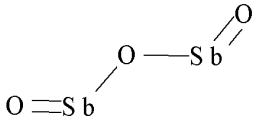
SIDS INITIAL ASSESSMENT PROFILE

CAS No.	1309-64-4 (same as 12412-52-1 and 1317-98-2)
Chemical Name	Diantimony trioxide, Sb_2O_3
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Analogue/Category rationale

For the environment, data on antimony trichloride and antimony hydroxide have been used in the aquatic ecotoxicity assessment, since they all release the biologically active form, i.e. antimony ion. An important difference between different antimony compounds, as observed in toxicity tests, is the time needed to dissolve and liberate ions able of exerting toxicity. Antimony chlorides, being more soluble, will dissolve faster than oxides (the liberation of ions will be slower for oxides). Dissolution of antimony compounds will be faster in the aquatic compartment, as compared to the terrestrial compartment. Since most toxicity tests of antimony are performed under oxygenated conditions using trivalent antimony compounds such as $SbCl_3$ and Sb_2O_3, the toxicity exerted will, depending on the duration of the test, reflect a mixture of toxicity from trivalent and pentavalent antimony ions. There is no conclusive evidence supporting a significant difference in toxicity between the two valencies, and it is decided not to differentiate between relevant and reliable toxicity results originating from toxicity studies with tri- or pentavalent antimony studies. It however needs to be recognised in this context that for human health, there are discrete differences in toxicokinetics and toxicity between tri- and pentavalent antimony species.

Physical-chemical properties

Diantimony trioxide (Sb_2O_3) is solid and is commercialized as a white, odourless, crystalline powder. Based on handbook-data, the melting point is 655°C and boiling point is 1550°C, and vapour pressure at ambient temperature is considered to be negligible. The solubility in reconstituted standard water (= ISO 6341 medium; temperature 22.2ºC) is 2.76 mg Sb/L. Dissolution of the substance in reconstituted standard water decreases constantly from pH 1 to pH 7. Above pH 7, the trend changes and the solubility of diantimony trioxide increases rapidly to pH 8, where a new equilibrium is established and the increase in solubility becomes much slower. The octanol-water partition coefficient (log K_{OW}) is not relevant for this type of substance.

Diantimony trioxide has two molecular arrangements, Senarmontite (CAS No. 12412-52-1) and Valentinite (CAS No, 1317-98-2), under environmental conditions. Since no data are available to differentiate between the two as regards exposure and effects, the intent is to cover both with the CAS Number for diantimony trioxide, i.e. 1309-64-4.

Human Health

In a rat study, the oral absorption was 0.3% and 0.05% at 100 mg/kg bw and 1000 mg/kg bw, respectively. However, at relevant human exposure levels an oral absorption of 1% is assumed, acknowledging both the poor solubility of diantimony trioxide and the higher intestinal absorption (3-8% on average) reported for more soluble antimony compounds. Dermal absorption of diantimony trioxide is considered negligible based on an *in vitro* human skin percutaneous study which showed 0.26% absorption. Based on particle size, the deposition of inhaled diantimony trioxide in the airways is calculated by the MPPD model resulting in an estimated total absorption via inhalation of 6.82 %.

After oral exposure of rats to diantimony trioxide suspension, antimony is distributed to most organs with the

highest concentrations found in whole blood, thyroid and bone marrow. Antimony is retained in the lungs for long periods of time (the biological elimination half time in humans has been estimated to 600-3700 days) and accumulates in lung tissue after repeated inhalation exposure to diantimony trioxide. Antimony has also been detected in low amounts in human foetal liver as well as in human breast milk, placenta, amniotic fluid and umbilical cord blood, indicating that antimony can be distributed to the foetus and excreted in breast milk. After oral exposure, most of the antimony is excreted in the faeces, due to low oral absorption. Antimony is excreted both in faeces and in urine, biliary excretion being higher than urinary excretion.

