THIS DOCUMENT HAS BEEN PREPARED ACCORDING TO THE PROVISIONS OF ARTICLE 136(3) “TRANSITIONAL MEASURES REGARDING EXISTING SUBSTANCES” OF REACH (REGULATION (EC) 1907/2006). IT IS NOT A PROPOSAL FOR A RESTRICTION ALTHOUGH THE FORMAT IS THE SAME

PROPOSAL FOR COMMUNITY-WIDE MEASURES TO REDUCE RISKS

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SUBMITTED BY: Swedish Chemicals Agency
DATE: 2008-11-26

SUBSTANCE NAME: Diantimony Trioxide
IUPAC NAME: Diantimony Trioxide
EC NUMBER: 215-175-0
CAS NUMBER: 1309-64-4

A. PROPOSAL

A.1 Proposed measures (includes no restriction(s))

A.1.1 The identity of the substance(s)

SUBSTANCE NAME: Diantimony Trioxide
IUPAC NAME: Diantimony Trioxide
EC NUMBER: 215-175-0
CAS NUMBER: 1309-64-4

A.1.2 Measures

Workers

The legislation for workers' protection currently into force at Community level is generally considered to give an adequate framework to limit the risks of the substance to the extent needed and shall apply.

Within this framework it is recommended:

- to establish at community level occupational exposure limit values for diantimony trioxide according to Directive 98/24/EEC[1].

Measures foreseen as a consequence of regulations already in place

Regulation (EC) 1907/2006 (Reach)

Diantimony trioxide is classified as dangerous in accordance with directive 67/548/EEC. An importer or producer that import or produces more than 10 tons of diantimony trioxide should therefore include an exposure assessment and a risk characterisation in the chemical safety assessment that is part of the required registration under Reach. The chemical safety assessment should show that the risks to the human population and the environment are adequately controlled. The description of how to control the risks will be included in the exposure scenario annexed to the safety data sheet (SDS). Exposure scenarios are sets of conditions that describe how substances are manufactured or used during their life-cycle and how the manufacturer or importer controls, or recommends others to control, exposures of humans and the environment. The exposure scenarios must include the appropriate risk management measures and operational conditions that, when properly implemented, ensure that the risks from the uses of the substance are adequately controlled. Exposure scenarios need to be developed to cover all "identified uses" which are the manufacturers' or importers' own uses, and uses which are made known to the manufacturer or importer by his downstream users and which the manufacturer or importer includes in his assessment. The downstream users will have to check that their use(s) are "covered" by the SDS, i.e. that they use a substance within the conditions described in the exposure scenarios in the Annex to the SDS, and apply these conditions.

Within this framework it is recommended:

[1] OJ L 131, 05.05.1998, p. 11

- that any importer, producer or downstream user takes into account relevant information in the EU RAR when performing the chemical safety assessment.
- that ECHA takes into account relevant information in the EU RAR in the compliance check of registrations.
- that national authorities take into account relevant information in the EU RAR when enforcing Reach.

Directive 2000/60/EC (WFD)
For the river basins where emissions of diantimony trioxide may cause a risk, the relevant Member State should establish Environmental Quality Standards (EQS) and the national pollution reduction measures to achieve those EQS in 2015 should be included in the river basin management plans in line with the provisions of Directive 2000/60/EC.

Directive 2008/1/EC (IPPC)
The competent authorities in the Member States concerned should lay down, in the permits issued under Directive 2008/1/EC, conditions, emission limit values or equivalent parameters or technical measures regarding diantimony trioxide in order for the installations concerned to operate by the end of October 2007 according to BAT and taking into account the technical characteristic of the installations concerned, their geographical location and the local environmental conditions.

Member States should carefully monitor the implementation of BAT regarding diantimony trioxide and report any important developments to the Commission in the framework of the exchange of information on BAT.

A.2 Summary of the justification

A.2.1 Identified hazard and risk

Introduction

Diantimony trioxide is a solid substance at room temperature and is mostly handled as solid powder; dry or in wetted form, pellets, paste, or granules. The particle size of diantimony trioxide differs between different technical products. The vapour pressure of solid diantimony trioxide is low and it has a low solubility in most solvents.

The major use of diantimony trioxide is as a flame-retardant. However, it does not itself have flame-retarding properties; instead it is a synergist for halogenated flame-retardants in plastics, paints, adhesives, sealants, rubber, and textile back coatings. Other uses of diantimony trioxide include: as polymerisation catalyst used in PET resin manufacture and as a clarifying aid in certain glasses, and in pigments. Approximately 25 000 tonnes per year are used in EU, mainly (>70%) in the production of flame-retarded plastics (PVC and non-PVC). Diantimony trioxide is presently produced in four plants in EU.

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.

The human population may be exposed to diantimony trioxide at the workplace, from use of consumer products containing diantimony trioxide and indirectly via the environment through contact with contaminated air. In the environment, diantimony trioxide will dissolve to the trivalent and pentavalent forms of antimony. Consequently, humans may also be exposed indirectly via the environment to the antimony ion through consumption of food, water and soil.

Environment

The compartments of concern are: fresh water sediment (generic scenarios for formulation and application of flame-retardant textile back-coating and one production site).

Sediment

There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

This applies to the generic scenarios for formulation and application of flame-retardant textile back-coating and to one production site (site P1).

There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

This conclusion applies to all other scenarios, including nineteen sites using diantimony trioxide in textile applications and three production sites, that all report releases.

Human health

Human health (toxicity)

Human populations exposed to diantimony trioxide include workers, consumers and humans exposed via the environment. Indirect exposure via the environment to the antimony ion may also occur as diantimony trioxide is readily dissolved to the trivalent and pentavalent antimony ions in the environment. However, the risk characterisation has shown that only exposure of workers is of concern. For exposure assessment, both measured data, analogues data, calculations and modelling have been used.

The endpoints of concern are: skin irritation, local pulmonary toxicity and carcinogenicity.

Repeated inhalation exposure to diantimony trioxide gives local toxic effects in the lung and a NOAEC of 0.51 mg/m^3 is derived from a 12 month inhalation exposure study in rat, supported by observations of acute pneumonia in a 19 days inhalation developmental toxicity study. No systemic toxicity was observed after repeated exposure.

Diantimony trioxide is considered to be a carcinogenic substance and is classified for carcinogenicity. Although the mechanism for pulmonary tumour formation is still unclear it may be assumed that particle deposition followed by macrophage infiltration, pulmonary inflammation and impaired clearance are pivotal initial steps in the process. Consequently, diantimony trioxide can be regarded as a threshold carcinogen and as a starting point for a

quantitative risk characterisation the NOAEC of 0.51 mg/m^3 derived for local repeated dose toxicity is also used for carcinogenicity.

Workers

There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

This applies to skin irritation for all scenarios to indicate the need for classification. Once classified, the risk is regarded to be adequately controlled.

The need for limiting the risks also applies to repeated dose toxicity (local pulmonary toxicity after inhalation) and carcinogenicity (pulmonary carcinogenicity) for the following scenarios: **Production of diantimony trioxide:** Conversion, Refuming and Final handling with and without RPE, **Use as a catalyst in production of PET**: Powder handling, **Use as flame-retardant in production of plastics**: Raw material handling, **Use as flame-retardant in treated textiles**: Formulation, **Use in pigments, paints, coatings and ceramics:** Loading and mixing, **Use as flame-retardant in production of rubber:** Formulation and Processing.

A.2.2 Justification that action is required at community-wide basis/

The proposed measures have been assessed and selected taking into account the principles of subsidiarity and proportionality and the established practice from the existing substances programme.

A need for further measures to reduce the risks for workers has been identified (according to the criteria of Regulation (EEC) 793/93) in several industry sectors and the potential effects give cause for concern. This justifies community-wide action within the existing legal framework.

A need for further measures to reduce the risks to the local environment has been identified (according to the criteria of Regulation (EEC) 793/93) near some industrial sites and the potential effects give cause for concern. This justifies community-wide action within the existing legal framework.

A.2.3 Justification that the proposed measures are the most appropriate measure

There is a need for measures to reduce risks for workers. An OEL and the existing legal framework for worker protection together with measures already required under the Reach-regulation (EC) 1907/2006 has been assessed to be effective and practical and with limited negative socio-economic effects. The exposure can be controlled by well-tried risk management measures that can be implemented in the relevant workplaces. Measures beyond what is proposed are therefore not justified. Measures such as restrictions on the production, placing on the market and use would lead to considerably more extensive negative socio-economic effects.

There is a need for measures to reduce risks for local environments near certain industrial sites. The inclusion of diantimony trioxide where relevant in the river basin management plans that are to be established under Directive 2000/60/EC; the inclusion of diantimony trioxide where relevant in permits issued under Directive 2008/1/EC; and the inclusion where relevant of information from the risk assessment in the Chemical Safety Assessment to be done under Regulation (EC) 1907/2006 are all part of existing legal obligations. These

measures are deemed to be effective and practical. Measures such as restrictions on the production, placing on the market and use would lead to considerably more extensive negative socio-economic effects.

B. INFORMATION ON HAZARD AND RISK

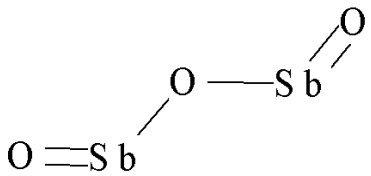
B.1 Identity of the substance(s) and physical and chemical properties

B.1.1 Name and other identifiers of the substance(s)

CAS No: 1309-64-4
EINECS No: 215-175-0
IUPAC Name: Diantimony Trioxide
Synonyms: Antimony (III) oxide
Antimony (3+) oxide
Antimony oxide (Sb2O3)
Antimony peroxide
Antimony trioxide
Antimony oxide
Antimony sesquioxide
Antimony white
Flowers of antimony
Senarmontite
Valentinite
Sesquioxide
C.I. Pigment White 11
C.I. 77052

B.1.2 Composition of the substance(s)

Molecular formula: Sb_2O_3
Structural formula:



Molecular weight: 291.52

B.1.3 Physico-chemical properties

The physico-chemical properties of diantimony trioxide are summarised in Table 1.

Table 1 Summary of physico-chemical properties

Property	Value	Comment	Reliability score
Physical state	Solid	The commercial product is a white, odourless, crystalline powder	
Melting point	655°C,	Budavari, 1996	4*
Boiling point	1550°C (1013 hPa), 1425°C (1013 hPa)	Gangolli, 1999, Budavari, 1996	4** 4*
Specific density	5.9 g/cm^3 (at 24ºC)	Smeykal, 2005 Density differs from crystalline structure.	1
Vapour pressure	1 mmHg (~133 Pa) at 574°C	Budavari, 1996	4*
Water solubility			2
Distilled water	pH 5: 19.7 mg Sb_2O_3 / l pH 7: 25.6 mg Sb_2O_3 / l pH 9: 28.7 mg Sb_2O_3 / l (at 20ºC)	UMWELTANALYTIK GMBH, 1993)	
Reconstituted standard water, 7 days	pH 8: 2.76 mg Sb/l (at 22.2ºC)	LISEC WE-14-018 Loading 100 mg Sb_2O_3/l	
Partition coefficient	Not relevant		
Granulometry	0.2-13.89 µm (particle size) 0.92-5.96 µm (D50)	Weidenfeller, 2005 Franke, 2005	1 1
Flash point	No data		
Autoflammability	No data		
Flammability	No data		
Explosive properties	No data		
Oxidizing properties	No data		
Heat of Vaporization	17.82 kcal/mol	Budavari, 1996	4*
Index of Refraction	2.087 - Senarmontite 2.18, 2.35 - Valentinite	Budavari, 1996	4*

* This reference refers to "The Merck Index" which is a peer-reviewed handbook of collected physico-chemical data.

** This reference refers to " The dictionary of substances and their effects" which is a peer-reviewed handbook of for instance collected physico-chemical data.

Physical state

The commercial product is a white, odourless, crystalline powder.
Diantimony trioxide has two molecular arrangement (Grund and Hanusch, 2000; Budavari, 1996; Kirk-Othmer, 1992a):

- Senarmontite [CAS No. 12412-52-1] below 570°C - colourless cubic crystals (Figure 1).

