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

Draft Report on Carcinogens Concept

Antimony Trioxide

Sb_2O_3; CAS No. 1309-64-4

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Summary and rationale

Antimony trioxide is proposed for review for possible listing in the Report on Carcinogens (RoC) based on the potential for widespread occupational exposure and an adequate database of cancer studies in experimental animals, including the recently completed NTP inhalation studies of antimony trioxide in mice and rats. In the United States, roughly 70 million pounds of antimony trioxide are used as a synergist for halogenated flame-retardants in plastics, rubber, and textiles, a catalyst in polyethylene terephthalate (PET) production, and as an additive in optical and art glass, pigments, paints, and ceramics. Up to 273 antimony trioxide companies were identified in EPA's Toxics Release Inventory Program. Thus, workers in many companies that produced a variety of consumer or industrial goods are potentially exposed to antimony trioxide. In addition, 11,635 lbs/yr of antimony are released into the air from antimony trioxide plants and antimony is persistent in the environment. OSHA's current permissible exposure limit for antimony is based on non-cancer health outcomes. The general public is potentially exposed to low levels of antimony trioxide from breathing contaminated air released from antimony industries (outdoor air) or from consumer products (indoor air). Some studies have reported that low levels of antimony in urine or cord blood have been associated with adverse non-cancer health outcomes although these studies are not specific for antimony trioxide.

1 Background

Antimony is a metalloid found in nature in over 100 mineral species, most commonly in stibnite (Sb_2S_3) and to a lesser extent in antimony trioxides ($Sb_2O_{3,}$) such as in the minerals valentinite and senarmontite (ATSDR 1992). Antimony exists in four oxidation states, -3, 0, +3, +5; the trivalent (Sb (III)) and pentavalent (Sb (V)) forms are the most common. Elemental antimony (Sb) is a silver white metal primarily used to make alloys. Other notable antimony species include antimony trioxide (trivalent) and medicinal antimonials – pentavalent antimonials used to treat leishmaniasis and antimony potassium tartrate (trivalent) formerly used to treat schistosomiasis (OEHHA 2016).

Antimony trioxide is the most commercially significant form of antimony, accounting for approximately 80% of antimony use in the United States (EPA 2014, NTP 2016). It is produced primarily by re-volatilization of crude antimony trioxide or by oxidation of antimony metal (EU 2008). In 2010, U.S. EPA identified one company manufacturing and 11 companies importing antimony trioxide; approximately 87% of the roughly 70 million pounds of antimony trioxide consumed in the United States between 2007 and 2011 was imported (EPA 2014).

The single predominant use of antimony trioxide (36% of antimony market share) is as a synergist for halogenated flame-retardants in plastics (including but not limited to polyvinyl chloride (PVC)), rubber, and textiles, which are used in a diversity of plastics and other products (see Figure 1). Although antimony trioxide is not a flame retardant itself, it decreases the amount of halogen needed for flame resistance by interacting with bromine or chlorine to form antimony halogens. Antimony trioxide can also be used as a catalyst in PET production (16% of antimony market share), as an additive in glass manufacture and in pigments, and as an additive in paints and ceramics (12% of antimony market share). Most (90%) PET production uses antimony as a catalyst (OEHHA 2016); antimony trioxide is chemically transformed into antimony glycolate

occupational monitoring data specific for exposure to antimony trioxide were reported by the European Union Risk Assessment (EU 2008). This report calculated integrated typical (or with personal protection equipment, PPE) and worst case scenario (or without PPE) exposure levels for both inhalation and dermal exposures across seven exposure scenarios – (1) production of antimony trioxide, (2) flame retardant in textiles, (3) flame retardant in plastics, (4) flame retardant in rubber, (5) catalyst in PET production, (6) use in paints, coatings and ceramics, and (7) use in production of crystal glass – using measured data from European industries or modelling. The air exposures across the exposure scenarios ranged from negligible to 130 $\mu g/m^3$ for typical exposures, and negligible to 940 $\mu g/m^3$ for the worst case scenarios (up to 2900 $\mu g/m^3$ for worst case scenarios without personal protection equipment). The highest inhalation and dermal exposure levels are for antimony trioxide production (without personal protection equipment), followed by flame retardant (formulation stage) industries.

