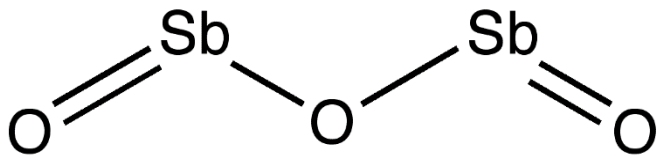
NTP
National Toxicology Program

Report on the Peer Review of the Report on Carcinogens (RoC) Draft Monograph on Antimony Trioxide



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Office of the Report on Carcinogens, Division of National Toxicology Program
National Institute of Environmental Health Sciences

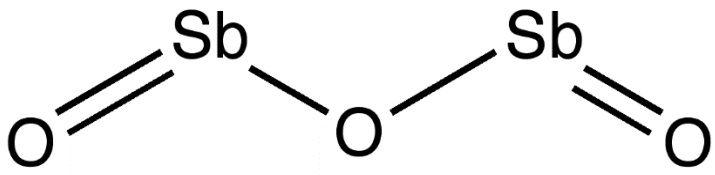
NTP Board of Scientific Counselors Meeting
October 9, 2018

Antimony trioxide

- Antimony is a metalloid found in nature

51
Sb
Antimony
121.76

- Antimony(III) trioxide is the most commercially significant form of processed antimony



Uses of Antimony(III) Trioxide

Formulation	Processing	Consumer products	
flame retardant synergist			
polyethylene terephthalate (PET) catalyst			
special glass manufacture additive			
pigments, paints, ceramics			

= Sb_2O_3 =no longer Sb_2O_3 = depends on circumstance

Slide courtesy of Sandy Garner, ILS

Peer Review Panel Members

Name	Affiliation
Rebecca Fry, PhD	University of North Carolina at Chapel Hill
Hao Zhu, PhD	Rutgers University-Camden
Elaine Symanski, PhD	The University of Texas Health Science Center at Houston
Elizabeth Ward, PhD	American Cancer Society (retired)
John Wise, Sr., PhD	University of Louisville
Michael Waalkes, PhD	NIEHS (retired)
Richard Peterson II, DVM, PhD, DACVP	AbbVie

NTP BSC liaison

Kenneth McMartin, PhD Louisiana State University

Public comments

- Public comments, including published and unpublished information, were received in several phases of the process
- ORoC staff considered technical and scientific issues at all phases
- Public comments on draft monograph were provided to the peer review panel

NTP Draft Recommendation: Exposure

A significant number of people in the United States are exposed to antimony(III) trioxide

- Highest levels of exposure occur in the workplace
- The general population is exposed
  - Primary releases (i.e., pollutant is antimony(III) trioxide) from industrial uses to air: Estimated 11,365 lb to air in year 2010
  - Secondary (i.e., pollutant is transformed from other antimony species into antimony(III) trioxide) releases to the environment
  - House dust from some consumer products
  - Antimony detected in urine (The National Health and Nutrition Examination Survey, or NHANES)

Panel: Concurred

NTP Draft Recommendation: Human Studies

Inadequate human evidence for determining carcinogenicity

- **Limited by:**
  - Few studies with small sample sizes for stomach and lung cancers
  - Potential confounding due to smoking and occupational co-exposures

