Report on Carcinogens Protocol: Methods for Preparing the Draft Report on Carcinogens Monograph on Antimony Trioxide and Other Antimony Compounds

Running title - Antimony: RoC Protocol

July 28, 2017

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National Institute of Environmental Health Sciences
U.S. Department of Health and Human Services

Table of Contents

Peer-Review

The Office of Reports on Carcinogens (ORoC) of the National Toxicology Program (NTP) gratefully acknowledges the following individuals for their peer review of the Report on Carcinogens (RoC) protocol on *Antimony Trioxide and Other Antimony Compounds*:

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Introduction

Objective

The objective of this protocol is to provide the methods and guidance that will be used to prepare the cancer hazard evaluation component of the draft Report on Carcinogens (RoC) monograph on *Antimony Trioxide and Other Antimony Compounds*. This monograph will evaluate whether exposure to antimony is a cancer hazard. This protocol applies the general methods outlined in the Handbook for Preparing RoC Monographs (hereinafter referred to as RoC Handbook) (NTP 2015) to issues specific for antimony.

Antimony trioxide is the most important antimony species in many aspects (production volume, use, general public potential exposure via inhalation, etc.), but antimony can transform in the environment and most biomonitoring data are for total antimony. Some studies have reported that antimony biomarkers may be associated with adverse biological effects or health outcomes (ATSDR 2017). Therefore, we seek to understand the contribution of antimony chemical species in biological effects.

Scope

- The monograph will focus on antimony trioxide because the database on animal carcinogenicity studies is only adequate for evaluating this compound.
- The monograph will also assess relevant information (e.g., properties, metabolism, and mechanistic data) on other antimony species and will attempt to use (quantitative) structure activity relationship ([Q]SAR) and read-across approaches to evaluate their potential carcinogenicity.

Key questions

- Is antimony trioxide carcinogenic?
- What role do antimony chemical species play in antimony carcinogenic potential?
    - To what extent does transformation between trivalent form of antimony, Sb(III), and pentavalent form of antimony, Sb(V), occur *in vivo*?
    - Is there a difference in toxicity or carcinogenic potential between Sb(V) and Sb(III)?
- Can antimony trioxide be considered a representative antimony species for cancer hazard evaluation?
- Are any other antimony compounds (excluding antimony trioxide) carcinogenic?

Background information

Antimony is a metalloid found in nature in over 100 mineral species, most commonly antimony trisulphide (Sb_2S_3) occurring as in the mineral stibnite and to a lesser extent antimony trioxides (Sb_2O_3) in the minerals valentinite and senarmontite (ATSDR 1992). Antimony exists in four oxidation states, -3, 0, +3, and +5; the Sb(III) and Sb(V) forms are the most common in nature. Elemental antimony is a silver white metal primarily used to make alloys.

Antimony trioxide is the most commercially significant form of processed antimony (EPA 2014, NTP 2017), and it is used as a synergist for halogenated flame-retardants in plastics (including but not limited to polyvinyl chloride [PVC]), rubber, and textiles. Antimony trioxide can also be used as a catalyst in polyethylene terephthalate (PET) production, as an additive in glass manufacture and in pigments, and as an additive in paints and ceramics.

Other notable antimony species include antimony trisulfide (Sb_2S_3) (trivalent) and medicinal antimonials – pentavalent antimony compounds (e.g., sodium antimony gluconate and meglumine antimoniate) used to treat leishmaniasis, and trivalent antimony potassium tartrate formerly used to treat schistosomiasis (OEHHA 2016). Antimony trisulfide is used as a plasticizer and pigment, and in pyrotechnics and explosives (IPCS 2017).

Both epidemiological studies and experimental animal studies play important roles in understanding potential carcinogenicity, and both types of studies will be systemically reviewed. Due to co-exposure to other known carcinogens in epidemiological studies, the mode of action of antimony trioxide and possibly other antimony compounds will rely on *in silico*, *in vitro*, and *in vivo* animal studies.

Cancer hazard evaluation

The purpose of the cancer hazard evaluation is (1) to assess the available scientific evidence, (2) to apply the RoC listing criteria[1] to this evidence, (3) to reach a preliminary level of evidence conclusion, and (4) to recommend a listing status in the RoC. Briefly, the RoC listing criteria for the two listing categories are as follows:

Known to be a human carcinogen

- Sufficient evidence of carcinogenicity from studies in humans

Reasonably anticipated to be a human carcinogen

Fulfill one of more of the criteria below when the body of evidence is not sufficient for listing as a known to be a human carcinogen:

- Limited evidence of carcinogenicity from studies in humans
- Sufficient evidence of carcinogenicity from studies in experimental animals
- Substance belongs to a structurally related class of substances that are listed in the RoC
- Convincing relevant information that the agent acts through a mechanism indicating it would likely cause cancer in humans

When none of the above listing criteria are fulfilled, the substance is not listed in the RoC.

Protocol components

This protocol discusses the methods that will be used to prepare the cancer hazard evaluation component of the draft monograph on *Antimony Trioxide and Other Antimony Compounds.*

- Part 1: Outline of the Draft RoC Monograph

[1] For the formal Report on Carcinogens listing criteria, see http://ntp.niehs.gov/go/15209.

1 Outline of the Draft RoC Monograph

The draft RoC monograph on *Antimony Trioxide and Other Antimony Compounds* focuses on the relationship between cancer and exposure to antimony. The cancer hazard evaluation component of the monograph is organized by topic and includes several sub-sections, as described below. Appendices to the monograph contain additional information, including descriptions of the quality evaluation of the human cancer studies and cancer studies in experimental animals.

The major sections in the cancer hazard evaluation are as follows:

1.1 Substance chemical properties and human exposure

This section includes details on the chemical properties of antimony trioxide and other antimony compounds. The section also provides an overview of the available information on human exposure to antimony in the United States of America.

1.2 Human cancer studies

This section separately reviews and assesses the quality and utility of the available studies of cancer in humans exposed to antimony to inform the cancer hazard evaluation. In Section 5, evidence from the human studies will be synthesized with evidence of mechanistic studies on antimony trioxide and other antimony compounds.

1.3 Experimental animal cancer studies

This section reviews and assesses the quality and utility of the available studies of cancer in experimental animals exposed to antimony compounds to inform the cancer hazard evaluation. It also integrates the evidence across studies and applies the RoC listing criteria to reach a preliminary level of evidence conclusion for the carcinogenicity of antimony in experimental animals.

1.4 Mechanisms, toxicokinetics, and other relevant data

This section assesses the strength of mechanistic and related evidence for carcinogenic effects from exposure to antimony compounds. Included in this section are (1) studies in humans and mammalian experimental animals that investigate hallmarks of cancer or characteristics of carcinogens, (2) studies investigating absorption, distribution, metabolism, and excretion of antimony in humans and mammalian experimental animals, (3) the roles of antimony chemical species in antimony potential carcinogenicity, and (4) a discussion of studies in humans, animal models, and *in vitro* models on potential mechanisms of antimony-related carcinogenicity.

1.5 Overall cancer hazard evaluation

The final section of the draft RoC monograph describes the methods used to integrate the evidence from the cancer studies in humans and mammalian experimental animals with mechanistic and other relevant data and applies the RoC listing criteria to reach the NTP preliminary listing recommendation for antimony exposure in the RoC. This section will also discuss the strength of evidence for grouping specific antimony compounds for cancer classification, and the RoC recommendation.