In the United States, monitoring data for antimony in general are available from the OSHA Chemical Exposure Health Dataset, which reported data from companies producing or using antimony and antimony compounds from 1984 to 2011. However, it is unclear which companies in the database used or produced antimony trioxide. Air monitoring data specific for antimony trioxide industries comes primarily from NIOSH walk-through surveys of a few smelters or antimony trioxide companies conducted largely in the 1970's which were usually conducted as part of health hazard evaluations or for an epidemiological study (Schnorr *et al.* 1995). In studies of smelters or antimony trioxide producers, antimony levels ranged from 50 to 6200 $\mu g/m^3$ in breathing zone samples and 140 to 5600 $\mu g/m^3$ in area samples (ATSDR 1992); antimony in smelter air samples is most likely in the form of antimony trioxide. Antimony levels were lower in a study of the fire retardant industry (non detectable to 200 $\mu g/m^3$), a survey of a rubber company (10 to 150 $\mu g/m^3$), and the glass industry (5 $\mu g/m^3$) (ATSDR 1992), which is consistent with the EU data.

Workers using or producing other types of antimony, such as antimony used in the battery industry, can also be exposed to antimony trioxide because the antimony oxidizes in the air to antimony trioxide (EU 2008). In addition, fire fighters may be exposed to antimony trioxide in smoke released from fire-retardant clothing during fires (NTP 2016).

1.1.2 General population

The general population is potentially exposed to antimony trioxide from consumer products or indirectly from releases to the environment, which can contaminate food, drinking water, and outdoor breathing air.

Data from the National Health and Nutrition Examination Survey (NHANES) and other biomonitoring studies in the United States indicate that the general public is exposed to low levels of antimony; antimony in urine ranged from 0.06 to 0.15 μg/L (CDC 2015). Some analyses of NHANES data show income disparities, e.g., higher antimony levels were found in individuals living in economically deprived neighborhoods or with lower income (Belova *et al.* 2013, Tyrrell *et al.* 2013, Gonzales *et al.* 2016). Because elemental antimony is measured in urine, the exposure that is specifically due to antimony trioxide is not clear (see Section 2.1.4). Although some reports have suggested that the low levels of antimony to which the general public is exposed may not be public health concerns (EPA 2014), 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, e.g., 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.

1.1.3 Consumer products

Consumers can potentially be exposed to antimony in several products based on its use as a flame retardant or in PET containers (see Figure 1). Potential exposure routes include dermal (e.g., from flame retardants used in upholstered furniture), oral (e.g., drinks in PET containers or from children's toys), and indoor air and dust (primarily from releases from flame retardant products). The EU noted that exposure from these products, with the exception of indoor air (estimated exposure 0.003 $\mu g/m^3$) and house dust (estimated exposure to children 0.60 $\mu g/kg/day$), is to the antimony ion and not to antimony trioxide itself (EU 2008). Higher indoor air antimony levels (0.017 $\mu g/m^3$ in the PM1 [particles < 1 μm] fraction) were reported in an elementary school in Arizona; antimony in air was most likely due to resuspension (from foot traffic) of embedded antimony in carpet as a result of its use as flame retardant (Majestic *et al.* 2012).

1.1.4 Environmental exposure

Antimony enters the environment through releases from industries producing, using, or recycling antimony or natural sources (e.g., volcanic activity, erosion). In 2014, 542 U.S. manufacturing, processing, and antimony-using facilities reported (as part of the Toxics Release Inventory data, TRI) that 8.6 million pounds of antimony and antimony compounds were released into the environment (e.g., land, water, and air) (TRI 2016).

