

Original research

Occupational exposure to antimony trioxide: a risk assessment

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ABSTRACT

Objectives The US National Toxicology Program (NTP) recently recommended in its Report on Carcinogens Monograph for Antimony Trioxide that antimony trioxide be listed as '*reasonably anticipated to be a human carcinogen*' based on sufficient evidence of carcinogenicity in experimental animals and supporting evidence from mechanistic studies. Our goal was to estimate the possible human cancer risk from occupational exposure to antimony trioxide.

Methods We selected data from 2-year inhalation studies in male and female mice conducted by the NTP and performed cancer dose–response analyses using cancer models and benchmark dose methods developed by the US Environmental Protection Agency. In these analyses, we generated benchmark doses and cancer slope factors for antimony trioxide, and then estimated human cancer risk under various exposure scenarios. Typical and worst-case inhalation scenarios in multiple occupational settings were used in risk estimation.

Results In typical case scenarios, the occupational cancer risk from antimony trioxide was estimated to be 0.025 (25 in 1000) for persons working with flame retardants in plastics and textiles for 40 years. Under worst-case scenarios, the occupational cancer risk was estimated to be 0.11 (110 in 1000) for persons working with flame retardants in plastics and textiles. At the current Occupational Safety and Health Administration Permissible Exposure Limit, the cancer risk for occupational inhalation exposure of antimony trioxide was estimated to be 0.096 (96 in 1000).

Conclusion The risk estimates calculated in this study suggest that exposure to antimony trioxide at levels present in certain occupational settings results in a large increase in the risk of developing cancer.

INTRODUCTION

Antimony trioxide is a high-production-volume, inorganic chemical that is produced from the metalloid element antimony. It accounts for 80% of total antimony in the USA used in the manufacturing of various consumer products.¹ Human exposure to antimony trioxide occurs through ambient air, consumer products and workplace settings.^{1,2} In consumer products, it is commonly used as a flame retardant synergist, a catalyst in polyethylene terephthalate (PET) production and as an opacifying agent in paints, glasses and ceramics.³ Occupationally exposed workers, particularly those in

Key messages

What is already known about this subject?

- Workers in certain occupational settings are exposed to high levels of antimony trioxide.
- Inhalation of antimony trioxide promotes the development of lung adenomas and carcinomas in experimental animals.
- At present, there is no quantitative occupational health risk assessment of the carcinogenic effects of antimony trioxide.

What are the new findings?

- To our knowledge, this study was the first quantitative carcinogenic risk assessment conducted for occupational antimony trioxide exposure.
- Our results provide evidence that chronic exposure to antimony trioxide in certain workplaces increases the risk of cancer development.
- Assuming occupational exposure to antimony trioxide for 40 years at the current US Occupational Safety and Health Administration (OSHA) Permissible Exposure Limit (PEL) of 0.5 mg/m³ for antimony, the associated risk of cancer is estimated to be 96 extra cases per 1000 exposed workers.

How might this impact on policy or clinical practice in the foreseeable future?

- Our study indicates that the cancer risk from exposure to occupational antimony trioxide is high at the current OSHA PEL.
- Our study underscores the necessity of personal protective equipment (PPE) in workplaces involved in antimony trioxide and flame-retardant production and manufacturing.
- Based on our risk calculations, we recommend that regulatory standards in the USA and European Union for antimony (and antimony trioxide) be revisited and lowered.

industries that manufacture products using antimony trioxide, have the highest exposure that occurs primarily through inhalation.^{1,3}

Antimony trioxide has been detected in the lungs, blood and urine of workers in occupational settings where antimony is processed, and biomonitoring data indicate that antimony compounds are

retained postinhalation exposure.⁴ Acute occupational exposure can lead to skin, eye and lung irritation, as well as headaches, nausea and vomiting.⁵ Prolonged occupational exposure has been associated with various chronic health effects. There is limited human evidence for reproductive and developmental toxicity of antimony trioxide, with one study reporting increases in spontaneous abortions and gynaecological issues among female workers.⁶ Immunological dysfunction, namely decreases in IgA, IgG and IgE immunoglobulins, has also been reported among occupationally exposed workers.⁷

