



# National Toxicology Program

U.S. Department of Health and Human Services

## **Draft Report on Carcinogens Monograph on Antimony Trioxide**

### **Peer-Review Draft**

November 29, 2017

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

*This information is distributed solely for the purpose of pre-dissemination peer review under applicable information quality guidelines. It has not been formally distributed by the National Toxicology Program. It does not represent and should not be construed to represent any NTP determination or policy.*

**This Page Intentionally Left Blank**

## Foreword

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

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

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

## Objectives and Methods

### Objective and scope

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

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

Scientific evidence stream	Exposure	Outcome
<b>Primary evidence</b>		
Experimental animal studies	Antimony trioxide	All reported neoplasms
Human studies	Antimony trioxide (primarily) and other antimony compounds	Lung and stomach cancer
<b>Supporting evidence</b>		
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
<i>In vitro</i> studies	Antimony(III) compounds	Biological effects related to carcinogenicity or toxicity

The monograph also assesses exposure information (summarized in the table below) to determine whether a significant number of people residing in the United States are currently exposed or were exposed in the past to antimony(III) trioxide.

Information	Antimony compounds
Uses, consumption, and production	Antimony(III) trioxide and other commercially important antimony compounds
Occupational exposure	Primarily antimony(III) trioxide
Consumer products	Products containing antimony(III) trioxide
Environmental exposure	Antimony (species mostly undefined)

## Methods for developing the RoC monograph

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

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

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

### *Monograph development*

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

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

- Physical and Chemical Properties (Section 1)
- Human Exposure (Section 2)
- Disposition and Toxicokinetics (Section 3)
- Human Cancer Studies (Section 4)

- Studies of Cancer in Experimental Animals (Section 5)
- Mechanistic and Other Relevant Data (Section 6)
- Evidence Integration and Preliminary Listing Recommendation (Section 7).

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

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

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

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

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

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

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

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

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

### Questions related to the evaluation of cancer studies in experimental animals

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

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

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

### *Methods for preparing the monograph*

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

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

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

**Data extraction and quality assurance procedures.** Information for the relevant cancer and mechanistic studies was systematically extracted in tabular format and/or summarized in the text from studies selected for inclusion in the monograph. All sections of the monograph underwent scientific review and quality assurance (i.e., assuring that all the relevant data and factual information extracted from the publications had been reported accurately) by a separate reviewer. Any discrepancies were resolved by the writer and the reviewer through discussion and reference to the original data source.

**Evaluation of human cancer studies.** The available epidemiological studies are not specific for exposure to antimony(III) trioxide. Based on the studies' descriptions, it is likely that the workers were exposed to other forms of antimony in addition to the trioxide. Two reviewers evaluated the quality of each study using a series of questions (and guidelines for answering the questions) related to risk of bias and to study sensitivity (as described in the Protocol). Any disagreements between the two reviewers were resolved through discussion or by consultation with a third reviewer and reference to the original data source. The approach to synthesizing the evidence across studies and reaching a conclusion on the level of evidence for carcinogenicity is also outlined in the Protocol. Level-of-evidence conclusions (inadequate, limited, or sufficient) were made by applying the RoC criteria (see below) to the body of evidence.

### **RoC Listing Criteria**

#### ***Known To Be Human Carcinogen:***

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

#### ***Reasonably Anticipated To Be Human Carcinogen:***

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

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

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

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

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

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

**Evaluation of mechanistic and other relevant data.** As mentioned in the protocol, the mechanistic data were organized by characteristics of carcinogens (such as genotoxicity,



oxidative stress, epigenetic alterations, and promotion of cell proliferation) to help inform understanding of the relevant biological effects potentially contributing to 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 all antimony compounds, to help inform the cancer evaluation of antimony(III) trioxide and whether there is sufficient information to identify the antimony species ultimately responsible for carcinogenicity.

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

## **Collaborators, Contributors and Acknowledgments**

### **Collaborators: Report on Carcinogens Monograph Evaluation Team**

*Responsible for execution and coordination of project activities, including conception, design, planning, conduct, or technical review of cancer hazard evaluation*

ORoC, NIEHS Staff

Amy Wang, PhD (Project Lead)

Ruth M. Lunn, DrPH

Suril S. Mehta, MPH

*Contributed to design, conduct, technical review, and interpretation of studies for the cancer hazard evaluation*

Contractor Staff

Sanford C. Garner, PhD, ILS

Joanne Trgovcich, PhD, ICF

Andrew D. Ewens, PhD, DABT, ILS

Alton F. Peters, MS, ILS

NIEHS Staff

Kristine L. Witt, MS

### **Contributors: Report on Carcinogens Monograph Evaluation Team**

*Provided significant technical input or review (by affiliation, and then in alphabetic order)*

NIEHS Staff

Gloria D. Jahnke, DVM, DABT

Stephen S. Ferguson, PhD

Gordon P. Flake, MD

Michelle J. Hooth, PhD, DABT

Jui-Hua Hsieh, PhD

Daniel L. Morgan, PhD, DABT

Arun K.R. Pandiri, BVSc, MS, PhD

Matthew D. Stout, PhD, DABT

Kyla W. Taylor, PhD

Erik J. Tokar, PhD

Suramya Waidyanatha, PhD

Contractor Staff

Whitney D. Arroyave, PhD, ILS

Jessica A. Jeter, MSLS, ILS  
Government Staff  
Linda M. Sargent, PhD, CDC  
Kristina M. Hatlelid, PhD, MPH, CPSC  
Melanie C. Buser, MPH, ATSDR  
Yin-tak Woo, PhD, DABT, EPA

**Acknowledgement:***Provided technical input or review*

Stanley T. Atwood, MS, DABT, ILS  
Alison H. Harrill, PhD, NIEHS  
Nisha S. Sipes, PhD, NIEHS  
Sharon L. Oxendine, PhD, EPA  
Michael A. Babich, PhD, CPSC

*Organized the peer review of the monograph*

Mary S. Wolfe, PhD, NIEHS

*Developed web-based databases and data visualization*

Andy J. Shapiro, MSPH, NIEHS

*Scientific and copy editing of specific sections of the monograph*

Susan Dakin, PhD, independent consultant<sup>a</sup>

*Administrative support for the preparation of the monograph*

Ella J. Darden, BS, ILS  
Tracy L. Saunders, BS, ILS

*Administrative support for the peer-review meeting*

F. Louise Assem, PhD, ICF  
Canden N. Byrd, BS, ICF  
Susan E. Blaine, BA, ICF  
Anna N. Stamatogiannakis, BS, ICF

ICF = ICF Incorporated, LLC (Support provided through NIEHS Contract Number (GS00Q14OADU417/HHSN273201600015U).

ILS = Integrated Laboratory Systems, Inc. (Support provided through subcontract number 16EDBO0078 with ICF).

ORoC = Office of the Report on Carcinogens, DNTP, NIEHS.

**The Page Left Intentionally Blank**

## Table of Contents

1	Chemical identification and properties .....	1
1.1	Properties of antimony(III) trioxide and other antimony compounds .....	1
1.2	Antimony speciation and variability of valence .....	8
1.3	Detection of antimony and antimonial species .....	9
1.4	Summary .....	9
2	Human Exposure.....	11
2.1	Uses, manufacturing processes, and production-related information.....	11
2.1.1	Uses.....	11
2.1.2	Other notable uses for major antimony forms .....	12
2.2	Manufacturing processes .....	13
2.2.1	Production, consumption, and trade of antimony and antimony(III) trioxide in the United States .....	13
2.3	Occupational exposure.....	15
2.4	General population exposure .....	19
2.4.1	Consumer products .....	21
2.4.2	Environmental exposure .....	22
2.4.3	Food and drinking water .....	25
2.5	Summary and synthesis.....	25
3	Disposition and Toxicokinetics.....	27
3.1	Antimony(III) trioxide .....	27
3.1.1	Absorption and distribution .....	27
3.2	Other antimony compounds.....	31
3.2.1	Absorption and distribution .....	31
3.2.2	Excretion .....	33
3.3	Metabolism and valence states.....	34
3.4	Toxicokinetics.....	36
3.5	Summary and synthesis.....	39
3.5.1	Absorption and distribution .....	39
3.5.2	Metabolism .....	40
3.5.3	Excretion .....	40
3.5.4	Toxicokinetics.....	40
4	Human Cancer Studies.....	41
4.1	Selection of the relevant literature and overview of the study characteristics.....	41
4.2	Study quality and utility evaluation .....	43
4.3	Cancer hazard assessment.....	45
4.3.1	Lung cancer.....	46
4.3.2	Stomach cancer .....	53
4.3.3	Other types of cancers.....	55
4.4	NTP preliminary level of evidence conclusion.....	55
5	Studies of Cancer in Experimental Animals.....	57
5.1	Overview of the studies .....	57
5.2	Study quality assessment .....	58
5.3	Findings from carcinogenicity studies .....	60

5.3.1	Lung neoplasms .....	62
5.3.2	Other neoplasms.....	65
	Skin neoplasms .....	66
	Lymphomas.....	66
5.4	Synthesis and NTP preliminary level of evidence conclusion.....	67
5.4.1	Synthesis .....	67
5.4.2	NTP preliminary level of evidence conclusion.....	68
6	Mechanistic and Other Relevant Data .....	83
6.1	Other relevant data.....	83
6.1.1	Carcinogenicity studies of other antimony compounds.....	83
6.1.2	Non-cancer health outcomes.....	83
6.2	Electrophilic properties.....	84
6.3	Genotoxicity.....	84
6.3.1	Mutagenicity .....	84
6.3.2	Mutations in antimony(III) trioxide–induced lung tumors .....	85
6.3.3	DNA damage .....	85
6.3.4	Chromosomal aberrations, micronucleus, and sister chromatid exchange .....	86
6.3.5	Summary of genotoxicity results .....	87
6.4	Inhibition of DNA repair .....	87
6.5	Epigenetic alterations.....	89
6.6	Oxidative stress.....	90
6.7	Immunomodulation and inflammation .....	92
6.8	Alteration of cell proliferation and receptor-mediated effects.....	92
6.9	Transcriptomics and Tox21/ToxCast high-throughput screening .....	93
6.9.1	Transcriptomics.....	93
6.9.2	Tox21/ToxCast high-throughput screening.....	94
6.10	Integration of mechanistic information.....	95
7	Evidence Integration and Preliminary Listing Recommendation.....	97
7.1	Evidence of carcinogenicity from studies in experimental animals .....	97
7.2	Summary of mechanistic data.....	97
7.3	Evidence of carcinogenicity from studies in humans .....	98
7.4	Preliminary listing recommendation.....	98
	References.....	99
	Abbreviations.....	125
	Units of Measurement.....	132
	Glossary .....	134
	Draft Substance Profile.....	P-1
	Appendix A: Literature Search Strategy.....	A-1
A.1	General approach .....	A-1
A.2	Search strategies.....	A-3
A.3	Exclusion of treatment for leishmaniasis from human cancer searches .....	A-3
A.4	Updating the literature search .....	A-3
A.5	Review of citations using web-based systematic review software .....	A-3

Appendix B: ADME Tables.....	B-1
Appendix C: Human Studies Tables.....	C-1
Appendix D: Animal Study Quality Tables.....	D-1
Appendix E: Mechanistic and Other Relevant Information .....	E-1
E.1: Studies of antimony(III) potassium tartrate carcinogenicity in experimental animals ...	E-1
E.2: Genetox tables.....	E-7
E.3: Effects of antioxidants and inhibitors of oxidative stress related enzymes on cells exposed to compounds containing trivalent antimony.....	E-24
E.4: Immune effects from compounds containing pentavalent antimony .....	E-26
E.5 Top ten canonical pathways affected by 6-hours exposure to 20 $\mu$ M antimony(III) potassium tartrate trihydrate .....	E-28
E.6. Top 10 upstream regulators of antimony .....	E-30

### List of Tables

Table 1-1. Physical and chemical properties for antimony(III) trioxide .....	1
Table 1-3. Bioaccessibility of antimony(III) trioxide and other antimony compounds .....	2
Table 1-2. Physical and chemical properties for metallic (elemental) antimony and other antimony compounds with carcinogenicity or mechanistic data <b>Error! Bookmark not defined.</b>	
Table 1-4. Methods for detection of antimony and antimonial species in environmental and biological samples .....	9
Table 2-1. U.S. antimony(III) trioxide and antimony compound production volumes for 2015 exceeding 1,000,000 pounds per year ranked by quantity .....	15
Table 2-2. U.S. imports and exports of antimony metal and compounds for 2016 <sup>a</sup> .....	15
Table 2-3. Air levels and urine levels of total antimony in U.S. workers occupationally exposed to various antimony compounds in the air .....	16
Table 2-4. Antimony(III) trioxide occupational exposure level estimates (as antimony(III) trioxide) .....	19
Table 2-5. Ranges of geometric mean total antimony levels in urine, blood, and saliva samples of U.S. populations .....	20
Table 2-6. Sources of antimony(III) trioxide and the final forms of antimony ( $\text{Sb}^{\text{III}}_2\text{O}_3$ and others) to which people are exposed .....	21
Table 2-7. Estimated consumer exposure to antimony (as antimony(III) trioxide) directly and indirectly from products containing antimony(III) trioxide .....	22
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.....	25
Table 3-1. Antimony(III) trioxide levels <sup>a</sup> ( $\mu\text{g/g}$ ) in lung tissue during a 1-year chronic exposure (6 mo and 12 mo samples) and a 1-year observation period (6 mo and 12 mo samples) in Fischer 344 male and female rats.....	37
Table 3-2. Model-predicted values for Wistar Han rats exposed to antimony(III) trioxide via inhalation for 2 years.....	38
Table 4-1. Antimony exposure and human cancer studies .....	43
Table 4-2. Summary of ratings for concerns for potential bias, study quality, and study utility in antimony epidemiology studies.....	44

Table 4-3. Evidence from epidemiological cohort and case-control studies on lung and stomach cancers and exposure to antimony.....	47
Table 5-1. Experimental animal studies evaluated for carcinogenicity of antimony(III) trioxide	58
Table 5-2. Quality assessments of antimony trioxide cancer studies in experimental animals.....	58
Table 5-3. Neoplasms induced in experimental animal carcinogenicity studies of inhaled antimony(III) trioxide.....	61
Table 5-4. Lung tumors in the 2-year NTP 2017a studies.....	62
Table 5-5. Antimony and arsenic concentrations ( $\mu\text{g/g}$ freeze-dried tissue) in the lung and blood of Wistar rats exposed to antimony trioxide containing arsenic by inhalation.....	64
Table 5-6. Adrenal medulla neoplasms in Wistar Han rats in the NTP 2017 two-year study.....	66
Table 5-7. Neoplasms that had increased incidences in malignant tumors or combined (benign or malignant) tumors.....	68
Table 5-8. Cancer studies in experimental animals from exposure to antimony(III) trioxide.....	69
Table 6-1. Summary of genotoxicity data for antimony(III) trioxide and antimony(III) trichloride	87
Table 6-2. DNA repair pathways and molecules altered by exposure to antimony(III) compounds.....	89
Table A-1. Major topics searched.....	A-1
Table B-1. Antimony(III) trioxide levels <sup>a</sup> ( $\mu\text{g/g}$ ) in red blood cells during a 1-year chronic inhalation exposure (6 mo and 12 mo samples) and a 1-year observation period (6 mo and 12 mo samples) in Fischer 344 male and female rats.....	B-1
Table B-2. Blood antimony concentrations ( $\mu\text{g/g}$ blood) in female rats and mice exposed to antimony trioxide (N = 5 except where indicated).....	B-1
Table B-3. Tissue distribution of antimony ( $\mu\text{g}$ antimony/g tissue) in rats after oral exposure to antimony(III) trioxide by gavage or in the diet.....	B-2
Table C-1. Evaluation of selection bias in human cancer studies.....	C-1
Table C-2. Evaluation of exposure assessment methods in human cancer studies.....	C-1
Table C-3. Evaluation of outcome assessment in human cancer studies.....	C-2
Table C-4. Evaluation of study sensitivity in human cancer studies.....	C-2
Table C-5. Evaluation of potential for confounding bias for human cancer studies.....	C-3
Table C-6. Evaluation of analysis and selective reporting for human cancer studies.....	C-3
Table D-1. Kanisawa and Schroeder (1969) study of male and female (combined) mice exposed to antimony potassium tartrate in drinking water for the lifespan of the animals...	D-1
Table D-2. NTP (2017) study of male rats exposed to antimony trioxide by inhalation for 105 weeks.....	D-2
Table D-3. NTP (2017) study of female rats exposed to antimony trioxide by inhalation for 105 weeks.....	D-3
Table D-4. NTP (2017) study of male mice exposed to antimony trioxide by inhalation for 105 weeks.....	D-4
Table D-5. NTP (2017) study of female mice exposed to antimony trioxide by inhalation for 105 weeks.....	D-5
Table D-6. Groth <i>et al.</i> (1986) study of male rats exposed to antimony trioxide by inhalation for 53 weeks followed by post-exposure observation for 71 to 73 weeks.....	D-6
Table D-7. Groth <i>et al.</i> (1986) study of female rats exposed to antimony trioxide by inhalation for 53 weeks followed by post-exposure observation for 71 to 73 weeks.....	D-7
Table D-8. Newton <i>et al.</i> (1994) study of male rats exposed to antimony trioxide by inhalation for 12 months followed by post-exposure observation for 24 months.....	D-8



Table D-9. Newton <i>et al.</i> (1994) study of female rats exposed to antimony trioxide by inhalation for 12 months followed by post-exposure observation for 24 months.....	D-9
Table D-10. Watt (1983) study of female rats exposed to antimony trioxide by inhalation for 1 year followed by post-exposure observation for 2 years.....	D-10
Table E-1. Ten characteristics of carcinogens .....	E-1
Table E.1-1. Neoplasms induced in experimental animal carcinogenicity studies by drinking water studies of antimony potassium tartrate .....	E-2
Table E.1-2. Cancer studies in experimental animals exposed to antimony(III) potassium tartrate .....	E-2
Table E.1-3. Schroeder <i>et al.</i> (1970) study of male rats exposed to antimony(III) potassium tartrate in drinking water for the life span of the animals .....	E-4
Table E.1-4. Schroeder <i>et al.</i> (1970) study of female rats exposed to antimony(III) potassium tartrate in drinking water for the life span of the animals .....	E-5
Table E.1-5. Kanisawa and Schroeder (1969) study of male and female (combined) mice exposed to antimony potassium tartrate in drinking water for the lifespan of the animals.....	E-6
Table E.2-1. Genotoxicity of antimony compounds: Mutations <sup>a, b, c</sup> .....	E-7
Table E.2-2. Mutations in the lung of mice and rats after two-year inhalation exposure to antimony trioxide (NTP 2016). .....	E-9
Table E.2-3. Genotoxic DNA damaging effects of antimony compounds.....	E-10
Table E.2-4. Genotoxicity of antimony compounds – chromosomal aberrations, micronucleus, and sister chromatic exchange <sup>a, b, c</sup> .....	D-16
Table E.3-1. Effects of antioxidants and inhibitors of oxidative stress related enzymes on cells exposed to compounds containing trivalent antimony .....	D-24
Table E.4-1. Effects of compounds containing pentavalent antimony on immunity.....	D-26
Table E.5-1. Top ten canonical pathways affected by 6-hour exposure to 20 $\mu$ M antimony(III) potassium tartrate trihydrate .....	D-28
Table E.6-1. Top 10 upstream regulators for antimony.....	D-30

## List of Figures

Figure 1-1. Structure for antimony(III) trioxide .....	1
Figure 1-2. Antimony speciation for antimony(III) and antimony(V) species over a range of pH values.....	8
Figure 2-1. Antimony(III) trioxide used in manufacturing processes .....	14
Figure 3-1. Blood antimony levels ( $\mu$ g/L) in female mice (panel A) and rats (panel B) exposed to antimony(III) trioxide by inhalation at 0, 3, 10, or 30 $\text{mg}/\text{m}^3$ in a 2-year study .....	29
Figure 3-2. Lung antimony(III) trioxide burdens in female rats in the 2-year inhalation study.....	39
Figure 3-3. Lung antimony(III) trioxide burdens in female mice in the 2-year inhalation study.....	39
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 .....	52
Figure 6-1. Antimony increases oxidative stress. ....	91
Figure A-1. Literature search strategy and review.....	A-2

**This Page Intentionally Left Blank**

# 1 Chemical identification and properties

This section provides information on the physical and chemical properties of antimony(III) trioxide ( $\text{Sb}^{(\text{III})}_2\text{O}_3$ ) and on antimony compounds with toxicological and other relevant information (Sections 3, 4, 5, and 6). As mentioned in the Objectives and Methods, toxicological information (Section 6) and information on properties for other antimony compounds (see below) may inform the cancer hazard evaluation of antimony(III) trioxide.

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

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

Figure 1-1. Structure for antimony(III) trioxide

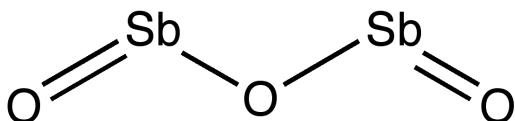


Table 1-1. Physical and chemical properties for antimony(III) trioxide

Property	Information
Chemical formula	$\text{Sb}^{(\text{III})}_2\text{O}_3^{\text{a}}$
CAS No.	1309-64-4 <sup>b</sup>
InChi key	ADCOVFLJGNWWNZ-UHFFFAOYSA-N <sup>c</sup>
Molecular weight	291.5 <sup>a</sup>
% Antimony by weight	83.6
Antimony charge	+3 <sup>a</sup>
Specific gravity, at 24°C	5.9 <sup>c</sup>
Melting point	655°C <sup>c</sup>
Boiling point	1425°C <sup>c</sup>
Water solubility, at 22.2°C [3.3 x 10 <sup>-4</sup> ] g/100 mL <sup>d,e</sup>	
Vapor pressure, at 574°C	1 mm Hg <sup>c</sup>

Sources: <sup>a</sup>ChemIDplus 2017, <sup>b</sup>EPA 2017a, <sup>c</sup>PubChem 2017, <sup>d</sup>IPCS 2017.

<sup>e</sup>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 (Section 4 and 5), mechanistic (Section 6), or disposition (Section 3) data. In addition to elemental antimony (valence = 0), most antimony compounds have valences of either +3 (11 compounds) or +5 (5 compounds) although one compound with valence -3 is also included in the table. Compounds with +3 valence are likely to share more similarity with antimony(III) oxide but as discussed in Sections 2 and 3, interconversion between antimony(III) and antimony(V) occurs during manufacturing processes, in the environment, and *in vivo*. Both the +3 and +5 valence states include both inorganic antimony compounds, e.g., antimony(III)

trisulfide and antimony(V) pentasulfide, and organic antimony compounds, primarily those used as anti-leishmanial drugs, such as sodium antimony 2,3-mesodimercaptosuccinate (the active ingredient in Astiban) and sodium stibogluconate(III) (the active ingredient in Pentostam).

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

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

Antimony compound	Percent (%) solubility in simulated human fluid after 24 hours of exposure				
	GMB <sup>a</sup> (pH = 7.4)	PBS <sup>b</sup> (pH = 7.4)	ASW <sup>c</sup> (pH = 6.5)	ALF <sup>d</sup> (pH = 4.5)	GST <sup>e</sup> (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.

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

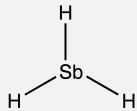
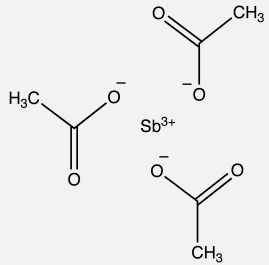
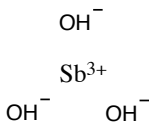
<sup>b</sup>PBS = Phosphate-buffered saline. PBS mimics the ionic strength of human blood serum.

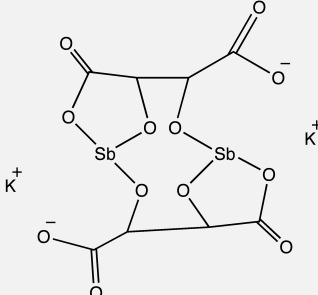
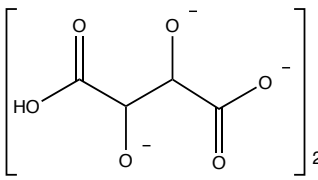
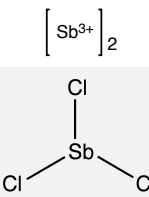
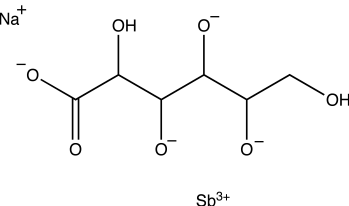
<sup>c</sup>ASW = Artificial sweat. ASW mimics hypoosmolar fluid excreted upon sweating.

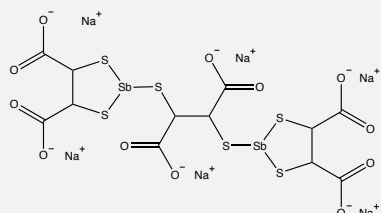
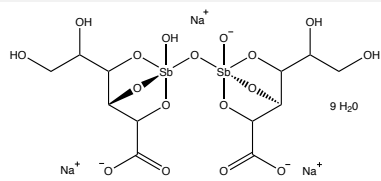
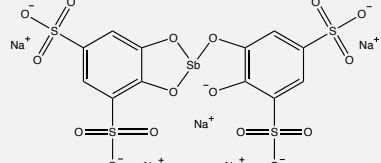
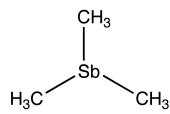
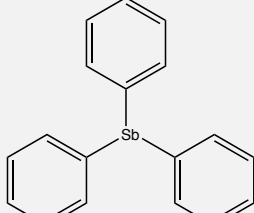
<sup>d</sup>ALF = Artificial lysosomal fluid. ALF mimics intracellular conditions in lung cells during phagocytosis.

<sup>e</sup>GST = Artificial gastric fluid. GST mimics stomach acid.

Table 1-2. Physical and chemical properties for metallic (elemental) antimony and other antimony compounds with carcinogenicity or mechanistic data

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 <sup>c</sup>
<i>Valence = 0</i>						
<b>Antimony (elemental)</b>	7440-36-0 <sup>a</sup> (WATWJIUSRGPENY-UHFFFAOYSA-N <sup>a</sup> )	Sb <sup>a</sup>	Sb	121.8 <sup>a</sup> (100.0 <sup>a</sup> )	6.68 <sup>a, b</sup>	Insoluble <sup>a</sup>
<i>Valence = -3</i>						
<b>Stibine</b>	7803-52-3 <sup>a</sup> (OUULRIDHGPHMNQ-UHFFFAOYSA-N <sup>a</sup> )	SbH <sub>3</sub> <sup>a</sup>		124.8 <sup>a</sup> (97.6 <sup>a</sup> )	2.26 <sup>a, d</sup>	[4.1 × 10 <sup>-1</sup> ] <sup>a, e</sup> Slightly soluble
<i>Valence = +3</i>						
<b>Antimony acetate; acetic acid antimony (+3) salt</b>	6923-52-0 <sup>a</sup> (JVLRYPRBKSMEEBF-UHFFFAOYSA-K <sup>a</sup> )	C <sub>6</sub> H <sub>9</sub> O <sub>6</sub> Sb <sup>a</sup>		298.9 <sup>a</sup> (40.7 <sup>a</sup> )	—	—
<b>Antimony hydroxide</b>	39349-74-1 <sup>f</sup> (SZOADBKOANDULT-UHFFFAOYSA-K <sup>a</sup> )	H <sub>3</sub> O <sub>3</sub> Sb <sup>a</sup>		172.8 <sup>a</sup> (70.5 <sup>a</sup> )	—	—

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 <sup>e</sup>
<b>Antimony potassium tartrate<sup>g</sup></b>	28300-74-5 <sup>a</sup> (WBTCZEPSIIFINA-MSFWTACDSA-J <sup>a</sup> )	C <sub>8</sub> H <sub>4</sub> K <sub>2</sub> O <sub>12</sub> Sb <sub>2</sub> <sup>g</sup>		667.8 <sup>a</sup> (36.5 <sup>a</sup> )	2.6 <sup>a</sup>	[8.3 × 10 <sup>0</sup> ] <sup>a, h</sup> Soluble
<b>Antimony tartrate<sup>i</sup></b>	12544-35-3 <sup>f</sup> (JFVMOLRNQCNLCHI-WZZCOQPSA-J <sup>f</sup> )	C <sub>8</sub> H <sub>4</sub> O <sub>12</sub> Sb <sub>2</sub> <sup>f</sup>		535.6 <sup>f</sup> (45.5 <sup>f</sup> )	—	[2.8 × 10 <sup>2</sup> ] <sup>j</sup> Very soluble
<b>Antimony trichloride</b>	10025-91-9 <sup>a</sup> (FAPDDOBMIUGHIN-UHFFFAOYSA-K <sup>a</sup> )	SbCl <sub>3</sub> <sup>a</sup>		228.1 <sup>a</sup> (53.4 <sup>a</sup> )	3.14 <sup>a, k</sup>	10 × 10 <sup>0a, l</sup> Soluble
<b>Sodium antimony(III) gluconate (antimony(III) sodium gluconate)</b>	12550-17-3 <sup>f</sup> (JEKOQEIHGHQVEI-ZBHRUSISSA-M <sup>f</sup> )	C <sub>6</sub> H <sub>8</sub> NaO <sub>7</sub> Sb <sup>f</sup>		336.9 <sup>f</sup> (36.2 <sup>f</sup> )	—	—

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 <sup>e</sup>
<b>Sodium antimony 2,3-mesodimercaptosuccinate</b> (active ingredient in Astiban)	1986-66-9 <sup>a</sup> (AOGOCZMBIYQOF E-UHFFFAOYSA-B <sup>a</sup> )	C <sub>12</sub> H <sub>6</sub> Na <sub>6</sub> O <sub>12</sub> S <sub>6</sub> Sb <sub>2</sub> <sup>a</sup>		916.0 <sup>a</sup> (26.6 <sup>a</sup> )	—	—
<b>Sodium stibogluconate</b> (active ingredient in Pentostam)	16037-91-5 <sup>f</sup> (CUEDNFKBTFCOSV -UZVLBLASSA-L <sup>f</sup> )	C <sub>12</sub> H <sub>20</sub> O <sub>17</sub> Sb <sub>2</sub> 3Na•9H <sub>2</sub> O <sup>f</sup>		908.9 <sup>f</sup> (26.8 <sup>f</sup> )	—	—
<b>Stibophen<sup>m</sup></b>	15489-16-4 <sup>f</sup> (ZDDUXABBRATYFS-UHFFFAOYSA-F <sup>f</sup> )	C <sub>12</sub> H <sub>4</sub> O <sub>16</sub> S <sub>4</sub> Sb•7H <sub>2</sub> O•5Na <sup>f</sup>		895.2 <sup>f</sup> (13.6 <sup>f</sup> )	—	—
<b>Trimethylstibine</b>	594-10-5 <sup>a</sup> (PORFVJURJXKREL-UHFFFAOYSA-N <sup>a</sup> )	C <sub>3</sub> H <sub>9</sub> Sb <sup>a</sup>		166.9 <sup>a</sup> (73.0 <sup>a</sup> )	—	—
<b>Triphenylstibine</b>	603-36-1 <sup>a</sup> (HVYVMSPJIWUNA-UHFFFAOYSA-N <sup>a</sup> )	C <sub>18</sub> H <sub>15</sub> Sb <sup>a</sup>		353.1 <sup>a</sup> (34.5 <sup>a</sup> )	—	[4.3 × 10 <sup>-6</sup> ] <sup>f, n</sup> Insoluble

*Valence* = +5

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 <sup>c</sup>
<b>Antimony pentachloride</b>	7647-18-9 <sup>a</sup> (VMPVEPPRYRXYN P-UHFFFAOYSA-I <sup>a</sup> )	SbCl <sub>5</sub> <sup>a</sup>		299.0 <sup>a</sup> (40.7 <sup>a</sup> )	2.35 <sup>a, k</sup>	–
<b>Antimony pentasulfide</b>	1315-04-4 <sup>a</sup> (PPKVREKQVQREQ D-UHFFFAOYSA-N <sup>a</sup> )	S <sub>5</sub> Sb <sub>2</sub> <sup>a</sup>		403.8 <sup>a</sup> (60.3 <sup>a</sup> )	–	[9.9 × 10 <sup>-6</sup> ] <sup>o</sup> Insoluble
<b>Antimony pentoxide</b>	1314-60-9 <sup>f</sup> (LJCFOYOSGPHIOO UHFFFAOYSA-N <sup>f</sup> )	Sb <sub>2</sub> O <sub>5</sub> <sup>f</sup>		323.5 <sup>f</sup> (75.3 <sup>f</sup> )	–	[4.3 × 10 <sup>-6</sup> ] <sup>p</sup> Insoluble
<b>Meglumine antimoniate</b>	133-51-7 <sup>a</sup> (XOGYVDXPYPVAAQ -SESJOKTNSA-M <sup>a</sup> )	C <sub>7</sub> H <sub>18</sub> NO <sub>8</sub> Sb <sup>a</sup>		366.0 <sup>a</sup> (33.3 <sup>a</sup> )	–	–
<b>Potassium hexahydroxy antimonate</b>	12208-13-8 <sup>q</sup> (IAYJQRROUBIPRX- UHFFFAOYSA-H <sup>l</sup> )	H <sub>6</sub> KO <sub>6</sub> Sb <sup>q</sup>		262.9 <sup>q</sup> (46.3 <sup>q</sup> )	–	–

– = No data found, CAS = Chemical Abstracts Service, InChi = IUPAC International Chemical Identifier.

<sup>a</sup>PubChem 2017.

<sup>b</sup>At 77°F.

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

<sup>d</sup>At -25°C.

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

<sup>f</sup>ChemIDplus 2017.

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

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

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

<sup>j</sup>EPA CompTox Chemistry Dashboard 2017 (<https://comptox.epa.gov/dashboard/dsstoxdb/results?utf8=%E2%9C%93&search=12544-35-3>). Reported as mean of 5.55 mol/L. Brackets denote unit conversion. Accessed 11/16/2017.

<sup>k</sup>At 68°F.

<sup>l</sup>At 25°C.

<sup>m</sup>The anhydrous form of Stibophen is C<sub>12</sub>H<sub>4</sub>Na<sub>5</sub>O<sub>16</sub>S<sub>4</sub>Sb (CAS number = 23940-36-5, molecular weight = 769.1 g/mol).



<sup>b</sup>Reported as 0.043 mg/L at 25°C. Brackets denote unit conversion. Accessed 11/29/2017.

<sup>c</sup>EPA CompTox Chemistry Dashboard 2017 (<https://comptox.epa.gov/dashboard/dsstoxdb/results?utf8=%E2%9C%93&search=1315-04-4>). Reported as  $2.46 \times 10^{-7}$  mol/L. Brackets denote unit conversion. Accessed 11/14/2017.

<sup>d</sup>EPA CompTox Chemistry Dashboard 2017 (<https://comptox.epa.gov/dashboard/dsstoxdb/results?utf8=%E2%9C%93&search=1314-60-9>). Reported as  $1.32 \times 10^{-7}$  mol/L by EpiSuite 2017. Brackets denote unit conversion. Accessed May 30, 2017.

<sup>e</sup>ChemSpider 2017 (<http://www.chemspider.com/Chemical-Structure.11311229.html>). Accessed 11/20/2017.

