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

Revised Draft:
Report on Carcinogens Monograph on Antimony Trioxide

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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

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 14th Edition (2016), 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
Primary evidence		
Experimental animal studies	Antimony(III) trioxide	All reported neoplasms
Human studies	Antimony(III) trioxide (primarily) and other antimony(III) compounds	Lung and stomach cancer
Supporting evidence		
Human studies	Antimony(III) compounds	Biological effects related to carcinogenicity or toxicity
Experimental animal studies	Antimony(III) compounds	Carcinogenicity and biological effects related to carcinogenicity or toxicity
In vitro studies	Antimony(III) compounds	Biological effects related to carcinogenicity or toxicity

The monograph also assesses exposure information (summarized in 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 (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?

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 were 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 other inorganic trivalent antimony compounds to help inform the cancer evaluation of antimony(III) trioxide and whether there is sufficient information to identify the antimony species ultimately responsible for carcingenicity.

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

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ILS = Integrated Laboratory Systems, Inc. (Support provided through subcontract number 16EDBO0078 with ICF).
DNTP = Division of National Toxicology Program.
NIEHS = National Institute of Environmental Health Sciences.

Peer Review

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

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

1. Comment on whether the Draft RoC Monograph on Antimony Trioxide is technically correct, clearly stated, and objectively presented.
2. Provide opinion on whether there is currently or was in the past significant human exposure to antimony trioxide.

The Panel was asked to vote on the following questions:

1. Whether the scientific evidence supports the NTP's conclusions on the level of evidence for carcinogenicity from cancer studies in animals for antimony trioxide.
2. Whether the scientific evidence supports the NTP's preliminary policy decision on the listing status of antimony trioxide.

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

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1 Chemical identification and properties

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

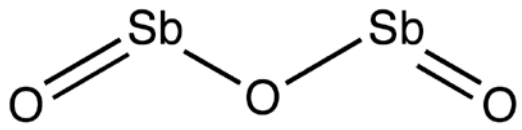


Table 1-1. Physical and chemical properties for antimony(III) trioxide

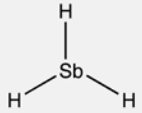
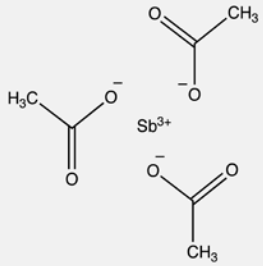
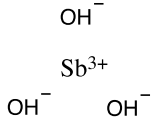
Property	Information
Chemical formula	Sb_2O_3[a]
CAS No.	1309-64-4[b]
InChi key	GHPGOEFPKIHBNM-UHFFFAOYSA-N[c]
Molecular weight	291.5[a]
% Antimony by weight	83.6
Antimony charge	+3[a]
Specific gravity, at 24°C	5.9[c]
Melting point	655°C[c]
Boiling point	1425°C[c]
Water solubility, at 22.2°C	[3.3 x 10^{-4}] g/100 mL[d,e]
Vapor pressure, at 574°C	1 mm Hg[c]

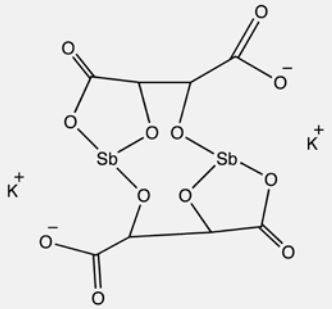
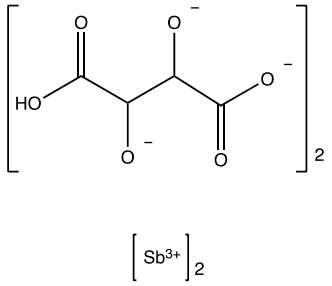
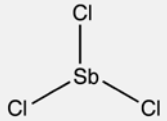
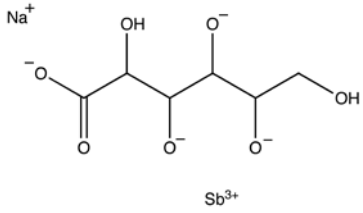
Sources: [a]ChemIDplus 2017, [b] EPA 2017b, [c]PubChem 2017, [d]IPCS 2017.

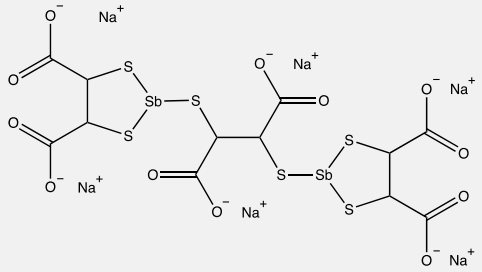
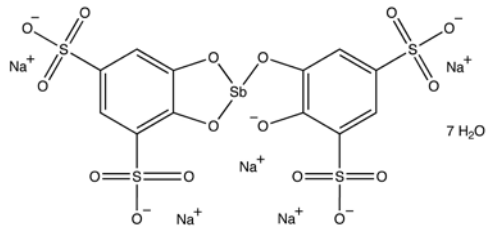
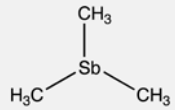
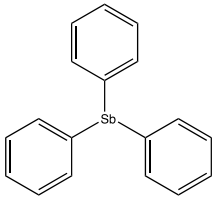
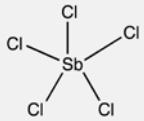
[e]Reported as 0.0033 g/L; brackets denote conversion of units.

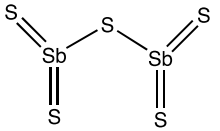
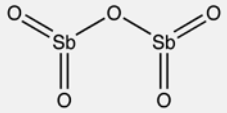
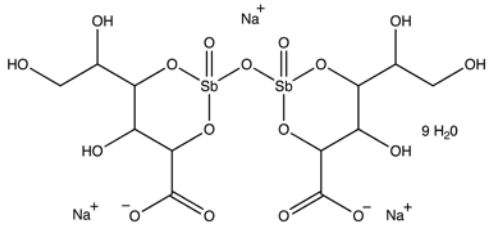
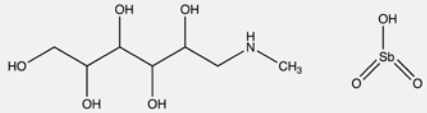
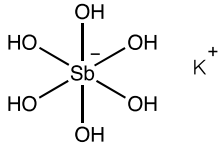
Physical and chemical properties for other antimony compounds discussed in this monograph are listed in Table 1-2 together with their structures; the compounds listed are those with carcinogenicity (Section 4 and 5), mechanistic (Section 6), or disposition (Section 3) data. In addition to elemental antimony (valence = 0), most antimony compounds have valences of either +3 (11 compounds) or +5 (6 compounds) although one compound with valence -3 is also included in the table. Compounds with +3 valence are likely to share more similarity with antimony(III) oxide but as discussed in Sections 2 and 3, interconversion between antimony(III)

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

Name	CAS No. (InChI Key)	Formula	Chemical structure	Molecular weight (% Sb by weight)	Density or specific gravity	Solubility in water (g/100 mL), descriptive level[c]
Valence = 0						
Antimony (elemental)	7440-36-0[a] (WATWJIUSRGPENY-UHFFFAOYSA-N[a])	Sb[a]	Sb	121.8[a] (100.0[a])	6.68[a, b]	Insoluble[a]
Valence = -3						
Stibine	7803-52-3[a] (OUULRIDHGPHMNQ-UHFFFAOYSA-N[a])	SbH_3[a]		124.8[a] (97.6[a])	2.26[a, d]	$[4.1 \times 10^{-1}]$[a,e] Slightly soluble
Valence = +3						
Antimony acetate; acetic acid antimony (+3) salt	6923-52-0[a] (JVLRYPRBKSMEBF-UHFFFAOYSA-K[a])	$C_6H_9O_6Sb$[a]		298.9[a] (40.7[a])	–	–
Antimony hydroxide	39349-74-1[f] (SZOADBKOANDULT-UHFFFAOYSA-K[a])	H_3O_3Sb[a]		172.8[a] (70.5[a])	–	–

Name	CAS No. (InChI Key)	Formula	Chemical structure	Molecular weight (% Sb by weight)	Density or specific gravity	Solubility in water (g/100 mL), descriptive level[c]
Antimony potassium tartrate[g]	28300-74-5[a] (WBTCZEPSIIFINA-MSFWTACDSA-J[a])	$C_8H_4K_2O_{12}Sb_2$[g]		667.8[a] (36.5[a])	2.6[a]	$[8.3 \times 10^0]$[a,h] Soluble
Antimony tartrate[i]	12544-35-3[f] (JFVMOLRNQCNLCHI-WZZCOQPSA-J[f])	$C_8H_4O_{12}Sb_2$[f]		535.6[f] (45.5[f])	–	$[2.8 \times 10^2]$[j] Very soluble
Antimony trichloride	10025-91-9[a] (FAPDDOBMIUGHIN-UHFFFAOYSA-K[a])	$SbCl_3$[a]		228.1[a] (53.4[a])	3.14[a,k]	$[10 \times 10^0]$[a,l] Soluble
Sodium antimony(III) gluconate (antimony(III) sodium gluconate)	12550-17-3[f] (JEKOQEIHGHQVEI-ZBHRUSISSA-M[f])	$C_6H_8NaO_7Sb$[f]		336.9[f] (36.2[f])	–	–

Name	CAS No. (InChI Key)	Formula	Chemical structure	Molecular weight (% Sb by weight)	Density or specific gravity	Solubility in water (g/100 mL), descriptive level[c]
Sodium antimony 2,3-mesodimercaptosuccinate (active ingredient in Astiban)	3064-61-7[a] (AOGOCZMBIYQOFE-UHFFFAOYSA-B[a])	$C_{12}H_6Na_6O_{12}S_6Sb_2$[a]		916.0[a] (26.6[a])	–	–
Stibophen[m]	15489-16-4[f] (ZDDUXABBRATYFS-UHFFFAOYSA-F[f])	$C_{12}H_4O_{16}S_4Sb\bullet 7H_2O.5Na$[f]		895.2[f] (13.6[f])	–	–
Trimethylstibine	594-10-5[a] (PORFVJURJXKREL-UHFFFAOYSA-N[a])	C_3H_9Sb[a]		166.9[a] (73.0[a])	–	–
Triphenylstibine	603-36-1[a] (HVYVMSPIJIWUNA-UHFFFAOYSA-N[a])	$C_{18}H_{15}Sb$[a]		353.1[a] (34.5[a])	–	$[4.3 \times 10^{-6}]$[f,n] Insoluble
Valence = +5						
Antimony pentachloride	7647-18-9[a] (VMPVEPPRYRXYNP-UHFFFAOYSA-I[a])	$SbCl_5$[a]		299.0[a] (40.7[a])	2.35[a, k]	–

Name	CAS No. (InChI Key)	Formula	Chemical structure	Molecular weight (% Sb by weight)	Density or specific gravity	Solubility in water (g/100 mL), descriptive level[c]
Antimony pentasulfide	1315-04-4[a] (PPKVREKQVQREQD-UHFFFAOYSA-N[a])	S_5Sb_2[a]		403.8[a] (60.3[a])	–	[9.9×10^{-6}][o] Insoluble
Antimony pentoxide	1314-60-9[f] (LJCFOYOSGPHIOO-UHFFFAOYSA-N[f])	Sb_2O_5[f]		323.5[f] (75.3[f])	–	[4.3×10^{-6}][p] Insoluble
Sodium stibogluconate (active ingredient in Pentostam)	16037-91-5[f] (CUEDNFKBTFCOSV-UZVLBLASSA-L[f])	$C_{12}H_{20}O_{17}Sb_2 \cdot 3Na \cdot 9H_2O$[f]		908.9[f] (26.8[f])	–	–
Meglumine antimoniate	133-51-7[a] (XOGYVDXPYVPAAQ-SESJOKTNSA-M[a])	$C_7H_{18}NO_8Sb$[a]		366.0[a] (33.3[a])	–	–
Potassium hexahydroxy antimonate	12208-13-8[q] (IAYJQRROUBIPRX-UHFFFAOYSA-H[f])	H_6KO_6Sb[q]		262.9[q] (46.3[q])	–	–

– = No data found, CAS = Chemical Abstracts Service, InChI = IUPAC International Chemical Identifier.
[a] PubChem 2017.
[b] At 77ºF.
[c] Descriptive levels are converted from solubility in water (Solubility of Things 2018).
[d] At -25ºC.
[e] Reported as 4.1 g/L at 0ºC in water. Brackets denote unit conversion.
[f] ChemIDplus 2017.
[g] Formula and structure shown are for anhydrous form of antimony potassium tartrate.
[h] Reported as 83,000 mg/L at 20ºC. Brackets denote unit conversion.
[i] Antimony tartrate ion. Felicetti *et al.* (1974a) reported starting solution as ^{124}Sb-tartrate complex.
[j] EPA CompTox Chemistry Dashboard 2017a. Reported as mean of 5.55 mol/L. Brackets denote unit conversion.

[k]At 68ºF.
[l]At 25ºC.
[m]The anhydrous form of Stibophen is $C_{12}H_4Na_5O_{16}S_4Sb$ (CAS number = 23940-36-5, molecular weight = 769.1 g/mol).
[n]Reported as 0.043 mg/L at 25ºC. Brackets denote unit conversion. Accessed 11/29/2017.
[o]EPA CompTox Chemistry Dashboard 2017a. Reported as 2.46×10^{-7} mol/L. Brackets denote unit conversion.
[p]EPA CompTox Chemistry Dashboard 2017a. Reported as 1.32×10^{-7} mol/L by EpiSuite 2017. Brackets denote unit conversion.
[q]ChemSpider 2017.

and antimony(V) occurs during manufacturing processes, in the environment, and *in vivo*. Both the +3 and +5 valence states include both inorganic antimony compounds, e.g., antimony(III) trisulfide and antimony(V) pentasulfide, and organic antimony compounds, primarily those used as anti-leishmanial drugs, such as sodium antimony 2,3-mesodimercaptosuccinate (the active ingredient in Astiban) and sodium stibogluconate(V) (the active ingredient in Pentostam).

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

	Percent (%) solubility in simulated human fluid after 24 hours of exposure				
Antimony compound	Gamble's solution[a] (pH = 7.4)	Phosphate-buffered saline[b] (pH = 7.4)	Artificial sweat[c] (pH = 6.5)	Artificial lysosomal fluid[d] (pH = 4.5)	Artificial gastric fluid[e] (pH = 1.6)
Antimony(III) trioxide	56.7	41.5	60.8	81.7	13.6
Antimony(V) pentoxide	32.5	29.2	60.8	71.4	94.3
Antimony(III) sulfide	3.9	8.5	3.6	5.1	4

Source: ECHA 2017.

[a] Gamble's solution mimics interstitial fluid within the deep lung under normal health conditions.

[b] Phosphate-buffered saline mimics the ionic strength of human blood serum.

[c] Artificial sweat mimics hypo-osmolar fluid excreted upon sweating.

[d] Artificial lysosomal fluid mimics intracellular conditions in lung cells during phagocytosis.

[e] Artificial gastric fluid mimics stomach acid.

1.2 Antimony speciation and variability of valence

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

Elemental antimony exists in four primary oxidation states; -3, 0, +3, and +5; Sb(III) (trivalent form) and Sb(V) (pentavalent form) are the most common in environmental, biological, and geochemical systems. Thermodynamic equilibrium calculations indicate that antimony(V) predominates in oxic systems, and antimony(III) predominates in anoxic systems. However, antimony(III) concentrations at higher than calculation-predicted values have been detected in oxic systems; similarly, higher than calculation-predicted antimony(V) concentrations have been detected in anoxic systems (Filella *et al.* 2002a). Both trivalent (III) and pentavalent (V) antimony ions hydrolyze readily. When any form of antimony dissolves in water, it exists as the hydroxide forms, $Sb(OH)_3$ (uncharged) or $Sb(OH)_6^-$ (charged) (Herath *et al.* 2017). Antimony(III) is present as the neutral species $Sb(OH)_3$ (or H_3SbO_3) for pH values from 2 to approximately 10 (Krupka and Serne 2002) and antimony(V) is present as the anion $Sb(OH)_6^-$ (or $H_2SbO_4^-$) for pH values from 2.7 to 10.4 (EU 2008, Herath *et al.* 2017). As shown in Figure 1-2, these forms are the major ones at physiologic pH around 7.4. Figure 1-2 also illustrates antimony speciation for antimony(III) and antimony(V) species over a pH range of 0 to 12. Positively charged species are reported to generally exist only under very acidic conditions (i.e., pH < 2) (Herath *et al.* 2017).

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

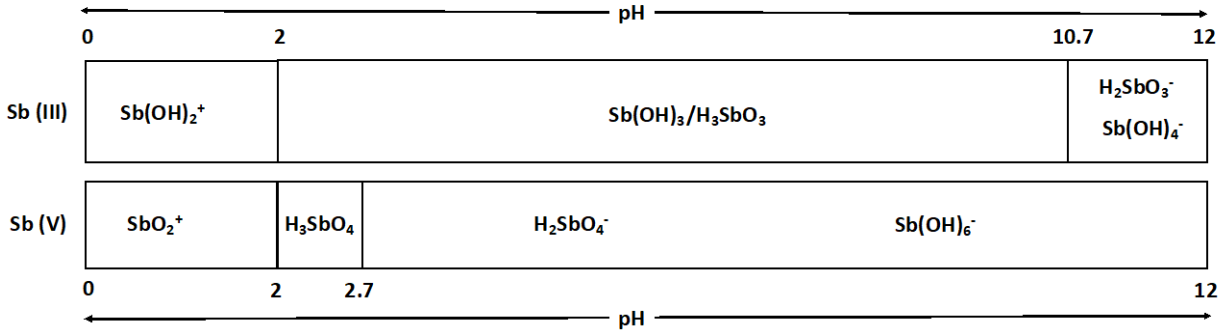


Figure 1-2. Antimony speciation for antimony(III) and antimony(V) species over a range of pH values

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

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 *et al.* 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 *et al.* 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 *et al.* 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 *et al.* 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 *et al.* 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, $Sb(OH)_3$.

2 Human Exposure

In the United States, antimony(III) trioxide (Sb_2O_3) is the most commercially significant form of processed antimony. In nature, Sb_2O_3 exists in minerals such as valentinite and senarmontite (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 antimony(III) trioxide is the focus of this section. However, evaluating exposure data specific to antimony(III) trioxide is complicated by the fact that antimony species can be interconverted in the environment and *in vivo*; thus, people can be exposed to antimony(III) trioxide from sources releasing other forms of antimony and to other forms of antimony from sources releasing antimony(III) trioxide. In addition, environmental and biomonitoring studies generally use methods that measure total elemental antimony (Sb) and not specific species of antimony. Data on exposure for specific antimony compounds are consequently limited. This section starts with antimony and antimony(III) trioxide consumption in the U.S. (Section 2.1), discusses exposure specifically to antimony(III) trioxide, and also briefly reviews exposure to other forms of inorganic antimony that might lead to exposure to antimony(III) trioxide.

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

2.1 Manufacturing processes, uses, and production-related information

2.1.1 Manufacturing processes

The lifecycle of antimony trioxide from raw material to consumer product is depicted in Figure 2-1. Antimony(III) trioxide for manufacturing processes may either be imported in that form (second box by the number 1 in Figure 2-1) or produced in the United States by oxidation of imported antimony metal (box 2 in Figure 2-1). Antimony trioxide is used to make various products and may change forms during the manufacturing of those products (see section 2.2.2) 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 2018), as no marketable antimony has been mined in the United States since 2015 (USGS 2018). The most recent U.S. mine production was in Nevada in 2013 and 2014, when about 800 tons of stibnite (Sb_2S_3), the principal antimony ore, was extracted. That mine has been on care-and-maintenance status (i.e., production has ceased but management for public health and safety continues) since 2015 (USGS 2018).

Antimony trioxide changes its chemical form during the formulation and processing stages for many products. The changes in chemical form for antimony are illustrated in Figure 2-1 by the grey shading in the boxes, which indicates the likelihood that antimony(III) trioxide is present at that stage of the process as described in the figure legend.