– Valentinite [CAS No 1317-98-2] above 570°C – white orthorhombic crystals which becomes yellow when heated but turns white again on cooling (Figure 2).

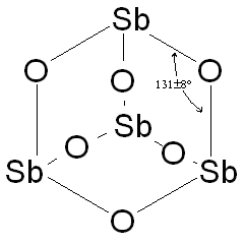


Figure 1 Senarmontite

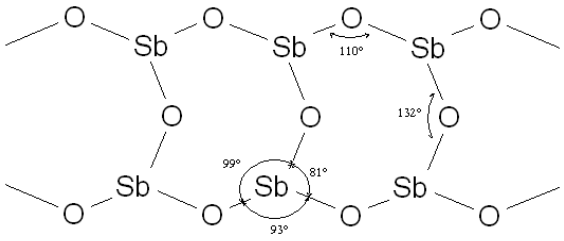


Figure 2 Valentinite

At higher temperatures, the stable form is the orthorhombic valentinite, which consists of infinite double chains. The orthorhombic modification is metastable below 570°C; however it is sufficiently stable to exist as a mineral.

Since diantimony trioxide can and will exist in both these modifications at environmental conditions, and no data are available to differentiate between the two as regards exposure and effects, the intention of the RAR will be to cover both with the CAS Number for diantimony trioxide, i.e. 1309-64-4.

Melting point

A melting point of 655°C is reported (Budavari, 1996).

Boiling point

The boiling point of diantimony trioxide is quoted as 1550°C (Gangolli, 1999; IUCLID), however there is also a reported boiling point of 1425°C (Budavari, 1996; Kirk-Othmer, 1992a).

Density

The specific density of diantimony trioxide has been reported to be 5.9 g/cm^3 at 24ºC (Smeykal, 2005).

Density differs from crystalline structure:

– *Senarmontite:* 5.2 g/cm^3 (Budavari, 1996; Kirk-Othmer, 1992a) 5.252 g/cm^3 (Grund and Hanusch, 2000)

– *Valentinite:* 5.67 g/cm^3 (Kirk-Othmer, 1992a), 5.72 g/cm^3 (Grund and Hanusch, 2000).

Vapour pressure

The vapour pressure of diantimony trioxide has been reported to be 1 mm Hg at 574°C (Budavari, 1996) which approximately corresponds to 133 Pa..

Solubility

Water solubility

Information on water solubility of Sb_2O_3 is limited. There are no studies performed according to the OECD guidelines. The available data contain one study that has measured solubility of the substance in distilled water and ten studies that have investigated solubility of diantimony trioxide in reconstituted standard water. Overall, the temperature in these studies varied between 17.8 – 23.6ºC.

Solubility of Sb_2O_3 in distilled water

The solubility of Sb_2O_3 was determined at pH 5.0, 7.0 and 9.0. Ten grams of the substance was mixed with 100 ml distilled water. The pH was adjusted and the solution agitated for 24 hr at 20°C. The resulting solid matter was filtered off and the Sb content of the filtrate was determined by the hydride-AA technique. The values reported are calculated as Sb_2O_3. The solubility of Sb_2O_3 at the different pH-values was: 19.7 mg Sb_2O_3/l at pH 5, 25.6 mg Sb_2O_3/l at pH 7, and 28.7 mg Sb_2O_3/l at pH 9 (UMWELTANALYTIK GMBH, 1993) performed at 20°C.

Solubility of Sb_2O_3 in reconstituted standard water (ISO 6341)[2]

The solubility of Sb_2O_3 has been measured in: (i) five 24-hr Screening tests transfomation/dissolution, i.e. WE-14-012e at 22ºC (LISEC, 2000), WE-14-030 at 20.6-20.65ºC (LISEC, 2002b), WE-14-021 at 20.7-20.8ºC (LISEC, 2002d), WE-14-018 at 23.6 ºC (LISEC, 2002e), and WE-14-020 at 17.8ºC (2002f); (ii) in three 7 days full tests WE-14-018 at 22.2ºC, (LISEC, 2002e) WE-14-020 at 17.8ºC (LISEC, 2002f) and CanMET, 2004 at 22ºC (Skeaff and Hardy, 2004) and in (iii) a 28 days full test WE-14-020 at 17.8ºC (LISEC, 2002f) (following the Transformation/Dissolution Protocol (GHS, 2005) In these tests the solubility is determined by measuring total dissolved concentration.

pH dependent dissolution pattern of Sb_2O_3

The test WE-14-021 (2002d) was performed in the ISO 6341 medium at seven different pH levels (i.e. from pH 1 to pH 10) performed at 20.7-20.8ºC. The loading of Sb_2O_3 was 100 mg l^{-1}. The solutions were agitated for 24 hr at 100 rpm. This does not fulfil the protocol, which states that the solutions should be agitated rapidly and vigorously. However, the speed of agitation applied in the tests seemed to have little influence on the results. Sampling and Sb analyses were carried out after 24 hr. The dissolved Sb concentration after 24 hr is given in

[2] Reconstituted standard water (i.e. ISO 6341 medium) is used in the Transformation/Dissolution Protocol that aims to determine the rate and extent to which metals and sparingly soluble metal compounds can produce soluble available ionic and other metal-bearing species in aqueous media at the rate of concern under environmental conditions. This medium is sterilised by filtration (0.2 μm) before use in the test.

Table 2, where also the actual pH values (for pH 7 and pH 8) that were measured during the test are presented

Table 2 Concentration of dissolved Sb (mg/l)) in reconstituted standard water (ISO 6341) after 24 hr (WE-14-021 (LISEC, 2002), WE-14-018 (LISEC, 2000) with a loading of 100 mg Sb_2O_3/l.

Test	pH	pH measured (mean)	Concentration of dissolved Sb (mg/l)
WE-14-021	1		4.37
	3		2.18
	5		1.11
	6		0.858
	7	0 hr = 7.01 24 hr = 6.98	0.618
WE-14-018	8	0 hr = 8.38 24 hr = 8.27	1.86
WE-14-021	10		2.16

The results from the study reveal the following dissolution pattern of Sb_2O_3 (see Figure 3).

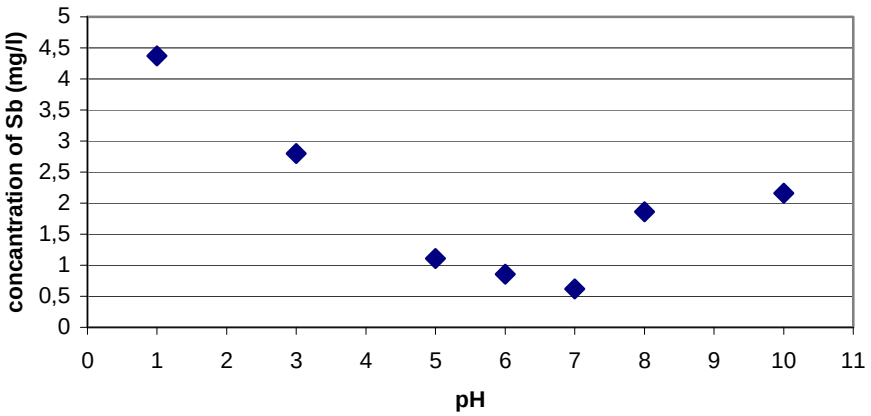


Figure 3 Mean dissolved Sb concentration after 24 hr in function of the pH.

According to the results from the test, dissolution of the substance in the test medium decreases constantly from pH 1 to pH 7. Above pH 7 the trend changes and the solubility of Sb_2O_3 increases rapidly to pH 8, where a new equilibrium is established and the increase in solubility becomes much slower.

Dissolution of diantimony trioxide between pH 7 and pH 8

Ten studies were performed in reconstituted standard water (ISO 6341) for 24 hr, 7 days and 28 days with high, medium and low loadings to investigate water solubility of the substance in the pH range 7 to 8. The results and pH conditions during these tests are reported in Table 3.

Table 3 Dissolved Sb concentration in reconstituted standard water (ISO 6341) after 24 hr , 7 days and 28 days with high, medium and low loadings

Test	Time	Loading (mg Sb_2O_3/l)	rpm	pH (measured, mean)	Dissolved Sb concentration [mg Sb/l]
WE-14-030 (LISEC, 2002b)	24 hr	100	200	0 hr = 7.15 24 hr = 7.16	0.812
	24 hr	100	200	0 hr = 7.52 24 hr = 7.55	1.06
	24 hr	100	200	0 hr = 7.87 24 hr = 7.86	1.54
WE-14-012e (LISEC, 2000)	24 hr	100	200	0 hr = 8.01 24 hr = 8.07	1.86
WE-14-018 (LISEC, 2002e)	24 hr	100	100	0 h = 8.4 24 h = 8.3	**1.86**
	7 d	100	100	0 h = 8.52 7 days = 8.11	**2.76**
CanMET (Skeaff and Hardy, 2004)	7 d	10	100	0 h = 7.90 7 d =7.95	0.370
WE-14-020 (LISEC, 2002f)	24 hr	1	100	0 h = 8.06 24 h = 8.06	0.016
	7 d	1	100	0 h = 8.06 7 d = 7.90	0.058
	28 d	1	100	0 h = 8.06 28 d = 7.90	0.118

These results confirm the solubility pattern of Sb_2O_3 that has been revealed by the study WE-14-021 (LISEC, 2002) performed at a broad range of pH-values (i.e. the increase of solubility of diantimony trioxide from pH 7 - the lowest concentration of free Sb ions- with increasing pH).
Besides that, graphical plotting of the actual pH conditions recorded during the 24-hr screening tests against concentrations of free Sb ions achieved at corresponding pH levels (see Figure 4) produces a line showing, in more detail, dissolution pattern of the substance between pH 7 and 8.

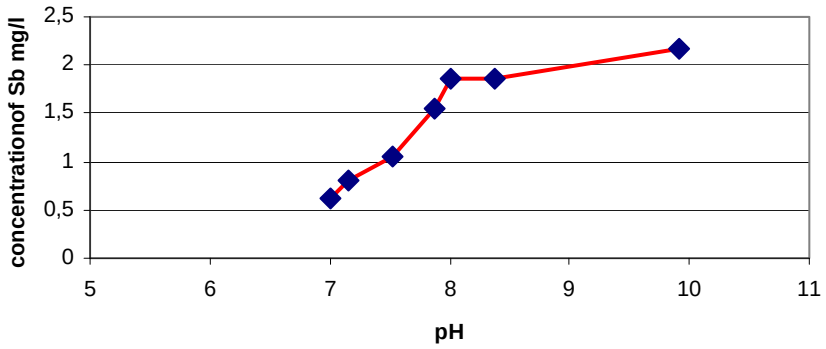


Figure 4 Mean dissolved Sb concentration after 24 hr at pH interval 7-8 (10)

Again, in correspondence with Figure 3 the results presented in Figure 4 show changes in dissolution trends around pH 7 (i.e. rapid increase of solubility) and pH 8 (i.e. reduction of the increase rate of solubility). The speed of agitation applied in the tests seemed to have little influence on the results.

The results from the WE-14-018 test (7-days Full test; loading of 100 mg Sb_2O_3/l) reveal the following dissolution pattern of Sb_2O_3 (see Figure 5).

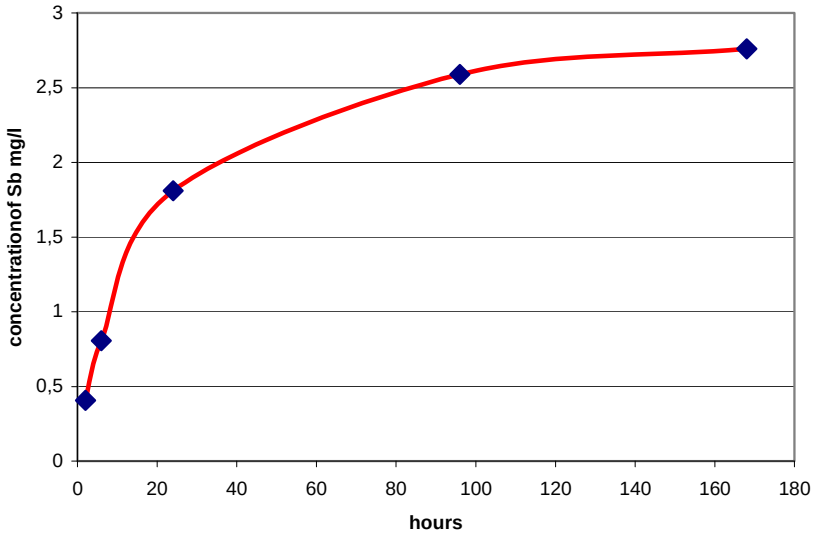


Figure 5 Transformation/dissolution curve for the 7-days test in reconstituted standard water (ISO 6341).

