参考資料３

NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS

STUDIES OF ANTIMONY TRIOXIDE

(CAS NO. 1309-64-4)

IN WISTAR HAN [Crl:WI (Han)] RATS AND B6C3F1/N MICE

(INHALATION STUDIES)

Scheduled Peer Review Date: February 16, 2016

NTP TR 590

National Toxicology Program

National Institutes of Health
Public Health Service
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOREWORD

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ABSTRACT

Sb_2O_3

ANTIMONY TRIOXIDE

CAS No. 1309-64-4

Chemical Formula: Sb_2O_3 Molecular Weight: 291.5

Synonyms: A1530; A1582; a1588 lp; antimonious oxide; antimony oxide; antimony (III) oxide; antimony peroxide; antimony sesquioxide; antimony white; AP 50; biantimony trioxide; C.I. pigment white 11; dechlorane a-o; diantimony trioxide; exitelite; flowers of antimony; nyacol a 1530; senarmontite; valentinite; weisspiessglanz
Trade names: FireShield®, Microfine®, Montana Brand, Thermoguard®, Timonox; TMS®, Trutint®, Ultrafine®, White Star

Antimony trioxide (Sb_2O_3) is used as a flame retardant in canvas, textiles, paper, and plastics and in combination with some chlorinated or brominated flame retardants on commercial furniture, draperies, wall coverings, and carpets. It is also used in batteries, enamels and paint pigment, and ceramics and fiberglass. Occupationally, the major sources of exposure to antimony exist in the metal ore smelting and mining industries. Antimony trioxide was nominated by the Consumer Products Safety Commission and The National Institute of Environmental Health Sciences for National Toxicology Program testing due to the potential for substantial human exposure in occupational settings and the lack of adequate 2-year exposure carcinogenicity studies. Male and female Wistar Han [Crl:WI (Han)] rats and B6C3F1/N mice were exposed to antimony trioxide (greater than 99.9% pure) by inhalation for 2 weeks or 2 years. Genetic toxicology studies were conducted in rat and mouse peripheral blood erythrocytes, peripheral blood leukocytes, and lung cells.

2-WEEK STUDY IN RATS

Groups of five male and five female core study rats were exposed by whole body inhalation to antimony trioxide aerosol at concentrations of 0, 3.75, 7.5, 15, 30, or 60 mg/m^3 for 6 hours plus T_{90} (12 minutes) per day, 5 days per week for 12 exposure days during a 16-day period. Additional groups of five female tissue burden study rats were exposed to the same concentrations for 16 days then held for 28 days without exposure. All rats survived to the end of the study. The mean body weights of exposed groups of males and females were similar to those of the respective chamber control groups. Lung weights of 60 mg/m^3 males and 30 and 60 mg/m^3 females were significantly greater than those of the chamber controls.

Incidences of chronic active inflammation in the lungs were significantly increased in 30 and 60 mg/m^3 males and females.

2-WEEK STUDY IN MICE

Groups of five male and five female core study mice were exposed by whole body inhalation to antimony trioxide aerosol at concentrations of 0, 3.75, 7.5, 15, 30, or 60 mg/m^3 for 6 hours plus T_{90} (12 minutes) per day, 5 days per week for 13 exposure days during a 17-day period. Additional groups of five female tissue burden study mice were exposed to the same concentrations for 17 days then held for 28 days without exposure. All mice survived to the end of the study. The mean body weights of exposed groups of males and females were similar to those of the respective chamber control groups. Lung weights were significantly increased in 60 mg/m^3 males and 15 mg/m^3 or greater females.

In the larynx, there were significantly increased incidences of squamous metaplasia of the epiglottis in the 30 and 60 mg/m^3 males and females compared to those in the chamber control groups.

2-YEAR STUDY IN RATS

Groups of 60 male and 60 female rats were exposed by whole body inhalation to antimony trioxide aerosol at concentrations of 0, 3, 10, or 30 mg/m^3 for 6 hours plus T_{90} (12 minutes) per day, 5 days per week for up to

105 weeks. Additional groups of 25 tissue burden study female rats were exposed to the same concentrations of antimony trioxide for up to 79 weeks. Survival of 10 and 30 mg/m^3 females was significantly less than that of the chamber control group. The decreased survival in females was attributed primarily to lung proteinosis. In males, the trend towards reduced survival was attributed primarily to lung inflammation and proteinosis. Mean body weights of 30 mg/m^3 males were at least 10% less than those of the chamber control group after week 69 and decreased to 80% of that of the chamber controls by the end of the study. Mean body weights of 3, 10, and 30 mg/m^3 females were at least 10% less than those of the chamber control group after weeks 99, 81, and 65, respectively, and those of 10 and 30 mg/m^3 females were 20% and 28% less, respectively, than that of the chamber control group by the end of the study. Exposure-related clinical findings included abnormal breathing, cyanosis, and thinness in males and females. Lung weights were significantly increased in all exposed groups of males and females at the 12-month interim evaluation.