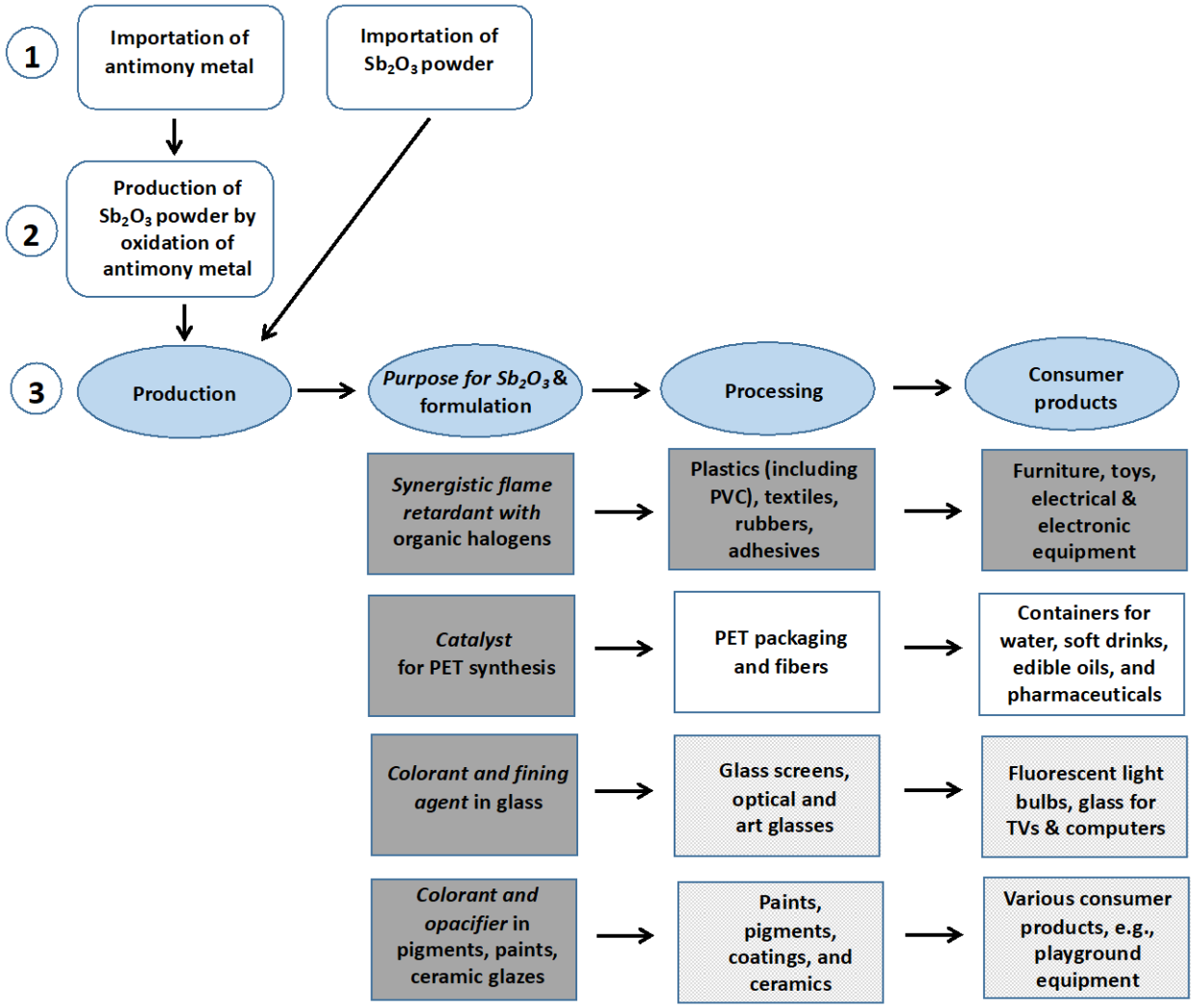


Figure 2-1. Antimony(III) trioxide used in manufacturing processes

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

2.1.2 Uses

Antimony(III) trioxide

The major industrial use of antimony(III) trioxide (EPA 2014, NTP 2017a) is as a synergist for halogenated flame retardants in plastics, rubber, and textiles, all of which are used in a wide variety of consumer products. Other uses include as a catalyst for polyethylene terephthalate (PET) production, and an additive in art and specialized glasses, pigments, paints, and ceramics.

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

PET production: Antimony(III) trioxide used as a catalyst for polyethylene terephthalate (PET) production in Japan and China has been shown to be present in the finished plastic as antimony(III) glycolate with antimony concentration ranging from below the detection limit to above 300 mg/kg in the PET bottles (Takahashi *et al.* 2008). While the major current use for PET plastic is in bottles for water and other beverages, often intended for single use and then disposal, the major use for recycled PET is as PET fibers for fleece fabrics for clothing, in soft toys, rugs, carpets, and upholstery, including in automobiles. Antimony is not generally removed from the PET to recycle antimony (Grund *et al.* 2011).

Specialty glass, paints, and pigments: Antimony(III) trioxide is also used in art and other specialty glasses as a fining agent to remove gaseous inclusions that could leave bubbles in the glass product. Antimony is also used in paints and pigments as a white pigment and an opacifier. The resulting pigments are used in a broad range of industries and consumer products such as plastics, coatings, enamels, ceramics, and building materials. During the production process of specialty glass and pigments, antimony(III) trioxide may be chemically transformed to antimony(V) pentoxide by oxidation, and the resulting antimony(V) form may either present as antimony(V) pentoxide in glass or be chemically bonded in a crystal matrix in pigments. Approximately 0.8% antimony is found in finished glass.

An additional minor use of antimony(III) trioxide is in cement to reduce chromium(VI) to chromium(III). However, only those individuals working with cement as a powder would likely be exposed to antimony(III) trioxide because of the intended chemical reaction, which will change its chemical form (without changing antimony's trivalent oxidation status) from Sb_2O_3 to the SbO_3^{3-} ion (antimonite) in the finished concrete (Mapei Group 2017).

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

shifting to sodium antimoniate(V) so that use of antimony(III) trioxide will likely decrease in the future.

Other notable uses for major antimony forms

Major uses of elemental antimony, i.e., the metal, are to make metal alloys, such as lead-based alloys used in lead-acid batteries, lead pipe, cable sheathing, and ammunition; other alloys are used in electrical equipment, and plumbing. Antimony compounds (e.g., antimony(V) pentoxide and sodium(III) antimonite) are used as synergists for flame retardant additives in plastics (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(III) diamyldithiocarbamate is used in lubricating compositions, such as grease, to provide extreme pressure protection (Hiza *et al.* 2006).

Medical uses of antimony compounds include as emetics (e.g., potassium antimonyl(III) tartrate or tartar emetic) (NTP 2017a) and to treat leishmaniasis (pentavalent antimonials, such as sodium stibogluconate(V)). However, the use of these drugs in the United States has declined. Pentavalent antimonials are no longer licensed for U.S. commercial use to treat leishmaniasis (CDC 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.

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

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

Antimony(III) trioxide accounts for 80% of total antimony use in the United States (EPA 2014, NTP 2017a). Reports under the U.S. Environmental Protection Agency's (EPA's) Chemical Data Reporting rule indicate that approximately 1 million to 10 million pounds of antimony(III) trioxide is produced in the United States (see Table 2-1); however, the actual consumption of antimony(III) trioxide is likely much higher. In 2017, U.S. imports for consumption were approximately 52.8 million pounds of antimony oxide (weight of antimony content) (USGS 2018). EPA (2014) reported that most (approximately 87%) of the roughly 70 million pounds (gross weight) of antimony(III) trioxide consumed in the United States each year between 2007

and 2011 was imported (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 2018). 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[a]	Antimony compound	Quantity (lb)[a]
68937-20-2	1,2-Ethanediol, reaction products with antimony(III) trioxide	28,926,800
7440-36-0	Antimony (elemental)	10,000,000–50,000,000
1309-64-4	Antimony(III) trioxide	1,000,000–10,000,000
1314-60-9	Antimony(V) pentoxide	1,000,000–10,000,000
15890-25-2	Antimony(III) diamyldithiocarbamate[b]	1,000,000–10,000,000

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

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

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

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

2.2 Occupational exposure

The highest exposures to antimony(III) trioxide and total antimony occur in the workplace including transportation workers exposed to antimony trioxide in the air. Historic data for the number of workers exposed to antimony were reported for the National Occupational Exposure Survey (NOES) conducted by the National Institute for Occupational Safety and Health (NIOSH) from 1981 to 1983, during which an estimated 209,773 male and female workers were potentially exposed to antimony(III) trioxide (CDC 2017c). 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 (measured personal breathing zone values), as total antimony, ranged from 0.2 $\mu g/m^3$ to 54,500 $\mu g/m^3$ across all facilities. Facilities with the highest antimony air concentrations were in the following industries: standard industrial classification (SIC) Code 2899, chemicals and chemical preparations, not elsewhere classified (this category would likely include antimony-containing flame retardants) (3.3 $\mu g/m^3$ to 54,500 $\mu g/m^3$); SIC Code 3341, secondary smelting and refining of nonferrous metals (this category would likely include antimonial lead refining) (1.8 $\mu g/m^3$ to 47,700 $\mu g/m^3$), and SIC Code 3339, primary smelting and refining of nonferrous metals (including antimony) (5 $\mu g/m^3$ to 18,500 $\mu g/m^3$). All of these industries are likely to involve exposure to antimony(III) trioxide as either a primary product or through oxidation of elemental antimony during smelting and refining processes; however, the levels most likely reflect other antimony compounds in addition to antimony trioxide.

Workers in the United States and other countries producing or using antimony(III) trioxide, as well as workers in occupations exposed to other antimony compounds, can be exposed to antimony(III) trioxide through inhalation of airborne solid dust or by skin contact resulting in increased excretion in the urine (see Table 2-3). The studies reported in Table 2-3 were identified primarily from the ATSDR (2017) draft toxicological profile for antimony and compounds and supplemented by literature searches. All results are reported from the primary publication cited.

Among industries using or producing antimony(III) trioxide, the highest levels (up to 5,000 to 6,000 $\mu g/m^3$, levels 10 times higher than the threshold limit value [TLV]), are found among smelters or antimony manufacturing industries (see Table 2-3). The European Union (EU) (2008) risk assessment report (RAR) for antimony trioxide (Sb_2O_3) considered metal smelting and refining to be one of the major anthropogenic sources of antimony release to the atmosphere. U.S. air monitoring data specific for antimony(III) trioxide industries come primarily from NIOSH walk-through surveys of a few smelters or antimony(III) trioxide companies conducted largely in the 1970s, which usually were conducted as part of health hazard evaluations (CDC 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).

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

Urinary excretion of antimony by exposed workers generally increases with the level of exposure, although relatively few studies have reported both exposure and urinary excretion for the same workers. A few studies that reported both parameters are summarized in Table 2-4 together with studies that reported air levels only. The current TLV for elemental antimony and antimony compounds in air is 500 $\mu g/m^3$ (ACGIH 2017) and levels above as well as below this value have been reported. Bailly *et al.* (1991) measured urine and air concentrations of total

antimony for workers manufacturing pentavalent antimony compounds (antimony(V) pentoxide and sodium antimoniate(V)) and reported a significant correlation ($r = 0.83$, $P < 0.0001$) between airborne antimony concentrations (log value) and both post-shift urinary antimony concentrations (log value) and an increase in urinary antimony concentrations during the work shift ($r = 0.86$, $P < 0.0001$). Air concentrations and pre-shift and post-shift urinary antimony levels are also reported in Table 2-3.

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

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

Exposure scenario (N)	Location[#]	Year of monitoring	Form of Sb used	Air Sb levels (as total Sb) (μg/m^3), mean ± standard deviation (range)	Urine Sb levels (as total Sb below, mean ± standard deviation (range)	Reference
Glass industry- batch bunker	Germany*	NR	Sb_2O_3			Lüdersdorf *et al.* 1987
Personal air (3)				< 50, 720, 840		
Stationary air (4)				40, 60, 70, 290		
Batch Mixer (45)					5.0 (1.5–15.7) μg/L	
Art glass production (10)	Italy*	NR	Sb_2O_3	NR	12.49 ± 13.68 (3.7–50) μg/L	Goi *et al.* 2003
Rubber company	**U.S.A. (Marysville, MI)**	**1979**	**Antimony oxide**			**Salisbury 1980**
Compounding area				**(100–150)**	**NR**	
Other Industries						
Lead battery production	Germany	NR				Kentner *et al.* 1995
Personal samples:						
Casters (7)			Sb_2O_3	4.5 (1.18–6.6)	3.9 (2.8–5.6) μg/g creatinine	
Formers (14)			SbH_3	12.4 (0.6–41.5)	15.2 (3.5–23.4) μg/g creatinine	
Lead-acid battery plant			**SbH_3**			
Area samples (10) (Jones and Gamble 1984)	**U.S.A.**	**NR**		**(ND[c]–2,500)**	**NR**	**Jones and Gamble 1984**
Area samples (1) (Young 1979a)	**U.S.A. (San Antonio, TX)**	**1978**			**7.0 μg/g creatinine**	**Young 1979a**
Area samples (1) (Young 1979b)	**U.S.A. (Dallas, TX)**	**1978**			**350 μg/g creatinine**	**Young 1979b**
Secondary lead smelter (reclaiming scrap batteries)	**U.S.A.**	**1979**	**NR**			**Craig *et al.* 1981**
Breathing zone (2 of 21 time-weighted averages (TWAs))				**37, 51**	**NR**	
Manufacture of pentavalent antimony compounds	Belgium*	NR	Sb_2O_5 Na_3SbO_4			Bailly *et al.* 1991
Personal samples:						
Wet process (26)				86 ± 78	12.3 ± 5.0 μg/g creatinine	
Dry process (14)				927 ± 985	110 ± 76 μg/g creatinine	
Refinery workers	United Kingdom*	NR				Smith *et al.* 1995

Exposure scenario (N)	Location[#]	Year of monitoring	Form of Sb used	Air Sb levels (as total Sb) (μg/m^3), mean ± standard deviation (range)	Urine Sb levels (as total Sb below, mean ± standard deviation (range)	Reference
Static and personal monitoring within the working areas of the refinery (NR)			NR	(< 10–80)	(0.08–32.6 μg/L urine)	
Chemical manufacturers (NR)			NR	NR	(0.1–36.1 μg/L)	
Battery manufacturers (NR)			NR	NR	(1.5–149.2 μg/L)	
Resinoid grinding wheel manufacture (NR)	**U.S.A.***	**NR**	**Sb_2S_3**	**~3,000**	**(800–9,600 μg/L)**	**Brieger *et al.* 1954**
Iron foundry (NR)	Belgium*	NR	NR	0.15	NR	Zhang *et al.* 1985

[#] U.S. locations are in bold.

* Location not specifically reported in publication, but likely location inferred from content of paper.

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

[b] BDL = below detection limit; level of detection reported as 0.3 μg/m^3, NR = not reported.

[c] ND = not detectable.

[d] All operators, beginning of shift (N = 39).

[e] All operators, end of shift (N = 39).

[f] BLQ = below lower limit of quantification.

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

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

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

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

Source: EU 2008.

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

[b]Job-specific typical exposure is equal to the median (50th percentile) exposure level.

[c]Job-specific (reasonable) worst-case exposure is equal to the 90th percentile exposure level.

[d]The body weight of the worker is 70 kg and the exposed dermal area is 2000 cm^2.

[e]Exposure levels for inhalation and dermal exposure during antimony(III) trioxide production were measured as Sb_2O_3 (inhalation) or as total Sb (dermal) with conversion to equivalent concentration of Sb_2O_3.

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

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

2.3 General population exposure

Evidence for exposure of the U.S. general population to antimony is provided by biomonitoring data showing its presence in urine, whole blood, and saliva. Data from the National Health and Nutrition Examination Survey (NHANES) indicate low level of exposure to antimony, with antimony (all forms of antimony) geometric means urine concentration of 0.132 μg/L for years 1999 to 2000 and 0.043 μg/L for years 2013 to 2014 (Table 2-5). Although the mean concentration (not considering the samples with antimony at below detection limit) appeared to be decreasing over time, this could reflect the use of more sensitive analytical methods, primarily inductively coupled plasma mass spectrometry (ICP-MS) in recent years, rather than an actual decrease in exposure, an explanation supported by reports of values close to the lower detection limits for the methods used (Filella *et al.* 2013a). On the other hand, Pang *et al.* (2016) (see Table 2-5) analyzing urine samples collected from 1998 to 2003 with a sensitive ICP-MS method

reported urine antimony concentrations of 0.1 μg/L or higher, suggesting the exposure was higher.

Based on analysis of NHANES data, higher urinary antimony levels were found in individuals with lower socioeconomic status, defined as either low income or living in economically deprived neighborhoods (Belova *et al.* 2013, 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, as well as for younger people (6 to 11 years old, and 12 to 19 years old) than 20 years and older in 1999 to 2000 data and in 2013 to 2014 data. Total antimony measured in urine as the elemental form can be from various forms of antimony, not just antimony(III) trioxide (see Table 2-5). Antimony concentrations in whole blood (Filella *et al.* 2013a, b, Whitworth *et al.* 2017) and saliva (Olmez *et al.* 1998) were available in only few samples, and the concentrations were much higher than that in urine.

Several studies have reported an association between biomonitoring data in the general population (e.g., urinary antimony, cord blood antimony) and adverse biological effects (Scinicariello and Buser 2016) or non-cancer endpoints, such as cardiovascular-related diseases (e.g., 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 and 95th percentile antimony levels in urine, blood, and saliva samples of U.S. populations

Sample	No. of individuals	Concentration (μg Sb/L) geometric mean with (95% confidence interval)	Concentration (μg Sb/L) 95th percentile with (95% confidence interval)	References
Urine				
Urine of general U.S. population in 1999–2000 (total)	**2,276**	**0.132 (0.120–0.145)**	**0.430 (0.390–0.470)**	NHANES (CDC 2017a)
6–11 years	316	0.176 (0.154–0.200)	0.440 (0.320–0.600)	
12–19 years	663	0.158 (0.141–0.178)	0.460 (0.350–0.510)	
20 years and older	1,297	0.123 (0.112–0.137)	0.430 (0.390–0.470)	
Urine of general U.S. population in 2013–2014 (total)	**2,664**	**0.043 (0.039–0.048)**	**0.189 (0.170–0.214)**	NHANES (CDC 2017a)
6–11 years	402	0.052 (0.045–0.060)	0.228 (0.168–0.254)	
12–19 years	451	0.051 (0.043–0.061)	0.203 (0.152–0.235)	
20 years and older	1,811	0.042 (0.038–0.045)	0.184 (0.161–0.215)	
Urine of adult (18–49 years) U.S. population in 2013–2014				NHANES (CDC 2017b)
Non-smokers	822	0.042 (0.037–0.047)	NR	
Smokers	592	0.053 (0.048–0.059)	NR	
Urine	15	0.061–0.74[a]	NR	Filella *et al.* 2013a, b
Urine of Multi-Ethnic Study of Atherosclerosis (MESA) participants in 2000–2002	308	0.10	NR	Pang *et al.* 2016

Sample	No. of individuals	Concentration (µg Sb/L) geometric mean with (95% confidence interval)	Concentration (µg Sb/L) 95th percentile with (95% confidence interval)	References
Urine of Strong Heart Study (SHS) participants in 1998–2003	277	0.15	NR	Pang *et al.* 2016
Blood				
Whole blood	9	2.53–4.07	NR	Filella *et al.* 2013a, b
Whole blood of Healthy Eating Active Living (HEAL) pilot study participants in Houston, TX	22	3.3	NR	Whitworth *et al.* 2017
Saliva				
Saliva of healthy volunteers	4	BDL to 3	NR	Olmez *et al.* 1998
Saliva of 3 patients with hypogeusia, 6 with hyposmia, and 3 with both hypogeusia and hyposmia	12	BDL to 10[b]	NR	Olmez *et al.* 1998

BDL = below detection limit; hypogeusia = decreased taste acuity; hyposmia = decreased smell acuity; NR = not reported.
[a]Filella *et al.* 2013a, Filella *et al.* 2013b also reported a single arithmetic (rather than geometric) mean that falls outside this range- 1.3 µg/L in urine.
[b]A mean ± SD of 110 ± 90 (N = 6) was reported for hyposmia, but this value was at least 10 times higher than the other data and is not included in the range above.

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

The general population is potentially exposed to antimony directly from consumer products (Section 2.4.1) 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 (antimony(III) trioxide and others) to which people are exposed

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

Sources: EU 2008, ATSDR 2017.

2.3.1 Consumer products

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

Because antimony(III) trioxide can change its form during the manufacture of many products, exposure may be to other forms of antimony. For instance, if antimony is released in liquid (e.g., water, sweat, or saliva) at near-neutral pH, it will exist as hydrolyzed forms in solution (see Figure 1-1 in Section 1), Sb(III) as $Sb(OH)_3$ or H_3SbO_3 and Sb(V) as $Sb(OH)_6^-$ or $H_2SbO_4^-$ rather than as antimony cations (ATSDR 1992). The antimony in house dust is mainly antimony(III) trioxide (from wear and tear of flame-retardant-treated fabric) (EU 2008). Table 2-7 shows exposure levels for consumer products evaluated in the EU antimony trioxide (i.e., antimony(III) trioxide) risk assessment report, which converted all exposure levels to the equivalent mass of antimony(III) trioxide (i.e., converting measured antimony to corresponding antimony(III) trioxide based on molecular weight).

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

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

Source: EU 2008.