1.6 References

1.7 Appendices

The appendices in the Draft RoC Monograph will contain important supplementary information such as the literature search strategy, study quality tables, and study descriptions, and results from key studies.

2 Methods for Evaluating Chemical Properties and Human Exposure

2.1 Introduction and objectives

Antimony exposure to humans in the United States will be assessed in this section of the monograph by reviewing available data on production, use, sources, environmental releases, and measured levels for occupational exposure and for the general population, who are potentially exposed to antimony compounds from the environment or consumer products.

2.1.1 Key questions

- What are the sources of exposure? How are people exposed to antimony compounds?
- Is a significant number of people residing in the United States exposed to antimony?
- What are the antimony chemical forms that occur in human exposure? Can the current analytical methods and available monitoring studies address this question?

2.1.2 Approach

The approach for planning, literature search strategy, section contents, and drafting is detailed in Part C of the Handbook for Preparing Report on Carcinogens Monographs (2015) (i.e., the RoC Handbook).

Data related to methods, properties, occurrence, and human exposure to antimony are collected from secondary sources, authoritative reviews, and online resources outlined in the RoC Handbook (see Part C: Section 1 and Table C-1).

Concepts used in the search for potentially relevant literature are provided in Table 2-1 below. A detailed description of the substance-specific search strings is included in Appendix A of this protocol. The search strategy uses terms related to antimony combined (using "and") with "speciation" in three scientific databases (PubMed, Scopus, and Web of Science), and with "occurrence" in PubMed only.

Table 2-1. Literature search strategy for exposure

Substance-specific search concepts[a]	Exposure and properties search concepts[b]
Antimony, antimony trioxide, antimonial, antimoniate, CAS numbers, synonyms (stibine)	Occurrence, speciation

[a]See Appendix A, Table A-1 for the detailed search strings.
[b]See Appendix A, Tables A-2 (occurrence) and A-3 (speciation) for the detailed search strings.

3 Methods for Evaluating Human Cancer

3.1 Introduction

The human cancer hazard evaluation component of the draft monograph on antimony trioxide and other antimony compounds will evaluate relevant epidemiologic studies on antimony exposure and cancer.

The available human studies generally do not provide specific information on the antimony species to which occupational study populations were exposed; however, workers in smelters were reportedly exposed to antimony trioxide, as well as other antimony oxides and antimony sulfides. Because specific antimony species or antimony groups are not available in human cancer studies, the generic term “antimony” is used in this section.

The available studies on exposure to antimony and human cancer consist primarily of (1) cohort studies of exposed workers in antimony and tin smelter plants, (2) a case-control study of art glass workers exposed to elemental mixtures containing antimony, and (3) a population-based cohort study of urinary antimony.

3.1.1 Objective

The objective of this section is to reach a preliminary level of evidence conclusion for the carcinogenicity of antimony from studies in humans by applying the RoC listing criteria to the body of evidence. If the evidence is inadequate to reach either *Sufficient* or *Limited* evidence level, it will be described as not meeting the RoC listing criteria.

Sufficient evidence of carcinogenicity from studies in humans: indicates a causal relationship between exposure to the agent, substance, or mixture, and human cancer.

Limited evidence of carcinogenicity from studies in humans: a causal interpretation is credible, but alternative explanations, such as chance, bias, or confounding factors, could not adequately be excluded.

3.1.2 Key questions

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

3.1.3 Approach: Steps in the cancer hazard evaluation process

The steps for conducting the human cancer hazard evaluation are outlined below. The procedures and guidelines for conducting each step are described in Sections 3.2 through 3.6 of this protocol.

1. Selection of the literature to be included in the cancer hazard evaluation of the human studies (Section 3.2)
2. Systematic extraction of data from the epidemiologic studies (Section 3.3)
3. Assessment of the utility of the individual epidemiologic studies (Section 3.4)
4. Assessment of the level of evidence for carcinogenicity (sufficient, limited, or inadequate) of antimony from human studies (Section 3.5)
5. Integration of the scientific evidence across human cancer studies (Section 3.6)

3.2 Selection of the literature included in the human cancer hazard evaluation

Concepts used in searches of three scientific databases (PubMed, Scopus, and Web of Science) for potential antimony exposures and cancer studies in humans are provided in Table 3-1 below. The search strategy used terms related to antimony combined (using "and") with search terms for epidemiological studies and with search terms for the outcome, i.e., cancer. A detailed description of the substance-specific search strings is included in Appendix A of this protocol, and the RoC standard search strings used for this and other searches are provided in the RoC Handbook Appendix: Standard search strings for databases searches). Citation analysis of articles, reports, and reviews identified from this search strategy are used to identify any additional primary studies or other relevant literature.

The use of antimony for the treatment of Leishmaniasis is considered an intentional medical exposure and out of the scope of this monograph. The large corpus of literature related to leishmaniasis treatment was excluded when identifying human studies.

Table 3-1. Literature search strategy for human cancer studies

Substance-specific search concepts[a]	Epidemiologic search concepts[b]	Cancer search concepts[b]
Antimony, antimony trioxide, antimonial, antimoniate, CAS numbers, synonyms (stibine) **Exposure scenarios:** Smelting, art glass, flame retardants **Excluded:** Leishmaniasis, Leishmania	RoC Epidemiological (Human) Search Strings	RoC Cancer Search Strings

[a]See Appendix A, Tables A-1 (substance-specific terms) and A-4 (exposure-scenario terms) for the detailed search strings.
[b]See RoC Handbook Appendix: Standard search strings for databases searches for search terms for human epidemiological studies and cancer.

Retrieved citations are screened and selected using Health Assessment Workspace Collaborative (HAWC) software according to the procedures outlined in the RoC Handbook, Part B, Section 2. HAWC software is an open-source, modular, content-management system designed to facilitate synthesis of multiple data sources, integrating and documenting workflow from literature search to data extraction, synthesis, and interpretation.

3.3 Systematic extraction of data from the epidemiologic studies

The latest published or most comprehensive follow-up or update for each of the studies is extracted. Additional relevant information (such as exposure data or other analyses) from earlier and related publications on the same or overlapping study population is also included if these publications provide unique or additional data to inform the cancer hazard evaluation of the primary study under review.

Detailed information regarding study data and methods abstraction from individual studies is described in the RoC Handbook, Part D, Section 3.

3.4 Assessment of the utility of the individual epidemiologic studies

3.4.1 Overview of approach

Each primary study is systematically evaluated by two independent reviewers for its ability to inform the cancer hazard evaluation using five domains related to risk of bias (selection and attrition bias, exposure assessment, outcome assessment, potential confounding, and analysis and selective reporting) and one domain related to study sensitivity. General methods used to assess the utility of the individual epidemiologic studies are described in detail in the RoC Handbook, Part D, Section 4.

Domain-level judgment terms: Responses for core questions

The evaluation of the potential for bias in each domain is captured by the core questions. A series of signaling and follow-up questions are used to address specific issues related to the core question and are used to provide transparency for the domain-level judgment provided below; the responses to the questions are captured in the rationale for the response to the core question. These questions are not meant to be a checklist. When adequate information is available, a judgment is made for the direction and distortion of each bias. For detailed description of each judgment (low/minimal concern, some concern, major concern, critical concern or inadequate, and inadequate information), see the RoC Handbook, Part D, Section 4.1.2.

