

Antimony oxide (Sb₂O₃): Human health tier II assessment

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Preface

This assessment was carried out by staff of the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) using the Inventory Multi-tiered Assessment and Prioritisation (IMAP) framework.

The IMAP framework addresses the human health and environmental impacts of previously unassessed industrial chemicals listed on the Australian Inventory of Chemical Substances (the Inventory).

The framework was developed with significant input from stakeholders and provides a more rapid, flexible and transparent approach for the assessment of chemicals listed on the Inventory.

Stage One of the implementation of this framework, which lasted four years from 1 July 2012, examined 3000 chemicals meeting characteristics identified by stakeholders as needing priority assessment. This included chemicals for which NICNAS already held exposure information, chemicals identified as a concern or for which regulatory action had been taken overseas, and chemicals detected in international studies analysing chemicals present in babies' umbilical cord blood.

Stage Two of IMAP began in July 2016. We are continuing to assess chemicals on the Inventory, including chemicals identified as a concern for which action has been taken overseas and chemicals that can be rapidly identified and assessed by using Stage One information. We are also continuing to publish information for chemicals on the Inventory that pose a low risk to human health or the environment or both. This work provides efficiencies and enables us to identify higher risk chemicals requiring assessment.

The IMAP framework is a science and risk-based model designed to align the assessment effort with the human health and environmental impacts of chemicals. It has three tiers of assessment, with the assessment effort increasing with each tier. The Tier I assessment is a high throughput approach using tabulated electronic data. The Tier II assessment is an evaluation of risk on a substance-by-substance or chemical category-by-category basis. Tier III assessments are conducted to address specific concerns that could not be resolved during the Tier II assessment.

These assessments are carried out by staff employed by the Australian Government Department of Health and the Australian Government Department of the Environment and Energy. The human health and environment risk assessments are conducted and published separately, using information available at the time, and may be undertaken at different tiers.

This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.


For more detail on this program please visit: www.nicnas.gov.au

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Acronyms & Abbreviations

Chemical Identity

Synonyms	antimony trioxide diantimony trioxide dioxodistiboxane valentinite C.I. Pigment White 11
Structural Formula	 Structural formula of Antimony oxide (Sb ₂ O ₃)
Molecular Formula	O ₃ Sb ₂
Molecular Weight (g/mol)	291.52
Appearance and Odour (where available)	White, odourless, crystalline powder.
SMILES	O([Sb]=O)[Sb]=O

Import, Manufacture and Use

Australian

The following Australian industrial uses were reported under previous mandatory and/or voluntary calls for information.

The chemical has reported domestic use including in flame retardants and fire-preventing agents.

The total volume introduced into Australia, reported under previous mandatory and/or voluntary calls for information, was between 100 and 1000 tonnes.

International

The following international uses have been identified through European Union Registration, Evaluation, Authorisation and Restriction of Chemicals (EU REACH) dossiers; the Organisation for Economic Cooperation and Development Screening Information Dataset Initial Assessment Report (OECD SIAR); Galleria Chemica; Substances and Preparations in the Nordic countries (SPIN) database; the European Commission Cosmetic Ingredients and Substances (CosIng) database; United States (US) Personal Care Product Council International Nomenclature of Cosmetic Ingredients (INCI) dictionary; and eChemPortal: OECD High Production Volume chemical program (OECD HPV), the US Environmental Protection Agency's Aggregated Computational Toxicology Resource (ACToR), and the US National Library of Medicine's Hazardous Substances Data Bank (HSDB).

The chemical has reported domestic use including:

- in adhesives (binding) agents;
- in colouring agents;
- in paints, lacquers and varnishes;
- in flame retardants and extinguishing agents;
- in insulating materials (>0.1 %); and
- as a filler.

The US Household Products Database notes that the chemical has domestic uses, mainly as an insulation material, at a concentration of >0.1 %.

The chemical has reported commercial use including:

- in construction materials;
- in lubricants and additives;
- as a process regulator; and
- as a reprographic agent.

The chemical has reported site-limited use including as an intermediate.

The chemical has reported non-industrial use including in pharmaceutical preparations.

Restrictions

Australian

The chemical, under the category of 'antimony compounds', is listed in the *Poisons Standard* (Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP, 2013)) in Schedule 6 as follows:

'ANTIMONY COMPOUNDS **except**:

- (a) when included in Schedule 4;
- (b) antimony chloride in polishes;
- (c) antimony titanate pigments in paint; or
- (d) in paints or tinters containing 5 per cent or less of antimony calculated on the non-volatile content of the paint or tinter'.

The chemical, as antimony or antimony compounds other than antimony titanate pigments (>5 %), is also listed in Appendix 1 (Uniform Paint Standard).

Antimony and its compounds are also listed in Schedule 10 (prohibited carcinogens, restricted carcinogens and restricted hazardous chemicals) of the Work Health and Safety Regulations (WHS) for restricted use. The Schedule 10 entry states the restriction as 'for abrasive blasting at a concentration of greater than 0.1% as antimony' (WHS, 2011).