In its more than 30-year-old 1989 monograph, the International Agency for Research on Cancer (IARC) classified antimony trioxide as possibly carcinogenic to humans (group 2B), finding there was inadequate evidence in humans and sufficient evidence of carcinogenicity in experimental animals.⁸ Four cancer epidemiology studies published since that time have reported associations of occupational exposure to antimony compounds (including various antimony oxides and antimony sulfides) with lung cancer in humans,^{9–12} including three studies in UK and US smelter workers.^{9–12} Furthermore, Jones *et al*¹² reported a dose-dependent increase in lung cancer mortality with increasing antimony exposure. Although the primary target of inhalation occupational exposure is the lung, three of these studies also observed increased gastric cancer mortality among workers.^{9–11} These findings are supported by evidence illustrating the potential genotoxic effects of antimony trioxide among occupationally exposed workers.¹³ A recent meta-analysis examining the carcinogenicity of antimony trioxide concluded that increased lung cancer in workers is possible,¹⁴ though the human evidence is limited by methodological concerns, including small sample sizes, residual confounding and exposure misclassification.^{8,14}

In animals, chromosomal aberrations and alveolar/bronchiolar hyperplasia were observed following oral exposure to antimony trioxide.¹⁴ Furthermore, several inhalation studies reported increases in lung (including alveolar and bronchiolar) carcinoma,¹⁵ adenoma,¹⁵ hyperplasia and metaplasia,^{15,16} lymphocytes¹⁵ and macrophages.¹⁶ Lymphoma¹⁵ and leukaemia¹⁶ were also reported following inhalation exposure. At the time of its monograph, IARC concluded that there was sufficient evidence for carcinogenicity from antimony trioxide in experimental animals based on lung tumour development.⁸ However, the studies used in IARC's determination had one or more methodological limitations, including starting exposure at older ages (eg, 15 weeks of age), exposure or study durations of considerably less than the lifetime of the animal (eg, 52 weeks), multiple early interim sacrifices (eg, at 3, 6, 9 and 12 months) and testing fewer than three dose levels.⁸ Recently, the National Toxicology Program (NTP) conducted more robust animal exposure studies of antimony trioxide and, in its review of antimony trioxide for the Report on Carcinogens, the NTP recommended that the chemical be listed as reasonably anticipated to be a human carcinogen based on sufficient evidence of carcinogenicity from studies in experimental animals and supporting evidence from mechanistic studies.³

Despite this evidence of carcinogenicity, no regulatory or other governmental entity has conducted a quantitative dose–response analysis or risk assessment of occupational exposure to antimony trioxide. Such an analysis is pertinent given the widespread use of antimony trioxide in workplace settings and the high prevalence of lung cancer worldwide,¹⁷ as well as the potential to enact known mitigation strategies to reduce antimony trioxide exposure in the workplace.

METHODS

Study selection

As noted previously, several animal studies examining the carcinogenic effects of antimony trioxide were limited by their methodologies.⁸ Therefore, we chose results from a recent set of controlled animal studies conducted by the NTP for modelling.¹⁵ Wistar Han rats and B6C3F/N mice were exposed to antimony trioxide through inhalation for 6 hours per day, 5 days per week, for 2 years in these studies. Groups of 60 male and 60 female animals were exposed to antimony trioxide concentrations of 0, 3, 10 or 30 mg/m³, with interim sacrifices of 10 animals per group at week 53. Animals in all dose groups were examined grossly and histologically for tumours in all tissues. Tumour incidence was determined at interim sacrifice at week 53, terminal sacrifice at the end of the 105 week period or at unscheduled death. Treatment-related increases in tumours, for example, increases in tumour incidence above the spontaneous levels observed in concurrent controls, were observed in both mice and rats. In evaluating the level of evidence of carcinogenicity in these studies, the NTP concluded there was clear evidence in male mice, based on treatment-related increases in alveolar/bronchiolar carcinoma of the lung and in fibrous histiocytoma or fibrosarcoma of the skin; clear evidence in female mice based on treatment-related increases in alveolar/bronchiolar adenoma and carcinoma of the lung and in malignant lymphoma; some evidence in male rats based on treatment-related increases in alveolar/bronchiolar adenoma or carcinoma of the lung and in benign pheochromocytoma of the adrenal medulla; and some evidence in female rats based on treatment-related increases in alveolar/bronchiolar adenoma in the lung and in benign or malignant pheochromocytoma of the adrenal medulla.