The results from the 28-days full test; loading of 1 mg Sb_2O_3/l) reveal the following dissolution pattern of Sb_2O_3 (see Figure 6).

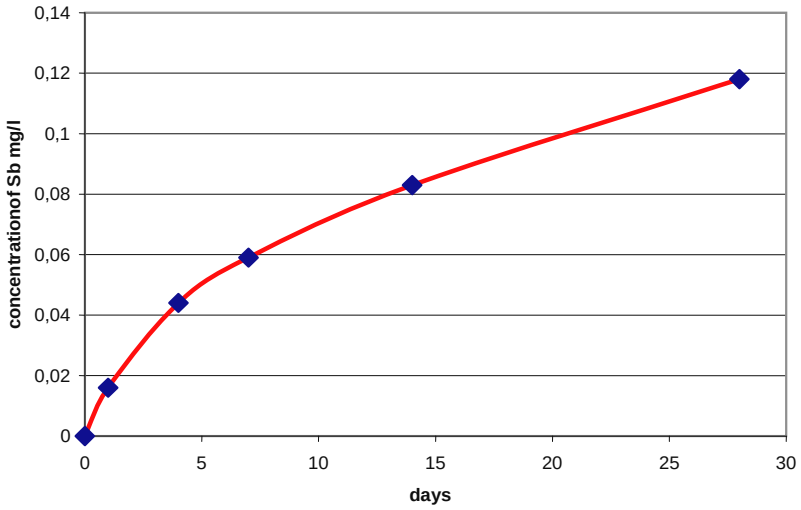


Figure 6 Transformation/dissolution curve for the 28-d test in reconstituted standard water (ISO 6341).

Selection of water solubility for modelling purposes

The results from the water solubility study in distilled water do not correspond to the results with the studies that measured water solubility of the substance in reconstituted standard water (ISO 6341). The study performed in distilled water suggests that the water solubility of Sb_2O_3 increases with the increasing pH over the range of 5 to 7 (and 9). The opposite picture was revealed by the tests in the ISO medium. In addition it is difficult to conclude from the test report why the study performed in distilled water resulted in so much higher water solubility of Sb_2O_3.

The discrepancy between water solubility studied in distilled water and in reconstituted standard water (ISO 6341) might be explained by the larger Ca concentration (2mM) in the reconstituted standard water and precipitation of $Ca[Sb(OH)_6]_2$. Upon dissolution in oxic systems Sb(III) is easily oxidized to Sb(V), which easily hydrolyse and form the anion $Sb(OH)_6^-$ (see also section 3.1.3.1.2, aquatic transformation). Johnson *et al.* (2005) present a solubility product (Kso = $[Ca^{2+}][Sb(OH)_6]_2$) of 10-12.55, which predicts a maximal Sb concentration of 0.012 mM or 1.44 mg Sb/l at 2 mM Ca. This corresponds to 1.73 mg Sb_2O_3 /l which is remarkably close to the maximum solubility observed in the ISO 6341 medium. Since the ISO medium is considered more relevant for natural conditions, the value for water solubility resulting from the tests conducted in ISO medium will be used for modelling purposes.

For modelling purposes a water solubility of 2.76 mg Sb/l will be used in the risk assessment.

Solubility in other solvents

Diantimony trioxide is insoluble in organic solvent (Kirk-Othmer, 1992a).

Granulometry

Weidenfeller reported particle sizes from 0.2 to 13.89 µm. Franke reported D50s of 0.92 to 5.96 µm. An assessment of the dustiness and particle size distribution of diantimony trioxide relevant for the potential inhalation toxicity has been made. (EBRC Consulting GmbH, 2006k) and the study and the results are presented and discussed in Chapter 4.

Autoflammability

An entry of autoflammability (year 1987) is included in IUCLID, but no value is reported. (IUCLID)

B.1.4 Justification for grouping

The diantimony trioxide in use will be the result of a production process which always will result in a mixture of Senarmontite and Valentinite. There are no data available to differentiate between these two as regards exposure and effects. In addition, in the environment the diantimony trioxide will dissolve and thereby generate antimony ions.

B.2 Manufacture and uses

B.2.1 Manufacture and import of a substance

Introduction to production

Import of diantimony trioxide into the EU is mainly from China (more than 90% of imported quantity in 2000) and USA. The quantity of diantimony trioxide imported/exported as a component of finished products, e g electrical and electronic articles, is not known.

Global diantimony trioxide production in 2005 was 120 000 tonnes (IAOIA, 2006b) Up from 112 600 tonnes in 2002, with China producing the largest part (47%) followed by US/Mexico (22%), Europe (17%), Japan (10%) and South Africa (2%) and other countries (2%). (EURAS bvba, 2003).

Production processes

Diantimony trioxide is currently (2006) being produced at four sites in EU15. Two sites ceased production in recent years.

Diantimony trioxide is produced via two routes:

a) Re-volatilizing of crude diantimony trioxide

b) Oxidation of antimony metal

Oxidation of antimony metal dominates in EU. Diantimony trioxide manufacturers typically buy antimony metal on the open market.

There are several processes for the production of crude diantimony trioxide or metallic antimony from virgin material. The choice of process depends on the composition of the ore and other factors. Typical steps include mining, crushing and grinding of ore, sometimes followed by flotation and separation of the metal using pyrometallurgical processes (smelting

or roasting) or in a few cases (e.g. when the ore is rich in precious metals) by hydrometallurgical processes. These steps do not take place in EU but closer to the mining location.

Re-volatizing of crude diantimony trioxide

1) Crude stibnite is oxidised to crude diantimony trioxide using furnaces operating at approximately 850 to 1 000°C according to the following reaction:

$$2\ Sb_2S_3 + 9\ O_2 \rightarrow 2\ Sb_2O_3 + 6\ SO_2$$

2) The crude diantimony trioxide from the first step is vaporised and condensed according to the following schematic formula (detailed process conditions are considered confidential):

$$Sb_2O_3\ (solid) + heat \rightarrow Sb_2O_3\ (gas)$$

Oxidation of antimony metal

Antimony metal is oxidized to diantimony trioxide in furnaces. The reaction is exothermic. Diantimony trioxide is formed through sublimation and recovered in bag filters (bag house). The size of the formed particles is controlled by process conditions (in furnace and gas flow). The reaction can be schematically described by:

$$4\ Sb + 3\ O_2 \rightarrow 2\ Sb_2O_3$$

(Grund and Hanusch, 2000; EURAS bvba, 2003; Swedish National Testing and Research Institute, SP, 2000).

Steps in the production

1) Reduction of oxide or sulphide to antimony metal (not always done on site) if metal is used as raw material.
2) If metal is used it is sometimes, but not always, crushed.
3) Loading of furnace with antimony metal or crude diantimony trioxide.
4) Oxidation of metal to diantimony trioxide in furnace or re-volatization of crude Antimony Trioxide.
5) Mixing/blending of master-batches or premixes. These may be dry or in wetted forms (e g with ethylene glycol or plasticizers). This step is not done on all production-sites. Not all the diantimony trioxide is mixed/blended with other components at the production site.
6) Packaging, typical packaging is big-bags (inner plastic bag typically containing 500 to 1200 kg of product with outer supporting bag) or 25 kg paper or plastic sacks. (EURAS bvba, 2003).

B.2.2 Uses

Introduction

An overview of the main uses of diantimony trioxide in the EU is summarised in Table 4 below.

Table 4 Use of diantimony trioxide in EU15

Use	Quantity (tonnes/year) and percentage of total quantity	
	Year 2005 (EURAS, 2006a)	Year 2000 (Docherty, 2001)
Flame-retardant in plastics (except PVC)	9 200 (38 %)	12 800 (51 %)
Flame-retardant in PVC	8 800 (36 %)	9 000 (36 %)
Flame-retardant in rubber	2 200 (9 %)	not specified
Flame-retardant in textiles	1 750 (7 %)	1 800 (7 %)
Catalyst in PET production	950 (4 %)	650 (3 %)
Additive in glass manufacture	250 (1 %)	250 (1 %)
In pigments, paint and ceramics	1 100 (5 %)	500 (2 %)
Total:	24 250	25 000

Use as flame-retardant

Combustion occurs through a chemical reaction that is sustained by free radicals. It is characterised by two principal stages:

1. A heat source initiates degradation of the polymer to yield volatile products of low mass, which migrate to the polymer surface and enter the gas phase.
2. The volatile products are oxidised by free radical reactions (burning), which evolves further heat to produce more volatile components from the polymer

Halogenated (based upon bromine or chlorine) flame retardants break down when heated. This leads to the formation of chlorine and bromine free radicals. These free radicals react with the free radicals formed in the combustion, yielding stable products and thereby terminating the combustion process. Diantimony trioxide acts synergistically through the formation of an antimony halide that scavenges free radicals. The exact mechanism of this synergistic action is not known. (Risk and policy analysts Limited, 2000)

Diantimony trioxide has limited fire-retardant properties of its own, but is an effective synergist for halogenated compounds such as halogenated flame-retardants or polymers containing halogens such as PVC. The addition of diantimony trioxide makes it possible to reduce the amount of halogenated flame-retardant that is added. Antimony pentoxide (Sb_2O_5) and sodium antimonite ($Na[Sb(OH)_6]$) are also used as synergistic flame-retardants. The synergistic effect of diantimony trioxide with organic halogen compounds was discovered in the 1930's. (Kirk-Othmer, 1992b, 1993a; Slooff *et al.*, 1992)

The consumption of diantimony trioxide in flame-retardant applications per country in EU is shown in Table 5 below (IAOIA, 2006b).

Table 5 Consumption of diantimony trioxide in flame retardant application per country in EU Europe (2005)

Country	Consumption (%)
Germany	16

Belgium	6
Switzerland	2
Spain	5
France	22
Finland	2
Italy	22
Netherlands	4
Sweden	4
UK	12
Other	3

Use as flame-retardant in plastics and rubber

According to EuPC – the European Plastics Converters, there are more than 27 000 companies in EU specialised in processing plastics. The processing of plastics and rubber containing diantimony trioxide does not require specialised equipment. Diantimony trioxide is used as flame-retardant in rubber by approximately 40 companies, in non-PVC plastics by approximately 220 companies and in PVC by approximately 200 companies (EBRC Consulting, 2006c; EBRC Consulting, 2006g; EBRC Consulting, 2006e).

Flame-retarded plastics are typically used in electrical and electronic equipment, in cables, in automotive parts, in some building materials and in some packaging. The industry estimates that 12% (210 000 tonnes) (APME, Association of Plastic Manufacturers in Europe, 2001b)or in another source 30% (450 000 tonnes) (APME, Association of Plastic Manufacturers in Europe, 2002)of the plastics used in the electrical and electronic sector contains flame-retardants, mainly in PC´s, monitors, printers, copiers, TV's and small and large household appliances. The latter source estimates that some 59% of the plastics use non-halogenated flame-retardants and 41% use halogenated. The flame-retardant system used depends on a number of considerations. Diantimony trioxide is only a synergist with halogenated flame-retardants; consequently it cannot be assumed that all flame-retardant systems in use contain diantimony trioxide.

Flame-retardants are used in cables and paints to prevent the conversion of a spark into a fire and subsequently to prevent the spread of a fire throughout a structure along the wiring or paint.

PVC is flame-retardant in itself, addition of diantimony trioxide improves the flame-retardant properties. The flame-retardant properties are reduced as non-flame retardant plasticizers are added.

Flame-retarded rubber is used in some automotive items (e g matting) electrical equipment and in some special industrial rubber applications where fire risk reduction is critical, e g conveyor belts in coalmines. Flame-retardant systems without diantimony trioxide (e g aluminium trihydrate) are typically used.