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

[b]ND = not determined.

[c]Reported as 0.82×10^{-6} mg/m^3.

[d]Reported as 3.2×10^{-6} mg/m^3.

The only U.S. data on indoor air antimony levels are from an elementary school in Arizona (Majestic *et al.* 2012), where the particles less than 1 µm in diameter (PM_1) fraction of air samples averaged 0.017 µg antimony/m^3. Antimony in air was most likely resuspended from flame-retardant-treated carpet by foot traffic.

A study measuring antimony in costume cosmetic products purchased in the San Francisco Bay area reported measurements of antimony in eyeshadows (mean = 0.34 mg/kg; range = 0.13 to 0.57 mg/kg; N = 5) and in body paint (mean = 1.5 mg/kg; range = 0.12 to 6.2 mg/kg; N = 5) (Perez *et al.* 2017).

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

2.3.2 Environmental exposure

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

concentrations in the local environment, which may be carried by air or water beyond the immediate area of those activities.

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

Air

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

Antimony can change oxidation state in the environment and during industrial use. Aerosolized elemental antimony oxidizes to antimony(III) trioxide through reactions with atmospheric oxidants (ATSDR 1992, EU 2008, ATSDR 2017). During coal combustion, antimony forms antimony oxides, regardless of the form of antimony present in the coal (Health Canada 2010); Pavageau *et al.* (2004) also reported formation of antimony(V) pentoxide from coal combustion. Similarly, antimony(III) trioxide is the primary species released to the atmosphere from other high-temperature industrial processes, such as smelting, combustion of petroleum and petroleum products, and incineration of products that contain antimony (Health Canada 2010, NTP 2017a). 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.* 2011, Dupont *et al.* 2016). Antimony(III) trisulfide (used as automobile brake lubricant) and antimony(III) trisulfate (used as automobile brake filler) have been reported to oxidize to antimony(III) trioxide at temperatures reached in the braking process (above 300°C) (EU 2008). Antimony concentration measurements taken at a roadside site in London, England were 6.73 ± 3.49 ng/m^3 (0.00673 ± 0.00348 μg/m^3) while the background level was 1.31 ± 0.807 ng/m^3 (0.00131 ± 0.000807 μg/m^3) (Gietl *et al.* 2010). People thus can inhale antimony(III) trioxide transformed from other antimony compounds.

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

Water, rain, and soil

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

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

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

2.3.3 Food and drinking water

Levels of antimony (form not specified) in food in the United States range from not detectable (limit of detection not reported) to 1.7 µg/g of dry weight (Belzile *et al.* 2011). Antimony(V) is the most prevalent antimony species in drinking water, as the result of oxidative treatments

(chlorination or ozonation) used in water disinfection processes. Antimony levels in U.S. drinking water range from 0.02 µg/L to 9.6 µg/L. The value of 9.6 µg/L was reported for bottled water heated in PET bottles at 80°C for 48 hours.

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

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

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

Source: EU 2008.

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

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

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

[d]ND = not determined.

2.4 Summary and synthesis

A significant number of people in the United States are exposed to antimony(III) trioxide (Sb_2O_3), as evidenced by occupational exposure data and supporting data on production, consumption, and releases into the environment and exposures from consumer products. In addition to exposure to antimony(III) trioxide in the workplace from its use as a synergist with flame retardant chemicals, as a catalyst in production of PET plastic, as a pigment and fining agent in glass production, and as a colorant and opacifier in pigments for paints and ceramic glazes, people are potentially exposed from using consumer products containing antimony(III) trioxide, and by breathing contaminated air, or a combination of these sources. The chemical form of antimony changes during manufacturing, in the environment, and *in vivo*, and detection methods typically measure total antimony rather than specific forms of antimony, so identifying exposure specifically to antimony(III) trioxide is presently difficult.

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

to 1983 U.S. National Occupational Exposure Survey, indicating extensive past exposure to antimony(III) trioxide.

The highest occupational exposure to antimony(III) trioxide in the United States, exceeding current regulatory levels by at least 10-fold, occurred during smelting and refining operations and production of antimony(III) trioxide in the 1970s and 1980s. Antimony is no longer mined in the United States and smelting and refining of metallic antimony and production of antimony(III) trioxide was limited to one company in the United States in 2017. More recent European data suggest that the highest exposure to antimony(III) trioxide occurs during production of antimony(III) trioxide, followed by the flame retardant industry. Lower levels of exposures occur during the use of Sb_2O_3 in the glass and PET industries.

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

3 Disposition and Toxicokinetics

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

3.1 Antimony(III) trioxide

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

3.1.1 Absorption and distribution

The main sources for information on absorption and distribution of antimony(III) trioxide are authoritative reports from governmental and international agencies (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 (2017a), conducted according to U.S. Food and Drug Administration GLP.

Human studies

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

Inhalation. The highest exposures of people to antimony by inhalation are from occupational exposure. Antimony has been detected in the lungs, blood, and urine of workers who had inhaled antimony identified as antimony(III) trioxide or likely to be antimony(III) trioxide; inhaled antimony compounds are retained long term in the lung (HSDB 2013, NTP 2017a). Elevated urinary excretion of antimony has been reported for workers exposed to antimony(III) trioxide in

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

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

Oral exposure. Antimony(III) trioxide is generally considered to be poorly absorbed from the GI tract (Stemmer 1976). No data for oral exposure to antimony(III) trioxide in humans was identified, but absorption is likely low. The EU (2008) calculated a rate of 0.3% for oral absorption from antimony(III) trioxide; however, concerns were expressed because the absorption was based on one study of oral exposure of rats to antimony(III) trioxide, with antimony levels 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 (2017a). In the Newton (1994) study, antimony (III) trioxide levels were detected at several timepoints in red blood cells, but not plasma, from male and female Fisher 344 rats exposed to antimony trioxide by inhalation (at 0.055, 0.51, or 4.50 mg/m^3) for up to 12 months and observed for another 12 months (Table B-1). The antimony levels increased proportionally with exposure level and nearly so with an exposure duration of 12 months compared with 6 months. Lung burdens also increased with exposure concentrations during the 2-year study in male and female Fischer 344 rats (Newton *et al.* 1994) (see Table 3-1 in Section 3.4, Toxicokinetics).

The NTP (2017a) exposed rats and mice of both sexes to antimony(III) trioxide by inhalation with either short-term inhalation exposure (2 weeks plus a 4-week recovery period) to 0, 3.75, 7.5, 15, 30, or 60 mg/m^3 for 6 hours plus T90 (12 minutes) per day, 5 days per week, or long-term exposure for 2 years at concentrations of 0, 3, 10, or 30 mg/m^3 with the same 5 days per week exposure. Blood levels increased with exposure concentration in rats and mice for both the short-term (data not shown) and the long-term exposure periods. Blood levels for the long-term exposure period were measured on days 61, 124, 269, 369, and 551 (see Appendix B, Table B-2 and Figure 3-1). Blood concentrations increased with exposure duration for rats by approximately 4 to 5-fold when concentration at day 551 was compared with that at day 61. Although the NTP (2017a) concluded that the increase over time was not as clear for mice in the

2-year study, no statistical comparisons for different time points were reported. Blood concentrations were also normalized by division of the blood levels by the exposure concentration; the normalized blood levels decreased with increasing exposure concentration, particularly at higher concentrations (data not shown).

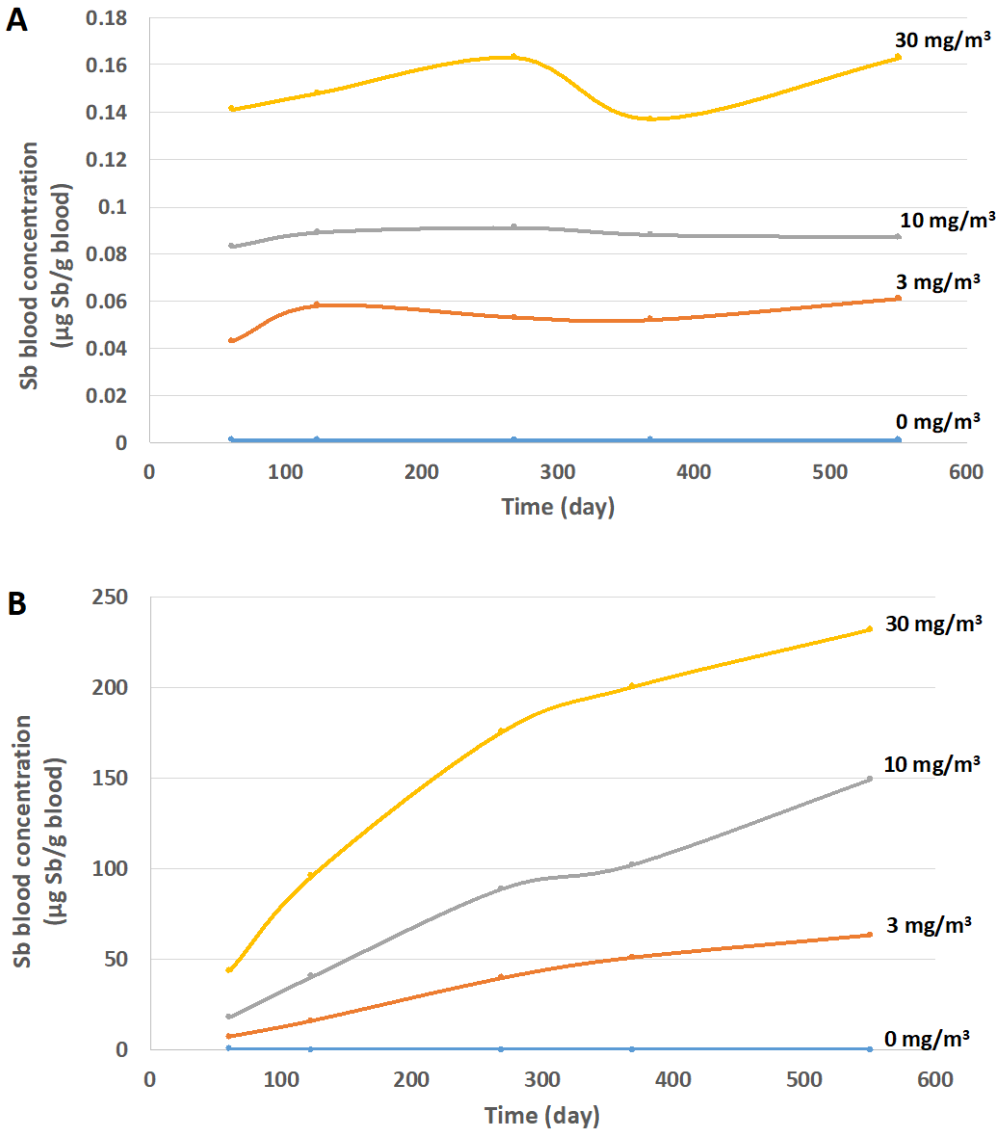


Figure 3-1. Blood antimony levels (µg/L) in female mice (panel A) and rats (panel B) exposed to antimony(III) trioxide by inhalation at 0, 3, 10, or 30 mg/m³ in a 2-year study

Source: NTP 2017a. 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. Leffler *et al.* (1984) exposed adult male Syrian golden hamsters to 19.5-μm or 7-μm particles of antimony(III) trioxide by intratracheal instillation. In addition to a large percentage in the lung, antimony was detected in the liver (12.6% of 19.5-μm particles and 7.2% of 7-μm particles), with lesser amounts in the kidney, stomach, and trachea (the only other tissues examined). Based on this study, the EU (2008) risk assessment concluded that absorption following intratracheal instillation was greater than 12.6%.

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

In a study of oral exposure to antimony(III) trioxide (TNO Quality of Life 2005), rats exposed to a single dose of 100 mg/kg showed little increase in tissue concentrations above control levels (data not shown), but at a dose of 1,000 mg/kg for 14 days, tissue levels increased at least 10 fold, and sometimes greater than 100-fold in thyroid, lung, spleen, heart, kidney, liver, bone marrow, bone or femur, muscle and whole blood levels in males and females (see Appendix B, Table B-3). Two additional studies, Westrick (1953), which exposed male Sprague-Dawley rats to 2% antimony(III) trioxide in the diet for 49 days, and Gross *et al.* (1955), which also exposed rats (sex and strain not specified) to 2% antimony(III) trioxide in the diet but for a total period of 8 months, reported tissue levels of antimony. If food consumption by the rats is assumed to be 5 g per day per 100 g body weight (Johns Hopkins University 2017) then the exposures by either gavage or dietary consumption would be approximately 0.1 g per 100 g body weight and the tissue levels can be compared across the different studies (see Appendix B, Table B-3). The oral exposure of rats to antimony(III) trioxide in the diet for 49 days (Westrick 1953) resulted in a general increase in tissue antimony levels compared with rats exposed by repeated gavage for 14 days (TNO Quality of Life 2005), but the differences between tissue levels at 49 days and 8 months (Gross *et al.* 1955) were relatively small and levels were lower after 8 months of exposure in some tissues. Different experimental conditions likely contributed to differences across these studies, but the general pattern of increasing tissue levels with increasing duration of oral exposure is likely meaningful.

3.1.2 Excretion

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

cells than antimony(V) and antimony(III) is preferentially excreted in the feces compared with antimony(V), which is more likely to be excreted in the urine (Tylenda and Fowler 2015).

Human studies (occupational exposures)

Urinary levels of antimony resulting from exposure to antimony(III) trioxide by inhalation have been reported for a few occupational uses of antimony(III) trioxide. Urinary excretion of antimony by exposed workers generally increases with the exposure level. Three studies were identified that reported both exposure to antimony(III) trioxide in air and urinary excretion for the same workers (see Section 2.2 and Table 2-4). The geometric mean or median air levels reported in these studies were mostly below the current threshold limit value for antimony and antimony compounds in air of 500 μg/m^3 (ACGIH 2017), but one study (Kim *et al.* 1999) reported a geometric mean air level of 766 μg/m^3, which was associated with a urinary excretion level of ~420 μg/L. This level was much higher than the 15.2 μg/g creatine excretion reported by Kentner *et al.* (1995) for a mean air level of 12.4 μg/m^3 in a starter battery factory using antimony(III) trioxide. The half-life for elimination of antimony in the urine following inhalation of antimony(III) trioxide was estimated as 95.1 hours for these 14 employees (Kentner *et al.* 1995).

Experimental animal studies

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

3.2 Other antimony compounds

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

3.2.1 Absorption and distribution

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

Human studies

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

necessary condition for cure of leishmaniasis and thus may be related to therapeutic effects of antimony.

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

Inhalation. Occupational and environmental exposure to antimony is mainly via inhalation. Elevated urinary excretion of antimony was reported in workers exposed to antimony trisulfide in the production of resinoid grinding wheels (Brieger *et al.* 1954) or to stibine (SbH_3) in lead battery production (Kentner *et al.* 1995). (Exposure to antimony(III) trioxide in this facility was discussed in Section 3.1.2.) Pregnant or lactating women in an antimony plant were exposed occupationally to unspecified amounts of antimony(III) trioxide, metallic antimony, or antimony(V) pentasulfide as aerosols, and antimony was detected in breast milk (3.3 ± 2.2 mg/L), placenta (3.2 to 12.6 mg% [units as reported in EU 2008 and HSDB 2013]), amniotic fluid (0.62 ± 0.28 mg/L), and umbilical cord blood, indicating absorption and potential exposure to fetuses and breast-fed infants (Belyaeva 1967). Mean levels in blood and urine were generally higher for workers in areas with high dust levels.

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

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

Oral exposure. Belzile *et al.* (2011) reported poisoning from either accidental or intentional consumption of antimony compounds, indicating absorption sufficient to cause toxicity (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 male and female Sprague-Dawley rats, the levels in thyroid, bone marrow, liver, spleen, and whole blood ranged from 0.028 (2.8 ng Sb/g in whole blood) to 0.195 μg/g (195 ng Sb/g in thyroid) (TNO Quality of Life 2005) (see Table B-3, column for controls [M/F]). Higher levels in liver were reported for 50 dogs (26 females, 23 males, and one of unknown sex) (12.2 μg/kg [ng/g] in males and 135 μg/kg [ng/g] in females) (Paßlack *et al.* 2015) and for 47 cats (22 males and 25 females) (132 μg/kg [ng/g] for males and females combined) (Paßlack *et al.* 2014). However, the tissue samples were collected from dogs and cats euthanized for medical reasons and no information on the animals was reported by the authors except for the age range of 3 days to 15 years for the dogs and 2 months to 18 years for the cats. The diet consumed by the dogs and cats could have been an important factor in the difference in antimony levels compared with rats, but the dietary composition was not specified.

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

Inhalation and intratracheal instillation. In general, aerosols of antimony oxides with small particle sizes and low water solubility (Newton *et al.* 1994) were retained in the lungs longer than larger particles with high water solubility (antimony tartrates) (Felicetti *et al.* 1974b). Large differences in blood levels of antimony following intratracheal instillation have been reported for different species. For example, following exposure to antimony(III) trichloride, blood levels in rabbits and dogs were 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 μg/g with 273 mg/kg antimony(III) potassium tartrate in drinking water or with 50 mg/kg by i.p. injection) and spleen (5 μg/g with 50 mg/kg by i.p. injection).

3.2.2 Excretion

Human studies

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

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

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

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

Experimental animal studies

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

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

Other routes. Oral ingestion of radiolabeled antimony(III) potassium tartrate by rats resulted in slow excretion, primarily in the feces but also in the urine (NTP 1992). In rats, i.v. injection of antimony(III) trichloride ($SbCl_3$) resulted in excretion of 30% of total antimony in feces and 12% in urine during the first 24 hours, indicating that biliary excretion exceeded urinary excretion (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. Evidence for methylation of antimony *in vivo* is limited to one study of two workers occupationally exposed to antimony during lead battery production (Krachler and Emons 2001). However, other studies in humans (Miekeley *et al.* 2002, Quiroz *et al.* 2011) and animals (Bailly *et al.* 1991) were negative for formation of methylated antimony.

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

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

Reduction of antimony(V) to antimony(III) occurs *in vitro*, and perhaps also in cell cytoplasm or in lysosomes, by reaction with GSH, cysteine, or cysteinyl-glycine. Evidence for reduction of antimony(V) to antimony(III) in humans is based on detection of both antimony(III) and

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

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

The valence state also affects the distribution of antimony in tissues. Felicetti *et al.* (1974a) reported that hamsters exposed to radioactive antimony (^{124}Sb) aerosols, one antimony(III) and one antimony(V), both with median aerodynamic diameters of 1.6 μm, had similar average body burdens on the day after exposure. However, slightly more antimony(III) than antimony(V) accumulated in the liver while more antimony(V) accumulated in the skeleton; reduction of antimony(V) to antimony(III) was not extensive. Antimony(III) tartrate inhaled as aerosols by mice (Thomas *et al.* 1973) or beagle dogs (Felicetti *et al.* 1974b) was distributed primarily to the lung, bone, 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 (2017a) report on lung accumulation and clearance in rats and mice exposed to antimony(III) trioxide via inhalation. No studies on the toxicokinetics of antimony in humans were identified.

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

Kinetic parameters were determined for inhaled antimony(III) trioxide in female rats and mice exposed at 0.0, 3.75, 7.5, 15, 30, or 60 mg/m^3 for 2 weeks followed by recovery for 4 weeks (NTP 2017a). Clearance half-lives in lung ranged from 73 to 122 days in rats and 47 to 62 days in mice. The shortest half-life was for the lowest exposure concentration, but no clear concentration-response trend was seen. Deposition rates (micrograms of antimony(III) trioxide per day) were approximately proportional or slightly less than proportional to exposure concentrations; deposition rates increased 15-fold in rats and 13-fold in mice when exposure increased 16-fold. Steady-state lung burdens were not reached during the 2-week exposure, but half-lives to steady state were estimated to be 365 to 610 days in rats and 235 to 310 days in mice.

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

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

Source: Newton *et al*. (1994).
mo = months.
[a]Total antimony in lung tissue was reported as total antimony(III) trioxide.

