NTP
National Toxicology Program

Draft Report on Carcinogens Concept
Antimony Trioxide

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NTP Board of Scientific Counselors
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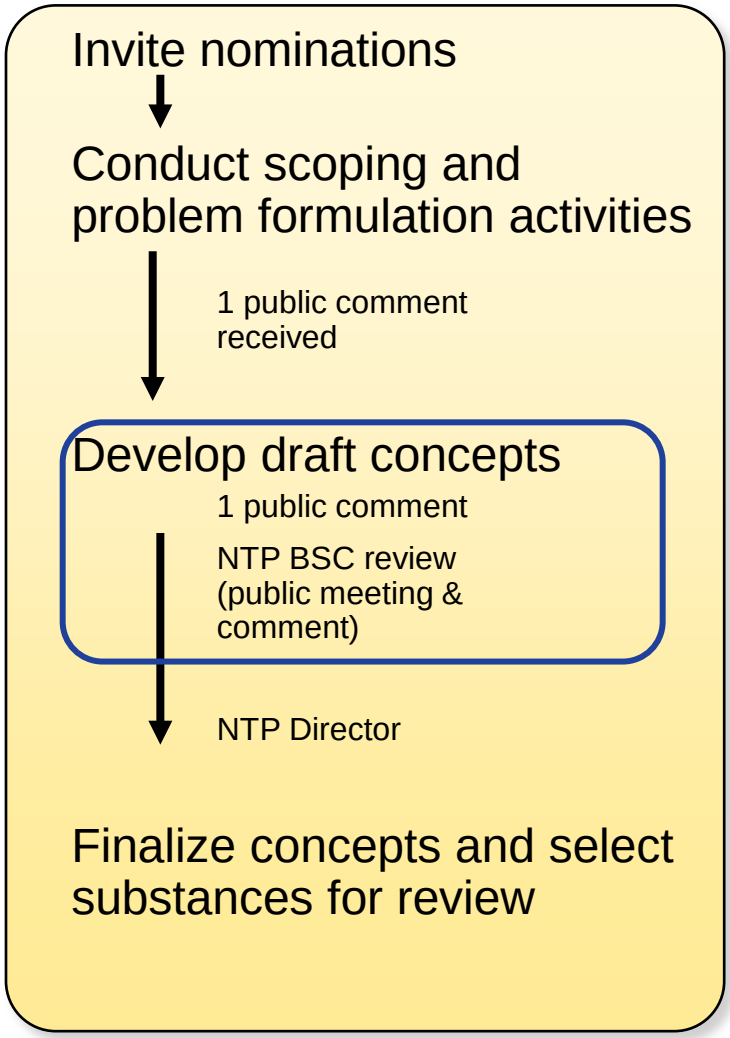
NTP is proposing one substance for review

Draft concept is a planning and communication tool

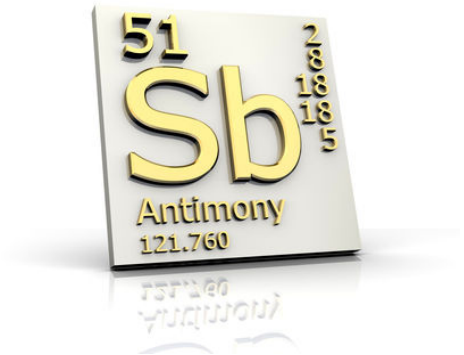


- Background information
- Rationale
- Scoping/problem formulation activities
  - Overview of exposure
  - Overview of carcinogenicity database
  - Key questions and scientific issues
- Objective and proposed approach for monograph development

BSC = Board of Scientific Counselors; FR = Federal register;

Antimony and antimony compounds

- Metalloid found in nature in over 100 mineral species
  - Most commonly in stibnite (Sb_2S_3); lesser extent in antimony oxides
- Exists as four oxidation states: -3, 0, +3, and +5
  - Antimony species undergo transformation in the environment and *in vivo*
- Antimony forms with commercial interest
  - Antimony metal; primary used to make alloys as lead batteries
  - Pentavalent antimonials and antimony potassium tartrate (trivalent) used to treat parasites
  - Antimony trioxide