The amount of diantimony trioxide added depends on several factors such as type of halogenated compound and polymer, required physical properties of the final polymer, flame retarding requirement, cost considerations etc. Typical content in the final polymer is up to

8% but percentages up to 25% are mentioned. Diantimony trioxide is incorporated into the polymer but is present as a separate phase. The potential for migration of diantimony trioxide out of the polymer is discussed in the exposure part of the chapter on human health. (Kirk-Othmer, 1993b; Kirk-Othmer, 1992b; Slooff *et al.*, 1992). Where tetrabromobisphenol A is used as an additive flame retardant, it is generally used with diantimony oxide for maximum performance. Diantimony trioxide is generally **not** used in conjunction with tetrabromobisphenol A in reactive flame retardant applications (where tetrabromobisphenol A becomes covalently bound to epoxy or polycarbonate resins), e g in printed circuit boards. (RAR, 2003)

Manufacturing of cables and other plastic products principally involve two main steps, mixing and forming. The mixing is either of granules/powder or powder additives to e g rubber slabs. The forming involves heating and a forming operation that depends on polymer and article produced. In practice diantimony trioxide is normally mixed into the polymer compounds as powder additives, either directly or by first making a master-batch of this and other components. The powder is sometimes supplied in pre-dosed bags that are added without opening to the mixing process. During forming e g extrusion, the temperature of the polymer may be up to 300°C, but may be much lower depending on type of polymer. The forming is done in partially closed systems. The time at which the polymer is subject to high temperatures is kept as short as possible to avoid degradation of the material.

The life expectancy for plastic articles varies widely depending on application and user. Because of the scarce information, no attempt has been made to estimate the service life for the various products containing plastic with diantimony trioxide. For the emission assessment it has been assumed that the amount of diantimony trioxide in use is constant over time.

Standard grades of diantimony trioxide for this application have particle sizes of 1 to 2 μm, but most producers have finer grades of around 0.5 μm. The latter can give benefits in engineering polymers in terms of impact strength. Coarser grades of 2.5 to 10 μm have benefits mainly in darker, highly coloured or pigmented PVC formulations because of their lower tinting properties (Docherty, 2001).

Use as flame-retardant in textiles

Approximately 30 companies in EU15 use diantimony trioxide to produce flame-retarded textiles (EBRC Consulting, 2006f).

Flame-retarded textiles are used in textiles that are used in vehicles, in protective clothing, mats, curtains, upholstered furniture, tents, canvas, straps etc. Requirements vary depending on national legislation. Flame-retardant systems without diantimony trioxide are also used in textiles. (Kirk-Othmer, 1996)

Textiles are given flame-retardant properties through a number of different approaches. Diantimony trioxide is used in back-coating, where a fire-resistant layer is attached to one side of the finished textile. This textile is then typically used in textile-covered articles (e g furniture, mattresses). Flame-retarded textiles typically contain 4 to 6 percent of diantimony trioxide, with content in the (dry) back-coating of up to 24 % (when a flame-retardant system including diantimony trioxide is used) (European IPPC bureau, 2002; EBRC Consulting, 2006f).

Use in glass

Five glass manufacturers in EU25 use diantimony trioxide. Sodium antimonate is replacing diantimony trioxide in this sector and is more commonly used than diantimony trioxide (EBRC Consulting, 2006b).

Diantimony trioxide is used as fining agent or as a degasser in the manufacture of art, optical and fluorescent light bulb glass, and in glass for screens for television and computers etc. It is added to the glass during manufacture and helps the removal of bubbles from the glass. The mechanism involves several steps. In the final step (part of) the trioxide is oxidised to the pentoxide, it is therefore likely that the antimony in the final glass is primarily in the pentoxide form. Total content of Sb in the finished glass is typically around 0.8%. (Sternbeck *et al.*, 2002a) It is usually mixed with the glass and other additives in a dry form. To reduce exposure to man and environment at many smaller sites, the mixing and sometimes also pelletizing may be done at one site and the mixture then sent to the various glass manufacturing sites.

The powder containing diantimony trioxide is melted in furnaces and formed either in machine processes or in the case of art glass sometimes by manual glass blowing. The glass melt is heated to a temperature around 1 400°C. Production is traditionally in batches, the furnace is typically loaded in the evening and the melt then processed the following day. Modern large facilities have 24-hour continuous tank smelters, balancing the take-off of crystal at one end with the raw-material charging at the other to maintain a constant level of molten glass within the system.

Use in pigments

Diantimony trioxide is used in the manufacturing of "Complex Inorganic Coloured Pigments" (CICP), which are further used in subsequent industries such as plastics (50%), coatings (35%), enamels and ceramics (10%) and building materials (5%). The pigment production process involves chemical transformation of the input materials into a crystal (rutile) host matrix in which various metals (e.g., Ti, Ni, Cr) apart from Sb are incorporated. Antimony is chemically bonded (as Sb(V) in the rutile lattice, taking the place of some of the Ti-ions.

Once incorporated into these rutile structures, antimony is no longer present as diantimony trioxide. For this reason, this report is restricted to the relevant process stages involving releases of diantimony trioxide itself. Apart from the use in pigment production, only two other uses have been reported, namely as pigment in the ceramics industry and as flame retardant in special paints. No exact split of tonnage per use is available, these uses will therefore be handled together (EBRC Consulting, 2006i).

Various antimony compounds are part of pigments used in ceramics decoration colours together with e g lead-, cadmium-, zinc- and chromium-compounds. They are applied dry and "fired" at temperatures up to 1 250°C.

Catalyst in PET-manufacture

There are 22 production sites (2005) for PET container resin in the EU, with a total production capacity of 2.94 million tonnes/year. Capacities range from 30 to 345 thousand tonnes/year. Annual EU25 consumption was estimated to 2.8 million tonnes for 2005. diantimony trioxide is used at 11 sites (involving 13 plants). (EURAS, 2006a)

In Europe, PET container resin is mainly (approximately 82%) used in bottles and containers for (in order of quantity) bottled waters, soft-drink bottles, edible oils and pharmaceuticals.

Other uses include containers for household cleaners and other non-foods, APET and CPET sheet and industrial strapping. About 200 kt of post-consumer recyclate are expected to be used in these applications. On top of the PET container resin production, EU25 has production capacities for 412 kt of Polyester Staple Fibre, 437 kt Polyester Filament Fibre and 296 kt of Polyester Film. This gives a total demand of 4.1 million tonnes of virgin and recycled PET. (IAOIA, 2006a)

PET resins are produced commercially by two similar processes, using ethylene glycol (EG) and either (i) dimethyl terephthalate (DMT) or (ii) terephthalic acid (TPA). In both cases, the bis-(2-hydroxyethyl)- terephthalate (BHET) monomer is first produced as an intermediate, yielding either methanol (DMT process) or water (TPA process) as by-products. The BHET monomer is then polymerised at low pressure under heating and the presence of the antimony catalyst to the PET resin. (EBRC Consulting, 2006h). Diantimony trioxide is used as polymerisation catalyst. Other catalysts are also in use, but diantimony trioxide dominates.

The final concentration of diantimony trioxide in PET is typically around 180 to 220 ppm, but can be up to 550 ppm.

The diantimony trioxide used in this application must have:

- Low impurity levels of lead and arsenic (around max 100 ppm of each element) and other impurities, typically Fe < 100 ppm; Cl < 100ppm; Cu < 0.01%; Zn 0.002%; Pb 0.001%; Ni < 0.1%; SO_4 < 0.01%. With a total impurity specification of max 0.05%.
- Good solubility in MEG, i.e. low levels of insolubles such as higher oxidation steps of antimony oxide.
- Small fluctuations over time in physical properties.

Diantimony trioxide was, and in some cases still is chemically purified in order to reduce the level of impurities. It is supplied as powder or powder wetted with some 3% MEG.

Diantimony trioxide is handled when preparing the catalyst solution. The preparation consists of the following activities: diantimony trioxide is dissolved in monoethylene glycol in a heated, stirred feed vessel and forms antimony glycolate. The antimony glycolate solution is then injected into the process vessel and the PET polymerisation reaction begins. In the initial stages of the reaction, excess water is removed and then as the reaction progresses and the polymer viscosity increases, excess monoethylene glycol is removed. When a specified viscosity is achieved the amorphous polymer is cooled and pelletised. Following this first process a secondary process is then employed. This process takes amorphous PET pellets and whilst in the solid phase crystalises the polymer. This is then transferred to a solid phase polymerisation process where more monoethylene glycol and other volatile species are removed and the viscosity of the polymer increases to a required level. The PET pellets are then formed, using a range of standard polymeric processing techniques into an article or precursor article. In the case of PET bottles a precursor article called a preform and is made on an injection moulding machine. This preform is then reheated and blown into a bottle shape in specially designed processing equipment which is called a blow moulding machine.

Bottles of PET are used as either single trip or multitrip bottles. In a few countries a proportion of bottles are used for multitrip purposes. These bottles are filled, consumed, collected washed and refilled (can be done in 7 to 15 cycles). Single trip bottles are collected and recycled in various ways. A rough estimate based on statistics from Petcore (PET container recycling Europe, 2003) indicates that around a third of the PET used in containers

is collected and recycled. This proportion is growing. Currently the biggest outlet for recovered PET is the fibre market (70%). The fibre market uses recovered PET in a number of different applications, e g padding to stuff anoraks, sleeping bags and soft toys, fleece fabric for sweatshirts, jackets and scarves, geotextiles, non-woven fabrics used in shoes, backpacks and umbrellas. PET fibres are used in car carpets and upholstery, and carpets and rugs. Other uses of recovered PET are for extruded sheets (both for food and non-food packaging) and for strapping tape (industrial use). Less than 10 percent is used to manufacture PET bottles, both for food and non-food applications, but that share is increasing. A proportion of the PET bottles will end up in household waste or as litter, when municipal solid waste is incinerated with energy recovery, PET bottles will significantly contribute to the calorific value of the waste. This fraction will decrease as recovery of packaging waste is improved. This improvement should also be driven by EU's packaging waste directive, 2004/12/EC. (Anonymous, 2006; Anonymous, 2000; PET container recycling Europe, 2003; IAOIA, written communication, 2000).

B.2.3 Uses advised against by the registrants

Not relevant for this proposal.

B.2.4 Description of targeting

This proposal has been targeted on where there are identified needs to reduce risks (a conclusion iii) in the risk assessment carried out in accordance with Council Regulation (EEC) 793/93. This document therefore focus on skin irritation, repeated dose toxicity (local pulmonary toxicity after inhalation) and carcinogenicity (pulmonary carcinogenicity) for workers, and local risks for aquatic compartment (sediment) at a limited number of industrial sites.

B.3 Classification and labelling

B.3.1 Classification in Annex I of Directive 67/548/EEC

Diantimony trioxide is classified as a dangerous substance within the meaning of Directive 67/548/EEC and is listed in Annex 1 of this directive, being assigned the following risk and safety phrases:

Category 3 carcinogen
Xn Harmful
R40 Limited evidence of a carcinogenic effect
S36/37 Wear suitable protective clothing and gloves
S2 Keep out of reach of children
S22 Do not breathe dust

B.3.2 Classification in classification and labelling inventory/Industry's self classification(s) and labelling

In the EU Risk Assessment Report on diantimony trioxide, the rapporteur proposes the following classification in addition to the current classification:

Xi; R38 (Irritating to skin)

B.4 Environmental fate properties

B.4.1 Degradation

In the environment diantimony trioxide will dissolve and thereby generate antimony ions. Antimony, being a natural element, cannot by definition be degraded. However, it can be transformed between different binding/speciation forms and oxidation states.

B.4.2 Environmental distribution

Not relevant for this proposal.

B.4.3 Bioaccumulation

Not relevant for this proposal.

B.4.4 Secondary poisoning

Not relevant for this proposal.

B.5 Human health hazard assessment

B.5.1 Toxicokinetics

Not relevant for this proposal.

B.5.2 Acute toxicity

Not relevant for this proposal.

B.5.3 Irritation

Skin

Studies in animals

The skin-irritating or penetrating properties of diantimony trioxide were studied in eight albino rabbits (Gross *et al.*, 1955a). The method of application was adapted from the procedure of Draize with minor modifications. The day before dosing the animals were clipped over the entire trunk with an electric clipper, care being taken to avoid cutting or abrading the skin. 25,000 mg of diantimony trioxide dust was incorporated into an aqueous methylcellulose paste and lightly applied to the denuded skin, which comprised about two-thirds of the animals' torso. The area was covered by an impervious membrane (Vinylite) and allowed to remain in contact for one week. No significant local reaction resulted from this single application, nor was there any apparent sign of systemic toxicity.

