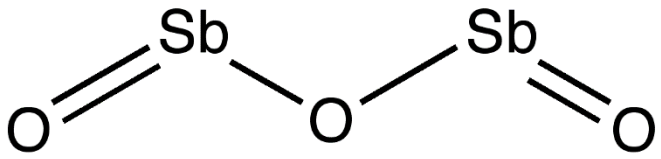
Overall Cancer Evaluation



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Summary of NTP's preliminary conclusions

- **A significant number of people living in the United States are or were exposed to antimony trioxide**
- **Studies in humans are inadequate for evaluating the relationship between human cancer and exposure to antimony trioxide and other antimony compounds**
- **Sufficient evidence of carcinogenicity for antimony trioxide from cancer studies in experimental animals**
  - **Multiple tissue sites in multiple species**
- **Supporting mechanistic information**
- **Biologically plausible in humans**

Human exposure

- **A significant number of people in the United States are exposed to antimony(III) trioxide**
- **Highest levels of exposure to antimony(III) trioxide occur in the workplace**
- **The general population is exposed to antimony**
  - From some consumer products
  - From primary (i.e., pollutant is antimony(III) trioxide) and secondary (i.e., pollutant is transformed from other antimony species into antimony(III) trioxide) environmental releases

Inadequate human evidence for determining carcinogenicity

Limited by:

- **Number of studies with small sample sizes for stomach and lung cancers.**
- **Potential confounding due to smoking and occupational co-exposures.**

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.

Mice had increased incidences of

lung tumors

Benign	Alveolar/bronchiolar adenoma (F)
Malignant	Alveolar/bronchiolar carcinoma (M and F)
Combined	Alveolar/bronchiolar adenoma or carcinoma (F)

skin tumors

Benign	Fibrous histiocytoma (M)
Combined	Fibrous histiocytoma or fibrosarcoma (M)

lymphoma

Malignant	Lymphoma (F)

Rats had increased incidences of

lung tumors

Benign	Alveolar/bronchiolar adenoma (M* & F)	NTP 2017
Combined	Alveolar/bronchiolar adenoma or carcinoma (M*)	
Benign	Bronchiolar/alveolar adenoma (F)	Groth et al. 1986
Malignant	Squamous-cell carcinoma (F)	
Malignant	Scirrhous carcinoma (F)	Watt 1983
Malignant	Scirrhous carcinoma (F)	

adrenal gland tumors

Benign	Pheochromocytoma (M & F)	
Combined	Pheochromocytoma (F)	NTP 2017

Newton et al. 1994 reported no increase in tumors.

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

Cancer Evaluation: Integration of Animal, Human, and Mechanistic Data

- Comment on the overall cancer evaluation (Section 7: Overall Cancer Evaluation and Preliminary Listing Recommendation) and whether the available mechanistic data provide support for the relevance of the cancer studies in experimental animals to human carcinogenicity.
  - Provide any scientific criticism of the NTP's overall assessment and integration of the human cancer, experimental animal, and mechanistic data.