In the NTP studies, greater tumour responses, that is, increases in the incidence of treatment-related tumours per increased increment of dose, were apparent in mice exposed to antimony trioxide, as compared with rats, based on inspection of the cancer dose response data (eg, online supplemental table 1). The greater sensitivity of the mouse to the carcinogenic effects of antimony trioxide was confirmed by a preliminary set of dose–response analyses of the NTP rat and mouse studies (results not shown). Thus, we chose to use mouse data for risk modelling as mice were found to be the more sensitive species. Specifically, we chose to model the dose–response data for alveolar/bronchiolar carcinoma in male mice (the low incidence of treatment-related skin tumours in male mice (0, 1, 3 and 4 fibrous histiocytomas or fibrosarcomas combined in the control, low, mid and high dose groups, respectively) was not modelled, as it was not anticipated to contribute substantially to the cancer potency estimate.) and for alveolar/bronchiolar adenoma or carcinoma (combined) and malignant lymphoma in female mice (online supplemental tables S1 and S3).

Survival rates and model corrections

Prior to modelling, we assessed the survival rates of the mice in all concentration groups. Poor survival has been shown to bias risk estimates where early deaths from causes other than treatment-related tumours reduce the time at risk of tumour for the animal's treatment group.¹⁸ In cases of poor survival associated with treatment (approximately >15% difference in survival between the control and one or more treatment groups), it can be necessary to use survival-corrected tumour incidences. Survival in the NTP mouse studies was assessed by comparing the survival in the control groups with the midexposure groups (10 mg/m³) and high-exposure groups (30 mg/m³) at week 85.

Table 1 Equations used to calculate the animal dose, human dose, human exposure factor (EF), human cancer slope factors (CSF_h), human cancer risks and intakes for reduced risk levels

| Equation number | Equation name (units) | Equation description |
|-----------------|---|--|
| {1} | Animal dose (mg/kg-day) | $C_a \times (IR_a \div BW_a) \times EF_a$ |
| {2} | Human dose (mg/kg-day) | $C_h \times (IR \div BW_h) \times EF_h$ |
| {3} | Animal exposure factor | $(6.2 \text{ hours} \div 24 \text{ hours}) \times (5 \text{ days} \div 7 \text{ days})$ |
| {4} | Human exposure factor | $(8 \text{ hours} \div 24 \text{ hours}) \times (5 \text{ days/week} \times 50 \text{ weeks/year} \times \text{ED}) \div (\text{ED} \times 365 \text{ days/year})$ |
| {5} | CSF _h (mg/kg-day) ⁻¹ | $CSF_a \times (BW_h \div BW_a)^{1/4}$ |
| {6} | Human cancer risk | $D_h \times CSF_h \times (\text{ED} \div \text{AT})$ |
| {7} | Intake level (IL) associated with a cancer risk of one in a million (µg/day); | $((10^{-6} \times BW_h) \div CSF_h) \times 1000 \text{ (µg/mg)}$ |
| {8} | Workplace air concentration (mg/m ³) associated with IL | $(\text{IL} \times 0.001 \text{ mg/µg}) \div IR_o$ |

Concentrations used to estimate animal doses were obtained from the NTP study (0, 3, 10, and 30 mg/m³), and the OSHA PEL and EU antimony occupational estimates were used as human concentrations. Default values were used for human and animal inhalation rates and body weights. The animal exposure factor reflects the time per day and days per week that animals were exposed in the NTP studies, and the human exposure factor reflects exposure across a typical occupational career. An exposure duration of 20 or 40 years and averaging time of 70 years were used in estimating cancer risk.