From this study it can be concluded that diantimony trioxide is not irritating to the skin of rabbits.

Studies in humans

White and co-workers reported three cases of dermatitis in workers exposed to antimony in a melting process (White *et al.*, 1993). Three men, between 28 and 33 years of age were employed at a brazing rod manufacturing plant. After changes at their workplace they were assigned the task of melting antimony metal and due to insufficient precautionary measures

they were exposed to fumes from the melted antimony. Shortly after the process changes they noted the onset of skin lesions. Physical examination revealed crusted follicular papules and pustules of the arms (accentuated in the antecubital fossae), trunk and forehead in two of the workers. One of these also had a dry eczematous patch on the left trunk. In the third worker erythematous follicular papules were noted on the ventral and dorsal aspects of both forearms and on the posterior legs and back. The urinary antimony level, which was measured in one worker, was 53.2 μg/L, which is in the range for exposed individuals (levels in unexposed persons are less than 1.0 μg/L). None of the workers had any history of skin disease or atopy. In all three workers the dermatitis resolved with the avoidance of antimony-related work.

The authors concluded that the three workers present strong evidence for antimony related dermatoses: these workers were exposed to other metal fumes for many years without skin manifestations; lesions appeared when antimony was introduced to the process, and resolved when antimony exposure was avoided. Two of the workers had exposure only to molten metal fume, and not to metallic dust. During site visit it was noted that the temperature in the work area was quite high, and the skin of employees was damp with perspiration.

This study indicates that fumes from melted antimony, presumably diantimony trioxide, may cause dermatitis in humans.

The occurrence of a skin eruption in 23 persons amongst a population of about 150 men employed in the manufacture of diantimony trioxide has also been reported and the morphology and histology of the rash known as ”antimony spots” is described (Stevenson, 1965). Intense itching preceded the skin eruption. A diffuse blotchy erythema may occur but most commonly the early lesions are small erythematous papules and may be associated with much excoriation. The papules enlarge and in some cases become frankly pustular. The sites most commonly involved in the 23 cases were antecubital area, shins, back of neck, forearms, trunk, back of knees and face. In general, the lesions were present on those dust-laden areas most exposed to heat and therefore to sweating. Two furnacemen who presented one side of their body to heat when working had lesions only on the limbs of that side. The rash subsides in from 3 to 14 days when the worker is transferred to a cooler part of the factory. The eruption occurs in the warm summer months and is rarely seen in the winter. 17 of the 23 men affected were furnace workers and 5 were doing a different job but also under hot conditions.

Histologically, the early lesions showed epidermal cellular necrosis with associated acute dermal inflammatory cellular reaction. The lesions appear to be closely associated with sweat ducts.

This study suggests that workers exposed to diantimony trioxide are liable to develop a transient skin eruption affecting areas most exposed to heat and where sweating occurs.

In another paper severe discomfort from skin irritation in warm weather was described in men working with the production of antimony oxide and the pure metal from sulphide ore by various smelting processes (McCallum, 1963). The rash consisted of papules and pustules around sweat and sebaccous glands and was compared in appearance to the lesions of chickenpox or smallpox. It affected particularly the fore arms and thighs and the flexures and did not appear on the face, hands or feet. The spots disappeared rapidly over a weekend or public holiday, but reappeared on return to work. Over hundred men were employed but the frequency of dermatitis was not stated.

This study indicates that work in various smelting processes in the production of diantimony trioxide and the pure metal is connected with dermatitis in warm weather.

The clinical examination of 51 male workers employed in an antimony smelting plant has been reported (Potkonjak and Pavlovich, 1983). The entire study is also reported in the 4.1.2.6. Repeated dose toxicity section. The subjects were aged between 31 and 54 years (mean 45.23), they were exposed to dust containing predominantly antimony oxide [Sb_2O_3 (38.73-88.86%), Sb_2O_5 (2.11-7.82%), SiO_2 (0.82-4.72), Fe_2O_3 (0.90-3.81%) and As_2O_3 (0.21-6.48%)], had worked in the factory from 9-31 years (mean 17.91) and had pneumoconiotic changes. Over a 25-year period they were examined 2-5 times; the evaluation included among other things a physical examination (specialist consultations were obtained when appropriate).

"Antimony dermatosis", characterised by vesicular or pustular lesions with residual hyperpigmentation, were present in 32 of 51 exposed workers (63%), especially during the summer season and when working near the furnace where temperatures were excessively high.

This study indicates that antimony related dermatosis may occur in humans exposed to diantimony trioxide at high temperatures.

A combined test was conducted to determine the irritation and sensitisation potential of a fibre treated with a mixture of antimony oxide (Sb_2O_3) and a substance of which the identity was deleted from the report (Haskell Laboratory for Toxicology and Industrial Medicine, 1970). The fibre contained 1% antimony oxide (by weight). One-inch squares of the test fabric were applied to the arms of ten men and to the arms or legs of ten women and held in place with adhesive tape for six days. Two weeks after removal, new patches were applied for 48 hours. Skin under the patches was examined at two and six days and on final day at patch removal. No skin reactions were seen at any of the examinations.

This study shows that one-inch squares of a test fabric of unknown identity containing 1% antimony oxide (by weight) was not irritating to the skin of 10 men and 10 women. However, the amount of diantimony trioxide applied was not given and there is no information on how much of the diantimony trioxide in the fibre that came into contact with the skin. Therefore, no conclusions on the irritation potential of diantimony trioxide can be drawn from this study.

A similar patch test was performed with fibre containing Sb_2O_3 and a substance of which the identity was deleted from the report (the concentration of antimony oxide was not specified) (Haskell Laboratory for toxicity and Industrial Medicin., 1970). One-inch squares of the test material were applied to the arms of 46 men and to the arms or legs of 127 women and held in place with adhesive tape for six days. Two weeks after removal, new patches were applied as a challenge for skin sensitisation and were removed after 48 hours. Skin under the patches was examined at two and six days and on final day at patch removal. After six days of occluded wear one subject had papules along the edge of patch area, however, similar papules were also seen under the tape area. Subjects had small indented areas under patch that appeared as red spots that coincided with the crimped pattern of this fibre. No conclusions on the irritation potential of diantimony trioxide can be drawn from this study.

This study shows that one-inch squares of a test fabric of unknown identity containing an unknown amount of diantimony trioxide were not irritating to the skin of 46 men and 127 women. Since the amount of diantimony trioxide applied was not given and there is no information on how much of the diantimony trioxide in the fibre that came into contact with the skin no conclusions on the irritation potential of diantimony trioxide can be drawn from this study.

Summary of irritation

The only animal study which can be used for risk assessment of the skin irritation potential of antimony oxide shows that antimony oxide is not irritating to rabbit skin. However, several human case report studies indicate that diantimony trioxide may cause dermatitis on skin damp with perspiration and thus the lesions appear to be closely associated with sweat ducts. The lack of dermal irritation in rabbits may be explained by the fact that rabbits lack sweat glands (Brewer and Cruise, 1994). In conclusion, diantimony trioxide should be regarded as a skin irritant in humans under conditions that evoke sweating.

Classification proposal: Xi; 38 (Irritating to skin)

Rationale for the classification

The classification proposal is based on practical experience in humans.

B.5.4 Corrosivity

Not relevant for this proposal.

B.5.5 Sensitisation

Not relevant for this proposal.

B.5.6 Repeated dose toxicity

Inhalation

Studies in animals

In a whole-body inhalation study, the sub-chronic toxicity of diantimony trioxide was evaluated (Newton et al., 1994). Fischer 344 rats, 50 males and 50 females per dose group, were exposed to diantimony trioxide in exposure chambers for 6 hours/day, 5 days/week for up to 13 weeks followed by a 27-week observation period. 30 rats/sex/dose group were exposed for the full 13 weeks, with 5 rats/sex/group killed after 1, 2, 4 and 8 weeks of exposure. The diantimony trioxide exposure concentrations were 0, 0.25, 1.08, 4.92, or 23.46 mg/m^3. Control animals were exposed to clean air only. The flow rate was 18-25 complete air changes per hour (the recommended flow rate in OECD guideline 412, 413 and 453 is 12-15 air changes per hour, Rapporteur comment). The test sample was a mix of equal-sized lots of diantimony trioxide obtained from nine different suppliers. The purity of the 9 lots was 99.68 ± 0.10 % and the mass medium aerodynamic diameter (MMAD) was 3.05 ± 0.21 micrometers with a geometric standard deviation (GSD) of 1.57±0.06.

Animals were observed twice daily for viability and overt signs of toxicity. Detailed observations were conducted weekly and body weights were measured weekly throughout the exposure and observation period. Ophtalmoscopic examinations were performed on all animals pretest and on the day before their scheduled sacrifice. Sacrifices were conducted on

5 animals/sex/group at exposure weeks 1, 2, 4, 8, and 13 and at recovery weeks 1, 3, 9, 18, and 27. Complete gross postmortem examinations of all major organs were performed in all animals. Histological examinations were performed on hematoxylin-eosin-stained tissue sections of heart, nasal turbinates, larynx, trachea, lung and peribronchial lymph node. Hematology and clinical chemistry analyses were conducted on five animals/sex/group at exposure weeks 1, 2, 4, 8, and 13.

No exposure-related mortalities were reported. Corneal irregularities were observed with about equal incidence, 30%, in all groups, including controls. According to the authors these effects were similar to a spontaneous degenerative condition reported in Fischer 344 rats and were, therefore, not considered to be treatment related. The irregularities appeared after about 2 weeks of exposure and did not abate during the 27-week observation period. Male body weight gains were significantly lower in the highest dose group compared to the controls. The difference was small, approximately 6% and statistically significant from week 3 to the end of the study, except for week 12. Female body weight gains were unaffected by diantimony trioxide exposure. No exposure-related changes in hematological parameters were noted. In both sexes, the mean absolute and relative lung weights were significantly increased at the two highest dose levels by week 13 of exposure but returned to normal after the 3rd week of the observation period. Microscopic changes observed in the lungs are shown in Table 6 and Table 7. Chronic interstitial inflammation (minimal to moderate severity) and interstitial fibrosis (minimal to slight severity) were seen in the lungs of both control and treated animals from the exposure and observation periods. During the observation period, these effects were most frequent in the highest dose group. Also, granulomatous inflammation (minimal to moderate severity) in the lungs was most frequent in the highest dose group during the observation period. Bronchiolar/alveolar hyperplasia (minimal to mild severity) was seen in only two males from the highest dose group terminated following the exposure period of the study. Alveolar macrophages were more numerous (minimal to moderate severity) in the lungs of the treated animals than in their comparable controls. The exposed rats had scattered macrophages containing small particles of foreign material in the lungs and in the peribronchial lymph nodes (minimal to moderate severity). The incidence and severities of these findings were greater during the observation period than during the exposure period. For both periods, the animals in the highest two dose groups were most severely affected. No histopathologic findings were reported in any other tissues examined.

In conclusion, this study did not indicate any systemic toxic effects of diantimony trioxide after sub-chronic inhalation exposure in rats. For the local effects, chronic interstitial inflammation, granulomatous inflammation and fibrosis are observed in the lungs of the animals of the highest dose group. However, it should be noted that the incidence of interstitial chronic inflammation and interstitial fibrosis in controls (17 and 12 out of 25 males and 15 and 8 out of 25 females, for the respective conditions) after 13 weeks is high and too severe in degree as to be completely satisfying. Thus, the study might reflect sub-chronic disease of moderate severity due to other causative agent than diantimony trioxide.

Table 6. Microscopic findings after a 13-week inhalation exposure period to diantimony trioxide.