There is one acute inhalation toxicity OECD guideline study in rats, which shows no signs of toxicity for diantimony trioxide, indicating a 4-hour (nose-only) LC_{50} > 5.20 mg/L (5 200 mg/m^3). The animal studies on acute oral exposure do not comply with current standards. Still, they indicate that the oral LD_{50} was in excess of 20 000 mg/kg bw in rats. There is one study on dermal exposure in rabbits that indicates that the LD_{50} for dermal exposure is higher than 8 300 mg/kg bw. The overall conclusion is that, despite the poor quality of the available acute oral and dermal toxicity studies with diantimony trioxide in laboratory animals, diantimony trioxide is considered to be of low acute inhalation, oral and dermal toxicity.

No reliable data were available for skin irritation to diantimony trioxide. Several human case study reports indicate that diantimony trioxide may cause dermatitis on skin damp with perspiration and the lesions appear to be closely associated with sweat ducts. Two eye irritation studies in rabbits, show that diantimony trioxide causes mild eye irritation, which was reversible. There is one acute inhalation toxicity animal study available, which also assessed the irritation potential to the respiratory tract, indicating that diantimony trioxide was not irritating to the respiratory system.

A skin sensitisation study, performed according to TG 406, showed that diantimony trioxide was not skin sensitising in guinea pigs.

The repeated dose toxicity of diantimony trioxide has been investigated in several animal studies via the inhalation and oral routes of exposure. The majority of these studies are considered inconclusive because they do not comply with current test guidelines, but those that are conclusive showed that diantimony trioxide is toxic to lung. In an inhalation repeated dose toxicity study (not following OECD test guideline), the substance was administered via whole body inhalation to 65 rats/sex/dose at 0, 0.06, 0.51 or 4.50 mg/m^3, for 5 days/week for 12 months, followed by a 12-month observation period. Interstitial fibrosis, granulomatous inflammation and bronchiolar/alveolar hyperplasia occurred in a number of animals during the observation period, most pronounced in the high-dose group. Increased numbers of alveolar/intraalveolar macrophages and particulate material in alveolar/intraalveolar macrophages were seen in all dose groups during both the exposure and the observation periods. The data showed a lung burden-dependent effect on the diantimony trioxide clearance rate in the high-dose group. It was calculated that with a lung containing approximately 2 mg of diantimony trioxide after 52 weeks of exposure, pulmonary clearance was decreased by 80% with an increase in the clearance halftime from 2 to 10 months. The clearance mechanism was significantly impaired at this exposure level and was interpreted as an intrinsic toxic effect of diantimony trioxide rather than a general effect due to particle overload. Absolute and relative lung weights were unaffected in all exposure groups. Based on impaired lung clearance, the LOAEC and NOAEC for repeated dose inhalation toxicity were considered to be 4.50 mg/m^3 and 0.51 mg/m^3, respectively. The NOAEC was determined in a study with a high background incidence of lung inflammation in controls; therefore there is some uncertainty regarding the reliability of the numerical values. In an OECD guideline 90-day oral study, diantimony trioxide did not cause systemic toxicity at doses up to 1686 and 1879 mg/kg bw/day in male and female rats, respectively.

Diantimony trioxide is not considered to induce gene mutations *in vitro*, but induces structural chromosome aberrations in cultured mammalian cells *in vitro*. Oral *in vivo* studies on the induction of chromosome aberrations and micronuclei in the bone marrow and unscheduled DNA synthesis in the liver have produced negative results. It is believed that a possible local genotoxic effect of diantimony trioxide would only be biologically relevant at concentration levels that also cause particle overload. Therefore, there is also no concern for local genotoxicity of diantimony trioxide in the lung.

Three chronic toxicity/carcinogenicity studies in rats with inhalation exposure to diantimony trioxide were available. The exposure duration in all three animal studies was 12 months only. In the study by Watt, inhalation of 5.0 mg/m^3 diantimony trioxide produced lung neoplasms in 44% of the animals tested (only females were exposed). In the study by Groth et al., 45 mg/m^3 diantimony trioxide produced pulmonary

neoplasms in 32% of the female rats exposed but none in the male rats. The study by Newton et al., showed no lung tumours at any dose level up to 4.5 mg/m^3. A comparison of the histopathology tissue sections from the Watt- and the Newton-studies indicated higher lung deposition of antimony and more severe lung damage in exposed rats in the Watt-study than in the Newton-study, which allegedly were conducted at similar exposure levels (1.9-5.0 and 0.06-4.50 mg/m^3, respectively). This suggests that the exposure levels in the Watt study were likely higher (5-fold) than those reported, and consequently make the study unsuitable for derivation of a NOAEC.