In the lung, there was a positive trend in the incidences of alveolar/bronchiolar adenoma in females in the 2-year study, and the incidences were significantly increased in females exposed to 10 or 30 mg/m^3; 30 mg/m^3 females also had one squamous cell carcinoma and two cystic keratinizing epitheliomas. In all exposed groups of males, the incidences of alveolar/bronchiolar adenoma and of alveolar/bronchiolar adenoma or carcinoma (combined) exceeded the historical control ranges for inhalation studies and for all routes of administration.

Incidences of chronic active inflammation, alveolar epithelium hyperplasia, proteinosis, and fibrosis in the lung were significantly increased in all exposed groups of males and females at the 12-month interim evaluation and in the 2-year study. Incidences of lymphocytic perivascular cellular infiltration were significantly increased in 3 and 10 mg/m^3 males and females at the 12-month interim evaluation and in 3 and 10 mg/m^3 males and all exposed groups of females in the 2-year study. Incidences of bronchiole epithelium hyperplasia were significantly increased in all exposed groups of males at the 12-month interim evaluation and in all exposed groups of males and females in the 2-year study. The incidences of suppurative alveolar inflammation were significantly increased in all exposed groups of males and females in the 2-year study. The incidence of squamous metaplasia of the alveolar epithelium was significantly increased in 3 mg/m^3 females in the 2-year study.

In the adrenal medulla, the incidences of benign pheochromocytoma were significantly increased in 30 mg/m^3 males and females and the incidence of benign or malignant pheochromocytoma (combined) was significantly increased in 30 mg/m^3 females in the 2-year study. Incidences of adrenal medullary hyperplasia occurred with a positive trend in both males and females in the 2-year study, and the incidences were significantly increased in 30 mg/m^3 males and females.

In the 2-year study, incidences of respiratory epithelium hyperplasia in the nose were significantly increased in 3 and 30 mg/m^3 males and 30 mg/m^3 females. The incidences of respiratory epithelium squamous metaplasia in 30 mg/m^3 males and females were significantly increased in the 2-year study.

In the 2-year study, the incidence of chronic active inflammation was significantly increased in the larynx of 3 mg/m^3 females.

In the bone marrow, incidences of hyperplasia were significantly increased in 30 mg/m^3 males and females in the 2-year study.

Incidences of lymphoid hyperplasia in the bronchial and mediastinal lymph nodes were significantly increased in 10 mg/m^3 males and 3 mg/m^3 females at the 12-month interim evaluation and in all exposed groups of males and females in the 2-year study. The incidence of pigmentation was significantly increased in the bronchial lymph nodes of 30 mg/m^3 males in the 2-year study.

Chronic active arterial inflammation was observed in multiple tissues in males and females in the 2-year study, including the mediastinum, pancreas, mesentery, lung, and kidney. The combined incidences of chronic active arterial inflammation in all tissues were increased in 10 and 30 mg/m^3 males and females. These increases were significant in 30 mg/m^3 males and 10 and 30 mg/m^3 females.

In the kidney, the incidences of renal tubule hyaline droplet accumulation were significantly increased in 30 mg/m^3 males and 10 and 30 mg/m^3 females in the 2-year study. The incidence of nephropathy was significantly increased in 30 mg/m^3 females in the 2-year study.

Incidences of retinal atrophy were significantly increased in all exposed groups of females in the 2-year study. Incidences of acute inflammation of the ciliary body of the eye were significantly increased in 30 mg/m^3 males and females in the 2-year study.