Default values: IR_a=0.0345 m³/day; IR_h=20 m³/day; BW_a=weighted average BW of the control; BW_h=70 kg; ED=20 or 40 years; AT=70 years; IR_o=10 m³/day. AT, averaging time (year); BW_a, animal body weight (kg); BW_h, human body weight (kg); C_a, animal concentration (mg/m³); C_h, human concentration (mg/m³); CSF_a, animal cancer slope factor (mg/kg-day)⁻¹; CSF_h, human cancer slope factor (mg/kg-day)⁻¹; D_h, human dose (mg/kg-day); ED, exposure duration (year); EF_a, animal exposure factor; EF_h, human exposure factor; IL, intake level associated with cancer risk of one in a million (µg/day); IR_a, animal inhalation rate (m³/day); IR_h, human inhalation rate (m³/day); IR_o, human occupational intake rate (m³/day); OSHA, Occupational Safety and Health Administration; PEL, Permissible Exposure Limit.

Among females, the difference in survival between the control and high-exposure and midexposure groups was 16% and 12%, respectively. Among males, the difference in survival between the control and high-exposure and midexposure groups was 22% and 14%, respectively. Less than 85% of early deaths in the high-exposure group for males and females were due to treatment-related tumours. Given the severe mortality among treated males, a multistage Weibull time-to-tumour model was used to account for mortality. Mortality was also high among treated females but occurred later in the study. Therefore, a poly3 correction was applied to the female tumour incidence data to account for treatment-related mortality.¹⁹

Benchmark dose (BMD) models

Prior to modelling, inhalation concentrations were converted to relevant animal doses (online supplemental table S2) using equation {1} in table 1. The average body weight of the controls was used to calculate doses for all exposure groups. The inhalation rate was calculated using the equation of Anderson, and the lifetime average doses were determined by dividing the inhalation rate by the body weight and multiplying by the chamber air concentration of antimony trioxide, accounting for the number of days per week and hours per day of exposure.²⁰ The US Environmental Protection Agency's (EPA) Benchmark Dose Software Version (BMDS) 3²¹ was used to estimate BMDs and cancer slope factors for alveolar/bronchiolar adenoma or carcinoma and malignant lymphoma among females using the poly3

corrected incidences (online supplemental table S3). The multistage polynomial model for cancer was used to derive cancer potency estimates for female mice, as there was no evidence to suggest that another model was more appropriate.

For alveolar/bronchiolar adenomas or carcinomas, BMDS did not recommend any degree of polynomial using all four exposure doses. Following US EPA BMDS guidance,²² we removed the highest dose (30 mg/m³) to achieve better model fit. The p value for the model with the three lowest doses was less than the recommended 0.05; however, the visual fit and scaled residuals were adequate, and thus we decided to use this model in order to preserve the middle dose that informs the dose-response. Furthermore, while malignant lymphoma likely shortened the lifespan of a number of high dose females, such that they did not live long enough to develop alveolar/bronchiolar tumours, this was not the case with the middle dose group. Therefore, there was no biological reason to remove the middle dose from the modelled data. The first-degree polynomial model was chosen for the alveolar/bronchiolar adenoma or carcinoma data, and the second-degree polynomial model was chosen for the malignant lymphoma data. A multisite cancer model using BMDS V.2 was used to derive cancer potency estimates for female mice, thereby incorporating the data for alveolar/bronchiolar adenoma or carcinoma and malignant lymphoma in the analysis. BMDS results for the individual tumour sites/types observed in females are provided in the online supplemental table S4.

The US EPA's Weibull time-to-tumour model for fatal tumours, which characterises the probability of death from a tumour, was used to derive cancer potency for males. A benchmark response of 0.05 and CI of 0.95 was used for both the multistage model and the Weibull time-to-tumour model.²³