Panel: Agreed unanimously

Key issues discussed at the peer review panel meeting

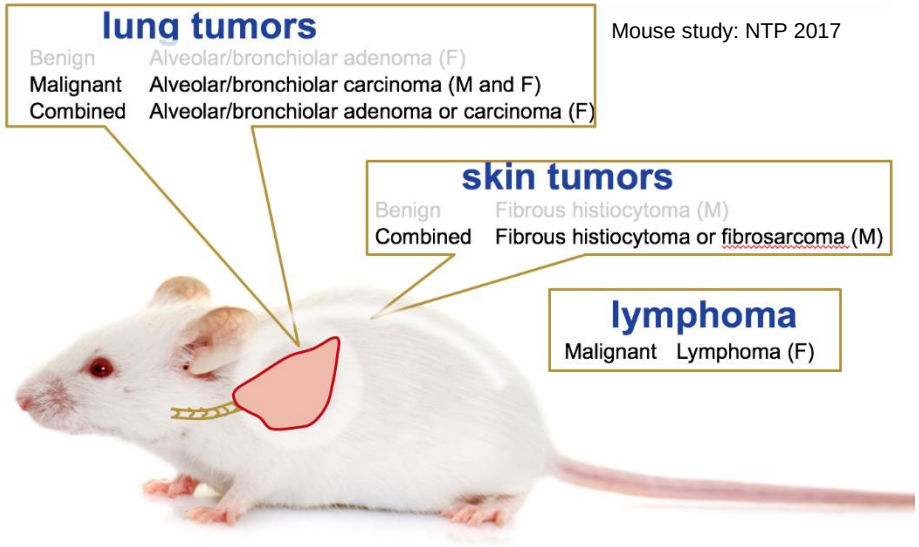
- Male rat lung tumors
  - Overload alone does not explain the observed carcinogenicity in rats
    - Increased lung tumors in mice at Sb_2O_3 concentrations below overload threshold
    - Genotoxicity in exposed mice, indicating Sb_2O_3 has intrinsic toxicity
  - Incidences of alveolar/bronchiolar adenoma exceed current and historical controls
  - Adenoma can progress to carcinoma

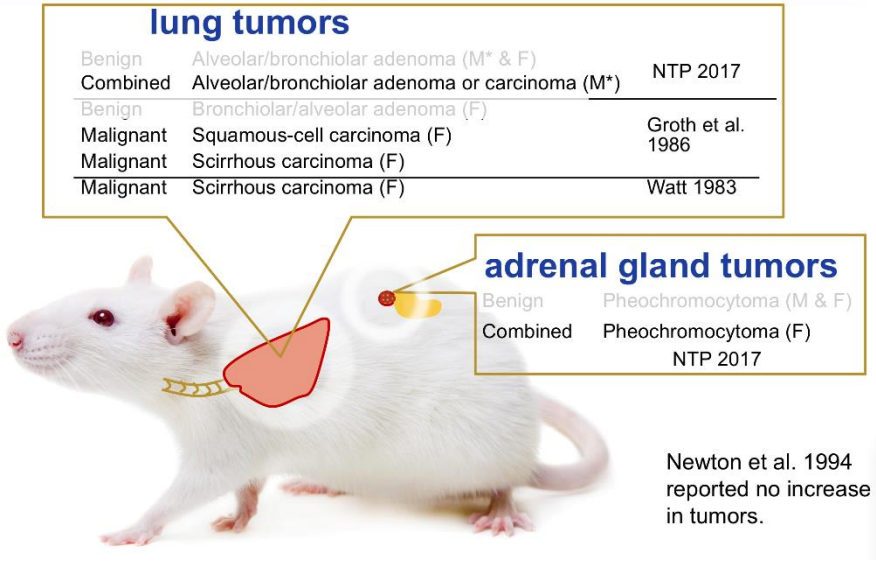
→ Rat lung tumors are evidence of carcinogenicity (i.e., agree with NTP 2017)

NTP Draft Recommendation: Animal Studies

Sufficient animal evidence for antimony trioxide carcinogenicity

Increased incidences of malignant tumors and combined incidences of malignant and benign tumors at multiple tissue sites in multiple species





Panel: Agreed unanimously

Supporting mechanistic information

- Electrophilicity
- Affinity to vicinal thiol groups

Interact with
- Peptides (e.g., GSH)
- Proteins/ enzymes (including zinc finger)