2-YEAR STUDY IN MICE

Groups of 60 male and 60 female mice were exposed by whole body inhalation to antimony trioxide aerosol at concentrations of 0, 3, 10, or 30 mg/m^3 for 6 hours plus T_{90} (12 minutes) per day, 5 days per week for up to 105 weeks. Additional groups of 25 tissue burden study female mice were exposed to the same concentrations of antimony trioxide for up to 79 weeks. Survival of 10 and 30 mg/m^3 males and females was significantly less than that of the chamber control groups. Decreases in survival were attributed primarily to alveolar/bronchiolar carcinomas and inflammation of the lung in males and malignant lymphoma and lung inflammation in females. Mean body weights of 30 mg/m^3 males were 10% to 25% less than those of the chamber control group after week 73; mean body weights of 30 mg/m^3 females were at least 10% less than those of the chamber control group after week 85. Exposure-related clinical findings included abnormal breathing and thinness in males and females.

Lung weights were significantly increased in all exposed groups of males and in 10 and 30 mg/m^3 females at the 12-month interim evaluation. Thymus weights of 10 and 30 mg/m^3 males and females were significantly increased at the 12-month interim evaluation.

Significantly increased incidences of alveolar/bronchiolar carcinoma and alveolar/bronchiolar adenoma or carcinoma (combined) occurred in all exposed groups of males in the 2-year study; these incidences occurred with a positive trend and exceeded the historical control ranges for inhalation studies and for all routes of administration. The incidences of multiple alveolar/bronchiolar carcinoma were also significantly increased in exposed male rats. In female mice, incidences of alveolar/bronchiolar adenoma, alveolar/bronchiolar carcinoma, and

alveolar/bronchiolar adenoma or carcinoma (combined) were significantly increased in all exposed groups in the 2-year study and exceeded the historical control ranges for inhalation studies and for all routes of administration. The incidences of multiple carcinoma were significantly increased in all exposed groups of females.

In the lung, incidences of lymphocytic cellular infiltration, chronic active inflammation, pleura fibrosis, pleura inflammation, alveolar epithelium hyperplasia, and bronchiole epithelium hyperplasia were significantly increased in all exposed groups of males and females at the 12-month interim evaluation and in the 2-year study. Incidences of alveolus fibrosis were significantly increased in all exposed groups of males and in 10 and 30 mg/m^3 females at the 12-month interim evaluation; incidences of this lesion were significantly increased in all exposed groups of males and females in the 2-year study.

Incidences of malignant lymphoma occurred with a positive trend in females, and were significantly increased in all exposed groups in the 2-year study.

In the skin, the incidences of fibrous histiocytoma and fibrous histiocytoma or fibrosarcoma (combined) were significantly increased in 30 mg/m^3 males in the 2-year study. In females, the incidence of squamous cell carcinoma was slightly increased at 30 mg/m^3.

In the nose, incidences of chronic active inflammation of the respiratory epithelium were significantly increased in 3 and 10 mg/m^3 males in the 2-year study. The incidence of squamous metaplasia of the respiratory epithelium was significantly increased in 30 mg/m^3 females in the 2-year study.

In the larynx, incidences of respiratory epithelium hyperplasia were significantly increased in 10 and 30 mg/m^3 males and 10 mg/m^3 females at the 12-month interim evaluation and in 10 and 30 mg/m^3 males and females in the 2-year study. Incidences of respiratory epithelium squamous metaplasia were significantly increased in 30 mg/m^3 females at the 12-month interim evaluation and in 10 and 30 mg/m^3 males and 30 mg/m^3 females in the 2-year study. Incidences of squamous epithelium hyperplasia were significantly increased in 30 mg/m^3 males and females in the 2-year study.

In the trachea, the incidence of epithelium hyperplasia was significantly increased in 30 mg/m^3 males in the 2-year study.

In the hematopoietic system, incidences of lymphoid hyperplasia in the bronchial lymph nodes were significantly increased in all exposed groups of males and females at the 12-month interim evaluation and in the 2-year study. Incidences of this lesion in the mediastinal lymph node were significantly increased in 30 mg/m^3 males at the 12-month interim evaluation and in 10 and 30 mg/m^3 males and females in the 2-year study. Incidences of this lesion were also significantly increased in the spleen of all exposed groups of females at the 12-month interim evaluation.

Also in the hematopoietic system, the incidences of histiocytic cellular infiltration were significantly increased in the bronchial lymph node of 10 mg/m^3 females at the 12-month interim evaluation and 30 mg/m^3 males and 10 and 30 mg/m^3 females in the 2-year study. Incidences of this lesion were also significantly increased in the mediastinal lymph node of 10 and 30 mg/m^3 males and all exposed groups of females in the 2-year study. The incidence of hematopoietic cell proliferation was significantly increased in the spleen of 30 mg/m^3 females in the 2-year study. Incidences of bone marrow hyperplasia were significantly increased in all exposed groups of males and in 10 and 30 mg/m^3 females in the 2-year study. Incidences of cellular depletion were significantly increased in the thymus of 10 and 30 mg/m^3 males and all exposed groups of females in the 2-year study.