Lifecycle

Antimony trioxide is the most commercially significant antimony form

Import or production	Formulation	Processing	Consumer products
Companies: 1 producer; 11 importers ~ 70 million lbs. consumed	flame retardant synergist	flame retardant plastics (including PVC), textiles, rubbers	furniture, electrical and electronic equipment (e.g., TV backing/circuit boards, PC monitors, printers, copiers), cables
	PET catalyst	PET packaging and fibers	PET containers: drinks, pharmaceuticals, edible oils, household cleaners
	special glass manufacture additive	glass screens, optical art	fluorescent light bulb, glass for TV and computers
	pigments, paints, ceramics	application of adhesive, paints, and coatings	

247 companies (TRI database)
waste disposal
recycling
incineration
landfill

Blue – Sb_2O_3; green – no longer Sb_2O_3; yellow – depends on circumstance

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Concerns for antimony carcinogenicity

Historical perspective and NTP interest

1970–80's initial concerns

- Excess lung cancer in UK antimony smelter workers
- Lung tumors in NIOSH sponsored study in female rats (Sb_2O_3; Sb ore, Sb_2S_3)
- Lung tumors in female rats in thesis study (Sb_2O_3)
- IARC 1989 review
  - Sb_2O_3: 2B
  - Sb_2S_3: 3

1990's AOIA Study

- Inhalation study in rats: Sb_2O_3
- No increases in tumor incidences

Early 2000 NTP nominations

- RoC nomination
  - Inadequate database
  - NIOSH
- NTP testing nomination
  - CPSC[a]

2008 European Union

- Sb_2O_3 suspected carcinogen
- Need to limit risk to workers

2016 NTP study

- Inhalation (whole body) study in rats and mice: Sb_2O_3
- Lung tumors mice and rats

On going activities:

- EU Reach Environmental classification 2018: Sb_2O_3
- EPA TSCA Sb_2O_3 ecological toxicity
- ATSDR toxicological profile
- **Proposed RoC evaluation**
- OEHHA PHG: Sb in drinking water

Blue: Sb_2O_3

[A] Consumer PrSC also sponsored NAS evaluation of flame retardants and conducted a risk assessment on flame

Rationale and considerations

- Rationale for reviewing antimony trioxide
  - Interest reinitiated by 2016 NTP technical report on two bioassays
  - Adequate database of cancer studies in experimental animals
  - Evidence for occupational exposure in the United States
- Consideration of other antimony species