Increase oxidative stress O_2^-

Decrease DNA damage repair capacity

Cause receptor-mediated effects

e.g., Prevent cell differentiation → Preserve proliferation potential

Genotoxicity
- DNA damage
- Chromosomal aberrations
- Sister chromatid exchange

= direct evidence from Sb_2O_3

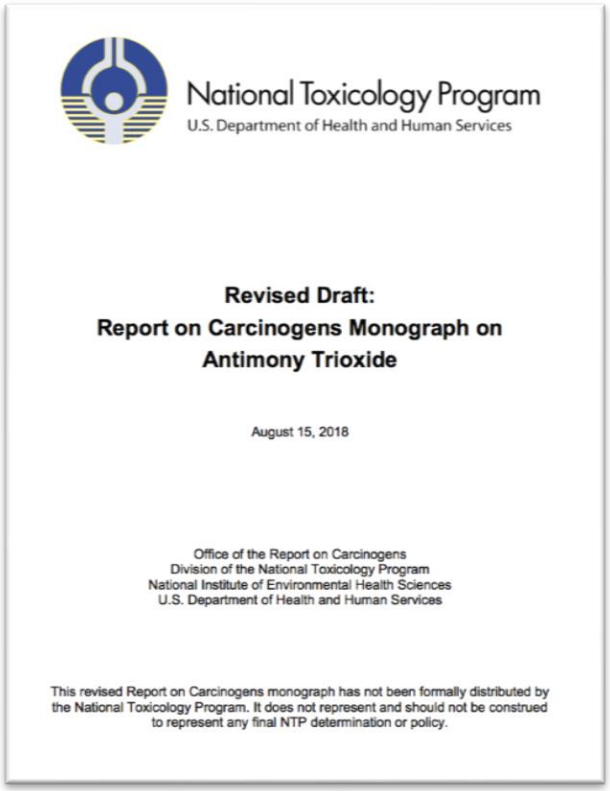
= direct evidence from compounds containing Sb(III)

NTP Preliminary Listing Recommendation

Antimony trioxide should be listed in the RoC as *reasonably anticipated to be a human carcinogen* based on sufficient evidence from studies in experimental animals and supporting mechanistic data.

Panel: Agreed unanimously

Revised Draft RoC Monograph



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

Revised Draft:
Report on Carcinogens Monograph on Antimony Trioxide

August 15, 2018

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

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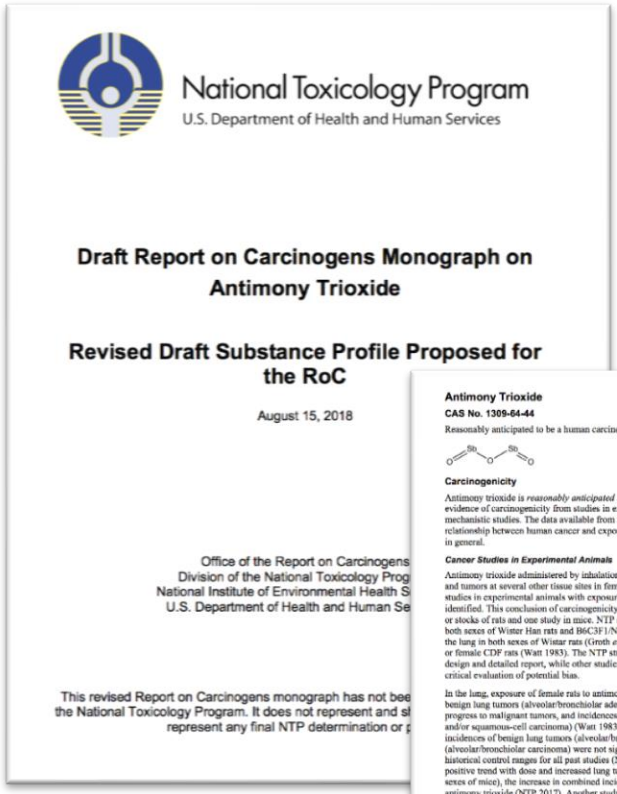

National Toxicology Program
U.S. Department of Health and Human Services

Draft Report on Carcinogens Monograph on Antimony Trioxide

Revised Draft Substance Profile Proposed for the RoC

August 15, 2018

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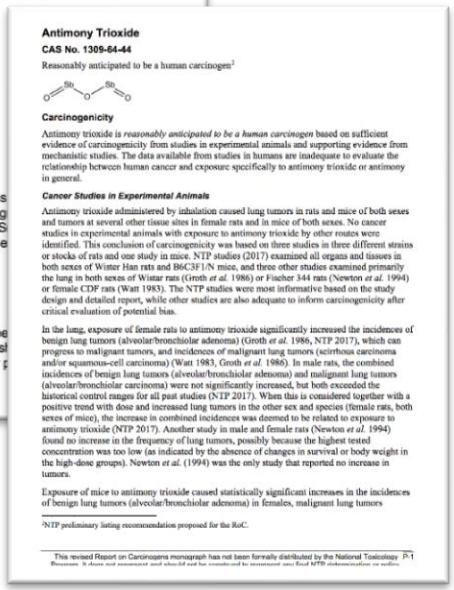