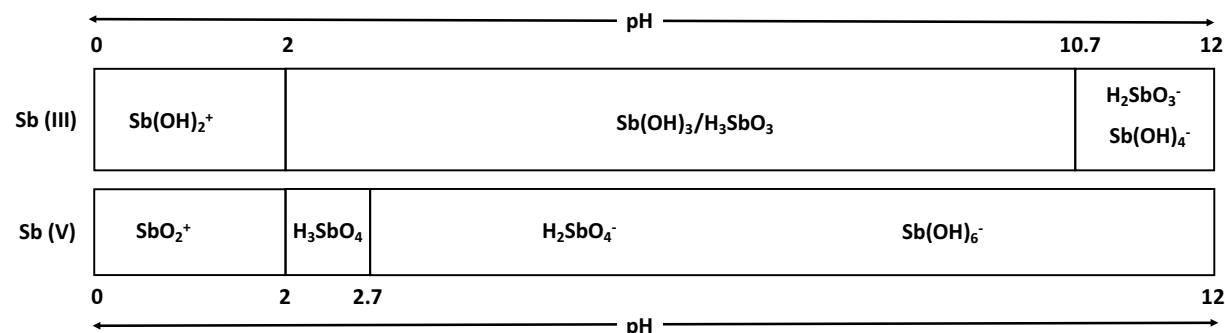
## 1.2 Antimony speciation and variability of valence

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

Elemental antimony exists in four primary oxidation states; -3, 0, +3, and +5; Sb(III) (trivalent form) and Sb(V) (pentavalent form) are the most common in environmental, biological, and geochemical systems. Thermodynamic equilibrium calculations indicate that antimony(V) predominates in oxic systems, and antimony(III) predominates in anoxic systems. However, antimony(III) concentrations at higher than calculation-predicted values have been detected in oxic systems; similarly, higher than calculation-predicted antimony(V) concentrations have been detected in anoxic systems (Filella *et al.* 2002b). Both trivalent (III) and pentavalent (V) antimony ions hydrolyze readily. When any form of antimony dissolves in water, it exists as the hydroxide forms, Sb(OH)<sub>3</sub> (uncharged) or Sb(OH)<sub>6</sub><sup>-</sup> (charged) (Herath *et al.* 2017).

Antimony(III) is present as the neutral species Sb(OH)<sub>3</sub> (or H<sub>3</sub>SbO<sub>3</sub>) for pH values from 2 to approximately 10 (Krupka and Serne 2002) and antimony(V) is present as the anion Sb(OH)<sub>6</sub><sup>-</sup> (or H<sub>2</sub>SbO<sub>4</sub><sup>-</sup>) 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,b).



**Figure 1-2. Antimony speciation for antimony(III) and antimony(V) species over a range of pH values**

Source: Herath *et al.* 2017. Sb(OH)<sub>2</sub><sup>+</sup> = dihydroxoantimony (III); Sb(OH)<sub>3</sub>/H<sub>3</sub>SbO<sub>3</sub> = trihydroxy antimony (III)/Antimonous acid (III); H<sub>2</sub>SbO<sub>3</sub><sup>-</sup> = dissociated form of Sb<sub>2</sub>O<sub>3</sub> (III); Sb(OH)<sub>4</sub><sup>-</sup> = tetrahydroxoantimony (III), dissociated form of Sb<sub>2</sub>O<sub>3</sub>; SbO<sub>2</sub><sup>+</sup> = cation (V); H<sub>3</sub>SbO<sub>4</sub> = antimonous acid (V); H<sub>2</sub>SbO<sub>4</sub><sup>-</sup> = dihydrogen antimonate (V); Sb(OH)<sub>6</sub><sup>-</sup> = antimonate ion (V), hexahydroxoantimonate.

Inorganic forms generally are found more often than organic forms in many environmental systems (EU 2008, Herath *et al.* 2017). However, antimony can form organic compounds via biological methylation (i.e., the chemical combination of methyl groups with metals or metalloids through the action of a living organism such as bacteria, fungi, or plants) (Filella *et al.* 2007). Evidence for *in vivo* methylation of antimony in mammals is limited (see Section 3).

### 1.3 Detection of antimony and antimonial species

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

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

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	–	Zheng <i>et al.</i> 2006, ATSDR 2017
Liquid chromatography-hydride generation-atomic fluorescence spectrometry (LC-HG-AFS)	Sb(III) and Sb(V) in tap water and river water	–	Vinas <i>et al.</i> 2006, ATSDR 2017
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)	Ulrich 1998, Müller <i>et al.</i> 2009
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	Quiroz <i>et al.</i> 2011, ATSDR 2017
High-performance liquid chromatography-ultraviolet-hydride generation-atomic fluorescence spectrometry (HPLC-UV-HG-AFS)	–	Sb(III) and Sb(V) in marine algae and mollusks	De Gregori <i>et al.</i> 2007, ATSDR 2017

### 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,  $\text{Sb}(\text{OH})_3$ .

## 2 Human Exposure

In the United States, antimony(III) trioxide ( $\text{Sb}^{\text{III}}_2\text{O}_3$ ) is the most commercially significant form of processed antimony. In nature,  $\text{Sb}^{\text{III}}_2\text{O}_3$  exists in minerals such as valentinite and senarmontite (Roper *et al.* 2012, ATSDR 2017). Antimony is found in nature in these and other mineral species, often in association with arsenic compounds due to their similar geochemical properties.

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

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

### 2.1 Uses, manufacturing processes, and production-related information

#### 2.1.1 Uses

##### Antimony(III) trioxide

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

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

**PET production:** The use of antimony(III) trioxide (EU 2008, EPA 2014) as a catalyst for PET plastics results in final concentrations of 180 to 550 ppm antimony in the plastic. While the major current use for PET plastic is in bottles for water and other beverages, often intended for

single use and then disposal, the major use for recycled PET is as PET fibers for fleece fabrics for clothing, in soft toys, rugs, carpets, and upholstery, including in automobiles. Antimony is not generally removed from the PET to recycle antimony (Grund *et al.* 2006).

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

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

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

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

### 2.1.2 Other notable uses for major antimony forms

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

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

## 2.2 Manufacturing processes

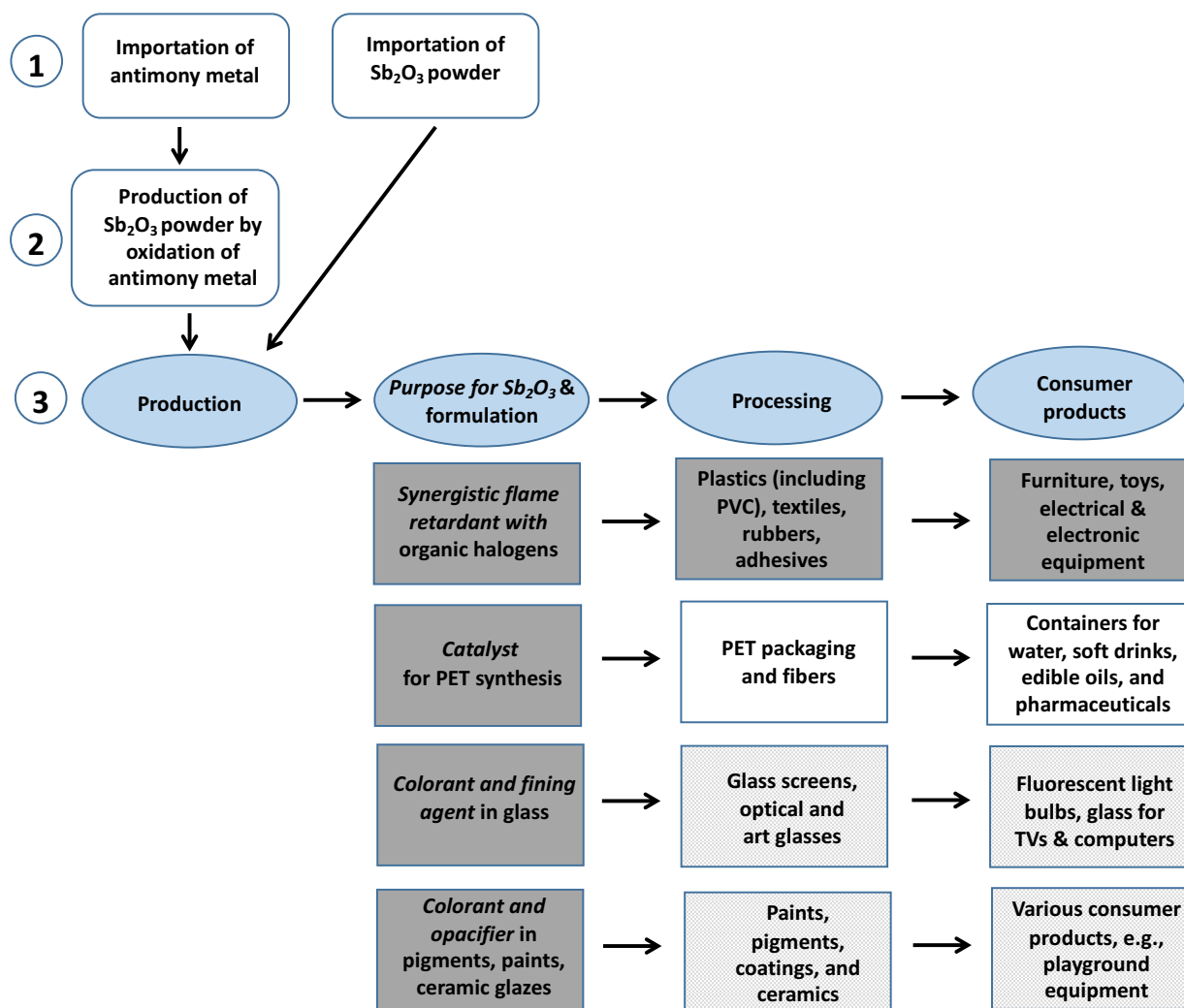
Antimony(III) trioxide for manufacturing processes may either be imported in that form (second box by the number 1 in Figure 2-1) or produced in the United States by oxidation of imported antimony metal (box 2 in Figure 2-1). The lifecycle for antimony and antimony(III) trioxide often ends at disposal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

Antimony(III) trioxide is produced primarily by re-volatilization of crude antimony(III) trioxide or by oxidation of antimony metal (EU 2008). The only domestic producer of primary antimony metal and oxide identified is a company in Montana that uses imported feedstock (USGS 2017), as no marketable antimony has been mined in the United States since 2015 (USGS 2017). The most recent U.S. mine production was in Nevada in 2013 and 2014, when about 800 tons of stibnite ( $\text{Sb}^{\text{III}}_2\text{S}_3$ ), the principal antimony ore, was extracted. That mine has been on care-and-maintenance status (i.e., production has ceased but management for public health and safety continues) since 2015 (USGS 2017).

Antimony trioxide changes its chemical form during the formulation and processing stages for many products. For example, antimony(III) trioxide may be chemically transformed to antimony(V) pentoxide by oxidation during the production process, and the resulting antimony(V) form may either be chemically bonded in a crystal matrix in pigments or present as antimony(V) pentoxide in glass. Antimony(III) trioxide used as a catalyst for polyethylene terephthalate (PET) production in Japan and China has been shown to be present in the finished plastic as antimony glycolate (Takahashi *et al.* 2008). An exception to transformation during production is the use of antimony(III) trioxide as a synergist for flame retardants, in which  $\text{Sb}^{\text{III}}_2\text{O}_3$  retains the trioxide form in finished consumer products. However, transformation of antimony(III) trioxide does occur if the product is burned. The changes in chemical form for antimony are illustrated in Figure 2-1 by the grey shading in the boxes, which indicates the likelihood that antimony(III) trioxide is present at that stage of the process as described in the figure legend.

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

Antimony(III) trioxide, elemental antimony, and several other antimony compounds (e.g., antimony(V) pentoxide, and antimony diamyldithiocarbamate) are high-production-volume chemicals, based on their production in, or import into, the United States in quantities of 1 million pounds or more per year (see Table 2-1 for U.S. antimony(III) trioxide and antimony compound production volumes for 2015 and Table 2-2 for import and export information). Elemental (i.e., metallic) antimony may be converted to antimony(III) trioxide by oxidation, and various forms of antimony, such as antimony(III) trisulfide in brake lubricants oxidize to antimony(III) trioxide at the high temperature achieved during the use of vehicle brakes. Other forms do not generally give rise to the trioxide form except through incineration. The EU (2008) risk assessment report noted that combustion or incineration processes produce antimony(III) trioxide from all forms of pre-incinerated antimony.



**Figure 2-1. Antimony(III) trioxide used in manufacturing processes**

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.

Antimony(III) trioxide accounts for 80% of total antimony use in the United States (EPA 2014, NTP 2016c). Reports under the U.S. Environmental Protection Agency's (EPA's) Chemical Data Reporting rule indicate that approximately 1 million to 10 million pounds of antimony(III) trioxide is produced in the United States (see Table 2-1); however, the actual consumption of antimony(III) trioxide is likely much higher. EPA (2014) reported that most (approximately 87%) of the roughly 70 million pounds of antimony(III) trioxide consumed in the United States each year between 2007 and 2011 was imported (EPA 2014). The majority of total antimony (83%) used in the United States is also imported, mostly from China, and the remainder (17%) is recovered from antimony-lead batteries (USGS 2017). In 2012, the U.S. EPA identified three companies manufacturing and ten companies importing antimony(III) trioxide (EPA 2012).



**Table 2-1. U.S. antimony(III) trioxide and antimony compound production volumes for 2015 exceeding 1,000,000 pounds per year ranked by quantity**

CAS Number <sup>a</sup>	Antimony compound	Quantity (lb) <sup>a</sup>
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 diamyldithiocarbamate <sup>b</sup>	1,000,000–10,000,000

<sup>a</sup>EPA 2017a.<sup>b</sup>Antimony diamyldithiocarbamate is a form of antimony dialkyldithiocarbamate with 5-carbon alkyl chains.**Table 2-2. U.S. imports and exports of antimony metal and compounds for 2016<sup>a</sup>**

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 <sup>b</sup>	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.

<sup>a</sup>Quantities converted from kilograms by NTP.<sup>b</sup>USITC harmonized tariff schedule (HTS) code 28258000 does not distinguish between antimony(III) trioxide and antimony(V) pentoxide.

### 2.3 Occupational exposure

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

U.S. monitoring data from the Occupational Safety and Health Administration (OSHA) Chemical Exposure Health Dataset during a period of more than 30 years (1984 to 2017) reported data from 2,126 personal breathing zone samples collected from companies producing or using “antimony and compounds (as Sb)” (forms of antimony not specified) (OSHA 2017). The antimony air levels (breathing zone), as total antimony, ranged from 0.2  $\mu\text{g}/\text{m}^3$  to 54,500  $\mu\text{g}/\text{m}^3$  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 (e.g., antimony-containing flame retardants) (3.3  $\mu\text{g}/\text{m}^3$  to

54,500  $\mu\text{g}/\text{m}^3$ ); SIC Code 3341, secondary smelting and refining of nonferrous metals (e.g., antimonial lead refining) (1.8  $\mu\text{g}/\text{m}^3$  to 47,700  $\mu\text{g}/\text{m}^3$ ), and SIC Code 3339, primary smelting and refining of nonferrous metals (including antimony) (5  $\mu\text{g}/\text{m}^3$  to 18,500  $\mu\text{g}/\text{m}^3$ ). 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.

Workers in the United States producing or using antimony(III) trioxide, as well as workers in occupations exposed to other antimony compounds, can be exposed to antimony(III) trioxide through inhalation of airborne solid dust or by skin contact. Among industries using or producing antimony(III) trioxide, the highest levels (up to 5,000 to 6,000  $\mu\text{g}/\text{m}^3$ , 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 ( $\text{Sb}^{\text{III}}_2\text{O}_3$ ) considered metal smelting and refining to be one of the major anthropogenic sources of antimony release to the atmosphere. U.S. air monitoring data specific for antimony(III) trioxide industries come primarily from NIOSH walk-through surveys of a few smelters or antimony(III) trioxide companies conducted largely in the 1970s, which usually were conducted as part of health hazard evaluations (CDC 2016b) or industrial hygiene surveys, the results for two of which were also reported in an epidemiological study (Schnorr *et al.* 1995) (see Table 2-3). Workers using or producing other types of antimony, such as elemental antimony used in the battery industry, can also be exposed to antimony(III) trioxide because metallic antimony oxidizes to antimony(III) trioxide in the air (EU 2008).

Urinary excretion of antimony by exposed workers generally increases with the level of exposure, although relatively few studies have reported both exposure and urinary excretion for the same workers. A few studies that reported both parameters are summarized in Table 2-3 together with studies that reported air levels only. The current TLV for elemental antimony and antimony compounds in air is 500  $\mu\text{g}/\text{m}^3$  (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 U.S. workers occupationally exposed to various antimony compounds in the air**

Exposure scenario (N)	Form of Sb used	Air Sb levels (as total Sb) ( $\mu\text{g}/\text{m}^3$ )	Urine Sb levels (as total Sb), $\mu\text{g}/\text{g}$ creatinine unless specified	Reference
<b>Industries that produce or use producing antimony(III) trioxide</b>				
Antimony(III) trioxide production	$\text{Sb}^{\text{III}}_2\text{O}_3$			Donaldson and Gentry 1975 <sup>a</sup>
Personal samples (2)		2,700–5,000	NR	
General area samples (2)		1,800– 5,600	NR	

Exposure scenario (N)	Form of Sb used	Air Sb levels (as total Sb) ( $\mu\text{g}/\text{m}^3$ )	Urine Sb levels (as total Sb), $\mu\text{g}/\text{g}$ creatinine unless specified	Reference
Antimony & antimony(III) trioxide production (smelting and refining) Breathing zone (55) Area samples (NR)	$\text{Sb}^{\text{III}}\text{S}_3$ & $\text{Sb}^{\text{III}}_2\text{O}_3$	50–6,210 140–2,120	NR NR	Donaldson 1976 <sup>a</sup>
Antimony oxide production (5)	$\text{Sb}^{\text{III}}\text{S}_3$ & $\text{Sb}^{\text{III}}_2\text{O}_3$	210–3,200	NR	Cassady and Etchison 1976
Antimony(III) trioxide production (12)	$\text{Sb}^{\text{III}}_2\text{O}_3$	766	419.8 $\mu\text{g}/\text{L}$	Kim <i>et al.</i> 1999
Flame retardant industry (NR)	NR	BDL <sup>b</sup> –200		ATSDR 1992
Glass production facility (NR)	NR	5	NR	Burroughs and Horan 1981
Glass industry- batch bunker Personal air (3) Stationary air (4)	$\text{Sb}^{\text{III}}_2\text{O}_3$	< 50, 720, 840 40, 60, 70, 290		Lüdersdorf <i>et al.</i> 1987
Batch Mixer (45)			5.0 (1.5–15.7) $\mu\text{g}/\text{L}$	
Rubber company Compounding area	Antimony oxide	10–150	NR	Salisbury 1980
<b>Other exposures</b>				
Lead battery production	$\text{Sb}^{\text{III}}_2\text{O}_3$ $\text{Sb}^{\text{III}}\text{H}_3$	4.5–12.4	3.9–15.2	Kentner <i>et al.</i> 1995
Lead-acid battery plant (NR)	$\text{Sb}^{\text{III}}\text{H}_3$	ND <sup>c</sup> –2,500	NR	Jones and Gamble 1984, Young 1979a, b
Secondary lead smelter (reclaiming scrap batteries) Breathing zone (2 of 21 TWAs)	NR	37, 51	NR	Craig <i>et al.</i> 1981
Manufacture of pentavalent antimony compounds Wet process (26) Dry process (14)	$\text{Sb}^{\text{V}}_2\text{O}_5$ $\text{Na}_3\text{Sb}^{\text{V}}\text{O}_4$	86 $\pm$ 3.9 927 $\pm$ 985	812.3 $\pm$ 5.0 110 $\pm$ 76	Bailly <i>et al.</i> 1991
Refinery workers	NR	< 10–80	0.08–32.6 $\mu\text{g}/\text{L}$	Smith <i>et al.</i> 1995
Chemical manufacturers	NR	NR	0.1–36.1 $\mu\text{g}/\text{L}$	
Battery manufacturers	NR	NR	1.5–149.2 $\mu\text{g}/\text{L}$	
Resinoid grinding wheel manufacture (NR)	$\text{Sb}^{\text{III}}\text{S}_3$	~3,000	800–9,600 $\mu\text{g}/\text{L}$	Brieger <i>et al.</i> 1954
Iron foundry (NR)	NR	0.15	NR	Zhang <i>et al.</i> 1985

Exposure scenario (N)	Form of Sb used	Air Sb levels (as total Sb) ( $\mu\text{g}/\text{m}^3$ )	Urine Sb levels (as total Sb), $\mu\text{g}/\text{g}$ creatinine unless specified	Reference
Injection molding of ignition resistant polystyrene (NR)	NR	0.03–200	NR	Willets <i>et al.</i> 1982

<sup>a</sup>Also reported by Schnorr *et al.* 1995 (see Section 5).

<sup>b</sup>BDL = below detection limit; level of detection reported as  $0.3 \mu\text{g}/\text{m}^3$ , NR = not reported.

<sup>c</sup>ND = not detectable. No detection limit reported in ATSDR 1992.

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

Inhalation exposure can also occur when antimony(III) trioxide powder is used in cement mixing (or cement powder-based product blending) applications (see Section 2.3) (Mapei Group 2017).

**Table 2-4. Antimony(III) trioxide occupational exposure level estimates (as antimony(III) trioxide)**

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

Source: EU 2008.

<sup>a</sup>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.

<sup>b</sup>Job-specific typical exposure is equal to the median (50<sup>th</sup> percentile) exposure level.

<sup>c</sup>Job-specific (reasonable) worst-case exposure is equal to the 90<sup>th</sup> percentile exposure level.

<sup>d</sup>The body weight of the worker is 70 kg and the exposed dermal area is 2000  $\text{cm}^2$ .

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

<sup>f</sup>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.

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

## 2.4 General population exposure

Evidence for exposure of the U.S. general population to antimony is provided by biomonitoring data showing its presence in urine, whole blood, and saliva. Data from the National Health and Nutrition Examination Survey (NHANES) indicate low exposure to antimony, with geometric means of 0.132  $\mu\text{g}/\text{L}$  urine for years 1999 to 2000 and 0.043  $\mu\text{g}/\text{L}$  urine for years 2013 to 2014 (Table 2-5). Although the most recent data suggest that levels might be decreasing over time, this could reflect the use of more sensitive analytical methods in recent years, rather than actual decreasing exposure, an explanation supported by reports of values close to the lower detection limits for the methods used (Filella *et al.* 2013a). Older publications tended to report higher

concentrations of total antimony in urine. Based on analysis of NHANES data, higher urinary antimony levels were found in individuals with lower socioeconomic status, defined as either low income or living in economically deprived neighborhoods (Belova *et al.* 2013, Tyrrell *et al.* 2013, Gonzales *et al.* 2016). Slightly higher urinary antimony levels were reported for smokers than non-smokers in 2013 to 2014 data. Total antimony measured in urine as the elemental form can be from various forms of antimony, not just antimony(III) trioxide (see Table 2-6).

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

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

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

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

<sup>a</sup>Filella *et al.* 2013a,b also reported a single arithmetic (rather than geometric) mean that falls outside this range- 1.3  $\mu\text{g/L}$  in urine.

<sup>b</sup>A mean  $\pm$  SD of  $110 \pm 90$  (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  $\mu\text{g/L}$ ] (Filella *et al.* 2013a).

The general population is potentially exposed to antimony directly from consumer products (Section 2.4.1) or indirectly from the environment by inhaling contaminated air (Section 2.4.2) or by consuming contaminated food or drinking water (Section 2.4.3). Because antimony can

change its form in the environment, the form of antimony to which people are exposed may not be the same form initially released into the environment.

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

**Table 2-6. Sources of antimony(III) trioxide and the final forms of antimony ( $\text{Sb}^{\text{III}}_2\text{O}_3$  and others) to which people are exposed**

Source	Exposure route	Expected form of antimony exposure
Antimony(III) trioxide ( $\text{Sb}^{\text{III}}_2\text{O}_3$ ) (e.g., industrial facility releases)	Inhalation of $\text{Sb}^{\text{III}}_2\text{O}_3$	$\text{Sb}^{\text{III}}_2\text{O}_3$
	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
$\text{Sb}^{\text{III}}_2\text{O}_3$ in flame retardant	Inhalation (from breathing indoor air containing house dust)	Mainly $\text{Sb}^{\text{III}}_2\text{O}_3$ 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
$\text{Sb}^{\text{III}}_2\text{O}_3$ in PET	Ingestion (from drinking liquid in PET bottles)	Sb ions

Sources: EU 2008, ATSDR 2017.

#### 2.4.1 Consumer products

Consumers are potentially exposed to antimony from consumer products as a result of the use of antimony(III) trioxide as a synergist with flame retardants or in PET containers. Exposure of the general population from consumer products is generally to antimony(III) trioxide by inhalation of dust from these products although some exposure could also occur orally to antimony(III) trioxide or other forms of antimony. Exposure is likely higher for children, especially infants, because of their direct skin contact with carpet material containing antimony(III) trioxide as a flame-retardant synergist while crawling, their mouthing of other fabrics containing flame retardants or toys with antimony-containing paint or plastic, and their potential to inhale more dust containing antimony from carpets because they are closer to the floor than adults (see Table 2-7). A 1998 study (Jenkins *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  $\text{Sb}^{\text{(III)}}(\text{OH})_3$  or  $\text{H}_3\text{Sb}^{\text{(III)}}\text{O}_3$  and Sb(V) as  $\text{Sb}^{\text{(V)}}(\text{OH})_6^-$  or

$\text{H}_2\text{Sb}^{(\text{V})}\text{O}_4^-$  rather than as antimony cations (ATSDR 1992). The antimony in house dust is mainly antimony(III) trioxide (from wear and tear of flame-retardant-treated fabric) (EU 2008). Table 2-7 shows exposure levels for consumer products evaluated in the EU antimony trioxide (i.e., antimony(III) trioxide) risk assessment report, which converted all exposure levels to the equivalent mass of antimony(III) trioxide (i.e., converting measured antimony to corresponding antimony(III) trioxide based on molecular weight).

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

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

Source: EU 2008.

<sup>a</sup>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.

<sup>b</sup>ND = not determined.

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

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

The only U.S. data on indoor air antimony levels are from an elementary school in Arizona (Majestic *et al.* 2012), where the particles less than 1  $\mu\text{m}$  in diameter ( $\text{PM}_{10}$ ) fraction of air samples averaged 0.017  $\mu\text{g}$  antimony/ $\text{m}^3$ . Antimony in air was most likely resuspended from flame-retardant-treated carpet by foot traffic.

A study in the United Kingdom measured antimony in 750 consumer products (rubber, textile, and foamed materials) (Turner and Filella 2017), and detected antimony in 18% of over 800 measurements of those products at approximately 60  $\mu\text{g}/\text{g}$  to 60,000  $\mu\text{g}/\text{g}$ . 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  $\mu\text{g}/\text{g}$  to 16,000  $\mu\text{g}/\text{g}$  (Turner *et al.* 2016). Similar products in the United States would likely have similar levels.

#### 2.4.2 Environmental exposure

Antimony enters the environment through releases from industries producing, using, or recycling antimony and from natural sources (e.g., volcanic activity or erosion). An estimate for antimony emissions to the air from natural sources in the 1980s indicated that 41% could be accounted for



from wind-borne soil particles, volcanoes, sea salt spray, forest fires, and biogenic sources (ATSDR 2017). Anthropogenic activities such as mining, fossil fuel combustion (coal or petroleum), smelting, waste incineration, and other human activities increase antimony concentrations in the local environment, which may be carried by air or water beyond the immediate area of those activities.

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

### Air

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

Antimony can change oxidation state in the environment and during industrial use. Aerosolized elemental antimony oxidizes to antimony(III) trioxide through reactions with atmospheric oxidants (ATSDR 1992, EU 2008, ATSDR 2017). During coal combustion, antimony forms antimony oxides, regardless of the form of antimony present in the coal (Health Canada 2010); Pavageau *et al.* (2004) also reported formation of antimony(V) pentoxide from coal combustion. Similarly, antimony(III) trioxide is the primary species released to the atmosphere from other high-temperature industrial processes, such as smelting, combustion of petroleum and petroleum products, and incineration of products that contain antimony (Health Canada 2010, NTP 2016c). Recycling of antimony as part of 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 (Grund *et al.* 2006, Dupont *et al.* 2016). Antimony(III) trisulfide (used as automobile brake lubricant) and antimony(III) trisulfate (used as automobile brake filler) have been reported to oxidize to antimony(III) trioxide at temperatures reached in the braking process (above  $300^\circ\text{C}$ ) (EU 2008). Port workers in Valparaiso, Chile were exposed to elevated air concentrations of antimony from heavy vehicular traffic due to oxidation of antimony sulfide or sulfate in brake pads to antimony(III) trioxide at temperatures achieved

during braking (Quiroz *et al.* 2009). People thus can inhale antimony(III) trioxide transformed from other antimony compounds.

Antimony is present almost entirely in the particulate matter in air. ATSDR summarized these data from various U.S. cities for 2014, reporting daily mean concentrations as total antimony ranging from 0.00037 to 0.002  $\mu\text{g}/\text{m}^3$  for total suspended particulate, 0.0013 to 0.0206  $\mu\text{g}/\text{m}^3$  for particles less than 10  $\mu\text{m}$  in diameter ( $\text{PM}_{10}$ ), and 0.0019 to 0.022  $\mu\text{g}/\text{m}^3$  for particles less than 2.5  $\mu\text{m}$  in diameter ( $\text{PM}_{2.5}$ ) (see Table 6-4 in ATSDR 2017.) Antimony levels in areas unpolluted by anthropogenic activity are low (approximately 0.001  $\mu\text{g}/\text{m}^3$ ) (ATSDR 2017). The EU (2008) estimated that the reasonable worst-case background concentration of antimony in outdoor air is 0.0026  $\mu\text{g}/\text{m}^3$ .

### **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.* 2002b).

According to the National Water-Quality Assessment (NAWQA) program, which surveyed groundwater between 1992 and 2003, U.S. groundwater had generally low concentrations of antimony, with a median concentration of less than 1  $\mu\text{g}/\text{L}$  (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  $\mu\text{g}/\text{L}$  while the nearby North Fork River was considered unpolluted with a mean level of 0.9  $\mu\text{g}/\text{L}$  (ATSDR 2017). Increased levels of antimony in rainwater likely depend on release of antimony from industrial sites. The mean total antimony concentration in rainwater collected downwind from a copper smelter in Tacoma, Washington was 1.3 ppb while that collected upwind during the same storms was only 0.03 ppb (ATSDR 1992).

Exposure to antimony in the soil is expected to be minimal because of low solubility and mobility of antimony (EPA 2014, Li *et al.* 2014). However, both trivalent and pentavalent antimony compounds are present in dust and soil carried into houses (EU 2008). Although the levels of antimony in the earth's crust average 0.2  $\mu\text{g}/\text{g}$  to 0.3  $\mu\text{g}/\text{g}$ , levels in soil vary more widely when samples are taken at different locations within the United States. A survey of soils by the United States Geological Survey (USGS) found levels from less than 1  $\mu\text{g}/\text{g}$  to 8.8  $\mu\text{g}/\text{g}$  with an average concentration of 0.48 ppm ( $\mu\text{g}/\text{g}$ ), (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  $\mu\text{g}/\text{g}$ ) than the other sites with more traffic (6.30  $\mu\text{g}/\text{g}$  and 2.74  $\mu\text{g}/\text{g}$ ) (Amereih *et al.* 2005).

### 2.4.3 Food and drinking water

Levels of antimony (form not specified) in food in the United States range from not detectable (limit of detection not reported) to 1.7  $\mu\text{g/g}$  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  $\mu\text{g/L}$  to 9.6  $\mu\text{g/L}$ . The value of 9.6  $\mu\text{g/L}$  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  $\text{Sb}^{(\text{III})}(\text{OH})_3$ , or the pentavalent form as charged  $\text{Sb}(\text{OH})_6^-$  (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 <sup>a</sup>	Typical ( $\mu\text{g Sb}^{\text{III}}_2\text{O}_3/\text{kg b.w./day}$ ) <sup>b</sup>	Worst case ( $\mu\text{g Sb}^{\text{III}}_2\text{O}_3/\text{kg b.w./day}$ ) <sup>b</sup>
Food	0.074	0.096
Breast milk (children 0–3 months)	0.023	0.087
Drinking water <sup>c</sup>	ND <sup>d</sup>	0.029

Source: EU 2008.

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

<sup>b</sup>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.

<sup>c</sup>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.

<sup>d</sup>ND = not determined.

## 2.5 Summary and synthesis

A significant number of people in the United States are exposed to antimony(III) trioxide ( $\text{Sb}^{\text{III}}_2\text{O}_3$ ), as evidenced by occupational exposure data and supporting data on production, consumption, and releases into the environment and exposures from consumer products. In addition to exposure to antimony(III) trioxide in the workplace from its use as a synergist with flame retardant chemicals, as a catalyst in production of PET plastic, as a pigment and fining agent in glass production, and as a colorant and opacifier in pigments for paints and ceramic glazes, people are potentially exposed from using consumer products containing antimony(III) trioxide, and by breathing contaminated air, or a combination of these sources. The chemical form of antimony changes during manufacturing, in the environment, and *in vivo*, and detection methods typically measure total antimony rather than specific forms of antimony, so identifying exposure specifically to antimony(III) trioxide is presently difficult.

The highest occupational exposure to antimony(III) trioxide occurs in workplaces that produce or use antimony(III) trioxide (e.g., smelting and refining operations and production of antimony(III) trioxide). During the 1970s, reported levels ranged from 50 to 5,000  $\mu\text{g}/\text{m}^3$ , compared with the current threshold limit value (TLV) of 500  $\mu\text{g}/\text{m}^3$ . In the United States, roughly 70 million pounds of antimony(III) trioxide are used annually as a synergist for halogenated flame

retardants in plastics, rubber, and textiles, as a catalyst in PET production, and as an additive in optical and art glass, pigments, paints, and ceramics. Workers at an estimated 273 U.S. facilities (based on information from EPA's Toxics Release Inventory) were exposed to antimony(III) trioxide in 2010. More than 200,000 workers were exposed to antimony(III) trioxide in the 1981 to 1983 U.S. National Occupational Exposure Survey, indicating extensive past exposure to antimony(III) trioxide.

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

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

## 3 Disposition and Toxicokinetics

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

### 3.1 Antimony(III) trioxide

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

#### 3.1.1 Absorption and distribution

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

#### Human studies

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

*Inhalation.* The highest exposures of people to antimony by inhalation are from occupational exposure. Antimony has been detected in the lungs, blood, and urine of workers who had inhaled antimony identified as antimony(III) trioxide or likely to be antimony(III) trioxide; inhaled antimony compounds are retained long term in the lung (HSDB 2013, NTP 2016c). Elevated urinary excretion of antimony has been reported for workers exposed to antimony(III) trioxide in

lead battery production (Kentner *et al.* 1995) (see Table 2-3) and for port workers in Valparaiso, Chile exposed to elevated air concentrations of antimony from heavy vehicular traffic when antimony sulfide or sulfate in brake pads is oxidized to antimony(III) trioxide at temperatures achieved during braking (see Sections 2.1 and 2.3.2) (Quiroz *et al.* 2009). Accumulation of antimony in the lung was demonstrated for seven workers accidentally exposed to radioactive antimony ( $^{125}\text{Sb}$ , described as antimony oxides, but likely including antimony(III) trioxide). Biomonitoring of whole-body radioactivity found the antimony to be almost entirely confined to the lungs (Garg *et al.* 2003). However, workers occupationally exposed to antimony(III) trioxide had detectable antimony in urine as well as lungs even after their exposure ceased (HSDB 2013).