Antimony undergoes changes in its oxidation states; thus, people can be exposed to antimony trioxide from releases into the air of other antimony compounds with transformation to antimony trioxide and releases of antimony trioxide can also be transformed into different antimony species. Most monitoring studies measured total antimony and few studies have measured specific antimony species. Releases into air are the most relevant antimony exposure that are specific to antimony trioxide. In 2010, 273 facilities with antimony trioxide-related activities reported a total of 11,635 lb/yr released into the air (EPA 2014). The European Union (2008) estimated that antimony trioxide levels in outdoor air are 0.003 $\mu g/m^3$ resulting from releases by companies producing or using antimony trioxide. Antimony trioxide can also be released into the air from high-temperature industrial processes such as combustion of petroleum, petroleum products, and coal and incineration of products that contain antimony (NTP 2016), and from oxidation of other antimony compounds. Individuals living close to industrial facilities may be exposed to much higher levels of antimony in the air; a study from the 1970s in the United States reported that antimony air levels downstream of a copper smelter were in excess of 300 ppm [300,000 $\mu g/m^3$] (NTP 2016).

Antimony is persistent in the environment and may form different species, such as Sb_2S_3, Sb_2O_5, that can impact bioaccessibility. Environmental exposure to antimony from the soil is expected to be minimal because of its low solubility and mobility (EPA 2014, Li *et al.* 2014). Based on thermodynamic principles, antimony is expected to exist primarily as the pentavalent form in oxic systems and trivalent forms in anoxic systems. Some studies have observed a greater

proportion than expected of the trivalent form in oxic systems although the pentavalent form is still the predominant form (OEHHA 2016).

1.2 Concerns for carcinogenicity

Concerns for the potential for antimony carcinogenicity were largely initiated by a report by the Factory Inspectorate in Great Britain in the 1970s, which suggested that lung cancer incidence among antimony smelter workers was higher than for the general population (Davies 1973 as cited by Groth *et al.* 1986). This report prompted NIOSH to conduct an inhalation study of antimony ore and antimony trioxide in male and female rats (Groth *et al.* 1986). Based on the findings of increased incidences of lung neoplasms in exposed female rats in this study and in another inhalation study of antimony trioxide, reported as a thesis, IARC (1989) classified antimony trioxide as probably carcinogenic to humans (Group 2B). Subsequent to the IARC evaluation, the Antimony Oxide Industry Association (AOIA) conducted an inhalation exposure to antimony trioxide that did not find an increase of lung or other types of neoplasms in exposed female and male rats. This study was conducted as part of a negotiated self-rule between AOIA and U.S. EPA (Newton *et al.* 1994).

In the early and mid 2000s, the National Institute of Occupational Safety and Health (NIOSH) nominated antimony for review for the RoC and the Consumer Product Safety Commission (CPSC) nominated it to the NTP testing program. Because of limitations in the database of carcinogenicity studies in experimental animals (e.g., conflicting findings, only one species tested, one of the studies was unpublished), NTP conducted an inhalation two-year bioassay of antimony trioxide. The NTP Technical Report of these studies was peer reviewed in 2016; the report found increases in the incidences of lung tumors in rats and mice. Increased incidences of other types of tumors – adrenal gland neoplasia in rats, and skin neoplasias and lymphomas in mice – were also reported (NTP 2016).

2 Problem formulation activities

NTP conducted preliminary literature searches to determine the scope of the available databases. To identify cancer studies in humans or experimental animals, literature searches were conducted using concepts for antimony and exposure scenarios associated with antimony combined with standard search strings for cancer and either epidemiological or animal studies. For mechanistic studies, search strings for antimony were combined with standard search strings for 10 characteristics of carcinogens as discussed by Smith *et al.* (2016). Standard search terms are available at http://ntp.niehs.nih.gov/go/rochandbook. Relevant references were screened and tagged using Health Assessment Workplace Collaborative (HAWC; https://hawcproject.org/), which is a web-based content management system.