> ***Low/minimal concern***: Information from the study design and methodology indicate that the study is close to ideal and that the potential for bias is unlikely, recognizing general limitations of observational studies.
>
> ***Some concern***: The study design or methodology is less than ideal, and there are some concerns about potential bias.
>
> ***Major concern***: The study design or methodology suggests that the potential for a specific type of bias is likely.
>
> ***Critical concern or inadequate***: Distortion of estimates due to bias makes the study unreliable for hazard identification.
>
> ***Inadequate information***.

The core questions, domain level ratings, and guidelines below will be used to evaluate study quality for antimony.

3.4.2 Selection and attrition bias

Core question, domain level ratings, and guidelines for the domain level ratings are provided below. For more information on selection bias including signaling and follow-up questions and examples of domain level rating, see the RoC Handbook, Part D, Section 4.2.1 and Table D-2.

Core question:

Is there a concern that selection into the study or out of the study was related to both antimony exposure and to outcome?

Domain level ratings:

Low/minimal concerns: (***) rating

Cohort is clearly defined (e.g., includes the relevant exposed and non-exposed) for a specific time period/location with no evidence that follow-up differs between exposed and non-exposed.

Case and controls selected from the same population used similar methods and criteria. No evidence that selection of the subjects is related to both antimony exposure and disease.

No evidence of healthy worker effect (HWE), such as left truncation, was present, or appropriate measures were used to address the potential bias.

Critical concerns: Inadequate rating

Strong evidence that selection or attrition of subjects is clearly related to both exposure to antimony and cancer.

Guidelines for reaching domain level ratings:

Potential biases in antimony occupational cohort studies include systemic bias, HWE, including healthy worker survival effect (HWSE) and left truncation, and incomplete follow-up, were present.

3.4.3 Information bias: Potential exposure misclassification

One of the most important aspects of a study is the ability to characterize exposure at the individual level. Core question, domain level ratings, and guidelines for the domain level ratings are provided below. For more information on exposure misclassification including signaling and follow-up questions, and examples of domain level rating, see the RoC Handbook, Part D, Section 4.2.2 and Table D-3.

Core question:

Is there a concern that methods to assess exposure to antimony do not distinguish between exposed and non-exposed subjects or exposure categories?

Domain level ratings:

Low/minimal concerns: (***) rating

Exposure assessment methods have good sensitivity and specificity leading to reliable classification (or discrimination) with respect to both ever exposure, exposure level, timing, or other relevant metrics (see guidelines for characteristics of ideal exposure assessments). Alternatively, exposure assessment methods may be less than ideal, but detailed information on exposure assessment allows for discrimination between exposed and non-exposed and exposure category.

Critical concerns: Inadequate rating

Exposure is not at the individual level or not likely to reflect individual exposure. Study has poor sensitivity and specificity resulting in poor discrimination between exposed and non-exposed and exposure category.

Guidelines for reaching domain level ratings:

Detailed exposure assessment is desirable primarily to reduce measurement error. The ideal study would include quantitative estimates of exposure to various antimony compounds alone and relevant co-exposures for each individual that are based on monitoring data (e.g., ambient or personal air levels or biological monitoring).

Studies using only job titles that have been probabilistically ranked as likely to have been exposed to antimony would be assigned a lower quality rating than studies that gather more data about detailed work patterns from individuals or employment records or job-exposure matrices although details on the working environment may increase confidence in the exposure assessment. Ideally, classfication of exposure should be at the individual level.

Urinary antimony was identified as a useful biomarker for antimony exposure given rapid excretion in occupational settings (Lüdersdorf *et al.* 1987). In a sample of battery workers, the elimination half-life of antimony was 93.2 to 95.1 hours (Kentner *et al.* 1995). Median urinary antimony concentrations in a nationally representative sample of the U.S. population ranges from 0.13 µg/L (or 0.12 µg/g of creatinine) in 1999 to 2000 to 0.05 µg/L (or 0.06 µg/g of creatinine) in 2011 to 2012 (CDC 2015). Personal air sampling of low-levels of antimony trioxide in an occupational study ranging from 0.01 to 0.55 $\mu g/m^3$ corresponded with mean urinary antimony concentrations of 0.31 ± 0.24 µg/L and 0.36 ± 0.29 µg/L measured at the beginning and end of a work shift, respectively (Iavicoli *et al.* 2002).

Misclassification of exposure in cohort studies is almost always non-differential and usually results in a bias towards the null, i.e., an underestimation of the true risk estimate. In general, exposure is better characterized in most occupational cohort studies than in geographical cohort studies or population-based case-control studies.

Ideally, exposure assessment investigators and interviewers should be blinded to the status of cases and controls. Of these, the blinding of the investigators conducting exposure assessments is considered the most important; blinding in-person interviewers may not be feasible (e.g., the health of the subject with cancer).

3.4.4 Informational bias: Potential outcome misclassification

Studies are evaluated for their adequacy in measuring disease outcomes, including missing data and the probability of misclassification of disease. Outcome as all cancer (without site specific information) is not very informative, because cancer is a collection of related diseases and thus a risk estimate for all cancer is insensitive to detected associations with a specific type of cancer(s). Similar to exposure misclassification, the effects of non-differential misclassification of a binary endpoint will produce bias towards the null, provided that the misclassification is independent of other errors.

Core question, domain level ratings, and guideline for reaching the domain level ratings are provided below. For a discussion of potential biases, signaling, follow-up questions, and examples of domain level rating, see the RoC Handbook, Part D, Section 4.2.3 and Table D-4.

Core question:

Is there a concern that the outcome measure does not reliably distinguish between the presence or absence (or degree of severity) of the outcome?

Domain level ratings:

Low/minimal concerns: (***) rating

Outcome methods clearly distinguish diseased and non-diseased subjects. Follow-up and diagnoses are conducted independent of exposure status.

Critical concerns: Inadequate rating

There is strong evidence that the methods do not discriminate between diseased and non-diseased subjects and/or follow-up and diagnoses are likely related to exposure status.

Guidelines for reaching domain level ratings:

Based on preliminary epidemiological literature search results, the major human cancer sites of interest are the lung and stomach. The Surveillance, Epidemiology, and End Results (SEER) database of the National Cancer Institute is used to examine the utility of mortality data based on historical U.S. population statistics for specific cancer sites.

For lung cancer, 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 (Table 15.6, Howlader *et al.* 2017; https://seer.cancer.gov). 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 SEER age-adjusted data (Table 15.12, Howlader *et al.* 2017; https://seer.cancer.gov, suggesting incidence and mortality data may be of similar utility).

For stomach cancer, from 1975 to 2014, age-adjusted incidence rates for men in the United States were 12.6 per 100,000 men (Table 24.5, Howlader *et al.* 2017; https://seer.cancer.gov). Similar to lung cancer, stomach cancer has comparable low five-year survival rate (30.3%) based on 2007 to 2013 SEER age-adjusted data (Table 24.8, Howlader *et al.* 2017; https://seer.cancer.gov). Given the low survival for stomach cancer, mortality data may of similar utility to incidence data.