Antimony Trioxide
CAS No. 1309-64-44
Reasonably anticipated to be a human carcinogen[1]

Carcinogenicity

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

Cancer Studies in Experimental Animals

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

In the lung, exposure of female rats to antimony trioxide significantly increased the incidences of benign lung tumors (alveolar/bronchiolar adenoma) (Groth *et al.* 1986, NTP 2017), which can progress to malignant tumors, and incidences of malignant lung tumors (scirrhous carcinoma and/or squamous-cell carcinoma) (Watt 1983, Groth *et al.* 1986). In male rats, the combined incidences of benign lung tumors (alveolar/bronchiolar adenoma) and malignant lung tumors (alveolar/bronchiolar carcinoma) were not significantly increased, but both exceeded the historical control ranges for all past studies (NTP 2017). When this is considered together with a positive trend with dose and increased lung tumors in the other sex and species (female rats, both sexes of mice), the increase in combined incidences was deemed to be related to exposure to antimony trioxide (NTP 2017). Another study in male and female rats (Newton *et al.* 1994) found no increase in the frequency of lung tumors, possibly because the highest tested concentration was too low (as indicated by the absence of changes in survival or body weight in the high-dose groups). Newton *et al.* (1994) was the only study that reported no increase in tumors.

Exposure of mice to antimony trioxide caused statistically significant increases in the incidences of benign lung tumors (alveolar/bronchiolar adenoma) in females, malignant lung tumors

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

This revised Report on Carcinogens monograph has not been formally distributed by the National Toxicology P-1

+ appendices
+ supplemental material

B	C	D	E	F	G	H	I	J	K	L	M	N	O
Reference	(additional) References	Data class	Species	Strain		Age at start	Duration	Historical data available?	Transgenic model?	Randomization bias rating	Randomization bias rationale	Concurrent controls bias rating	Concurrent controls bias rationale
NTP 2017		Full carcinogenicity	Rat	Wistar Han [Crl:WI (Han)]	M	6 weeks	105 weeks	TRUE	FALSE	+++	Animals were randomly assig	+++	Concurrent chamber control was u

New: Supplemental Material

Detailed risk of bias information on animal studies

	Adequacy of study duration bias rating	Adequacy of study duration bias rationale	Confounding bias rating	Confounding bias rationale	Reporting and statistics bias rating
oups	+++	The study duration was 2 years, with 12 m	+++	Material of high purity. Animal husbandry	+++
ot h	+++	The study duration was 2 years, with 1 ye	++	Animals in high dose group were heavier th	++

Animal cancer study results ready for further analysis

Non-neoplastic findings	Other comments	Dose	N at start	Incidence
Lung were examined after 12 months and after 24 month.	12 Month results:	0	65	1/52
Lung were examined after 12 months and after 24 month.	12 Month results:	0.06	65	0/52
Lung were examined after 12 months and after 24 month.	12 Month results:	0.51	65	0/53
Lung were examined after 12 months and after 24 month.	12 Month results:	4.5	65	1/52
Lung were examined after 12 months and after 24 month.	12 Month results:	0	50	0/49
Lung were examined after 12 months and after 24 month.	12 Month results:	0.06	50	0/52
Lung were examined after 12 months and after 24 month.	12 Month results:	0.51	50	1/54
Lung were examined after 12 months and after 24 month.	12 Month results:	4.5	50	0/50
Lungs from exposed animals grossly appeared mottled – wit	Only the incidenc	0		0/13
Lungs from exposed animals grossly appeared mottled – wit	Only the incidenc	1.6		0/17
Lungs from exposed animals grossly appeared mottled – wit	Only the incidenc	4.2		9/18
Lungs from exposed animals grossly appeared mottled – wit	Only the incidenc	0		0/13
Lungs from exposed animals grossly appeared mottled – wit	Only the incidenc	1.6		0/17

Immediate next steps after BSC meeting

- Present to NTP director
- Finalize RoC monograph

Acknowledgements

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