International

The chemical is listed on the following (Galleria Chemica):

- EU Cosmetics Regulation 1223/2009 Annex II—List of substances prohibited in cosmetic products;
- New Zealand Cosmetic Products Group Standard—Schedule 4: Components cosmetic products must not contain;
- Health Canada List of prohibited and restricted cosmetic ingredients (The Cosmetic Ingredient "Hotlist");
- The Association of Southeast Asian Nations (ASEAN) Cosmetic Directive Annex II Part 1: List of substances which must not form part of the composition of cosmetic products;
- China List of banned substances for use in cosmetics; and
- Philippines Restricted ingredients for use in cosmetics—List of substances which must not form part of the composition of cosmetic products.

Existing Work Health and Safety Controls

Hazard Classification

The chemical is classified as hazardous, with the following risk phrase for human health in the Hazardous Substances Information System (HSIS) (Safe Work Australia):

Xn; R40 (Carcinogenicity Cat. 3)

Exposure Standards

Australian

The chemical has an exposure standard of 0.5 mg/m³ time weighted average (TWA).

International

The following exposure standards are identified (Galleria Chemica):

An exposure limit (TWA) of 0.1–0.5 mg/m³ in different countries such as Canada, Denmark, Iceland, Ireland, Japan, New Zealand, Singapore, South Africa, Spain, Switzerland, Sweden, United Kingdom, and the USA.

A short-term exposure limit (STEL) of 0.75–2 mg/m³ in countries such as Argentina, Austria, and Hungary.

Health Hazard Information

Toxicokinetics

The absorption of the chemical has been reported to be low following acute oral exposure; 0.3 % and 0.05 % following administration of 100 and 1000 mg/kg bw, respectively. Absorption following oral dosing is also a slow process, with a C_{max} (maximum absorption) at approximately 24 hours, followed by an even slower elimination phase from the blood. Following absorption, the chemical undergoes significant distribution to most tissues. The highest levels were found in the whole blood, thyroid, and bone marrow followed by ovaries, spleen, liver, lung, heart, femur and skin (EU, 2008; REACH).

In an in vitro percutaneous study with human skin conducted in accordance with OECD Test Guideline (TG) 428, dermal absorption of the chemical was considered negligible (0.26 %). The deposition of inhaled chemical in the airways, based on particle size, is calculated by the Multiple Path Particle Deposition (MPPD) model resulting in an estimated total deposition via inhalation of 6.82 % (EU, 2008; ECHA, 2009). Due to the low solubility, systemic absorption is expected to be low.

Studies in humans and animals have shown that the chemical may be retained in the lungs for long periods of time following repeated inhalation exposure. The biological elimination half-life in humans is estimated to be 600–1100 days for non-smokers and 1700–3700 days for smokers. Lung clearance efficiency depends on the particle size and solubility. Elimination from the lung occurs in two phases, a rapid initial phase followed by a slower second phase (IARC, 1989; EU, 2008; REACH). As the chemical has also been detected in the human foetal liver, breast milk, placenta and umbilical cord blood, exposure to the chemical in utero and through breast-feeding can occur (EU, 2008).

Following oral gavage, 80–100 % of the antimony was recovered in faeces after 72 hours. While 30 % of the total antimony was excreted in the faeces within the first 24 hours following intravenous injection, around 12 % was recovered from the urine 24 hours after dosing. Following intraperitoneal injection, 36 % of the antimony was recovered from the faeces 72 hours after dosing (REACH).

Acute Toxicity

Oral

The chemical had low acute toxicity in animal tests following oral exposure. The median lethal dose (LD₅₀) in rats is greater than 2000 mg/kg bw. Observed sub-lethal effects included lethargy, piloerection, diarrhoea and wet fur (EU, 2008; REACH).

Dermal

The chemical had low acute toxicity in animal tests following dermal exposure. The LD₅₀ in rabbits is greater than 2000 mg/kg bw (EU, 2008; REACH).

Inhalation

The chemical had low acute toxicity in animal tests following inhalation exposure. The median lethal concentration (LC₅₀) in rats is greater than 5.2 mg/L/4-hours (EU, 2008; REACH).

Observation in humans

Although acute poisoning is rare as the chemical is poorly soluble and is not readily absorbed following ingestion, reports of poisoning have been noted when the chemical has leached into acidic beverages or has been converted into a more soluble form. Nausea, vomiting, and diarrhoea have been seen following ingestion of a substantial quantity of the chemical (IPCS, 1998).

A case study reports that 56/70 people, who drank lemonade from preparations left overnight in white enamelware buckets (the enamel contained 2.88 % antimony oxide), were hospitalised suffering from burning stomach pains, colic, nausea and vomiting.

Most of the affected patients recovered within three hours. Analysis found that the lemonade contained 0.013 % antimony (equivalent to 36 mg/person ingesting 300 mL lemonade) (IPCS, 1998; HSDB).

In another report, 150 children developed nausea, vomiting, abdominal pain, and diarrhoea 15 minutes after drinking lemonade contaminated with antimony. An estimated 30 mg/L antimony was leached into lemonade (pH 2.5–3.1) from an agate pot in which the lemonade was stored for 20–22 hours. While most of the affected children recovered within few hours, the remaining children took several days to recover. An 18th century author (Oliver Goldsmith) is reputed to have died 18 hours following ingestion of tartar emetic (mixture of antimony trioxide and potassium tartrate), with severe vomiting and diarrhoea. The estimated dose of antimony was 132–198 mg (IPCS, 1998).