Very few antimony exposure studies examined other cancer endpoints such as colorectal cancer.

3.4.5 Potential confounding bias

Core question, domain level ratings, and guideline for reaching the domain level ratings are provided below. For more information on evaluating how studies assessed confounding, including signaling and follow-up questions, and examples of domain level ratings, see the RoC Handbook, Part D, Section 4.2.4 and Table D-5. For information on evaluating whether confounding exists in the study, see Part D, Section 5.1.1.

Core question:

Is there a concern that either the methods are inadequate or there is inadequate information to evaluate potential confounding?

Domain level ratings:

Low/minimal concerns: (***) rating

Studies measured all relevant potential confounders and/or used appropriate statistical analyses or designs to address them. Final statistical models should, however, only include "actual" confounders and not variables that have minimal effect on the risk estimate.

Critical concerns: Inadequate rating

Studies did not provide any information on potential confounders.

Guidelines for reaching domain level ratings:

Potential confounders evaluated in relevant antimony exposure studies include (1) occupational co-exposures and (2) non-occupational exposures or lifestyle factors. Critical common confounders, defined in this assessment, are factors associated with exposure and strongly associated with disease that are not in the causal pathway, and are not correlated with other risk factors. In addition, it may not be possible to identify common confounders across studies because the relationship between activity and exposure may vary by population and comparison group.

Occupational co-exposures:

Studies should ideally provide quantitative exposure data for each potential confounder as part of a job-exposure matrix or expert assessment for each worker. However, some studies provide quantitative or qualitative data on co-exposures for subsets of workers, which can be used to evaluate potential confounding.

In metal smelting and glass working settings, multiple occupational co-exposures are highly likely given the nature of the products being manufactured. Knowledge of antimony manufacturing processes or patterns of use in glass working, smelting, battery facilities, and fire-retardants in textiles may also be helpful in understanding the potential co-exposures likely to be present in the workplace.

Manufacturing of art glass is considered to be a carcinogenic agent for lung cancer. Known occupational agents for stomach cancer include rubber production, asbestos, and lead (IARC 2017); of these agents, lead is a co-exposure for antimony and thus a potential confounder.

Among antimony smelter workers (Jones 1994; Schnorr *et al.* 1995), lung carcinogens most likely to be present in the occupational setting include arsenic and lead (lead is also a stomach carcinogen), possibly polycyclic aromatic hydrocarbons (PAHs), and possibly asbestos. Tin smelter workers (Jones *et al.* 2007) are also potentially exposed to lead and arsenic as well as cadmium and radiation.

Non-occupational exposures or lifestyle factors:

Ideally, quantitative information on other non-occupational exposures or lifestyle factors should be assessed, and preferably by in-person interview by interviewers blinded to the status of the respondent in cancer incidence studies, rather than via proxy respondents, work records, or other indirect methods. Residual confounding is more likely when only limited qualitative information (e.g., dichotomous yes or no) on a given risk factor is available.

Smoking is an important risk factor for both lung and stomach cancer. Occupational lung and stomach cancer studies should assess smoking prevalence among exposed and non-exposed participants. When available, data on nonmalignant respiratory diseases (e.g., hard-metal pneumoconiosis or pulmonary fibrosis) or smoking-related diseases (e.g., chronic bronchitis, emphysema) may provide indirect information about risk factors for specific cancer endpoints of concern. However, retrospective occupational cohorts often do not have information on smoking patterns of participants although they sometimes have smoking information from subsets of the cohort.

In addition to demographic factors, important lifestyle potential risk factors (identified by IARC 2017) for stomach cancer include consumption of processed meat, salted fish, pickled vegetables, nitrate or nitrite (ingested under conditions that cause endogenous nitration), and infection with *Helicobacter pylori* (*H. pylori*) (IARC 2012) or with Epstein-Barr virus (NTP 2016). However, none of these are suspected to correlate with occupational exposure to antimony and thus would not be a potential confounder.

3.4.6 Potential bias from selective reporting and analysis

Core questions are provided below. No antimony exposure-specific issues, guidelines, or ratings were identified. For more information including signaling and follow-up questions, and examples of domain level ratings, see the RoC Handbook, Part D, Sections 4.2.5 and 4.2.6 and Tables D-6 and D-7.

Selective reporting

Core question:

Is there a concern that the study does not provide results for all relevant measures and participants biasing its interpretation?

Analyses bias

Core question:

Is there a concern that the data assumptions and analysis are not adequate or the study does not conduct relevant analysis on available data?

3.4.7 Evaluation of study sensitivity

Core question, domain level ratings, and guidelines are provided below. For more information including signaling and follow-up questions, and examples of domain level ratings, see the RoC Handbook, Part D, Section 4.2.7 and Table D-8.

Core question:

Does the study have adequate sensitivity to detect an effect from exposure (if present)?

Domain level ratings:

High utility (***) rating

Study has an adequate number of exposed subjects, with substantial (level, duration, or range) exposure and adequate duration of follow-up for latency.

Inadequate utility

Study is moderate or small with few exposed subjects and/or exposure is unlikely to be substantial enough (based on other knowledge) to detect an effect.

Guidelines for domain level ratings:

Detection of cancer endpoints requires a relatively large cohort and/or higher exposure prevalence for an adequate ability to detect an effect.

Studies evaluating exposure groups in which the majority of workers classified as "exposed" have very low exposure, very short duration of employment, or limited evidence of actual exposure may be inadequate to detect an effect due to a dilution effect. Further, the ability to evaluate exposure-response relationships depends on an adequate range of exposure (in intensity or duration) among the study participants, and adequate numbers of subjects in each exposure category.

Inadequate duration of follow-up may bias findings toward the null for cancer endpoints with longer latencies. Using cancer incidence data to model approximate latency periods for various cancer subtypes, Nadler and Zubenko (2014) estimated latency (approximate time from cancer initiation to diagnosis, not from exposure to cancer occurrence) for lung cancer to be 13.6 years and for stomach cancer 22.3 years. Minimum latency estimates have been reported in the literature for lung cancer associated with exposure to asbestos (19 years; Selikoff *et al.* 1980, Magnani *et al.* 2008, Harding *et al.* 2009), and chromium (5 years; Harding *et al.* 2009).

3.4.8 Study-level judgment for overall utility for health hazard evaluation

The overall study utility is based on consideration of both the potential for biases (i.e., study quality) and consideration of study sensitivity. Serious concerns about risk of biases would result in lower utility ranking; however, a well-designed study with low study sensitivity (such as few exposed/expected cases for a specific endpoint) could be given a lower utility ranking. When adequate information is available, a judgment is made for the direction and distortion from the overall biases for a study or whether it has low sensitivity to detect an effect. Studies with critical concern for bias in a domain are usually considered to be uninformative and are not brought forward to the cancer hazard evaluation. This evaluation occurs prior to the cancer assessment (e.g., interpreting the finding of the study).

- High (low/minimal concerns for bias and high sensitivity rating)
- Moderate (low/minimal or some concerns for bias, high or moderate sensitivity rating)
- Moderate/low (major to low concerns for bias, sensitivity rating varies)
- Low (major concerns, sensitivity rating varies)
- Inadequate (critical concerns for bias, sensitivity rating varies)

3.5 Cancer hazard evaluation

Detailed information regarding the methods for cancer hazard evaluation is described in the RoC Handbook, Part D, Section 5.1.