In the heart, incidences of chronic active inflammation of the epicardium were significantly increased in 10 and 30 mg/m^3 males and females in the 2-year study.

The incidence of chronic active inflammation of the forestomach was significantly increased in 30 mg/m^3 males in the 2-year study.

GENETIC TOXICOLOGY

Antimony trioxide induced small but significant increases in micronucleated erythrocytes in male and female B6C3F1/N mice following exposure for 12 months by inhalation. Significant increases in the percentage of

reticulocytes (immature erythrocytes) were also seen in both male and female mice. In addition, increased levels of DNA damage, assessed using the comet assay, were observed in these same male and female mice in lung tissue samples, but not in peripheral blood leukocytes. No increases in micronucleated red blood cells, percentage of reticulocytes, or DNA damage in lung tissue samples or blood leukocytes were observed in male or female Wistar Han rats following exposure to antimony trioxide for 12 months.

TISSUE BURDEN

Total antimony trioxide lung burdens and blood antimony concentrations increased with increasing exposure concentration in rats and mice in the 2-week and 2-year studies. Based on the observed deposition of antimony trioxide in the lung, it is presumed that foreign body observed in the lungs of rats and mice in the 2-week studies and the lungs, nose, larynx, trachea, bronchial and mediastinal lymph nodes, and mandibular lymph node (mice only) in the 2-year studies is consistent with the presence of antimony trioxide particles in these tissues.

MOLECULAR PATHOLOGY

In Wistar Han rats exposed to antimony trioxide by inhalation for 2 years, there was a high incidence of *Egfr* mutations (13/26) but not *Kras* mutations (1/26) in alveolar/bronchiolar tumors. The *Egfr* mutations were localized within exons 18 to 21 and all of them were transitions (G to A or C to T). No *Kras* or *Egfr* mutations were noted in the alveolar/bronchiolar tumors that arose spontaneously or in age-matched nontumor lung tissues.

Compared to the rats, the mice had higher frequencies of point mutations within hot spot regions of *Kras* (34/80) in alveolar/bronchiolar tumors. However, the mice also had a relatively high incidence of *Kras* mutations in the spontaneous alveolar/bronchiolar carcinomas in the chamber controls (3/9), and as a result, the increased incidences of *Kras* mutations within the exposed groups did not achieve statistical significance. In addition, the majority of *Kras* mutations in both spontaneous and chemically induced alveolar/bronchiolar tumors were within codon 12 and were G to A transitions. Incidences of *Egfr* mutations increased with exposure concentration and occurred with a positive trend across the exposure concentration groups. The *Egfr* mutations were mainly located within exons 18 and 20, and were G to A or C to T transitions.

CONCLUSIONS

Under the conditions of these 2-year inhalation studies, there was *some evidence of carcinogenic activity** of antimony trioxide in male Wistar Han rats based on increased combined incidences of alveolar/bronchiolar adenoma or carcinoma in the lung and on increased incidences of benign pheochromocytoma of the adrenal medulla. There was *some evidence of carcinogenic activity* of antimony trioxide in female Wistar Han rats based on increased incidences of alveolar/bronchiolar adenoma in the lung and on increased combined incidences of benign or malignant pheochromocytoma of the adrenal medulla. The combined occurrence of cystic keratinizing epithelioma and squamous cell carcinoma in the lung may have been related to exposure. There was *clear evidence of carcinogenic activity* of antimony trioxide in male B6C3F1/N mice based on increased incidences of alveolar/bronchiolar carcinoma of the lung. Increases in the combined incidences of fibrous histiocytoma or fibrosarcoma in the skin of male mice were also considered to be related to exposure. There was *clear evidence of carcinogenic activity* in female B6C3F1/N mice based on increases in the incidences of alveolar/bronchiolar adenoma and alveolar/bronchiolar carcinoma of the lung and on increased incidences of malignant lymphoma. The occurrence of squamous cell carcinoma of the skin may have been related to exposure.