Corrosion / Irritation

Respiratory Irritation

The chemical is not irritating to the respiratory system. In an acute inhalation toxicity study, rats exposed to the chemical for four hours at a concentration of 5.20 mg/L revealed no adverse effects in the nose, larynx or trachea; respiratory tract infection symptoms (dyspnoea, rhinitis) were also not observed (EU, 2008).

Skin Irritation

The available information indicate that the chemical is not a skin irritant.

In a skin irritation study, the chemical (25 g) was incorporated into an aqueous methylcellulose paste and applied on the abraded skin (two-thirds of the torso) of eight albino rabbits. The method of application was adapted from the Draize procedure with minor modifications. The applied area was covered by an impervious membrane and the chemical was allowed to remain in contact with the skin for one week. No significant local skin reaction or signs of systemic toxicity were observed. Conclusions could not be drawn from other skin irritation studies in animals due to quality concerns (EU, 2008; REACH).

Although the chemical is not considered to be a skin irritant in animal studies, several human case studies have reported skin irritation in occupational settings (see **Observations in humans**). Skin irritation in these cases has been reported to be mainly on skin damp with perspiration (under high temperature) and the lesions appear to be closely associated with sweat ducts. The lack of dermal irritation in rabbits could be due to the fact that rabbits lack sweat glands. It was therefore concluded that the chemical should be regarded as a skin irritant in humans under conditions that evoke sweating (IPCS, 1998; EU, 2008).

Following a proposal to classify the chemical as a skin irritant, the EU Committee for Risk Assessment concluded that the chemical should not be classified as skin irritant. This conclusion was based on the facts that the skin irritation is not due to the inherent (intrinsic) capacity of the chemical to cause skin irritation and special conditions, namely substantial heat and sweat, were also required. It was also noted that the skin irritation is significantly less or not present at all in less hot and non-sweaty conditions. There was also no evidence in animal studies to suggest that the chemical should be classified as a skin irritant (ECHA, 2009).

Eye Irritation

The chemical is reported to be a slight eye irritant in animal studies. Effects were not sufficient to warrant a hazard classification.

In an acute eye irritation study conducted according to the OECD TG 405, 100 mg of the chemical (99.93 % purity) was administered into the conjunctival sac of each of three Himalayan rabbits. Observations were made at one, 24, 48, 72 hours and four days following administration. Only mild conjunctival redness was observed in two animals at the 24 hours time interval (EU, 2008; REACH).

In another acute eye irritation study conducted according to the OECD TG 405, 100 mg of the chemical was administered into the conjunctival sac of each of five New Zealand White rabbits. Observations were made at six hours and at days one, two, three, four, seven, 10, and 14 following administration. Thirty seconds after application, the treated eyes of two male and two female rabbits were washed with distilled water for one minute. The chemical caused necrosis of the lower conjunctivae and the

nictitating membrane in 7/10 animals 48 hours after application. As the necrosis was observed only at 48 hours following exposure, the relevance of this finding is questionable. Mean score values for the ocular lesions at 24, 48, and 72 hours of the unwashed eyes were 0.39 for cornea opacity, 0.17 for iris lesion, 1.56 for conjunctivae and 1.39 for oedema. The effects were reversible at the end of the observation period at day 14 and the chemical was considered to be a mild irritant (EU, 2008; REACH).

Observation in humans

Although many cases of irritation (dermatitis) have been reported in occupational settings, the observations also indicated that workers exposed to the chemical were more susceptible to developing transient skin irritation when sweating occurred. It was also noted that the skin lesions appeared to be associated with sweat ducts and were observed to happen primarily during warm summer months and rarely seen in the winter (EU, 2008).

Skin eruptions called 'antimony spots' have been reported on the antecubital area, shins, back of neck, forearms, trunk, back of knees and faces of 23 workers exposed to fumes of the chemical. The rash subsided within 3–14 days when the workers were transferred to cooler areas in the factory. Among these workers, 17/23 men affected were furnace workers and the remainder were doing different jobs but also under hot conditions. Two furnace men, who only had one side of their body exposed to heat when working, had lesions only on the limbs of that side (EU, 2008; REACH).

Another case of dermatitis was reported in three workers exposed to the chemical in a melting process at a manufacturing plant. Due to insufficient precautionary measures, they were exposed to fumes of the molten chemical, which caused acute skin lesions. Crusted follicular papules and pustules of the arms, trunk and forehead were observed on two workers and the third showed erythematous follicular papules on the ventral and dorsal aspects of forearms, posterior legs and back. The urinary measurements in one worker revealed a concentration of 53.2 µg/L of the chemical, compared with the concentration in an unexposed worker of 1.0 µg/L. The effects were reversible when work associated with the chemical was avoided. Furthermore, the temperature in the work area was noted to be quite high and the employees were perspiring. The authors concluded that the irritation potential of the chemical appeared to be associated with sweat ducts and the chemical was an irritant on skin damp with perspiration (EU, 2008).

In another occupational study, physical examinations were conducted on 51 male workers employed (9–31 years) in an antimony smelting plant, who were exposed to airborne dust containing the chemical (up to 88 %). These workers were examined 2–5 times over a 25-year period. Skin, respiratory tract and eye irritation symptoms such as chronic bronchitis (37.3 %), chronic coughing without expectoration (23.5 %), upper airway inflammation (35.3 %), conjunctivitis (27.5 %) and dermatosis (63 %) were observed. However, due to exposure to mixed chemical fumes and lack of further data, firm conclusions were not drawn regarding the respiratory and eye irritation potential of the chemical (EU, 2008; HSDB; REACH).