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

NTP (2017a) also attempted to fit a lung-burden model to data for rats and mice based on assumptions of a zero-order (constant) deposition rate and a first-order (with respect to lung burden) clearance rate. Model-predicted values are shown in Table 3-2 and lung burdens are shown in 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 yrs

	Exposure level (mg/m^3)		
Parameter	**3**	**10**	**30**
Deposition rates (μg Sb_2O_3 per total lung per day)	17.0	44.0	119.0
Percent deposition efficiency (%)	3.3	3.7	4.7
Clearance half-life (days)	136.0	203.0	262.0
Time to steady state (days)	680.0	1,015.0	1,3100.0

Source: NTP 2017a

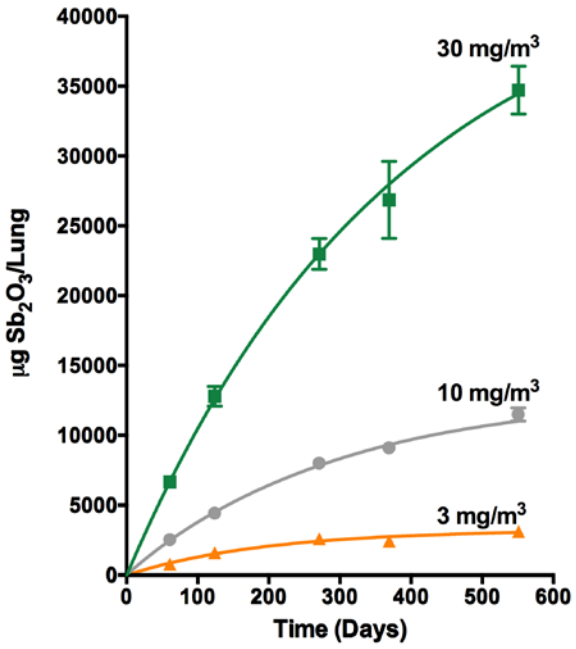


Figure 3-2. Lung antimony(III) trioxide burdens in female rats in the 2-year inhalation study

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

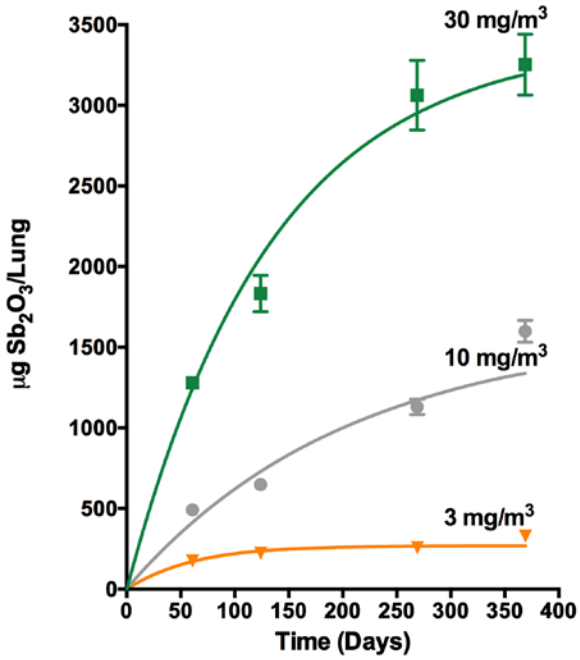


Figure 3-3. Lung antimony(III) trioxide burdens in female mice in the 2-year inhalation study

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

Based on relatively longer clearance half-lives at the higher doses and an unexpectedly high lung burden in mice after 551 days of exposure, NTP (2017a) concluded that the reduced pulmonary clearance was associated with lung overload at 10 mg/m^3 and 30 mg/m^3, but not 3 mg/m^3. Two theories to explain overload in relation to inhalation exposure to particulates have been proposed, one based on particle volume and the second on particle surface area. Volumetric overload is initiated when individual alveolar macrophages accumulate a particulate volume exceeding 60 µm^3 per macrophage (Morrow 1988, 1992). When the particulate volume per macrophage exceeds 600 µm^3, all macrophage-mediated clearance ceases, and the dust accumulates linearly with continued inhalation. Tran *et al.* (2000) proposed a second hypothesis for clearance impairment based on the total particle surface area of ultrafine particulates. This particle surface area hypothesis proposes that ultrafine particles with high surface area will cause macrophages to release proinflammatory mediators (chemokines), such as tumor necrosis factor, that attract macrophages and could prevent their migration. The NTP concluded that volume-based overload occurred at 10 mg/m^3 by day 418 in rats and day 369 in mice and at 30 mg/m^3 by day 94 in rats and day 124 in mice.

3.5 Summary

3.5.1 Absorption and distribution

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

Information from studies with exposure to antimony(III) trioxide and other forms of antimony indicated that this element is distributed through the body via the blood, and distribution to tissues is generally similar for different routes of exposure. Both antimony(III) and antimony(V) forms tend to accumulate mainly in red blood cells, although antimony(V) is initially present in plasma during the first few hours after exposure. The highest levels of antimony are generally in organs rich in reticuloendothelial cells, such as the spleen, liver, and bone marrow. In rats, dogs, and some studies in humans, high levels have also been reported in the thyroid. However, the relative accumulation of inhaled antimony in liver and skeleton differs by valence; antimony(III) is distributed more rapidly than antimony(V) to the liver, while antimony(V) is delivered more rapidly than antimony(III) to the skeleton. Both forms were also found in the kidneys and other organs. In humans exposed to radioactive antimony, it was still detected in tissues, particularly the liver, weeks or months after exposure ended. During pregnancy and lactation, both humans and rats passed antimony to the fetus via the placenta and to infants via milk.

3.5.2 Metabolism

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

3.5.3 Excretion

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

3.5.4 Toxicokinetics

Toxicokinetics data for antimony are mainly from the NTP (2017a) report on studies in rats and mice exposed to antimony(III) trioxide by inhalation for 2 weeks plus 4 weeks' recovery or for 2 years. Clearance half-lives from lung were calculated from 2-week exposure data as 73 to 122 days for rats and 47 to 62 days for mice. The models that NTP used fit the data for rats relatively well, but not those for mice. Model-estimated clearance half-lives for 2-year exposure data in rats increased with exposure concentration with durations of 136 for 3 mg/m^3, 203 days for 10 mg/m^3, and 262 days for 30 mg/m^3. (Data for mice could not be modeled.) The NTP also considered the question of lung overload during the 2-year exposure, concluding that lung overload was not reached at the lowest concentration tested (3 mg/m^3), but was reached in both rats and mice at the middle (10 mg/m^3) and high concentrations (30 mg/m^3).

4 Human Cancer Studies

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

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

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

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

1. Selection and overview of the human cancer studies (Section 4.1 and Antimony Protocol [NTP 2017b]).
2. Evaluation of risk of bias and study sensitivity (Section 4.2, and Appendix C, 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 2017b).

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

A U.S. population-based cohort study on urinary antimony concentrations and cancer (Guo *et al.* 2016) and a Turkish geospatial study on antimony exposure from drinking water and cancer incidence (Colak *et al.* 2015) were excluded from the cancer evaluation because only all malignant neoplasms, not site-specific cancers, were reported. Two Swedish post-mortem studies comparing antimony concentrations in various tissue types in deceased metal smelter workers and deceased controls (Gerhardsson *et al.* 1982, Gerhardsson and Nordberg 1993) were excluded

because no point estimates were reported and exposure measurements did not precede cancer outcomes.

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

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

4.2 Study quality and utility evaluation

This section assesses the adequacy of the identified cohort and case-control studies to evaluate cancer hazard of antimony. This assessment considers factors relating to study quality (potential for selection and attrition bias, information bias regarding exposure and outcome, and concern for inadequate analytical methods, selective reporting, and inadequate methods or information to

evaluate confounding) and study sensitivity (e.g., adequate numbers of individuals exposed to substantial levels of antimony). The ratings for each of these factors are provided in Table 4-2 and the rationale for the rating is described in detail in Appendix C, 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[a]						Quality[a]	Utility[b]
	Selection	Exposure	Outcome	Confounding methods	Adequacy of analysis	Selective reporting	Sensitivity	Integration
Cohort studies								
Antimony smelter workers								
Jones 1994	++	+++/++	+++	+	+++	+++	++	+++/++
Schnorr *et al.* 1995	++	++	+++	+++	++	+++	++	+++/++
Tin smelter workers								
Jones *et al.* 2007	++	++	+++	++	++	+++	+	++
Case-control study								
Wingren and Axelson 1993	+++	+	++	+	++	++	+	+

[a]Levels of concern for bias and for study quality rating. Equal column width for types of bias does not imply they have equal weight (see RoC Handbook for description of terms): +++ = low/minimal concern or high quality; +++/++ = minimal/some concern or high/medium quality; ++ = some concern or medium quality; + = major concern or low quality; 0 = critical concern.
[b]Utility of the study to inform the hazard evaluation (see RoC Handbook for description of terms): +++ = high utility; +++/++ = high/moderate utility; ++ = moderate utility; ++/+ = moderate/low utility; + = low utility; 0 = inadequate utility.

All three retrospective cohort studies (Jones 1994, 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. It should be noted that while individual-level exposure estimates are generally more precise than imprecise group-level estimates, they may be more subject to bias which may impact the validity of the results (Tielemans *et al.* 1998). Regardless, exposure misclassification in all four studies is non-differential and would likely attenuate effect estimates.

Major concerns for confounding bias were found in studies of antimony smelter workers (Jones 1994) and the art glass worker case-control study (Wingren and Axelson 1993), some concern in the study of tin smelter workers (Jones *et al.* 2007), and minimal concern in the study of antimony smelter workers (Schnorr *et al.* 1995) (see Appendix C, Table C-5). No studies controlled for lifestyle-related confounders such as smoking, or occupational co-exposures, e.g., arsenic, lead, asbestos, or polycyclic aromatic hydrocarbons (PAHs). Although smoking prevalence was not directly controlled for in the three occupational cohort studies, smoking rates were assessed. Occupational co-exposure to lead, arsenic, and PAHs were identified or concurrently examined, but were not adequately controlled for in all occupational metal-working cohorts; however, in some studies, available monitoring data on co-exposures and antimony helped inform the evaluation of confounding bias. Lead and asbestos were suspected occupational co-exposures in the case-control study involving art glass workers. Given there is either some concern (Jones *et al.* 2007) or major concern (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 2017).

Evidence from individual studies

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

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

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

Reference, location, study-design and year	Population description & exposure assessment method	Exposure category	Risk estimate (95% CI)	Exposed cases	Covariates	Comments, strengths and limitations
Jones 1994 Cohort Northeast England, United Kingdom **Enrollment or follow-up:** 1961–1992 (study enrollment and follow-up period)	**Population:** Antimony smelter workers N = 1,420 men **Exposure assessment method:** company records	**Lung cancer: Ever employed antimony workers, SMR (95% CI)**			Age	**Exposure information:** *Exposure level:* Ever exposure to antimony defined as employment in antimony plant for 3+ months. *Exposure duration:* 6–50 years based on employment. **Confounding concern**: Likely co-exposure to arsenic and PAHs (lung carcinogens). Smoking not controlled for despite 72% prevalence. **Strengths:** Antimony workers exposed primarily to antimony compounds. Stratified by hiring date, years since first exposure. Additional analysis on other job titles. **Limitations:** External analysis only. Small number of exposed cases for lung and stomach cancers. Potential confounding by smoking and occupational co-exposures. Individual-level data on exposure not available. **Level of evidence:** Inconclusive (lung), inconclusive (stomach)
		Ever antimony worker	[1.55 (1.11–2.11)]	37		
		Before 1/1/1961	[2.18 (1.49–3.07)]	32		
		After 12/31/1960	[0.54 (0.18–1.27)]	5		
		Stomach cancer: Ever employed antimony workers, SMR (95% CI)				
		Ever antimony worker	[0.42 (0.05–1.51)]	2		
Schnorr *et al.* 1995 Cohort Southern Texas, United States	**Population:** Antimony smelter workers N = 1,014 men	**Lung cancer: External analysis - U.S. white male mortality rates, SMR (95% CI)**			Age, calendar year, latency period	**Exposure information:** *Exposure level:* Ever exposure to antimony defined as employment in antimony plant for 3+ months from 1937–1971. *Exposure duration:* < 5 years to > 10 years based on employment.
		Ever antimony worker	[0.75 (0.51–1.07)]	30		
		Lung cancer: External analysis - Texas ethnic-specific mortality rates, SMR (90% CI)				
		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
Enrollment or follow-up: 1937–1989 (employment and follow-up period)	**Exposure assessment method:** company records	< 5 years employment	SMR only: 0.83	11		**Confounding concern**: Minimal concern from smoking, arsenic, and lead exposure. **Strengths**: Antimony workers primarily exposed to antimony compounds; both national and local ethnic-specific expected mortality rates were calculated; two-time air sampling of antimony and arsenic. **Limitations**: External analysis only; small number of exposed cases for lung and stomach cancers; individual-level data on exposure not available. **Level of evidence**: Some evidence (lung); some evidence (stomach)
		5–10 years employment	SMR only: 2.24	8		
		> 10 years employment	SMR only: 2.73	9		
		Stomach cancer: External analysis – U.S. white male mortality rates, SMR (95% CI)				
		Ever antimony worker	1.49 (0.71–2.74)	10		
		Stomach cancer: External analysis – Texas ethnic-specific mortality rates, SMR (95% CI)				
		Ever antimony worker	1.24 (0.50–2.55)	7		
Jones *et al*. 2007 Cohort Northern England, United Kingdom **Enrollment or follow-up:** 1937–2001 (Employment and follow-up period)	**Population:** Tin smelter workers N = 1,462 men **Exposure assessment method:** job-exposure matrix and air sampling measurements	**Lung cancer: Cumulative exposure, RR (90% CI)**			Age, calendar year, time since exposure	**Exposure information:** *Exposure level:* cumulative antimony inhalation over employment duration. *Exposure duration:* Modeled three exposure scenarios from 1937–1971 using annual air sampling estimates from 1972–1991. **Confounding concern**: Highly correlated antimony, lead, and arsenic air concentrations; minimal concern for smoking, but not controlled for in analysis. **Strengths**: Concentration-response relationship examined; use of JEM from work histories and 20 years of air measurements; antimony exposure cumulatively estimated. **Limitations**: Small number of exposed cases for lung cancer. No information on smoking status; did not control for highly correlated occupational co-exposures.
		Model 1[a] (unweighted)	[1.23 (0.79–1.92)]	62		
		Model 1[a] (weighted)	[5.26 (1.75–43.38)]			
		Model 2[b] (unweighted)	[1.13 (0.80–1.60)]			
		Model 2[b] (weighted)	[3.25 (1.32–21.76)]			
		Model 3[c] (unweighted)	[1.12 (0.80–1.55)]			
		Model 3[c] (weighted)	[3.32 (1.42–8.08)]			
		Lung cancer: Cumulative exposure, beta coefficient (β) (90% CI)				
		Model 1[a] (unweighted)	0.21 (-0.24–0.65)	62		
		Model 1[a] (weighted)	1.66 (0.56–3.77)			
		Model 2[b] (unweighted)	0.12 (0.22–0.47)			
		Model 2[b] (weighted)	1.18 (0.28–3.08)			
		Model 3[c] (unweighted)	0.11 (-0.22–0.44)			
		Model 3[c] (weighted)	1.20 (0.35–2.09)			

Reference, location, study-design and year	Population description & exposure assessment method	Exposure category	Risk estimate (95% CI)	Exposed cases	Covariates	Comments, strengths and limitations
						Exposure not at an individual level; air concentrations modeled over 34-year period. **Level of evidence**: Inconclusive (lung)
Wingren and Axelson 1993 Case-control Southeast Sweden **Enrollment or follow-up:** 1950–1982 (mortality period)	**Population:** Population-based study of art-glass producing area N cases = NR (~ 73 cases of stomach cancer, Wingren and Axelson 1985). N controls: NR (~833 controls, Wingren and Axelson 1985) **Exposure assessment method:** occupation (i.e., art-glass worker) listed on death records	**Stomach cancer: Antimony use in parish of subject death, OR (90% CI)**			Age	**Exposure information:** Occupation listed as glass worker on death record, and subject died in a parish where antimony use was reported. *Exposure level:* Reported antimony usage levels from companies within study's geographic area. **Confounding concern**: Likely co-exposure to lead; minimal concern for smoking and asbestos. **Strengths**: Population-based study; cases and controls from same geographic area. **Limitations**: Unknown number of cases and controls; exposure status based on factory antimony use at one time point; likely confounding from occupational co-exposure to lead. **Level of evidence**: Inconclusive (stomach)
		No use	2.00 (1.30–3.10)	NR		
		Low level of use	1.60 (0.90–2.60)			
		High level of use	0.80 (0.30–2.00)			
		Any level of use (pooled estimate)	[1.36 (0.85 to 2.15)]			

NR = Not reported; [ ] = NTP calculated risk estimates and CI.
[a]Model 1: back-extrapolated missing air concentrations, holding 1972–1974 concentrations constant.
[b]Model 2: back-extrapolated missing air concentrations, assuming two-fold higher concentrations than 1972–1974.
[c]Model 3: back-extrapolated missing air concentrations by increasing (1937–1960) then decreasing (1960s–1970s) linear trends.

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

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

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

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

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

Limitations of the Jones *et al.* 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. Furthermore, the use of weighting factors (time since exposure and attained age) to modify cumulative exposure estimates are less than ideal as they were based on assumptions from a prior study of uranium workers (National Research Council 1999). It is unclear whether weighted or unweighted estimates are the best metric to evaluate the relationship.

The reported association between antimony exposure and lung cancer is potentially due to confounding from occupational arsenic and lead exposures. Based on air monitoring data at the smelter site, median estimated cumulative air lead concentrations (1.5 mg/m^3-year) were higher than either arsenic (0.28 mg/m^3-year) or antimony (0.37 mg/m^3-year) from 1972 to 1991. Besides reporting increased lung cancer risk from antimony exposure, Jones *et al.* (2007) reported an increased risk of lung cancer mortality for weighted cumulative exposure to lead and arsenic, but not cadmium or polonium-210, in three exposure scenarios. A high level of correlation between lead, arsenic, and antimony air concentrations was seen at the smelter site, suggesting concurrent exposure. It is possible that arsenic, a known and potent lung carcinogen, is driving the observed incident lung cancer in this cohort. Since all three metals are highly correlated and offer similar slopes in their exposure-response relationships, the causality of one exposure over the other cannot be separated.

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

Integration of evidence across studies

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

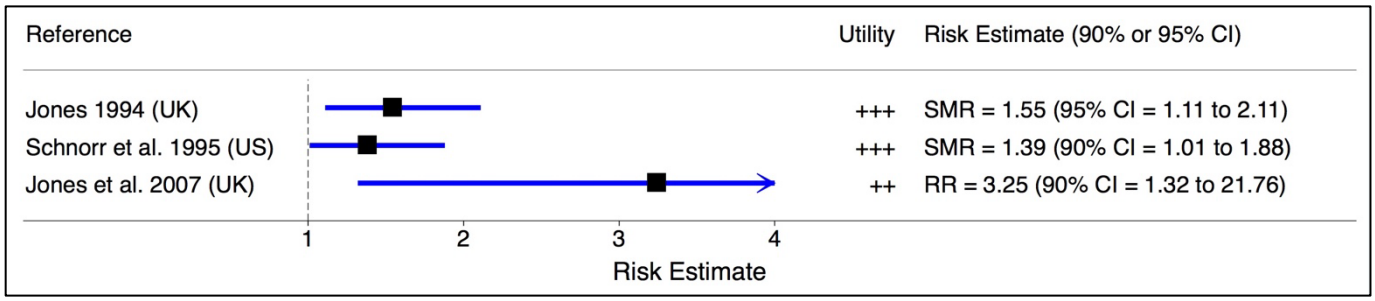


Figure 4-1. Forest plot of effect estimates of lung cancer mortality (SMR or RR, 90% or 95% CI) in metal smelter workers exposed to antimony in available cohort studies

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

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

4.3.2 Stomach cancer

In 2017, there will be approximately 28,000 cases and 10,960 deaths of stomach cancer in the United States (SEER 2018). For stomach cancer from 1975 to 2014, age-adjusted incidence rates for men in the United States were 12.6 per 100,000 men (see Table 24.5 of Howlader *et al.* 2017). Similar to lung cancer, stomach cancer has comparable low 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. Since there was likely substantial exposure misclassification between the low and high consumption estimates due to imprecise assessment methods, in a post-hoc analysis NTP pooled both the low and high exposure for an ever-exposure risk estimate, which resulted in a weighted odds ratio of 1.36 which was not statistically significant (95% CI = 0.85 to 2.15). The highest risk of stomach cancer mortality was actually found in glass workers who died in parishes with no reported antimony consumption (OR = 2.00, 90% CI = 1.30 to 3.10), compared with unexposed controls in these parishes.

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

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

Integration of evidence across studies

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

4.3.3 Other types of cancers

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

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

A prospective mortality linkage study of National Health and Nutrition Examination Survey (NHANES) participants by Guo *et al.* (2016) saw an increased risk of death from malignant neoplasms when comparing the highest quartile of urinary antimony concentrations to the lowest quartile (fully-adjusted hazard ratio [HR] = 1.20, 95% CI = 0.70 to 2.06). However, no trend was seen across quartiles (*P*-value for trend test = 0.20). Furthermore, as noted in Section 4.1, all malignant neoplasms (i.e., all sites as one outcome) are insensitive for evaluating potential cancer hazards.

4.4 NTP 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; however, it is not clear whether the increased risk was due to exposure to antimony. Results may be impacted due to non-differential exposure misclassification and confounding bias due to concurrent exposure from other metals.