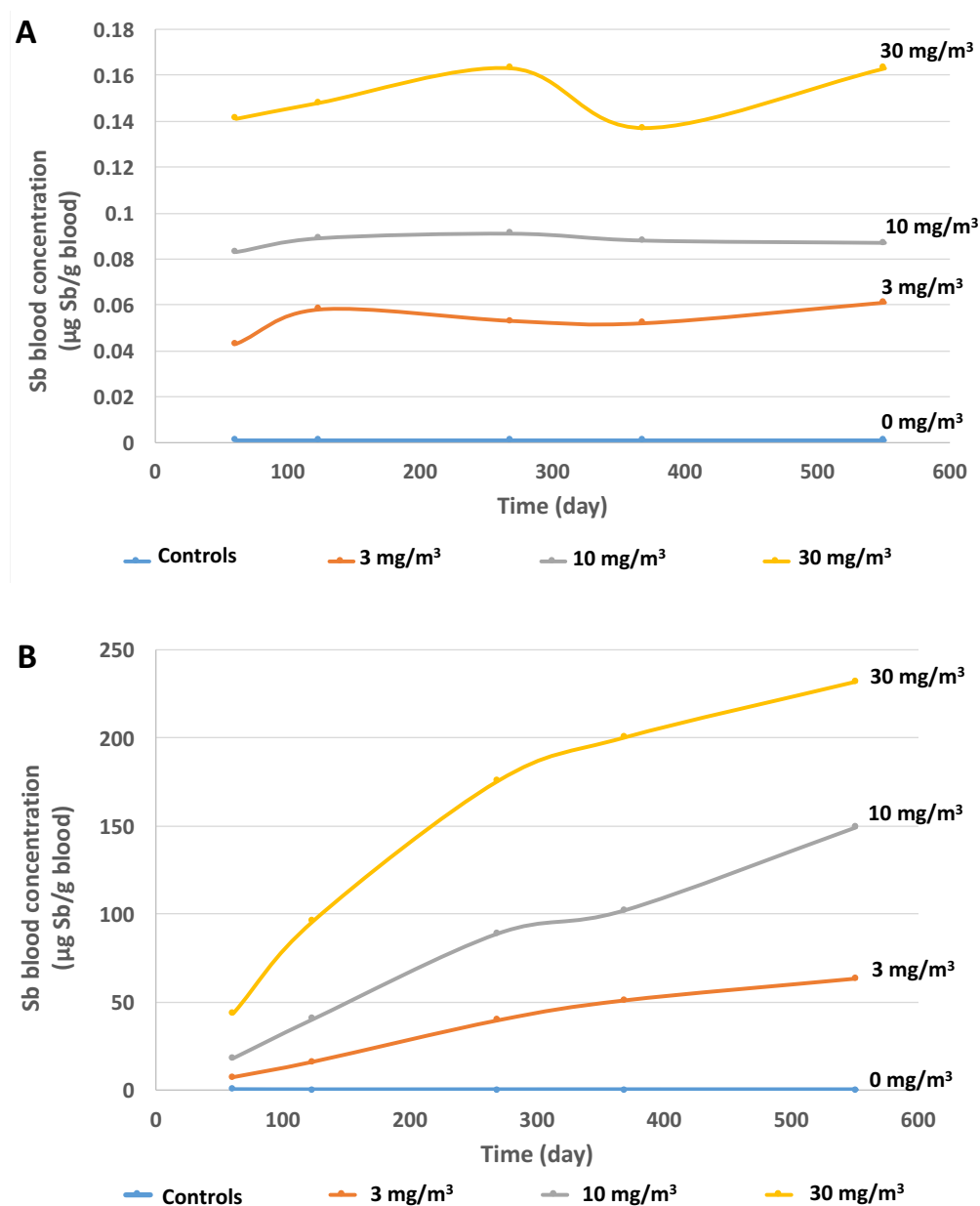
The EU (2008) risk assessment report used data from humans to predict absorption from inhalation exposure based on the Multiple Path Particle Deposition (MPPD) model prediction using particle size and density from collected antimony(III) trioxide samples and gastrointestinal tract absorption in humans.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

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

### Experimental animal studies

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

The NTP (2016c) exposed rats and mice of both sexes to antimony(III) trioxide by inhalation with either short-term inhalation exposure (2 weeks plus a 4-week recovery period) to 0, 3.75, 7.5, 15, 30, or 60 mg/m<sup>3</sup> 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<sup>3</sup> with the same 5 days per week exposure. Blood levels (see Appendix B, Table B-2 and Figure 3-1) increased with exposure concentration in rats and mice for both exposure periods. Blood concentrations increased with exposure duration for rats but not as clearly for mice in the 2-year study. Blood concentrations normalized to exposure concentrations decreased with increasing exposure concentration, particularly at higher concentrations. Lung burdens also increased with exposure concentrations during the 2-year study (see Table 3-1 in Section 3.4, Toxicokinetics)



**Figure 3-1. Blood antimony levels ( $\mu\text{g/L}$ ) in female mice (panel A) and rats (panel B) exposed to antimony(III) trioxide by inhalation at 0, 3, 10, or 30  $\text{mg/m}^3$  in a 2-year study**

Source: NTP 2016c. Blood antimony levels are reported in Appendix B, Table B-1.

Another difference observed for the short-term exposure was a continued increase in blood antimony concentrations relative to the concentrations in lung. During the 4-week recovery period in rats the percentage in blood relative to lung concentrations increased from 0.8% in both sexes at the end of exposure to 2% in female rats at 4 weeks post exposure [only females were examined post exposure]). In contrast, the blood concentrations in mice were only 0.004% of lung concentrations in the same animals for males and 0.005% for females at both time points. In the 2-year study, blood concentration was 7% of lung concentration in rats, but only 0.002% in mice.

*Intratracheal instillation (i.t.).* Leffler *et al.* (1984) exposed adult male Syrian golden hamsters to 19.5- $\mu\text{m}$  or 7- $\mu\text{m}$  particles of antimony(III) trioxide by i.t. instillation. In addition to a large percentage in the lung, antimony was detected in the liver (12.6% of 19.5- $\mu\text{m}$  particles and 7.2% of 7- $\mu\text{m}$  particles), with lesser amounts in the kidney, stomach, and trachea (the only other tissues examined). Based on this study, the EU (2008) risk assessment concluded that absorption following i.t. instillation was greater than 12.6%.

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

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

### **Excretion**

Antimony is eliminated mainly in the urine, regardless of the exposure route, but it can also appear in the feces when some ingested antimony passes through the GI tract without being absorbed or is absorbed and then excreted in the bile where it fails to form a complex with glutathione (GSH) and is not reabsorbed via 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 2-3). The geometric mean or median air levels reported in these studies were mostly below the current threshold limit value for antimony and antimony compounds in air of 500  $\mu\text{g}/\text{m}^3$  (ACGIH 2017), but one study (Kim *et al.* 1999) reported a geometric mean air level of 766  $\mu\text{g}/\text{m}^3$ , which was associated with a urinary excretion level of  $\sim 420$   $\mu\text{g}/\text{L}$ . This level was much higher than the 15.2  $\mu\text{g}/\text{g}$  creatine excretion reported by



Kentner *et al.* (1995) for a mean air level of 12.4  $\mu\text{g}/\text{m}^3$  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).

### Laboratory animal studies

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

### 3.2 Other antimony compounds

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

#### 3.2.1 Absorption and distribution

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

### Human studies

When humans are exposed to antimony, usually by occupational exposure, the initial retention of antimony(V) in blood is primarily in the plasma rather than in red blood cells in contrast with antimony(III), but equilibration of antimony between plasma and cells occurs over a period of hours, and intracellular antimony concentrations increase (see Section 3.3). Repeated administration results in both higher plasma levels and increased urinary excretion.

Antimony(III) concentration is generally highest in liver, while antimony(V) concentration is higher than that of antimony(III) in the spleen. A high concentration in spleen is considered a necessary condition for cure of leishmaniasis and thus may be related to therapeutic effects of antimony.

For people without known exposure to antimony, potential reference ranges for blood or serum levels of total antimony and either whole-body burden or levels in individual organs include a mean body burden of 0.7 mg, with the highest levels in skin and hair for a Japanese autopsy study (Sumino *et al.* 1975), the presence of 28% of the body's antimony content in the skeleton in Chinese men (Zhu *et al.* 2010), and serum antimony levels of 0.09 to 0.25  $\mu\text{g}/\text{L}$  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 ( $\text{Sb}^{(\text{III})}\text{H}_3$ ) 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 ( $3.3 \pm 2.2$  mg/L), placenta (3.2 to 12.6 mg% [units as reported in EU 2008 and HSDB 2013]), amniotic fluid ( $0.62 \pm 0.28$  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 ( $^{125}\text{Sb}$ ); 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 ( $315 \mu\text{g}/\text{kg}$ ) as in 11 controls ( $26 \mu\text{g}/\text{kg}$ ) (Gerhardsson *et al.* 1982).

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

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

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

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

### Experimental animal studies

A few publications have reported levels of antimony in blood and tissues of control animals that had not been experimentally exposed to antimony. In rats, the levels in thyroid, bone marrow, liver, spleen, and whole blood ranged from 0.028 (2.8 ngSb/g in whole blood) to 0.195  $\mu\text{g}/\text{g}$  (195

ngSb/g in thyroid) (TNO Quality of Life 2005) (see Table B-3). Higher levels in liver were reported in dogs (12.2  $\mu\text{g}/\text{kg}$  [ng/g] in males and 135  $\mu\text{g}/\text{kg}$  [ng/g] in females) (PaBlack *et al.* 2015) and in cats (132  $\mu\text{g}/\text{kg}$  [ng/g] for males and females combined) (PaBlack *et al.* 2014).

Numerous studies have reported that antimony binds to red blood cells and that tissue concentrations are generally highest in spleen, liver, bone marrow, and thyroid; however, the order varies among studies, which used various species, routes of exposure, and forms of antimony. For example, in mice exposed to antimony (as antimony tartrate) by inhalation, i.p. injection (tartar emetic [antimony(III) potassium tartrate] or Astiban [sodium antimony(III) 2,3-mesodimercaptosuccinate]), or oral administration (tartar emetic), up to half of antimony that entered the systemic circulation was deposited in the liver, but the fraction was smaller in rats, hamsters, and dogs (ICRP 1981). In dogs, inhaled antimony also accumulated in the thyroid.

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

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

Blood levels of antimony in rats exposed to antimony(III) potassium tartrate by oral exposure (in drinking water) or by intraperitoneal (i.p.) injection were compared in the NTP (1992) study. Blood levels following administration in drinking water (14 days) were only about twice those observed after repeated daily i.p. injections (12 injections over 16 days) even though the oral exposure was 10 times higher, suggesting limits on absorption from the GI tract (NTP 1992). No blood levels were detected in mice exposed via drinking water or i.p. injection following the same protocol as for rats, but antimony was detected in liver (24  $\mu\text{g}/\text{g}$  with 273 mg/kg antimony(III) potassium tartrate in drinking water or with 50 mg/kg by i.p. injection) and spleen (5  $\mu\text{g}/\text{g}$  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  $\leq 0.1 \mu\text{g}/\text{L}$ , 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  $\mu\text{g/L}$  were associated with air levels that the authors reported as mostly exceeding 3,000  $\mu\text{g/m}^3$ , far above the current threshold limit value for antimony and antimony compounds in air of 500  $\mu\text{g/m}^3$  (ACGIH 2017).

In seven workers exposed to radioactive antimony (reported as  $^{124}\text{Sb}$  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, Tylanda and Fowler 2015).

### Laboratory animal studies

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

*Inhalation and intratracheal instillation.* Following exposure by inhalation or intratracheal instillation, larger and more soluble particles were generally cleared most quickly from the lungs (EU 2008). A study in 20 hamsters compared two soluble radioactive ( $^{124}\text{Sb}$ ) antimony aerosols, one Sb(III) and one Sb(V), each with median aerodynamic diameters of 1.6  $\mu\text{m}$  (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 ( $\text{Sb}^{(\text{III})}\text{Cl}_3$ ) 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 (TNO Quality of Life 2005). Enterohepatic cycling occurs due to binding of antimony(III) to GSH; in adult rats, depletion of GSH decreased fecal excretion and increased urinary excretion after i.v. or i.p. injection of antimony(III) trichloride (Bailly *et al.* 1991).

### 3.3 Metabolism and valence states

Mammalian metabolism of antimony consists primarily of interconversion of the valence state between +3 and +5. Methylation is a well-known pathway for metabolism of arsenic *in vivo*, but

evidence for methylation of antimony *in vivo* is limited to one study of two workers occupationally exposed to antimony during lead battery production (Krachler and Emons 2001). However, other studies in humans (Miekeley *et al.* 2002, Quiroz *et al.* 2011) and animals (Bailly *et al.* 1991) were negative for formation of methylated antimony.

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

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

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

Data for interconversion between antimony(III) and antimony(V) in experimental animals are generally limited, but one study in dogs injected s.c. with a single dose of meglumine antimoniate(V) reported systemic conversion of 23.62% of antimony(V) to antimony(III) in blood in 24 hours (de Ricciardi *et al.* 2008). In rhesus monkeys injected i.m. with meglumine antimoniate(V) daily for 21 days, the proportion of antimony(V) remained in the range of 11% to

20% of total antimony, while that of antimony(III) increased from 5% on day 1 to 50% on day 9, which could indicate reduction of antimony(V) to antimony(III) within cells (Friedrich *et al.* 2012). The authors did not report what form of antimony made up the balance of the total concentration.

The valence state also affects the distribution of antimony in tissues. Felicetti *et al.* (1974a) reported that hamsters exposed to radioactive antimony ( $^{124}\text{Sb}$ ) aerosols, one antimony(III) and one antimony(V), both with median aerodynamic diameters of 1.6  $\mu\text{m}$ , 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 ~70%. Although the initial excretion rate was slower for antimony(III), the difference decreased over 48 hours. In hamsters, i.p. injection resulted in urinary excretion of 15% for antimony(III) and 65% for antimony(V), while fecal excretion was 50% for antimony(III) and < 10% for antimony(V).

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

### 3.4 Toxicokinetics

The available information on the toxicokinetics of antimony is from Newton *et al.* (1994) and a recent NTP (2016c) report on lung accumulation and clearance in rats and mice exposed to

antimony(III) trioxide via inhalation. No studies on the toxicokinetics of antimony in humans were identified.

Newton *et al.* (1994) exposed F344 male and female rats to antimony(III) trioxide for either 13 weeks followed by 27 weeks of observation (0.0, 0.25, 1.08, 4.92, or 23.46 mg/m<sup>3</sup>) or 1-year exposure followed by 1-year observation (0.0, 0.055, 0.51, or 4.5 mg/m<sup>3</sup>) with intermediate sample collection at 6 months for each period. The authors reported near steady-state lung burdens by 6 months of exposure for the 12-month exposure period (see Table 3-3). Semilogarithmic plots of clearance data ( $\mu\text{g}$  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  $\sim 2$  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<sup>a</sup> ( $\mu\text{g/g}$ ) in lung tissue during a 1-year chronic exposure (6 mo and 12 mo samples) and a 1-year observation period (6 mo and 12 mo samples) in Fischer 344 male and female rats**

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

Source: Newton *et al.* (1994).

mo = months.

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

Lung burdens were expressed as mass rather than concentration because lung weights increased in exposed animals. NTP also reported that normalized antimony(III) trioxide lung burdens

increased in approximate proportion to exposure concentration and with exposure duration during the two-year bioassay in rats and mice. The lung burden in female rats increased steadily over time. The 3 mg/m<sup>3</sup> and 10 mg/m<sup>3</sup> exposure groups nearly reached steady state, but the 30 mg/m<sup>3</sup> exposure group did not. The results in rats were consistent with the clearance rates from the lungs progressively decreasing.

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

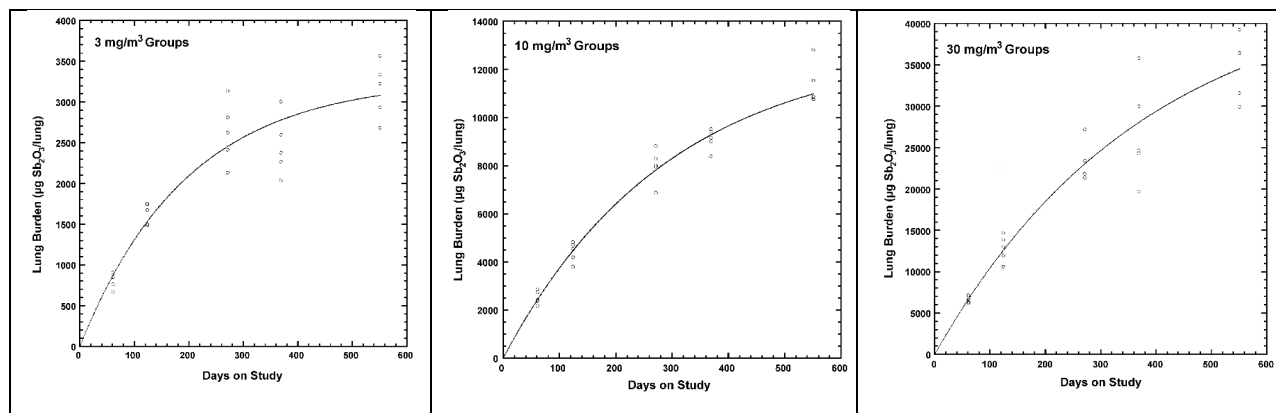
**Table 3-2. Model-predicted values for Wistar Han rats exposed to antimony(III) trioxide via inhalation for 2 years**

Parameter	Exposure level (mg/m <sup>3</sup> )		
	3	10	30
Deposition rates (µg Sb <sub>2</sub> O <sub>3</sub> 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

Source: NTP 2016c.

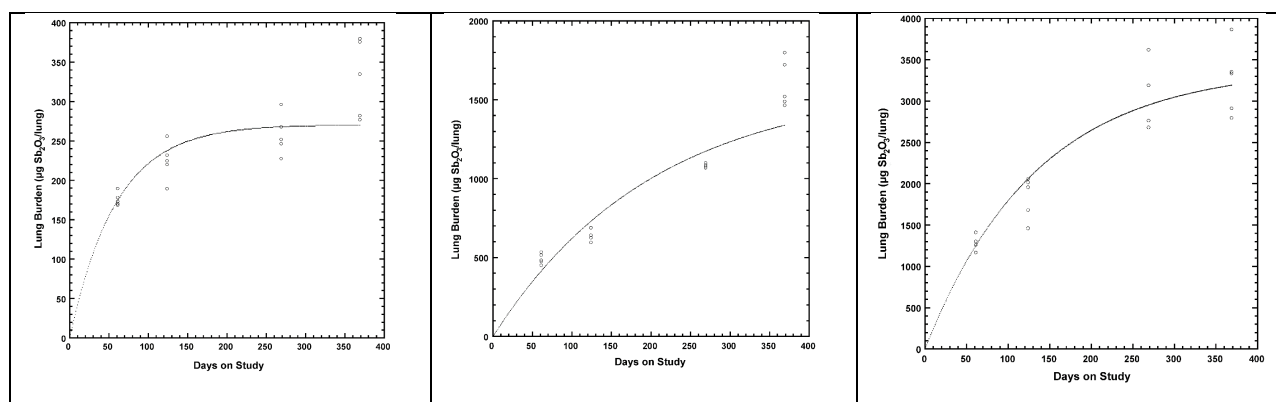
Based on relatively longer clearance half-lives at the higher doses and an unexpectedly high lung burden in mice after 551 days of exposure, NTP (2016c) concluded that the reduced pulmonary clearance was associated with lung overload at 10 mg/m<sup>3</sup> and 30 mg/m<sup>3</sup>, but not 3 mg/m<sup>3</sup>. 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<sup>3</sup> per macrophage (Morrow 1988, 1992). When the particulate volume per macrophage exceeds 600 µm<sup>3</sup>, all macrophage-mediated clearance ceases, and the dust accumulates linearly with continued inhalation. Tran *et al.* (2000) proposed a second hypothesis for clearance impairment based on the total particle surface area of ultrafine particulates. This particle surface area hypothesis proposes that ultrafine particles with high surface area will cause macrophages to release proinflammatory mediators (chemokines), such as tumor necrosis factor, that attract macrophages and could prevent their migration. The NTP concluded that volume-based overload occurred at 10 mg/m<sup>3</sup> by day 418 in rats and day 369 in mice and at 30 mg/m<sup>3</sup> by day 94 in rats and day 124 in mice.





**Figure 3-2. Lung antimony(III) trioxide burdens in female rats in the 2-year inhalation study**

The lines represent the fit of the lung deposition and clearance data to models used by NTP (2016c).



**Figure 3-3. Lung antimony(III) trioxide burdens in female mice in the 2-year inhalation study**

The lines represent the fit of the lung deposition and clearance data, without the results for day 551, to models used by NTP (2016c). NTP (2016c) noted that the day 551 lung burdens were considerably higher than the curves generated with the model fit.

### 3.5 Summary and synthesis

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

## 4 Human Cancer Studies

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

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

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

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

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

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

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

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

A U.S. population-based cohort study on urinary antimony concentrations and cancer (Guo *et al.* 2016) and a Turkish geospatial study on antimony exposure from drinking water and cancer incidence (Colak *et al.* 2015) were excluded from the cancer evaluation because only all malignant neoplasms, not site-specific cancers, were reported. Two Swedish post-mortem studies comparing antimony concentrations in various tissue types in deceased metal smelter workers

and deceased controls (Gerhardsson *et al.* 1982, Gerhardsson and Nordberg 1993) were excluded because no point estimates were reported and exposure measurements did not precede cancer outcomes.

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

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

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

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

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

**Table 4-1. Antimony exposure and human cancer studies**

Reference	Study design (location), years, population	Outcome, including cancer sites, data analysis	Exposure: antimony compounds, source of information, assessment, metrics
Jones 1994	<b>Antimony smelter worker cohort (United Kingdom)</b> 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 <i>Exposed:</i> ever employed in U.K. antimony smelter <i>External referent:</i> local population Duration of employment, years of exposure
Schnorr <i>et al.</i> 1995	<b>Antimony smelter worker cohort (United States)</b> 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 <i>Exposed:</i> ever employed in U.S. antimony smelter <i>External referents:</i> national and ethnic-specific local U.S. population Duration of employment
Jones <i>et al.</i> 2007; methods described in Binks <i>et al.</i> 2005	<b>Tin smelter worker cohort (United Kingdom)</b> 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 <i>Exposure sources:</i> area and personal air sampling, JEM Quantitative cumulative inhalation exposure (mg-year/m <sup>3</sup> )
Wingren and Axelson 1993; methods described in Wingren and Axelson 1985	<b>Case-control study of men in art glass-producing area (Sweden)</b> 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, Tables C-1 to C-6.

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

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

Study type, citation	Concern for potential bias <sup>a</sup>						Quality <sup>a</sup>	Utility <sup>b</sup>
	Selection	Exposure	Outcome	Confounding methods	Adequacy of analysis	Selective reporting	Sensitivity	Integration
<b>Cohort studies</b>								
<b>Antimony smelter workers</b>								
Jones 1994	++	+++/>++	+++	+	+++	+++	++	+++/>++
Schnorr <i>et al.</i> 1995	++	++	+++	+++	++	+++	++	+++/>++
<b>Tin smelter workers</b>								
Jones <i>et al.</i> 2007	++	++	+++	++	++	+++	+	++
<b>Case-control study</b>								
Wingren and Axelson 1993	+++	+	++	+	++	++	+	+

<sup>a</sup>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.

<sup>b</sup>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, Schnorr *et al.* 1995, Jones *et al.* 2007) had low risk of selection bias because they all had clearly defined cohorts by exposure status during specific time periods and geographic locations associated with the antimony and tin smelters. All cohort studies had minimal (3.0% to 5.7%) loss to follow-up, and relied on death certificates to trace workers' outcome status. Bias due to healthy worker survival effect (HWSE) is possible in all studies, though unlikely. Observed all-cause mortality rates in study participants did not differ from the general population. All three cohort studies enrolled workers already employed by the smelter companies and likely already exposed to antimony before enrollment, although all three studies accounted for time-since-exposure in their analyses.

The cohort studies of metal smelter workers (Jones 1994, Schnorr *et al.* 1995, Jones *et al.* 2007) were deemed to have some concern for non-differential exposure misclassification, and the case-control study of Swedish art glass workers (Wingren and Axelson 1993) had major concerns for exposure misclassification (see Appendix C, Table C-2). Reasons for these concerns include lack of individual-level exposure data (Wingren and Axelson 1993, Jones *et al.* 2007), lack of exposure information prior to enrollment date, and reliance on ever-exposure to antimony. Furthermore, antimony exposure likely varied over time as changes in occupational smelting practices and different source materials were reported in studies. To better characterize exposure, reliance on job titles (Jones 1994) and worker functions (Jones *et al.* 2007) allowed for greater specificity. Regardless, exposure misclassification in all four studies is non-differential and would likely attenuate effect estimates.

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

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

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

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

### 4.3 Cancer hazard assessment

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

### 4.3.1 Lung cancer

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

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

#### Evidence from individual studies

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

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



Table 4-3. Evidence from epidemiological cohort and case-control studies on lung and stomach cancers and exposure to antimony

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 <b>Enrollment or follow-up:</b> 1961–1992 (study enrollment and follow-up period)	<b>Population:</b> Antimony smelter workers N = 1,420 men  <b>Exposure assessment method:</b> company records	<b>Lung cancer: Ever employed antimony workers, SMR (95% CI)</b>			Age	<b>Exposure information:</b> <i>Exposure level:</i> Ever exposure to antimony defined as employment in antimony plant for 3+ months. <i>Exposure duration:</i> 6–50 years based on employment. <b>Confounding concern:</b> Likely co-exposure to arsenic and PAHs (lung carcinogens). Smoking not controlled for despite 72% prevalence. <b>Strengths:</b> Antimony workers exposed primarily to antimony compounds. Stratified by hiring date, years since first exposure. Additional analysis on other job titles. <b>Limitations:</b> 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. <b>Level of evidence:</b> 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		
		<b>Stomach cancer: Ever employed antimony workers, SMR (95% CI)</b>				
Ever antimony worker	[0.42 (0.05–1.51)]	2				
Schnorr <i>et al.</i> 1995 Cohort Southern Texas, United States <b>Enrollment or</b>	<b>Population:</b> Antimony smelter workers N = 1,014 men  <b>Exposure</b>	<b>Lung cancer: External analysis - U.S. white male mortality rates, SMR (95% CI)</b>			Age, calendar year, latency period	<b>Exposure information:</b> <i>Exposure level:</i> Ever exposure to antimony defined as employment in antimony plant for 3+ months from 1937–1971. <i>Exposure duration:</i> < 5 years to > 10
		Ever antimony worker	[0.75 (0.51–1.07)]	30		
		<b>Lung cancer: External analysis - Texas ethnic-specific mortality rates, SMR (90% CI)</b>				
		Ever antimony worker	1.39 (1.01–1.88)	28		

Reference, location, study-design and year	Population description & exposure assessment method	Exposure category	Risk estimate (95% CI)	Exposed cases	Covariates	Comments, strengths and limitations
<b>follow-up:</b> 1937–1989 (employment and follow-up period)	<b>assessment method:</b> company records	< 5 years employment	SMR only: 0.83	11		years based on employment. <b>Confounding concern:</b> Minimal concern from smoking, arsenic, and lead exposure. <b>Strengths:</b> 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. <b>Limitations:</b> External analysis only; small number of exposed cases for lung and stomach cancers; individual-level data on exposure not available. <b>Level of evidence:</b> Some evidence (lung); some evidence (stomach)
		5–10 years employment	SMR only: 2.24	8		
		> 10 years employment	SMR only: 2.73	9		
		<b>Stomach cancer: External analysis – U.S. white male mortality rates, SMR (95% CI)</b>				
		Ever antimony worker	1.49 (0.71–2.74)	10		
		<b>Stomach cancer: External analysis – Texas ethnic-specific mortality rates, SMR (95% CI)</b>				
Ever antimony worker	1.24 (0.50–2.55)	7				
Jones <i>et al.</i> 2007 Cohort Northern England, United Kingdom <b>Enrollment or follow-up:</b> 1937–2001 (Employment and follow-up period)	<b>Population:</b> Tin smelter workers N = 1,462 men <b>Exposure assessment method:</b> job-exposure matrix and air sampling measurements	<b>Lung cancer: Cumulative exposure, RR (90% CI)</b>			Age, calendar year, time since exposure	<b>Exposure information:</b> <i>Exposure level:</i> cumulative antimony inhalation over employment duration. <i>Exposure duration:</i> Modeled three exposure scenarios from 1937–1971 using annual air sampling estimates from 1972–1991. <b>Confounding concern:</b> Highly correlated antimony, lead, and arsenic air concentrations; minimal concern for smoking, but not controlled for in analysis. <b>Strengths:</b> Concentration-response relationship examined; use of JEM from work histories and 20 years of air measurements; antimony exposure
		Model 1 <sup>a</sup> (unweighted)	[1.23 (0.79–1.92)]	62		
		Model 1 <sup>a</sup> (weighted)	[5.26 (1.75–43.38)]			
		Model 2 <sup>b</sup> (unweighted)	[1.13 (0.80–1.60)]			
		Model 2 <sup>b</sup> (weighted)	[3.25 (1.32–21.76)]			
		Model 3 <sup>c</sup> (unweighted)	[1.12 (0.80–1.55)]			
		Model 3 <sup>c</sup> (weighted)	[3.32 (1.42–8.08)]			
		<b>Lung cancer: Cumulative exposure, beta coefficient (β) (90% CI)</b>				
		Model 1 <sup>a</sup> (unweighted)	0.21 (0.24–0.65)	62		
		Model 1 <sup>a</sup> (weighted)	1.66 (0.56–3.77)			
		Model 2 <sup>b</sup> (unweighted)	0.12 (0.22–0.47)			
		Model 2 <sup>b</sup> (weighted)	1.18 (0.28–3.08)			

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 3 <sup>c</sup> (unweighted)	0.11 (-0.22–0.44)			cumulatively estimated. <b>Limitations:</b> 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. <b>Level of evidence:</b> Inconclusive (lung)
		Model 3 <sup>c</sup> (weighted)	1.20 (0.35–2.09)			
Wingren and Axelson 1993 Case-control Southeast Sweden <b>Enrollment or follow-up:</b> 1950–1982 (mortality period)	<b>Population:</b> 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) <b>Exposure assessment method:</b> occupation (i.e., art-glass worker) listed on death records	<b>Stomach cancer: Antimony use in parish of subject death, OR (90% CI)</b>			Age	<b>Exposure information:</b> Occupation listed as glass worker on death record, and subject died in a parish where antimony use was reported. <i>Exposure level:</i> Reported antimony usage levels from companies within study's geographic area. <b>Confounding concern:</b> Likely co-exposure to lead; minimal concern for smoking and asbestos. <b>Strengths:</b> Population-based study; cases and controls from same geographic area. <b>Limitations:</b> 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. <b>Level of evidence:</b> 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)			

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

<sup>a</sup>Model 1: back-extrapolated missing air concentrations, holding 1972–1974 concentrations constant.

<sup>b</sup>Model 2: back-extrapolated missing air concentrations, assuming two-fold higher concentrations than 1972–1974.

<sup>c</sup>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 less than 1% arsenic and lead, and 32% to 60% antimony. Furthermore, arsenic air concentrations were orders of magnitude lower than antimony concentrations: in 1975, mean airborne concentrations were  $2 \mu\text{g}/\text{m}^3$  arsenic and  $551 \mu\text{g}/\text{m}^3$  for 8-hour area samples; in 1976, mean airborne concentrations were  $5 \mu\text{g}/\text{m}^3$  arsenic and  $747 \mu\text{g}/\text{m}^3$  antimony for 8-hour personal (breathing zone) samples. Therefore, arsenic exposure is unlikely to fully account for the excess lung cancer mortality seen in this population. Overall, this study provides some evidence that antimony exposure is associated with an increased risk of lung cancer mortality, despite its limited sample size and lack of individual-level exposure data.

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

between cumulative exposure to antimony air concentrations and lung cancer mortality was seen for all three scenarios.

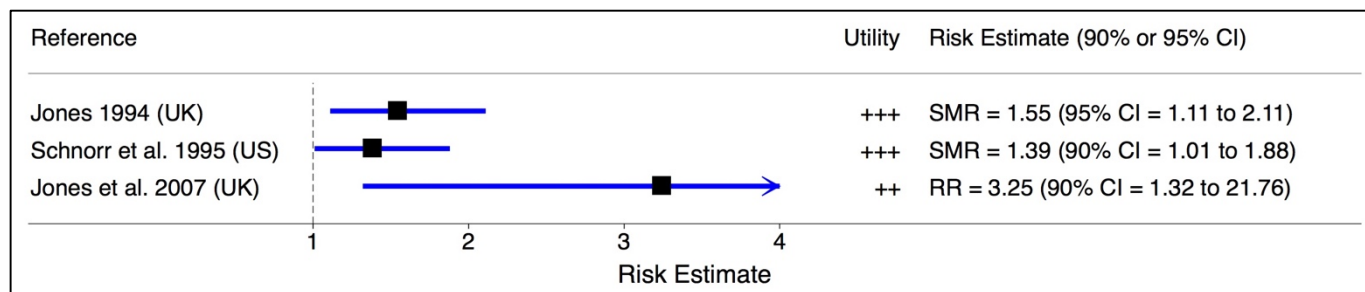
Limitations of the Jones *et al.* study (2007) included a small number of exposed cases and moderate concerns for potential biases (e.g., exposure misclassification and confounding). Although the study attempted to estimate missing antimony exposure measurements spanning over 30 years via data extrapolation,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

The reported association between antimony exposure and lung cancer is potentially due to confounding from occupational arsenic and lead exposures. Based on air monitoring data at the smelter site, median estimated cumulative air lead concentrations ( $1.5 \text{ mg/m}^3\text{-year}$ ) were higher than either arsenic ( $0.28 \text{ mg/m}^3\text{-year}$ ) or antimony ( $0.37 \text{ mg/m}^3\text{-year}$ ) 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 (<https://seer.cancer.gov/>). For stomach cancer from 1975 to 2014, age-adjusted incidence rates for men in the United States were 12.6 per 100,000 men (see Table 24.5 of Howlader *et al.* 2017). Similar to lung cancer, stomach cancer has comparable low five-year survival rate (30.3%) based on 2007 to 2013 SEER age-adjusted data (see Table 24.8 of Howlader *et al.* 2017). Given the low survival for stomach cancer, mortality data may have similar utility as incidence data do.

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

#### Evidence from individual studies

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

A non-statistically significant increase in the risk of stomach cancer mortality was seen in exposed workers from a U.S. antimony smelter, compared with both the national white male mortality rate (SMR = 1.49, 95% CI = 0.71 to 2.74; 10 cases) and state ethnic-specific male mortality rate (SMR = 1.24, 95% CI = 0.50 to 2.55; 7 cases) (Schnorr *et al.* 1995). As noted in

Section 4.2.3, limitations of this study include a small number of stomach cancer deaths and lack of individual-level exposure data. The likelihood of confounding bias from smoking and lead exposure (both stomach cancer carcinogens) was minimal. Although lead exposure was concomitantly present, lead made up < 1% of the antimony ore used at this plant. This study offers some evidence that antimony exposure increases risk of stomach cancer mortality.

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

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

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

### Integration of evidence across studies

The available studies do not indicate a consistent pattern of increased stomach cancer mortality associated with antimony exposure. In similar populations of antimony smelter workers, two studies offered conflicting results for antimony exposure and risk of stomach cancer mortality. The case-control study of a Swedish art glass region only showed nonsignificantly increased odds of stomach cancer mortality for cases who died in parishes with low antimony



consumption, but not in parishes with high antimony consumption. Additionally, co-exposure to other stomach cancer carcinogens, including lead, and smoking, may be confounding the reported associations.