Based on these data it is concluded that diantimony trioxide induces tumours in rat lung. The most likely mechanism for the lung carcinogenicity is impaired lung clearance and particle overload followed by an inflammatory response, fibrosis and tumours. Consequently, diantimony trioxide can be regarded as a threshold carcinogen and the NOAEC of 0.51 mg/m^3, derived for local repeated dose toxicity and based on impaired clearance of particles, is also used for carcinogenicity. The NOAEC was determined in a study with a high background incidence of lung inflammation in controls, therefore there is some uncertainty regarding the reliability of the numerical value.

No reproductive toxicity studies have been conducted for diantimony trioxide. However, detailed examination of male and female reproductive organs from repeated-dose toxicity studies via the oral route of exposure has been done. Testicular toxicity of diantimony trioxide has been investigated in male mice and male rats. In this 4-week study, diantimony trioxide was administered via gavage to 10 mice and 8 rats/dose at 0, 12.0 and 1 200 mg/kg bw/day, for 5 and 3 days/week, respectively. An oral NOAEL = 1 200 mg/ kg bw/day for testicular toxicity was determined. In a rat 90-day oral feeding study performed according to OECD TG 408 no histopathological changes were observed in testes up to a dose of 1686 mg/kg bw/day, or in ovaries and uterus up to a dose of 1879 mg/kg bw/day. Based on these results, diantimony trioxide was not toxic to male or female reproductive tissues.

The developmental toxicity of diantimony trioxide has been investigated, following a test protocol based on the OECD TG 414. However, some alterations in the conduct of the study have been made. Twenty-six mated rats per group were exposed (nose-only) from day 0 to day 19 of gestation at concentrations of 0, 2.6, 4.4 or 6.3 mg diantimony trioxide/m^3. No evidence of developmental toxicity was observed in rats at doses up to 6.3 mg diantimony trioxide/m^3 and the NOAEC for developmental toxicity was 6.3 mg/m^3, the highest exposure level tested. The LOAEC for maternal toxicity (acute pneumonia and significantly increased absolute and relative lung weights relative to controls) in this study was 2.6 mg/m^3. However, body weight and food intake were not affected at any dose level.

Environment

In the environment diantimony trioxide will slowly dissolve and transform into $Sb(OH)_3$, which is oxidized to $Sb(OH)_6^-$ under oxygenated (or oxic) conditions. Antimony, being a natural element, cannot by definition be degraded. However, it can be transformed between different binding/speciation forms and oxidation states.
Combustion/incineration processes transform antimony compounds to diantimony trioxide regardless of the pre-incinerated form of antimony. There are indications that diantimony trioxide may dissolve in the atmosphere and that the trivalent form will oxidize to the pentavalent form. Antimony is deposited from the atmosphere predominantly dissolved in rain, but also as particulate matter in wet and dry deposition.

In natural waters dissolved antimony exists almost exclusively in the two valency states +3 and +5 as $Sb(OH)_3$ and $Sb(OH)_6^-$, respectively. According to thermodynamic calculations, antimony should almost exclusively be present as Sb(V) in oxic systems, and as Sb(III) in anoxic systems. Even though the dominant species in oxic waters is Sb(V), Sb(III) has been detected in concentrations much greater than predicted concentrations, and the reverse is true for Sb(V) in anoxic systems.