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

5 Studies of Cancer in Experimental Animals

This section reviews and assesses the evidence from carcinogenicity studies in experimental animals exposed to antimony(III) trioxide, and applies the RoC listing criteria to reach a 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 Jr 1984). The effects from antimony alone cannot be identified for these papers, and thus these three papers were excluded.

Among the seven studies for antimony(III) trioxide reported in four papers (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 *et al.* 1994
Rat, CDF (F)	Inhalation	1 year/2 years	Watt 1983
Rat, Wistar (M&F)	Inhalation	53 weeks /71–73 weeks	Groth *et al.* 1986

M = male, F = female.

5.2 Study quality assessment

Each primary carcinogenicity study was systematically evaluated for its utility in informing the cancer hazard evaluation. A series of questions related to the following elements of study potential bias and study sensitivity were used: study design, exposure conditions, outcome, confounding, reporting, and analysis (NTP 2015). The following subsections discuss antimony(III) trioxide studies. Each study was evaluated individually and is presented in descending order of overall utility in determining carcinogenicity (Table 5-2). For details of each study assessment, see Appendix D.

All studies used concurrent negative controls, and two studies (NTP 2017a) also included historical control data. Two studies reported that animals were randomly assigned to treatment groups (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.

The two most recent antimony trioxide studies (NTP 2017a) presented no concerns regarding the utility to assess the cancer hazard and were considered of high overall utility.

Three antimony(III) trioxide studies were considered of moderate overall utility for assessing cancer hazard. The Groth *et al.*(1986) study used antimony(III) trioxide that was estimated to be 95.8% pure based on the assumption that all of the antimony (80% by weight) was in the trioxide form, which is consistent with the grade of antimony tested. Trace amounts of arsenic and lead contaminated the antimony(III) trioxide, but the low levels were not thought to contribute significantly to carcinogenicity. The Watt (1983) study used fewer than 10 CDF rats per group, limiting the statistical power of the study, and also used only females, eliminating the ability to detect cancer increases in males or differences between sexes. Furthermore, only a few organs were reported to have been examined during necropsy. The statistical methods used for tumor incidences were not reported. In the Newton *et al.* (1994) study, the highest exposure level caused no changes in body weight, survival, or tumor incidence, so the dose levels might not have reached the maximally tolerated dose.

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

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

In the row for species, R = rats, M = mice. In the row for sex, M = males, F = females. In rows for each signaling question, NR = not reported, +++ = high utility, ++ = moderate utility, + = low utility.
[a]Elements related primarily to the sensitivity of the study.

5.3 Findings from carcinogenicity studies

Increased neoplastic lesions were observed in antimony(III) trioxide studies (see Table 5-3). Four of five studies showed increased neoplasms, and all four reported increases in lung neoplasms in rats or mice (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-. 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[a], strain or stock	Site	Classification	Neoplasms (Sex of animal)	Reference
Rat, Wistar Han	Adrenal gland	Benign	Pheochromocytoma (M and F)	NTP 2017a
	Adrenal gland	Combined	Pheochromocytoma (F)	
	Lung	Benign	Alveolar/bronchiolar adenoma (M* 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 or carcinoma (F)	Groth *et al.* 1986
	Lung	Malignant	Squamous-cell carcinoma (F)	
	Lung	Malignant	Scirrhous carcinoma (F)	
Rat, Fischer 344	None	None	None (M and F)	Newton *et al.* 1994
Rat (F only), CDF	Lung	Malignant	Scirrhous carcinoma (F)	Watt 1983

F = female, M = male.

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

[a] 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 (2017a) study is discussed below in an order that follows the progression of lung tumor development, i.e., from preneoplastic hyperplasia to benign adenoma and then to malignant carcinoma.

Nonneoplastic lesions of the lung relevant to the carcinogenic process were increased in treated groups compared with vehicle controls. Both sexes of B6C3F1/N mice and Wistar Han rats had

increased incidences of preneoplastic hyperplasia of alveolar and/or bronchiolar epithelium (see Table 5-4), in all exposed groups (3, 10, and 30 mg/m^3) after two years (NTP 2017a).

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

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

* Considered evidence of antimony(III) trioxide carcinogenicity based on multiple factors, although the increase in incidence was not statistically significant.
↑ = Significant increase
F = in females
M = in males.
[a] Increased hyperplasia of both alveolar and bronchiolar epithelium.
[b] Hyperplasia only increased in bronchiolar epithelium, not in alveolar epithelium.
[c] Findings include an equivocal finding of benign cystic keratinizing epithelioma and some evidence for alveolar/bronchiolar adenoma.

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

In female Wistar Han rats, incidences of alveolar/bronchiolar adenoma, which were not seen in 300 historical control female Wistar Han rats, were higher (though not statistically significant) at 3 mg/m^3, and were significantly increased at 10 and 30 mg/m^3 in the 2-year study. Additionally,

at the 12-month interim evaluation, one female Wistar Han rat exposed to 30 mg/m^3 had alveolar/bronchiolar adenoma. Alveolar/bronchiolar adenoma is known to progress to carcinoma, but no alveolar/bronchiolar carcinoma was seen, and the combined incidence was not increased. The incidence of lung cystic keratinizing epithelioma or squamous-cell carcinoma combined was not significantly increased, but there was a significant positive trend and it was considered an equivocal finding. NTP [2017a] noted that "cystic keratinizing epitheliomas are considered part of a spectrum of lesions that form a continuum considered to progress from squamous metaplasia to keratin cysts to cystic keratinizing epithelioma to squamous cell carcinoma." NTP also reported lung squamous-cell carcinoma in male or female rats as part of the evidence for carcinogenicity of 5 substances with exposure by inhalation (tetranitromethane [NTP 1990], nickel(II) oxide [NTP 1996b], nickel subsulfide [NTP 1996a], cobalt sulfate heptahydrate [NTP 1998], and indium phosphide [NTP 2001]) and 2 substances with exposure by oral gavage (dimethyl hydrogen phosphide [NTP 1985] and 3,3',4,4',5-pentachlorobiphenyl (PCB 126), a type of polychlorinated biphenyl (PCB) compound [NTP 2006]).

Overall, these data were considered to be some evidence of carcinogenic activity in the lung based on benign alveolar/bronchiolar adenoma in female Wistar Han rats (NTP 2017a). Because the RoC listing criteria requires malignant and/or combined benign and malignant tumors in experimental animal studies, the findings in female Wistar Han rat lung do not meet the RoC listing criteria.

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

For mice, females in all treated groups showed increased incidences in alveolar and bronchiolar epithelium hyperplasia, alveolar/bronchiolar adenoma, alveolar/bronchiolar carcinoma, and alveolar/bronchiolar adenoma or carcinoma (combined) at two years. Carcinomas were increased in both sexes of mice and adenomas were increased in female mice. Compared to rats that had incidence rates of adenomas and carcinomas lower then 20% at all dose levels, mice had incidence rates that were all greater than 20% and carcinomas that were over 60% at 30 mg/m^3 in males. The incidences of carcinomas exceeded historical controls at all dose levels in both sexes and adenomas exceeded historical control at all dose levels in females. During the 1-year interim sacrifice a low frequency of alveolar/bronchiolar adenoma were seen in female mice. Males showed increased alveolar and bronchiolar epithelium hyperplasia in all treated groups, slightly (not significantly) higher incidence of alveolar/bronchiolar adenoma in the 3 and 30 mg/m^3 groups, increased incidences of alveolar/bronchiolar carcinoma in all treated groups, and increased combined incidence of alveolar/bronchiolar adenoma or carcinoma in all treated groups after two years. After just one year males had a low frequency of alveolar/bronchiolar adenoma and alveolar/bronchiolar carcinoma. These early findings indicate lung carcinogenesis related to antimony exposure (NTP 2017a). Significant increases in the incidences of adenomas

and carcinomas were observed at exposure concentrations as low as 3 mg/m^3, which did not cause pulmonary overload.

In the Groth *et al.* (1986) study, incidences of alveolar hyperplasia and cuboidal and columnar-cell metaplasia were increased (statistical significance not reported) in female and male Wistar rats, and incidences of benign alveolar/bronchiolar adenoma as well as incidence of malignant lung neoplasms (squamous-cell carcinoma and scirrhous carcinoma) were increased significantly in female rats. Tumor incidences were not increased in male rats. Neoplasms occasionally developed from metaplastic foci, suggesting that metaplastic foci are preneoplastic. As mentioned above, the antimony(III) trioxide used in this study was only 80% pure and was contaminated with arsenic and lead. The concentrations of lead (0.1035 mg/m^3) and arsenic (0.0018 mg/m^3) in the air were both considered too low to have been the cause of neoplasms. Further, in animal studies, lead predominantly causes kidney neoplasms, which were not observed with antimony(III) trioxide exposure, thus, lead is not likely to have contributed to the carcinogenicity seen in the Groth *et al.* study (1986). Arsenic causes mice and hamsters to develop lung neoplasms, which were seen in Wistar rats after exposure to antimony. Compared to the concentration of antimony(III) trioxide (36 mg/m^3), the concentration of arsenic (0.0018 mg/m^3) was inconsequential, which is further supported by (1) much higher levels of antimony than that of arsenic found in the lung in exposed animals (Table 5-5), and (2) higher levels of arsenic in the lung of males, which did not develop lung tumors, compared to that of females, which developed lung tumors. These data suggest that neither arsenic nor lead contributed greatly to the observed incidences of lung cancer in this study, but interaction and other effects cannot be ruled out. Although this assessment is for hazard identification, it is noted that exposure concentrations in the Groth *et al.* study (1986) varied dramatically (average daily concentrations ranged from less than 10 mg/m^3 to more than 80 mg/m^3) due to technical difficulties in generating the aerosol, leading to questions about aerosol size and actual exposure level.

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

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

Source: Groth *et al.* 1986.

No increased incidences of neoplasms were observed in the 1-year exposure plus 1-year post-exposure recovery study in male and female F344 rats (Newton *et al* 1994). The concentrations in that study, 0.06, 0.51, and 4.5 mg/m^3, were much lower than the high concentrations used in previously discussed studies (i.e., 45 mg/m^3 in Groth *et al.* [1986], and 30 mg/m^3 in NTP 2017a]) but the high concentration was comparable to the high dose used by Watt (1983) of 4.2 mg/m^3. The aerosol size used in the Newton *et al.* (1994) study was large, ranging from 3.76 to 4.55 μm (depending on the instrument used) and included less respirable aerosols than if they had been < 4.0 μm (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. 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^3 (Watt 1983). It is worth noting that scirrhous carcinoma is not a term that NTP currently uses, and it is possible that the same lesions might be classified currently as alveolar/bronchiolar carcinoma. Exposed CDF rats also had significant increases in pneumocyte hyperplasia at 1.6 and 4.2 mg/m^3, and adenomatous hyperplasia in the lung at 4.2 mg/m^3.

5.3.2 Other neoplasms

Besides lung neoplasms, benign or malignant pheochromocytoma of the adrenal gland in Wistar Han rats, and benign fibrous histiocytoma or malignant fibrosarcoma of the skin in B6C3F1/N mice, and malignant lymphoma in B6C3F1/N mice, also were increased after antimony(III) trioxide exposure (NTP 2017a).

Adrenal gland neoplasms

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

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

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

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

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

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

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

Skin neoplasms

Skin neoplasms were seen in B6C3F1/N mice, but not in Wistar Han rats, in the NTP (2017a) two-year study. Male B6C3F1/N mice had increased incidences (also exceeding historical control ranges) of benign fibrous histiocytoma at 30 mg/m^3 and had a significant positive trend. Two incidences (not significantly increased) of malignant fibrosarcoma were seen at 10 mg/m^3, and increased combined incidences of fibrous histiocytoma or fibrosarcoma at 30 mg/m^3 which had a significant positive trend also occurred. Overall, there is some evidence of skin carcinogenicity in male B6C3F1/N mice based on increased combined incidences of fibrous histiocytoma or fibrosarcoma. Female B6C3F1/N mice had two incidences (not significantly increased, but exceeding the historical control ranges) of squamous-cell carcinoma at 30 mg/m^3 which was considered equivocal evidence of skin carcinogenesis in females.

Lymphomas

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

sacrifice. Overall, malignant lymphoma in female B6C3F1/N mice is considered to be clear evidence of carcinogenicity.

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

5.4 Synthesis and NTP preliminary level of evidence conclusion

5.4.1 Synthesis

The evidence for the carcinogenic potential from inhalation exposure to antimony(III) trioxide (Table 5-7 and Table 5-8) in experimental animals is strong.

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

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

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

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

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

↑ = Significant increase; – = no increase reported; F = in females; M = in males.

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

[a]Squamous-cell carcinoma, scirrhous carcinoma.

[b]Alveolar/bronchiolar adenoma or carcinoma.

[c]Alveolar/bronchiolar carcinoma.

[d]Benign or malignant pheochromocytoma.

[e]Fibrous histiocytoma or fibrosarcoma.

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

Reference and study design	Exposure	Tumor site – Tumor type		Comments
		Dose levels (mg/m^3)	Tumor incidence (n/N) (%)	
NTP 2017a **Animal:** Rat — Wistar Han [Crl:WI (Han)] M **Animal age at the beginning of exposure:** 6 weeks **Study duration:** 105 weeks	**Agent and purity:** Antimony(III) trioxide (crystalline form: crystalline, diamond cubic crystal structure) 99.9% Aerosol size: Mass median aerodynamic diameter (MMAD) 0.9–1.5 µm, GSD 1.7–2.2 **Exposure route:** Inhalation **Exposure concentrations, frequency, and duration:** 0 3 10 30 mg/m^3 6 hours/day, 5 days/week x 105 weeks	**Adrenal gland – Benign pheochromocytoma[a]**		**Survival:** Survival had a significant negative trend (P = 0.025), but was not significantly different compared to controls at any exposure level: 30/50, 30/50, 28/50, 18/50. **Body weight:** Body weight of the 30-mg/m^3 group was lower than untreated controls after 69 weeks. **Significantly increased preneoplastic lesions:** Lung alveolar epithelium hyperplasia: 4/50, 50/50**, 48/50**, 49/50** Lung bronchiole epithelium hyperplasia: 3/50, 34/50**, 36/50**, 33/50** Adrenal medulla hyperplasia: 1/49, 2/50, 4/49, 8/50* **Other comments**: 12 Month interim evaluation: Perivascular lymphocytic infiltrate 0/10, 4/10*, 4/10*, 3/10. **Overall utility: [+++]** There were no concerns of confounding as the chemical was pure and stable, the exposure was well characterized, and all groups were treated the same. The study had a high level of sensitivity to detect neoplasms as it used large numbers of both sexes of rats, exposed at three dose levels, which reached the maximally tolerated level, for a near life-span duration. However, the stock of rat used was new to NTP and so few historical control data exist compared to other strains. Complete necropsies with histological examination of most organs was performed, so the ability to detect neoplasms was high. **Footnotes:** * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$. [a]Adjusted percent incidence based on Poly-3 estimated neoplasm incidence after adjustment for concurrent mortality. [b]Exceeds historical controls from inhalation studies: 5/149 (range 0%–8%); - exceeds historical controls from studies of all routes: 6/297 (range 0%–8%).
		0	1/49 (2.5%)	
		3	0/50	
		10	2/49 (4.8%)	
		30	7/50*[b] (17.2%)	
		Trend P-value: < 0.001		
		Lung – Alveolar/bronchiolar adenoma[a]		
		0	3/50[c] (7.1%)	
		3	4/50[c] (9.8%)	
		10	6/50[c] (13.8%)	
		30	8/50[c] (19.7%)	
		Trend P-value: = 0.057		
		Lung – Alveolar/bronchiolar carcinoma[a]		
		0	0/50	
		3	0/50	
		10	2/50[d] (4.7%)	
		30	0/50	
		Lung – Alveolar/bronchiolar adenoma or carcinoma[a]		
		0	3/50[c] (7.1%)	
		3	4/50[c] (9.8%)	
		10	8/50[c] (18.4%)	
		30	8/50[c] (19.7%)	

Reference and study design	Exposure	Tumor site – Tumor type		Comments
		Dose levels (mg/m^3)	Tumor incidence (n/N) (%)	
				[c]Exceeds historical controls from inhalation studies: 4/150 (range 0%–6%); - exceeds historical controls from studies of all routes: 4/299 (range 0%–6%). [d]Exceeds historical controls from inhalation studies: 0/150; exceeds historical controls from studies of all routes: 0/299.
NTP 2017a **Animal:** Rat — Wistar Han [Crl:WI (Han)] F **Animal age at the beginning of exposure:** 6 weeks **Study duration:** 105 weeks	**Agent and purity**: Antimony trioxide (crystalline form: crystalline, diamond cubic crystal structure) 99.9% Aerosol size: MMAD 0.9–1.5 µm, GSD 1.7–2.2 **Exposure route**: Inhalation **Exposure concentrations, frequency, and duration:** 0 3 10 30 mg/m^3 6 hours/day, 5 days/week x 105 weeks	**Adrenal gland – Benign pheochromocytoma[a]**		**Survival**: Survival was significantly decreased at 10 and 30 mg/m^3 and there was a significant negative trend ($P < 0.001$): 39/50, 38/50, 28/50 ($P = 0.032$), 20/50 ($P < 0.001$). **Body weight**: Body weight was lower than controls in the groups exposed to 30, 10, and 3 mg/m^3 after 65, 81, and 99 weeks, respectively. **Significantly increased preneoplastic lesions**: Lung alveolar epithelium hyperplasia: 5/50, 50/50**, 49/50**, 50/50** Lung bronchiole epithelium hyperplasia: 6/50, 26/50**, 25/50**, 27/50** Lung alveolar epithelium squamous metaplasia: 0/50, 5/50*, 3/50, 1/50 Adrenal medulla hyperplasia: 0/49, 0/49, 3/49, 5/50* **Other comments**: 12 Month interim evaluation: Alveolar/bronchiolar adenoma 0/10, 0/10 0/10, 1/10; Perivascular lymphocytic infiltrate 0/10, 4/10*, 5/10*, 3/10. **Overall utility: [+++]** There were no concerns of confounding as the chemical was pure and stable, the exposure was well characterized, and all groups were treated the same. The study had a high level of sensitivity to detect neoplasms as it used large numbers of both sexes of rats, exposed at three dose levels, which reached the maximally tolerated level, for a near life-span duration. However, the stock of rat used was new to NTP and so few historical control data exist compared to other strains. Complete necropsies with histological examination of most organs were performed, so the ability to detect neoplasms was high.
		0	0/49	
		3	2/49[b] (4.5%)	
		10	2/49[b] (4.8%)	
		30	6/50**[b] (15.2%)	
		Trend *P*-value: = 0.004		
		Adrenal gland – Malignant pheochromocytoma		
		0	0/49	
		3	0/49	
		10	0/49	
		30	1/50 (2%)	
		Adrenal gland – Benign or malignant pheochromocytoma[a]		
		0	0/49	
		3	2/49[c] (4.5%)	
		10	2/49[c] (4.8%)	
		30	7/50**[c] (17.6%)	
		Trend *P*-value: < 0.001		
		Lung – Alveolar/bronchiolar adenoma[a]		
		0	0/50	
		3	2/50[d] (4.4%)	