	Males					Females				
Dose (mg/m^3)	0	0.25	1.08	4.92	23.46	0	0.25	1.08	4.92	23.46
Number of animals examined	25	25	25	25	25	25	25	25	25	25
Effect										
Interstitium: chronic inflammation	17	15	11	13	16	15	11	13	11	15

	Males					Females				
Granulomatous inflammation	0	0	0	0	1	0	1	0	0	1
Interstitium: fibrosis	12	13	8	10	10	8	7	6	4	12
Bronchiolar/alveolar hyperplasia	0	0	0	0	2	0	0	0	0	0
Alveolar/intraalveolar macrophages	3	1	5	11	9	2	0	4	10	11
Alveolar/intraalveolar macrophages: foreign particulate material	0	8	11	17	23	0	4	11	20	23
Peribronchial lymph node macrophages: foreign particulate material	0	1	0	1	3	0	0	0	3	3

Table 7. Microscopic findings related to the 13-week inhalation exposure period to diantimony trioxide seen during the 1- to 27-week observation period.

	Males					Females				
Dose (mg/m^3)	0	0.25	1.08	4.92	23.46	0	0.25	1.08	4.92	23.46
Number of animals examined	25	25	25	25	25	25	25	25	25	25
Effect										
Interstitium: chronic inflammation	15	13	17	17	25	9	14	12	16	25
Granulomatous inflammation	2	0	4	1	6	1	0	0	5	7
Interstitium: fibrosis	8	12	6	9	21	7	5	4	11	20
Bronchiolar/alveolar hyperplasia	0	0	0	0	0	0	0	0	0	0
Alveolar/intraalveolar macrophages	6	10	5	21	24	1	3	11	21	25
Alveolar/intraalveolar macrophages: foreign particulate material	0	17	22	25	25	0	13	23	25	25
Macrophages in the perivascular/peribronchiolar aggregates of lymphoid cells: foreign particulate material	0	0	0	0	3	0	0	0	3	2
Peribronchial lymph node macrophages: foreign particulate material	0	0	2	15	15	0	0	4	16	18

In a subsequent whole-body inhalation study, performed by Bio/dynamics Inc. (Newton and Daly, 1990) and published by Newton and co-workers (1994), the oncogenicity of diantimony trioxide was evaluated (Newton and Daly, 1990; Newton et al., 1994). This study is also reported in the 4.1.2.1 Toxicokinetics and 4.1.2.8. Carcinogenicity sections. Fisher 344 rats, 65 males and 65 females per group, 8 weeks of age, were exposed to diantimony trioxide at 0, 0.06, 0.51 or 4.50 mg/m^3 for 6hr/d, 5d/wk for 12 months followed by a 12-month observation period. Control animals were exposed to clean air only. The flow rate was 18-25 complete air changes per hour (the recommended flow rate in OECD guideline 412, 413 and 453 is 12-15 air changes per hour, Rapporteur comment). Five animals per sex per group were sacrificed at 6 and 12 months of exposure and at 6 months post-exposure. All surviving animals were sacrificed at 24 months (12 months post-exposure). The purity of the diantimony trioxide was 99.68 % and the particle MMAD was 3.76±0.84 µm with a geometric standard deviation of 1.79±0.32 for all concentrations. The concentrations of diantimony trioxide were determined by atomic absorption.

Animals were observed twice daily for viability and overt signs of toxicity. Detailed observations were conducted weekly and body weights were measured twice pre-test, weekly for the first 13 weeks, monthly thereafter and at termination. Ophtalmoscopic examinations were performed on all animals pre-test and on the day before their scheduled sacrifice. Hematological effects were evaluated at 12, 18 and 24 months. Complete gross postmortem examinations of all major organs were performed in all animals. Histological examinations were performed on hematoxylin-eosin-stained tissue sections of heart, nasal turbinates, larynx, trachea, lung and peribronchial lymph node. At each sacrifice, the left lung lobe was frozen for later diantimony trioxide analyses and blood samples were collected. Fecal samples were collected at the 18- and 24-month sacrifices.

Survival was not affected by the exposures to diantimony trioxide. At termination, there was 56 % survival of the males and 48 % survival of the females in the control groups with 56-58 % (males) and 40-66 % (females) survival in the exposed groups.

Detailed weekly observations showed a dose related increase in chromodacryorrhea (shedding of bloody tears) in the males, which did not change during the post exposure recovery period (data not shown). This effect was also confirmed during the ophtalmoscopic evaluation. According to the full study report by Bio/dynamics Inc., chromodacryorrhea was not seen in the females. In contrast, Newton and co-workers reported that chromodacryorrhea was also found in the females. Chromodacryorrhea is a sign of discomfort caused e.g. by stress, aging and illness. Thus, in this particular study it is difficult to asses what might have caused the condition. An increase in corneal scars was observed in both the males and females. However, the definitive ophtalmoscopic evaluation found these scars to be nearly equally distributed among all groups, similar to a spontaneous degenerative condition reported in Fischer 344 rats and were therefore not considered to be treatment related. Ophthalmoscopic evaluation at 6 months found compound related ocular irritation but this was not indicated at 12 or 18 months. Ophthalmoscopic examination at 24 months revealed an increase in cataracts (including focal posterior polar cataract, posterior subcapsular cataract and complete cataract) with respective incidences in the control, low-, mid- and high-dose groups of 11, 15, 21 and 18 % in males and 13, 40, 36 and 47 % in females. A microscopic evaluation of the eyes was performed on the animals in the control and the highest dose group. Moderate or severe lens degeneration was observed in 14 and 11 % of the males and in 13 and 33 % of the females for the control and high dose group, respectively. No statistical calculations were presented, but the cataracts in high-exposure-level females was well above normal and judged, by the authors, to be diantimony trioxide exposure related.

No significant differences in body weight gains were observed among the dose groups.

Absolute and relative lung weights were also unaffected in all exposure groups.

No diantimony trioxide related hematologic effects were found. Elevated total leukocyte counts and atypical lymphocytes in some animals in all groups at the terminal euthanization indicated, according to the authors, the presence of leukemia a common finding in aged Fischer 344 rats (authors' comment).

Effects observed in the lungs and peribronchial lymph nodes are shown in Table 8 and

Table 9. Chronic interstitial inflammation (minimal to moderate severity) was observed in the lungs of several control and treated animals during both the exposure and the observation periods. Interstitial fibrosis, granulomatous inflammation and bronchiolar/alveolar hyperplasia

(all of minimal to moderate severity) occurred in a small number of animals during the observation period and was 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 (but not in the control group) during both the exposure and the observation periods. However, the increase in alveolar macrophages may be regarded as a normal pulmonary response to the foreign particles entering the lung.

Other post mortem findings, not further specified, were by the authors considered not to be treatment related.

The diantimony trioxide lung burden data show 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. Thus, the clearance mechanism was significantly impaired at this exposure level and was interpreted by the authors as an intrinsic toxic effect of diantimony trioxide rather than a general effect due to particle overload. This was assumed since the rate of clearance from the lungs of deposited benign or slightly toxic insoluble particles has been reported to be reduced by 50 % at a dust volume of about 1000 nl/lung (Muhle et al., 1990). In the current study a 50 % inhibition of clearance was seen at 400 µg of diantimony trioxide/lung. Volumetrically, with a diantimony trioxide density of 5.5 g/cm^3, this is according to Newton and coworkers (1994) equal to a dust volume of about 270 nl/lung. However, according to the rapporteur, 400 µg of diantimony trioxide is equal to about 73 nl (calculated as 400 µg / 5.5 g/cm^3).

In conclusion, this study indicates that diantimony trioxide exposure causes impaired clearance and chronic interstitial inflammation in the lung. However, there was also a high (62% and 67% for males and females, respectively) frequency of chronic interstitial inflammation in the lung of control animals, indicating that the lung inflammation also had other cause than the diantimony trioxide exposure. However, Newton and co-workers stated that the lung inflammation observed in controls is commonly seen in rats of this age and strain and judged that it did not compromise the health status of these animals and consequently it did not affect the results of the study. An elevated total leukocyte count was also observed in both control and diantimony trioxide exposed animals. The elevated total leukocyte count was by the authors explained by the presence of leukaemia. However, no supportive data for this explanation was presented. A dose related increase in chromodacryorrhea was observed in the males throughout the whole study. Since no data was presented it is not clear if chromodacryorrhea occurred also in the control group. Due to the discrepancy between the two reports on the occurrence of chromodacryorrhea in the females, it is not clear if this effect was also observed in the females. According to the authors, chromodacryorrhea can be secondary to dental abnormality, infectious disease or xerosis in rats. Although not seen in all animals (the teeth were not specifically examined) microscopic periodontal disease was seen in some rats and could according to the authors explain the presence of chromodacryorrhea. However, considering the interstitial inflammation in the lung and the elevated total leukocyte count it cannot be excluded, that the chromodacryorrhea was a result of the pulmonary inflammation. However, the causative agents to chromodacryorrhea are multiple, thus it is not possible to conclude if these animals were suffering from infectious disease or stressful condition in general.

The cataract findings in this study are present in both controls as well as in treated animals. Although cataracts have been reported to occur after oral exposure to other metallic compounds, (Ginsburg and Buschke, 1923; Alagna and D´Aquino, 1956; Schaumberg et al., 2004) there is, in this study, no dose-response relationship and statistical evaluation is lacking

for this observation. Therefore, the cataract finding is inconclusive and will not be forwarded to the risk characterisation.

Table 8. Non-neoplastic microscopic findings seen after a 1-year inhalation exposure period to diantimony trioxide.

	Males				Females			
Dose (mg/m³)	0	0.06	0.51	4.5	0	0.06	0.51	4.5
Number of animals examined	13	13	12	13	16	13	11	14
Effect								
Interstitium: chronic inflammation	10	8	11	12	10	11	10	14
Granulomatous inflammation	0	0	0	1	1	0	0	0
Interstitium: fibrosis	0	0	0	0	0	0	0	0
Bronchiolar/alveolar hyperplasia	0	0	0	0	0	0	0	0
Alveolar/intraalveolar macrophages	6	11	9	13	6	10	8	14
Alveolar/intraalveolar macrophages: foreign particulate material	0	13	12	13	0	13	11	14
Macrophages in the perivascular/peribronchiolar aggregates of lymphoid cells: foreign particulate material	0	2	6	7	0	6	4	7
Peribronchial lymph node macrophages: foreign particulate material	0	3	5	13	0	0	6	13

Table 9. Non-neoplastic microscopic findings related to the 1-year inhalation exposure period to diantimony trioxide seen during the 1-year observation period.

	Males				Females			
Dose (mg/m³)	0	0.06	0.51	4.5	0	0.06	0.51	4.5
Number of animals examined	52	52	53	52	49	52	54	50
Effect								
Interstitium: chronic inflammation	32	37	36	48	33	40	48	48
Granulomatous inflammation	3	2	5	7	2	2	5	3
Interstitium: fibrosis	0	0	1	2	0	1	1	4
Bronchiolar/alveolar hyperplasia	3	1	2	4	1	0	0	6
Alveolar/intraalveolar macrophages	31	44	46	52	28	40	48	50
Alveolar/intraalveolar macrophages: foreign particulate material	0	15	38	51	0	24	49	48
Macrophages in the perivascular/peribronchiolar aggregates of lymphoid cells: foreign particulate material	0	22	46	47	0	31	47	47
Peribronchial lymph node macrophages: foreign particulate material	0	6	34	39	0	6	29	39

A NOAEC of 0.51 mg/m^3 is derived from this study based on impaired lung clearance observed at 4.50 mg/m^3. Although there might be some uncertainty regarding the accuracy of

the LOAEC and NOAEC numerical values, as the study had a high background incidence of lung inflammation in control animals, the NOAEC of 0.51 mg/m^3 is brought forward to the risk characterisation.