Problem formulation

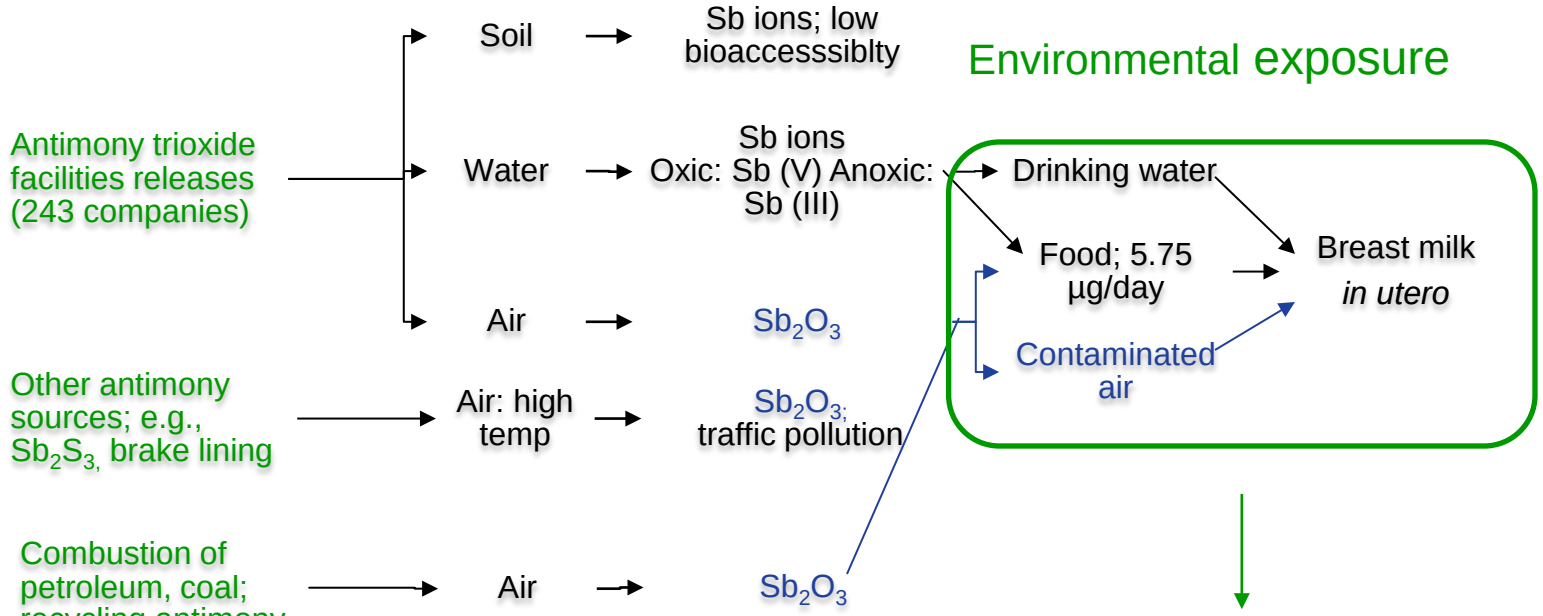
- Literature sources
  - Authoritative reviews such as European Union Risk Assessment Report, U.S. EPA TSCA report, OEHHA PWG, IARC Monograph
  - Exposure sources: NIOSH HHE, OSHA database, ATSDR
- Literature search strategy
  - Searches conducted in PubMed, Scopus, and Web of Science, uploaded and screened using HAWC

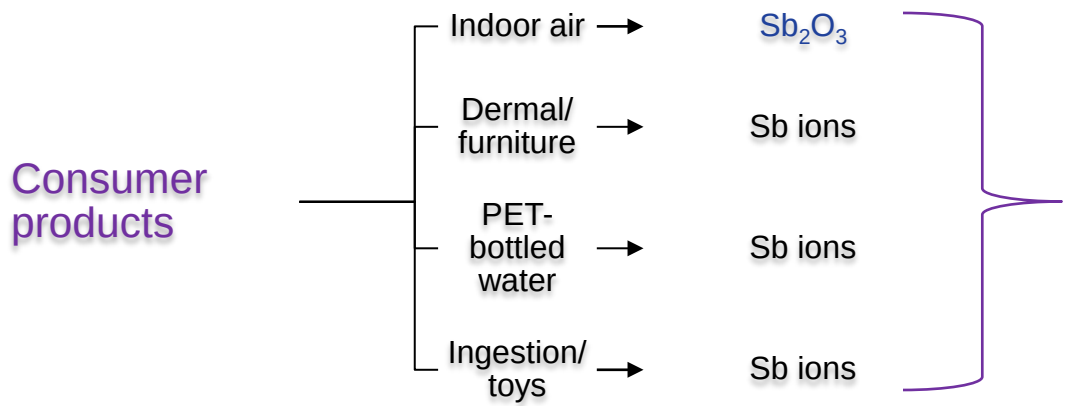
Type of evidence	Approach
Human cancer studies	Antimony or exposure scenarios + cancer search string + epidemiology standard search string[a]
Animal cancer studies	Antimony + cancer search string + animal standard search string[a]
Mechanistic	Antimony search terms + 10 carcinogen characteristics standard search strings[a]

[a]RoC handbook; http://ntp.niehs.nih.gov/go/rochandbook

Human exposure

U.S. residents are exposed to antimony trioxide from the environment and consumer products primarily via inhalation