#### 4.3.3 Other types of cancers

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

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

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

#### 4.4 NTP preliminary level of evidence conclusion

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

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

For lung cancer, elevated mortality was seen in all studies of antimony-exposed smelter worker cohorts. Results may be impacted due to non-differential exposure misclassification and confounding bias due to concurrent exposure from other metals.

An increased risk of stomach cancer was found in the U.S. antimony smelter cohort study (Schnorr *et al.* 1995) and the Swedish case-control study (Wingren and Axelson 1993), but not in the U.K. antimony smelter cohort study (Jones 1994).

## 5 Studies of Cancer in Experimental Animals

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

Experimental animal carcinogenicity studies of antimony(III) trioxide were identified using methods described in the protocol and literature search strategy document (see Appendix A). Briefly, besides having a concurrent or historical control group, and reporting study design and results with sufficient detail, studies to be included need to meet one of the three following inclusion criteria (NTP 2015): (1) had an exposure duration of 12 months or greater for rats and mice and reported on the presence or absence of neoplastic and related nonneoplastic lesions (e.g., preneoplastic lesions or lesions considered part of the morphological continuum of neoplasia); (2) had a less than 12-month exposure, but showed increased neoplastic lesions; or (3) were cocarcinogen exposure studies (initiation/promotion and other cocarcinogen studies). Among 16 papers initially identified, four papers met the inclusion criteria. Among the 12 excluded papers, nine were not carcinogenicity studies, while three were carcinogenicity studies, but they tested antimony combined with nickel (Sunderman and McCully 1983, Sunderman *et al.* 1984, Sunderman 1984). The effects from antimony alone cannot be identified for these papers, and thus these three papers were excluded.

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

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

### 5.1 Overview of the studies

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

study, in which only female rats were used. The studies in rats were conducted in four different strains or stocks.

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

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

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 <i>et al.</i> 1994
Rat, CDF (F)	Inhalation	1 year/2 years	Watt 1983
Rat, Wistar (M&F)	Inhalation	53 weeks /71–73 weeks	Groth <i>et al.</i> 1986

M = male, F = female.

## 5.2 Study quality assessment

Each primary carcinogenicity study was systematically evaluated for its utility in informing the cancer hazard evaluation. A series of questions related to the following study performance elements was used: study design, exposure conditions, outcome, confounding, reporting, and analysis (see Protocol for Preparing RoC Monographs at [https://ntp.niehs.nih.gov/ntp/roc/handbook/roc\\_handbook\\_508.pdf](https://ntp.niehs.nih.gov/ntp/roc/handbook/roc_handbook_508.pdf)). The following subsections discuss antimony(III) trioxide studies. Each study was evaluated individually and is presented in descending order of overall utility in determining carcinogenicity (Table 5-2). For details of each study assessment, see Appendix D.

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

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

Areas	NTP 2017	NTP 2017	Newton <i>et al.</i> 1994	Watt 1983	Groth <i>et al.</i> 1986
Species	R	M	R	R	R
Sex	MF	MF	MF	F	MF
<b>Study design</b>					
Animal randomization	+++	+++	+++	NR	NR

Areas	NTP 2017	NTP 2017	Newton <i>et al.</i> 1994	Watt 1983	Groth <i>et al.</i> 1986
Concurrent controls	+++	+++	+++	+++	+++
Animal model	+++	+++	+++	++	+++
Statistical power	+++	+++	+++	+	+++
<b>Exposure</b>					
Chemical characterization	+++	+++	+++	+++	+
Dosing regimen	+++	+++	+++	++	+
Exposure duration	+++	+++	+++	+++	++
Dose/response	+++	+++	++	+++	++
<b>Outcome</b>					
Outcome methodology	+++	+++	++	+++	++
Group methodology consistency	+++	+++	+++	+++	++
Adequacy of study duration	+++	+++	+++	+++	+++
<b>Confounding</b>					
Consideration of confounding	+++	+++	+++	++	+
<b>Analysis and reporting</b>					
Reporting and statistics	+++	+++	+++	++	+++
Tumor combining	+++	+++	+++	++	NR
<b>Study judgment</b>					
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. The two most recent antimony trioxide studies (NTP 2017a) presented no concerns regarding the utility to assess the cancer hazard and were considered of high overall utility.

Two antimony(III) trioxide studies were considered of moderate overall utility for assessing cancer hazard. The Watt (1983) study used fewer than 10 CDF rats per group, limiting the statistical power of the study, and also used only females, eliminating the ability to detect cancer increases in males or differences between sexes. Furthermore, only a few organs were reported to have been examined during necropsy. The statistical methods used for tumor incidences were not reported. In the Newton *et al.* (1994) study, the highest exposure level caused no changes in body weight, survival, or tumor incidence, so the dose levels might not have reached the maximally tolerated dose.

One antimony(III) trioxide study (Groth *et al.* 1986) is considered to have a low utility for the cancer hazard evaluation due to several concerns. The antimony(III) trioxide used was only 80% pure and was contaminated with arsenic (a known human carcinogen and animal carcinogen [NTP 2016b]) and lead (a reasonably anticipated human carcinogen and animal carcinogen [NTP 2016a]). Arsenic and lead are potential confounders depending on the tumor site. For instance, lung tumors (benign adenoma and malignant carcinoma), lymphocytic leukemia, and lymphoma were seen in animals exposed to arsenic (NTP 2016b). Lung was one of tumor sites in animals after lead exposure (NTP 2016a).

### **5.3 Findings from carcinogenicity studies**

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

**Table 5-3. Neoplasms induced in experimental animal carcinogenicity studies of inhaled antimony(III) trioxide.**

Studies are presented in the order of descending overall utility.

Species <sup>a</sup> , 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* and F)	
	Lung	Combined	Alveolar/bronchiolar adenoma or carcinoma (M*)	
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 (F)	Groth <i>et al.</i> 1986
	Lung	Malignant	Squamous-cell carcinoma (F)	
	Lung	Malignant	Scirrhous carcinoma (F)	
Rat, Fischer 344	None	None	None (M and F)	Newton <i>et al.</i> 1994
Rat (F only), CDF	Lung	Malignant	Scirrhous carcinoma (F)	Watt 1983

F = female, M = male.

\*Considered evidence of antimony trioxide based on multiple factors, although the increase in incidence was not statistically significant.

<sup>a</sup> Both sexes, unless specified.

In the Classification column, combined = benign or malignant (total number of animals with tumors).

### 5.3.1 Lung neoplasms

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

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

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

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

Antimony trioxide concentration →	3 mg/m <sup>3</sup>	10 mg/m <sup>3</sup>	30 mg/m <sup>3</sup>
<b>Mouse</b>			
Pulmonary overload	No	Yes	Yes
Preneoplastic <sup>a</sup>	↑ F, ↑ M	↑ F, ↑ M	↑ F, ↑ M
Benign	↑ F	↑ F	↑ F
Malignant	↑ F, ↑ M	↑ F, ↑ M	↑ F, ↑ M
Combined	↑ F, ↑ M	↑ F, ↑ M	↑ F, ↑ M
<b>Rat</b>			
Pulmonary overload	No	Yes	Yes
Preneoplastic <sup>a</sup>	↑ F, ↑ M	↑ F <sup>b</sup> , ↑ M	↑ F <sup>b</sup> , ↑ M
Benign	*M	↑ F, *M	↑ F <sup>c</sup> , *M
Malignant			↑ F <sup>d</sup>
Combined	*M	*M	*M

\* Considered evidence of antimony(III) trioxide carcinogenicity based on multiple factors, although the increase in incidence was not statistically significant.

↑ F = increase in females.

↑ M = increase in males.

<sup>a</sup> Increased hyperplasia of both alveolar and bronchiolar epithelium.

<sup>b</sup> Hyperplasia only increased in bronchiolar epithelium, not in alveolar epithelium.

<sup>c</sup> Findings include an equivocal finding of benign cystic keratinizing epithelioma and some evidence for alveolar/bronchiolar adenoma.

<sup>d</sup> Equivocal finding was seen for malignant squamous-cell carcinoma.

Male Wistar Han rats exposed to 10 or 30 mg/m<sup>3</sup> 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<sup>3</sup>. While alveolar/bronchiolar carcinoma was seen in only two



Wistar Han rats in the 10 mg/m<sup>3</sup> 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<sup>3</sup>, and were significantly increased at 10 and 30 mg/m<sup>3</sup> in the 2-year study. Additionally, at the 12-month interim evaluation, one female Wistar Han rat exposed to 30 mg/m<sup>3</sup> had alveolar/bronchiolar adenoma. Adenoma is known to progress to carcinoma, but no alveolar/bronchiolar carcinoma was seen, and the combined incidence was not increased. The incidence of lung cystic keratinizing epithelioma or squamous-cell carcinoma combined was not significantly increased, but was considered an equivocal finding (i.e., might have been related to exposure). Overall, these data were considered to be some evidence of carcinogenic activity in the lung based on benign alveolar/bronchiolar adenoma in female Wistar Han rats (NTP 2017a). Because the RoC listing criteria requires malignant and/or combined benign and malignant tumors in experimental animal studies, the findings in female Wistar Han rat lung do not meet the RoC listing criteria.

In the NTP (2017a) studies, as discussed in Section 3 (ADME), pulmonary overload was seen at 10 and 30 mg/m<sup>3</sup>, but not at 3 mg/m<sup>3</sup> 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<sup>3</sup>, 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<sup>3</sup>, in all groups except female Wistar Han rats, indicates that pulmonary overload is not required to induce carcinogenesis and is supportive of the RoC listing criteria.

For mice, females in all treated groups showed increased incidences in alveolar and bronchiolar epithelium hyperplasia, alveolar/bronchiolar adenoma, alveolar/bronchiolar carcinoma, and alveolar/bronchiolar adenoma or carcinoma (combined) at two years. During the 1-year interim sacrifice a low frequency of alveolar/bronchiolar adenoma were seen in female mice and prominent peribronchial lymphoid infiltrates were seen in the lung providing additional support for antimony(III) trioxide-induced tumorigenesis. Males showed increased alveolar and bronchiolar epithelium hyperplasia in all treated groups, slightly (not significantly) higher incidence of alveolar/bronchiolar adenoma in the 3 and 30 mg/m<sup>3</sup> groups, increased incidences of alveolar/bronchiolar carcinoma in all treated groups, and increased combined incidence of alveolar/bronchiolar adenoma or carcinoma in all treated groups after two years. After just one year males had a low frequency of alveolar/bronchiolar adenoma and alveolar/bronchiolar carcinoma. Males treated for one year also had prominent peribronchial lymphoid infiltrates. These early findings indicate lung carcinogenesis related to antimony exposure (NTP 2017a). Tumors were observed at exposure concentration as low as 3 mg/m<sup>3</sup>.

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 ( $0.1035 \text{ mg/m}^3$ ) and arsenic ( $0.0018 \text{ mg/m}^3$ ) in the air were both considered too low to have been the cause of neoplasms. Further, in animal studies, lead predominantly causes kidney neoplasms, which were not observed with antimony(III) trioxide exposure, thus, lead is not likely to have contributed to the carcinogenicity seen in the Groth *et al.* study (1986). Arsenic causes mice and hamsters to develop lung neoplasms, which were seen in Wistar rats after exposure to antimony. Compared to the concentration of antimony(III) trioxide ( $36 \text{ mg/m}^3$ ), the concentration of arsenic ( $0.0018 \text{ mg/m}^3$ ) was inconsequential, which is further supported by (1) much higher levels of antimony than that of arsenic found in the lung in exposed animals (Table 5-5), and (2) higher levels of arsenic in the lung of males, which did not develop lung tumors, compared to that of females, which developed lung tumors. These data suggest that neither arsenic nor lead contributed greatly to the observed incidences of lung cancer in this study, but interaction and other effects cannot be ruled out. Although this assessment is for hazard identification, it is noted that exposure concentrations in the Groth *et al.* study (1986) varied dramatically (average daily concentrations ranged from less than  $10 \text{ mg/m}^3$  to more than  $80 \text{ mg/m}^3$ ) due to technical difficulties in generating the aerosol, leading to questions about aerosol size and actual exposure level.

**Table 5-5. Antimony and arsenic concentrations ( $\mu\text{g/g}$  freeze-dried tissue) in the lung and blood of Wistar rats exposed to antimony trioxide containing arsenic by inhalation**

Tissue conc.↓ Metal and site↓	Antimony(III) trioxide		Ratio <sup>a</sup>
	0	45	
<b>Male</b>			
Antimony in lung	9.2	38,300	4,160
Antimony in blood	12.0	1,160	97
Arsenic in lung	6.5	213	33
Arsenic in blood	60.0	115	< 2
<b>Female</b>			
Antimony in lung	10.5	25,600	2,400
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

<sup>a</sup>Ratio = Concentration in  $45 \text{ mg/m}^3$  group/concentration in  $0 \text{ mg/m}^3$  group. Conc. = concentration.

No increased incidences of neoplasms were observed in the 1-year exposure plus 1-year post-exposure recovery study in male and female F344 rats (Newton *et al.* 1994). The concentrations in that study,  $0.06$ ,  $0.51$ , and  $4.45 \text{ mg/m}^3$ , were much lower than the high concentrations used in previously discussed studies (i.e.,  $45 \text{ mg/m}^3$  in Groth *et al.* [1986], and  $30 \text{ mg/m}^3$  in NTP

[2017a]) but the high concentration was comparable to the high dose used by Watt (1983) of 4.2 mg/m<sup>3</sup>. The aerosol size used in the Newton *et al.* (1994) study was large, ranging from 2.92 to 4.60 μm and included less respirable aerosols than if they had been < 4.0 μm (EPA 1988, OECD 2017). However, the Watt (1983) study used aerosols that were even larger, averaging 5.06 μm, and Watt reported significant increases in lung tumor incidences. Nonsignificant increases in nonneoplastic alveolar/bronchiolar hyperplasia were found in females, but not in males and significant increases in interstitial inflammation occurred at the termination of the study (Newton *et al.* 1994). Significant increases in nonneoplastic lesions of alveolar/intra-alveolar macrophages, with or without foreign particulate material, perivascular/peribronchiolar macrophages with lymphoid cells and foreign particulate material, and peribronchial lymph node macrophages with foreign particulate material occurred at both the beginning and the end of the exposure period and at the end of the study in both sexes. Lungs appeared with pinpoint black foci, which the authors believed to be aggregates of macrophages containing antimony(III) trioxide. The strain or stock of rats also differs from that used in the positive studies.

Scirrhous carcinoma in the lung was increased in female CDF rats in a study with one-year exposures at 4.2 mg/m<sup>3</sup> (Watt 1983). It is worth noting that scirrhous carcinoma is not a term that NTP currently uses, and it is possible that the same lesions might be classified currently as alveolar/bronchiolar carcinoma. Exposed CDF rats also had significant increases in nonneoplastic lesions of the lung, including focal fibrosis, pneumocyte hyperplasia, and multinucleated giant cells at 1.6 and 4.2 mg/m<sup>3</sup>, and adenomatous hyperplasia at 4.2 mg/m<sup>3</sup>.

### 5.3.2 Other neoplasms

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

#### Adrenal gland neoplasms

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

Female Wistar Han rats in the 30 mg/m<sup>3</sup> 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<sup>3</sup> had higher (but not significant) incidences of adrenal medullary hyperplasia, and the trend for all concentrations was positive. Overall, there is some evidence of adrenal medulla carcinogenicity in female Wistar Han rats (NTP 2017a). The increase in the combined incidences of benign or malignant pheochromocytoma in female Wistar Han rats supports the RoC listing criteria.

**Table 5-6. Adrenal medulla neoplasms in Wistar Han rats in the NTP 2017 two-year study.**

Antimony trioxide concentration →	3 mg/m <sup>3</sup>	10 mg/m <sup>3</sup>	30 mg/m <sup>3</sup>
Observations ↓			
Pulmonary overload	No	Yes	Yes
Pre-neoplastic <sup>a</sup>	*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.

<sup>a</sup> Increased incidences of hyperplasia in adrenal medulla.

Male Wistar Han rats in the 30 mg/m<sup>3</sup> group had increased incidences of adrenal medullary hyperplasia and increased incidences of benign pheochromocytoma. Incidences of benign pheochromocytoma at 10 mg/m<sup>3</sup> were higher, but not significantly increased, compared to concurrent controls. Overall, there is some evidence of adrenal medullary carcinogenicity in female Wistar Han rats (NTP 2017a) based on the increased incidences of benign pheochromocytoma and combined malignant or benign pheochromocytoma.

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

### Skin neoplasms

Skin neoplasms were seen in B6C3F1/N mice, but not in Wistar Han rats, in the NTP (2017a) two-year study. Male B6C3F1/N mice had increased incidences (also exceeding historical control ranges) of benign fibrous histiocytoma at 30 mg/m<sup>3</sup> and had a significant positive trend. Two incidences (not significantly increased) of malignant fibrosarcoma were seen at 10 mg/m<sup>3</sup>, and increased combined incidences of fibrous histiocytoma or fibrosarcoma at 30 mg/m<sup>3</sup> 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<sup>3</sup> 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<sup>3</sup>), with a significant positive dose-response trend

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

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

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

##### **5.4.1 Synthesis**

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

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

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

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

**Table 5-7. Neoplasms that had increased incidences in malignant tumors or combined (benign or malignant) tumors**

Sites	Rat		Mouse	
	Malignant	Combined	Malignant	Combined
Lung	↑ F <sup>a</sup>	*M <sup>b</sup>	↑ M <sup>c</sup> , ↑ F <sup>c</sup>	↑ F <sup>b</sup>
Adrenal gland	–	↑ F <sup>d</sup>	–	–
Skin	–	–	–	↑ M <sup>c</sup>
Lymphoma (whole body)	–	–	↑ F	–

↑ F = significant increase in females.

↑ M = significant increase in males.

– = No increase reported.

\*Considered evidence of antimony(III) trioxide carcinogenicity based on multiple factors, although the increase in incidence was not statistically significant (NTP 2017a).

<sup>a</sup>Squamous-cell carcinoma, scirrhus carcinoma.

<sup>b</sup>Alveolar/bronchiolar adenoma or carcinoma.

<sup>c</sup>Alveolar/bronchiolar carcinoma.

<sup>d</sup>Benign or malignant pheochromocytoma.

<sup>e</sup>Fibrous histiocytoma or fibrosarcoma.

#### 5.4.2 NTP preliminary level of evidence conclusion

Sufficient evidence of carcinogenicity from studies in experimental animals based on the combined increase in the incidences of malignant and benign tumors at several tissue sites in rats and mice.

Table 5-8. Cancer studies in experimental animals from exposure to antimony(III) trioxide

Reference and study design	Exposure	Tumor site – Tumor type		Comments
		Dose levels	Tumor incidence (n/N) (%)	
<b>NTP 2017a</b>  <b>Animal:</b> Rat — Wistar Han [CrI:WI (Han)] M  <b>Animal age at the beginning of exposure:</b> 6 weeks  <b>Study duration:</b> 105 weeks	<b>Agent and purity:</b> Antimony(III) trioxide (crystalline form: crystalline, diamond cubic crystal structure) 99.9%  <b>Aerosol size:</b> MMAD = 0.9–1.5 µm, GSD 1.7–2.2  <b>Exposure route:</b> Inhalation  <b>Exposure concentrations, frequency, and duration:</b> 0 3 10 30 mg/m <sup>3</sup> 6 hours/day, 5 days/week x 105 weeks	<b>Adrenal gland – Benign pheochromocytoma<sup>a</sup></b>		<b>Survival:</b> 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.  <b>Body weight:</b> Body weight of the 30-mg/m <sup>3</sup> group was lower than untreated controls after 69 weeks.  <b>Significantly increased preneoplastic lesions:</b> 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*  <b>Overall utility:</b> [+++] There were no concerns of confounding as the chemical was pure and stable, the exposure was well characterized, and all groups were treated the same. The study had a high level of sensitivity to detect neoplasms as it used large numbers of both sexes of rats, exposed at three dose levels, which reached the maximally tolerated level, for a near life-span duration. However, the stock of rat used was new to NTP and so few historical control data exist compared to other strains. Complete necropsies with histological examination of most organs was performed, so the ability to detect neoplasms was high.  <b>Footnotes:</b> * $P < 0.05$ , ** $P < 0.01$ , *** $P < 0.001$ . <sup>a</sup> Adjusted percent incidence based on Poly-3 estimated
		0	1/49 (2.5%)	
		3	0/50	
		10	2/49 (4.8%)	
		30	7/50* (17.2%)	
		Trend $P$ -value: $< 0.001$		
		<b>Lung – Alveolar/bronchiolar adenoma<sup>a</sup></b>		
		0	3/50 <sup>b</sup> (7.1%)	
		3	4/50 <sup>b</sup> (9.8%)	
		10	6/50 <sup>b</sup> (13.8%)	
		30	8/50 <sup>b</sup> (19.7%)	
		Trend $P$ -value: = 0.057		
		<b>Lung – Alveolar/bronchiolar carcinoma<sup>a</sup></b>		
		0	0/50	
		3	0/50	
		10	2/50 <sup>c</sup> (4.7%)	
		30	0/50	
<b>Lung – Alveolar/bronchiolar adenoma or carcinoma<sup>a</sup></b>				
0	3/50 (7.1%)			
3	4/50 (9.8%)			
10	8/50 (18.4%)			

Reference and study design	Exposure	Tumor site – Tumor type		Comments
		Dose levels	Tumor incidence (n/N) (%)	
		30	8/50 (19.7%)	neoplasm incidence after adjustment for concurrent mortality. <sup>b</sup> Exceeds historical controls from inhalation studies: 4/150 (range 0%–6%); exceeds historical controls from studies of all routes: 4/299 (range 0%–6%). <sup>c</sup> Exceeds historical controls from inhalation studies: 0/150; exceeds historical controls from studies of all routes: 0/299.
<b>NTP 2017a</b>  <b>Animal:</b> Rat — Wistar Han [CrI:WI (Han)] F  <b>Animal age at the beginning of exposure:</b> 6 weeks  <b>Study duration:</b> 105 weeks	<b>Agent and purity:</b> Antimony trioxide (crystalline form: crystalline, diamond cubic crystal structure) 99.9%  <b>Aerosol size:</b> MMAD = 0.9-1.5 µm, GSD 1.7–2.2  <b>Exposure route:</b> Inhalation  <b>Exposure concentrations, frequency, and duration:</b> 0 3 10 30 mg/m <sup>3</sup> 6 hours/day, 5 days/week x 105 weeks	<b>Adrenal gland – Benign pheochromocytoma<sup>a</sup></b>		<b>Survival:</b> Survival was significantly decreased at 10 and 30 mg/m <sup>3</sup> and there was a significant negative trend ( $P < 0.001$ ): 39/50, 38/50, 28/50 ( $P = 0.032$ ), 20/50 ( $P < 0.001$ ).  <b>Body weight:</b> Body weight was lower than controls in the groups exposed to 30, 10, and 3 mg/m <sup>3</sup> after 65, 81, and 99 weeks, respectively.  <b>Significantly increased preneoplastic lesions:</b> 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*  <b>Overall utility:</b> [+++] 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 (4.5%)	
		10	2/49 (4.8%)	
		30	6/50** (15.2%)	
		Trend $P$ -value: = 0.004		
		<b>Adrenal gland – Malignant pheochromocytoma</b>		
		0	0/49	
		3	0/49	
		10	0/49	
		30	1/50 (2%)	
		<b>Adrenal gland – Benign or malignant pheochromocytoma<sup>a</sup></b>		
		0	0/49	
		3	2/49 (4.5%)	
		10	2/49 (4.8%)	
		30	7/50** (17.6%)	
Trend $P$ -value: < 0.001				
<b>Lung – Alveolar/bronchiolar adenoma<sup>a</sup></b>				
0	0/50			
3	2/50 (4.4%)			
10	6/50* (13.8%)			



Reference and study design	Exposure	Tumor site – Tumor type		Comments
		Dose levels	Tumor incidence (n/N) (%)	
		30	5/50* (12.4%)	<b>Footnotes:</b> * $P < 0.05$ , ** $P < 0.01$ , *** $P < 0.001$ . <sup>a</sup> Adjusted percent incidence based on Poly-3 estimated neoplasm incidence after adjustment for concurrent mortality.
		Trend $P$ -value: = 0.029		
		<b>Lung – Cystic keratinizing epithelioma or squamous-cell carcinoma<sup>a</sup></b>		
		0	0/50	
		3	0/50	
		10	0/50	
		30	3/50 (7.4%)	
		Trend $P$ -value: = 0.006		
		<b>Lung – Alveolar/bronchiolar adenoma<sup>a</sup></b>		
		0	10/50 (21.5%)	
		3	14/50 (32.9%)	
		10	9/50 (21.8%)	
		30	14/50 (34.6%)	
		<b>NTP 2017a</b>  <b>Animal:</b> Mouse — B6C3F1/N M  <b>Animal age at the beginning of exposure:</b> 6 weeks  <b>Study duration:</b> 105 weeks	<b>Agent and purity:</b> Antimony(III) trioxide (crystalline form: crystalline, diamond cubic crystal structure) 99.9%  Aerosol size: MMAD = 0.9–1.5 $\mu\text{m}$ , GSD 1.7–2.2  <b>Exposure route:</b>	
0	4/50 (8.5%)			
3	18/50 <sup>***</sup> (40.9%)			
10	20/50 <sup>***</sup> (46.2%)			
30	27/50 <sup>***</sup> (62.8%)			
Trend $P$ -value: < 0.001				
<b>Lung – Alveolar/bronchiolar carcinoma, multiple only</b>				
0	0/50			
3	5/50* (10%)			
10	6/50 <sup>**</sup> (12%)			
30	11/50 <sup>**</sup> (22%)			
Lung – Alveolar/bronchiolar adenoma or carcinoma <sup>a</sup>				

Reference and study design	Exposure	Tumor site – Tumor type		Comments
		Dose levels	Tumor incidence (n/N) (%)	
	Inhalation  <b>Exposure concentrations, frequency, and duration:</b> 0 3 10 30 mg/m <sup>3</sup> 6 hours/day, 5 days/week × 105 weeks	0	13/50 (27.5%)	exposure was well characterized, and all groups were treated the same. The study had a high level of sensitivity to detect neoplasms as it used large numbers of both sexes of mice, exposed at three dose levels, which reached the maximally tolerated level, for a near life-span duration. Complete necropsies with histological examination of most organs was performed, so the ability to detect neoplasms was high.  <b>Footnotes:</b> * $P < 0.05$ , ** $P < 0.01$ , *** $P < 0.001$ . <sup>a</sup> Adjusted percent incidence based on Poly-3 estimated neoplasm incidence after adjustment for concurrent mortality.
		3	29/50*** (64.5%)	
		10	28/50*** (63.6%)	
		30	34/50*** (75.3%)	
		Trend $P$ -value: < 0.001		
		<b>Skin – Benign fibrous histiocytoma<sup>a</sup></b>		
		0	0/50	
		3	1/50 (2.5%)	
		10	1/50 (2.5%)	
		30	4/50* (10.6%)	
		Trend $P$ -value: = 0.012		
		<b>Skin – Fibrosarcoma</b>		
		0	0/50	
		3	0/50	
		10	2/50 (4%)	
		30	0/50	
		<b>Skin – Fibrous histiocytoma or fibrosarcoma<sup>a</sup></b>		
		0	0/50	
		3	1/50 (2.5%)	
		10	3/50 (7.3%)	
30	4/50* (10.6%)			
Trend $P$ -value: = 0.023				
<b>NTP 2017a</b>	<b>Agent and purity:</b> Antimony(III) trioxide (crystalline form:	<b>Whole body – Malignant lymphoma<sup>a</sup></b>		<b>Survival:</b> Survival was significantly decreased at 10 and 30 mg/m <sup>3</sup> and there was a significant negative trend ( $P < 0.001$ ): 36/50, 31/50, 26/50 ( $P = 0.032$ ), 15/50 ( $P < 0.001$ ).  <b>Body weight:</b> Body weights were lower than controls in the
<b>Animal:</b> Mouse — B6C3F1/N		0	7/50 (15.6%)	
		3	17/50* (38.1%)	
		10	20/50*** (47.5%)	

Reference and study design	Exposure	Tumor site – Tumor type		Comments
		Dose levels	Tumor incidence (n/N) (%)	
F  <b>Animal age at the beginning of exposure:</b> 6 weeks  <b>Study duration:</b> 105 weeks	crystalline, diamond cubic crystal structure) 99.9% Aerosol size: MMAD = 0.9–1.5 µm, GSD 1.7–2.2  <b>Exposure route:</b> Inhalation  <b>Exposure concentrations, frequency, and duration:</b> 0 3 10 30 mg/m <sup>3</sup> 6 hours/day, 5 days/week × 105 weeks	30	27/50*** (60.7%)	30-mg/m <sup>3</sup> group after 85 weeks.  <b>Significantly increased preneoplastic lesions: Lung lymphocyte infiltration: 7/50, 37/50<sup>l***l</sup>, 37/50<sup>l***l</sup>, 26/50<sup>l***l</sup>;</b> Lung alveolar epithelium hyperplasia: 1/50, 36/50**, 49/50**, 48/50** Lung bronchiole epithelium hyperplasia: 1/50, 34/50**, 48/50**, 45/50**.  <b>Overall utility: [+++]</b> There were no concerns of confounding as the chemical was pure and stable, the exposure was well characterized, and all groups were treated the same. The study had a high level of sensitivity to detect neoplasms as it used large numbers of both sexes of mice, exposed at three dose levels, which reached the maximally tolerated level, for a near life-span duration. Complete necropsies with histological examination of most organs was performed, so the ability to detect neoplasms was high.  <b>Footnotes:</b> * $P < 0.05$ , ** $P < 0.01$ , *** $P < 0.001$ . <sup>a</sup> Adjusted percent incidence based on Poly-3 estimated neoplasm incidence after adjustment for concurrent mortality.
		Trend $P$ -value: < 0.001		
		<b>Lung – Alveolar/bronchiolar adenoma<sup>a</sup></b>		
		0	1/50 (2.3%)	
		3	10/50** (22.8%)	
		10	19/50*** (44.9%)	
		30	8/50** (20.3%)	
		<b>Lung – Alveolar/bronchiolar carcinoma<sup>a</sup></b>		
		0	2/50 (4.4%)	
		3	14/50*** (31.2%)	
		10	11/50** (26.8%)	
		30	11/50** (28.8%)	
		<b>Lung – Alveolar/bronchiolar carcinoma, multiple only</b>		
		0	0/50	
		3	7/50** (14%)	
		10	6/50* (12%)	
		30	4/50* (8%)	
		<b>Lung – Alveolar/bronchiolar adenoma or carcinoma<sup>a</sup></b>		
		0	3/50 (6.6%)	
		3	22/50*** (48.8%)	
		10	27/50*** (62.6%)	
		30	18/50*** (43.5%)	
		Trend $P$ -value: = 0.019		
<b>Skin – Squamous cell carcinoma</b>				
0	0/50			

Reference and study design	Exposure	Tumor site – Tumor type		Comments
		Dose levels	Tumor incidence (n/N) (%)	
		3	0/50	
		10	0/50	
		30	2/50 (4%)	
<b>Groth <i>et al.</i> 1986</b>  <b>Animal:</b> Rat — Wistar M, F  <b>Animal age at the beginning of exposure:</b> 8 months  <b>Study duration:</b> 71 to 73 weeks	<b>Agent and purity:</b> 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  <b>Exposure route:</b> Inhalation	<b>Lung – Total neoplasms (M)</b>		<b>Survival:</b> Survival was similar to controls.  <b>Body weight:</b> Body weights were similar to controls, although males did weigh 6.2% less than controls at 26 to 50 weeks.  <b>Significantly increased preneoplastic lesions:</b> 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.  <b>Other comments:</b> 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.  <b>Overall utility:</b> [++] The chemical was well characterized,
		0	None	
		45	None	
		<b>Lung – Total neoplasms (F)</b>		
		0	0/89	
		45	19/89 <sup>[***]</sup> (21%)	
		<b>Lung – Squamous cell carcinoma (F)</b>		
		0	0/89	
		45	9/89 <sup>[**]</sup> (10%)	
		<b>Lung – Scirrhous carcinoma (F)</b>		
0	0/89			
45	5/89 <sup>[*]</sup> (5.6%)			
<b>Lung – Bronchioalveolar adenoma (F)</b>				
0	0/89			

Reference and study design	Exposure	Tumor site – Tumor type		Comments								
		Dose levels	Tumor incidence (n/N) (%)									
	<p><b>Exposure concentrations, frequency, and duration:</b> 0 45 mg/m<sup>3</sup> 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].</p> <p>Intermediate sacrifices were made to examine distribution of antimony in tissue.</p>	45	11/89 <sup>[***]</sup> (12%)	<p>but was found to be only 80% pure, with lead and arsenic as contaminants. The low purity makes distinguishing effects caused by antimony from possible effects caused by the contaminants difficult. The sensitivity of the study to detect neoplasms was low as only one dose level was used and it was based on the level of exposure to workers and not the maximally tolerated dose. Further, the exposure concentration varied widely until 5 months into the study when the target concentration was reached. The exposure duration was more than a year and full necropsies with histological examinations were performed. Neoplasms were reported with statistical analysis as total neoplasms combined per organ site.</p> <p><b>Footnotes:</b> * <math>P &lt; 0.05</math>, ** <math>P &lt; 0.01</math>, *** <math>P &lt; 0.001</math>. [ ] = Statistical significance calculated by NTP, using Fisher's Exact test.</p>								
<p><b>Newton et al. 1994</b></p> <p><b>Animal:</b> Rat — Fischer 344 (CDF F344)</p>	<p><b>Agent and purity:</b> Antimony(III) trioxide (crystalline form: not reported)</p>	<p><b>Lung – Carcinoma</b></p> <table border="1"> <tr> <td>0</td> <td>1/52 (1.9%)</td> </tr> <tr> <td>0.06</td> <td>0/52 (0%)</td> </tr> <tr> <td>0.51</td> <td>0/53 (0%)</td> </tr> <tr> <td>4.5</td> <td>1/52 (1.9%)</td> </tr> </table>		0	1/52 (1.9%)	0.06	0/52 (0%)	0.51	0/53 (0%)	4.5	1/52 (1.9%)	<p><b>Survival:</b> Survival was similar to controls.</p> <p><b>Body weight:</b> Similar to controls.</p> <p><b>Significantly increased preneoplastic lesions:</b> Bronchiolar/alveolar hyperplasia, interstitial inflammation,</p>
0	1/52 (1.9%)											
0.06	0/52 (0%)											
0.51	0/53 (0%)											
4.5	1/52 (1.9%)											

Reference and study design	Exposure	Tumor site – Tumor type		Comments
		Dose levels	Tumor incidence (n/N) (%)	
CrI BR) M  <b>Animal age at the beginning of exposure:</b> 8 weeks (140–169 g males; 99–122 g females)  <b>Study duration:</b> 24 months	99.68% Aerosol size: MMAD = 3.76 ± 0.84 μm, GSD 1.79 ± 0.32 <b>Exposure route:</b> Inhalation  <b>Exposure concentrations, frequency, and duration:</b> 0 0.06 (target 0.05) 0.51 (target 0.5) 4.50 mg/m <sup>3</sup> (target 5.0) 6 hours/day, 5 days/week x 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.	Alveolar/intra-alveolar macrophages (12 months)		interstitial fibrosis, and granulomatous inflammation were increased in the exposed groups.  An increase in opacities of the eye was seen predominantly in females, but also occurred to a lesser extent in males.  <b>Overall utility: [++]</b> 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 <sub>2</sub> O <sub>3</sub> accumulation and increased clearance half-life in the lung (by 80% in the 4.5 mg/m <sup>3</sup> group). The pulmonary overload was observed at relatively low exposure concentrations (compared to inert particles, such as TiO <sub>2</sub> ) and Sb <sub>2</sub> O <sub>3</sub> 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).
		0	6/13 (46.2%)	
		0.06	11/13 <sup>[*]</sup> (84.6%)	
		0.51	9/12 (75%)	
		4.5	13/13 <sup>[**]</sup> (100%)	
		Alveolar/intra-alveolar macrophages with foreign particulates (12 months)		
		0	0/13 (0%)	
		0.06	13/13 <sup>[***]</sup> (100%)	
		0.51	12/12 <sup>[***]</sup> (100%)	
		4.5	13/13 <sup>[***]</sup> (100%)	
		Perivascular/peribronchiolar macrophages with lymphoid cells and foreign particulates (12 months)		
		0	0/13 (0%)	
		0.06	2/13 (15.3%)	
		0.51	6/12 <sup>[**]</sup> (50%)	
		4.5	7/13 <sup>[**]</sup> (53.8%)	
		Peribronchial lymph node macrophages with foreign particulates (12 months)		
		0	0/13 (0%)	
		0.06	3/13 (23%)	
		0.51	5/12 <sup>[*]</sup> (41.7%)	
		4.5	13/13 <sup>[***]</sup> (100%)	
Lung – Interstitial inflammation (24 months)				
0	32/52 (61.5%)			
0.06	37/52 (71.1%)			
0.51	36/53 (67.9%)			

Reference and study design	Exposure	Tumor site – Tumor type		Comments
		Dose levels	Tumor incidence (n/N) (%)	
		4.5	48/52 <sup>[***]</sup> (92.3%)	
		Bronchiolar/alveolar hyperplasia (24 months)		
		0	3/52 (5.8%)	
		0.06	1/52 (1.9%)	
		0.51	2/53 (3.8%)	
		4.5	4/52 (7.7%)	
		Alveolar/intra-alveolar macrophages (24 months)		
		0	31/52 (59.6%)	
		0.06	44/52 <sup>[**]</sup> (84.6%)	
		0.51	46/53 <sup>[**]</sup> (86.8%)	
		4.5	52/52 <sup>[***]</sup> (100%)	
		Alveolar/intra-alveolar macrophages with foreign particulates (24 months)		
		0	0/52 (0%)	
		0.06	15/52 <sup>[***]</sup> (28.8%)	
		0.51	38/53 <sup>[***]</sup> (71.7%)	
		4.5	51/52 <sup>[***]</sup> (98.1%)	
		Perivascular/peribronchiolar macrophages with lymphoid cells and foreign particulates (24 months)		
		0	0/52 (0%)	
		0.06	22/52 <sup>[***]</sup> (42.3%)	
		0.51	46/53 <sup>[***]</sup> (86.8%)	
		4.5	47/52 <sup>[***]</sup> (90.4%)	
		Peribronchial lymph node macrophages with foreign particulates (24 months)		
		0	0/52 (0%)	
		0.06	6/52 <sup>[*]</sup> (11.5%)	

This information is distributed solely for the purpose of pre-dissemination peer review under applicable information quality guidelines. It has not been formally distributed by the National Toxicology Program. It does not represent and should not be construed to represent any NTP determination or policy.