Sensitisation

Skin Sensitisation

Although the data are limited, the available information indicate that the chemical is not a skin sensitizer.

In a preliminary maximisation test conducted similarly to OECD TG 406, eight female guinea pigs were administered (intradermally) the chemical (99.93 % purity) with concentrations of 0.001, 0.01 and 0.1 % in one animal and 1, 5 and 10 % in the second animal. For topical administration, concentrations of 0.5, 1, 5, 10, 25 and 50 % of the chemical were applied to the shaved skin of three animals each and removed after 24 or 48 hours. No skin sensitisation effects were observed at any concentration at any time point. In the main experiment, 20 animals were exposed (intradermally) to 10 % of the chemical followed by a 48-hour topical application of the chemical at 50 % concentration after seven days. The animals were challenged two weeks after the topical application at 50 % concentration on the left flank for 24 hours. No skin sensitisation reactions were observed following the challenge (EU, 2008; REACH).

In two poorly-documented studies conducted similarly to the Buehler test, 10 guinea pigs were exposed (topically) to 1:8 or 1:6 mixtures of the chemical over three weeks. After a two-week rest period, the animals were challenged with 25 % and 50 % suspensions of the chemical on both intact and abraded skin (volumes and duration not reported). They were evaluated after 24 and 48 hours and no skin sensitisation reactions were reported. Mixtures and not the pure substance were tested. Although mild

erythema was observed at 50 % suspension in one of the studies, the response could correspond to irritation effects instead of sensitisation (EU, 2008; REACH).

Repeated Dose Toxicity

Oral

Although data are limited, the chemical is not considered to cause serious damage to health from repeated oral exposure.

In a 30-day oral feeding study, male Sherman rats (10/group) were fed a diet containing the chemical at 0, 0.1, 0.45 or 1.8 % (equivalent to 0, 60, 270 or 1070 mg/kg bw/day). A no observed adverse effect level (NOAEL) of 270 mg/kg bw/day was reported. Effects observed at the highest concentration (1070 mg/kg bw/day) included: decreased growth, decreased appetite and histopathological changes (data not stated)(REACH).

In a repeated dose oral toxicity study, Wistar rats (12/sex/group) were fed a diet containing the chemical at 0, 1000, 5000 or 20000 ppm (equivalent to 84/97, 421/494 or 1686/1879 mg/kg bw/day in males/females) for 90 days. A NOAEL of 1686/1879 mg/kg bw/day was determined in males/females for the study, based on the lack of any adverse effect observed at the highest tested dose (EU, 2008; REACH).

Dermal

No data are available.

Inhalation

The chemical may cause serious damage to the lungs from repeated inhalation exposure. Adverse effects were found at concentrations within the hazard classification range under both the HSIS Approved Criteria and the GHS. During the public comment period, information was received suggesting that such effects could be considered to be species-specific due to susceptibility of rats to lung/particle overload. Further analysis of the available information is required to determine whether classification is warranted. In addition, results from new repeated dose toxicity studies in both rats and mice will inform this analysis and are expected to be available in the near future (US EPA, 2014).

In a repeated dose inhalation toxicity study, Fischer 344 (F344) rats (65/sex/group) were exposed (whole body) to the chemical at concentrations of 0, 0.06, 0.51 or 4.50 mg/m³ for six hours/day, five days/week for 12 months followed by a 12 month observation period. There was no effect on survival, body weight gains, or lung weights following treatment with the chemical. The lungs of several control and treated animals had chronic interstitial inflammation (minimal to moderate severity) during the exposure and observation periods. Interstitial fibrosis, granulomatous inflammation and bronchiolar/alveolar hyperplasia were seen in a number of treated animals during the observation period, most pronounced in the high dose group. A lung burden-dependent effect was noted on the clearance of the chemical in the high-dose group. The pulmonary clearance was decreased by 80 %, in the 4.50 mg/m³ group, with approximately 2 mg of chemical per lung after 52 weeks of exposure. This was interpreted as an intrinsic toxic effect of the chemical rather than a general effect due to particle overload. A LOAEC and a no observed adverse effect concentration (NOAEC) of 4.50 mg/m³ and 0.51 mg/m³, respectively, were established, based on impaired lung clearance (IRIS, 1995; EU, 2008).

In another repeated dose inhalation study, Wistar rats (90/sex/group) were exposed to the chemical as a dust at concentrations of 0 and 45 mg/m³ for seven hours/day, five days/week for 52 weeks (see **Carcinogenicity**). There was no treatment related mortality. Following six months of exposure, the lungs from the female rats contained particles evenly scattered throughout all lobes of the lung and in more than 90 % of the alveoli. Dense particle aggregates resembling macrophages were noted in about 10 % of the alveoli and the particles were embedded in dense, pink, homogeneous protein in some alveoli. Thickening of alveolar-wall in the form of interstitial fibrosis, alveolar-wall cell hypertrophy and hyperplasia was noted in about 50 % of the alveolar duct regions, affecting about 5–10 % of all alveoli.