Exposure to antimony trioxide resulted in increased incidences of nonneoplastic lesions of the lung, nose, larynx, trachea, bronchial and mediastinal lymph nodes, and bone marrow of male and female rats and mice; the adrenal medulla, arteries of multiple tissues (mesentery, pancreas, mediastinum, kidney, and lung), and eye of male and female rats; the thymus and heart of male and female mice; the forestomach of male mice; and the spleen of female mice.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 19.

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Antimony Trioxide

	Male Wistar Han Rats	Female Wistar Han Rats	Male B6C3F1/N Mice	Female B6C3F1/N Mice
Concentrations in air	0, 3, 10, or 30 mg/m^3	0, 3, 10, or 30 mg/m^3	0, 3, 10, or 30 mg/m^3	0, 3, 10, or 30 mg/m^3
Survival rates	30/50, 30/50, 28/50, 18/50	39/50, 38/50, 28/50, 20/50	38/50, 30/50, 27/50, 17/50	36/50, 31/50, 26/50, 15/50
Body weights	30 mg/m^3 group at least 10% less than the chamber control group after week 69 and decreased to 80% of that of the chamber controls by the end of the exposure.	3, 10, and 30 mg/m^3 groups at least 10% less than the chamber control group after weeks 99, 81, and 65, respectively, and were 20% or 28% less than those of the chamber control group in 10 and 30 mg/m^3 by the end of the exposure.	30 mg/m^3 group at least 10% less than the chamber control group after week 73 and 25% less than the chamber control group by the end of the exposure.	30 mg/m^3 group at least 10% less than the chamber control group after week 85 and 21% less than the chamber control group by the end of the exposure.
Nonneoplastic effects	Lung: foreign body (1/50, 50/50, 50/50, 50/50); inflammation, chronic active (18/50, 50/50, 50/50, 50/50); alveolus, inflammation, suppurative (0/50, 12/50, 24/50, 28/50); perivascular, infiltration cellular, lymphocyte (3/50, 25/50, 19/50, 9/50); proteinosis (0/50, 47/50, 50/50, 50/50); alveolar epithelium, hyperplasia (4/50, 50/50, 48/50, 49/50); bronchiole, epithelium, hyperplasia (3/50, 34/50, 36/50, 33/50); fibrosis (2/50, 50/50, 49/50, 49/50) Adrenal medulla: hyperplasia (1/49, 2/50, 4/49, 8/50) Nose: foreign body (0/50, 0/49, 17/50, 40/50); respiratory epithelium, hyperplasia (6/50, 15/49, 13/50, 25/50); respiratory epithelium, metaplasia, squamous (0/50, 0/49, 2/50, 6/50) Larynx: foreign body (0/50, 50/50, 50/50, 50/50)	Lung: foreign body (0/50, 50/50, 50/50, 50/50); inflammation, chronic active (21/50, 50/50, 50/50, 50/50); alveolus, inflammation, suppurative (0/50, 5/50, 6/50, 5/50); perivascular, infiltration cellular, lymphocyte (0/50, 18/50, 11/50, 8/50); proteinosis (0/50, 50/50, 50/50, 50/50); alveolar epithelium, hyperplasia (5/50, 50/50, 49/50, 50/50); bronchiole, epithelium, hyperplasia (6/50, 26/50, 25/50, 27/50); alveolar epithelium, metaplasia, squamous (0/50, 5/50, 3/50, 1/50); fibrosis (1/50, 50/50, 50/50, 49/50) Adrenal medulla: hyperplasia (0/49, 0/49, 3/49, 5/50) Nose: foreign body (0/50, 5/50, 26/50, 45/50); respiratory epithelium, hyperplasia (4/50, 6/50, 7/50, 16/50); respiratory epithelium, metaplasia, squamous (0/50, 2/50, 3/50, 5/50) Larynx: foreign body (0/50, 50/50, 50/50, 50/50); inflammation, chronic active (0/50, 8/50, 0/50, 3/50)	Lung: infiltration cellular, lymphocyte (13/50, 47/50, 48/50, 45/50); foreign body (0/50, 50/50, 50/50, 50/50); inflammation, chronic active (0/50, 48/50, 50/50, 50/50); alveolus, fibrosis (0/50, 12/50, 30/50, 37/50); pluera, fibrosis (0/50, 36/50, 46/50, 50/50); pleura, inflammation (1/50, 40/50, 47/50, 48/50); alveolar epithelium, hyperplasia (6/50, 39/50, 45/50, 49/50); bronchiole, epithelium, hyperplasia (0/50, 32/50, 44/50, 44/50) Bone marrow: hyperplasia (10/49, 19/50, 27/48, 33/49) Thymus: depletion cellular (15/41, 14/38, 32/43, 32/39) Nose: foreign body (0/50, 48/49, 48/49, 49/50); respiratory epithelium, inflammation, chronic active (3/50, 9/49, 9/49, 6/50)	Lung: infiltration cellular, lymphocyte (7/50, 37/50, 37/50, 26/50); foreign body (0/50, 50/50, 50/50, 50/50); inflammation, chronic active (1/50, 50/50, 50/50, 50/50); alveolus, fibrosis (0/50, 13/50, 30/50, 38/50); pluera, fibrosis (1/50, 39/50, 50/50, 50/50); pleura, inflammation (4/50, 27/50, 42/50, 38/50); alveolar epithelium, hyperplasia (1/50, 36/50, 49/50, 48/50); bronchiole, epithelium, hyperplasia (1/50, 34/50, 48/50, 45/50) Spleen: hematopoietic cell proliferation (17/50, 19/50, 20/50, 35/50) Bone marrow: hyperplasia (3/50, 5/50, 15/50, 28/50) Thymus: depletion cellular (9/47, 18/49, 23/49, 29/49) Nose: foreign body (1/50, 44/49, 45/50, 48/50); respiratory epithelium, metaplasia, squamous (0/50, 3/49, 2/50, 4/50)