Reference and study design	Exposure	Tumor site – Tumor type		Comments
		Dose levels	Tumor incidence (n/N) (%)	
		0.51	34/53 <sup>[***]</sup> (64.2%)	
		4.5	39/52 <sup>[***]</sup> (75%)	
<b>Newton <i>et al.</i> 1994</b>  <b>Animal:</b> Rat — Fischer 344 (CDF F344 CrI BR) F  <b>Animal age at the beginning of exposure:</b> 8 weeks (140–169 g males; 99–122 g females)  <b>Study duration:</b> 24 months	<b>Agent and purity:</b> Antimony(III) trioxide (crystalline form: not reported) 99.68%  Aerosol size: MMAD = 3.76 ± 0.84 µm, GSD 1.79 ± 0.32  <b>Exposure route:</b> Inhalation  <b>Exposure concentrations, frequency, and duration:</b> 0 0.06 (target 0.05) 0.51 (target 0.5) 4.50 mg/m <sup>3</sup> (target 5.0) 6 hours/day, 5 days/week x 12 months  5 animals/sex were sacrificed at 6 (5/sex), 12	Lung – Carcinoma		<b>Survival:</b> Survival was similar to controls.  <b>Body weight:</b> Similar to controls.
		0	0/49 (0%)	
		0.06	0/52 (0%)	
		0.51	1/54 (1.9%)	
		4.5	0/50 (0%)	
		Alveolar/intra-alveolar macrophages (12 months)		
		0	6/16 (37.5%)	
		0.06	10/13 <sup>[*]</sup> (76.9%)	
		0.51	8/11 (72.7%)	
		4.5	14/14 <sup>[***]</sup> (100%)	
		Alveolar/intra-alveolar macrophages with foreign particulates (12 months)		
		0	0/16 (0%)	
		0.06	13/13 <sup>[***]</sup> (100%)	
		0.51	11/11 <sup>[***]</sup> (100%)	
		4.5	14/14 <sup>[***]</sup> (100%)	
		Perivascular/peribronchiolar macrophages with lymphoid cells and foreign particulates (12 months)		
		0	0/16 (0%)	
0.06	6/13 <sup>[**]</sup> (46.2%)			
0.51	4/11 <sup>[*]</sup> (36.4%)			
4.5	7/14 <sup>[**]</sup> (50%)			
Peribronchial lymph node macrophages with foreign particulates (12 months)				



Reference and study design	Exposure	Tumor site – Tumor type		Comments		
		Dose levels	Tumor incidence (n/N) (%)			
	(5/sex), 18 (5/sex) months and the rest (50/sex) were sacrificed at 24 months.	0	0/16 (0%)			
		0.06	0/13 (0%)			
		0.51	6/11 <sup>[**]</sup> (54.5%)			
		4.5	13/14 <sup>[***]</sup> (92.9%)			
		Lung – Interstitial inflammation (24 months)				
		0	33/49 (67.3%)			
		0.06	40/52 (76.9%)			
		0.51	48/54 <sup>[**]</sup> (88.9%)			
		4.5	48/50 <sup>[***]</sup> (96%)			
		Bronchiolar/alveolar hyperplasia (24 months)				
		0	1/49 (2%)			
		0.06	0/52 (0%)			
		0.51	0/54 (0%)			
		4.5	6/50 (12%)			
		Alveolar/intra-alveolar macrophages (24 months)				
		0	28/49 (57.1%)			
		0.06	40/52 <sup>[*]</sup> (76.9%)			
		0.51	48/54 <sup>[***]</sup> (88.9%)			
		4.5	50/50 <sup>[***]</sup> (100%)			
		Alveolar/intra-alveolar macrophages with foreign particulates (24 months)				
		0	0/49 (0%)			
		0.06	24/52 <sup>[***]</sup> (46.2%)			
		0.51	49/54 <sup>[***]</sup> (90.7%)			
		4.5	48/50 <sup>[***]</sup> (96%)			

Reference and study design	Exposure	Tumor site – Tumor type		Comments
		Dose levels	Tumor incidence (n/N) (%)	
		Perivascular/peribronchiolar macrophages with lymphoid cells and foreign particulates (24 months)		
		0	0/49 (0%)	
		0.06	31/52 <sup>[***]</sup> (59.6%)	
		0.51	47/54 <sup>[***]</sup> (87%)	
		4.5	47/50 <sup>[***]</sup> (94%)	
		Peribronchial lymph node macrophages with foreign particulates (24 months)		
		0	0/49 (0%)	
		0.06	6/52 <sup>[*]</sup> (11.5%)	
		0.51	29/54 <sup>[***]</sup> (53.7%)	
		4.5	39/50 <sup>[***]</sup> (78%)	
<b>Watt 1983</b>  <b>Animal:</b> Rat — CDF F  <b>Animal age at the beginning of exposure:</b> NR (Possibly 3 to 5 months)  <b>Study duration:</b> 2 years	<b>Agent and purity:</b> Antimony(III) trioxide (crystalline form: 99.4% Aerosol size: MMAD = 5.06 μm  <b>Exposure route:</b> Inhalation	<b>Lung – Scirrhous carcinoma</b>		<b>Survival:</b> Not reported.  <b>Body weight:</b> Body weight gain in exposed rats was greater than controls.  <b>Significantly increased pre-neoplastic lesions:</b> 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
		0	0/13	
		1.6	0/17	
		4.2	9/18 <sup>**</sup> (50%)	
		<b>Lung – Squamous cell carcinoma</b>		
		0	0/13	
		1.6	0/17	
		4.2	2/18 (11%)	
		<b>Lung – Alveolar/bronchiolar adenoma</b>		
		0	0/13	
1.6	1/17 (5.9%)			

Reference and study design	Exposure	Tumor site – Tumor type		Comments
		Dose levels	Tumor incidence (n/N) (%)	
	<p><b>Exposure concentrations, frequency, and duration:</b></p> <p>0  <math>1.6 \pm 1.5</math>            [avg Feret's diameter = 0.44 <math>\mu\text{m}</math> w/ geometric std dev 2.23]  <math>4.2 \pm 3.2 \text{ mg/m}^3</math>            [avg Feret's diameter = 0.4 <math>\mu\text{m}</math> 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.</p>	4.2	3/18 (16.7%)	<p>study.</p> <p>Significant increases in adenomatous hyperplasia occurred in the high dose group after 9 months to the end of the study.</p> <p>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.</p> <p><b>Other comments:</b> 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.</p> <p><b>Overall utility:</b> [++] The chemical purity was high and exposure was characterized, although the particle size (converted by Newton <i>et al.</i> [1994] to be MMAD of approximately 5 <math>\mu\text{m}</math>) was over the recommended (1-4 <math>\mu\text{m}</math>). 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<sub>2</sub>O<sub>3</sub> particles (and possible metabolism alternation due to pine shavings and therefore affecting susceptibility).</p> <p><b>Footnotes:</b> * <math>P &lt; 0.05</math>, ** <math>P &lt; 0.01</math>, *** <math>P &lt; 0.001</math>.</p>

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

**This Page Intentionally Left Blank**

## 6 Mechanistic and Other Relevant Data

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

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

### 6.1 Other relevant data

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

#### 6.1.1 Carcinogenicity studies of other antimony compounds

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

#### 6.1.2 Non-cancer health outcomes

Non-carcinogenic health effects resulting from exposure to antimony are described elsewhere. ATSDR (2017) conducted a systematic review of non-cancer effects in workers and animals exposed to antimony (elemental antimony, antimony ore, and various antimony compounds) and

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

## 6.2 Electrophilic properties

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

## 6.3 Genotoxicity

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

### 6.3.1 Mutagenicity

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

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

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

### 6.3.2 Mutations in antimony(III) trioxide–induced lung tumors

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

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

### 6.3.3 DNA damage

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

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

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

*In vitro* studies of human whole blood and peripheral blood lymphocytes (Schaumlöffel and Gebel 1998) and V79 Chinese hamster cells (Gebel *et al.* 1998) exposed to antimony(III) trichloride showed increased DNA damage (single-strand breaks). DNA damage was detected below cytotoxic concentrations and did not involve DNA-protein crosslinks. The latter observation is in contrast to results with arsenic, which is a potent inducer of DNA-protein crosslinks in both hamster and human cells.

In prokaryotes, evidence for DNA damage has been reported from experiments with sensitive detection capacity. In modified *rec* assay protocols that increased the sensitivity of the *Bacillus subtilis* *rec* assay 20- to 50-fold (Kada 1976, Hirano *et al.* 1982), antimony(III) trioxide (Kuroda *et al.* 1991) and antimony(III) trichloride (Kanematsu *et al.* 1980, Kuroda *et al.* 1991) both gave positive results. In the very sensitive plasmid pBR322 DNA-nicking assay, trimethylstibine ( $\text{Sb}^{\text{III}}(\text{CH}_3)_3$ ) 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).

#### 6.3.4 Chromosomal aberrations, micronucleus, and sister chromatid exchange

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

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

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

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

Antimony(III) trioxide increased micronuclei in mature erythrocytes (normochromatic erythrocytes) in mice, but not in rats, after 12 months of inhalation exposure; the increase in mice showed a significant dose-related trend and was significant at the highest dose ( $30 \text{ mg/m}^3$ ) (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 cells (Gebel *et al.* 1998). Following *in vitro* exposure to antimony(III) trichloride, micronuclei were seen in human peripheral blood lymphocytes (Schaumlöffel and Gebel 1998), V79 Chinese hamster cells (Gebel 1998, Gebel *et al.* 1998), BES-6 human bronchial epithelial cells, human fibroblasts, and Chinese hamster ovary (CHO)-K1 cells (Huang *et al.* 1998). Because co-incubation with either superoxide dismutase or catalase did not affect the number of micronuclei detected in human lymphocytes, superoxide or peroxide oxygen species might not have a prominent role in promoting chromosomal damage (Schaumlöffel and Gebel 1998).

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

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

### 6.3.5 Summary of genotoxicity results

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

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

Endpoint (test system)	Antimony(III) trioxide		Antimony(III) trichloride	
	<i>in vitro</i>	<i>in vivo</i>	<i>in vitro</i>	<i>in vivo</i>
<b>Mutation</b>				
Any mutation (prokaryotes)	N	–	N	–
Any mutation (eukaryotes)	N	*	–	–
<b>DNA Damage</b>				
Any DNA damage (prokaryotes)	P	P	P	–
Any DNA damage (eukaryotes)	P	P	P	–
DNA-protein crosslinks	–	–	N	–
<b>Chromosomal damage/cytogenetic effects</b>				
Chromosomal aberrations	P	N <sup>a</sup>	–	<sup>b</sup>
Micronucleus induction	–	P	P	P
Sister chromatid exchange	P	–	P	–

Results: P = positive, N = negative. – = not reported.

\*Mutations were detected in antimony(III) trioxide-induced lung tumors (NTP 2017a). <sup>a</sup> Negative in rats; uncertain in mice due to severe study limitations. <sup>b</sup> Uncertain because only available study has severe study limitations.

#### 6.4 Inhibition of DNA repair

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

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

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

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

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

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

**Table 6-2. DNA repair pathways and molecules altered by exposure to antimony(III) compounds**

DNA repair pathway(s)	Effects on DNA repair	Molecules affected	Reference
<b>Antimony(III) trichloride</b>			
<b>NER</b>	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 <i>et al.</i> 2010
<b>NHEJ and HR</b>	Inhibition of repair of $\gamma$ -irradiation-induced DSBs in HeLa cells	Prolonged associated of histone H2AX and TP53-binding protein 1 at foci of DSBs Diminished phosphorylation of Chk1, but not Chk2, and prolonged DNA-damage-induced cell-cycle arrest at the G2/M checkpoint Prolonged association of the phosphorylated form of ATM at DSB foci Diminished phosphorylation and recruitment of repair-associated regulator BRCA1 to DSB foci	Koch <i>et al.</i> 2017
<b>HR</b>	Inhibition of repair of $\gamma$ -irradiation-induced DSBs in HeLa cells	Diminished association of the HR-specific marker RAD51 at DSB foci	Koch <i>et al.</i> 2017
<b>Antimony(III) potassium tartrate</b>			
<b>NHEJ and HR</b>	Inhibition of repair of $\gamma$ -irradiation-induced DSBs in CHO-K1 cells	Not reported	Takahashi <i>et al.</i> 2002a

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

## 6.5 Epigenetic alterations

Only two studies on DNA and RNA methylation were identified.

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

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

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

## 6.6 Oxidative stress

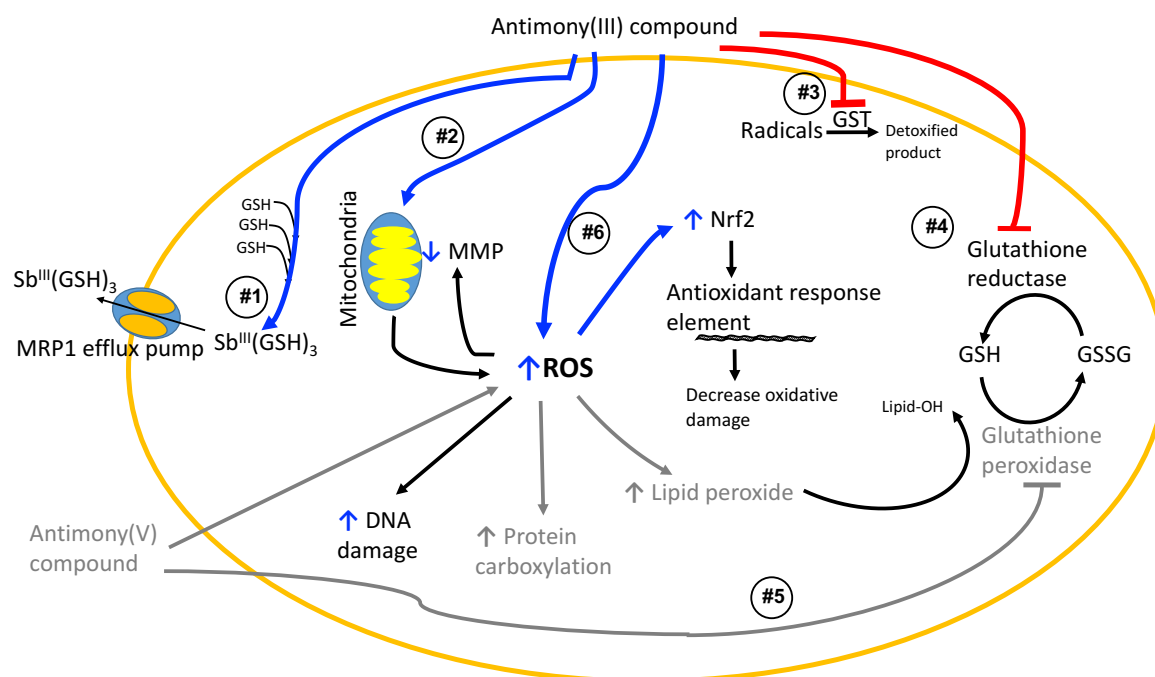
Cellular redox imbalance leads to excess accumulation of reactive oxygen species (ROS) and reactive nitrogen species, and causes oxidative stress. Oxidative stress can cause cell damage, affect normal cell processes, and contribute to carcinogenicity (reviewed by Jones 2008, Kim *et al.* 2015, Smith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

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

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

**Figure 6-1. Antimony increases oxidative stress.**

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



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

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

both antimony(III) trichloride and ROS scavengers prevented the antimony(III) trichloride-induced decrease in mitochondrial membrane potential.

### 6.7 Immunomodulation and inflammation

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

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

### 6.8 Alteration of cell proliferation and receptor-mediated effects

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

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

The potential role of EGFR in antimony(III) trioxide carcinogenicity is further supported by the increased *Egfr* mutation in the alveolar/bronchiolar tumors of mice and rats after long-term inhalation exposure to antimony(III) trioxide, not seen in non-tumor lung tissue or in spontaneous lung tumors (NTP 2017a). *EGFR* is commonly mutated in human lung neoplasms.

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  $\mu\text{mol/L}$  (Wang *et al.* 2015). Moreover, antimony(III) potassium tartrate suppressed the phosphorylation of Src and focal adhesion kinase

in the presence of phosphorylation triggers. These findings support the notion that antimony(III) potassium tartrate has anti-angiogenic properties in endothelial cells; indeed, antimony(III) potassium tartrate inhibited vascularization of non-small-cell lung cancer xenografts in mice.

## 6.9 Transcriptomics and Tox21/ToxCast high-throughput screening

### 6.9.1 Transcriptomics

One DNA microarray study (Kawata *et al.* 2007) of *in vitro* effects of an antimony(III) compound on a human cell line was found in the National Center for Biotechnology Information Gene Expression Omnibus (NCBI GEO) database (NCBI 2017). HepG2 (human liver carcinoma) cells were exposed to bis[(+)-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  $\mu\text{M}$  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  $\mu\text{M}$  and nickel(III) chloride hexahydrate at 6.5 nM. The gene expression profile after antimony(III) potassium tartrate trihydrate exposure was most similar to that after nickel(III) chloride hexahydrate exposure.

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

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

### 6.9.2 Tox21/ToxCast high-throughput screening

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

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

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

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

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

In summary, the activities of antimony compounds in Tox21 assays were mostly antagonistic to nuclear receptors, possibly because of displacement of Zn(II) in the zinc finger structures of these receptors by antimony(III) ions. These assays also indicated an oxidative stress response. Because only one antimony(V) compound was screened, and some of the trivalent compounds



had very little activity in the Tox21 assays, it is unclear whether antimony(III) compounds are in general more active than antimony(V) compounds.

#### 6.10 Integration of mechanistic information

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

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

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

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

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

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

**The Page Left Intentionally Blank**

## 7 Evidence Integration and Preliminary Listing Recommendation

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

### 7.1 Evidence of carcinogenicity from studies in experimental animals

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

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

### 7.2 Summary of mechanistic data

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

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

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

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

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

### 7.3 Evidence of carcinogenicity from studies in humans

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

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

### 7.4 Preliminary listing recommendation

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

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

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

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

## References

1. ACGIH. 2017. *TLVs and BEIs Based on the Documentation of the Threshold Limit Values for Chemical Substances and Physical Agents & Biological Indices*, Cincinnati, OH: Association Advancing Occupational and Environmental Health.
2. Al Jaser MH, Radwan MA, Zaghoul IY. 2006. Pharmacokinetics and tissue distribution of antimony(V) after multiple intramuscular administrations in the hamster. *Saudi Pharma J* 14(1): 52-58. (Support not reported. Authors affiliated with King Saud University, Saudi Arabia.)
3. Amereih S, Meisel T, Scholger R, Wegscheider W. 2005. Antimony speciation in soil samples along two Austrian motorways by HPLC-ID-ICP-MS. *J Environ Monit* 7(12): 1200-1206. (Supported by the Austrian Exchange Service. Authors affiliated with University of Leoben, Austria.)
4. Andrewes P, Kitchin KT, Wallace K. 2004. Plasmid DNA damage caused by stibine and trimethylstibine. *Toxicol Appl Pharmacol* 194(1): 41-48. (Supported by the National Research Council and the US EPA. Authors affiliated with U.S. Environmental Protection Agency, NC.)
5. Asakura K, Satoh H, Chiba M, Okamoto M, Serizawa K, Nakano M, Omae K. 2009. Genotoxicity studies of heavy metals: lead, bismuth, indium, silver and antimony. *J Occup Health* 51(6): 498-512. (Supported by the IMS (Intelligent Manufacturing Systems) Promotion Center, Manufacturing Science and Technology Center. Authors affiliated with Keio University School of Medicine, Japan; Tohoku University Graduate School of Medicine, Japan; International University of Health and Welfare, Japan; Hitachi Ltd., Japan.)
6. ATSDR. 1992. *Toxicological Profile for Antimony and Compounds*. Atlanta, GA: Agency for Toxic Substances and Disease Registry. 160 pp.
7. ATSDR. 2017. *Draft Toxicological Profile for Antimony and Compounds*. Atlanta, GA: Agency for Toxic Substances and Disease Registry. 328 pp.
8. Bailly R, Lauwerys R, Buchet JP, Mahieu P, Konings J. 1991. Experimental and human studies on antimony metabolism: their relevance for the biological monitoring of workers exposed to inorganic antimony. *Br J Ind Med* 48(2): 93-97. (Support not reported. Authors affiliated with Catholic University of Louvain, Belgium; Medische Dienst, Belgium.)
9. Barrera C, López S, Aguilar L, Mercado L, Bravo M, Quiroz W. 2016. Pentavalent antimony uptake pathway through erythrocyte membranes: molecular and atomic fluorescence approaches. *Anal Bioanal Chem* 408(11): 2937-2944. (Supported by FONDECYT. Authors affiliated with Pontificia Universidad Católica de Valparaíso, Chile.)
10. Basu JM, Mookerjee A, Sen P, Bhaumik S, Sen P, Banerjee S, Naskar K, Choudhuri SK, Saha B, Raha S, Roy S. 2006. Sodium antimony gluconate induces generation of reactive oxygen species and nitric oxide via phosphoinositide 3-kinase and mitogen-activated protein kinase activation in *Leishmania donovani*-infected macrophages. *Antimicrob Agents Chemother* 50(5): 1788-1797. (Supported by the Council of Scientific and Industrial Research. Authors affiliated with Indian Institute of Chemical Biology, India; Saha Institute of Nuclear Physics, India; Chittaranjan National Cancer Institute, India; National Centre for Cell Science, India; Institute of Microbial Technology, India.)

11. Belova A, Greco SL, Riederer AM, Olsho LE, Corrales MA. 2013. A method to screen U.S. environmental biomonitoring data for race/ethnicity and income-related disparity. *Environ Health* 12: 114. (Supported by the U.S. EPA and the Abt Associates' Daniel McGillis Development and Dissemination Grant Program. Authors affiliated with Abt Associates, MD and MA; Emory University, GA; US EPA, Washington, D.C.)
12. Belyaeva AP. 1967. The effect produced by antimony on the generative function. *Labor Hyg Occup Dis* 11: 32-37. (as cited in EU 2008)
13. Belzile N, Chen YW, Filella M. 2011. Human exposure to antimony: I. Sources and intake. *Crit Rev Environ Science Tech* 41(14): 1309-1373. (Supported by the Natural Sciences and Engineering Research Council of Canada. Authors affiliated with Laurentian University, Canada; Institut F.-A. Forel, Switzerland; SCHEMA, Luxembourg.)
14. Bento DB, de Souza B, Steckert AV, Dias RO, Leffa DD, Moreno SE, Petronilho F, de Andrade VM, Dal-Pizzol F, Romão PR. 2013. Oxidative stress in mice treated with antileishmanial meglumine antimoniate. *Res Vet Sci* 95(3): 1134-1141. (Supported by the Programa de Pós-graduação em Ciências da Saúde – Universidade do Extremo Sul Catarinense (UNESC) and the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq). Authors affiliated with Universidade do Extremo Sul Catarinense, Brazil; Universidade Católica Dom Bosco, Brazil; Universidade Federal de Ciências da Saúde de Porto Alegre, Brazil.)
15. Beyersmann D, Hartwig A. 2008. Carcinogenic metal compounds: recent insight into molecular and cellular mechanisms. *Arch Toxicol* 82(8): 493-512. (Support not reported. Authors affiliated with University of Bremen, Germany; Technical University of Berlin, Germany.)
16. Binks K, Doll R, Gillies M, Holroyd C, Jones SR, McGeoghegan D, Scott L, Wakeford R, Walker P. 2005. Mortality experience of male workers at a UK tin smelter. *Occup Med (Lond)* 55(3): 215-226. (Supported by Rio Tinto plc. Authors affiliated with Westlakes Scientific Consulting, UK; University of Oxford, UK; Rio Tinto plc, UK; British Nuclear Fuels plc, UK.)
17. Borborema SE, Osso Jr JA, Andrade Jr HF, Nascimento N. 2013. Biodistribution of meglumine antimoniate in healthy and *Leishmania (Leishmania) infantum* chagasi-infected BALB/c mice. *Mem Inst Oswaldo Cruz* 108(5): 623-630. (Supported by CNPq (134047/2003-6), LIM-HC-FMUSP-49. Authors affiliated with Comissão Nacional de Energia Nuclear, Brazil; Comissão Nacional de Energia Nuclear, Brazil.)
18. Brieger H, Semisch CW, Stasney J, Piatnek DA. 1954. Industrial antimony poisoning. *Ind Med Surg* 23: 521-523. (Support not reported. Authors affiliated with Jefferson Medical College of Philadelphia, PA.)
19. Burroughs GE, Horan J. 1981. *Health Hazard Evaluation Report. Becton-Dickinson Company, Columbus, Nebraska*. HE 80-023-804. National Institutes for Occupational Health and Safety. 17 pp.
20. Cantanhêde LF, Almeida LP, Soares REP, Branco PVGC, Pereira SRF. 2015. Soy isoflavones have antimutagenic activity on DNA damage induced by the antileishmanial Glucantime (*Meglumine antimoniate*). *Drug Chem Toxicol* 38(3): 312-317. (Supported by FAPEMA (Fundação de Amparo à Pesquisa e ao Desenvolvimento Científico e Tecnológico do Maranhão). Authors affiliated with Federal University of Maranhão, Spain.)

21. Cassady ME, Etchison B. 1976. *Walk-through Survey of Chemetron Corporation Inorganic Chemicals Division*. Cincinnati, OH: Industrial Hygiene Section, Division of Surveillance, Hazard Evaluations, and Field Studies, National Institute for Occupational Safety and Health.
22. Cavallo D, Iavicoli I, Setini A, Marinaccio A, Perniconi B, Carelli G, Iavicoli S. 2002. Genotoxic risk and oxidative DNA damage in workers exposed to antimony trioxide. *Environ Mol Mutagen* 40(3): 184-189. (Support not reported. Authors affiliated with ISPESL-National Institute for Occupational Safety and Prevention, Italy; Università Cattolica del Sacro Cuore, Italy.)
23. CDC. 1978. *Criteria for a Recommended Standard. Occupational Exposure to Antimony*. Washington, D.C.: U.S. Department of Health, Education, and Welfare, Center for Disease Control. 136 pp.
24. CDC. 2016a. *Leishmaniasis. Resources for Health Professionals*. Centers for Disease Control and Prevention. Updated on 1/9/16. [https://www.cdc.gov/parasites/leishmaniasis/health\\_professionals/index.html](https://www.cdc.gov/parasites/leishmaniasis/health_professionals/index.html). Accessed on 6/9/17.
25. CDC. 2016b. *Health Hazard Evaluations (HHEs) Search*. Centers for Disease Control and Prevention. Last updated 4/11/16. <https://www2a.cdc.gov/hhe/search.asp>. Accessed on 11/20/17.
26. CDC. 2017a. *Fourth National Report on Human Exposure to Environmental Chemicals, Updated Tables, January 2017, Volume 2*. Atlanta, GA: Centers for Disease Control and Prevention. 588 pp. [https://www.cdc.gov/exposurereport/pdf/FourthReport\\_UpdatedTables\\_Volume2\\_Jan2017.pdf](https://www.cdc.gov/exposurereport/pdf/FourthReport_UpdatedTables_Volume2_Jan2017.pdf).
27. CDC. 2017b. *National Occupational Exposure Survey (NOES)*. Centers for Disease Control and Prevention. Last updated 5/28/17. <https://www.cdc.gov/noes/default.html>. Accessed on 11/20/17.
28. CDC. 2017c. *Fourth National Report on Human Exposure to Environmental Chemicals, Updated Tables, January 2017, Volume 1*. Atlanta, GA: Centers for Disease Control and Prevention. 656 pp. <https://www.cdc.gov/exposurereport/>.
29. Chandra S, Hoenerhoff MJ, Peterson R. 2013. Chapter 17: Endocrine Glands. In *Toxicologic Pathology: Nonclinical Safety Assessment*. Sahota PS, Popp JA, Hardisty JF, Gopinath C, eds. Boca Raton, FL: CRC Press. p. 691.
30. ChemIDplus. 2017. *ChemIDplus Advanced*. National Library of Medicine. <http://chem.sis.nlm.nih.gov/chemidplus/chemidheavy.jsp> and select Registry Number and search on CAS number. Accessed on 5/22/17.
31. Chiu WA, Guyton KZ, Martin MT, Reif DM, Rusyn I. 2017. Use of high-throughput *in vitro* toxicity screening data in cancer hazard evaluations by IARC Monograph Working Groups. *ALTEX*: 14 pp.
32. Coelho DR, De-Carvalho RR, Rocha RCC, Saint'Pierre TD, Paumgarten FJR. 2014. Effects of *in utero* and lactational exposure to Sb-V on rat neurobehavioral development and fertility. *Reprod Toxicol* 50: 98-107. (Supported by the Rio de Janeiro State Agency for Supporting Research, the the Brazilian National Research Council, and the National School of Public Health. Authors affiliated with Oswaldo Cruz Foundation (FIOCRUZ), Brazil; Pontifical Catholic University of Rio de Janeiro, Brazil.)