Cancer risk calculation

Cancer slope factors from the BMD models were used to calculate human cancer risk. Human cancer slope factors were first estimated from animal cancer slope factors using the average animal body weight of the control group and default human adult body weight of 70 kg (equations {2}–{5}, table 1).²⁴ The most sensitive study was chosen as the basis for the animal cancer slope factor. Human relevant doses were calculated using the default human adult body weight and an occupational exposure factor that assumes employees work an average of 8 hours per day, 5 days per week, 50 weeks per year (assuming 2 weeks of vacation time), for both 20 and 40 working years.²⁵ Human exposure concentrations were based on typical and worst-case inhalation exposure scenarios in common occupational settings with antimony trioxide exposure from an exposure assessment conducted in the European Union (EU) reported in the NTP's Antimony Trioxide Monograph (online supplemental table S5).²⁶ The human cancer slope factor and estimated average daily human doses were used to calculate human cancer risks (equation {6}, table 1) for 20 or 40 years of occupational exposure. Lastly, we calculated daily intake levels of antimony trioxide associated with an estimated risk of no more than 1 case of cancer per 1 000 000 individuals over 70 years of exposure (equation {7}, table 1).

RESULTS

Model predictions

In the male mouse model output, the BMD associated with a 5% increased risk of developing a treatment-related tumour (alveolar/bronchiolar carcinoma) was 1.34 mg/kg-day, and the lower bound of this dose (BMD level) was 0.78 mg/kg-day. The animal

Table 2 Results calculated with Benchmark Dose Software Version 3 for male and female mouse models.

| Tumour type | BMD (mg/kg-day) | BMDL (mg/kg-day) | CSF _a (mg/kg-day) ⁻¹ | CSF _h (mg/kg-day) ⁻¹ |
|--------------------------------|-----------------|------------------|--|--|
| Male | | | | |
| Alveolar/bronchiolar carcinoma | 1.34 | 0.78 | 0.064 | 0.40 |
| Female | | | | |
| Multisite* | 0.078 | 0.061 | 0.82 | 5.17 |

Model outputs include the benchmark dose (BMD), benchmark dose level (BMDL), animal cancer slope factor (CSF_a) and the calculated human cancer slope factor (CSF_h).

*Alveolar/bronchiolar carcinoma or adenoma and malignant lymphoma.

cancer slope factor, which is the ratio of the 5% risk level to the lower bound on dose, was 0.064 (mg/kg-day)⁻¹. In the female mouse model output, the BMD associated with a 5% increased risk of developing a treatment-related tumour (alveolar/bronchiolar adenoma or carcinoma and/or malignant lymphoma) was 0.078 mg/kg-day, and the BMD level was 0.061 mg/kg-day. The animal cancer slope factor was 0.82 (mg/kg-day)⁻¹ (table 2).

Cancer slope factors

Human cancer slope factors were calculated based on animal cancer slope factors for the male and female mouse models (equation {5}, table 1). Human cancer slope factors were 5.17 (mg/kg-day)⁻¹ based on the female mouse study, using the multisite (alveolar/bronchiolar adenoma or carcinoma and malignant lymphoma) cancer model, and 0.40 (mg/kg-day)⁻¹, based on the male mouse study, using the Weibull time-to-tumour model for fatal tumours (alveolar/bronchiolar carcinoma). As female mice were the more sensitive sex and species, the cancer slope factor based on females was used to estimate human cancer risks.

Human cancer risk results

Risk at OSHA PEL

The current US OSHA PEL for antimony is 0.5 mg/m³.²⁷ Based on this permissible limit, we estimate the cancer risk is 96 cases per 1000 individuals for 40 years of occupational exposure across the life course.

Risk at typical case exposure scenarios

The typical case exposure scenarios for occupationally exposed workers were based on EU estimates made in 2008 and were reported in the NTP Antimony Trioxide Monograph (online supplemental table S5).²⁶ Exposure scenarios were given for several occupational settings, including antimony trioxide production, handling of flame retardants in textiles and plastics and handling of flame retardants in the formulation and processing of rubber. The industrial processes using antimony trioxide in the USA are likely similar to the EU,³ indicating the exposure estimates from the EU are applicable to the USA. Under the typical case scenarios, the highest observed cancer risk was 25 cases per 1000 individuals for 40 years of occupational exposure to flame retardants for plastics and textiles. The lowest cancer risk was observed for antimony trioxide refining in the production process, with the lowest observed risk, approximately 1 case per 1000 individuals for 20 years of occupational exposure (table 3).