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Antimony Trioxide

	Male Wistar Han Rats	Female Wistar Han Rats	Male B6C3F1/N Mice	Female B6C3F1/N Mice
Nonneoplastic effects (continued)	Trachea: foreign body (0/50, 28/50, 43/50, 48/50) Bone marrow: hyperplasia (0/50, 3/50, 4/50, 8/50) Lymph node, bronchial: foreign body (0/41, 35/40, 45/48, 42/47); hyperplasia, lymphoid (0/41, 21/40, 29/48, 26/47); pigmentation (1/41, 4/40, 5/48, 10/47) Lymph node, mediastinal: foreign body (0/42, 41/45, 41/49, 43/49); hyperplasia, lymphoid (1/42, 24/45, 30/49, 26/49) Mediastinum: artery, inflammation, chronic active (0/0, 1/1, 2/2, 10/10) Pancreas: artery, inflammation, chronic active (1/50, 0/50, 2/50, 8/50) Mesentery: artery, inflammation, chronic active (0/50, 0/50, 0/50, 6/50) Lung: artery, inflammation, chronic active (0/50, 0/50, 1/50, 1/50) Kidney: renal tubule, accumulation, hyaline droplet (0/50, 1/50, 3/50, 14/50); artery, inflammation, chronic active (0/50, 0/50, 1/50, 4/50) Artery (all tissues combined): inflammation, chronic active (1/50, 1/50, 5/50, 16/50) Eye: ciliary body, inflammation, acute (0/49, 0/49, 1/50, 6/49)	Trachea: foreign body (0/50, 39/50, 47/50, 49/50) Bone marrow: hyperplasia (8/50, 5/50, 11/50, 20/50) Lymph node, bronchial: foreign body (0/35, 35/36, 23/28, 36/41); hyperplasia, lymphoid (0/35, 21/36, 9/28, 11/41) Lymph node, mediastinal: foreign body (0/46, 27/46, 32/46, 33/46); hyperplasia, lymphoid (0/46, 14/46, 10/46, 15/46) Mediastinum: artery, inflammation, chronic active (0/0, 0/0, 2/2, 9/9) Pancreas: artery, inflammation, chronic active (0/50, 0/50, 3/50, 8/50); artery, necrosis (0/50, 0/50, 0/50, 4/50) Mesentery: artery, inflammation, chronic active (0/50, 0/50, 0/50, 6/50) Lung: artery, inflammation, chronic active (0/50, 0/50, 1/50, 2/50) Kidney: renal tubule, accumulation, hyaline droplet (0/50, 0/50, 5/50, 11/50); nephropathy (16/50, 15/50, 20/50, 24/50); artery, inflammation, chronic active (0/50, 0/50, 0/50, 2/50) Artery (all tissues combined): inflammation, chronic active (0/50, 0/50, 5/50, 15/50) Eye: retina, atrophy (6/49, 21/50, 18/49, 19/49); ciliary body, inflammation, acute (0/49, 0/50, 1/49, 6/49)	Larynx: foreign body (0/50, 15/50, 29/50, 44/50); respiratory epithelium, hyperplasia (1/50, 3/50, 15/50, 30/50); respiratory epithelium, metaplasia, squamous (0/50, 0/50, 8/50, 18/50); squamous epithelium, hyperplasia (2/50, 0/50, 4/50, 13/50) Trachea: foreign body (0/49, 3/50, 1/50, 20/50); epithelium, hyperplasia (0/49, 0/50, 2/50, 5/50) Lymph node, bronchial: hyperplasia, lymphoid (2/30, 21/43, 26/47, 13/41); foreign body (0/30, 34/43, 47/47, 38/41); infiltration cellular, histiocyte (0/30, 2/43, 4/47, 6/41) Lymph node, mediastinal: hyperplasia, lymphoid (2/37, 8/45, 17/48, 34/49); foreign body (0/37, 32/45, 42/48, 48/49); infiltration cellular, histiocyte (0/37, 4/45, 13/48, 34/49) Heart: epicardium, inflammation, chronic active (0/50, 2/50, 7/50, 16/50) Stomach, forestomach: inflammation, chronic active (2/50, 4/50, 4/49, 7/50)	Larynx: foreign body (0/50, 25/50, 39/50, 48/50); respiratory epithelium, hyperplasia (2/50, 0/50, 14/50, 18/50); respiratory epithelium, metaplasia, squamous (1/50, 0/50, 5/50, 24/50); squamous epithelium, hyperplasia (4/50, 1/50, 1/50, 12/50) Trachea: foreign body (0/50, 7/50, 14/50, 20/50) Lymph node, bronchial: hyperplasia, lymphoid (2/41, 15/47, 17/48, 11/49); foreign body (0/41, 34/47, 46/48, 43/49); infiltration cellular, histiocyte (0/41, 2/47, 7/48, 7/49) Lymph node, mediastinal: hyperplasia, lymphoid (0/46, 3/48, 16/49, 18/50); foreign body (0/46, 28/48, 45/49, 44/50); infiltration cellular, histiocyte (0/46, 6/48, 11/49, 16/50) Heart: epicardium, inflammation, chronic active (0/50, 2/50, 7/50, 7/50)