33. Colak EH, Yomralioglu T, Nisanci R, Yildirim V, Duran C. 2015. Geostatistical analysis of the relationship between heavy metals in drinking water and cancer incidence in residential areas in the Black Sea region of Turkey. *J Environ Health* 77(6): 86-93. (Supported by the Scientific and Technical Research Council of Turkey. Authors affiliated with Karadeniz Technical University, Turkey; Istanbul Technical University, Turkey.)
34. Craig ABJ, Vandervort R, Burton DJ, Coleman RT. 1981. *Environmental and Occupational Protection in the Secondary Lead Industry*. DHHS (NIOSH) Pub1 ISS 81-114. p. 315-353.
35. Cullen A, Kiberd B, Matthews T, Mayne P, Delves HT, O'Regan M. 1998. Antimony in blood and urine of infants. *J Clin Pathol* 51(3): 238-240. (Supported by the National Sudden Infant Death Register of the Irish Sudden Infant Death Association funded by the National Lottery through the Department of Health Authors affiliated with University College Dublin, Ireland; The Irish Sudden Infant Death Association, Ireland; The Children's Hospital, Ireland; University of Southampton, UK; Trinity College, Ireland.)
36. Daskalos A, Nikolaidis G, Xinarianos G, Savvari P, Cassidy A, Zakopoulou R, Kotsinas A, Gorgoulis V, Field JK, Liloglou T. 2009. Hypomethylation of retrotransposable elements correlates with genomic instability in non-small cell lung cancer. *Int J Cancer* 124(1): 81-87.
37. Daskalos A, Logotheti S, Markopoulou S, Xinarianos G, Gosney JR, Kastania AN, Zoumpourlis V, Field JK, Liloglou T. 2011. Global DNA hypomethylation-induced DeltaNp73 transcriptional activation in non-small cell lung cancer. *Cancer Lett* 300(1): 79-86.
38. De Gregori I, Quiroz W, Pinochet H, Pannier F, Potin-Gautier M. 2007. Speciation analysis of antimony in marine biota by HPLC-(UV)-HG-AFS: Extraction procedures and stability of antimony species. *Talanta* 73(3): 458-465. (Supported by the FONDECYT, Pontificia Universidad Católica de Valparaíso, the thecProgram ECOS-CONICYT. Authors affiliated with Pontificia Universidad Católica de Valparaíso, Chile; Université de Pau et des Pays de l'Adour, France.)
39. De Oliveira FB, Schettini DA, Ferreira CS, Rates B, Rocha OGF, Frézard F, Demicheli C. 2006. Kinetics of antimony(V) reduction by L-cysteine. Pharmacological implications and application to the determination of antimony in pentavalent antimonial drugs. *J Brazil Chem Soc* 17(8): 1642-1650. (Supported by CNPq, MCT, CAPES and FAPEMIG. Authors affiliated with Universidade Federal de Minas Gerais, Brazil; Fundação Centro Tecnológico de Minas Gerais, Brazil.)
40. de Ricciardi LV, Vicuña-Fernández N, de Peña YP, López S, Scorza JV, Scorza-Dager JV, Villegas E, Pérez B. 2008. Pharmacokinetic disposition of antimony species in dogs after a dose of meglumine antimonate (Glucantime®). *Bol Malar Salud Ambient* 48(1): 27-33. (Supported by Al Consejo de Desarrolla Científico Humanístico y Tecnológico de la Universidad de Los Andes. Authors affiliated with Escuela de Medicina Extensión Valera, Venezuela; Instituto de Investigaciones Parasitológicas "José Witremundo Torrealba" NURR Trujillo, Venezuela; Universidad de Los Andes, Venezuela; Universidad Autónoma de Barcelona, Spain.)
41. de Thé H, Lavau C, Marchio A, Chomienne C, Degos L, Dejean A. 1991. The PML-RAR alpha fusion mRNA generated by the t(15;17) translocation in acute promyelocytic leukemia encodes a functionally altered RAR. *Cell* 66(4): 675-684. (Supported by the



- Fondation pour la Recherche Médicale, the Ligue Nationale Française contre le Cancer, and the Association pour la Recherche contre le Cancer. Authors affiliated with INSERM, France.)
42. Donaldson H, Gentry S. 1975. *Air Sampling Industrial Hygiene Survey: The Harshaw Chemical Company, Gloucester City, New Jersey*. Cincinnati, OH: Department of Health, Education and Welfare, Division of Surveillance, Hazard Evaluations, and Field Studies, National Institute for Occupational Safety and Health.
  43. Donaldson H. 1976. *Industrial Hygiene Survey of Texas Smelting and Refining Division of National Lead Industries, Laredo, Texas*. Cincinnati, OH: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health.
  44. Dopp E, Hartmann LM, Florea AM, von Recklinghausen U, Rabieh S, Shokouhi B, Hirner AV, Rettenmeier AW. 2006. Trimethylantimony dichloride causes genotoxic effects in Chinese hamster ovary cells after forced uptake. *Toxicol Vitro* 20(6): 1060-1065. (Supported by the German Research Foundation. Authors affiliated with University Hospital Essen, Germany; University of Duisburg-Essen, Germany.)
  45. Dunn JT. 1928. A curious case of antimony poisoning. *Analyst* 53: 532-533. (as cited in Belzille *et al.* 2011)
  46. Dupont D, Arnout S, Jones PT, Binnemans K. 2016. Antimony recovery from end-of-life products and industrial process residues: A critical review. *J Sustain Metall* 2: 79-103. (Supported by the KU Leuven and the FWO Flanders. Authors affiliated with KU Leuven, Belgium; InsPyro, Belgium.)
  47. ECHA. 2017. *Diantimony pentoxide*. European Chemicals Agency. <https://echa.europa.eu/registration-dossier/-/registered-dossier/16264/7/2/2>. Accessed on 10/3/17.
  48. Edel J, Marafante E, Sabbioni E, Manzo L. 1983. Metabolic behaviour of inorganic forms of antimony in the rat. In *International Conference on Heavy Metals in the Environment, Heidelberg, West Germany, September 1983*. Edinburgh, UK: CEP Consultants. pp. 574-577. (Support not reported. Authors affiliated with Commission of the European Communities, Italy; University of Pavia, Italy.)
  49. El Shanawany S, Foda N, Hashad DI, Salama N, Sobh Z. 2017. The potential DNA toxic changes among workers exposed to antimony trioxide. *Environ Sci Pollut Res Int* 24(13): 12455-12461. (Support not reported. Authors affiliated with University of Alexandria, Egypt.)
  50. Ellegaard L, Cunningham A, Edwards S, Grand N, Nevalainen T, Prescott M, Schuurman T, Steering Group of the Rethink Project. 2010. Welfare of the minipig with special reference to use in regulatory toxicology studies. *J Pharmacol Toxicol Methods* 62(3): 167-183. (Supported by the RETHINK project, a Specific Support Action funded by the European Community 6th Framework Programme. Authors affiliated with Ellegaard Göttingen Minipigs A/S, Denmark; GSK, UK; University of Newcastle School of Agriculture, Food and Rural Development, UK; University of Kuopio, Finland; National Centre for the Replacement, Refinement and Reduction of Animals in Research, UK; Biomedical Research of Wageningen University, Netherlands.)
  51. Elliott BM, Mackay JM, Clay P, Ashby J. 1998. An assessment of the genetic toxicology of antimony trioxide. *Mutat Res* 415(1-2): 109-117. (Support not reported. Authors affiliated with Central Toxicology Laboratory, UK.)

52. El Nahas S, Temtamy SA, de Hondt HA. 1982. Cytogenetic effects of two antimonial antibilharzial drugs: Tartar emetic and bilharacid. *Environ Mut* 4:83-91.
53. Elshafie AI, Åhlin E, Mathsson L, ElGhazali G, Rönnelid J. 2007. Circulating immune complexes (IC) and IC-induced levels of GM-CSF are increased in sudanese patients with acute visceral *Leishmania donovani* infection undergoing sodium stibogluconate treatment: implications for disease pathogenesis. *J Immunol* 178(8): 5383-5389. (Supported by the Swedish Society of Medicine, King Gustav V's 80-years Fund, Swedish League against Rheumatism, Ugglas Foundation, Groschinsky Foundation, Viberg Foundation, and Swedish Fund for Research Without Animal Experiments. Authors affiliated with Uppsala University, Sweden; Alribate University Hospital, Sudan; University of Khartoum, Sudan; King Fahad Medical City, Saudi Arabia.)
54. EPA. 1988. *Health Effects Test Guidelines: OPPTS 870.3465 90-Day Inhalation Toxicity*. EPA 712-C-98-204. Washington, DC: U.S. Environmental Protection Agency. 17 pp. <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2009-0156-0014>.
55. EPA. 2012. *Chemical Data Reporting*. [https://java.epa.gov/oppt\\_chemical\\_search/](https://java.epa.gov/oppt_chemical_search/) and search for antimony. Accessed on 3/28/16.
56. EPA. 2014. *TSCA Work Plan Chemical Risk Assessment. Antimony Trioxide*. EPA Document # 740 - Z1 - 4001. U.S. Environmental Protection Agency. 87 pp.
57. EPA. 2017a. *ChemView*. U.S. Environmental Protection Agency. <https://java.epa.gov/chemview> and search by CAS number. Accessed on 2/22/17.
58. EPA. 2017b. *iCSS ToxCast Dashboard*. U.S. Environmental Protection Agency. <https://actor.epa.gov/dashboard/>. Accessed on 10/10/17.
59. EpiSuite. 2017. *Antimony pentoxide*. U.S. Environmental Protection Agency. <https://comptox.epa.gov/dashboard/dsstoxdb/results?utf8=%E2%9C%93&search=1314-60-9>.
60. EU. 2008. *European Union Risk Assessment Report. Diantimony Trioxide*. Luxembourg: European Communities. 556 pp.
61. Fabian T, Borgerson JL, Kerber SI, Gandhi PD, Baxter CS, Ross C, S., Lockey JE, Dalton JM. 2010. *Firefighter Exposure to Smoke Particulates* Project Number: 08CA31673, File Number: IN 15941. Underwriter Laboratories, Inc. 390 pp. <https://ulfirefightersafety.org/assets/EMW-2007-FP-02093-cebf37283b5f736fe7dd535dcf26382e5b5b5d5e911d8b28af6fed60ad0b6e6a.pdf>.
62. Fan K, Borden E, Yi T. 2009. Interferon-gamma is induced in human peripheral blood immune cells *in vitro* by sodium stibogluconate/interleukin-2 and mediates its antitumor activity *in vivo*. *J Interferon Cytokine Res* 29(8): 451-460. (Support not reported. Authors affiliated with Lerner Research Institute, OH; Cleveland Clinic Foundation, OH; Taussig Cancer Center, OH.)
63. Felicetti SA, Thomas RG, McClellann RO. 1974a. Metabolism of two valence states of inhaled antimony in hamsters. *Am Ind Hygiene Assoc J* 35(5): 292-300. (Supported by the U.S. Atomic Energy Commission. Authors affiliated with Lovelace Foundation for Medical Education and Research, NM.)
64. Felicetti SW, Thomas RG, McClellan RO. 1974b. Retention of inhaled antimony-124 in the beagle dog as a function of temperature of aerosol formation. *Health Physics* 26(6): 525-531. (Supported by the USAEC. Authors affiliated with Lovelace Foundation for Medical Education and Research, NM.)

65. Fernandes FR, Ferreira WA, Campos MA, Ramos GS, Kato KC, Almeida GG, Corrêa Jr JD, Melo MN, Demicheli C, Frézard F. 2013. Amphiphilic antimony(V) complexes for oral treatment of visceral leishmaniasis. *Antimicrob Agents Chemother* 57(9): 4229-4236. (Supported by CNPq, FAPEMIG, and CAPES. Authors affiliated with Universidade Federal de Minas Gerais, Brazil.)
66. Filella M, Belzile N, Chen YW. 2002a. Antimony in the environment: A review focused on natural waters II. Relevant solution chemistry. *Earth Sci Rev* 59(1-4): 265-285.
67. Filella M, Belzile N, Chen YW. 2002b. Antimony in the environment: A review focused on natural waters I. Occurrence. *Earth Sci Rev* 57(1-2): 125-176. (Supported by the Agence Universitaire de la Francophonie (Programme d'invitation de professeur/chercheur), the Natural Sciences and Engineering Research Council of Canada and the Elliot Lake Research Field Station of Laurentian University. Authors affiliated with University of Geneva, Switzerland; Laurentian University, Canada.)
68. Filella M, Belzile N, Lett MC. 2007. Antimony in the environment: A review focused on natural waters. III. Microbiota relevant interactions. *Earth Sci Rev* 80: 195-217. (Support not reported. Authors affiliated with University of Geneva, Switzerland; Laurentian University, Canada; ULP-CNRS, France.)
69. Filella M, Belzile N, Chen Y-W. 2013a. Human exposure to antimony. III. Contents in some human excreted biofluids (urine, milk, saliva). *Crit Rev Environ Sci Technol* 43: 162-214. (Support not reported. Authors affiliated with University of Geneva, Switzerland; Laurentian University, Canada.)
70. Filella M, Belzile N, Chen YW. 2013b. Human exposure to antimony. IV. Contents in human blood. *Crit Rev Environ Sci Technol* 43(19): 2071-2105. (Support not reported. Authors affiliated with University of Geneva, Switzerland; SCHEMA, Luxembourg; Laurentian University, Canada.)
71. Friedrich K, Vieira FA, Porrozzini R, Marchevsky RS, Miekeley N, Grimaldi G, Jr., Paumgartten FJ. 2012. Disposition of antimony in rhesus monkeys infected with *Leishmania braziliensis* and treated with meglumine antimoniate. *J Toxicol Environ Health A* 75(2): 63-75. (Supported by INOVA-ENSP (National School of Public Health), PAPES-V grants (CNPq-FIOCRUZ) and the the Brazilian National Research Council (CNPq). Authors affiliated with National School of Public Health, Brazil; Oswaldo Cruz Institute, Brazil; Oswaldo Cruz Foundation, Brazil; Pontifical Catholic University of Rio de Janeiro, Brazil.)
72. Garg SP, Singh IS, Sharma RC. 2003. Long term lung retention studies of  $^{125}\text{Sb}$  aerosols in humans. *Health Phys* 84(4): 457-468. (Support not reported. Authors affiliated with Bhabha Atomic Research Centre, India.)
73. Gebel T, Christensen S, Dunkelberg H. 1997. Comparative and environmental genotoxicity of antimony and arsenic. *Anticancer Res* 17(4a): 2603-2607. (Support not reported. Authors affiliated with University of Goettingen, Germany.)
74. Gebel T. 1998. Suppression of arsenic-induced chromosome mutagenicity by antimony. *Mutat Res* 412(3): 213-218. (Support not reported. Authors affiliated with Medical Institute of General Hygiene and Environmental Health, Germany.)
75. Gebel T, Birkenkamp P, Luthin S, Dunkelberg H. 1998. Arsenic(III), but not antimony(III), induces DNA-protein crosslinks. *Anticancer Res* 18(6a): 4253-4257. (Support not reported. Authors affiliated with University of Goettingen, Germany.)

76. Gerhardsson L, Brune D, Nordberg GF, Wester PO. 1982. Antimony in lung, liver and kidney tissue from deceased smelter workers. *Scand J Work Environ Health* 8(3): 201-208. (Supported by the Swedish Work Environment Fund. Authors affiliated with Umeå University, Sweden; Scandinavian Institute of Dental Medicine, Norway.)
77. Gerhardsson L, Nordberg GF. 1993. Lung cancer in smelter workers--interactions of metals as indicated by tissue levels. *Scand J Work Environ Health* 19 Suppl 1: 90-94. (Support not reported. Authors affiliated with University of Umeå, Sweden; University Hospital - Lund, Sweden.)
78. Ghosh M, Roy K, Roy S. 2013. Immunomodulatory effects of antileishmanial drugs. *J Antimicrob Chemother* 68(12): 2834-2838. (Supported by the Network Project and CSIR India. Authors affiliated with CSIR-Indian Institute of Chemical Biology, India.)
79. Gonzales FA, Jones RR, Deardorff J, Windham GC, Hiatt RA, Kushi LH. 2016. Neighborhood deprivation, race/ethnicity, and urinary metal concentrations among young girls in California. *Environ Int* 91: 29-39. (Supported by the Breast Cancer and the Environment Research Program, NIEHS, NCI, and NCCR. Authors affiliated with NCI, MD; University of California at Berkeley, CA; California Department of Public Health, CA; University of California at San Francisco, CA; Kaiser Permanente, CA.)
80. Gosney JR. 1985. Adrenal corticomedullary hyperplasia in hypobaric hypoxia. *J Pathol* 146(1): 59-64.
81. Gross P, Brown JH, Westrick ML, Srsic RP, Butler NL, Hatch TF. 1955. Toxicologic study of calcium halophosphate phosphors and antimony trioxide. I. Acute and chronic toxicity and some pharmacologic aspects. *AMA Arch Ind Health* 11(6): 473-478. (Supported by General Electric Company and Sylvania Electric Products, Inc. Authors affiliated with Mellon Institute, PA; Emory University, GA.)
82. Grosskopf C, Schwerdtle T, Mullenders LH, Hartwig A. 2010. Antimony impairs nucleotide excision repair: XPA and XPE as potential molecular targets. *Chem Res Toxicol* 23(7): 1175-1183. (Supported by the DFG. Authors affiliated with Technische Universität Berlin, Germany; Westfälische Wilhelms-Universität Münster, Germany; Leiden University Medical Center, Netherlands.)
83. Groth DH, Stettler LE, Burg JR, Busey WM, Grant GC, Wong L. 1986. Carcinogenic effects of antimony trioxide and antimony ore concentrate in rats. *J Toxicol Environ Health* 18(4): 607-626. (Supported by NIOSH and Midwest Research Institute. Authors affiliated with NIOSH, OH; Experimental Pathology Laboratories, VA; College of William and Mary, VA; Midwest Research Institute, MO.)
84. Grund SC, Hanusch K, Breunig HJ, Wolf HU. 2006. *Antimony and Antimony Compounds*. Ullmann's Encyclopedia of Industrial Chemistry. [http://onlinelibrary.wiley.com/doi/10.1002/14356007.a03\\_055.pub2/full](http://onlinelibrary.wiley.com/doi/10.1002/14356007.a03_055.pub2/full). Accessed on 11/28/17.
85. Guan D, Kao HY. 2015. The function, regulation and therapeutic implications of the tumor suppressor protein, PML. *Cell Biosci* 5: 60. (Supported by RO1 HL093269 and DK078965. Authors affiliated with Case Western Reserve University, OH.)
86. Guo J, Su L, Zhao X, Xu Z, Chen G. 2016. Relationships between urinary antimony levels and both mortalities and prevalence of cancers and heart diseases in general US population, NHANES 1999-2010. *Sci Total Environ* 571: 452-460. (Support not reported. Authors affiliated with Zhejiang University School of Medicine, China.)

87. Gurnani N, Sharma A, Talukder G. 1992a. Cytotoxic effects of antimony trichloride on mice *in vivo*. *Cytobios* 70(281): 131-136. (Supported by the Council of Scientific and Industrial Research, Government of India. Authors affiliated with University of Calcutta, India; Vivekananda Institute of Medical Sciences, India.)
88. Gurnani N, Sharma A, Talukder G. 1992b. Comparison of the clastogenic effects of antimony trioxide on mice *in vivo* following acute and chronic exposure. *Biometals* 5(1): 47-50. (Supported by the Council of Scientific and Industrial Research. Authors affiliated with University of Calcutta, India; Vivekananda Institute of Medical Sciences, India.)
89. Hansen C, Hansen EW, Hansen HR, Gammelgaard B, Stürup S. 2011. Reduction of Sb(V) in a human macrophage cell line measured by HPLC-ICP-MS. *Biol Trace Elem Res* 144(1-3): 234-243. (Support not reported. Authors affiliated with University of Copenhagen, Denmark; University of Aberdeen, UK.)
90. Hantson P, Leonard ED, Crutzen-Fayt MC, Leonard A, Vandercam B, Delaere B, Mahieu P. 1996. Cytogenetic observations after meglumine antimoniate therapy for visceral leishmaniasis. *Pharmacotherapy* 16(5): 869-871. (Support not reported. Authors affiliated with Universitaires St-Luc, Belgium; Catholic University of Louvain, Belgium.)
91. Hashemzaei M, Pourahmad J, Safaeinejad F, Tabrizian K, Akbari F, Bagheri G, Hosseini MJ, Shahraki J. 2015. Antimony induces oxidative stress and cell death in normal hepatocytes. *Toxicol Environ Chem* 97(2): 256-265. (Supported by the Zabol University of Medical Sciences. Authors affiliated with Zabol University of Medical Sciences, Iran; Shahid Beheshti University of Medical Sciences, Iran; Zanjan University of Medical Sciences, Iran.)
92. Health Canada. 2010. *Screening Assessment for the Challenge: Antimony Trioxide*. Health Canada. 90 pp.
93. Hebeisen M, Baitsch L, Presotto D, Baumgaertner P, Romero P, Michielin O, Speiser DE, Rufer N. 2013. SHP-1 phosphatase activity counteracts increased T cell receptor affinity. *J Clin Invest* 123(3): 1044-1056. (Supported by the Swiss National Center of Competence in Research Molecular Oncology, the Ludwig Institute for Cancer Research, and the Swiss Cancer League. Authors affiliated with Lausanne University Hospital Center, Switzerland; University of Lausanne, Switzerland.)
94. Herath I, Vithanage M, Bundschuh J. 2017. Antimony as a global dilemma: Geochemistry, mobility, fate and transport. *Environ Pollut* 223: 545-559. (Support not reported. Authors affiliated with University of Southern Queensland, Australia; National Institute of Fundamental Studies, Sri Lanka.)
95. Hirano K, Hagiwara T, Ohta Y, Matsumoto H, Kada T. 1982. *rec*-Assay with spores of *Bacillus subtilis* with and without metabolic activation. *Mutat Res* 97(5): 339-347. (Supported by the Ministry of Education, the Ministry of Welfare, the Science and Technology Agency of Japan, the Takamatsunomiya Cancer Research Fund, the Nissan Science Foundation, and the National Institute of Genetics. Authors affiliated with National Institute of Genetics, Japan; Sankyo Co. Ltd., Japan.)
96. Hirano S, Tadano M, Kobayashi Y, Udagawa O, Kato A. 2015. Solubility shift and SUMOylation of promyelocytic leukemia (PML) protein in response to arsenic(III) and fate of the SUMOylated PML. *Toxicol Appl Pharmacol* 287(3): 191-201. (Supported by the Japan Society for the Promotion of Science. Authors affiliated with National Institute for Environmental Studies, Japan; Chiba University, Japan.)

97. Hiza RJ, Aguilar GA, Donnelly SG, Cheng FS, Tepper RJ. 2006. Patent US 2006/0183648 A1. *Lubricating greases containing antimony dithiocarbamates*.
98. Howlader N, Noone AM, Krapcho M, Miller D, Bishop K, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA. 2017. *SEER Cancer Statistics Review, 1975-2014*. National Cancer Institute, Bethesda, MD. [https://seer.cancer.gov/csr/1975\\_2014/](https://seer.cancer.gov/csr/1975_2014/), based on November 2016 SEER data submission, posted to the SEER web site, April 2017.
99. HSDB. 2013. *Hazardous Substances Data Bank: Antimony Trioxide*. National Library of Medicine. Updated on 3/8/13. <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB> and search on CAS number or compound name. Accessed on 5/19/17. (as cited in NTP 2016)
100. Huang H, Shu SC, Shih JH, Kuo CJ, Chiu ID. 1998. Antimony trichloride induces DNA damage and apoptosis in mammalian cells. *Toxicology* 129(2-3): 113-123. (Supported by the National Science Council, Republic of China. Authors affiliated with National Tsing-Hua University, Taiwan.)
101. Huang W, Qi CB, Lv SW, Xie M, Feng YQ, Huang WH, Yuan BF. 2016. Determination of DNA and RNA Methylation in Circulating Tumor Cells by Mass Spectrometry. *Anal Chem* 88(2): 1378-1384.
102. IARC. 1989. Antimony Trioxide and Antimony Trisulfide. In *Some Organic Solvents, Resin Monomers and Related Compounds, Pigments and Occupational Exposures in Paint Manufacture and Painting*. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, vol. 47. Lyon, France: International Agency for Research on Cancer. pp. 291-305.
103. IARC. 2006. Metallic Cobalt Particles (with or without Tungsten Carbide). In *Cobalt in Hard Metals and Cobalt Sulfate, Gallium Arsenide, Indium Phosphide and Vanadium Pentoxide*. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, vol. 86. Lyon, France: International Agency for Research on Cancer. pp. 39 - 155.
104. IARC. 2017a. *List of classifications by cancer sites with sufficient or limited evidence in humans, Volumes 1 to 119*. International Agency for Research on Cancer. Updated 4/13/17. <http://monographs.iarc.fr/ENG/Classification/Table4.pdf>. Accessed on 5/15/17.
105. IARC. 2017b. *Some Organophosphate Insecticides and Herbicides*, IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. vol. 112, Lyon, France: International Agency for Research on Cancer. 464 pp.
106. ICRP. 1981. Metabolic data for antimony. *Ann ICRP* 6(42403): 46-49. (Support and authors not reported.)
107. ICRP. 2012. *Draft Report: Occupational Intakes of Radionuclides, Part 3*. ICRP ref 4838-4528-4881. International Commission on Radiological Protection. 321 pp.
108. IPCS. 2017. *Antimony trioxide*. International Programme on Chemical Safety. <http://www.inchem.org/documents/icsc/icsc/eics0012.htm>. Accessed on 10/26/17.
109. Jeanne M, Lallemand-Breitenbach V, Ferhi O, Koken M, Le Bras M, Duffort S, Peres L, Berthier C, Soilihi H, Raught B, de Thé H. 2010. PML/RARA oxidation and arsenic binding initiate the antileukemia response of As<sub>2</sub>O<sub>3</sub>. *Cancer Cell* 18(1): 88-98. (Supported by the Ligue Nationale contre le Cancer, INSERM, CNRS, University Paris Diderot (formerly known as Paris-7), the Institut Universitaire de France, EPITRON (an integrated project funded by the European union under the 6th framework program

- (LSHC-CT-2005- 518417)), the Cancerpole programs, and the Leukemia and Lymphoma Society of Canada. Authors affiliated with INSERM/CNRS, France; Hôpital St. Louis, France; Ontario Cancer Institute and McLaughlin Centre for Molecular Medicine, Canada.)
110. Jenkins RO, Craig PJ, Goessler W, Irgolic KJ. 1998. Antimony leaching from cot mattresses and sudden infant death syndrome (SIDS). *Hum Exp Toxicol* 17(3): 138-139. (as cited in ATSDR 2017)
111. Jiang X, An Z, Lu C, Chen Y, Du E, Qi S, Yang K, Zhang Z, Xu Y. 2016. The protective role of Nrf2-Gadd45b against antimony-induced oxidative stress and apoptosis in HEK293 cells. *Toxicol Lett* 256: 11-18. (Supported by the Strategic Priority Research Program of the Chinese Academy of Science and the National Nature Science Foundation of China. Authors affiliated with Second Hospital of Tianjin Medical University, China.)
112. Johns Hopkins University. 2017. *Species Specific Information: Rat*. Johns Hopkins University. <http://web.jhu.edu/animalcare/procedures/rat.html>. Accessed on 8/18/17.
113. Jones DP. 2008. Radical-free biology of oxidative stress. *Am J Physiol Cell Physiol* 295(4): C849-868. (Supported by NIEHS. Author affiliated with Emory University School of Medicine, GA.)
114. Jones RD. 1994. Survey of antimony workers: mortality 1961-1992. *Occup Environ Med* 51(11): 772-776. (Support not reported. Authors affiliated with Corporate Health Limited, Slough.)
115. Jones SR, Atkin P, Holroyd C, Lutman E, Batlle JV, Wakeford R, Walker P. 2007. Lung cancer mortality at a UK tin smelter. *Occup Med (Lond)* 57(4): 238-245. (Supported by Rio Tinto plc. Authors affiliated with Westlakes Research Institute, UK; Rio Tinto plc, UK; University of Manchester, UK.)
116. Jones W, Gamble J. 1984. Epidemiological-environmental study of lead acid battery workers. I. Environmental study of five lead acid battery plants. *Environ Res* 35(1): 1-10. (Support not reported. Authors affiliated with NIOSH, WV.)
117. Kada T. 1976. Rec assay with cold incubation with and without metabolic reactivation *in vitro* [proceedings]. *Mutat Res* 38(5): 340. (Support not reported. Author affiliated with National Institute of Genetics, Japan.)
118. Kanematsu N, Hara M, Kada T. 1980. Rec assay and mutagenicity studies on metal compounds. *Mutat Res* 77(2): 109-116. (Supported by the Ministry of Welfare, the Ministry of Education, the Science and Technology Agency of Japan, the Takamatsunomiya Cancer Foundation and the Nissan Science Foundation. Authors affiliated with Gifu College of Dentistry, Japan; National Institute of Genetics, Japan.)
119. Kanisawa M, Schroeder HA. 1969. Life term studies on the effect of trace elements on spontaneous tumors in mice and rats. *Cancer Res* 29(4): 892-895. (Supported by the USPHS, the US Army, the American Cancer Society, and the CIBA Pharmaceutical Company. Authors affiliated with Dartmouth Medical School, NH; Brattleboro Memorial Hospital, VT.)
120. Kavlock R, Dix D. 2010. Computational toxicology as implemented by the U.S. EPA: providing high throughput decision support tools for screening and assessing chemical exposure, hazard and risk. *J Toxicol Environ Health B Crit Rev* 13(2-4): 197-217.

121. Kavlock R, Chandler K, Houck K, Hunter S, Judson R, Kleinstreuer N, Knudsen T, Martin M, Padilla S, Reif D, Richard A, Rotroff D, Sipes N, Dix D. 2012. Update on EPA's ToxCast program: providing high throughput decision support tools for chemical risk management. *Chem Res Toxicol* 25(7): 1287-1302.
122. Kawata K, Yokoo H, Shimazaki R, Okabe S. 2007. Classification of heavy-metal toxicity by human DNA microarray analysis. *Environ Sci Technol* 41(10): 3769-3774. (Supported by the 21st Century COE Program "Sustainable Metabolic System of Water and Waste for Area-Based Society," and the Ministry of Education, Science, and Culture of Japan. Authors affiliated with Hokkaido University, Japan.)
123. Kentner M, Leinemann M, Schaller KH, Weltle D, Lehnert G. 1995. External and internal antimony exposure in starter battery production. *Int Arch Occup Environ Health* 67(2): 119-123. (Supported by the VB Autobatterie GmbH. Authors affiliated with University of Gottingen, Germany; University of Erlangen-Nürnberg, Germany.)
124. Kim HA, Heo Y, Oh SY, Lee KJ, Lawrence DA. 1999. Altered serum cytokine and immunoglobulin levels in the workers exposed to antimony. *Hum Exp Toxicol* 18(10): 607-613. (Support not reported. Authors affiliated with Catholic University of Korea, Korea; New York State Department of Health, NY; Korean Industrial Health Association, Korea.)
125. Kim HS, Kim YJ, Seo YR. 2015. An overview of carcinogenic heavy metal: Molecular toxicity mechanism and prevention. *J Cancer Prev* 20(4): 232-240. (Supported by the the Korea Ministry of Environment. Authors affiliated with Dongguk University Biomedical Campus, Korea.)
126. Kirkland D, Whitwell J, Deyo J, Serex T. 2007. Failure of antimony trioxide to induce micronuclei or chromosomal aberrations in rat bone-marrow after sub-chronic oral dosing. *Mutat Res* 627(2): 119-128. (Supported by the International Antimony Oxide Industry Association (IAOIA) and the Antimony Trioxide Stakeholders (ATOS). Authors affiliated with Covance Laboratories Ltd., UK; Eastman Chemical Company, TN; Blasland, Bouck & Lee Inc., CA.)
127. Koch B, Maser E, Hartwig A. 2017. Low concentrations of antimony impair DNA damage signaling and the repair of radiation-induced DSB in HeLa S3 cells. *Arch Toxicol*. (Supported by the Deutsche Forschungsgemeinschaft. Authors affiliated with Karlsruhe Institute of Technology, Germany.)
128. Kocyigit A, Gur S, Gurel MS, Bulut V, Ulukanligil M. 2002. Antimonial therapy induces circulating proinflammatory cytokines in patients with cutaneous leishmaniasis. *Infect Immun* 70(12): 6589-6591. (Support not reported. Authors affiliated with University of Harran Medical School, Turkey; University of Firat Medical School, Turkey.)
129. Krachler M, Emons H. 2001. Urinary antimony speciation by HPLC-ICP-MS. *J Anal At Spectrom* 16(1): 20-25. (Supported by the European Community through the Research Program TMR and the Research Centre Jülich. Authors affiliated with Institute of Applied Physical Chemistry, Germany.)
130. Krupka KM, Serne RJ. 2002. *Geochemical Factors Affecting the Behavior of Antimony, Cobalt, Europium, Technetium, and Uranium in Vadose Sediments*. PNNL-14126. Oak Ridge, TN: Pacific Northwest Laboratory. 95 pp.
131. Kuroda K, Endo G, Okamoto A, Yoo YS, Horiguchi S. 1991. Genotoxicity of beryllium, gallium and antimony in short-term assays. *Mutat Res* 264(4): 163-170.



- (Supported by the Ministry of Education, Science and Culture of Japan. Authors affiliated with Osaka City Institute of Public Health and Environmental Sciences, Japan; Osaka City University Medical School, Japan; Seoul Health Junior College, Korea.)
132. Labeledzka M, Gulyas H, Schmidt N, Gercken G. 1989. Toxicity of metallic ions and oxides to rabbit alveolar macrophages. *Environ Res* 48(2): 255-274. (as cited in MAK 2007)
133. Lantzsch H, Gebel T. 1997. Genotoxicity of selected metal compounds in the SOS chromotest. *Mutat Res* 389(2-3): 191-197. (Support not reported. Authors affiliated with University of Goettingen, Germany.)
134. Lauwers LF, Roelants A, Rosseel PM, Heyndrickx B, Baute L. 1990. Oral antimony intoxications in man. *Crit Care Med* 18(3): 324-326. (Support not reported. Authors affiliated with Stuivenberg General Hospital, Belgium; State University of Ghent, Belgium.)
135. Lecureur V, Lagadic-Gossmann D, Fardel O. 2002. Potassium antimonyl tartrate induces reactive oxygen species-related apoptosis in human myeloid leukemic HL60 cells. *Int J Oncol* 20(5): 1071-1076. (Support not reported. Authors affiliated with INSERM, France.)
136. Leffler P, Gerhardsson L, Brune D, Nordberg GF. 1984. Lung retention of antimony and arsenic in hamsters after the intratracheal instillation of industrial dust. *Scand J Work Environ Health* 10(4): 245-251. (Supported by the Swedish Work Environment Fund. Authors affiliated with University of Umeå, Sweden; Scandanavian Institute of Dental Materials, Norway.)
137. Li J, Wei Y, Zhao L, Zhang J, Shangguan Y, Li F, Hou H. 2014. Bioaccessibility of antimony and arsenic in highly polluted soils of the mine area and health risk assessment associated with oral ingestion exposure. *Ecotoxicol Environ Saf* 110: 308-315. (Supported by the National Natural Science Foundation of China, the Special Environmental Protection Foundation for Public Welfare Projects, THE National Science Foundation for Post-doctoral Scientists of China, and the State Key Laboratory Program. Authors affiliated with Chinese Research Academy of Environmental Sciences, China.)
138. Lian CG, Xu S, Guo W, Yan J, Frank MY, Liu R, Liu C, Chen Y, Murphy GF, Chen T. 2015. Decrease of 5-hydroxymethylcytosine in rat liver with subchronic exposure to genotoxic carcinogens riddelliine and aristolochic acid. *Mol Carcinog* 54(11): 1503-1507.
139. Lima MI, Arruda VO, Alves EV, de Azevedo AP, Monteiro SG, Pereira SR. 2010. Genotoxic effects of the antileishmanial drug Glucantime. *Arch Toxicol* 84(3): 227-232. (Supported by the CAPES/PET—Biology (Coordenação de Aperfeiçoamento de Pessoal de Nível Superior, Programa de Educação Tutorial—Biologia) from Federal University of Maranhão. Authors affiliated with Federal University of Maranhão, Brazil.)
140. López S, Aguilar L, Mercado L, Bravo M, Quiroz W. 2015. Sb(V) reactivity with human blood components: Redox effects. *Plos One* 10(1): 12. (Supported by FONDECYT. Authors affiliated with Pontificia Universidad Católica de Valparaíso, Chile.)
141. Lösler S, Schlieff S, Kneifel C, Thiel E, Schrezenmeier H, Rojewski MT. 2009. Antimony-trioxide- and arsenic-trioxide-induced apoptosis in myelogenic and lymphatic cell lines, recruitment of caspases, and loss of mitochondrial membrane potential are enhanced by modulators of the cellular glutathione redox system. *Ann Hematol* 88(11):

- 1047-1058. (Support not reported. Authors affiliated with Charité Universitätsmedizin Berlin, Germany; Universität Ulm, Germany; Institut für klinische Transfusionsmedizin und Immungenetik, Germany.)
142. Lüdersdorf R, Fuchs A, Mayer P, Skulsuksai G, Schäcke G. 1987. Biological assessment of exposure to antimony and lead in the glass-producing industry. *Int Arch Occup Environ Health* 59(5): 469-474. (Support not reported. Authors affiliated with Freien Universität Berlin, Germany; Berufsgenossenschaft der keramischen und Glas-Industrie, Germany.)
143. Ma DK, Guo JU, Ming GL, Song H. 2009. DNA excision repair proteins and Gadd45 as molecular players for active DNA demethylation. *Cell Cycle* 8(10): 1526-1531. (Supported by NIH, March of Dimes, NARSAD and MSCRF. Authors affiliated with Johns Hopkins University School of Medicine, MD.)
144. Majestic BJ, Turner JA, Marcotte AR. 2012. Respirable antimony and other trace-elements inside and outside an elementary school in Flagstaff, AZ, USA. *Sci Total Environ* 435-436: 253-261. (Supported by the Camille and Henry Dreyfus Foundation and the National Science Foundation,. Authors affiliated with University of Denver, CO; Northern Arizona University, AZ; Arizona State University, AZ.)
145. MAK. 2007. Antimony and its inorganic compounds (inhalable fraction). In *The MAK-Collection Part I: MAK Value Documentations*. vol. 23. Weinheim, Germany: WILEY-VCH Verlag GmbH & Co. KGaA. (Support and author affiliations not reported.)
146. Mann KK, Davison K, Colombo M, Colosimo AL, Diaz Z, Padovani AM, Guo Q, Scrivens PJ, Gao W, Mader S, Miller WH, Jr. 2006. Antimony trioxide-induced apoptosis is dependent on SEK1/JNK signaling. *Toxicol Lett* 160(2): 158-170. (Supported by the CIHR, the Montreal Centre for Experimental Therapeutics in Cancer/CIHR/FRSQ, BCRP, Department of the Army, and the U.S. Army Medical Research Acquisition Activity. Authors affiliated with Montreal Centre for Experimental Therapeutics in Cancer and Lady Davis Institute for Medical Research, Canada; Université de Montréal, Canada.)
147. Mansour TE, Bueding E. 1954. The actions of antimonials on glycolytic enzymes of *Schistosoma mansoni*. *Br J Pharmacol Chemother* 9(4): 459-462. (Supported by the Office of Naval Research and NIH. Authors affiliated with Western Reserve University, OH.)
148. Mapei Group. 2017. *Technical Notebook: Hexavalent Chromium Reducing Agents for Portland Cements and Cement-Based Materials*. Milan, Italy: C-ADD Division, Mapei Group. <http://cadd.mapei.com/wp-content/uploads/2016/02/mapei-dam-cement-reducing-agents-technical-notebook.pdf>.
149. Miekeley N, Mortari SR, Schubach AO. 2002. Monitoring of total antimony and its species by ICP-MS and on-line ion chromatography in biological samples from patients treated for leishmaniasis. *Anal Bioanal Chem* 372(3): 495-502. (Supported by CNPq, FAPERJ, and CAPES. Authors affiliated with Pontifical Catholic University, Brazil; Center of Hospital Research Evandro Chagas, Brazil.)
150. Migliore L, Cocchi L, Nesti C, Sabbioni E. 1999. Micronuclei assay and FISH analysis in human lymphocytes treated with six metal salts. *Environ Mol Mutagen* 34(4): 279-284. (Support not reported. Authors affiliated with Università di Pisa, Italy; ECVAM, Italy.)

