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

- **skin tumors**
  - Benign
  - Combined
  - Fibrous histiocytoma (M)
  - Fibrous histiocytoma or fibrosarcoma (M)

- **lymphoma**
  - Malignant
  - Lymphoma (F)

Rats had increased incidences of

- **lung tumors**
  - Benign
  - Combined
  - Alveolar/bronchiolar adenoma (M* & F)
  - Alveolar/bronchiolar adenoma or carcinoma (M*)
  - Bronchiolar/alveolar adenoma (F)
  - Squamous-cell carcinoma (F)
  - Scirrhous carcinoma (F)

- **adrenal gland tumors**
  - Benign
  - Combined
  - Pheochromocytoma (M & F)
  - 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

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

DNA damage
- Increase oxidative stress
- Decrease DNA damage repair capacity
Reviewer Questions

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.