Reference and study design	Exposure	Tumor site – Tumor type		Comments
		Dose levels (mg/m^3)	Tumor incidence (n/N) (%)	
		10	6/50*[d] (13.8%)	**Footnotes:** * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.
		30	5/50*[d] (12.4%)	[a]Adjusted percent incidence based on Poly-3 estimated neoplasm incidence after adjustment for concurrent mortality.
		Trend *P*-value: = 0.029		[b]Exceeds historical controls from inhalation studies: 1/148 (range 0%–2%); exceeds historical controls from studies of all routes: 5/297 (range 0%–4%).
		Lung – Cystic keratinizing epithelioma or squamous-cell carcinoma[a,f]		[c]Exceeds historical controls from inhalation studies: 2/148 (range 0%–2%); exceeds historical controls from studies of all routes: 7/297 (range 0%–4%).
		0	0/50	[d]Exceeds historical controls from inhalation studies: 0/150; exceeds historical controls from studies of all routes: 0/300.
		3	0/50	[e]Includes 2 cystic keratinizing epithelioma and 1 squamous-cell carcinoma, tumors that NTP considered to be part of a continuum of lesions.
		10	0/50	
		30	3/50[d,e] (7.4%)	
		Trend *P*-value: = 0.006		
NTP 2017a **Animal:** Mouse — B6C3F1/N M **Animal age at the beginning of exposure:** 6 weeks **Study duration:** 105 weeks	**Agent and purity**: Antimony(III) trioxide (crystalline form: crystalline, diamond cubic crystal structure) 99.9% Aerosol size: MMAD 0.9–1.5 µm, GSD 1.7–2.2 **Exposure route:** Inhalation **Exposure concentrations, frequency, and**	**Lung – Alveolar/bronchiolar adenoma[a]**		**Survival:** Survival was significantly decreased at 10 and 30 mg/m^3 and there was a significant negative trend ($P < 0.001$): 38/50, 30/50, 27/50 ($P = 0.027$), 17/50 ($P < 0.001$). **Body weight:** Body weights were lower than controls in the 30-mg/m^3 group after 73 weeks. **Significantly increased preneoplastic lesions: Lung lymphocyte infiltration: 13/50, 47/50[***], 48/50[***], 45/50[***];** Lung alveolar epithelium hyperplasia: 6/50, 39/50**, 45/50**, 49/50** Lung bronchiole epithelium hyperplasia: 0/50, 32/50**, 44/50**, 44/50**. **Other comments**: 12 Month interim evaluation: Alveolar/bronchiolar adenoma 0/10, 0/10, 2/10, 0/10; Alveolar/bronchiolar carcinoma 0/10, 0/10, 1/10, 2/10; Lung lymphocyte infiltration 0/10, 10/10**, 10/10**, 10/10**. **Overall utility: [+++]** There were no concerns of confounding as the chemical was pure and stable, the exposure was well characterized, and all groups were
		0	10/50 (21.5%)	
		3	14/50 (32.9%)	
		10	9/50 (21.8%)	
		30	14/50 (34.6%)	
		Lung – Alveolar/bronchiolar carcinoma[a]		
		0	4/50 (8.5%)	
		3	18/50***[b] (40.9%)	
		10	20/50***[b] (46.2%)	
		30	27/50***[b] (62.8%)	
		Trend *P*-value: < 0.001		
		Lung – Alveolar/bronchiolar carcinoma, multiple only		
		0	0/50	
		3	5/50* (10%)	
		10	6/50** (12%)	

Reference and study design	Exposure	Tumor site – Tumor type		Comments
		Dose levels (mg/m^3)	Tumor incidence (n/N) (%)	
	duration: 0 3 10 30 mg/m^3 6 hours/day, 5 days/week × 105 weeks	30	11/50** (22%)	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. **Footnotes:** * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$. [ ] = Statistical significance calculated by NTP, using Fisher's Exact test. [a]Adjusted percent incidence based on Poly-3 estimated neoplasm incidence after adjustment for concurrent mortality. [b]Exceeds historical controls from inhalation studies: 42/250 (range 8%–22%); exceeds historical controls from studies of all routes: 75/550 (range 4%–22%). [c]Exceeds historical controls from inhalation studies: 1/250 (range 0%–2%); exceeds historical controls from studies of all routes: 2/550 (range 0%–2%). [d]Exceeds historical controls from inhalation studies: 2/250 (range 0%–2%); exceeds historical controls from studies of all routes: 5/550 (range 0%–2%).
		Lung – Alveolar/bronchiolar adenoma or carcinoma[a]		
		0	13/50 (27.5%)	
		3	29/50*** (64.5%)	
		10	28/50*** (63.6%)	
		30	34/50*** (75.3%)	
		Trend *P*-value: < 0.001		
		Skin – Benign fibrous histiocytoma[a]		
		0	0/50	
		3	1/50[c] (2.5%)	
		10	1/50[c] (2.5%)	
		30	4/50*[c] (10.6%)	
		Trend *P*-value: = 0.012		
		Skin – Fibrosarcoma		
		0	0/50	
		3	0/50	
		10	2/50[c] (4%)	
		30	0/50	
		Skin – Fibrous histiocytoma or fibrosarcoma[a]		
		0	0/50	
		3	1/50[d] (2.5%)	
		10	3/50[d] (7.3%)	
		30	4/50*[d] (10.6%)	
		Trend *P*-value: = 0.023		

Reference and study design	Exposure	Tumor site – Tumor type		Comments
		Dose levels (mg/m^3)	Tumor incidence (n/N) (%)	
NTP 2017a **Animal:** Mouse — B6C3F1/N F **Animal age at the beginning of exposure:** 6 weeks **Study duration:** 105 weeks	**Agent and purity:** Antimony(III) trioxide (crystalline form: crystalline, diamond cubic crystal structure) 99.9% Aerosol size: MMAD 0.9–1.5 µm, GSD 1.7–2.2 **Exposure route**: Inhalation **Exposure concentrations, frequency, and duration:** 0 3 10 30 mg/m^3 6 hours/day, 5 days/week × 105 weeks	**Whole body – Malignant lymphoma[a]**		**Survival:** Survival was significantly decreased at 10 and 30 mg/m^3 and there was a significant negative trend ($P < 0.001$): 36/50, 31/50, 26/50 ($P = 0.032$), 15/50 ($P < 0.001$). **Body weight:** Body weights were lower than controls in the 30-mg/m^3 group after 85 weeks. **Significantly increased preneoplastic lesions: Lung lymphocyte infiltration: 7/50, 37/50[***], 37/50[***], 26/50[***];** Lung alveolar epithelium hyperplasia: 1/50, 36/50**, 49/50**, 48/50** Lung bronchiole epithelium hyperplasia: 1/50, 34/50**, 48/50**, 45/50**. **Other comments**: 12 Month interim evaluation: Alveolar/bronchiolar adenoma 0/10, 0/10, 0/10, 1/10; peribronchial and perivascular lymphoid infiltrates 3/10, 10/10**, 10/10**, 9/10**; malignant lymphoma 0/10, /10, 0/10, 3/10. **Overall utility: [+++]** There were no concerns of confounding as the chemical was pure and stable, the exposure was well characterized, and all groups were treated the same. The study had a high level of sensitivity to detect neoplasms as it used large numbers of both sexes of mice, exposed at three dose levels, which reached the maximally tolerated level, for a near life-span duration. Complete necropsies with histological examination of most organs was performed, so the ability to detect neoplasms was high. **Footnotes:** * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$. [ ] = Statistical significance calculated by NTP, using Fisher's Exact test. [a]Adjusted percent incidence based on Poly-3 estimated neoplasm incidence after adjustment for concurrent mortality.
		0	7/50 (15.6%)	
		3	17/50*[b] (38.1%)	
		10	20/50***[b] (47.5%)	
		30	27/50***[b] (60.7%)	
		Trend P-value: < 0.001		
		Lung – Alveolar/bronchiolar adenoma[a]		
		0	1/50 (2.3%)	
		3	10/50**[c] (22.8%)	
		10	19/50***[c] (44.9%)	
		30	8/50**[c] (20.3%)	
		Lung – Alveolar/bronchiolar carcinoma[a]		
		0	2/50 (4.4%)	
		3	14/50***[d] (31.2%)	
		10	11/50**[d] (26.8%)	
		30	11/50**[d] (28.8%)	
		Lung – Alveolar/bronchiolar carcinoma, multiple only		
		0	0/50	
		3	7/50** (14%)	
		10	6/50* (12%)	
		30	4/50* (8%)	
		Lung – Alveolar/bronchiolar adenoma or carcinoma[a]		
		0	3/50 (6.6%)	
		3	22/50***[e] (48.8%)	

Reference and study design	Exposure	Tumor site – Tumor type		Comments
		Dose levels (mg/m^3)	Tumor incidence (n/N) (%)	
		10	27/50***[e] (62.6%)	[b]Exceeds historical controls from inhalation studies: 63/250 (range 14%–36%); exceeds historical controls from studies of all routes: 109/550 (range 12%–36%).
		30	18/50***[e] (43.5%)	
		Trend *P*-value: = 0.019		[c]Exceeds historical controls from inhalation studies: 12/249 (range 2%–8%); exceeds historical controls from studies of all routes: 27/549 (range 0%–10%).
		Skin – Squamous cell carcinoma		[d]Exceeds historical controls from inhalation studies: 17/249 (range 2%–10%); exceeds historical controls from studies of all routes: 24/549 (range 0%–10%).
		0	0/50	[e]Exceeds historical controls from inhalation studies: 28/249 (range 6%–18%); exceeds historical controls from studies of all routes: 50/549 (range 2%–18%).
		3	0/50	[f]Exceeds historical controls from inhalation studies: 0/250; exceeds historical controls from studies of all routes: 0/550.
		10	0/50	
		30	2/50[f] (4%)	
Groth *et al.* 1986 **Animal**: Rat — Wistar M, F **Animal age at the beginning of exposure:** 8 months **Study duration**: 71 to 73 weeks	**Agent and purity**: Antimony(III) trioxide (crystalline form: not reported) 80% (23 other metals, including Pb 2,300 μg/g, As 40 μg/g, and Ni 1.6 μg/g) Aerosol size: MMAD 2.80 μm **Exposure route**: Inhalation **Exposure concentrations, frequency, and duration**:	**Lung – Total neoplasms (M)**		**Survival:** Survival was similar to controls. **Body weight**: Body weights were similar to controls, although males did weigh 6.2% less than controls at 26 to 50 weeks. **Significantly increased preneoplastic lesions**: Interstitial fibrosis and alveolar-wall cell hypertrophy and hyperplasia, as well as cuboidal and columnar cell metaplasia occurred at lung foci. Occasionally, neoplasms developed from these foci, suggesting a pre-neoplastic lesion. **Other comments**: Total neoplasms included squamous-cell carcinoma, bronchioalveolar adenoma, bronchioalveolar carcinoma, and scirrhous carcinoma. Incidences of lung neoplasms were not reported in males, but were said not to have been significantly different from controls. **Overall utility: [++]** The chemical was well characterized, but was found to be only 80% pure, with lead and arsenic as contaminants. The low purity makes distinguishing effects caused by antimony from possible effects caused by the contaminants difficult. The sensitivity of the study to detect neoplasms was low as only one dose level was used and it was based on the level of exposure to workers and not the maximally tolerated dose. Further, the exposure concentration varied widely until 5 months into the study when the target concentration was reached. The exposure duration was more than a year and full necropsies with histological examinations were performed. Neoplasms
		0	None	
		45	None	
		Lung – Total neoplasms (F)		
		0	0/89	
		45	19/89[***] (21%)	
		Lung – Squamous cell carcinoma (F)		
		0	0/89	
		45	9/89[**] (10%)	
		Lung – Scirrhous carcinoma (F)		
		0	0/89	
		45	5/89[*] (5.6%)	
		Lung – Bronchioalveolar adenoma or carcinoma combined (F)		
		0	0/89	
		45	11/89[***] (12%)	

Reference and study design	Exposure	Tumor site – Tumor type		Comments
		Dose levels (mg/m^3)	Tumor incidence (n/N) (%)	
	0 45 mg/m^3 time-weighted average 7 hours/day, 5 days/week for 6 [5/sex], 9 [5/sex], and 12 [5/sex] months. After 53 weeks (~12 months) the remaining rats [75/sex] were kept unexposed for 18–20 additional weeks before sacrifice [Total time of 71–73 weeks]. Intermediate sacrifices were made to examine distribution of antimony in tissue.			were reported with statistical analysis as total neoplasms combined per organ site. **Footnotes**: * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$. [ ] = Statistical significance calculated by NTP, using Fisher's Exact test.
Newton *et al.* 1994 **Animal:** Rat — Fischer 344 (CDF F344 Crl BR) M	**Agent and purity**: Antimony(III) trioxide (crystalline form: not reported) 99.68% Aerosol size: MMAD = 3.76 ±	**Lung – Carcinoma**		**Survival**: Survival was similar to controls. **Body weight**: Similar to controls. **Significantly increased preneoplastic lesions**: Lung were examined after 12 months and after 24 month. 12 Month results: **Alveolar/intraalveolar macrophage:** 6/13 (46.2%), 11/13 (84.6%)[*], 9/12 (75.0%), 13/13 (100.0%)[**]; **Alveolar/intraalveolar macrophage with**
		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 (mg/m^3)	Tumor incidence (n/N) (%)	
Animal age at the beginning of exposure: 8 weeks (140–169 g males; 99–122 g females) **Study duration**: 24 months	0.84 μm, GSD 1.79 ± 0.32 **Exposure route**: Inhalation **Exposure concentrations, frequency, and duration:** 0 0.06 (target 0.05) 0.51 (target 0.5) 4.50 mg/m^3 (target 5.0) 6 hours/day, 5 days/week 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.			**foreign particulates:** 0/13, 13/13 (100.0%)[***], 12/12 (100.0%)[***], 13/13 (100.0%)[***]; **Perivascular/peribronchiolar macrophage with lymphoid cells and foreign particulates:** 0/13, 2/13 (15.3%), 6/12 (50.0%)[**], 7/13 (53.8%)[**]; **Peribronchial lymph node macrophage with foreign particulates:** 0/13, 3/13 (23.1%), 5/12 (41.7%)[*], 13/13 (100.0%)[***]. 24 Month results: **Interstitial inflammation:** 32/52 (61.5%), 37/52 (71.2%), 36/53 (67.9%), 48/52 (92.3%)[***]; **Bronchiolar/alveolar hyperplasia:** 3/52 (5.8%), 1/52 (1.9%), 2/53 (3.8%), 4/52 (7.7%); **Alveolar/intraalveolar macrophage:** 31/52 (59.6%), 44/52 (84.6%)[**], 46/53 (86.8%)[**], 52/52 (100.0%)[***]; **Alveolar/intraalveolar macrophage with foreign particulates:** 0/52, 15/52 (28.8%)[***], 38/53 (71.7%)[***], 51/52 (98.1%)[***]; **Perivascular/peribronchiolar macrophage with lymphoid cells and foreign particulates:** 0/52, 22/52 (42.3%)[***], 46/53 (86.8%)[***], 47/52 (90.4%)[***]; **Peribronchial lymph node macrophage with foreign particulates:** 0/52, 6/52 (11.5%)[*], 34/53 (64.2%)[***], 39/52 (75.0%)[***]. **Overall utility: [++]** There was little concern for confounding as the chemical was pure, exposure conditions were well characterized, and groups were treated consistently with animals randomly assigned to exposure groups. The sensitivity of detecting neoplasms was good as high numbers of both sexes were tested. Exposures were at three concentrations for about half a life-span duration (1 year), though observations (1 year) continued to a near life-span total study duration. However, the highest exposure level did not reach the maximally tolerated level. Most organs were histologically examined, so most neoplasms would have been detected. Although aerosol size was not ideal (slightly over the current upper limit of test guidelines), this study did show Sb_2O_3 accumulation and decreased clearance in the lung (by 80% in the 4.5 mg/m^3 group). The pulmonary overload was observed at relatively low exposure concentrations (compared to inert particles, such as TiO_2) and Sb_2O_3 toxicity was suspected. It appears conditions that could lead to cancer did persist (Table 9, page 572 of Newton *et al.*), post-exposure, chronic

Reference and study design	Exposure	Tumor site – Tumor type		Comments
		Dose levels (mg/m^3)	Tumor incidence (n/N) (%)	
				inflammation in most animals, although hyperplasia was observed in very few animals). **Footnotes**: [ ] = Statistical significance calculated by NTP, using Fisher's Exact test.
Newton *et al.* 1994 **Animal:** Rat — Fischer 344 (CDF F344 Crl BR) F **Animal age at the beginning of exposure:** 8 weeks (140–169 g males; 99–122 g females) **Study duration**: 24 months	**Agent and purity**: Antimony(III) trioxide (crystalline form: not reported) 99.68% Aerosol size: MMAD = 3.76 ± 0.84 μm, GSD 1.79 ± 0.32 **Exposure route**: Inhalation **Exposure concentrations, frequency, and duration:** 0 0.06 (target 0.05) 0.51 (target 0.5) 4.50 mg/m^3 (target 5.0) 6 hours/day, 5 days/week x 12 months 5 animals/sex were sacrificed	Lung – Carcinoma		**Survival**: Survival was similar to controls. **Body weight**: Similar to controls. **Significantly increased preneoplastic lesions**: Lung were examined after 12 months and after 24 month. 12 Month results: **Alveolar/intraalveolar macrophage:** 6/16 (37.5%), 10/13 (76.9%)[*], 8/11 (72.7%), 14/14 (100.0%)[***]; **Alveolar/intraalveolar macrophage with foreign particulates:** 0/16, 13/13 (100.0%)[***], 11/11 (100.0%)[***], 14/14 (100.0%)[***]; **Perivascular/peribronchiolar macrophage with lymphoid cells and foreign particulates:** 0/16, 6/13 (46.2%)[**], 4/11 (36.4%)[*], 7/14 (50.0%)[**]; **Peribronchial lymph node macrophage with foreign particulates:** 0/16, 0/13, 6/11 (54.5%)[**], 13/14 (92.9%)[***]. 24 Month results: **Interstitial inflammation:** 33/49 (67.3%), 40/52 (76.9%), 48/54 (88.9%)[**], 48/50 (96.0%)[***]; **Bronchiolar/alveolar hyperplasia:** 1/49 (2.0%), 0/52, 0/54, 6/50 (12.0%); **Alveolar/intraalveolar macrophage:** 28/49 (57.1%), 40/52 (76.9%)[*], 48/54 (88.9%)[***], 50/50 (100.0%)[***]; **Alveolar/intraalveolar macrophage with foreign particulates:** 0/49, 24/52 (46.2%)[***], 49/54 (90.7%)[***], 48/50 (96.0%)[***]; **Perivascular/peribronchiolar macrophage with lymphoid cells and foreign particulates:** 0/49, 31/52 (59.6%)[***], 47/54 (87.0%)[***], 47/50 (94.0%)[***]; **Peribronchial lymph node macrophage with foreign particulates:** 0/49, 6/52 (11.5%)[*], 29/54 (53.7%)[***], 39/50 (78.0%)[***].
		0	0/49 (0%)	
		0.06	0/52 (0%)	
		0.51	1/54 (1.9%)	
		4.5	0/50 (0%)	

Reference and study design	Exposure	Tumor site – Tumor type		Comments
		Dose levels (mg/m^3)	Tumor incidence (n/N) (%)	
	at 6 (5/sex), 12 (5/sex), 18 (5/sex) months and the rest (50/sex) were sacrificed at 24 months.			**Overall utility: [++]** There was little concern for confounding as the chemical was pure, exposure conditions were well characterized, and groups were treated consistently with animals randomly assigned to exposure groups. The sensitivity of detecting neoplasms was good as high numbers of both sexes were tested. Exposures were at three concentrations for about half a life-span duration (1 year), though observations (1 year) continued to a near life-span total study duration. However, the highest exposure level did not reach the maximally tolerated level. Most organs were histologically examined, so most neoplasms would have been detected. Although aerosol size was not ideal (slightly over the current upper limit of test guidelines), this study did show Sb_2O_3 accumulation and decreased clearance in the lung (by 80% in the 4.5 mg/m^3 group). The pulmonary overload was observed at relatively low exposure concentrations (compared to inert particles, such as TiO_2) and Sb_2O_3 toxicity was suspected. It appears conditions that could lead to cancer did persist (Table 9, post-exposure, chronic inflammation in most animals, although hyperplasia was observed in very few animals). **Footnotes**: [ ] = Statistical significance calculated by NTP, using Fisher's Exact test.
Watt 1983 **Animal**: Rat — CDF F **Animal age at the beginning of exposure:** NR (Possibly 3 to 5 months)	**Agent and purity**: Antimony(III) trioxide (crystalline form: not reported) 99.4% Aerosol size: MMAD 5.06 µm **Exposure route**: Inhalation	**Lung – Scirrhous carcinoma**		**Survival:** Not reported. **Body weight:** Body weight gain in exposed rats was greater than controls. **Significantly increased pre-neoplastic lesions:** Lungs from exposed animals appeared grossly mottled – with foci of fibrosis. Focal fibrosis occurred as early as 3 months in the high-dose group and the incidence was significantly increased over controls in the high dose group from 9 months to the end of the study and in the low dose group from 12 months to the end of the study. Significant increases in pneumocyte hyperplasia occurred in both the low and high dose from 12 months to the end of the study. Significant increases in adenomatous hyperplasia occurred in the high dose group after 9 months to the end of the study.
		0	0/13	
		1.6	0/17	
		4.2	9/18** (50%)	
		Lung – Squamous cell carcinoma		
		0	0/13	
		1.6	0/17	
		4.2	2/18 (11%)	
		Lung – Alveolar/bronchiolar adenoma		
		0	0/13	

Reference and study design	Exposure	Tumor site – Tumor type		Comments
		Dose levels (mg/m^3)	Tumor incidence (n/N) (%)	
Study duration: 2 years	**Exposure concentrations, frequency, and duration:** 0 1.6 ± 1.5 [avg Feret's diameter = 0.44 µm w/ geometric std dev 2.23] 4.2 ± 3.2 mg/m^3 [avg Feret's diameter = 0.4 µm w/ geometric std dev 2.13] for 6 hours/day, 5 days/week, for up to 1 year. Sacrifices at 0, 3, 6, 9, 12, and 24 months.	1.6	1/17 (5.9%)	The onset of multinucleated giant cells in the high dose group occurred after 6 months and in the low dose group after 1 year. Significant increases in the incidence of multinucleated giant cells were seen in the high dose group after 9 months and in the low-dose-group after 1 year. **Other comments:** Only the incidence at 2 years is reported here as the denominators of the other time points were all fewer than 10 rats. Scirrhous carcinomas were associated with an unusually large amount of fibrous connective tissue. **Overall utility: [++]** The chemical purity was high and exposure was characterized, although the particle size (converted by Newton *et al.* [1994] to be MMAD of approximately 5 µm) was over the recommended (1-4 µm). Only female rats were used, which eliminates the ability to detect sex differences. The sensitivity to detect neoplasms was low as a small number of rats were used at only two dose levels, though the exposure was near life-span duration. The ability to detect neoplasms, if they exist, was moderate as the organs examined during necropsy were not fully reported. The statistical methods used were not reported. The use of large exposure chamber with pigs inside and pine shavings also increased the chance of exposure to non-Sb_2O_3 particles (and possible metabolism alternation due to pine shavings and therefore affecting susceptibility). **Footnotes:** * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.
		4.2	3/18 (16.7%)	

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

6 Mechanistic Data

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

Most of the section discusses mechanistic data on antimony(III) trioxide and antimony(III) trichloride, which is similar to antimony(III) trioxide, and is generally organized according to the 10 key characteristics of human carcinogens (Smith *et al.* 2016) (see Characteristics in Table 6-1), with minor exceptions (see next paragraph). The order of the presentation is by both possible chronological sequence of events (e.g., being electrophilic leads to binding with GSH, and the efflux of antimony GSH complex in turn causes oxidative stress) and the weight of evidence (evidence from antimony(III) trioxide carries more weight than evidence from other antimony compounds). No metabolic activation is needed for the antimony effects seen.