The carcinogenic effects of one concentration of diantimony trioxide and antimony ore were evaluated in an inhalation study in Wistar rats, 90 males and 90 females per group (Groth *et al.*, 1986a). This study is also described in section 4.1.2.8., Carcinogenicity. The animals (free of endemic respiratory disease stated by the supplier, Charles River Breeding Labs, Wilmington, Mass.), 8 months of age, were exposed to diantimony trioxide [time-weighted average (TWA) 45 mg/m^3 (range = 0-191.1)], antimony ore [TWA 36-40 mg/m^3 (range = 0-91.1)] or filtered air (controls) in exposure chambers, 7 h/day, 5 days/week for up to 52 weeks. The MMADs for diantimony trioxide and antimony ore were 2.80 and 4.78 µm, respectively (GSD not reported). The Sb content in the diantimony trioxide was 80% and in the antimony ore it was 46%. Major contaminants in the diantimony trioxide were lead (0.23%), tin (0.21%) and arsenic (0.004%) and in the antimony ore they were aluminium (0.48%), iron (0.33%), lead (0.25%), tin (0.16%) and arsenic (0.079%). At 6, 9, and 12 months after initiating exposures 5 animals/sex/group were sacrificed and autopsied, the remainder of the animals were sacrificed 18-20 weeks post-exposure. In addition, all animals that died or were sacrificed due to ill health were autopsied. At autopsy all organs were examined grossly and tissue sections from the lungs, liver, kidneys, pancreas, spleen, adrenal, thyroid, pituitary, bladder, brain, eye, bone marrow, skin, lymph nodes (mesenteric and tracheobronchial), stomach and colon (ascending and descending) from each rat were fixed in buffered 10% formalin, embedded, sectioned and stained with hematoxylin and eosin for examination by light microscopy. Samples from the testes and prostate from males and mammary gland, ovary, uterus and cervix from females were also examined as well as any abnormal tissue. In addition, at the final sacrifice heart tissue was sampled and examined by light microscopy. At sacrifices, portions of liver, lungs, kidneys, brains, spleens and blood from five animals/sex/group were sampled for antimony concentration analysis.

The data indicate that there was no treatment related mortality. The mean body weight of the males exposed to diantimony trioxide and the females exposed to antimony ore was slightly but statistically significantly reduced (6.2% and 6.4%, respectively). Sporadic bleeding from eyes and hematuria occurred in all groups, but appeared to occur more frequently in the Sb_2O_3 and Sb ore groups (data not shown).

The concentration of antimony in the lungs of the male rats (38,300 µg Sb/g dry weight) after 9 months of exposure to diantimony trioxide was significantly higher than in the females (25,600 µg Sb/g dry weight). The concentrations of antimony in the lungs of these groups were considerably greater (males: 5.4 times; females 5.7 times) than in animals exposed to antimony ore. The concentration of arsenic in the lungs of animals exposed to diantimony trioxide was 213 µg/g dw for males and 150 µg/g dw for females. This was considerable more arsenic than measured in the lungs of males and females exposed to Sb ore (in males 21 times as much and in females 10.8 times as much, $p < 0.05$)

Gross pathology at the final sacrifice showed that the lungs of all animals from both exposure groups had slightly elevated, confluent, white and yellow foci on the pleural surfaces of all lobes.

Histopathological examination of the lungs at 6 months showed that the lungs from the female rats exposed to Sb_2O_3 contained particles evenly scattered throughout all lobes of the lung and

in more than 90% of the alveoli. Several dense particle aggregates about the size of macrophages were present in about 10 % of the alveoli. Individual macrophages were obscured by the particles. In some alveoli the particles were embedded in dense, pink, homogeneous protein. Alveolar-wall thickening, consisting of interstitial fibrosis, alveolar-wall cell hypertrophy and hyperplasia appeared in about 50% of the alveolar duct regions, affecting about 5-10% of all alveoli. Cuboidal and columnar cell metaplasia occurred in some of these foci. All these effects increased with the time of exposure. In addition, foci containing cholesterol clefts were seen. At the sacrifice, 4-5 months postexposure, the density of particles and amount of protein in the alveoli had significantly decreased. However, the extent of interstitial fibrosis had increased. In some rats it affected over 80% of the alveoli. The number of foci containing cholesterol clefts had also increased and in some rats dense scars that appeared to be confluent areas of interstitial fibrosis were present. At 6 months, the lungs of male rats exposed to Sb_2O_3 had the same amount of interstitial thickening as the female rats, however, there was less alveolar protein. At 12 months, the severity of the interstitial fibrosis was the same as in the females. In some interstitial areas, there was, in addition, dense eosinophilic material. The cuboidal, alveolar-wall cell metaplasia was, however, not as extensive as in the females and there were fewer foci with cholesterol clefts. At 4 months post-exposure a diminution in the amount of alveolar-wall metaplasia was observed and it was less severe than that observed in females. There were fewer foci with cholesterol clefts and less alveolar protein. In interstitial spaces there were more mononuclear cells, lymphocytes and plasma cells than observed in the female rat lungs. The extent and severity of the interstitial fibrosis was the same as in the females. The histopathology of the lungs in female rats exposed to Sb ore was similar to that seen in Sb_2O_3-exposed females, except that there were fewer particles and less alveolar protein visible at all sacrifice intervals. In addition, they contained mononuclear cell granulomas similar to those that are seen in the early stages of silicosis or sarcoidosis. In Sb ore exposed males the alterations in the lungs were similar to those seen in Sb_2O_3-exposed males. None of these effects were seen in the control animals. No other exposure-related non-neoplastic effects were observed.

According to the authors, no significant pathological alterations were seen in any of the control lungs. Occasional foci containing lymphocytes, typical of chronic pneumonia, were seen in a few rats.

In conclusion, even though all animals were free of endemic respiratory disease at the start of the study, occasional foci containing lymphocytes, typical of chronic pneumonia, were seen in a few control rats. In addition, sporadic bleeding from eyes and hematuria occurred in all groups, but appeared to occur more frequently in the diantimony trioxide and antimony ore groups. These findings may indicate that some animals had some non-treatment related sickness. However, the lung changes described after diantimony trioxide and antimony ore exposure was not observed in the control group and therefore it can be assumed that the lung effects observed were treatment related and a LOAEC of 45 mg/m^3 is suggested from this study based on pleural plaques, lung fibrosis and cholesterol clefts.

A chronic inhalation toxicity study of diantimony trioxide has also been performed in female rats and miniature swine (Watt, 1983). 148 female Fischer rats from the Charles River Laboratories, 14 weeks of age, were divided into three groups (the number per group was not specified) and exposed to 0, 1.9 ± 1.8 and 5.0 ± 3.8 mg diantimony trioxide /m^3 for 6 h/day, 5 days/week for one year in whole body exposure chambers. Similarly, eight female Sinclair S-1 miniature swine were divided into control (n = 2), low dose (n = 3) and high dose (n = 3) groups and exposed in the same way as the rats. The exposure concentrations have been

recalculated from the values in the study report as they were reported as Sb, 1.6 ± 1.5 and 4.2 ± 3.2 mg Sb/ m^3 respectively. Control animals were treated the same as exposure animals, that is, moved to exposure chambers during each exposure period. Rats and swine of the same exposure group were exposed in the same chamber; the swine free on the floor and the rats in pairs in cages suspended from the walls of the chamber. Air samples were taken within the exposure chambers at the same level as the suspended rat cages. The diantimony trioxide used was 99.4% pure with arsenic (0.02%) and lead (0.2%) as the major contaminants. Only particles with mean aerodynamic diameter of 15 μm or less would pass into the chamber. The particle size (Ferret's diameter) was 0.44 and 0.40 μm for the low and high concentrations (GSD 2.23 and 2.13, respectively). Surviving animals were kept up to 15 months post-exposure.

Prior to and after 3, 6, and 12 months of exposure animals were evaluated for evidence of toxicity and blood samples were taken. The rats were also evaluated at approximately 9 months exposure. The rats were anesthetized ip with Surital or V-Pento and sacrificed through exsanguinations. The swine were anesthetized with V-Pento and sacrificed at the end of the exposure period by anesthetizing with V-Pento and opening the chest cavity. Differential count, red and white blood cell count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin and mean corpuscular hemoglobin volume, serum enzymes and chemistry were determined in both rats and swine. Animals were weighed periodically throughout the exposure. At sacrifice, the heart, lung, liver, spleen and kidney were weighed and fixed in 10% buffered formalin for subsequent light microscopic examination. Prior to exposure, at 6 months and at the end of exposure the swine were subjected to roentgenograms and electrocardiograms.

No exposure-related effects on survival, haematology or clinical chemistry were noted in either rats or swine. Roentgenograms and electrocardiograms showed no abnormalities. T-waves generally had a negative deflection, but no change in amplitude was observed, throughout the study, which according to the authors is normal for miniature swine. The body weights of the exposed rats were significantly higher than the controls at pre-exposure and throughout the exposure period. At the end of exposure and post exposure there was no significant difference in body weights between exposed and control rats. No effect was observed on swine body weight. There was no effect on organ weights except for lung. For the rat, the lungs were significantly heavier than the controls at nine months in the high dose group and at 12 months in both exposure groups. No significant difference was observed at one year post exposure. The swine lungs show the same dose-response pattern after 12 months of exposure, however, the differences were not statistically significant. No exposure related histopathological alterations were observed in the swine. However, a number of effects were observed in the lungs of exposed rats (Table 10). These included focal fibrosis, adenomatous hyperplasia, multinucleated giant cells, cholesterol clefts, pneumonocyte hyperplasia, and pigmented macrophages. The severity of the effects increased with both time and exposure concentration. Postmortem findings that appeared to be treatment related included discoloration and increased pulmonary alveolar-intralveolar macrophages in both exposure groups and focal subacute-chronic interstitial inflammation and granulomatous inflammation in the high-exposure group.

Focal fibrosis was the earliest non-neoplastic effect, observed already after three months in the high-dose group. The effect was time- and dose-dependent. After one year of exposure, focal fibrosis was seen in 10/21 animals of the low dose and 17/20 animals in the high dose group.

Table 10 Non-neoplastic microscopic alteration seen after inhalation exposure to diantimony trioxide.

		Focal fibrosis			Pneumocyte hyperplasia			Adenomatous hyperplasia			Multinucleated giant cells			Cholesterol clefts		
Group	Death or sacrifice	Control	Low	High	Control	Low	High	Control	Low	High	Control	Low	High	Control	Low	High
A	Pre-exposure	0/3	0/1	0/0	0/3	1/1	0/0	0/4	0/1	0/0	0/4	0/1	0/0	0/4	0/1	0/0
B	From start through 5 months of exposure	0/2	0/4	1/3	0/2	3/4	3/3	0/2	0/4	0/3	0/2	0/4	0/3	0/2	0/4	0/3
C	From 6 through 9 months of exposure	0/4	0/3	3/3	0/4	3/3	3/3	0/4	0/3	0/3	0/4	0/3	2/3	0/4	1/3	3/3 *
D	From 9 through 12 months of exposure	0/4	1/5	5/5 ***	4/4	5/5	4/5	0/4	0/5	5/5 ***	0/4	0/5	5/5 ***	0/4	2/5	5/5 ***
E	At the end of exposure (12 months)	0/9	9/9 ***	8/9 ***	0/9	8/9 **	9/9 ****	0/9	1/9	6/9 ***	0/9	4/9 **	8/9 ****	0/9	9/9 ****	8/9 **
F	Between 2 and 12 months post-exposure	0/6	4/5 ***	7/7 ***	0/6	2/5	5/7 **	0/6	0/5	5/7 **	0/6	2/5	5/7 **	0/6	2/5	4/7
G	12 to 15 months post-exposure	1/13	12/17 ****	17/18 *****	0/13	12/17 ****	12/18 ****	0/13	0/17	13/18 ****	0/13	5/17 *	11/18 ****	0/13	9/17 ***	14/18 ****
Total A-G		0/41	26/44	41/45	4/41	34/44	36/45	0/42	1/44	29/45	0/42	11/44	31/45	0/42	23/44	34/45

Statistically different from control: *p<0.05; ** p< 0.02; *** p< 0.01; **** p< 0.001; *****p<0.0001

A variety of neoplastic and non-neoplastic changes were observed in other tissues, most notably mammary glands, but they were not considered treatment-related since their incidence and severity were comparable among all groups. No exposure-related effects were observed in the swine.

A re-evaluation 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 may have been above those reported, but the difference could also be due to different particle generation techniques or different strains of rats. Although there is some uncertainty with regard to the actual exposure concentration, due to the occurrence of pulmonary effects in rats exposed 6 hours per day, 5 days a week for one year in this study, a LOAEC of 1.9 mg diantimony trioxide /m^3 is derived. This is based on findings indicative of endogenous lipoid pneumonia (focal fibrosis, pneumocyte hyperplasia, presence of giant cells and cholesterol clefts) observed in animals in this and the higher dose group.