Risk at worst-case exposure scenarios

Cancer risks based on worst-case occupational exposures to antimony trioxide were also estimated by the EU and included the same industries as the typical case scenarios.²⁶ Under the worst-case exposure scenarios, the highest cancer risk observed was 110 cases per 1000 individuals for 40 years of occupational exposure in textile formulation and plastics handling where

antimony trioxide was used as a flame retardant. Processing flame retardants in rubber had the lowest observed cancer, with the lowest observed risk, 4.5 case per 1000 individuals, for 20 years of occupational exposure (table 4).

Intakes for reduced risk levels

The estimated daily intake associated with a reduced risk level producing no more than one extra case of cancer in 1000 000 individuals exposed over a 40-year workplace exposure is 0.014 µg/day. This translates to a workplace air concentration of 1.4 × 10⁻⁶ mg/m³, which is more than 357 000 times lower than the current OSHA PEL (equation {8}, table 1).

DISCUSSION

This quantitative risk assessment on occupational exposure to antimony trioxide calculated cancer risk estimates for workers exposed chronically to antimony trioxide in certain occupational settings. Risk was calculated based on data from a controlled animal study using the US EPA's BMD modelling software and exposure estimates from prior assessments. Estimated cancer risk was as high as 96 cases per 1000 individuals for workers with inhalation exposure at the OSHA PEL. Cumulative impacts, resulting from exposure to other carcinogens (eg, those acting additively or synergistically with antimony trioxide), and exposures to antimony trioxide from ambient air^{28 29} and consumer products,^{2 30} as well as exposures occurring earlier in life (in utero through age 16 years), were not incorporated in the model. Thus, it is likely that our cancer risk estimates are actually underestimates. Although prior studies have found associations between occupational antimony exposure and lung cancer,^{9 10 12} this is the first study to attempt to quantify cancer risk to humans.

Mechanistically, antimony trioxide exhibits several key characteristics of carcinogens³¹ that support the cancer risk findings

Table 3 Cancer risks based on 2008 EU estimates of typical case scenario exposures in various industries that commonly used antimony trioxide²⁶

| Industry | 20-year exposure | 40-year exposure |
|---|------------------|------------------|
| Sb ₂ O ₃ production | | |
| Conversion | 0.0026 | 0.0052 |
| Refining/refuming | 0.0012 | 0.0023 |
| Product handling | 0.0039 | 0.0077 |
| Flame retardants in rubber | | |
| Formulation | 0.0049 | 0.0098 |
| Processing | 0.0062 | 0.012 |
| Flame retardants in plastics/textiles, handling/formulation | 0.013 | 0.025 |

Cancer risks were calculated for 20 and 40 years of exposure. Online supplemental table S5 provides EU occupational exposure estimates used in risk calculations. EU, European Union.

Table 4 Cancer risks based on 2008 EU estimates of worst-case scenario exposures in various industries that commonly used antimony trioxide²⁶

| Industry | 20-year exposure | 40-year exposure |
|--|------------------|------------------|
| Sb₂O₃ production | | |
| Conversion | 0.014 | 0.029 |
| Refining/refuming | 0.0045 | 0.0091 |
| Product handling | 0.011 | 0.021 |
| Flame retardants in rubber | | |
| Formulation | 0.021 | 0.042 |
| Processing | 0.013 | 0.027 |
| Flame retardants (plastics/textiles), handling/formulation | 0.055 | 0.11 |

Cancer risks were calculated for 20 and 40 years of exposure. Online supplemental table S5 provides EU occupational exposure estimates used in risk calculations. EU, European Union.