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

Table 6-1. Ten characteristics of carcinogens (Smith *et al.* 2016) and organization of Section 6

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

6.1 Electrophilic properties

Antimony compounds are electrophilic and might interact directly with nucleic acids (DNA and RNA) and proteins. Antimony, especially in its trivalent form, is highly reactive with sulfhydryl groups and, in particular, vicinal thiol groups (reviewed by Wysocki and Tamas 2010). Thiol reactivity may directly affect toxicity by disrupting protein structure, function, and stability.

While direct effects of antimony(III) trioxide electrophilicity were not found, antimony(III) potassium tartrate directly inhibits glutathione (GSH) reductase (Wyllie and Fairlamb 2006, Moreira *et al.* 2017) and glutathione *S*-transferase (GST) in red blood cells (Poon and Chu 2000) (see Section 6.2 for additional details). Antimony(III) potassium tartrate also reduced protein thiols by 15% to 40% in neonatal cardiac myocytes ([Tirmenstein *et al.* 1997] in Section 6.2). Reaction of antimony(III) with thiols can also target zinc finger domains of DNA-binding proteins and affect their functions, as seen in antimony(III) trichloride displacement of zinc in a DNA repair enzyme (Grosskopf *et al.* 2010) (see Section 6.4 for additional details). In the high-throughput screening using cultured cells, four antimony compounds, not including antimony(III) trioxide, were screened in various Tox21 assays (see Appendix E.1). They showed mostly antagonistic effects to nuclear receptors, possibly because of displacement of Zn(II) in the zinc finger structures of these receptors by antimony(III) ions.

6.2 Oxidative stress

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

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

In vitro studies showed that antimony(III) compounds can react with thiol groups on proteins and peptides (e.g., the reduced form of GSH) (see Section 6.1) and consequently inhibit cellular antioxidant defenses. Exposure to antimony(III) trioxide (Mann *et al.* 2006) and other antimony(III) compounds (antimony trichloride [Hashemzaei *et al.* 2015] and antimony potassium tartrate [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).

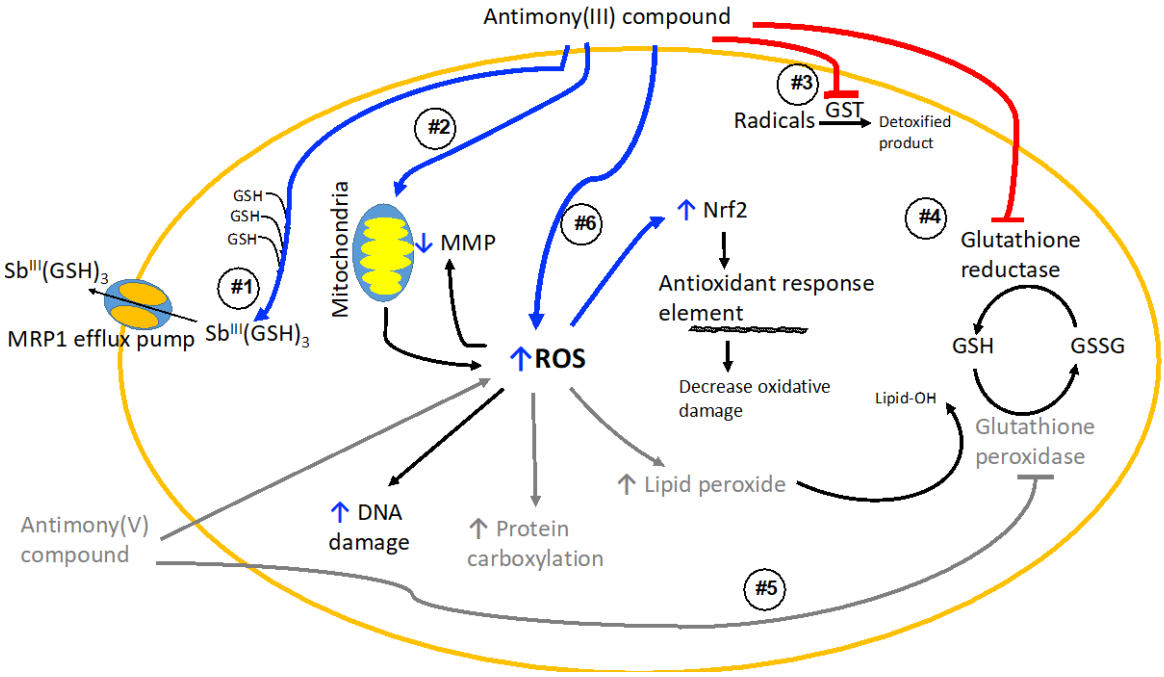


Figure 6-1. Antimony increases oxidative stress.

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.2). For example, antimony(III) trioxide–induced apoptosis was further increased by depletion of GSH or inhibition of enzymes (γ-glutamylcysteine synthetase, glutathione peroxidase, or catalase) (Lösler *et al.* 2009).

Mitochondria can be affected by ROS and can contribute to increased ROS. Antimony(III) trioxide (Lösler *et al.* 2009), antimony(III) trichloride (Hashemzaei *et al.* 2015), and antimony(III) potassium tartrate (Lecureur *et al.* 2002) disrupted mitochondrial membrane potential (Blond and Whittam 1965) (Figure 6-1, #2) and induced ROS. Mitochondria, in turn, are a source of antimony(III) trichloride–induced oxidative stress. When primary rat hepatocytes were exposed to both antimony(III) trichloride and a mitochondrial protective agent, the ROS production was less than with exposure to antimony(III) trichloride alone (Hashemzaei *et al.* 2015). Exposure of cells to both antimony(III) trichloride and ROS scavengers prevented the antimony(III) trichloride–induced decrease in mitochondrial membrane potential.

6.3 Genotoxicity

This section summarizes the results of *in vitro*, *in vivo*, and human genotoxicity studies of antimony compounds. The focus is on antimony(III) trioxide, followed by antimony(III) trichloride, and findings from other antimony(III) compounds.

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

Table 6-2. Summary of genotoxicity data for antimony(III) trioxide and antimony(III) trichloride

	Antimony(III) trioxide		Antimony(III) trichloride	
Endpoint (test system)	***in vitro***	***in vivo***	***in vitro***	***in vivo***
Mutation				
Any mutation (prokaryotes)	Neg	–	Neg	–
Any mutation (eukaryotes)	Neg	*	–	–
DNA Damage				
Any DNA damage (prokaryotes)	Pos	Pos	Pos	–
Any DNA damage (eukaryotes)	Pos	Pos	Pos	–
DNA-protein crosslinks	–	–	Neg	–
Chromosomal damage/cytogenetic effects				
Chromosomal aberrations	Pos	Neg[a]	–	[b]
Micronucleus induction	–	Pos	Pos	Pos
Sister chromatid exchange	Pos	–	Pos	–

Results: Pos = positive, Neg = negative. – = not reported.

*Mutations were detected in antimony(III) trioxide-induced lung tumors (NTP 2017a).

[a]Negative in rats; uncertain in mice due to severe study limitations.

[b]Uncertain because only available study has severe study limitations.

Studies with severe limitations are not used for the assessment or discussed in the text, but study details and limitations are summarized in the tables in Appendix E.3 along with studies discussed in the text. This section is organized by genotoxic end point, including mutations, and damage to DNA, chromatids, and chromosomes. Within each end point, the results are generally presented in the order of human studies, *in vivo* animal studies, *in vitro* mammalian cell studies, and *in vitro* bacterial cell studies.

6.3.1 Mutagenicity: base substitution and frame shift

Detailed results of the mutagenicity studies regarding base change and fame shift are shown in Appendix E.3, Table E.3-1.

No human cell study was found. In mouse lymphoma L5178Y $TK^{+/-}$ cells *in vitro* antimony(III) trioxide did not increase mutations with or without liver S9 metabolic enzymes and cofactors (Elliott *et al.* 1998).

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

6.3.2 DNA damage

Detailed results of DNA damage studies are shown in Appendix E.3, Table E.3-2. Antimony(III) trioxide exposure was associated with DNA damage in mice and in cultured cells. No study specifically measuring DNA adduct was found.

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

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

In vitro studies of human whole blood and peripheral blood lymphocytes (Schaumlöffel and Gebel 1998) and V79 Chinese hamster cells (Gebel *et al.* 1998) exposed to antimony(III) trichloride showed increased DNA damage (single-strand breaks). DNA damage was detected below cytotoxic concentrations and did not involve DNA-protein crosslinks.

In prokaryotes, evidence for DNA damage has been reported from experiments with sensitive detection capacity. In modified *rec* assay protocols that increased the sensitivity of the *Bacillus subtilis* rec assay 20- to 50-fold (Kada 1976, Hirano *et al.* 1982), antimony(III) trioxide (Kanematsu *et al.* 1980, Kuroda *et al.* 1991) and antimony(III) trichloride (Kanematsu *et al.* 1980, Kuroda *et al.* 1991) both gave positive results. In the very sensitive plasmid pBR322 DNA-nicking assay, trimethylstibine ($Sb(CH_3)_3$) was genotoxic, but antimony(III) potassium tartrate was not (Andrewes *et al.* 2004). In contrast, in the less sensitive assays, antimony(III) trichloride did not induce SOS DNA repair genes in *E. coli* (Lantzsch and Gebel 1997) or *S. typhimurium* (Yamamoto *et al.* 2002). In the traditional *B. subtilis* rec assay, antimony(III) trichloride did not inhibit the growth in the repair-deficient bacteria (Nishioka 1975).

6.3.3 Chromosomal aberrations, micronucleus, and sister chromatid exchange

Detailed results of chromosomal aberrations, micronucleus, and sister chromatid exchange (SCE) studies are shown in Appendix E.3, Table E.3-3.

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, b), including unknown test-substance purity, lack of positive controls, and mortality at the high dose, it is uncertain whether oral exposure to antimony(III) trioxide (Gurnani *et al.* 1992a) or antimony(III) trichloride (Gurnani *et al.* 1992b) induces chromosomal aberrations in mice. Antimony potassium tartrate (described as potassium antimonyl tartrate in the study) administered by intraperitoneal (i.p.) injections increased chromosomal aberrations (excluding gaps and including gaps) in the bone marrow of rats (El Nahas *et al.* 1982).

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

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

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

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

Studies showed that antimony(III) trioxide and other antimony(III) compounds increased chromosomal aberrations, micronuclei, and sister chromatid exchange. Chromosomal aberrations

included chromosome damage (excluding gaps) induced by antimony(III) trioxide by *in vitro* exposure of human cells (Elliott *et al.* 1998) and chromatid breaks induced by antimony(IIII) sodium tartrate by *in vitro* exposure of human cells (Paton and Allison 1972). Micronuclei were increased by antimony(III) trioxide *in vivo* and antimony(III) trichloride *in vitro* exposures. SCEs were increased by antimony(III) trioxide and antimony(III) trichloride in human cells (Gebel *et al.* 1997) and animal cells (Kuroda *et al.* 1991).

6.4 Inhibition of DNA repair

Although effects of antimony(III) trioxide on DNA repair was only investigated indirectly in an unscheduled DNA synthesis study (Elliott *et al.* 1998), those of antimony(III) trichloride and antimony(III) potassium tartrate have in assays directly measure DNA damage repair and enzymes. As summarized in Table 6-3, thee studies suggest that antimony(III) exposure leads to alterations in the abundance, phosphorylation, or localization of various proteins that regulate or mediate NER, NHEJ, and homologous recombination pathways. Whether antimony affects other repair pathways, including base-excision repair or mismatch repair, has not been investigated.

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

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

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

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

Table 6-3. DNA repair pathways and molecules altered by exposure to antimony(III) compounds

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

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

6.5 Alteration of cell proliferation and receptor-mediated effects

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

Among the many receptors related to tumor development, the epidermal growth factor receptor gene (*EGFR*) (an oncogene) is commonly mutated in human lung neoplasms, and so is *KRAS* (a proto-oncogene), which does not code for a receptor but a G-protein influencing cells to divide or differentiate. The mutations of *Egfr* and *Kras* genes were analyzed in the lungs of mice and rats after two-year inhalation exposure to antimony(III) trioxide at 3, 10, or 30 mg/m^3 (NTP 2017a). *Egfr* mutations were seen in the lung tumors of mice (46% of the tissues) and rats (50% of the tissues), whereas no *Egfr* mutations were seen in non-tumorous lung tissue or in spontaneous lung tumors in the control animals. No *Kras* mutations were seen in the control rats, and only one *Kras* mutation was seen in a single lung tumor in antimony(III) trioxide-exposed rats. The incidences of *Kras* mutations in exposed mice were similar to those in control mice. These data suggest that EGFR signaling might play an important role in pulmonary carcinogenesis resulting from chronic antimony(III) trioxide exposure in both rats and mice (NTP 2017a). Detailed results of the studies are shown in Appendix E.4, Table E.4-1.

Antimony(III) potassium tartrate inhibits cell differentiation in cultured skin cells, potentially increasing the chance of tumor development, but in endothelial cells it decreases angiogenesis, which facilitates tumor growth. It is possible that antimony(III) potassium tartrate has both pro- and anti-tumorigenic effects.

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

In cultured human umbilical-vein endothelial cells, antimony(III) potassium tartrate suppressed the activation of several critical receptor kinases involved in angiogenesis, including vascular endothelial growth factor receptor 2, fibroblast growth factor receptors 1 and 2, tyrosine kinase with immunoglobulin-like and epithelial growth factor-like domains 2, and erb-b2 receptor tyrosine kinase 2, at concentrations from 2.5 to 10 μmol/L (Wang *et al.* 2015). Moreover, antimony(III) potassium tartrate suppressed the phosphorylation of Src and focal adhesion kinase in the presence of phosphorylation triggers. In HepG2 (human liver carcinoma) cells, bis[(+)-tartato]diantimonate(III) dipotassium trihydrate (i.e., antimony(III) potassium tartrate trihydrate, equivalent to one molecule of antimony(III) potassium tartrate plus three water molecules), one of the top three affected regulators[1] based on upstream analysis of the microarray data (see Appendix E.5, Table E.5-1) was vascular endothelial growth factor (VEGF). These findings support the notion that antimony(III) potassium tartrate has anti-angiogenic properties in endothelial cells; indeed, antimony(III) potassium tartrate inhibited vascularization of non-small-cell lung cancer xenografts in mice.

6.6 Immunomodulation and inflammation

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

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.

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

In contrast to the lack of information of inorganic antimony immune effects, an organic compound containing antimony(III) was found to affect expression of many genes related to immune reactions. Based on the gene expression profile of HepG2 cells after 6-hour-exposure to bis[(+)-tartato]diantimonate(III) dipotassium trihydrate (equivalent to one molecule of antimony(III) potassium tartrate plus three water molecules) (Kawata *et al.* 2007) analyzed by ORoC (see Appendix E.5), of the top ten canonical pathways affected (see Table E.5-2), seven were related to immune reactions (agranulocyte adhesion and diapedesis, granulocyte adhesion and diapedesis, role of cytokines in mediating communication between immune cells, role of hypercytokinemia or hyperchemokinemia in the pathogenesis of influenza, crosstalk between dendritic cells and natural killer cells, role of interleukin-17A in psoriasis, and role of Wnt/GSK-3β signaling in the pathogenesis of influenza). These findings are consistent with the former use of antimony(III) potassium tartrate as an antiparasitic agent for leishmaniasis. In the upstream analysis (Appendix E.5, Table E.5-1**)**, besides VEGF, the top three affected regulators were colony-stimulating factor 2 (CSF2) (a cytokine), and the triggering receptor expressed on myeloid cells 1 (TREM1), which stimulates neutrophil- and monocyte-mediated inflammatory responses. Both CSF2 and TREM1 stimulate immune or inflammatory responses.

The majority of studies investigating antimony-mediated effects on immunity involve humans and animals with parasite infections undergoing treatment with antimony(V) compounds. Antimony(V) compounds can potentiate inflammatory cytokine responses, macrophage activity, and expression of interferon-γ by T lymphocytes *in vivo* and *in vitro* (Appendix E.6, Table E.6-1). This immune-stimulating effect of antimony(V) may be in part from inhibition of Src homology PTPase1, a key phosphatase involved in regulating cytokine responses and immune-cell activation (Pathak and Yi 2001).

6.7 Epigenetic alterations

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

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

In a study of U.S. Native Americans, antimony exposure was linked to increased global methylation of cytosines and, to a lesser extent, increased global methylation of hydroxycytosines of DNA (Tellez-Plaza *et al.* 2014). Global hypomethylation has been reported to be associated with lung cancer (not from antimony exposure) (Daskalos *et al.* 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).

6.8 Integration of mechanistic information

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

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

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

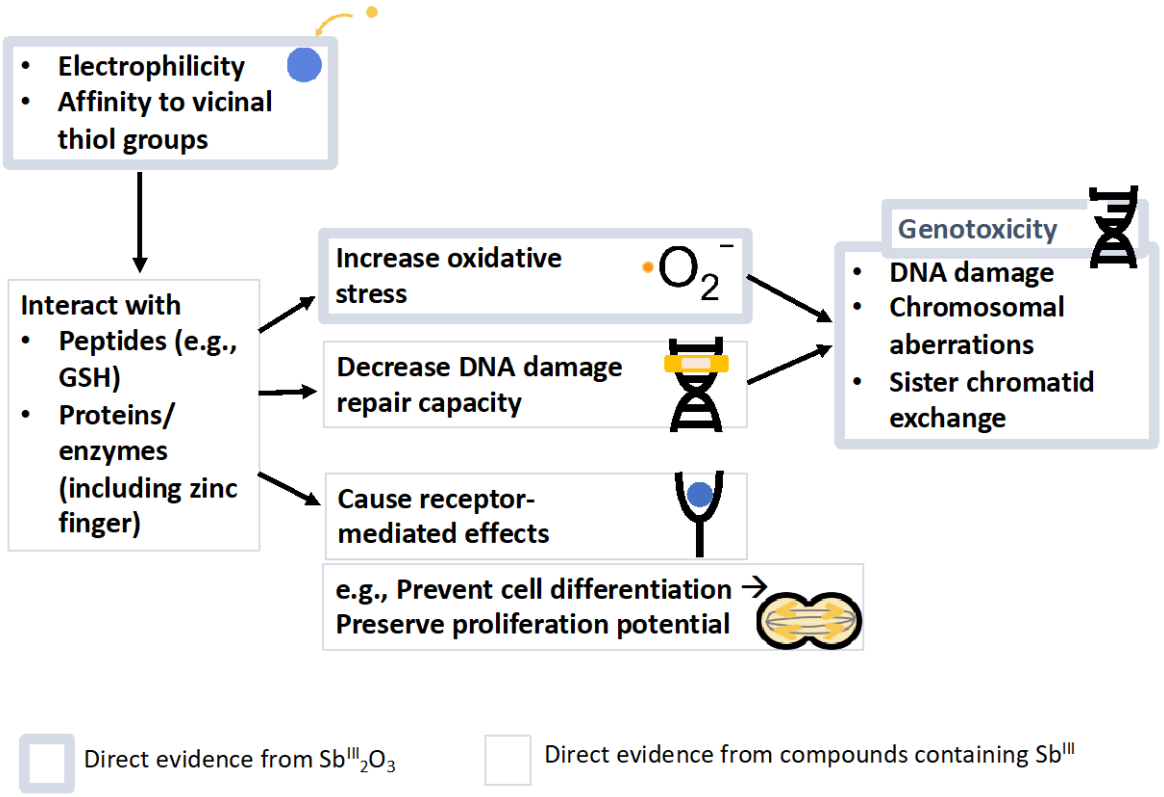


Figure 6-2. Key mechanistic information of antimony(III) trioxide carcinogenicity

Antimony(III) trioxide causes DNA damage, chromosomal aberrations, and micronucleus formation in rodents after *in vivo* exposure, Bacterial assays indicate it does not change the base-sequence in DNA, which is supported by the only available mammalian mutation study. Many studies have shown that various antimony compounds increase oxidative stress and cause oxidative damage. Antimony(III) trioxide also decreases levels of antioxidants in cells. Although antimony(III) trioxide was not used in the DNA repair study, two other antimony(III) compounds decreased DNA repair capacity in human cells *in vitro*, and the effect was due at least in part to displacement of the zinc(II) in zinc fingers of a DNA repair enzyme.