2.1 Human cancer studies

Six epidemiology studies (five in the peer-reviewed literature) were identified that reported risk estimates for antimony (see Table 1). Five of the studies are of occupational exposure – three of antimony smelter workers, one of tin smelter workers, and one of art glassworkers. Based on a description of the type of industry, workers were probably exposed to antimony trioxide, although not exclusively, in all the studies but the tin smelter workers; the smelter workers were exposed to other metals. The sixth study evaluated urinary antimony levels in the general population (NHANES data) and cancer mortality.

Table 1: Overview of human cancer studies on exposure to antimony[a]

Population/study design	Antimony species	Reference
Antimony smelter (cohort studies – reference group is the general population)	Prior to 1960, antimony, metals, antimony ore, antimony trioxide; After 1960 – antimony trioxide	Jones 1994
	Antimony ore (oxide or sulfide), metal and antimony oxide	Schnorr *et al.* 1995
Tin smelter workers (cohort study)	Not clear	Jones *et al.* 2007
Art glass workers (case-reference)	Probably antimony trioxide	Wingren and Axelson 1993
General public/NHANES (cross-sectional and prospective mortality analysis)	Antimony urinary levels Source of exposure unknown	Guo *et al.* 2016

[a]Studies in the peer-reviewed literature; does not include report by Davies 1973 (as cited by Groth *et al.* 1986).

2.2 Carcinogenicity studies in experimental animals

An overview of the animal carcinogenicity data on antimony is provided in Table 2. Most of the studies tested antimony trioxide, including four inhalation studies conducted in rats and one in mice. The NIOSH-sponsored inhalation study (Groth *et al.* 1986) also exposed rats to antimony ore. Two drinking water studies were identified on antimony potassium tartrate, one each in rats and mice.

Table 2. Carcinogenicity studies in experimental animals

Model	Exposure overview	Antimony	Reference
Fischer (CDF) female rats	Inhalation; 2 doses	Antimony trioxide	Watt 1983 (thesis; summarized by IARC 1989)
Wistar male and female rats	Inhalation; 1 dose	Antimony trioxide, Antimony ore	Groth *et al.* 1986 NIOSH-sponsored study

Model	Exposure overview	Antimony	Reference
Fischer 344 male and female rats	Inhalation; 4 doses	Antimony trioxide	Newton *et al.* 1994 AOIA study
Wistar Han male and female rats	Inhalation; 3 doses	Antimony trioxide	NTP 2016
B6C3F1/N male and female mice	Inhalation; 3 doses	Antimony trioxide	NTP 2016
CD-1 male and female mice	Drinking water; 1 dose	Antimony potassium tartrate	Kanisawa and Schroeder 1969
Long Evans male and female rats	Drinking water; 1 dose	Antimony potassium tartrate	Kanisawa and Schroeder 1969

2.3 Mechanistic and other relevant data

Studies identified by the preliminary literature search were tagged according to the 10 characteristics of carcinogens; most studies evaluated genotoxicity and DNA damage, oxidative stress and inflammation, and cellular proliferation. Based on a preliminary review of the literature, the mechanistic database is smaller and less established than for other metals, although antimony appears to be associated with some similar biological activities as other metals, such as oxidative damage.

Studies are also available on absorption, distribution, metabolism, excretion, and toxicity of different antimony species. Although some authors have proposed that antimony is more toxic than its salts, and trivalent antimony is more toxic than pentavalent antimony, the EU stated that the differences in toxicity between the two valence states is unclear because of few studies comparing the toxicity of both compounds under the same conditions. There are some differences in the distribution of the pentavalent and trivalent forms *in vivo*. Pentavalent antimony has been reported to be reduced to trivalent antimony *in vivo* by glutathione (Ferreira *et al.* 2003). Other studies in rats have found that the trivalent form is oxidized to the pentavalent form (reviewed by OEHHA 2016).