The application of the RoC listing criteria to the body of studies on antimony includes evaluating (1) whether there is credible evidence for an association between exposure to antimony and cancer, and (2) whether such an observed association can be explained by chance, bias, or confounding.

The most informative studies (i.e., lowest risk of bias and greatest sensitivity to detect an effect) are given the most weight in the evaluation. The identification of the potential for specific types of uncontrolled bias or confounding, the assessment of study sensitivity, and the presence of effect modification are also used to interpret the findings from studies and to help explain heterogeneity across studies.

Conclusions about the evidence from each study should consider the strengths and weaknesses of the study, the direction and distortion of the biases, the role of measured and unmeasured effect modifiers, and the strength of the association between exposure and the cancer endpoint.

The evidence from the studies is then synthesized across studies and several considerations – strength of the association, consistency across studies, evidence of an exposure-response gradient, and temporality of exposure – are used to help reach a level of evidence conclusion. While these factors are important for summarizing evidence across studies, it should be noted that they do not constitute absolute criteria.

3.5.1 Evaluation of confounding

There may be evidence from the study to suggest that although the risk estimate may be explained in part by confounding or bias, the bias cannot explain all excess risk. Thus, the evaluation of confounding is considered in several steps in the cancer hazard evaluation and therefore merits a cohesive discussion. In addition to considering the study methods for evaluating confounding discussed in Section 3.4.4, the evaluation of potential confounding may also consider (1) the distribution of the potential confounder in the exposed and non-exposed individuals or the correlation of the potential confounder with the exposure; (2) the strength of the association of the potential confounder with the endpoint of interest; and (3) the magnitude of the risk estimate or strength of exposure-response relationship for antimony and specific cancer endpoints. Findings on non-antimony workers (with similar co-exposures as antimony workers) can also inform the evaluation of potential confounders. Once such considerations are weighed, and the results are examined, bias may be ruled out.

3.5.2 Integration of evidence from human cancer studies

The emphasis in integrating scientific evidence across human cancer studies should be placed on evaluating the extent to which biases, or confounding by co-exposures that may also cause cancer, could explain observed increases in cancer risk.

A qualitative evaluation will be made that integrates the evidence across studies, giving the most weight to studies that have the highest utility, and applies the RoC listing criteria to reach a listing recommendation. The application of the RoC listing criteria to the body of studies on a specific substance includes evaluating (1) whether there is credible evidence for an association between exposure to the substance and cancer, and (2) whether such an observed association can be explained by chance, bias, or confounding. This evaluation considers temporality, consistency of findings across studies, strength of observed associations between antimony exposure and cancer, and evidence for an exposure-response gradient (Hill 1965).

4 Methods for Evaluating Cancer Studies in Experimental Animals

4.1 Introduction and objective

This section describes the procedures used to evaluate the cancer studies in the experimental animal section of the draft RoC monograph, and to reach a level of evidence conclusion on the carcinogenicity of antimony compounds with cancer data, namely antimony trioxide (via inhalation) (Watt 1983, Groth *et al.* 1986, Newton *et al.* 1994, NTP 2017) and antimony potassium tartrate (via oral exposure) (Kanisawa and Schroeder 1969, Schroeder *et al.* 1970).

The general approach for identification and selection of the relevant literature, systematic extraction of data from the experimental animal studies, assessment of the utility of the individual studies in experimental animals, cancer hazard evaluation, and examples of table templates and figures are described in Part E of the RoC Handbook.

The objective of the evaluation of the studies in experimental animals is to reach a preliminary level of evidence conclusion [sufficient, not sufficient] for the carcinogenicity of antimony compounds from studies in experimental animals by applying the RoC listing criteria to the body of evidence.

Key questions

- What is the level of evidence (sufficient or not sufficient) of carcinogenicity of antimony compounds from animal studies?
- What are the methodological strengths and limitations of the studies?
- What are the tissue sites with cancer?
- What role does lung overload, if it occurred in the study, play in observed cancer?

RoC listing criteria for sufficient evidence of carcinogenicity from studies in experimental animals

"Increased incidence of malignant and/or a combination of malignant and benign tumors

- in multiple species or at multiple tissue sites, OR
- by multiple routes of exposure, OR
- to an unusual degree with regard to incidence, site, or type of tumor, or age at onset."

4.1.1 Approach

The steps for conducting the cancer hazard evaluation include:

- Selection of the literature included in the cancer hazard evaluation of the experimental animal studies (RoC Handbook, Part E, Section 1; Section 4.2 of this protocol)
- Systematic extraction of the data from experimental animal studies (RoC Handbook, Part E, Section 3; Section 4.3 of this protocol)
- Assessment of the quality of the individual studies (RoC Handbook, Part E, Section 4; Section 4.4 of this protocol)

- Cancer hazard evaluation of the evidence from studies in experimental animals (RoC Handbook, Part E, Section 5; Section 4.5 of this protocol)

Details on the approach to be used to identify and report on relevant studies, including the factors used for study quality assessment, is provided following the brief description of the literature search.

4.2 Identification and selection of the literature included in the cancer hazard evaluation of experimental animal studies

Concepts used to search the three scientific databases (PubMed, Scopus, and Web of Science) for potential antimony exposures and cancer studies in experimental animals are provided in Table 4-1 below. The search strategy used terms related to antimony combined (using "and") with search terms for experimental animal studies and with search terms for the outcome, i.e., cancer. A detailed description of the substance-specific search strings is included in Appendix A of this protocol, and the RoC standard search strings used for this and other searches are provided in the RoC Handbook Appendix: Standard search strings for databases searches. Citation analysis of articles, reports, and reviews identified from this search strategy are used to identify any additional primary studies or other relevant literature.

The use of antimony for the treatment of leishmaniasis is considered an intentional medical exposure and out of the scope of this monograph. The large corpus of literature related to leishmaniasis treatment was excluded when identifying experimental animal studies. (In contrast, antimonials and antimoniates used in leishmaniasis treatment are considered for mechanism discussion.)

Table 4-1. Literature search strategy for cancer studies in experimental animals

Substance-specific search concepts[a]	Animal species concepts[b]	Cancer search concepts[b]
Antimony search strings Antimony search strings with exclusion of leishmaniasis	RoC Animal Studies Search Strings	RoC Cancer Search Strings

[a]See Appendix A, Table A-1 for the detailed search strings.
[b]See RoC Handbook Appendix: Standard search strings for databases searches for search terms for experimental animals and cancer.

Retrieved citations are screened for inclusion/exclusion using Health Assessment Workspace Collaborative (HAWC) software according to the procedures outlined in the RoC Handbook, Part B, Section 2.

4.3 Systematic extraction of data from the cancer studies in experimental animals

Detailed information regarding study data and methods abstraction from individual studies is described in the RoC Handbook, Part D, Section 3. Briefly, data are selected and entered into *NTP Table Builder*, a database specifically created for entering information from scientific publications in a systematic manner using standardized instructions and questions. The database contains "fields" that are specific for the different types of extracted information (e.g., such as species, strain, sex, route, dosing regimen, duration, and results). Questions and guidelines are available to describe the specific type of information that should be summarized or entered into each field; and selected fields are used to populate tables in the monograph.