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Antimony Trioxide

	Male Wistar Han Rats	Female Wistar Han Rats	Male B6C3F1/N Mice	Female B6C3F1/N Mice
Neoplastic effects	Lung: alveolar/bronchiolar adenoma (3/50, 4/50, 6/50, 8/50); alveolar/bronchiolar adenoma or carcinoma (3/50, 4/50, 8/50, 8/50) Adrenal medulla: benign pheochromocytoma (1/49, 0/50, 2/49, 7/50)	Lung: alveolar/bronchiolar adenoma (0/50, 2/50, 6/50, 5/50) Adrenal medulla: benign pheochromocytoma (0/49, 2/49, 2/49, 6/50); benign or malignant pheochromocytoma (0/49, 2/49, 2/49, 7/50)	Lung: alveolar/bronchiolar carcinoma (4/50, 18/50, 20/50, 27/50) Skin: fibrous histiocytoma (0/50, 1/50, 1/50, 4/50); fibrous histiocytoma or fibrosarcoma (0/50, 1/50, 3/50, 4/50)	Lung: alveolar/bronchiolar adenoma (1/50, 10/50, 19/50, 8/50); alveolar/bronchiolar carcinoma (2/50, 14/50, 11/50, 11/50); alveolar/bronchiolar adenoma or carcinoma (3/50, 22/50, 27/50, 18/50) All organs: malignant lymphoma (7/50, 17/50, 20/50, 27/50)
Equivocal findings	None	Lung: cystic keratinizing epithelioma or squamous cell carcinoma (0/50, 0/50, 0/50, 3/50)	None	Skin: squamous cell carcinoma (0/50, 0/50, 0/50, 2/50)
Level of evidence of carcinogenic activity	Some evidence	Some evidence	Clear evidence	Clear evidence
Genetic toxicology				
Micronucleated erythrocytes				
Rat peripheral blood *in vivo*:	Negative in males and females			
Mouse peripheral blood *in vivo*:	Positive in males and females			
DNA damage				
Rat	Negative in lung cells and leukocytes (males and females)			
Mouse	Positive in lung cells (males and females); negative in leukocytes (males and females)			