All the above stated effects increased with the duration of exposure. Foci containing cholesterol clefts (space formed by the dissolving of cholesterol crystals) were also noted. Although the density of particles and amount of protein in the alveoli had significantly decreased at sacrifice and at 4–5 months post exposure, the extent of interstitial fibrosis and the number of foci containing cholesterol clefts had increased. Male rats, compared with female rats, were stated to have:

- less alveolar protein following six months of exposure;
- following 12 months of exposure, less extensive cuboidal, alveolar-wall cell metaplasia and fewer foci with cholesterol clefts;
- a less severe diminution in the amount of alveolar-wall metaplasia along with fewer foci with cholesterol clefts and less alveolar protein was seen at four months post-exposure; and
- more mononuclear cells, lymphocytes and plasma cells in interstitial spaces were seen at four months post-exposure.

A LOAEC of 45 mg/m³ was established in this study, based on pleural plaques, lung fibrosis and cholesterol clefts (IRIS, 1995; EU, 2008).

In a repeated dose inhalation toxicity study, Fischer rats (41–45/sex/group) were exposed (whole body) to the chemical at 0, 1.9 and 5.0 mg/m³ for six hours/day, five days/week for 52 weeks. Surviving animals were followed for up to 15 months following cessation of exposure. Although there were no effects on survival, haematology or clinical chemistry in treated animals, a number of effects were observed in the lungs of exposed rats. The earliest non-neoplastic effect (focal fibrosis) was observed in the high dose group following three months of exposure. Focal fibrosis was time and dose dependent. Following one year of exposure, focal fibrosis was seen in 10/21 animals of the low dose group and 17/20 animals in the high dose group. The severity of the other effects also increased both with time and exposure concentration. Postmortem findings following 12 months of exposure included lung discolouration, increased pulmonary alveolar/intraalveolar macrophages in both exposure groups, focal subacute-chronic interstitial inflammation and granulomatous inflammation in the high exposure group. Similar lesions in the lungs (focal fibrosis, pneumocyte hyperplasia, adenomatous hyperplasia, multinucleated giant cells, cholesterol clefts) were also significantly increased following cessation of exposure for 12–15 months. A LOAEC of 1.9 mg/m³ was established, based on endogenous lipid pneumonia (focal fibrosis, pneumocyte hyperplasia, presence of giant cells and cholesterol clefts) in animals in both dose groups (IRIS, 1995; EU, 2008).

Observation in humans

Chronic occupational exposure to antimony is most commonly associated with “antimony pneumoconiosis”, shown as ‘diffuse, densely distributed punctate opacities that are round, polygonal, or irregular in shape; have a diameter of usually <1 mm; and do not tend to conglomerate’ (IRIS, 1995). Case studies have also shown effects such as pulmonary inflammation, lung emphysema following repeated inhalation exposure. These case studies were on workers employed in industries manufacturing the chemical. Although workers were probably subjected to inhalation, dermal and oral exposure in these case studies, it can be assumed that exposure via inhalation was the dominant route (IRIS, 1995; IPCS, 1998; EU, 2008; REACH).

A comprehensive radiological investigation conducted in antimony smelter workers in the UK studied magnified areas of the lungs of 274 workers and reported 26 new cases of antimony pneumoconiosis, in addition to 18 men already identified clinically with antimony pneumoconiosis. The ambient antimony concentrations were measured as 37 mg/m³ during tapping operations, and an average of 5 mg/m³ in other areas. A worker who died from lung carcinoma had an accumulation of dust particles and dust laden macrophages in the alveolar septa and perivascular tissues without inflammatory reaction.

In a case study, 78 employees of a mining company involved in antimony smelting operations or maintenance reported illness within the first five months of operation. The workers were exposed to an average antimony concentration of 4.69 and 11.81 mg/m³ in two different work areas. Arsenic was also present at 1.10 and 0.36 mg/m³, respectively. The illnesses reported among 69 out of 78 workers included nasal septal perforations, laryngitis, tracheitis and pneumonitis. Although the workers were co-exposed to arsenic trioxide, no early signs of arsenic intoxication were observed.

All 51 workers employed in an antimony smelting plant for 9–31 years in Serbia experienced pneumoconiotic changes. The airborne dust concentrations were measured as 17–86 mg/m³, and consisted of 38.73–88.86 % antimony trioxide. The

pneumoconiosis was characterised to be of diffuse densely distributed punctate opacities, concentrated in the mid-lung region and present in many of the workers employed over nine years. Although rhinitis (54.3 %), perforation of the septa (33.2 %), pharyngitis (76.5 %), bronchitis (54.3 %), pneumoconiosis (20.8 %) and emphysema (41.9 %) were noted, no systemic toxicity was observed.

Genotoxicity

Overall, the data indicate that the chemical has no mutagenic or genotoxic potential.

The chemical gave negative results in several in vitro bacterial reverse mutation assays with *Salmonella typhimurium*/*Escherichia coli* and a mammalian mutation assay with mouse lymphoma L5178Y cells. Although the chemical produced positive results in two bacterial DNA repair/recombination assays in *Bacillus subtilis*, as limited details were provided, it was difficult to draw conclusions on the reliability of this result. The chemical produced positive results for the induction of sister chromatid exchanges (SCE) in vitro in human lymphocytes and V79 Chinese hamster cells. The chemical also produced chromosomal aberrations as well as polyploidy and endoreduplication in an in vitro cytogenetic assay with human lymphocytes. Taken together, it is concluded that while the chemical did not induce gene mutations in vitro, it has clastogenic potential in mammalian cells in vitro (EU, 2008; REACH).