4.4 Assessment of the utility of the individual studies in experimental animals

Each primary study is systematically evaluated by two independent reviewers for its ability to inform the cancer hazard evaluation using a series of signaling questions related to the following study performance elements: study design, exposure conditions, outcome assessment and measurement, potential confounding, and reporting and analysis. Each element contains questions related to potential for bias as well as questions related to study sensitivity, which is the ability of the study to detect a neoplastic effect (see below for questions). Studies are also evaluated for elements relevant to external validity (interpreting the findings for relevance to humans). The response for answering the signaling question (see below) of whether there is a potential bias or limitation is based on a comparison of the study element with that of the "ideal" study for a specific endpoint and exposure to the candidate substance. General methods used to assess the utility of the individual epidemiologic studies are described in detail in the RoC Handbook, Part D, Section 4. This protocol briefly reviews the major questions in the RoC Handbook, and discusses issues specific for exposure to antimony.

Signaling questions[a]

Question	Type of question	Issues specific for antimony
Were animals randomized to control and dosed groups?	Study domain	None
Was a concurrent control group present? Is it adequate for evaluating effects across treatment groups?	Study domain	None
Are historical control data reported? (No rating given)	Study domain	None
Is the age of the animals at the start of dosing suitable for evaluating potential effects?	Study domain Sensitivity	None
Is the animal model sensitive for detecting an effect?	Study domain Sensitivity	None
Is statistical power (number of animals per dose and control group) sufficient to detect a neoplastic effect, if present?	Study domain Sensitivity	None
Are chemical characterization, dose formulations, and delivery of the chemical adequate to support attribution of any neoplastic effects to the substance?	Exposure conditions	None
Was dosing regimen adequate for detection of a neoplastic effect (if none was detected) or attribution of any neoplastic effects to the substance?	Exposure conditions	High dose might lead to particle overload in the lung[b]
Was the exposure duration period adequate for detection of a neoplastic effect, if not seen?	Exposure conditions Sensitivity	None
Is the study design adequate to evaluate dose-response relationships (e.g., more than one dose)	Exposure conditions Sensitivity	

Question	Type of question	Issues specific for antimony
Were the methods used to assess tumor outcome or the pathology procedures adequate for attribution of the effects to the exposure?	Outcome assessment	
Were all treatment and control groups assessed in the same way and in balanced blocks, to avoid bias?	Outcome assessment	None
Is the study duration (observation period) adequate to detect a neoplastic effect, if present?	Outcome assessment Sensitivity	None
Is there potential confounding?	Confounding	None
Are reporting of the data and statistical analysis adequate for evaluating the results?	Reporting and analysis	None
Were different types of tumors analyzed separately or accurately combined?	Reporting and analysis	None

[a]Questions here have been shortened; note that each question relates to whether there is concern about the potential bias or limitation, see RoC Handbook for further details.
[b]Guidelines for study design recommend that studies of insoluble particles include exposures that are likely to result in overload.

Response to signaling questions

- **Minimal concerns**: Information from study designs and methodologies indicate that they are close to the ideal study characteristics and that the potential for bias is unlikely or minimal (+++).
- **Some concerns**: Study designs or methodologies are less than ideal, indicating possible bias (++).
- **Major concerns**: Study designs or methodologies suggest that the potential for a specific type of bias is likely (+).
- **Inadequate**: Study designs or methodologies suggest that the bias is critical and would make the study not informative for cancer hazard evaluation.
- **No information**: Inadequate information in the study to evaluate the level of concern.

Study level judgment signaling questions

The overall utility (ability of the study to inform the cancer hazard evaluation) of a study is based on consideration of both the potential for bias (limitations) and study sensitivity:

- ***High*** (low concerns about most potential biases and high sensitivity)
- ***Moderate*** (some concerns about many potential biases)
- ***Low*** (major concerns about several biases)
- ***Inadequate*** (critical concerns about some potential biases)

4.5 Cancer hazard evaluation

The findings of each study are interpreted with respect to their limitations and strengths and the evidence from the studies is integrated across studies. The most informative studies (highest

quality and sensitivity) are given the most weight, and positive findings from these studies are considered to provide evidence of a treatment-related tumor effects. The evaluation also considers questions related to external validity including concerns whether the route of exposure was adequate for evaluating the potential for human carcinogenicity and whether the mechanism of observed tumor formation in experimental animals is human relevant. Findings in experimental animals are considered to be relevant to humans unless there is *compelling* evidence to suggest otherwise. Although the relevance of the route of the exposure to humans is considered, the findings of a similar tumor site by multiple routes of exposure strengthens the evidence for carcinogenicity.

Special attention should be given in evaluating lung overload and effects, and whether trend or neoplastic effects can be observed at conditions without significant lung overload. Pulmonary overload is characterized by overwhelmed alveolar macrophages leading to impaired alveolar clearance and increased particle accumulation in the lung of animals that are chronically exposed to very high concentrations of poorly soluble particles with no or low innate toxicity. The particle burdens continue to rise (instead of reaching a steady concentration) and clearance half-time continues to increase with the exposure. While overload has been seen in rats exposed to various chemicals at particle size raging from dust to nanoparticles, it is rarely, if ever, reported in mice (in spite of decreased clearance rates, the term overload is not used). Overload has been seen in human (see conditional evidence listed in Borm *et al.* 2015) in extreme conditions. While overload alone might lead to lung cancer, the presence of overload does not automatically mean observed lung cancer is from overload, because other mechanisms could be in action as well. Careful evaluation of pathological changes before overload occurs in animals, and changes at overload condition can provide clues of carcinogenic mechanisms.

The preliminary level of evidence for carcinogenicity is reached by applying the RoC listing criteria to the body of knowledge.

5 Methods for Evaluating Mechanisms, Toxicokinetics, and Other Relevant Data

The purpose of this section is to discuss and assess the potential mechanisms of carcinogenicity for antimony. It will include relevant discussions on the roles of absorption, distribution, metabolism, and excretion (ADME), toxicokinetics, genotoxicity, cancer mechanisms, and other data potentially involved in the carcinogenicity (e.g., ten characteristics of human carcinogens) of some or all of the antimony compounds.

5.1 Evaluation of ADME and toxicokinetics studies

5.1.1 Objectives

This section provides an overview of available information on the antimony ADME and toxicokinetics in humans and experimental animals. Antimony transportation and transformation at the cellular and subcellular levels will be considered. This information as it applies to potential mechanism(s) of chemical carcinogenicity will be discussed in the mechanistic section.

5.1.2 Key questions

- 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 toxicokinetic models (if any) inform biological plausibility, interspecies extrapolation, or other mechanistic questions for antimony?

5.1.3 Literature search strategy

The search strategy used terms related to antimony (i.e., substance-specific search strings in Appendix A of this protocol) combined with (using "and") search terms for absorption, metabolism, distribution, and excretion (i.e., ADME search strings in RoC Handbook Appendix: Standard search strings for databases searches). Three scientific databases (PubMed, Scopus, and Web of Science) were searched.

5.1.4 Evaluation approach

Given very limited information on antimony metabolism in the body identified in comprehensive agency reviews, the approach will focus on recent publications that measure different forms of antimony (in contrast to total antimony) in biological samples. The goal is a comprehensive review of all pertinent topics and not necessarily an exhaustive review of the literature.