151. Miranda ES, Miekeley N, De-Carvalho RR, Paumgarten FJ. 2006. Developmental toxicity of meglumine antimoniate and transplacental transfer of antimony in the rat. *Reprod Toxicol* 21(3): 292-300. (Supported by ANVISA, CNPq, and CAPES. Authors affiliated with Oswaldo Cruz Foundation, Brazil; Pontifical Catholic University of Rio de Janeiro, Brazil.)
152. Molokhia MM, Smith H. 1967. Trace elements in the lung. *Arch Environ Health* 15(6): 745-750. (Support not reported. Authors affiliated with University of Glasgow, UK.)
153. Moreira VR, de Jesus LCL, Soares RP, Silva LDM, Pinto BAS, Melo MN, Paes AMA, Pereira SRF. 2017. Meglumine antimoniate (glucantime) causes oxidative stress-derived DNA damage in BALB/c mice infected by *Leishmania (Leishmania) infantum*. *Antimicrob Agents Chemother* 61(6). (Supported by FAPEMA and CAPES. Authors affiliated with Universidade Federal do Maranhão, Brazil; Universidade Federal de Minas Gerais, Brazil)
154. Morrow PE. 1988. Possible mechanisms to explain dust overloading of the lungs. *Fundam Appl Toxicol* 10(3): 369-384. (Support not reported. Author affiliated with University of Rochester, NY.)
155. Morrow PE. 1992. Dust overloading of the lungs: update and appraisal. *Toxicol Appl Pharmacol* 113(1): 1-12. (Support not reported. Author affiliated with University of Rochester, NY.)
156. Müller K, Daus B, Mattusch J, Stärk HJ, Wennrich R. 2009. Simultaneous determination of inorganic and organic antimony species by using anion exchange phases for HPLC-ICP-MS and their application to plant extracts of *Pteris vittata*. *Talanta* 78(3): 820-826. (Supported by the Deutsche Bundesstiftung Umwelt DBU. Authors affiliated with UFZ Helmholtz Centre for Environmental Research, Germany.)
157. Müller S, Miller WH, Jr., Dejean A. 1998. Trivalent antimonials induce degradation of the PML-RAR oncoprotein and reorganization of the promyelocytic leukemia nuclear bodies in acute promyelocytic leukemia NB4 cells. *Blood* 92(11): 4308-4316. (Supported by the European Economic Community, the the Association pour la Recherche contre le Cancer, la Fondation pour la Recherche Médicale et le Ministère de la Recherche et de la Technologie, and the Medical Research Council of Canada. Authors affiliated with INSERM, France; McGill University, Canada.)
158. Murray HW, Delph-Etienne S. 2000. Roles of endogenous gamma interferon and macrophage microbicidal mechanisms in host response to chemotherapy in experimental visceral leishmaniasis. *Infect Immun* 68(1): 288-293. (Supported by NIH. Authors affiliated with Weill Medical College of Cornell University, NY.)
159. NCBI. 2017. *GEO Datasets*. National Center for Biotechnology Information, U.S. National Library of Medicine. <https://www.ncbi.nlm.nih.gov/gds/>. Accessed on 11/20/17.
160. Newton PE, Bolte HF, Daly IW, Pillsbury BD, Terrill JB, Drew RT, Ben-Dyke R, Sheldon AW, Rubin LF. 1994. Subchronic and chronic inhalation toxicity of antimony trioxide in the rat. *Fundam Appl Toxicol* 22(4): 561-576. (Supported by the Antimony Oxide Industry Association. Authors affiliated with Pharmaco LSR Inc., NJ; American Petroleum Institute, Washington, DC; Antimony Oxide Industry Association, Washington, DC; University of Pennsylvania, PA.)

161. Nielson KB, Atkin CL, Winge DR. 1985. Distinct metal-binding configurations in metallothionein. *J Biol Chem* 260(9): 5342-5350. (Supported by NIH. Authors affiliated with University of Utah, UT.)
162. Nishioka H. 1975. Mutagenic activities of metal compounds in bacteria. *Mutat Res* 31(3): 185-189. (Support not reported. Author affiliated with Doshisha University, Japan.)
163. NTP. 1992. *Toxicity Studies of Antimony Potassium Tartrate in F344/N Rats and B6C3F<sub>1</sub> Mice (Drinking Water and Intraperitoneal Injection Studies)*. NTP TOX 11, NIH Publication No. 92-3130. National Toxicology Program. 70 pp.
164. NTP. 2015. *Handbook for Preparing the Report on Carcinogens Monographs*. Research Triangle Park, NC: National Toxicology Program. 89 pp. [http://ntp.niehs.nih.gov/ntp/roc/handbook/roc\\_handbook\\_508.pdf](http://ntp.niehs.nih.gov/ntp/roc/handbook/roc_handbook_508.pdf).
165. NTP. 2016a. Lead and Lead Compounds. In *Report on Carcinogens, Fourteenth Edition*. Fourteenth Edition. Research Triangle Park, NC: National Toxicology Program, U.S. Department of Health and Human Services, Public Health Service. <https://ntp.niehs.nih.gov/ntp/roc/content/profiles/lead.pdf>.
166. NTP. 2016b. Arsenic and Inorganic Arsenic Compounds. In *Report on Carcinogens, Fourteenth Edition*. Fourteenth Edition. Research Triangle Park, NC: National Toxicology Program, U.S. Department of Health and Human Services, Public Health Service. <https://ntp.niehs.nih.gov/ntp/roc/content/profiles/arsenic.pdf>.
167. NTP. 2016c. *Peer Review Draft. Technical Report on the Toxicology and Carcinogenesis Studies of Antimony Trioxide (CAS No. 1309-64-4) in Wistar Han [CrI:Wi (Han)] Rats and B6C3F<sub>1</sub>/N Mice (Inhalation Studies)*. NTP TR 590. National Toxicology Program. 303 pp.
168. NTP. 2017a. *Draft Toxicology and Carcinogenesis Studies of Antimony Trioxide (CAS No. 1309-64-4) in Wistar Han [CrI:WI (Han)] Rats and B6C3F<sub>1</sub>/N Mice (Inhalation Studies)*. NTP TR 590. National Toxicology Program, National Institutes of Health. 303 pp.
169. NTP. 2017b. *Tox21 Toolbox*. U.S. Department of Health and Human Services. <https://ntp.niehs.nih.gov/results/tox21/tbox/>. Accessed on 10/10/17.
170. NTP. 2017c. *Report on Carcinogens Protocol: Methods for Preparing the Draft Report on Carcinogens Monograph on Antimony Trioxide and Other Antimony Compounds*. Research Triangle Park, NC: National Toxicology Program. 38 pp. [https://ntp.niehs.nih.gov/ntp/roc/protocols/antimonytrioxide\\_508.pdf](https://ntp.niehs.nih.gov/ntp/roc/protocols/antimonytrioxide_508.pdf).
171. OECD. 2016. *Test No. 474: Mammalian Erythrocyte Micronucleus Test*. Paris: OECD Publishing, Paris. <http://www.oecd-ilibrary.org/docserver/download/9716401e.pdf>.
172. OECD. 2017. *Test No. 413: Subchronic Inhalation Toxicity: 90-day Study*. Paris: OECD Publishing, Paris. <http://www.oecd-ilibrary.org/docserver/download/9741301e.pdf>.
173. Olmez I, Gulovali MC, Gordon GE, Henkin RI. 1998. Trace elements in human parotid saliva. *Biol Trace Elem Res* 17: 259-270. (Support not reported. Authors affiliated with University of Maryland, MD; Center for Molecular Nutrition and Sensory Disorders, Washington, DC; Massachusetts Institute of Technology, MA; Turkish Aerospace Industries, Inc., Turkey.)
174. OSHA. 2017. *Chemical Exposure Health Data*. United States Department of Labor. Go to <https://www.osha.gov/opengov/healthsamples.html> and enter the chemical's IMIS number; click "Submit." (IMIS numbers are available at

- [https://www.osha.gov/dts/chemicalsampling/toc/chmn\\_A.html](https://www.osha.gov/dts/chemicalsampling/toc/chmn_A.html); enter chemical name in Search box, click enter, and select "Chemical Sampling Information" link.). Accessed on 7/28/17.
175. Otto GF, Maren TH, Brown HW. 1947. Blood levels and excretion rates of antimony in persons receiving trivalent and pentavalent antimonials. *Am J Hyg* 46: 193-211. (as cited in CDC 1978)
  176. Ozaki K, Haseman JK, Hailey JR, Maronpot RR, Nyska A. 2002. Association of adrenal pheochromocytoma and lung pathology in inhalation studies with particulate compounds in the male F344 rat--the National Toxicology Program experience. *Toxicol Pathol* 30(2): 263-270. (as cited in NTP 2017)
  177. Paßlack N, Mainzer B, Lahrssen-Wiederholt M, Schafft H, Palavinskas R, Breithaupt A, Zentek J. 2014. Liver and kidney concentrations of strontium, barium, cadmium, copper, zinc, manganese, chromium, antimony, selenium and lead in cats. *BMC Vet Res* 10: 9. (Support not reported. Authors affiliated with Freie Universität Berlin, Germany; Federal Institute for Risk Assessment, Germany.)
  178. Paßlack N, Mainzer B, Lahrssen-Wiederholt M, Schafft H, Palavinskas R, Breithaupt A, Zentek J. 2015. Concentrations of strontium, barium, cadmium, copper, zinc, manganese, chromium, antimony, selenium, and lead in the liver and kidneys of dogs according to age, gender, and the occurrence of chronic kidney disease. *J Vet Sci* 16(1): 57-66. (Support not reported. Authors affiliated with Freie Universität Berlin, Germany; Federal Institute for Risk Assessment, Germany.)
  179. Pathak MK, Yi T. 2001. Sodium stibogluconate is a potent inhibitor of protein tyrosine phosphatases and augments cytokine responses in hemopoietic cell lines. *J Immunol* 167(6): 3391-3397. (Supported in part by Grants R01CA79891 and R01MG58893. Authors affiliated with Cleveland Clinic Foundation, OH.)
  180. Paton GR, Allison AC. 1972. Chromosome damage in human cell cultures induced by metal salts. *Mutat Res* 16(3): 332-336. (Support not reported. Authors affiliated with Clinical Research Centre, UK.)
  181. Patterson TJ, Ngo M, Aronov PA, Reznikova TV, Green PG, Rice RH. 2003. Biological activity of inorganic arsenic and antimony reflects oxidation state in cultured human keratinocytes. *Chem Res Toxicol* 16(12): 1624-1631. (Supported by the USPHS. Authors affiliated with University of California, CA.)
  182. Patterson TJ, Rice RH. 2007. Arsenite and insulin exhibit opposing effects on epidermal growth factor receptor and keratinocyte proliferative potential. *Toxicol Appl Pharmacol* 221(1): 119-128. (Supported by USPHS. Authors affiliated with University of California, CA.)
  183. Pavageau MP, Morin A, Seby F, Guimon C, Krupp E, Pecheyran C, Poulleau J, Donard OF. 2004. Partitioning of metal species during an enriched fuel combustion experiment. speciation in the gaseous and particulate phases. *Environ Sci Technol* 38(7): 2252-2263. (Supported by the A.D.E.M.E. Authors affiliated with UMR CNRS, France; Institut National de l'Environnement Industriel et des Risques, France.)
  184. Petit de Peña Y, Gallignani M, Burguera M, Burguera JL, Añez N, Lugo A. 1990. Selective determination of antimony (III) and antimony (V) in blood serum and urine by hydride generation and atomic absorption spectrometry. *J Braz Chem Soc* 1(2): 72-75. (Support not reported. Authors affiliated with Universidad de Los Andes, Venezuela.)

185. Poon R, Chu I. 2000. Effects of trivalent antimony on human erythrocyte glutathione-S-transferases. *J Biochem Mol Toxicol* 14(3): 169-176. (Support not reported. Authors affiliated with Bureau of Chemical Hazards, Canada.)
186. PubChem. 2017. *PubChem Compound Database*. National Library of Medicine. <http://pubchem.ncbi.nlm.nih.gov/> and search on antimony. Accessed on 6/29/17.
187. Quiroz W, De Gregori I, Basilio P, Bravo M, Pinto M, Lobos MG. 2009. Heavy weight vehicle traffic and its relationship with antimony content in human blood. *J Environ Monit* 11(5): 1051-1055. (Supported by FONDECYT. Authors affiliated with Pontificia Universidad Católica de Valparaíso, Chile; Universidad de Valparaíso, Chile.)
188. Quiroz W, Arias H, Bravo M, Pinto M, Lobos MG, Cortés M. 2011. Development of analytical method for determination of Sb(V), Sb(III) and TMSb(V) in occupationally exposed human urine samples by HPLC-HG-AFS. *Microchem J* 97(1): 78-84. (Supported by FONDECYT. Authors affiliated with Pontificia Universidad Católica de Valparaíso, Chile; Universidad de Valparaíso, Chile.)
189. Quiroz W, Aguilar L, Barria M, Veneciano J, Martínez D, Bravo M, Lobos MG, Mercado L. 2013. Sb(V) and Sb(III) distribution in human erythrocytes: speciation methodology and the influence of temperature, time and anticoagulants. *Talanta* 115: 902-910. (Supported by FONDECYT and “Dirección de Investigación” of the Pontificia Universidad Católica de Valparaíso. Authors affiliated with Pontificia Universidad Católica de Valparaíso, Chile; Universidad de Valparaíso, Chile.)
190. Ragaini RC, Ralston HR, Roberts N. 1977. Environmental metal contamination in Kellogg, Idaho, near a lead smelting complex. *Environ Sci Technol* 11: 773-781. (as cited in Belzille *et al.* 2011)
191. Ribeiro RR, Ferreira WA, Martins PS, Neto RL, Rocha OG, Le Moyec L, Demicheli C, Frézard F. 2010. Prolonged absorption of antimony(V) by the oral route from non-inclusion meglumine antimoniate-beta-cyclodextrin conjugates. *Biopharm Drug Dispos* 31(2-3): 109-119. (Supported by CNPq and FAPEMIG. Authors affiliated with Universidade Federal de Minas Gerais, Brazil; Universidade Federal do Recôncavo da Bahia, Brazil; Fundação Centro Tecnológico de Minas Gerais, Brazil; CNRS, France.)
192. Roper AJ, Williams PA, Filella M. 2012. Secondary antimony minerals: Phases that control the dispersion of antimony in the supergene zone. *Chem Erde - Geochem* 72: 9-14. (Support not reported. Authors affiliated with University of Western Sydney, Australia; University of Geneva, Switzerland; SCHEMA, Luxemborg.)
193. Sage AP, Minatel BC, Ng KW, Stewart GL, Dummer TJB, Lam WL, Martinez VD. 2017. Oncogenomic disruptions in arsenic-induced carcinogenesis. *Oncotarget* 8(15): 25736-25755. (Supported by the Canadian Institutes for Health Research. Authors affiliated with British Columbia Cancer Research Centre, Canada; University of British Columbia, Canada.)
194. Sahin U, de Thé H, Lallemand-Breitenbach V. 2014. PML nuclear bodies: assembly and oxidative stress-sensitive sumoylation. *Nucleus* 5(6): 499-507. (Support not reported. Authors affiliated with University Paris Diderot, France; INSERM, France; CNRS, France; Hôpital St. Louis, France; Collège de France, France.)
195. Salerno M, Petroutsas M, Garnier-Suillerot A. 2002. The MRP1-mediated effluxes of arsenic and antimony do not require arsenic-glutathione and antimony-glutathione complex formation. *J Bioenerg Biomembr* 34(2): 135-145. (Supported by La Ligue

- Nationale contre le Cancer, l'Université Paris Nord, and CNRS. Authors affiliated with Université Paris Nord, France.)
196. Salisbury S. 1980. *Health Hazard Evaluation. St. Clair Rubber Company, Marysville, Michigan*. HE 79-075-784. Cincinnati, OH: National Institute for Occupational Safety and Health. 25 pp.
  197. Schaumlöffel N, Gebel T. 1998. Heterogeneity of the DNA damage provoked by antimony and arsenic. *Mutagenesis* 13(3): 281-286. (Support not reported. Authors affiliated with University of Gottingen, Germany.)
  198. Schnorr TM, Steenland K, Thun MJ, Rinsky RA. 1995. Mortality in a cohort of antimony smelter workers. *Am J Ind Med* 27(5): 759-770. (Support not reported. Authors affiliated with NIOSH, OH; American Cancer Society, GA.)
  199. Schroeder HA, Mitchener M, Balassa JJ, Kanisawa M, Nason AP. 1968. Zirconium, niobium, antimony and fluorine in mice: effects on growth, survival and tissue levels. *J Nutr* 95(1): 95-101. (Supported by the Public Health Service, the National Heart Institute, the US Army and CIBA Pharmaceutical Products, Inc. Authors affiliated with Dartmouth Medical School, NH; Brattleboro Memorial Hospital, VT.)
  200. Schroeder HA, Mitchener M, Nason AP. 1970. Zirconium, niobium, antimony, vanadium and lead in rats: life term studies. *J Nutr* 100(1): 59-68. (Supported by the Public Health Service, the National Heart Institute, the U.S. Army, and Cooper Laboratories, Inc. Authors affiliated with Dartmouth Medical School, NH; Brattleboro Memorial Hospital, VT.)
  201. Scinicariello F, Buser MC. 2016. Urinary antimony and leukocyte telomere length: An analysis of NHANES 1999-2002. *Environ Res* 150: 513-518. (Support not reported. Authors affiliated with ATSDR, GA.)
  202. Shacklette HT, Boerngen JG. 1984. *Element Concentration in Soils and Other Surficial Materials of the Conterminous United States*. U.S. Geological Survey Professional Paper 1270. Alexandria, VA: U.S. Geological Survey. (as cited in ATSDR 2017)
  203. Shiue I, Hristova K. 2014. Higher urinary heavy metal, phthalate and arsenic concentrations accounted for 3-19% of the population attributable risk for high blood pressure: US NHANES, 2009-2012. *Hypertens Res* 37(12): 1075-1081. (Supported by the Global Platform for Research Leaders scheme. Authors affiliated with Heriot-Watt University, UK; University of Georgia, GA.)
  204. Smith MM, White Ma, Wilson HK. 1995. Determination of antimony in urine by solvent extraction and electrothermal atomization atomic absorption spectrometry for the biological monitoring of occupational exposure. *J Anal At Spectrom* 10: 349-352. (Support not reported. Authors affiliated with Health and Safety Executive, UK.)
  205. Smith MT, Guyton KZ, Gibbons CF, Fritz JM, Portier CJ, Rusyn I, DeMarini DM, Caldwell JC, Kavlock RJ, Lambert PF, Hecht SS, Bucher JR, Stewart BW, Baan RA, Coglianò VJ, Straif K. 2016. Key characteristics of carcinogens as a basis for organizing data on mechanisms of carcinogenesis. *Environ Health Perspect* 124(6): 713-721. (Supported by NIEHS. Authors affiliated with University of California Berkeley, CA; IARC, France; US EPA, Washington, D.C. and NC; ATSDR; Texas A&M University, TX; University of Wisconsin School of Medicine and Public Health, WI; University of Minnesota, MN; NIEHS, NC; University of New South Wales, Australia.)

206. Stemmer KL. 1976. Pharmacology and toxicology of heavy metals: antimony. *Pharmac Ther A* 1: 157-160. (Support not reported. Author affiliated with University of Cincinnati, OH.)
207. Sudhandiran G, Shaha C. 2003. Antimonial-induced increase in intracellular Ca<sup>2+</sup> through non-selective cation channels in the host and the parasite is responsible for apoptosis of intracellular *Leishmania donovani* amastigotes. *J Biol Chem* 278(27): 25120-25132. (Supported by the Indian Council of Medical Research, Department of Biotechnology, Government of India and the National Institute of Immunology, New Delhi. Authors affiliated with National Institute of Immunology, India.)
208. Sumino K, Hayakawa K, Shibata T, Kitamura S. 1975. Heavy metals in normal Japanese tissues. Amounts of 15 heavy metals in 30 subjects. *Arch Environ Health* 30(10): 487-494. (as cited in Tylanda and Fowler 2015)
209. Sunderman FW, Jr., McCully KS. 1983. Carcinogenesis tests of nickel arsenides, nickel antimonide, and nickel telluride in rats. *Cancer Invest* 1(6): 469-474. (Supported by NIEHS and the U.S. Department of Energy. Authors affiliated with University of Connecticut School of Medicine, CT.)
210. Sunderman FW, Jr., McCully KS, Hopfer SM. 1984. Association between erythrocytosis and renal cancers in rats following intrarenal injection of nickel compounds. *Carcinogenesis* 5(11): 1511-1517. (Supported by NIEHS and the U.S. Department of Energy. Authors affiliated with University of Connecticut School of Medicine, CT.)
211. Sunderman Jr FW. 1984. Carcinogenicity of nickel compounds in animals. *IARC Sci Publ* 53: 127-142. (Supported by NIEHS and the U.S. Department of Energy. Author affiliated with University of Connecticut School of Medicine, CT.)
212. Takahashi S, Okayasu R, Sato H, Kubota Y, Bedford JS. 2002a. Inhibition of radiation-induced DNA-double strand break repair by various metal/metalloid compounds. In *Radiation and Homeostasis, Proceedings*. International Congress Series, 1236. Sugahara T, Nikaido O, Niwa O, eds. Amsterdam: Elsevier Science Bv. 327-330. (Support not reported. Authors affiliated with National Institute of Radiological Sciences, Japan; Colorado St. University, CO.)
213. Takahashi S, Sato H, Kubota Y, Utsumi H, Bedford JS, Okayasu R. 2002b. Inhibition of DNA-double strand break repair by antimony compounds. *Toxicology* 180(3): 249-256. (Support not reported. Authors affiliated with National Institute of Radiological Sciences, Japan; Kyoto University, Japan; Colorado St. University, CO.)
214. Takahashi Y, Sakuma K, Itai T, Zheng G, Mitsunobu S. 2008. Speciation of antimony in PET bottles produced in Japan and China by X-ray absorption fine structure spectroscopy. *Environ Sci Technol* 42(24): 9045-9050. (Supported by the the Ministries of Education, Culture, Sports, Science, and Technology and Environment of Japan, the 100-Talent program from CAS, and Spring-8. Authors affiliated with Hiroshima University, Japan; Chinese Academy of Sciences, China.)
215. Tellez-Plaza M, Tang WY, Shang Y, Umans JG, Francesconi KA, Goessler W, Ledesma M, Leon M, Laclaustra M, Pollak J, Guallar E, Cole SA, Fallin MD, Navas-Acien A. 2014. Association of global DNA methylation and global DNA hydroxymethylation with metals and other exposures in human blood DNA samples. *Environ Health Perspect* 122(9): 946-954. (Supported by the National Heart, Lung, and Blood Institute, the Strong Heart Study, NIOSH, the Education and Research Center for



- Occupational Safety and Health at the Johns Hopkins Bloomberg School of Public Health, NIEHS, the Carlos the Third Health Institute at the Spanish Ministry of Economy and Innovation, and FEDER. Authors affiliated with Johns Hopkins Bloomberg School of Public Health, MD; INCLIVA, Spain; Second Military Medical University, China; MedStar Health Research Institute, MD; Georgetown-Howard Universities Center for Clinical and Translational Science, Washington, DC; Karl-Franzens University, Austria; Aragon Health Sciences Institute, Spain; CNIC, Spain; Johns Hopkins Medical Institutions, MD; Texas Biomedical Research Institute, TX.)
216. Tessier S, Martin-Martin N, de Thé H, Carracedo A, Lallemand-Breitenbach V. 2017. Promyelocytic leukemia protein, a protein at the crossroad of oxidative stress and metabolism. *Antioxid Redox Signal* 26(9): 432-444. (Supported by the the Ramón y Cajal, the Basque Department of Industry, Tourism and Trade, Health, and Education, Marie Curie, the Movember Foundation, FERO, ERC, INSERM, CNRS, the Spanish Association Against Cancer, Université Paris-Diderot, Ligue Contre le Cancer, Institut National du Cancer, ANR (PACRI, SLI, and SUMOPiv projects), Canceropole Ile de France, and the European Research Council. Authors affiliated with Collège de France, France; INSERM, France; CNRS, France; Université Paris Diderot, France; CIC bioGUNE, Spain; Hopital St. Louis, France; IKERBASQUE, Spain; University of the Basque Country, Spain.)
217. Thomas RG, Felicetti SW, Lucchino RV, McClellan RO. 1973. Retention patterns of antimony in mice following inhalation of particles formed at different temperatures. *Proceed Soc Exp Biol Med* 144(2): 544-550.
218. Tice RR, Austin CP, Kavlock RJ, Bucher JR. 2013. Improving the human hazard characterization of chemicals: a Tox21 update. *Environ Health Perspect* 121(7): 756-765.
219. Tirmenstein MA, Plews PI, Walker CV, Woolery MD, Wey HE, Toraason MA. 1995. Antimony-induced oxidative stress and toxicity in cultured cardiac myocytes. *Toxicol Appl Pharmacol* 130(1): 41-47. (Support not reported. Authors affiliated with NIOSH, OH.)
220. Tirmenstein MA, Mathias PI, Snawder JE, Wey HE, Toraason M. 1997. Antimony-induced alterations in thiol homeostasis and adenine nucleotide status in cultured cardiac myocytes. *Toxicology* 119(3): 203-211. (Support not reported. Authors affiliated with NIOSH, OH.)
221. TNO Quality of Life. 2005. A study on the biodistribution of antimony trioxide (Sb<sub>2</sub>O<sub>3</sub>) in rats. *TNO Rep* 6502: 1-63. (as cited in EU 2008)
222. Tran CL, Buchanan D, Cullen RT, Searl A, Jones AD, Donaldson K. 2000. Inhalation of poorly soluble particles. II. Influence of particle surface area on inflammation and clearance. *Inhal Toxicol* 12(12): 1113-1126. (Supported by the UK Health and Safety Executive. Authors affiliated with Institute of Occupational Medicine, UK; Napier University, UK.)
223. TRI. 2016. *TRI Explorer Chemical Report. On--site Disposal to Class I Underground Injection Wells, RCRA Subtitle C Landfills, and Other Landfills*. U.S. Environmental Protection Agency. <http://www.epa.gov/triexplorer>. Accessed on 8/18/16.
224. Turner A, Kearn ER, Solman KR. 2016. Lead and other toxic metals in playground paints from South West England. *Sci Total Environ* 544: 460-466. (Supported by the UoPMarine Institute. Authors affiliated with Plymouth University, UK.)

225. Turner A, Filella M. 2017. Field-portable-XRF reveals the ubiquity of antimony in plastic consumer products. *Sci Total Environ* 584-585: 982-989. (Supported by the UoP Marine Institute. Authors affiliated with Plymouth University, UK; University of Geneva, Switzerland.)
226. Tylanda CA, Fowler BA. 2015. Antimony. In *Handbook on the Toxicology of Metals*. 4th ed. Nordberg GF, Fowler BA, Nordberg M, eds. Waltham, MA: Elsevier. p. 565-579. (Support and author affiliations not reported.)
227. Tyrrell J, Melzer D, Henley W, Galloway TS, Osborne NJ. 2013. Associations between socioeconomic status and environmental toxicant concentrations in adults in the USA: NHANES 2001-2010. *Environ Int* 59: 328-335. (Supported by the University of Exeter internal support. Authors affiliated with University of Exeter Medical School, UK.)
228. Ulrich N. 1998. Speciation of antimony(III), antimony(V) and trimethylstiboxide by ion chromatography with inductively coupled plasma atomic emission spectrometric and mass spectrometric detection. *Anal Chim Acta* 359(3): 245-253. (Support not reported. Author affiliated with University of Hannover, Germany.)
229. USGS. 2017. *Mineral Commodity Summaries, January 2017. Antimony*. U.S. Department of Interior, U.S. Geological Survey. 2 pp.
230. USITC. 2017. *USITC Interactive Tariff and Trade Dataweb*. United States International Trade Commission. [http://dataweb.usitc.gov/scripts/user\\_set.asp](http://dataweb.usitc.gov/scripts/user_set.asp) and search on HTS no. 8110900000, 2617100000, 2825800000, 8110200000, 7801910000, 8110100000. Accessed on 8/22/17.
231. Vanoeteren C, Cornelis R, Dams R. 1986a. Evaluation of trace elements in human lung tissue. II. Recovery and analysis of inhaled particulates. *Sci Total Environ* 54: 231-236. (as cited in NTP 2016)
232. Vanoeteren C, Cornelis R, Verbeeck P. 1986b. Evaluation of trace elements in human lung tissue. III. Correspondence analysis. *Sci Total Environ* 54: 237-245. (as cited in NTP 2016)
233. Vanoeteren C, Cornelis R, Versieck J. 1986c. Evaluation of trace elements in human lung tissue. I. Concentration and distribution. *Sci Total Environ* 54: 217-230. (as cited in NTP 2016)
234. Verdugo M, Ogra Y, Quiroz W. 2016. Mechanisms underlying the toxic effects of antimony species in human embryonic kidney cells (HEK-293) and their comparison with arsenic species. *J Toxicol Sci* 41(6): 783-792. (Supported by the Chilean Government and JSPS KAKENHI. Authors affiliated with Chiba University, Japan; Avenida Universidad, Chile.)
235. Vinas P, López-García I, Merino-Meroño B, Hernández-Córdoba M. 2006. Liquid chromatography-hydride generation-atomic fluorescence spectrometry hybridation for antimony speciation in environmental samples. *Talanta* 68(4): 1401-1405. (Supported by CARM, the Spanish MEC, and S.A. Hero España. Authors affiliated with University of Murcia, Spain.)
236. Wang B, Yu W, Guo J, Jiang X, Lu W, Liu M, Pang X. 2015. The antiparasitic drug, potassium antimony tartrate, inhibits tumor angiogenesis and tumor growth in nonsmall-cell lung cancer. *J Pharmacol Exp Ther* 352(1): 129-138. (Supported by the National Basic Research Program of China, the National Natural Science Foundation of China, the Science and Technology Commission of Shanghai Municipality, the

- Chenguang Program from Shanghai Municipal Education Commission, and the Fundamental Research Funds for the Central Universities. Authors affiliated with East China Normal University, China; Texas A&M University Health Science Center, TX.)
237. Watt WD. 1983. *Chronic Inhalation Toxicity of Antimony Trioxide: Validation of the Threshold Limit Value*. Detroit, MI: Wayne State University, PhD Thesis. (Supported by ASARCO, Inc. Author affiliated with Wayne State University, MI.)
238. Westrick ML. 1953. Physiologic responses attending administration of antimony, alone or with simultaneous injections of thyroxin. *Proc Soc Exp Biol Med* 82(1): 56-60. (Support not reported. Author affiliated with University of Pittsburgh, PA.)
239. Whaley P, Halsall C, Agerstrand M, Aiassa E, Benford D, Bilotta G, Coggon D, Collins C, Dempsey C, Duarte-Davidson R, FitzGerald R, Galay-Burgos M, Gee D, Hoffmann S, Lam J, Lasserson T, Levy L, Lipworth S, Ross SM, Martin O, Meads C, Meyer-Baron M, Miller J, Pease C, Rooney A, Sapiets A, Stewart G, Taylor D. 2016. Implementing systematic review techniques in chemical risk assessment: Challenges, opportunities and recommendations. *Environ Int* 92-93: 556-564. WikiGenes. 2017. *Chemical Compound Review: Meglumine*. WikiGenes. <https://www.wikigenes.org/e/chem/e/8567.html>. Accessed on 10/9/17.
240. Willets P, Anderson RA, Farmer JG, et al. 1982. Inorganic elements in the tracheas of fire fatalities. *Fire Mater* 6: 32-37. (Supported by the Building Research Establishment Fire Research Station, Borehamwood, Hertfordshire. Authors affiliated with University of Glasgow, UK; West of Scotland Health Boards, UK.)
241. Wingren G, Axelson O. 1985. Mortality pattern in a glass producing area in SE Sweden. *Br J Ind Med* 42(6): 411-414. (Support not reported. Authors affiliated with Linköping University, Sweden.)
242. Wingren G, Axelson O. 1993. Epidemiologic studies of occupational cancer as related to complex mixtures of trace elements in the art glass industry. *Scand J Work Environ Health* 19 Suppl 1: 95-100. (Support not reported. Authors affiliated with University Hospital - Linköping, Sweden)
243. Witte T, Plass C, Gerhauser C. 2014. Pan-cancer patterns of DNA methylation. *Genome Med* 6(8): 66.
244. Wortmann GW, Aronson NE, Byrd JC, Grever MR, Oster CN. 1998. Herpes zoster and lymphopenia associated with sodium stibogluconate therapy for cutaneous leishmaniasis. *Clin Infect Dis* 27(3): 509-512. (Support not reported. Authors affiliated with Walter Reed Army Medical Center, Washington, D.C; Johns Hopkins University, MD.)
245. Wyllie S, Fairlamb AH. 2006. Differential toxicity of antimonial compounds and their effects on glutathione homeostasis in a human leukaemia monocyte cell line. *Biochem Pharmacol* 71(3): 257-267. (Supported by the Burroughs Wellcome Fund and Wellcome Trust Infectious Disease Initiative. Authors affiliated with University of Dundee, UK.)
246. Wysocki R, Tamas MJ. 2010. How *Saccharomyces cerevisiae* copes with toxic metals and metalloids. *FEMS Microbiol Rev* 34(6): 925-951. (Supported by the Swedish Research Council, the Swedish Research Links programme, and the Polish Ministry of Science and Higher Education. Authors affiliated with University of Wroclaw, Poland; University of Gothenburg, Sweden.)