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

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

7 Other Relevant Data

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

7.1 Carcinogenicity studies of other antimony compounds

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

7.2 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 experimental animals exposed to antimony trioxide via inhalation.

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

8.1 Evidence of carcinogenicity from studies in experimental animals

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

The conclusion that antimony(III) trioxide is carcinogenic is based on increased incidences of malignant tumors and increased combined incidences of benign and malignant tumors at several tissue sites in two rodent species exposed to antimony(III) trioxide by inhalation. Increased incidences were observed for lung tumors in rats and mice of both sexes, adrenal-gland tumors in female rats, skin tumors in male mice, and lymphoma in female mice (see Section 5, 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.

8.2 Summary of mechanistic data

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

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

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

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

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

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

8.3 Evidence of carcinogenicity from studies in humans

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

Elevated mortality was reported in three cohort studies of antimony-exposed workers in the United States (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.

8.4 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.

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Abbreviations

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

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

iCSS	interactive Chemical Safety for Sustainability (dashboard)
ILS	Integrated Laboratory Systems, Inc.
JEM	job-exposure matrix
K-562	chronic myelogenous leukemia cells
LC-HG-AFS	liquid chromatography-hydride generation-atomic fluorescence spectrometry
LEC	lowest effective concentration
LOUCY	T cell acute lymphoblastic leukemia cells
M	male(s)
MMAD	mass median aerodynamic diameter
MMP	mitochondrial membrane potential
mo	month(s)
MPPD	multiple path particle deposition (model)
N	number (e.g. total number of animals tested in a group)
n/N	number of animals with neoplasms divided by the total number of animals tested in that group
NAICS	North American Industry Classification System
NAWQA	National Water-Quality Assessment
NB4	acute promyelocytic leukemia cells
NB4-M-AsR3	arsenic resistant APL cells derived in Miller laboratory
NC	negative control
NCBI GEO	National Center for Biotechnology Information Gene Expression Omnibus
NCTR	National Center for Toxicological Research
ND	not determined
Neg	negative
NER	nucleotide excision repair
NHANES	National Health and Nutrition Examination Survey
NHEJ	non-homologous end joining
NIEHS	National Institute of Environmental Health Sciences
NIH	National Institutes of Health
NIOSH	National Institute for Occupational Safety and Health
NOES	National Occupational Exposure Survey

NOS	not otherwise specified
NR	not reported
NTP	National Toxicology Program
NVS	NovaScreen
OR	odds ratio
ORoC	Office of the Report on Carcinogens
OSHA	Occupational Safety and Health Administration
PAHs	polycyclic aromatic hydrocarbons
PC	positive control
PET	polyethylene terephthalate
pH	potential of hydrogen (a logarithmic scale used to specify the acidity or basicity of an aqueous solution)
PHS	Public Health Service
Pos	positive
PVC	polyvinyl chloride
r	correlation coefficient
R	rat(s)
REACH	European Union Registration, Evaluation and Authorisation of CHemicals
RNA	ribonucleic acid
RoC	Report on Carcinogens
ROS	reactive oxygen species
RR	relative risk
s.c.	subcutaneous(ly)
SCE	sister chromatid exchange
SD	standard deviation
SE	standard error
SEER	Surveillance, Epidemiology, and End Results (program)
SIC	standard industrial classification
SIK	a cell line from spontaneously immortalized human keratinocytes
SMR	standardized mortality ratio
std dev	(geometric) standard deviation
TK	toxicokinetics

TLV	threshold limit value
TREM1	triggering receptor expressed on myeloid cells 1
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
U.K.	United Kingdom
U.S.	United States of America
USGS	United States Geological Survey
UVC	ultraviolet C
VC	vehicle control
VEGF	vascular endothelial growth factor
XPA	xeroderma pigmentosum complementation group A
XPE	xeroderma pigmentosum complementation group E

Units of Measurement

Area

cm^2	square centimeter

Concentration

g/L	grams per liter
mg/kg b.w.	milligrams per kilogram body weight
mg/L	milligrams per liter
mg/m^3	milligrams per cubic meter
mg%	milligram percent (equivalent to milligrams per deciliter)
mol/L	moles per liter
ng/g	nanograms/gram
ppm	parts per million
μM	micromolar
μmol/L	micromoles per liter
μg/g	micrograms per gram
μg/kg	micrograms per kilogram
μg/L	micrograms per liter
$\mu g/m^3$	micrograms per cubic meter

Length

ft	feet
in	inch

Mass/Weight

kg	kilogram
lb	pound
mg	milligram
mol	mole
ng	nanogram
μg	microgram

Temperature

°C	degrees Celsius

Volume

dL	deciliter
L	liter
m^3	cubic meter
mL	milliliter

Glossary

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Hypogeusia: A partial loss of the ability to taste.

Hyposmia: A partial loss of the ability to perceive smells.

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

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

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

Loss of heterozygosity: If there is one normal and one abnormal allele at a particular locus, as might be seen in an inherited autosomal dominant cancer susceptibility disorder, loss of the normal allele produces a locus with no normal function. When the loss of heterozygosity

involves the normal allele, it creates a cell that is more likely to show malignant growth if the altered gene is a tumor suppressor gene.

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

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

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

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

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

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

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

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

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

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

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

Non-differential exposure misclassification: The probability of erroneous classification of an exposed individual into a category other than that to which they should be assigned is the same in all study groups.

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

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

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

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

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

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

Personal breathing zone: A sampling area as close as practical to an employee's nose and mouth, (i.e., in a hemisphere forward of the shoulders within a radius of approximately 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*$_{trend}$:** Level of statistical significance of a change over time in a group selected to represent a larger population.

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

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

Schistosomiasis: A disease caused by parasites (genus *Schistosoma*) that enter humans by attaching to the skin, penetrating it, and then migrating through the venous system to the portal

veins where the parasites produce eggs and eventually, the symptoms of acute or chronic disease (for example, fever, abdominal discomfort, blood in stools).

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

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

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

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

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

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

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

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

Toxicokinetics: The determination and quantification of the time course of absorption, distribution, biotransformation, and excretion of a chemical in the body.

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

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

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

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

Draft Report on Carcinogens Monograph on Antimony Trioxide

Revised Draft Substance Profile Proposed for the RoC

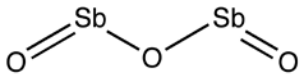
August 15, 2018

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

Antimony Trioxide

CAS No. 1309-64-44

Reasonably anticipated to be a human carcinogen[2]



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. No cancer studies in experimental animals with exposure to antimony trioxide by other routes were identified. This conclusion of carcinogenicity was based on three studies in three different strains or stocks of rats and one study in mice. NTP studies (2017) examined all organs and tissues in both sexes of Wister Han rats and B6C3F1/N mice, and three other studies examined primarily the lung in both sexes of Wistar rats (Groth *et al.* 1986) or Fischer 344 rats (Newton *et al.* 1994) or female CDF rats (Watt 1983). The NTP studies were most informative based on the study design and detailed report, while other studies are also adequate to inform carcinogenicity after critical evaluation of potential bias.

In the lung, exposure of female rats to antimony trioxide significantly increased the incidences of benign lung tumors (alveolar/bronchiolar adenoma) (Groth *et al.* 1986, NTP 2017), which can progress to malignant tumors, and incidences of malignant lung tumors (scirrhous carcinoma and/or squamous-cell carcinoma) (Watt 1983, Groth *et al.* 1986). 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 to be related to exposure to antimony trioxide (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.

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

[2]NTP preliminary listing recommendation proposed for the RoC.

(alveolar/bronchiolar carcinoma) in males and females, and combined benign and malignant lung tumors (alveolar/bronchiolar adenoma and carcinoma) in males and females (NTP 2017). These increases were significant at all three tested concentrations, including the low concentration with no lung clearance overload. In rats, high concentrations of inert particles could "overload" the lung clearance capacity and lead to increased lung cancer. In the case of antimony trioxide, evidence of suggested toxicity and increased cancer at concentration below the occurrence of lung clearance overload showed that observed lung cancer was not due to overload. The incidences of malignant and combined lung tumors in males also occurred with a positive trend.

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). The occurrences of adrenal gland pheochromocytoma might be secondary to hypoxia.

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

↑ = Significant increase
F = in females
M = in males.
* = Considered evidence of antimony trioxide based on multiple factors, although the increase in incidence was not statistically significant (NTP 2017).
– = No exposure-related increase in tumors.

Mechanisms of Carcinogenesis

Antimony trioxide induces several biological effects associated with carcinogenicity that are also observed with other carcinogenic metals; however, the available data did not provide adequate information to determine the overall mechanism by which antimony causes cancer. The relative abundance of the data in each type of characteristic of the substance or biological changes could be a reflection of available studies (e.g., genotoxicity has been studied much longer than epigenetic changes), and not the level of contribution to carcinogenicity. 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.

Overall, *in vivo* effects were increased DNA damage and micronucleus from exposure to antimony trioxide and increase oxidative stress by an antimony(V) compound. *In vitro* effects included increased oxidative stress (and consequently oxidative damage) by antimony trioxide or other antimony compounds, inhibition of DNA repair by antimony trichloride, another trivalent antimony compound, inhibition of cell differentiation by antimony trichloride or antimony potassium tartrate, which also contains trivalent antimony.

Antimony trioxide increases reactive oxygen species (ROS) and adversely affects mitochondria and DNA (Mann *et al.* 2006, Lösler *et al.* 2009), while other antimony compounds also cause oxidative damage to proteins and lipids. Antimony trioxide also decreases antioxidants in cells, which would make the cells more likely to be damaged by oxidants like ROS. Specifically, antimony trioxide lowered levels of reduced glutathione (GSH), an antioxidant, and inhibited the enzymes involved in GSH functions, which would disrupt the normal cellular balance between oxidation and reduction (redox). Cells could be partially protected from antimony(III)-induced oxidative damage by addition of external antioxidants and ROS scavengers. In mice treated with an antimony(V) compound, oxidative damages were seen as protein carbonylation, lipid peroxidation (Bento *et al.* 2013), and DNA damage (Cantanhêde *et al.* 2015, Moreira *et al.* 2017).

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 (small pieces of nucleus produced by incorrect chromosome segregation or other events), indicating genotoxicity and 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, the combination of both, or other changes.

DNA repair effects were not studied with antimony trioxide, but antimony trichloride 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.

Long-term inhalation of 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 may lead to increased cell survival, which in turn can lead to cancer growth. The fact that *Egfr* mutations were not seen in spontaneous alveolar/bronchiolar carcinomas in control animals or nontumor lung tissues in exposed 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 some analyses of all studies of antimony-exposed smelter worker cohorts; however, it is not clear whether the increased risk was due to exposure to antimony. Results may be impacted due to potential confounding bias from concurrent exposure to other lung carcinogens. An increased risk of stomach cancer was found in the U.S. antimony smelter cohort study (Schnorr *et al.* 1995) and the Swedish case-control study (Wingren and Axelson 1993), but not in the U.K. antimony smelter cohort study (Jones 1994).

Properties

Antimony trioxide is the oxide of trivalent (+3) antimony, and it occurs naturally as well as from human activities. Antimony exists in four main oxidation states: –3, 0, +3, and +5. The most common in environmental, biological, and geochemical systems are Sb(III) (the trivalent form) and Sb(V) (the pentavalent form). In nature, antimony trioxide (Sb_2O_3) exists in minerals such as valentinite and senarmontite (Roper *et al.* 2012, ATSDR 2017). Humans purposely oxidize elemental antimony to produce antimony trioxide for various industrial uses. Other forms of antimony can 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 can also be converted to other antimony forms in the environment.

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[a]
Specific gravity, at 24°C	5.9[b]
Melting point	655°C[b]
Boiling point	1425°C[b]
Water solubility, at 22.2°C	[3.3 x 10^{-4}] g/100 mL[b,c]
Vapor pressure, at 574°C	1 mm Hg[b]

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

Although antimony trioxide in water is relatively insoluble and not easily taken up by cells (low bioaccessibility), studies show antimony trioxide in some artificial fluids that mimic various body fluids have higher bioaccessibility. For example, the bioaccessibility of antimony trioxide was highest (81.7%) in artificial lysosomal fluid, followed by 60.8% in artificial sweat, 56.7% in artificial interstitial lung fluid, 41.5% in artificial blood serum, and was lowest (13.6%) in artificial gastric fluid. These are consistent with the observation that inhalation (via lung) of antimony trioxide lead to more adverse health effects than ingestion (via mouth, stomach, and intestine).

Use

The major industrial use of antimony trioxide (EPA 2014, NTP 2017) 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 the coating on back-coated textiles may contain up to 24% (EU 2008).

Antimony trioxide used in industrial processes often changes form during production. In the production of polyethylene terephthalate (PET) plastics, antimony trioxide, which is added in the preparation of the catalyst solution, is readily converted to antimony glycolate (Carneado *et al.* 2015). The final concentration of antimony in PET plastics, where it is bound as antimony glycolate complexes, is 180 to 550 ppm. 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 2018); no marketable antimony has been mined in the United States since 2015 (USGS 2018). The production of antimony trioxide in 2015 was reported to be between 1 million and 10 million pounds (EPA 2017). The U.S. mine production of antimony trioxide has ceased since 2015 (USGS 2018).

Antimony trioxide accounts for 80% of total antimony use in the United States (EPA 2014, NTP 2017). 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 much higher. In

2017, U.S. imports for consumption were approximately 52.8 million pounds of antimony oxide (weight of antimony content) (USGS 2018). In the earlier timeframe, each year between 2007 and 2011, U.S. imports were roughly 61 million pounds (equivalent to approximately 87% of yearly consumption - 70 million pounds) (EPA 2014). 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, 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. A summary of the major sources of antimony trioxide is presented in the table and text below.

Sources of antimony trioxide (Sb_2O_3) and the final forms of antimony (Sb_2O_3 and others) to which people are exposed

Source of antimony trioxide	Exposure route	Expected form of antimony exposure
Sb_2O_3 production: Occupational	Inhalation of Sb_2O_3	Sb_2O_3
	Dermal exposure	Sb_2O_3
Environmental Sb_2O_3: Sb_2O_3 and some non-Sb_2O_3 releasing sources	Inhalation of Sb_2O_3	Sb_2O_3
	Ingestion (from consuming contaminated soil)	Sb ions
	Ingestion (from drinking contaminated water)	Sb(V) ion in oxic environments, and Sb(III) ion in anoxic environments
Sb_2O_3 in flame retardant: Occupational and general population exposure	Inhalation (from breathing indoor air in the workplace and home from containing house dust)	Mainly Sb_2O_3
	Dermal (workplace and from sitting on flame-retardant-treated upholstery)	Sb ions
	Ingestion (from mouthing flame-retardant-treated toys)	Sb ions
Sb_2O_3 used in PET production: Occupational and consumer products	Inhalation: Workers in PET production	Sb_2O_3
	Inhalation: Workers in downstream PET operations	Sb ions
	Ingestion (from drinking liquid in PET bottles)	Sb ions
Sb_2O_3 used in glass, paint and other uses: occupational	Inhalation and dermal: Occupational	Sb_2O_3 and Sb ions (depending on process step)

Sources: EU 2008, ATSDR 2017.

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 $\mu g/m^3$) (Donaldson 1976). 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 $\mu g/m^3$ (ATSDR 2017), and worst-case exposure was estimated at 790 $\mu g/m^3$ (EU 2008). The next-highest exposures have been reported for the flame-retardant industry, at up to 200 $\mu g/m^3$ (ATSDR 1992), with worst-case exposure estimated at 570 $\mu g/m^3$ (EU 2008). Lower exposures occur during the use of antimony trioxide in the PET industries (with an estimated worst-case exposure of 26 $\mu g/m^3$ when used to generate the catalyst, antimony glycolate) and glass industries (1980s measurements were 40 to 840 $\mu g/m^3$, Lüdersdorff *et al.* (1987); estimated worst-case exposure is 15 $\mu g/m^3$ (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.* 2011, 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 due to automobile-generated air pollution in high traffic areas. Antimony trisulfide is used as a lubricant in the abrasive material of brakes and can be oxidized to antimony trioxide by the frictional heat resulting from braking (Quiroz *et al.* 2009). The study by Quiroz *et al.* in Valparaiso City, Chile reported very high levels of antimony in the blood (average concentration of 27 ± 9 ng antimony/kg) of port workers exposed to high vehicular traffic; the levels were 5 to 10 times higher than control groups from either another part of the city or a rural area outside Valparaiso.

Exposure of the General Population

Antimony has been detected in urine, whole blood, and saliva from U.S. residents. Data from the National Health and Nutrition Examination Survey reported low levels of urinary antimony (0.043 μg/L for 2013 to 2014), and levels might 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, Tyrrell *et al.* 2013, Gonzales *et al.* 2016) and in younger population (6-11 and 12-19 years old) than in adults (20 years and older) (CDC 2017). 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. Antimony is present almost entirely in the particulate matter in air. In 2010, EPA estimated from Toxics Release Inventory data that approximately 11,635 lb of antimony were released into the air from 273 U.S. facilities that likely produced, processed, or used antimony trioxide-containing flame retardants (EPA 2014). Antimony concentrations in outdoor air are highest near facilities that release antimony trioxide into the air, such as mines and smelting operations; levels reported in the 1970s ranged from 0.146 to 300,000 μg/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 (approximately 0.001 μg/m^3) (ATSDR 2017).

Exposure to antimony from surface water or soil likely does not result from antimony trioxide, because antimony trioxide is converted to different forms in the environment. Antimony trioxide in solution produces the trivalent antimony ion, which hydrolyzes to either the neutral trivalent species antimony (III) hydroxide, $Sb(OH)_3$, or the charged pentavalent species (the antimonate ion), $Sb(OH)_6^-$ (EU 2008). Exposure to antimony in the soil is expected to be minimal because of antimony's low solubility and mobility (EPA 2014, Li *et al.* 2014).

Drinking water and food are not considered sources of exposure to antimony trioxide. The European Union risk assessment for antimony trioxide noted that antimony present in drinking water and foods is not in the form of antimony trioxide (EU 2008).

General population are potentially exposed to antimony trioxide from consumer products containing antimony trioxide as a flame retardant synergist and more specifically from the dust generated from the wear and tear of 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^3 of air (EU 2008). The exposure in children, especially infants, is likely increased due to their proximity to carpet containing antimony trioxide than adults do and mouthing of toys with antimony-containing fabric, paint or plastics; the estimated worst-case daily exposure from eating house dust (e.g., from unwashed hands) is 0.6 μg/kg of body weight (EU 2008).

Regulations

Consumer Product Safety Commission

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

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

Department of Transportation (DOT)

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

Environmental Protection Agency (EPA)

Clean Air Act

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

Clean Water Act

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

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

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

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 5,000 lb for elemental antimony;

= 1,000 lb for antimony and other antimony compounds

as specified by EPA.

Emergency Planning and Community Right-To-Know Act

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

Resource Conservation and Recovery Act

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

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

Safe Drinking Water Act

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

Food and Drug Administration (FDA)

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

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

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

Occupational Safety and Health Administration (OSHA)

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

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

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 0.5 mg/m^3 for elemental antimony and compounds (as Sb).[3]

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) = 2×10^{-4} mg/m^3 for antimony trioxide.

Regional Screening Levels (formerly Preliminary Remediation Goals):

Residential soil = 3.1 mg/kg for elemental antimony;

= 28,000 mg/kg for antimony trioxide.

Industrial soil = 47 mg/kg for elemental antimony.

Residential air = 0.021 µg/m^3 for antimony trioxide.

Industrial air = 0.088 µg/m^3 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^3 (10-h TWA) for elemental antimony and other antimony compounds (as Sb).

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

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

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