After slow dissolution and subsequent oxidation of Sb_2O_3 in soil, its fate is controlled by sorption of $Sb(OH)_6^-$ on soil constituents and precipitation of $Ca[Sb(OH)_6]_2$. The solubility of antimony compounds depends on the soil conditions (Eh/pH) and the time given to dissolve. The most important soil characteristic as regards the mobility of antimony in soil (and sediments) appear to be pH and the presence of hydrous oxides of iron, manganese, and aluminium, to which antimony may adsorb with decreasing sorption at increasing pH In addition, hydrous oxides seem to oxidise dissolved trivalent antimonite ($Sb(OH)_3$) to the pentavalent antimonate ($Sb(OH)_6^-$). Due to the anionic character of the dissolved species ($Sb(OH)_6^-$), antimony is expected to have a low affinity for organic carbon. However, there exist results that indicate that the sorption of Sb(V)

by humic acid in acid soils with high proportions of organic matter may be more important than previously suspected, although the strong Sb(V) scavenging potential of $Fe(OH)_3$ probably results in a diminished role of organic matter binding in soils with high amounts of non-crystalline hydroxides. The cationic exchange reactions, which are the main sorption reactions on clay minerals, are not expected to be important for the anionic antimony.

Antimony released to the environment will eventually end up in either of the two compartments soil or sediment, depending on the release, the form of antimony, meteorological conditions, etc. The distribution of antimony between aqueous phase and soil/sediment/suspended matter is described using the partitioning coefficients log Kp_{soil} = 1.98 L/kg, log $Kp_{suspended\ matter}$ = 3.65 L/kg and log $Kp_{sediment}$ = 3.4 L/kg.

The bioaccumulation potential seems to be low to moderate. No reliable bioaccumulation studies were available and measured data from different aquatic organisms have been used to calculate tentative BCF values. For marine fish the BCFs vary between 40 and 15000 whereas for freshwater fish the BCF values are lower, the highest being 14. For invertebrates tentative BCFs below 1 up to 4000-5000 have been calculated. It should be noted that there is a considerable uncertainty in these BCF values. An assessment of secondary poisoning using the tentative BCF values raised no concern.

The lowest reliable acute and chronic toxicity data for different aquatic organisms are presented below. Except for the marine fish *Pargus major*, for which the source of antimony was $K[Sb(OH)_6]$, all these data were obtained using $SbCl_3$. The reported aquatic toxicity values are above the solubility limits of antimony when using diantimony trioxide at the pH levels used in these studies.

Acute toxicity test results:

Marine fish [*Pargus major*]	96 h LC50	= 6.9 mg Sb/L(measured total)
Freshwater fish [*Pimephales promelas*]	96 h LC50	= 14.4 mg Sb/L (measured filtered)
Invertebrates [*Chlorohydra viridissimus*]	96 h LC50	= 1.77 mg Sb/L (measured filtered)
Algae [*Raphidocelis subcapitata*]	72 h E_rC50 (growth rate)	> 36.6 mg Sb/L (measured total)

Chronic toxicity test results:

Fish [*Pimephales promelas*]	28 d NOEC/LOEC (growth; length)	= 1.13/2.31 mg Sb/L (measured total)
Invertebrates [*Daphnia magna*]	21 d NOEC/LOEC (reproduction)	= 1.74/3.13 mg Sb/L (measured total)
Algae [*Raphidocelis subcapitata*]	72 h NOEC/LOEC (growth rate)	= 2.11/4.00 mg Sb/L (measured total)

The lowest chronic toxicity data for sediment organisms were observed for the midge *Chironomus riparius*: 14-d NOEC (growth) = 78 mg Sb/kg ww ($SbCl_3$ used). The lowest reliable terrestrial toxicity data were determined in a soil spiked with Sb_2O_3 and aged for 31 weeks before testing.

Lowest chronic toxicity test results for terrestrial species:

Plants [*Hordeum vulgare*]	5 d NOEC (root elongation)	= 370 mg Sb/kg dw (measured*)
Invertebrates [*Folsomia candida*]	28 d NOEC (reproduction)	= 370 mg Sb/kg dw (measured*)
Microorganisms	7 d NOEC (nitrification)	= 710 mg Sb/kg dw (measured*)

*Recalculated in order to represent toxicity data in fully equilibrated diantimony trioxide amended soil (see below).

Since the equilibrium pore water concentration was not reached during the study period used, the NOEC values were recalculated using the pore water concentrations measured at the NOEC (9.7 mg Sb/L (plants and invertebrates) and 18.7 mg Sb/L (microorganisms)), and the equilibrium solid:liquid distribution coefficient (K_d) for antimony for this soil, i.e. 38 L/kg.