247. Xiong J, Liu X, Cheng QY, Xiao S, Xia LX, Yuan BF, Feng YQ. 2017. Heavy metals induce decline of derivatives of 5-methylcytosine in both DNA and RNA of stem cells. *ACS Chem Biol* 12(6): 1636-1643. (Supported by the National Natural Science Foundation of China. Authors affiliated with Wuhan University, China; University of Science and Technology of China, China; Southern Medical University, China; Chinese Academy of Sciences, China.)
248. Yamamoto A, Kohyama Y, Hanawa T. 2002. Mutagenicity evaluation of forty-one metal salts by the umu test. *J Biomed Mater Res* 59(1): 176-183. (Support not reported. Authors affiliated with National Institute for Materials Science, Japan.)
249. Yi T, Pathak MK, Lindner DJ, Ketterer ME, Farver C, Borden EC. 2002. Anticancer activity of sodium stibogluconate in synergy with IFNs. *J Immunol* 169(10): 5978-5985. (Supported by Grants R01CA7989, R01 MG58893 and CA90914. Authors affiliated with Cleveland Clinic Foundation, OH; Northern Arizona University Flagstaff, AZ.)
250. Young M. 1979a. *Walk-through Survey Report of General Battery and Ceramic Corporation, Dallas, Texas*. Cincinnati, OH: Division of Surveillance, Hazard Evaluations, and Field Studies, Industry-wide Studies Branch, Industrial Hygiene Section, National Institute for Occupational Safety and Health.
251. Young M. 1979b. *Walk-through Survey Report of Standard Industries, Inc. (Reliable Battery Company), San Antonio, Texas*. Cincinnati, OH: Division of Surveillance, Hazard Evaluations, and Field Studies, Industry-wide Studies Branch, Industrial Hygiene Section, National Institute for Occupational Safety and Health.
252. Zhang J, Billiet J, Dams R. 1985. Elemental composition and source investigation of particulates suspended in the air of an iron foundry. *Sci Total Environ* 41: 13-28. (Support not reported. Authors affiliated with Institute for Nuclear Sciences, Belgium.)
253. Zhang L, Li J, Wang Y, Wu G, Wei F. 2012. [Descriptive study of the environmental epidemiology of high lung cancer incidence rate in Qujing, Yunnan, China]. *Zhongguo Fei Ai Za Zhi* 15(3): 159-163. (Support unknown due to foreign language. Authors affiliated with National Environmental Monitoring Center, China; Qujing Centers for Disease Control and Prevention, China; China Gao Xin Investment Group Corporation, China.)
254. Zheng FY, Qian SH, Li SX, Huang XQ, Lin LX. 2006. Speciation of antimony by preconcentration of Sb(III) and Sb(V) in water samples onto nanometer-size titanium dioxide and selective determination by flow injection-hydride generation-atomic absorption spectrometry. *Anal Sci* 22(10): 1319-1322. (Supported by the National Natural Science Foundation of China and the Science & Technology Committee of Fujian Province, China. Authors affiliated with Wuhan University, China; Zhangzhou Teachers College, China.)
255. Zheng G, Zhong H, Guo Z, Wu Z, Zhang H, Wang C, Zhou Y, Zuo Z. 2014. Levels of heavy metals and trace elements in umbilical cord blood and the risk of adverse pregnancy outcomes: a population-based study. *Biol Trace Elem Res* 160(3): 437-444. (Supported by the Xiamen Science and Technology Program and the Fundamental Research Funds for the Central Universities. Authors affiliated with Xiamen University, China; Maternal and Child Health Hospital of Xiamen, China; Nanjing University of Science and Technology, China.)

256. Zhu H, Wang N, Zhang Y, Wu Q, Chen R, Gao J, Chang P, Liu Q, Fan T, Li J, Wang J, Wang J. 2010. Element contents in organs and tissues of Chinese adult men. *Health Phys* 98(1): 61-73. (as cited in ICRP 2012)

**The Page Left Intentionally Blank**

## Abbreviations

53BP1:	TP53-binding protein 1, 6-4PP = 6-4 photoproducts
6-4PP:	6-4 photoproducts
AAS	atomic absorption spectrometry
ACGIH:	American Conference of Governmental Industrial Hygienists
ADME:	absorption, distribution, metabolism, and excretion
ALF:	artificial lysosomal fluid
ALL	acute lymphoblastic leukemia
ANOVA:	analysis of variance
APL:	acute promyelocytic leukemia
APM	airborne particulate matter
APT	antimony potassium tartrate
AR:	androgen receptor
ASW:	Artificial sweat
AT:	3-amino-1,2,4-azole
ATG:	Attagene
ATM:	serine-protein kinase ATM
ATSDR:	Agency for Toxic Substances and Disease Registry
avg:	average
BDL:	below detection limit
BPDE:	benzo[ <i>a</i> ]pyrene diol epoxide
BPDE-DNA:	benzo[ <i>a</i> ]pyrene diol epoxide-DNA
BPDE-DNA adducts:	DNA adducts induced by (+)-anti- benzo[ <i>a</i> ]pyrene diol epoxide
BRCA1:	breast cancer type 1 susceptibility protein
BSC:	Board of Scientific Counselors
BSO:	DL-buthionine-[ <i>S,R</i> ]-sulfoximine
CAR:	androstane receptor
CAS:	Chemical Abstracts Service
CAT:	catalase
CCRF-CEM	acute lymphoblastic leukemia cells
CDC:	Centers for Disease Control and Prevention

---

CDR:	Chemical Data Reporting Rule
CHK:	serine/threonine-protein kinase Chk1 isoform 1
CHK2:	erine/threonine-protein kinase Chk1 isoform 2
CI:	confidence interval
Conc:	concentration
CPD:	cyclobutane pyrimidine dimers
<i>CSF2</i>	colony-stimulating factor 2
CYP:	cytochrome P450
DDB2	damage specific DNA binding protein 2 (see also XPE)
dGTP	deoxyguanosine triphosphate
DNA:	deoxyribonucleic acid
DSB:	double-strand breaks
EC50:	effective concentration at 50% maximal activity
EGF	epidermal growth factor
EGFR	epidermal growth factor receptor
EPA:	(United States) Environmental Protection Agency
ErbB2	erb-b2 receptor tyrosine kinase 2
EU	European Union
EU RAR	European Union risk assessment report
Exp.:	exposed
F:	female
FDA:	Food and Drug Administration
FXR:	farnesoid-X-receptor
GC/MS:	gas chromatography/mass spectroscopy
GI:	gastrointestinal
GM:	geometric mean
GMB:	Gamble's solution
GSD	geometric standard deviation
GSH:	glutathione
GSSG:	glutathione disulfide
GST:	glutathione-S-transferase
GST:	artificial gastric fluid



---

GTP:	guanosine triphosphate
H2AX:	histone H2AX
HBr:	hydrogen bromide
HCl:	hydrogen chloride
HG-AAS:	hydride generation-atomic absorption spectrometry
HHS:	Department of Health and Human Services
HL-60	acute promyelocytic leukemia cells
HPLC-HG-AFS:	high performance liquid chromatography-hydride generation-atomic fluorescence spectrometry
HPLC:	high-performance liquid chromatography
HR:	hazard ratio
HR:	homologous recombination repair
hr:	hour
HSDB:	Hazardous Substances Database
HTS:	harmonized tariff schedule
HWSE:	healthy worker survival (or survivor) effect
i.p.:	intraperitoneal
i.v.:	intravenous
IARC:	International Agency for Research on Cancer
IC-ICP-AES:	inductively coupled plasma atomic emission spectrometric
ICD:	International Classification of Diseases
ICD-8:	International Classification of Diseases, Eighth Revision
ICD-9:	International Classification of Diseases, Ninth Revision
ICP-AES:	inductively coupled plasma-atomic emission spectroscopy
ICP-MS:	inductively coupled plasma-mass spectrometry
IDLH:	immediately dangerous to life and health
IFN $\alpha$ :	interferon-alpha
IFN $\gamma$ :	interferon-gamma
Ig:	immunoglobulin
IM	infectious mononucleosis
InChi:	IUPAC International Chemical Identifier
iNOS KO:	inducible nitric oxide synthase knock out (mice)
IRIS:	Integrated Risk Information System

---

IUR:	Inventory Update Rule
JEM:	job-exposure matrix
K-562	chronic myelogenous leukemia cells
LC-HG-AFS:	liquid chromatography-hydrate generation-atomic fluorescence spectrometry
LOUCY	T cell acute lymphoblastic leukemia cells
M:	male or mice
MAP:	mitogen-activated protein
MCL:	maximum contaminant level
MeSH:	Medical Subject Headings
MMAD:	mass median aerodynamic diameter
MMP	mitochondrial membrane potential
MN:	micronuclei
mo:	month
MS:	mercaptosuccinic acid
N:	number
n/N:	number of animals with neoplasms divided by the total number of animals tested in that group
NaAsc:	sodium ascorbate
NAC	N-acetylcysteine
NAICS:	North American Industry Classification System
NB4	acute promyelocytic leukemia cells
NB4-M-AsR3 cells	arsenic resistant APL cells derived in Miller lab
nBP:	<i>n</i> -bromoheptane
NC:	negative control
NCATS:	National Center for Advancing Translational Sciences
NCBI GEO:	National Center for Biotechnology Information Gene Expression Omnibus database
NCE:	normochromatic erythrocyte
NCTR:	National Center for Toxicological Research
ND:	not detected; not determined; not done; patient and normal donor
NER:	nucleotide excision repair
NHANES:	National Health and Nutrition Examination Survey

---

NHEJ:	non-homologous end joining
NIEHS:	National Institute of Environmental Health Sciences
NIH:	National Institutes of Health
NIOSH:	National Institute for Occupational Safety and Health
NOES:	National Occupational Exposure Survey
NOS:	not otherwise specified
NR:	not reported; none reported
Nrf2:	nuclear factor (erythroid derived-2)-like 2
NS:	not significant
NT:	not tested
NTP:	National Toxicology Program
NVS:	NovaScreen
obs:	observations
OECD:	Organisation for Economic Co-Operation and Development
OR:	odds ratio
ORoC:	Office of the Report on Carcinogens
OSHA:	Occupational Safety and Health Administration
p.o.:	per os (oral administration)
PAHs:	polycyclic aromatic hydrocarbons
PBS:	phosphate-buffered saline
PC:	positive control
PCE:	polychromatic erythrocyte
PDF:	Portable Document Format
PEL:	permissible exposure limit
PET	polyethylene terephthalate
PM <sub>1</sub> :	particles less than 1 µm in diameter
PM <sub>10</sub> :	particles less than 10 µm in diameter
PPARδ:	peroxisome proliferator-activated receptor delta
PVC:	polyvinyl chloride
R:	rats
r:	correlation coefficient
RAD51:	DNA repair protein RAD51 homolog

---

RAHC:	reasonably anticipated to be a human carcinogen
REL:	recommended exposure limit
RNA:	ribonucleic acid
RoC:	Report on Carcinogens
ROS:	reactive oxygen species
RQ:	reportable quantity
RR:	relative risk
s.c.:	subcutaneous
Sb:	antimony
Sb(III):	trivalent form of antimony (valence = +3)
Sb(V):	pentavalent form of antimony (valence = +5)
SCE:	sister-chromatid exchange
SD:	standard deviation
SHP-1:	PTPases Src homology PTPase1
SIC:	Standard Industrial Classification
SMR:	standardized mortality ratio
SOD:	superoxide dismutase
std dev:	standard deviation
Tie2	tyrosine kinase with immunoglobulin like and EGF like domains 2
TK:	toxicokinetics
TLV:	threshold limit value
TLV-TWA:	threshold limit value time-weighted average
TM:	tail moment
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
USITC:	United States International Trade Commission
UV:	ultraviolet light
UVC:	ultraviolet C
VC	vehicle control

---

VEGF:	<i>vascular endothelial growth factor</i>
wAUC:	weighted area under the curve
X-CGD	X-linked chronic granulomatous disease
XPA:	xeroderma pigmentosum complementation group A
XPE:	xeroderma pigmentosum complementation group E

## Units of Measurement

### *Area*

cm<sup>2</sup>: square centimeter

### *Concentration*

g/L: grams per liter  
mg/dL: milligrams per deciliter  
mg/kg b.w.: milligrams per kilogram body weight  
mg/L: milligrams per liter  
mg/m<sup>3</sup>: milligrams per meter cubed  
mg%: milligram percent (milligrams per deciliter)  
mol/L: moles per liter  
mol/L: moles per liter  
ng/g: nanograms/gram  
ppm: parts per million  
ppt: parts per trillion  
wt%: weight percent  
μM: micromolar  
μmol/L: micromoles per liter  
μg/g: micrograms per gram  
μg/kg: micrograms per kilogram  
μg/L: micrograms per liter  
μg/m<sup>3</sup>: micrograms per meter cubed

### *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 <sup>3</sup> :	cubic meter
mL:	milliliter

## Glossary

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

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

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

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

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

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

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

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

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

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

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

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

**Diapedesis:** The movement of blood cells, particularly leukocytes, from the blood across blood vessel walls into tissues.



**Disposition:** The description of absorption, distribution, metabolism, and excretion of a chemical in the body.

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

**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 hyperrelease of inflammatory mediators in response to stimulation of T cells and macrophages by pathogens and immune insults.

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

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

**In silico:** An expression used to mean "performed on computer or via computer simulation".

**InChi key:** A 27-character compacted version of the InChI (IUPAC [International Union of Pure and Applied Chemistry] International Chemical Identifier) intended for Internet and database searching and indexing.

**Leishmaniasis:** A parasitic disease that is found in parts of the tropics, 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 (dec). The temperature is rounded off to the nearest °C.

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

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

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

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

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

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

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

**Mucocilliary transport:** The process by which cilia move a thin film of mucus from the upper and lower respiratory tracts towards the digestive tract. Particles of dust and microorganisms are trapped on the mucus and thereby removed from the respiratory tract.

**Mutations:** A change in the structure of a gene, resulting from the alteration of single base units in DNA, or the deletion, insertion, or rearrangement of larger sections of genes or chromosomes. The genetic variant can be transmitted to subsequent generations.

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

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

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

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

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

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

**Octanol/water partition coefficient (log *K<sub>ow</sub>*):** A measure of the equilibrium concentration of a compound between octanol and water.

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

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

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

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

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

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

**Primary mineral:** In an igneous rock, any mineral that is formed during the original solidification (i.e., crystallization) of the rock. Primary minerals include both the essential

minerals used to assign a classification name to the rock and the accessory minerals present in lesser abundance.

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

***P*<sub>trend</sub>:** Level of statistical significance of a change over time in a group selected to represent a larger population.

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

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

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

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

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

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

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

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

**Spot test:** Qualitative assay in which a small amount of test chemical is added directly to a selective agar medium plate seeded with the test organism, e.g., *Salmonella*. As the chemical diffuses into the agar, a concentration gradient is formed. A mutagenic chemical will give rise to

a ring of revertant colonies surrounding the area where the chemical was applied; if the chemical is toxic, a zone of growth inhibition will also be observed.

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

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

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

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

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

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

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

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

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

**This Page Intentionally Left Blank**



# National Toxicology Program

U.S. Department of Health and Human Services

## **Draft Report on Carcinogens Monograph on Antimony Trioxide**

### **Draft Substance Profile**

November 29, 2017

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

*This information is distributed solely for the purpose of pre-dissemination peer review under applicable information quality guidelines. It has not been formally distributed by the National Toxicology Program. It does not represent and should not be construed to represent any NTP determination or policy.*

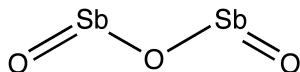
**This Page Intentionally Left Blank**



## Antimony Trioxide

**CAS No. 1309-64-44**

Reasonably anticipated to be a human carcinogen<sup>1</sup>.



### Carcinogenicity

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

#### **Cancer Studies in Experimental Animals**

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

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

---

<sup>1</sup>NTP preliminary listing recommendation proposed for the RoC.

Exposure of mice to antimony trioxide caused statistically significant increases in the incidences of benign lung tumors (alveolar/bronchiolar adenoma) in females, malignant lung tumors (alveolar/bronchiolar carcinoma) in males and females, and combined benign and malignant lung tumors (alveolar/bronchiolar adenoma and carcinoma) in females (NTP 2017).

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

	Rat		Mouse	
	Malignant	Combined	Malignant	Combined
Lung	↑F	*M	↑M, ↑F	↑F
Adrenal gland	–	↑F	–	–
Skin	–	–	–	↑M
Lymphatic system	–	–	↑F	–

↑F = Significant increase in tumors in females.

↑M = Significant increase in tumors in males.

\* = Increase not statistically significant but considered exposure-related (NTP 2017).

– = No exposure-related increase in tumors.

### ***Mechanisms of Carcinogenesis and Other Relevant Data***

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

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

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

Antimony trioxide causes damages in DNA, chromosome, and chromatid in experimental animals and/or cultured cells, although antimony trioxide does not cause mutations in classical bacterial tests except under very specific conditions. In mice exposed to antimony trioxide by inhalation, lung tissue showed increased DNA damage, and red blood cells showed increased

micronucleus formation, indicating chromosomal instability (NTP 2017). Increased chromosomal aberrations, micronucleus, and sister chromatid exchange were seen after antimony trioxide exposure in cultured cells. The genotoxicity could be the result of oxidative stress, decreased DNA repair, or the combination of both.

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

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

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

### **Cancer Studies in Humans**

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

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

### **Properties**

Antimony trioxide is the oxide of trivalent (+3) antimony, and it occurs naturally as well as from human activities. Antimony exists in four main oxidation states: -3, 0, +3, and +5. The most

common in environmental, biological, and geochemical systems are Sb(III) (the trivalent form) and Sb(V) (the pentavalent form). In nature, antimony trioxide ( $\text{Sb}_2\text{O}_3$ ) exists in minerals such as valentinite and senarmontite (ATSDR 2017, Roper *et al.* 2012). Humans purposely oxidize elemental antimony to produce antimony trioxide for various industrial uses. Other forms of antimony can also transform into antimony trioxide during the life cycles of products containing antimony. For instance, at high temperature (e.g., during incineration, combustion, or use of the brakes in vehicles), other forms of antimony can be oxidized and give rise to antimony trioxide.

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

Property	Information
Molecular weight	291.5 <sup>a</sup>
Specific gravity, at 24°C	5.9 <sup>b</sup>
Melting point	655°C <sup>b</sup>
Boiling point	1425°C <sup>b</sup>
Water solubility, at 22.2°C	[3.3 x 10 <sup>-4</sup> ] g/100 mL <sup>b,c</sup>
Vapor pressure, at 574°C	1 mm Hg <sup>b</sup>

Sources: <sup>a</sup>ChemIDplus 2017; <sup>b</sup>PubChem 2017, <sup>c</sup>IPCS 2017.

<sup>d</sup>Reported as 0.0033 g/L; brackets denote conversion of units.

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

## Use

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

materials. An additional minor use of antimony trioxide is to reduce the amount of hexavalent chromium used in cement.

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

## Production

Antimony trioxide is produced primarily by re-volatilization of crude antimony trioxide or by oxidation of antimony metal (EU 2008). The only current domestic producer of primary antimony metal and oxide identified was a company in Montana that used imported feedstock (USGS 2017); no marketable antimony has been mined in the United States since 2015 (USGS 2017). The production of antimony trioxide in 2015 was reported to be between 1 million and 10 million pounds (EPA 2017). The most recent U.S. mine production was in Nevada in 2013 and 2014, when about 800 tons of stibnite ( $Sb_2S_3$ ), 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 2017).

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

## Exposure

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

### Sources of antimony trioxide and the final forms of antimony (Sb<sub>2</sub>O<sub>3</sub> and others) to which people are exposed

Source of antimony trioxide	Exposure route	Expected form of antimony exposure
Sb <sub>2</sub> O <sub>3</sub> production: Occupational	Inhalation of Sb <sub>2</sub> O <sub>3</sub>	Sb <sub>2</sub> O <sub>3</sub>
	Dermal exposure	Sb <sub>2</sub> O <sub>3</sub>
Environmental antimony trioxide (Sb <sub>2</sub> O <sub>3</sub> ): Sb <sub>2</sub> O <sub>3</sub> and some non-Sb <sub>2</sub> O <sub>3</sub> releasing sources	Inhalation of Sb <sub>2</sub> O <sub>3</sub>	Sb <sub>2</sub> O <sub>3</sub>
	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 <sub>2</sub> O <sub>3</sub> in flame retardant: Occupational and general population exposure	Inhalation (from breathing indoor air in the workplace and home from containing house dust)	Mainly Sb <sub>2</sub> O <sub>3</sub>
	Dermal (workplace and from sitting on flame-retardant-treated upholstery)	Sb ions
	Ingestion (from mouthing flame-retardant-treated toys)	Sb ions
Sb <sub>2</sub> O <sub>3</sub> in PET: Occupational and consumer products	Inhalation: Workers in PET production	Sb <sub>2</sub> O <sub>3</sub>
	Inhalation: Workers in downstream PET operations	Sb ions
	Ingestion (from drinking liquid in PET bottles)	Sb ions
Sb <sub>2</sub> O <sub>3</sub> glass, paint and other uses:	Inhalation and dermal: Occupational	Sb <sub>2</sub> O <sub>3</sub> and Sb ions (depending on process step)

Sources: ATSDR 2017, EU 2008.

### Occupational Exposure

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

The highest occupational exposure to antimony trioxide in the United States, exceeding current regulatory levels by at least tenfold, occurred during smelting and refining operations and production of antimony trioxide in the 1970s and 1980s (antimony air levels ranged from 50 to over 5,000 µg/m<sup>3</sup>) (Donaldson 1976). Antimony is no longer mined in the United States, although three companies still produce antimony trioxide and twelve companies import it (EPA 2012). Global data collected since the 1980s suggest that the highest exposure to antimony

trioxide occurs during production of antimony trioxide; mean exposure at an antimony trioxide manufacturing facility was  $766 \mu\text{g}/\text{m}^3$  (ATSDR 2017), and worst-case exposure was estimated at  $790 \mu\text{g}/\text{m}^3$  (EU 2008). The next-highest exposures have been reported for the flame-retardant industry, at up to  $200 \mu\text{g}/\text{m}^3$  (ATSDR 1992), with worst-case exposure estimated at  $570 \mu\text{g}/\text{m}^3$  (EU 2008). Lower exposures occur during the use of antimony trioxide in the PET industries (with an estimated worst-case exposure of  $26 \mu\text{g}/\text{m}^3$ ) and glass industries (1980s measurements were 40 to  $840 \mu\text{g}/\text{m}^3$ , Lüdersdorff *et al.* (1987); estimated worst-case exposure is  $15 \mu\text{g}/\text{m}^3$  (EU 2008). Because other forms of antimony can be oxidized to antimony trioxide, workers in industries using other forms of antimony as raw material can also be exposed to antimony trioxide. For example, when antimonial lead in automobile batteries (antimony makes up as much as 2% of the battery's total weight) is recycled, the metals are frequently oxidized and produce antimony(III) trioxide (Grund *et al.* 2006, Dupont *et al.* 2016). The table above provides information on the form of antimony in these different industries.

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

### **Exposure of the General Population**

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

Members of the general population are exposed to antimony trioxide primarily by breathing contaminated indoor and outdoor air. In 2010, EPA estimated from Toxics Release Inventory data that approximately 11,635 lb of antimony were released into the air from 273 U.S. facilities that likely produced, processed, or used antimony trioxide-containing flame retardants (EPA 2014). Antimony concentrations in outdoor air are highest near facilities that release antimony trioxide into the air, such as mines and smelting operations; levels reported in the 1970s ranged from 0.146 to  $300,000 \mu\text{g}/\text{m}^3$ . People can also be exposed to antimony trioxide released into the air by oxidation of various forms of antimony, such as antimony trisulfide in brake pads oxidized during braking of automobiles, burning of coal and petroleum, and incineration of waste containing antimony. Levels of antimony in the air of U.S. cities (not associated with specific sources) are low ( $0.00037$  to  $0.002 \mu\text{g}/\text{m}^3$  for total suspended particulates).

Soil, water, drinking water and food are not major environmental sources of exposure to antimony trioxide, because it occurs at low concentrations. Environmental exposure is most likely to other forms of antimony, because antimony trioxide is converted to different forms in these media. Antimony trioxide in solution produces the trivalent antimony ion, which hydrolyzes to either the neutral trivalent species antimony (III) hydroxide,  $\text{Sb}(\text{OH})_3$ , or the charged pentavalent species (the antimonate ion),  $\text{Sb}(\text{OH})_6^-$  (EU 2008). Exposure to antimony in

the soil is expected to be minimal because of antimony's low solubility and mobility (EPA 2014, Li *et al.* 2014). Low levels of antimony have been found in U.S. groundwater (at a median concentration of less than 1 µg/L), drinking water (at concentrations ranging from 0.02 to 9.6 µg/L) (ATSDR 2017), and food (at concentrations ranging from not detected to 1.7 µg/g of dry weight) (Belzile *et al.* 2011).

Consumers are potentially exposed to antimony from consumer products as a result of the use of antimony trioxide as a flame retardant or in PET containers. Exposure of the general population to antimony trioxide from consumer products is generally by inhalation of dust from these products; the estimated worst-case daily exposure to antimony trioxide from inhalation of house dust is 60 µg/g of dust and 0.0032 µg/m<sup>3</sup> of air (EU 2008). Exposure is likely higher for children, especially infants, because of their direct contact with carpet material containing antimony trioxide as a fire retardant while crawling and their mouthing of other fabrics containing fire retardants or toys with antimony-containing paint or plastics; the estimated worst-case daily exposure from this source is 0.6 µg/kg of body weight (EU 2008). (See Table above for the route of exposure and most likely form of antimony.)

## Regulations

### **Consumer Product Safety Commission**

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

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

### **Department of Transportation (DOT)**

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

### **Environmental Protection Agency (EPA)**

#### *Clean Air Act*

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

#### *Clean Water Act*

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

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

Antimony trioxide and other antimony compounds as specified by EPA are designated as hazardous substances.



*Comprehensive Environmental Response, Compensation, and Liability Act*

Reportable quantity (RQ) = 5,000 lb for elemental antimony;  
= 1,000 lb for antimony and other antimony compounds

as specified by EPA.

*Emergency Planning and Community Right-To-Know Act*

*Toxics Release Inventory:* Elemental antimony and antimony compounds are listed substances subject to reporting requirements.

*Resource Conservation and Recovery Act*

*Listed Hazardous Waste:* Waste codes for which the listing is based wholly or partly on the presence of antimony or its compounds = K021, K161, K176, K177.

Elemental antimony and antimony compounds are listed as hazardous constituents of waste.

*Safe Drinking Water Act*

Maximum contaminant level (MCL) = 0.006 mg/L for elemental antimony.

***Food and Drug Administration (FDA)***

Test systems designed to measure antimony in urine, blood, vomitus, and stomach contents in the diagnosis and treatment of antimony poisoning are designated as Class I medical devices requiring a premarketing application for FDA clearance to market.

Maximum permissible level of elemental antimony in bottled water = 0.006 mg/L.

Antimony (as Sb) content of color additive mixtures for food use made with titanium dioxide may not exceed 2 parts per million.

***Occupational Safety and Health Administration (OSHA)***

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

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

**Guidelines*****American Conference of Governmental Industrial Hygienists (ACGIH)***

Threshold limit value – time-weighted average (TLV-TWA) = 0.5 mg/m<sup>3</sup> for elemental antimony and compounds (as Sb).<sup>2</sup>

---

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

Exposure to antimony trioxide by all routes should be carefully controlled to levels as low as possible.

**Environmental Protection Agency (EPA)**

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

Regional Screening Levels (formerly Preliminary Remediation Goals):

Residential soil = 3.1 mg/kg for elemental antimony;  
= 28,000 mg/kg for antimony trioxide.

Industrial soil = 47 mg/kg for elemental antimony.

Residential air = 0.021 µg/m<sup>3</sup> for antimony trioxide.

Industrial air = 0.088 µg/m<sup>3</sup> for antimony trioxide.

Tapwater = 0.78 µg/L for elemental antimony.

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

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

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

**References**

ATSDR. 1992. *Toxicological Profile for Antimony and Compounds*. Atlanta, GA: Agency for Toxic Substances and Disease Registry. 160 pp.

ATSDR. 2017. *Draft Toxicological Profile for Antimony and Compounds*. Atlanta, GA: Agency for Toxic Substances and Disease Registry. 328 pp.

Belova A, Greco SL, Riederer AM, Olsho LE, Corrales MA. 2013. A method to screen U.S. environmental biomonitoring data for race/ethnicity and income-related disparity. *Environ Health* 12: 114.

Belzile N, Chen YW, Filella M. 2011. Human exposure to antimony: I. Sources and intake. *Crit Rev Environ Science Tech* 41(14): 1309-1373.

ChemIDplus. 2017. *ChemIDplus Advanced*. National Library of Medicine. <http://chem.sis.nlm.nih.gov/chemidplus/chemidheavy.jsp> and select Registry Number and search on CAS number. Accessed on 5/22/17.

Donaldson H. 1976. Industrial Hygiene Survey of Texas Smelting and Refining Division of National Lead Industries, Laredo, Texas. Cincinnati, OH: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health.

Dupont D, Arnout S, Jones PT, Binnemans K. 2016. Antimony recovery from end-of-life products and industrial process residues: A critical review. *J Sustain Metall* 2: 79-103.

- ECHA. 2017. *Diantimony pentoxide*. European Chemicals Agency. <https://echa.europa.eu/registration-dossier/-/registered-dossier/16264/7/2/2>. Accessed on 10/3/17.
- EPA. 2012. *Chemical Data Reporting*. [https://java.epa.gov/oppt\\_chemical\\_search/](https://java.epa.gov/oppt_chemical_search/) and search for antimony. Accessed on 3/28/16.
- EPA. 2014. *TSCA Work Plan Chemical Risk Assessment. Antimony Trioxide*. EPA Document # 740-Z1-4001. U.S. Environmental Protection Agency. 87 pp.
- EPA. 2017. *ChemView*. U.S. Environmental Protection Agency. <https://java.epa.gov/chemview> and search by CAS number. Accessed on 2/22/17.
- EU. 2008. *European Union Risk Assessment Report. Diantimony Trioxide*. Luxembourg: European Communities. 556 pp.
- Gonzales FA, Jones RR, Deardorff J, Windham GC, Hiatt RA, Kushi LH. 2016. Neighborhood deprivation, race/ethnicity, and urinary metal concentrations among young girls in California. *Environ Int* 91: 29-39.
- Groth DH, Stettler LE, Burg JR, Busey WM, Grant GC, Wong L. 1986. Carcinogenic effects of antimony trioxide and antimony ore concentrate in rats. *J Toxicol Environ Health* 18(4): 607-626.
- Grund SC, Hanusch K, Breunig HJ, Wolf HU. 2006. Antimony and Antimony Compounds. Ullmann's Encyclopedia of Industrial Chemistry. [http://onlinelibrary.wiley.com/doi/10.1002/14356007.a03\\_055.pub2/full](http://onlinelibrary.wiley.com/doi/10.1002/14356007.a03_055.pub2/full). Accessed on 11/28/17.
- Guo J, Su L, Zhao X, Xu Z, Chen G. 2016. Relationships between urinary antimony levels and both mortalities and prevalence of cancers and heart diseases in general US population, NHANES 1999-2010. *Sci Total Environ* 571: 452-460.
- HSDB. 2013. *Hazardous Substances Data Bank: Antimony Trioxide*. National Library of Medicine. Updated on 3/8/13. <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB> and search on CAS number or compound name. Accessed on 5/19/17.
- IPCS. 2017. *Antimony trioxide*. International Programme on Chemical Safety. <http://www.inchem.org/documents/icsc/icsc/eics0012.htm>. Accessed on 10/26/17.
- Jones RD. 1994. Survey of antimony workers: mortality 1961-1992. *Occup Environ Med* 51(11): 772-776.
- Jones SR, Atkin P, Holroyd C, Lutman E, Batlle JV, Wakeford R, Walker P. 2007. Lung cancer mortality at a UK tin smelter. *Occup Med (Lond)* 57(4): 238-245.
- Li J, Wei Y, Zhao L, Zhang J, Shangguan Y, Li F, Hou H. 2014. Bioaccessibility of antimony and arsenic in highly polluted soils of the mine area and health risk assessment associated with oral ingestion exposure. *Ecotoxicol Environ Saf* 110: 308-315.
- Lovly C, Horn L, Pao W. 2015. *EGFR in Non-Small Cell Lung Cancer (NSCLC)*. My Cancer Genome. Updated on 6/18/15. <https://www.mycancergenome.org/content/disease/lung-cancer/egfr/>. Accessed on 10/26/17.

- Lüdersdorf R, Fuchs A, Mayer P, Skulsuksai G, Schäcke G. 1987. Biological assessment of exposure to antimony and lead in the glass-producing industry. *Int Arch Occup Environ Health* 59(5): 469-474.
- Newton PE, Bolte HF, Daly IW, Pillsbury BD, Terrill JB, Drew RT, Ben-Dyke R, Sheldon AW, Rubin LF. 1994. Subchronic and chronic inhalation toxicity of antimony trioxide in the rat. *Fundam Appl Toxicol* 22(4): 561-576.
- NTP. 2016. *Peer Review Draft. Technical Report on the Toxicology and Carcinogenesis Studies of Antimony Trioxide (CAS No. 1309-64-4) in Wistar Han [Crl:Wi (Han)] Rats and B6C3F1/N Mice (Inhalation Studies)*. NTP TR 590. National Toxicology Program. 303 pp.
- NTP. 2017. *Draft Toxicology and Carcinogenesis Studies of Antimony Trioxide (CAS No. 1309-64-4) in Wistar Han [Crl:WI (Han)] Rats and B6C3F1/N Mice (Inhalation Studies)*. NTP TR 590. National Toxicology Program, National Institutes of Health. 303 pp.
- PubChem. 2017. *PubChem Compound Database*. National Library of Medicine. <http://pubchem.ncbi.nlm.nih.gov/> and search on antimony. Accessed on 6/29/17.
- Quiroz W, De Gregori I, Basilio P, Bravo M, Pinto M, Lobos MG. 2009. Heavy weight vehicle traffic and its relationship with antimony content in human blood. *J Environ Monit* 11(5): 1051-1055.
- Roper AJ, Williams PA, Filella M. 2012. Secondary antimony minerals: Phases that control the dispersion of antimony in the supergene zone. *Chem Erde - Geochem* 72: 9-14.
- Schnorr TM, Steenland K, Thun MJ, Rinsky RA. 1995. Mortality in a cohort of antimony smelter workers. *Am J Ind Med* 27(5): 759-770.
- Scinicariello F, Buser MC. 2016. Urinary antimony and leukocyte telomere length: An analysis of NHANES 1999-2002. *Environ Res* 150: 513-518.
- Shiue I, Hristova K. 2014. Higher urinary heavy metal, phthalate and arsenic concentrations accounted for 3-19% of the population attributable risk for high blood pressure: US NHANES, 2009-2012. *Hypertens Res* 37(12): 1075-1081.
- Tyrrell J, Melzer D, Henley W, Galloway TS, Osborne NJ. 2013. Associations between socioeconomic status and environmental toxicant concentrations in adults in the USA: NHANES 2001-2010. *Environ Int* 59: 328-335.
- USGS. 2017. *Mineral Commodity Summaries, January 2017. Antimony*. U.S. Department of Interior, U.S. Geological Survey. 2 pp.
- Watt WD. 1983. *Chronic Inhalation Toxicity of Antimony Trioxide: Validation of the Threshold Limit Value*. Detroit, MI: Wayne State University, PhD Thesis.
- Wingren G, Axelson O. 1993. Epidemiologic studies of occupational cancer as related to complex mixtures of trace elements in the art glass industry. *Scand J Work Environ Health* 19 Suppl 1: 95-100.
- Zheng G, Zhong H, Guo Z, Wu Z, Zhang H, Wang C, Zhou Y, Zuo Z. 2014. Levels of heavy metals and trace elements in umbilical cord blood and the risk of adverse pregnancy outcomes: a population-based study. *Biol Trace Elem Res* 160(3): 437-444.