5.2 Evaluation of mechanistic studies

5.2.1 Objectives

The purpose of this section is to discuss and assess the potential mechanisms of carcinogenicity for antimony compounds. It will include relevant discussions on the characteristics of human

carcinogens and other key events that are potentially involved in the carcinogenicity of some or all of the antimony compounds.

5.2.2 Key questions

- What are the genotoxic effects due to antimony exposure?
    - How well do the predicted genotoxic effects from (Q)SAR, read-across, transcriptomics, or other assays that do not directly measure DNA damage or mutation, correlate with to empirical genotoxic effects?
- What are the major mechanistic modes of action for the carcinogenicity of antimony?
    - What are the common key events leading to cancer development across different antimony compounds?
    - Is the mode of action seen in animal studies biologically plausible in humans?
    - If similar key steps or carcinogenic modes of action are seen across different antimony compounds, should antimony trioxide and other antimony compounds be listed as a class in the assessment?
- What role does antimony chemical species play in antimony trioxide carcinogenic potential?
    - Is there a difference in toxicity or carcinogenic potential between the pentavalent (Sb(V)) and trivalent (Sb(III)) forms of antimony?

5.2.3 Literature search strategy

Literature search will be conducted in three scientific databases (PubMed, Scopus, and Web of Science) for potentially relevant information on the carcinogenic mechanisms of antimony. The search strategy used terms related to antimony (i.e., substance-specific search strings in Appendix A of this protocol) combined with (using "and") terms for mechanisms (i.e., mechanistic search strings in RoC Handbook Appendix: Standard search strings for databases searches). Unlike other parts of the monograph, in which leishmaniasis related content was excluded via search terms, the mechanisms section literature search did not exclude leishmaniasis via the use of search terms. The studies on the *Leishmania* parasite itself were excluded at levels 1 and 2 by reviewers, and studies on the host or cells not infected by leishmaniasis were included for information related to mechanism.

5.2.4 Evaluation approach

To identify potential mode(s) of action, literature searches will be performed to identify studies measuring endpoints that are considered characteristics of human carcinogens (Smith *et al.* 2016) and could contribute to carcinogenicity. Additionally, studies with a broad coverage of biological effects (e.g., transcriptomics, and screening of a large number of endpoints[2]) and predictive toxicological approaches will be evaluated to further direct secondary searches. The results might be organized by the prevailing mechanism or by the characteristics of carcinogens (if no prevailing mechanism is identified), and will be tabulated or graphed for easy comparison.

[2] Including ToxCast and Tox21 results from EPA and NTP websites.

The mode of action of antimony carcinogenicity is unclear based on available literature, although our preliminary literature review found studies supporting oxidative stress (Hashemzaei *et al.* 2015, Jiang *et al.* 2016) and potentially a decrease in DNA damage repair (Gebel 1997, Beyersmann and Hartwig 2008, Grosskopf *et al.* 2010) contributing to antimony carcinogenicity. Immune function alteration has also been reported (Kim *et al.* 1999, Ghosh *et al.* 2013).

5.3 Evaluation of read-across predictions

5.3.1 Objectives

The purpose of using a read-across approach is to estimate carcinogenicity of antimony compounds that lack sufficient animal studies to determine carcinogenic potential.

If computationally predicted data provide compelling evidence that some forms of antimony share the same mechanism with antimony compounds that meet RoC listing criteria, these antimony compounds (without sufficient empirical data on their own) might be considered for RoC listing.

5.3.2 Key questions

1. Which antimony compounds have structurally similar chemicals that have defined carcinogenicity from rodent studies?
2. What is the prediction of carcinogenicity when similar biological effects (measured activities that are relevant to carcinogenesis) and metabolism are included in the criteria for read-across analogue selection?
3. Can key events or mode(s) of action be suggested from information gathered via the read-across approach?

5.3.3 Read-across strategy

From preliminary testing of read-across of antimony compounds based on chemical structural similarity alone, we learned that identified analogs lack existing empirical carcinogenic results in the Organisation for Economic Co-operation and Development (OECD) QSAR toolbox. In other words, additional searches for the carcinogenicity of identified structurally similar analogues is needed.

The general approach is to use multiple tools (e.g., OECD QSAR toolbox and Leadscope®) for each step of the read-across, and evaluate the benefits of pulling additional information sources.

1. Identify analogues via varying combinations of the following criteria:
    a. Contain functional group(s) (limited to the ones potentially relevant to carcinogenesis) in the target chemical.
    b. Share overall chemical structural similarity with the target chemical (threshold to be defined).
    c. Show measured known biological effects that are relevant to carcinogenesis and measured in the target chemical.

   d. Trigger the same alerts of events/toxicities relevant to carcinogenicity that were seen in the target chemical.

2. For analogues that are very similar to the target chemical, we will search for the carcinogenicity of analogues identified in step 1, if carcinogenicity outcome is not already in the OECD QSAR toolbox database.

3. Predict carcinogenicity of target chemical based on the closest (five, if more than five are available) analogues' carcinogenicities identified in step 2.

The carcinogenicity of source chemicals will be based on classifications from widely recognized authorities (e.g., International Agency for Research on Cancer (IARC) and governmental agencies), rather than primary studies. Whenever possible, carcinogenicities for rats and mice will be predicted separately.

5.3.4 Evaluation approach

While it is being debated how to effectively justify the rational of categorization or analogue selection used in a read-across case, it is generally accepted that a read-across prediction based on mechanistic information is stronger than prediction based purely on chemical structure. The steps taken and interim results in the read-across process will be documented. Uncertainties will be provided, to the extent practically informative. No formal evaluation of read-across data will be attempted.

6 Overall Cancer Hazard Evaluation and NTP Listing Recommendation

The purpose of this section is to evaluate all the data on the antimony compounds and to determine whether antimony trioxide and other antimony compounds meet the RoC listing criteria for listing in the RoC and if so, for which listing category, based on (1) human and experimental animal data of each antimony compound, (2) mechanistic or other data supporting listing some antimony compounds as a class, or (3) the combination of both (1) and (2).

6.1 Key questions

- Do available human and animal cancer data for individual antimony compound meet the criteria for RoC listing? If so, what is the listing category?
- If similar modes of action are supported between or among antimony compounds, is the evidence strong enough to support listing some antimony compounds as a class or group?

6.2 Approach

For each antimony compound, the compound-specific human and animal cancer data will be evaluated to determine whether each antimony compound meet the RoC listing criteria. If so, for what category.

Based on mechanistic understanding from *in vivo* and *in vitro* studies, which, if any, antimony compounds share mode(s) of action and could be listed as a class?

Preliminary RoC listing recommendations for the antimony compounds will be reported based on these findings.

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Appendix A: Literature Search Strategy

This section provides the search strings for antimony that are specific for the draft RoC monograph (Table A-1). The literature search includes terms for the antimony trioxide specifically, other chemical names that include antimony, synonyms, database index terms (Medical Subject Headings [MeSH] terms), and CAS numbers.

Treatment of leishmaniasis with antimony is associated with large sets of results that were not relevant to most sections of this evaluation. Except for the mechanism section, targeted exclusion of such results was accomplished using a select set of terms combined with the Boolean term "Not".