in this study. Specifically, antimony trioxide reacts and depletes glutathione,³ which disrupts cellular redox metabolism and mitochondrial membrane potential.^{32–34} Disrupted redox metabolism leads to oxidative stress in cells, characterised by increased reactive oxygen species (ROS) and cellular damage.⁴ For example, ROS can react and cause mutations in genes common to lung tumours, including the epidermal growth factor receptor (EGFR).³ In the same set of controlled animal studies conducted by the NTP used for this risk assessment, alveolar and bronchiolar tumours in mice and rats chronically exposed to antimony trioxide had point mutations in EGFR. These mutations were not present in non-tumour lung tissue or spontaneous alveolar and bronchiolar carcinomas that developed in chamber control animals.³ Prior studies have also shown that the EGFR genes are upregulated in lung cancer cells,³⁵ leading to increased cell proliferation, decreased cell differentiation, angiogenesis, metastasis and decreased apoptosis.^{36–37} In addition to mutagenicity,¹³ antimony also causes chromosomal aberrations, sister chromatid exchanges and micronuclei formation.³ Furthermore, subchronic and chronic interstitial and granulomatous inflammation, as well as increased alveolar macrophages, have been reported in multiple animal studies following antimony trioxide exposure.^{3, 38}

In addition to the lung and lymphohematopoietic system, there is evidence for the carcinogenicity of antimony trioxide at other sites. The NTP reported tumours of the adrenal gland in female rats, skin in male mice and lymphatic system in female mice.³ Human studies have reported gastrointestinal cancer in occupational settings following antimony trioxide exposure,^{9–11} as well as mucous membrane irritation of the gastrointestinal tract, which may contribute to carcinogenesis.³ Taken together, this evidence supports the carcinogenic potential of antimony trioxide and highlights the salience of the cancer risk estimates reported in this study.

Strengths and limitations

Strengths of our risk assessment include the use of exposure assessment data for multiple workplace settings and scenarios and the use of controlled 2-year inhalation studies in male and female mice to generate BMD model output.³⁹

The main limitation of the risk assessment is that it is based on animal rather than human data, and we assume that humans are equally as sensitive as mice to antimony trioxide. This seems a reasonable assumption, especially as there are reasons why our methodology may underestimate risk. First among these is our

analysis excludes cumulative impacts. When ambient air exposure estimates were included in risk estimates, the estimates of risk did not change significantly. However, this does not imply that environmental exposures themselves are negligible, and it is likely that any additional exposure to antimony trioxide from ambient air and consumer products, combined with exposure to other carcinogens such as tobacco smoke, would increase the risk of cancer posed from high occupational exposures.⁴⁰ In addition, the exposure parameters used, including body weight, inhalation rate and average lifetime, assume little interindividual variability. However, the limitations in the risk assessment are inherent in the current methodology and may underestimate the true risk to vulnerable persons.

Conclusion

Our risk estimations demonstrate that occupational exposures to antimony trioxide at levels commensurate with the current US regulatory standards may pose a significant cancer risk. Furthermore, both typical and worst-case exposure estimates from the EU indicate that European workers may also be commonly exposed to unsafe levels of antimony trioxide. Therefore, regulatory standards in the USA and EU should be revisited and lowered. Moreover, this underscores the necessity for employers to reduce worker exposure by using validated protection measures, which include enclosing operations, implementing local exhaust ventilation, providing respirators and personal protective equipment and providing a water station for workers to wash immediately after exposure and at the end of the work shift.⁵ This is especially crucial given that risk estimates decreased when typical rather than worst-case exposure scenarios were used but increased in the worst exposure case. Based on these risk calculations, we recommend that OSHA consider lowering the current PEL for antimony in the USA.

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Occupational Exposure to Antimony Trioxide: A Risk Assessment

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SUPPLEMENTARY MATERIALS**Tables S1-S5**

S1: Incidences of tumors in male and female mice by exposure group.

S2: Calculated animal doses.

S3: Female tumor incidences following the Poly3 correction.

S4: BMDS model output for individual female tumors.

S5: European Union antimony trioxide exposure estimates for several occupational settings.