Exposure

Diantimony trioxide is commercially produced at four sites in the EU (2006). The annual production volume in year 2005 was 24 250 tonnes in the EU and approximately 120 000 tonnes worldwide. In 2002 the worldwide production was about 112 600 tonnes, with China producing the largest part (47%) followed by US/Mexico

(22%), Europe (17%), Japan (10%), South Africa (2%) and other countries (2%). Diantimony trioxide is mainly produced by re-volatilizing of crude stibnite or oxidation of antimony metal, with the latter process dominating in the EU. In the EU in 2005, diantimony trioxide was used as flame-retardant in plastics (38%), PVC (36%), rubber (9%) and textiles (7%), as a catalyst in polyethylene terephthalate production (4%), additive in glass manufacture (1%) and in pigments in paint and ceramics (5%).

Occupational exposure through inhalation of airborne dust and dermal contact with powder, pellets, paste, granules or final products is possible. Consumer exposure may occur through inhalation, ingestion and dermal contact with articles containing diantimony trioxide or domestic dust, but the exposure levels are low. (~60.000 times lower than the NOAEC established in long-term repeated dose inhalation study).

Diantimony trioxide is released to the environment via emissions to air, waste water, surface water and soil from manufacture, formulation, processing, use and disposal of diantimony trioxide, but also via coal combustion and refuse incineration, non-ferrous metal production (e.g. Cu), and road traffic. Humans may be exposed via the environment by inhalation of particles in air or ingestion of contaminated food and water, but the exposure levels are low.

Total estimated emissions of antimony into the environment in the EU from production of Sb_2O_3 are 1.36 tonnes per annum (tpa) to air, 0.006 tpa to surface water, 1.79 tpa to industrial urban soil. Total antimony emissions from formulation/industrial use/service life (of flame-retardants in plastic and rubber, flame-retardants in textiles, use as catalyst in the polyethylene terephthalate industry, use in paint and use in glass), were estimated to be 0.43 tpa to air, 1.75 tpa to surface water, 29.75 tpa to waste water and 34.49 tpa to industrial urban soil. Antimony emissions from disposal (100% incineration/100% landfill) were calculated to be 4.5/0 tpa to air, 5.4/0.38 tpa to waste water and 0/0.05 tpa to surface water. Total estimated emissions of antimony from unintentional sources are 16.67 tpa to air, 0.8 tpa to surface water and 2.5 tpa to industrial urban soil. Overall exposure is considered to be low compared to mammalian toxicity effect levels.

Realistic worst case (RWC) ambient concentrations were calculated as the median of the country specific 90^{th} percentile values using available ambient measured data from EU countries (and Norway). RWC ambient concentrations were derived for fresh water (0.72 µg Sb/L; dissolved), freshwater sediment (3 mg Sb/kg dw), soil (1.7 mg Sb/kg dw), air (2.6 ng Sb/m^3), marine water (0.20 µg Sb/L; dissolved) and marine sediment (3 mg Sb/kg dw).

RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health

The chemical is a candidate for further work. The chemical possesses properties indicating a hazard for human health (skin irritation, lung toxicity and lung carcinogenicity after repeated exposure). Member countries are invited to perform an exposure assessment for workers and if then indicated a risk assessment.

As all studies on chronic toxicity/carcinogenicity deviate from the OECD guideline, which prescribes an exposure period of 24 months for rats and because of other critical shortcomings in the data set on chronic toxicity/carcinogenicity, the US NTP (National Toxicology Program - see http://ntp.niehs.nih.gov) has initiated 2-year inhalation toxicology and carcinogenicity studies on diantimony trioxide in rats and mice.

Environment

This chemical is currently of low priority for further work. The chemical possesses properties indicating a hazard for the environment (acute aquatic toxicity values between 1 and 100 mg/L). However, based on data presented by the Sponsor Country, relating to production by 4 producers in Europe which accounts for ~1/6 of the global production and relating to the use pattern in EU countries, exposure to the environment is expected to be low. Countries may desire to investigate any

exposure scenarios that were not presented by the Sponsor country.