2.4 Key questions

The key issues (provided below) for the cancer assessment involve the interpretation of the animal cancer data and the scope of the cancer hazard assessment with respect to antimony species. The database on studies of carcinogenicity in experimental animals is only adequate for antimony trioxide. As discussed above, due to the complexity of antimony chemistry the contribution of antimony trioxide to exposure of the general public may not be clear. Health concerns to the general public from antimony may be important as some studies have reported that antimony biomarkers may be associated with adverse biological effects or health outcomes.

- What role does lung overload (impairment in alveolar macrophage clearance of particles inhaled due to excessive lung particle burden) play in interpretation of the cancer data in experimental animals?

- Should the evaluation be expanded to include antimony and antimony compounds?
    - To what extent does transformation between Sb(III) and Sb (V) occur *in vivo*? Is Sb(III) the ultimate carcinogenic species?
    - Is there a difference in toxicity or carcinogenic potential between the pentavalent (Sb (V)) and trivalent (Sb (III) forms of antimony?
    - Can Sb_2O_3 be considered a representative antimony species for cancer hazard evaluation?

3 Objective and approach for developing the RoC monograph

The objective of the NTP evaluation is to review and assess the carcinogenicity and exposure data on antimony trioxide for possible listing in the RoC. The RoC monograph, which captures the cancer assessment, will focus on the animal carcinogenic data specific for antimony trioxide. The monograph will review human exposure data to determine whether a significant number of people living in the United States are exposed to antimony trioxide and provide an overview of the major sources of exposure. Because studies of antimony may be informative to the assessment, human and animal cancer studies, and mechanistic studies on antimony in general will also be reviewed as supporting information; the evaluation process will consider the possibility of expanding the review to include other antimony species. The approach for the cancer assessment is provided in the table below.

Table 3: Approach for cancer evaluation

Evidence stream/study design	Exposure	Outcome
Human exposure	Antimony trioxide and antimony in general	Use, production, occupational, consumer and other products, environmental occurrence, biological monitoring data, and information on transformation of antimony species
Experimental animal studies/~2 year studies	Antimony trioxide	All reported neoplasms
Human studies	Antimony	All neoplasms; lung cancer is a target tissue
Human studies	Antimony trioxide/urinary antimony	Biological effects related to carcinogenicity or toxicity
Experimental studies	Antimony compounds	Biological effects related to carcinogenicity or toxicity

Evidence stream/study design	Exposure	Outcome
In vitro studies	Antimony compounds	Biological effects related to carcinogenicity or toxicity

3.1 Scientific input and protocol development

The first step in the process is to establish a monograph planning team. ORoC is soliciting technical support from experts on metals, NTP scientists, and interagency partners (ATSDR and CPSC) to provide input on key questions and protocol and monograph development.

The protocol will outline the literature search strategy, key issues, and focus of the monograph (as discussed above). Literature search strategies and identification of other evaluations will be developed with an information specialist and input from technical advisors. The protocol be reviewed by experts and posted on NTP/RoC website.

3.2 Monograph development and peer review

The cancer assessment, which is captured in the draft RoC monograph, will include an evaluation of the quality of scientific evidence and apply the RoC criteria to reach a preliminary listing recommendation for the RoC (for more information, see the Handbook for Preparing the RoC monographs available at http://ntp.niehs.nih.gov/go/rochandbook). Per the process for preparing the RoC, ORoC will release the draft RoC monograph on antimony trioxide for peer review. Similar to the peer review of other candidate substances, the peer reviewers will be asked to comment on whether (1) there is evidence that a significant number of people residing in the United States are exposed to antimony trioxide and (2) whether the carcinogenicity and mechanistic information in the substance profile is clear, objectively presented, and supports NTP's preliminary listing recommendation.

4 References

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