Table A-1. Substance-specific literature search strings for antimony

Database	Formatted search strings[a]
PubMed	Antimony[mh] OR "antimony trioxide"[nm] OR 7440-36-0[rn] OR 1309-64-4[rn] OR antimony[tiab] OR 28300-74-5[rn] OR 1345-04-6[rn] OR 7783-70-2[rn] OR 7783-56-4[rn] OR 10025-91-9[rn] OR 7647-18-9[rn] OR 7789-61-9[rn] OR 7790-44-5[rn] OR 7803-52-3[rn] OR stibine[tiab] OR stibine[nm] OR antimonial[tiab] OR antimoniate[tiab] **Excluding Leishmaniasis-related content:** (Antimony[mh] OR "antimony trioxide"[nm] OR 7440-36-0[rn] OR 1309-64-4[rn] OR antimony[tiab] OR 28300-74-5[rn] OR 1345-04-6[rn] OR 7783-70-2[rn] OR 7783-56-4[rn] OR 10025-91-9[rn] OR 7647-18-9[rn] OR 7789-61-9[rn] OR 7790-44-5[rn] OR 7803-52-3[rn] OR Stibine[tiab] OR stibine[nm] OR antimonial[tiab] OR antimoniate[tiab])) NOT ("Leishmaniasis"[Mesh] OR "Leishmania"[Mesh] OR leishmaniasis[ti] OR Leishmania[ti])
Scopus	((CASREGNUMBER (10025-91-9 OR 1309-64-4 OR 1345-04-6 OR 28300-74-5 OR 7440-36-0 OR 7647-18-9 OR 7783-56-4 OR 7783-70-2 OR 7789-61-9 OR 7790-44-5 OR 7803-52-3)) OR (CHEMNAME (antimony OR stibine)) OR (TITLE (antimony OR antimonial OR stibin* OR. stibo*)) OR (ABS (antimony OR stibine OR antimonial OR antimoniate OR stibin* OR stibo*)) **Excluding Leishmaniasis-related content:** ((CASREGNUMBER (10025-91-9 OR 1309-64-4 OR 1345-04-6 OR 28300-74-5 OR 7440-36-0 OR 7647-18-9 OR 7783-56-4 OR 7783-70-2 OR 7789-61-9 OR 7790-44-5 OR 7803-52-3)) OR (CHEMNAME (antimony OR stibine)) OR (TITLE (antimony OR stibine OR antimonial)) OR (ABS (antimony OR stibine OR antimonial OR antimoniate)) AND NOT (TITLE-ABS-KEY(leishmaniasis OR Leishmania OR leishmaniosis)))
Web of Science	(TS=("10025-91-9" OR "1309-64-4" OR "1345-04-6" OR "28300-74-5" OR "7440-36-0" OR "7647-18-9" OR "7783-56-4" OR "7783-70-2" OR "7789-61-9" OR "7790-44-5" OR "7803-52-3" OR antimony OR antimonial OR antimoniate OR antimon* OR stibin* OR stibo*)) **Excluding leishmaniasis-related content:**

Database	Formatted search strings[a]
	(TS=("10025-91-9" OR "1309-64-4" OR "1345-04-6" OR "28300-74-5" OR "7440-36-0" OR "7647-18-9" OR "7783-56-4" OR "7783-70-2" OR "7789-61-9" OR "7790-44-5" OR "7803-52-3" OR antimony OR stibine OR antimonial OR antimoniate)) NOT (TS=(Leishmaniasis OR Leishmania OR leishmaniosis))

[a] Search terms were developed in consultation with an information specialist.

Information on occurrence was searched for in PubMed only using the combined search terms in Table A-2.

Table A-2. Occurrence-specific literature search strings for antimony (PubMed only)

Database	Formatted search strings[a]
PubMed	((((Antimony[mh] OR "antimony trioxide"[nm] OR 7440-36-0[rn] OR 1309-64-4[rn] OR antimon*[tiab] OR 28300-74-5[rn] OR 1345-04-6[rn] OR 7783-70-2[rn] OR 7783-56-4[rn] OR 10025-91-9[rn] OR 7647-18-9[rn] OR 7789-61-9[rn] OR 7790-44-5[rn] OR 7803-52-3[rn] OR Stibin*[tiab] OR Stibo*[tiab] OR stibine[nm] OR Antimonial[tiab] OR antimoniate[tiab]))) AND *occur*[tiab]*

[a] Search terms were developed in consultation with an information specialist.

Information on speciation was searched for in all three databases using the combined search terms in Table A-3.

Table A-3. Speciation-specific literature search strings for antimony

Database	Formatted search strings[a]
PubMed	(Antimony[mh] OR "antimony trioxide"[nm] OR 7440-36-0[rn] OR 1309-64-4[rn] OR antimon*[tiab] OR 28300-74-5[rn] OR 1345-04-6[rn] OR 7783-70-2[rn] OR 7783-56-4[rn] OR 10025-91-9[rn] OR 7647-18-9[rn] OR 7789-61-9[rn] OR 7790-44-5[rn] OR 7803-52-3[rn] OR Stibin*[tiab] OR Stibo*[tiab] OR stibine[nm] OR Antimonial[tiab] OR antimoniate[tiab]) AND *(Speciat*[tiab])*
Scopus	((CASREGNUMBER (10025-91-9 OR 1309-64-4 OR 1345-04-6 OR 28300-74-5 OR 7440-36-0 OR 7647-18-9 OR 7783-56-4 OR 7783-70-2 OR 7789-61-9 OR 7790-44-5 OR 7803-52-3)) OR (CHEMNAME (antimony OR stibine)) OR (TITLE (antimony OR antimonial OR stibin* OR. Stibo*)) OR (ABS (antimony OR stibine OR antimonial OR antimoniate OR stibin* OR Stibo*)) AND *(TITLE-ABS-KEY (speciat*))*
Web of Science	(TS=("10025-91-9" OR "1309-64-4" OR "1345-04-6" OR "28300-74-5" OR "7440-36-0" OR "7647-18-9" OR "7783-56-4" OR "7783-70-2" OR "7789-61-9" OR "7790-44-5" OR "7803-52-3" OR antimony OR antimonial OR antimoniate OR Antimon* OR Stibin* OR Stibo*)) AND

Database	Formatted search strings[a]
	(TS=Speciat)*

[a] Search terms were developed in consultation with an information specialist.

Information on exposure scenarios (for human cancer) was searched for in PubMed only using the combined search terms in Table A-4.

Table A-4. Exposure-scenario-specific literature search strings for antimony (PubMed only)

Exposure scenario	Formatted search strings[a]
Smelting	smelting[tiab] OR smelter*[tiab] OR smelted[tiab]
Art glass	1. glass[tiab] AND (artisan[tiab] OR craftsman[tiab] OR craftsmen[tiab] OR artist[tiab] OR craftsperson[tiab] OR artist*[tiab] OR blower*[tiab]) 2. glass[tiab] AND ((decorative[tiab]) OR ("art glass"[tiab] OR "glass art"[tiab])) 3. glassworks[tiab] OR glassmaking[tiab] OR glassmaker*[tiab]
Flame retardants	"Flame Retardants"[Mesh] OR flame-retardant*[tiab] OR fire-retardant*[tiab] OR fire-resistant*[tiab]

[a] Search terms were developed in consultation with an information specialist.