The chemical was not clastogenic (no significant increase in the incidence of micronuclei) in a bone marrow micronucleus assay in mice following single or repeated doses of the chemical. A bone marrow study conducted in Sprague Dawley (SD) rats for micronuclei and chromosome aberrations following a 21-day oral repeated exposure to the chemical was also negative. A negative result was also obtained in the in vivo rat liver DNA repair (unscheduled DNA synthesis) (UDS) assay following a single administration (gavage) of the chemical. These studies show that the chemical is not genotoxic in vivo (EU, 2008; HSDB; REACH).

An epidemiology study also assessed genotoxic effects on 23 male workers occupationally exposed to low doses of the chemical in an industrial textile plant. Genotoxicity was evaluated by the SCE, micronucleus tests, and the enzyme (Fpg)-modified comet assay. There were no differences in the induction of micronuclei or SCE for the lymphocytes of exposed workers compared with the control. Oxidative DNA damage was observed in an enzyme modified comet assay for workers in the high exposure group (0.001 mg/m³). However, as the workers were exposed to diverse chemicals, no conclusion between DNA damage and exposure to the chemical could be drawn (EU, 2008, HSDB).

Carcinogenicity

The chemical is classified as hazardous—Category 3 carcinogenic substance—with the risk phrase 'Limited evidence of carcinogenic effect' (Xn; R40 in HSIS (Safe Work Australia). The available data support this classification (IARC, 1989; IRIS, 1995; NTP, 2005; EU, 2008).

The International Agency for Research on Cancer (IARC) has concluded that there is 'sufficient evidence' for the carcinogenicity of antimony trioxide in experimental animals and has classified antimony trioxide as 'possibly carcinogenic to humans (Group 2B)'. In a carcinogenicity study in male and female rats of one strain and in female rats of another strain, the chemical produced a significant increase in the incidence of lung tumours (scirrhous and squamous-cell carcinomas and bronchioloalveolar tumours) in females only in both studies following exposure via inhalation. It was also concluded that there is inadequate evidence for the carcinogenicity of antimony trioxide in humans (IARC, 1989).

Once inhaled, the chemical has also been reported to accumulate and be retained in the lung in humans and animals. The rate of clearance by the lungs is dose-dependent and therefore depends on lung burden (see **Toxicokinetics**) (IRIS, 1995). It has also been stated that 'the most likely mechanism for lung carcinogenicity is impaired lung clearance and particle overload followed by an inflammatory response, fibrosis and tumours' and that the chemical 'can be regarded as a threshold carcinogen' (EU, 2008).

In chronic/carcinogenicity inhalation toxicity study, female CDF Fischer rats were exposed (whole body) to the chemical at 1.9 and 5.0 mg/m³ for six hours/day, five days/week for one year. Post-exposure observations for the surviving animals were kept up to 15 months. An LOAEC of 5.0 mg/m³ was established, based on pulmonary scirrhous carcinoma observed in 44 % (15/34)

of the high dose rats. As tumours were not observed at the lower dose, an NOAEC of 1.9 mg/m³ was established. A comparison of the histopathology tissue sections from this and other one-year studies suggested that the exposure levels in this study were likely to be higher (five-fold) than those reported (EU, 2008).

In a one-year inhalation carcinogenicity study, Wistar rats (90/sex/group) were exposed to the chemical as a dust at concentrations of 0 and 45 mg/m³ for seven hours/day, five days/week (see **Repeat dose toxicity: inhalation**). There was no treatment-related mortality. Male rats accumulated significantly more antimony in the lung (38300 µg Sb/g dry weight) after nine months of exposure to the chemical than the female rats (25600 µg Sb/g dry weight). Control rats of either sex and the male rats exposed to the chemical did not develop any tumours. Female rats exposed to the chemical developed lung tumours, including squamous-cell carcinomas, bronchoalveolar adenomas and carcinomas and scirrhous carcinomas. The incidence of lung tumours for the female rats exposed to the chemical was 32 %. It was also noted that female rats were more susceptible to the induction of lung cancer. Based on lung neoplasms observed in female rats, a LOAEC of 45 mg/m³ was established (IRIS, 1995; EU, 2008).

Reproductive and Developmental Toxicity

The chemical does not show specific reproductive or developmental toxicity. Any developmental effects were only observed secondary to maternal toxicity (EU, 2008; REACH).

Although appropriate reproductive toxicity studies have not been conducted on the chemical, the available data indicated that the chemical is not toxic to male or female reproductive tissues. In a four-week fertility study (guideline not stated), male Wistar rats (eight/group) and CD-1 mice (10/group) were administered (gavage) the chemical at doses of 0, 12 or 1200 mg/kg bw/day for three and five days/week with rats and mice, respectively. No effects on body weights, reproductive organs or accessory sex organs and sperm parameters were observed in any of the two dose groups. An NOAEL of >1200 mg/kg bw was established in this study. In another 90-day feeding study, Wistar rats (12/sex/group) were administered the chemical at doses of 0, 84, 412 or 1686 mg/kg bw/day in males and 0, 97, 494 or 1879 mg/kg bw/day in females. An NOAEL of 1879 mg/kg bw/day was established, based on the absence of histopathological changes in the reproductive organs at the highest tested dose (EU, 2008; HSDB; REACH).