| Supplementary Table 1 Incidences [‡] of alveolar/bronchiolar adenoma and carcinoma in all treatment groups among male and female rats and mice reported in the NTP study. Mice were the more sensitive species. | | | | |
|---|-----------|-------------|-----------|-------------|
| | Male rats | Female rats | Male mice | Female mice |
| Alveolar/bronchiolar adenoma | | | | |
| 0 mg/m ³ | 3/60 | 0/60 | 10/60 | 1/60 |
| 3 mg/m ³ | 4/60 | 2/60 | 14/60 | 10/60 |
| 10 mg/m ³ | 6/60 | 6/60 | 11/60 | 19/60 |
| 30 mg/m ³ | 8/60 | 6/60 | 14/60 | 9/60 |
| Alveolar/bronchiolar carcinoma | | | | |
| 0 mg/m ³ | 0/60 | 0/60 | 4/60 | 2/60 |
| 3 mg/m ³ | 0/60 | 0/60 | 18/60 | 14/60 |
| 10 mg/m ³ | 2/60 | 0/60 | 21/60 | 11/60 |
| 30 mg/m ³ | 0/60 | 0/60 | 29/60 | 11/60 |

[‡]Note on the data: The numerator represents the number of tumor-bearing animals and the denominator represents the number of animals on which a necropsy was performed. In the two-year studies, groups of 60 animals per dose group were exposed to antimony trioxide. Ten animals per group were sacrificed at week 53. Some tables reported in the NTP antimony study include only the 50 animals per dose group that were designated to be kept on study for the full 105 weeks. We chose to include the data from the animals in the interim sacrifice groups because treatment-related tumors were observed at interim sacrifice, e.g. alveolar/bronchiolar carcinoma in 2/10 male mice in the 30 mg/m³ dose group.

| Supplementary Table 2 Calculated animal doses based on exposure concentrations for male and female mice. | | |
|---|------------------------------------|------------------|
| Sex | Concentration (mg/m ³) | Dose (mg/kg-day) |
| Female | | |
| | 0 | 0 |
| | 3 | 0.63 |
| | 10 | 2.12 |
| | 30 | 6.35 |
| Male | | |
| | 0 | 0 |
| | 3 | 0.62 |
| | 10 | 2.06 |
| | 30 | 6.19 |

| Supplementary Table 3 Incident tumors and animal sample sizes for female mice alveolar/bronchiolar adenoma/carcinoma and malignant lymphoma per dose group following Poly3 corrections. | | | |
|--|------------------------|-----------------|----------------------------|
| Tumor type | Dose group (mg/kg-day) | Incident tumors | Total animals [‡] |
| Alveolar/bronchiolar adenoma/carcinoma | | | |
| | 0 | 3 | 47 |
| | 0.63 | 22 | 46 |
| | 2.12 | 27 | 44 |
| | 6.35 | 19 | 44 |
| Malignant lymphoma | | | |
| | 0 | 7 | 46 |
| | 0.63 | 17 | 46 |
| | 2.12 | 20 | 43 |
| | 6.35 | 30 | 48 |

[‡]Number of animals alive at the time of first occurrence of tumor. Animals in the interim sacrifice groups were included because tumors were observed in interim sacrifice groups.

Supplementary Table 4 Results from the individual site alveolar/bronchiolar adenoma/carcinoma and malignant lymphoma in females. Model outputs include the benchmark dose (BMD), benchmark dose lower (BMDL), and animal cancer slope factor (CSF).

| Gender | Tumor type | BMD (mg/kg-day) | BMDL (mg/kg-day) | CSF (mg/kg-day) ⁻¹ |
|--------|---|-----------------|------------------|-------------------------------|
| Female | Alveolar/bronchiolar adenoma or carcinoma | 0.098 | 0.073 | 0.68 |
| Female | Malignant lymphoma | 0.39 | 0.27 | 0.65 |

Supplementary Table 5 Typical and worst-case exposure estimates for common occupational exposure settings for antimony trioxide. Exposure estimates were estimated by the European Union.[26] Typical exposure concentrations were set as the 50th percentile exposure level and the worst-case exposure concentrations were set as the 90th percentile exposure level.

| Industry | Typical-case exposure ($\mu\text{g}/\text{m}^3$) | Worst-case exposure ($\mu\text{g}/\text{m}^3$) |
|---|--|--|
| Sb₂O₃ production | | |
| Conversion | 27 | 150 |
| Refining / Refuming | 12 | 47 |
| Product handling | 40 | 110 |
| Flame retardants in rubber | | |
| Formulation | 51 | 220 |
| Processing | 64 | 140 |
| Flame retardants (plastics/textiles), handling/formulation | 130 | 570 |