- U.S. urinary Sb: Low levels: 0.06 to 0.15 (µg/L); economic disparity
- Contribution of Sb_2O_3 and Sb form unclear
- Potential link with non-cancer outcomes

Workers are exposed to the highest levels of antimony

- U.S companies: 1 antimony manufacturer; 11 antimony importers; up to 243 antimony trioxide users
- Exposure: inhalation and dermal
- Highest exposure measured in smelters and producers; next highest in flame retardant industries

Exposure source	Exposure level µg/m^3
Workplace	
EU: Sb_2O_3 industries, worst case	ND to 2900 (non-production 570)
US: 1970s NIOSH surveys selected companies	ND to 6210 (production high levels)
Environment	
EU data: Sb_2O_3 industries	0.003
Consumer products	
Dust: children	0.60 µg/kg/day
Indoor air: mostly flame retardant products	0.003 (EU); 0.017 (US school)

Cancer studies on antimony

Evidence stream/population	Antimony compound	Database
Experimental animals: Rodents	Antimony trioxide	Inhalation 3 studies in male and female rats 1 unpublished study in female rats 1 study in male and female mice
Experimental animals: Rodents	Antimony ore (sulfide)	Inhalation 1 study in male and female rats
Experimental animals: Rodents	Antimony potassium tartrate	Oral (low levels) 1 study in male and female rats 1 study in male and female mice
Humans: Workers	Assumed antimony trioxide or antimony trioxide and other Sb compounds	3 cohort studies: smelter and glass workers; exposure to other metals
Humans: Workers	Antimony: unclear	1 cohort study: tin smelter workers; exposure to other metals
Humans: General population	Urinary Sb (source of exposure unknown)	1 study: NHANES cross sectional and prospective mortality analysis

Mechanisms have not been elucidated although some mechanisms common to metals, such as oxidative DNA damage, are suggested

Overview of databases

Sb_2O_3

- Carcinogenicity/toxicity
  - Adequate database of carcinogenicity in experimental animals
  - Some studies on mechanisms
- U.S. Exposure
  - Occupational data; highest exposure from past production or smelters
  - General population is exposed to Sb: not clear contribution of Sb_2O_3

Sb

- Carcinogenicity/toxicity
  - Inadequate database of animal cancer studies for other Sb compounds
  - Greater number of mechanistic studies
- U.S. Exposure
  - Antimony metal industries may be associated with high exposure
  - Environmental exposure data on Sb
  - Non-cancer outcomes potentially linked to Sb in studies in the general population

Scientific issues

- Should the evaluation be expanded to include antimony and antimony compounds?
  - What extent does species transformation occur *in vivo*? Is Sb (III) the ultimate carcinogen species?
  - Is there a difference in toxicity or carcinogenic potential between Sb (III) and Sb (V)?
  - Can Sb_2O_3 be considered a representative antimony species for cancer hazard evaluation?
- What role does lung overload play in interpretation of the cancer data in experimental animals?

Objective and scope

Review and assess the carcinogenicity and exposure data on antimony trioxide for possible listing in the RoC; however, monograph will include relevant information on all antimony species

Evidence stream	Exposure	Outcome
Human exposure	Sb_2O_3 and Sb	Use, production, occupational, consumer products, environmental exposure, biological monitoring data, and transformation of antimony species
Experimental animals	Sb_2O_3	All reported neoplasms
Human cancer studies Experimental animals	Sb_2O_3 and Sb Other Sb species	Lung cancer target: all types of cancer
Mechanistic Human studies Experimental animal studies In vitro studies (supporting)	Sb_2O_3 and Sb	Biological effects related to carcinogenicity or toxicity

Blue: Focus
Black: Supporting information

Monograph development and peer review

- Monograph evaluation team: Metal experts, NTP and Interagency (ATSDR, CPSC, EPA) scientists will provide input on:
  - Sb speciation in the environment and *in vivo*
  - Protocol development
    - Outlines approach; applies method of handbook (http://ntp.niehs.nih.gov/go/rochandbook) to specific issues related to antimony
  - Monograph development and review
- Peer view of monograph by panel of experts