In an inhalation developmental toxicity study (OECD TG 414), SD rats (n = 26) were exposed (nose-only) to the chemical as a dust at concentrations of 0, 2.6, 4.4 or 6.3 mg/m³ for six hours/day during gestation days (GD) 0–19. As developmental effects were not noted at the highest tested dose, an NOAEC of 6.3 mg/m³ was established. Pregnancy rates were also comparable between the control and the treatment groups. A LOAEC of 2.6 mg/m³ for maternal toxicity was established, based on significantly increased absolute and relative lung weights. Microscopic examination of the lungs also revealed acute inflammation and type II cell hyperplasia at all doses. Body weight and food intake were not affected at any dose level (EU, 2008; REACH).

In a human case study, women occupationally exposed to dust containing the chemical over a period of two years were examined for fertility effects. The chemical was detected in the blood of exposed workers (12–16 times higher than controls), breast milk (3.3 ± 2.2 mg/L), amniotic fluid, placental tissue and umbilical cord blood. Observed sub-lethal effects included disturbed menstrual cycle, late spontaneous abortions and premature births. A lag in the body weight gain of the babies of exposed women up to 12 months was also observed, although no statistical calculations were provided.

Although the study indicated effects of the chemical following occupational exposure, no statistical calculations were presented and no information was given about the control group. This study also did not account for the concurrent exposure to other potentially toxic substances or workplace conditions (high temperatures, heavy work or stress) (IPCS, 1998; EU, 2008).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include long-term effects (carcinogenicity following inhalation exposure). The chemical caused serious damage to the lungs in animal studies following repeated inhalation exposure to low levels. The relevance of these effects to humans will be evaluated as a part of the Tier III assessment.

Public Risk Characterisation

The general public may be exposed to the chemical through dermal and/or inhalation routes when using domestic products containing the chemical. However, based on limited US information derived from the National Library of Medicine (NLM) Household Products Database, the chemical will be mainly used for home maintenance as an insulating material. Therefore, the risk to public health is not considered to be unreasonable and further risk management is not considered necessary for public safety.

Occupational Risk Characterisation

During product formulation, ocular and inhalation exposure of workers to the chemical may occur, particularly where manual or open processes are used. These may include transfer and blending activities, quality control analysis, and cleaning and maintenance of equipment. Worker exposure to the chemical at lower concentrations may also occur while using formulated products containing the chemical. The level and route of exposure will vary depending on the method of application and work practices employed.

Given the critical health effects, the chemical may pose an unreasonable risk to workers unless adequate control measures to minimise dermal, ocular and inhalation exposure to the chemical are implemented. The chemical should be appropriately classified and labelled to ensure that a person conducting a business or undertaking (PCBU) at a workplace (such as an employer) has adequate information to determine appropriate controls.

NICNAS Recommendation

The chemical is recommended for Tier III assessment to examine whether the chemical should be classified for repeat dose inhalation toxicity.

Regulatory Control

Work Health and Safety

The chemical is recommended for classification and labelling under the current approved criteria and adopted GHS as below. This assessment does not consider classification of physical hazards and environmental hazards.

Hazard	Approved Criteria (HSIS) ^a	GHS Classification (HCIS) ^b
Carcinogenicity	Carc. Cat 3 - Limited evidence of a carcinogenic effect (Xn; R40)*	Suspected of causing cancer - Cat. 2 (H351)

^a Approved Criteria for Classifying Hazardous Substances [NOHSC:1008(2004)].

^b Globally Harmonized System of Classification and Labelling of Chemicals (GHS) United Nations, 2009. Third Edition.

* Existing Hazard Classification. No change recommended to this classification

Advice for consumers

Products containing the chemical should be used according to the instruction on the label.

Advice for industry

Control measures

Control measures to minimise the risk from ocular and inhalation to the chemical should be implemented in accordance with the hierarchy of controls. Approaches to minimise risk include substitution, isolation and engineering controls. Measures required to eliminate or minimise risk arising from storing, handling and using a hazardous chemical depend on the physical form and the manner in which the chemical is used. Examples of control measures which may minimise the risk include, but are not limited to:

- using closed systems or isolating operations;
- using local exhaust ventilation to prevent the chemical from entering the breathing zone of any worker;
- health monitoring for any worker who is at risk of exposure to the chemical if valid techniques are available to monitor the effect on the worker's health;
- air monitoring to ensure control measures in place are working effectively and continue to do so;
- minimising manual processes and work tasks through automating processes;
- work procedures that minimise splashes and spills;
- regularly cleaning equipment and work areas; and
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with the chemical.

Guidance on managing risks from hazardous chemicals are provided in the *Managing risks of hazardous chemicals in the workplace—Code of practice* available on the Safe Work Australia website.

Personal protective equipment should not solely be relied upon to control risk and should only be used when all other reasonably practicable control measures do not eliminate or sufficiently minimise risk. Guidance in selecting personal protective equipment can be obtained from Australian, Australian/New Zealand or other approved standards.

Obligations under workplace health and safety legislation

Information in this report should be taken into account to assist with meeting obligations under workplace health and safety legislation as adopted by the relevant state or territory. This includes, but is not limited to:

- ensuring that hazardous chemicals are correctly classified and labelled;
- ensuring that (material) safety data sheets ((m)SDS) containing accurate information about the hazards (relating to both health hazards and physicochemical (physical) hazards) of the chemical are prepared; and
- managing risks arising from storing, handling and using a hazardous chemical.

Your work health and safety regulator should be contacted for information on the work health and safety laws in your jurisdiction.

Information on how to prepare an (m)SDS and how to label containers of hazardous chemicals are provided in relevant codes of practice such as the *Preparation of safety data sheets for hazardous chemicals—Code of practice* and *Labelling of workplace hazardous chemicals—Code of practice*, respectively. These codes of practice are available from the Safe Work Australia website.

A review of the physical hazards of the chemical has not been undertaken as part of this assessment.

References

European Chemical Agency (ECHA) 2009. Committee for Risk Assessment (RAC) Background document to the opinion of the committee for risk assessment on a proposal for harmonised classification and labelling of antimony trioxide (CAS No. 1309-64-4). Accessed June 2014 at <http://echa.europa.eu/documents/10162/be0237eb-1ee6-4e3b-a0ad-c4ba9474e292>

European Union (EU) 2008. Risk assessment report on diantimony trioxide (CAS No. 1309-64-4). Accessed August 2014 at <http://esis.jrc.ec.europa.eu/>

Galleria Chemica. Accessed June 2014 at <https://jr.chemwatch.net/galleria/>

Hazardous Substances Data Bank (HSDB). National Library of Medicine. Accessed July 2014 at <http://toxnet.nlm.nih.gov>.

Household Products Database: Health& Safety Information on Household Products from the US National Library of Medicine (NLM). Accessed July 2014 at <http://householdproducts.nlm.nih.gov/>

International Agency for Research on Cancer (IARC) 1989. IARC monographs on the evaluation of carcinogenic risks to humans. Volume 47. Some Organic Solvents, Resin Monomers and Related Compounds, Pigments and Occupational Exposures in Paint Manufacture and Painting. Accessed June 2014 at <http://monographs.iarc.fr/ENG/Monographs/vol47/mono47-16.pdf>

International Programme on Chemical Safety (IPCS) 1998. UKPID Monograph - antimony trioxide (CAS No. 1309-64-4). Accessed July 2014 at <http://www.inchem.org/documents/ukpids/ukpids/ukpid38.htm>

National Toxicology Program (NTP) 2005. Antimony Trioxide (CAS No. 1309-64-4) - Brief review of toxicological literature. Accessed July 2014 at http://ntp.niehs.nih.gov/ntp/htdocs/chem_background/exsumpdf/antimonytrioxide_508.pdf

REACH Dossier (REACH). Antimony oxide (CAS No. 1309-64-4). Accessed June 2014 at [http://apps.echa.europa.eu/registered/data/dossiers/DISS-9eb02d6b-39b7-666e-e044-00144f67d031/DISS-9eb02d6b-39b7-666e-e044-00144f67d031.html](http://apps.echa.europa.eu/registered/data/dossiers/DISS-9eb02d6b-39b7-666e-e044-00144f67d031/DISS-9eb02d6b-39b7-666e-e044-00144f67d031_DISS-9eb02d6b-39b7-666e-e044-00144f67d031.html) and [http://apps.echa.europa.eu/registered/data/dossiers/DISS-dffb4072-e41a-47ae-e044-00144f67d031/DISS-dffb4072-e41a-47ae-e044-00144f67d031.html](http://apps.echa.europa.eu/registered/data/dossiers/DISS-dffb4072-e41a-47ae-e044-00144f67d031/DISS-dffb4072-e41a-47ae-e044-00144f67d031_DISS-dffb4072-e41a-47ae-e044-00144f67d031.html)

Safe Work Australia (SWA). Hazardous Substances Information System (HSIS). Accessed June 2014 at <http://hsis.safeworkaustralia.gov.au/HazardousSubstance>

Substances in Preparations in Nordic Countries (SPIN). Accessed July 2014 at <http://195.215.202.233/DotNetNuke/default.aspx>

The Poisons Standard (the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP)) 2013. Accessed July 2014 at <http://www.comlaw.gov.au/Details/F2013L01607/Download>

US Environmental Protection Agency (US EPA) 2014. TSCA Work Plan Chemical Risk Assessment. Antimony Trioxide (CASRN: 1309-64-4). Accessed July 2015 at [http://www.epa.gov/oppt/existingchemicals/pubs/ATO%20RA_\(8-28-14\)_FINAL.PDF](http://www.epa.gov/oppt/existingchemicals/pubs/ATO%20RA_(8-28-14)_FINAL.PDF)

US EPA 1995. Antimony trioxide (CAS No. 1309-64-4). Accessed August 2014 via the US EPA Integrated Risk Information System (IRIS) at: <http://www.epa.gov/iris/subst/0676.htm>

US Household Products Database. Accessed August 2014 at <http://householdproducts.nlm.nih.gov/advancedsearch.htm>

Work Health and Safety (WHS) Regulations 2011. Schedule 10 - Prohibited carcinogens, restricted carcinogens and restricted hazardous chemicals. Accessed July 2014 at <http://www.comlaw.gov.au/Details/F2011L02664>

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