A group of 24 guinea pigs were exposed to diantimony trioxide dust via inhalation for 2 h per day, seven days a week, during the first three weeks, thereafter for 3 h per day for additional 27 weeks (Dernehl *et al.*, 1945). Eleven control animals were included. However, the way of treatment was not stated. Diantimony trioxide was generated by heating the metal at 700°C in the presence of large quantities of air. The fume was reported to contain 99.8% diantimony trioxide with a particle size of 1 μm or less. The average diantimony trioxide dust concentration in the exposure chambers was 45.5 mg/m^3, determined gravimetrically by means of an electrostatic precipitator. Fluctuations in dust concentration were reported to occur. No food was provided during the 2-3 hour diantimony trioxide exposure period. The animals were sacrificed, after a 12 h fasting period, at various time points, corresponding to exposures between 33 and 609 h. The laboratory studies included weight changes, blood changes and gross and microscopic pathology of the heart, lungs, liver, kidneys, spleen and gastro-intestinal tract.

Four of the treated animals died during the experiment (in week 10, 16, 17 and 21, respectively). These animals were exposed for 184, 298, 321 and 402 h. In each instance death occurred suddenly after a week or more of illness. A reduced weight gain was observed in treated animals. However, this was not related to diantimony trioxide exposure (data not shown). Blood cell counts in the six animals that were most heavily exposed showed a decrease in the overall number of white blood cells, a decrease in the relative amount of polymorphonuclear leucocytes and eosinophiles but a relative increase in lymphocytes and monocytes. No statistical details were provided. Red blood cell counts and haemoglobin was normal. An increase in the relative weight of liver and lung were observed in the treated animals. 95% of the livers from treated animals were above the average control liver weight and 50% were above the maximum control liver weight. Similarly, 84% of the lungs from treated animals were above the average control lung weight and 79 % were above the maximum control lung weight. However, no exposure time-dependent relationship was evident. No statistical calculations were presented but from the data presented for the liver on "% increase over average control weight" the calculated average liver weight increase was 30.0 ± 17.1%. The calculated average liver weight increase over maximal control liver weight was 14.6 ± 9.2.

Microscopy of all exposed animals revealed a thickening of the alveolar wall as found in interstitial pneumonitis, the severity ranged from areas of simple thickening to areas in which the process had practically obliterated the alveoli. According to the authors normal guinea pig lung often presents a mild pneumonitis, however, not as extensive or as severe as that found in the exposed animals. There was a hypertrophy of the pulmonary lymphoid tissue and particles of diantimony trioxide were visible in phagocytes in interstitial tissue spaces. Edema was also observed. Pneumonia was observed in 2 of the animals that died and 3 additional animals, of which one died, showed small areas of organizing pneumonia. The pneumonias were intensely hemorrhagic. Pneumonia was not noted in the controls. The lungs of the 15

animals exposed for 138 h or more were reported to show scattered sub-pleural petechial hemorrhages. Fatty degeneration of the liver occurred in 11 (45.8% of all treated animals) of the 15 animals having exposure for 138 h or longer. Only one of the 11 control animals (9%) showed any evidence of fat in the liver. In most cases the greatest concentration of fat was around the central vein with lesser quantities surrounding the portal vein and a relatively clear zone intervening the two. Two of the animals dying with pneumonia presented extensive fatty degeneration involving all three zones. The spleen showed hyperplasia of the lymph follicles in 50% of the cases. There was an abnormal amount of blood pigment present in 62% of the cases. In addition, phagocytes loaded with diantimony trioxide were present in small numbers. 50% of the spleens examined showed a marked reduction or absence of polymorphonuclear leucocytes. No abnormalities in either heart or kidney were observed.

This study indicates that diantimony trioxide may cause pulmonary toxic effects, liver weight increase, fatty degeneration of the liver and death in guinea pigs after repeated exposure of 45.5 mg diantimony trioxide/ m^3. However, since data for individual control liver and lung weights were not reported the study is regarded inconclusive and will not be used in the risk characterisation.

An inhalation toxicity study of diantimony trioxide was performed in rats and rabbits (strain and sex were not stated) (Gross *et al.*, 1955b). Diantimony trioxide was suspended in water, dispersed by a compressed air atomizer and heat dried. The dust-laden air was passed through an impinger which trapped particles larger than 1μm before being blown into inhalation chambers. The average particle size was 0.6μm as determined by electron microscope. 50 rats were exposed to 100-125 mg/m^3 for 14.5 months (100h/ month) and 20 rabbits were exposed to 89 mg/ m^3 for 10 months (100h/ month). No control animals were used. Beginning at two months and at varying intervals (not further specified) thereafter, groups of animals were killed. The lungs of these animals, as well as of those, which died of spontaneous pneumonia, were expanded with formalin.

Nine (18%) rats and 17 (85%) rabbits died spontaneously in the inhalation chambers. The predominant cause of death was bacterial pneumonia and it affected the rabbits to a higher degree than the rats. The lungs, in rabbits beginning with the fifth month and in rats from the ninth month, were mottled with chalk-white foci 1-2 mm in diameter upon the pleura and cut surface. The latter was also coarse-textured and dry. The white mottling of the lungs increased in intensity with longer exposure. Microscopically, the inhaled fine diantimony trioxide dust was early associated with swelling, proliferation and desquamation of alveolar macrophages. The dust was found within alveolar macrophages and as densely agglomerated deposits in the peribronchial and perivascular stroma. With longer exposure, fatty degeneration of macrophages became a prominent feature. This culminated in necrosis, cell rupture and a progressive increase in the alveolar lipid content. Finally, colourless, needle-shaped crystals formed in the air spaces. These crystals, soluble in fat solvents and giving a positive Lieberman-Burchard reaction for steroid, were found in sheaves and singly. Large numbers of coarse and fine sudanophilic droplets were demonstrable within macrophages and also in the alveolar debris. This debris contained finely dispersed diantimony trioxide. Collagenous thickening of alveolar walls and interstitial thickening occurred early and were preceded by increased tortuosity, arborescence and thickening of reticulum fibers. Such fibrosis, initially minimal became more extensive with increasing exposure. In the rabbit lungs the interstitial pneumonia was more pronounced than in rat lungs, and characterised by great widening of the alveolar septa. Initially this widening was caused by edema fluid. Later, septal histiocytes

increased in size and number and collagen fibers between the capillary and respiratory membrane made the septal thickening permanent. There was no indication of fibrosis in the pulmonary lymph nodes of neither rats nor rabbits, in spite of frequently considerable deposits of diantimony trioxide.

A high incidence (not further specified) of spontaneous deaths from bacterial pneumonia in the inhalation chambers was reported.

In conclusion, considering the reported high incidence of spontaneous deaths from bacterial pneumonia and the absence of control animals the study is considered inconclusive and it is not clear to what extent the diantimony trioxide exposure has contributed to the overall pathology of the lung. This study will not be used for the risk assessment of diantimony trioxide.

In a briefly described inhalation lung toxicity study, two groups of albino Sprague Dawley, C.D., rats were exposed to dust of diantimony trioxide or powdered antimony ore (Cooper *et al.*, 1968). Only the results from the diantimony trioxide exposure will be presented here. The group exposed to diantimony trioxide consisted of 10 male and 10 female rats, approximately 84 days old and weighing from 342 to 425 g (males) and 227 to 276 g (females). A specially constructed exposure chamber was used whereby only the nose of the animal came in contact with the aerolised diantimony trioxide at a concentration of 1700 mg antimony/m^3 of air. This corresponds to an exposure of 2000 mg diantimony trioxide/m^3. The purity or the particle size of the substance was not stated. All animals received 1 to 6 exposures, of 1 h each, every 2 months, during a period of time ranging from 66 to 311 days. Animals were sacrificed periodically for study of gross and microscopic pathology.

Initially, at 66 days after the first series of 1 h exposures the pulmonary pathology consisted of a phagocytic response. The dust-laden phagocytes were generally lying free within the alveolar spaces or they were intermingled with cells of the septa. In some situations there was a tendency for the cells to focalise the dust into small deposits throughout the lung. At more prolonged intervals of time after the first and subsequent exposures, this focalisation became increasingly prominent. At 311 days the phagocytic response persisted, without any appreciable chronic pneumonitis, neither cellular, collagenous nor fibrotic.

Non-pulmonary tissue, such as the tracheobronchial lymph nodes remained soft and without abnormal enlargement. Microscopically, they exhibited scattered deposits of intracellular antimony, attended by mild hyperplasia but without evidence of chronic inflammation. The spleens disclosed microscopic presence of scattered dust particles accompanied by a moderate proliferation of reticuloendothelial elements. There was no hepatic and renal pathology of significance (no data shown).

This study showed that repeated inhalation exposure of 2000 mg diantimony trioxide/m^3, 1 to 6 exposures, of 1 h each, every 2 months, during a period of time ranging from 66 to 311 days in rats caused pneumoconiosis without signs of chronic inflammation. However, since the purity of the diantimony trioxide given was not stated and the dosing regime was very different from current standard the study will not be used to derive a LOAEC.

The developmental toxicity properties of diantimony trioxide were recently investigated in a repeated inhalation toxicity study in rats, which is also presented in section 4.1.2.9., Toxicity

for reproduction (MPI, 2003). The study was conducted in accordance with Standard Operating Procedures and was based on a draft guideline published in the US EPA Health Effects Test Guidelines and the OECD Guideline Number 414.

Mated females were exposed to diantimony trioxide via nose-only inhalation from Day 0 (fertilization) to Day 19 (one day prior to scheduled euthanasia and laparohysterectomy) of gestation (6h/d) at concentrations of 2.6 (SD ± 2.43), 4.4 (SD ± 3.88), and 6.3 (SD ± 4.18) mg/m^3. A purity of Sb_2O_3 of 99.87% is stated. Control females received clean air by the same procedure and dosing regime as the treated females. Dust aerosol atmospheres of the test article were generated into the breathing air of the treated animals using a Wright Dust feeder. A chamber airflow of at least 0.6 liter per minute per animal resulted in at least 10 chamber air changes per hour. The mass median aerodynamic diameters (MMAD) and geometric standard deviations (GSD) ranged from 1.59 to 1.82 μm and 1.713 to 1.744, respectively. Observations of the dams included clinical signs, conducted daily following exposures, gestation body weights and gestation food consumption. Blood samples were collected from 10 dams/treatment group and the Sb concentration in RBC was determined. A complete necropsy was performed on all dams. The lungs and brain were weighed and the lungs then infused via the trachea with 10% neutral buffered formalin. Based on organ weight changes, the lungs of 10 females/group randomly selected were processed for histopathological examination.

All animals survived to scheduled euthanasia on Day 20 of gestation. The food consumption in the 4.4 and 6.3 mg/m^3 groups was statistically higher than controls over GD 15-18, 18-20 and 0-20. These increases in food consumption corresponded with slight increase in body weight gains over these same intervals, but the differences in weight gain compared to controls were not statistically significant and according to the author not considered toxicologically meaningful. The mean antimony level in RBC were (without a clear dose-response relationship) statistically higher than controls in each of the treated groups, 0.128 ± 0.0286, 3.275 ± 1.0391, 3.078 ± 0.5624 and 5.591 ± 1.3248 μg/g for the dose groups 0, 2.6, 4.4, 6.3 mg/m^3, respectively. A dose-related increase in lung weights, absolute and relative to brain weights, was seen in the diantimony trioxide-treated groups. These differences in lung weights from controls were statistically significant and considered indicative of a treatment-related response. The absolute lung weights were 24.2%, 31.1% and 38.6% heavier than control in the 2.6, 4.4, and 6.3 mg/m^3 groups, respectively. Lung weights relatively to brain weights were 20.3%, 26.3%, and 34.8% heavier, respectively. Test article-related microscopic findings were observed in the lungs of all animals evaluated at all exposure levels with a diffuse accumulation of pigmented alveolar macrophages, reflecting accumulation and phagocytosis of the test article particulate matter. Pulmonary alveoli contained variable numbers of macrophages with abundant eosinophilic cytoplasm with minimal to moderate quantities of brown granular pigment, as well as small to moderate quantities of extracellular eosinophilic proteinaceous material containing similar pigment. Throughout the lungs, scattered foci of acute inflammation (0/10, 7/10, 4/10 and 6/10 in control, 2.6, 4.4, and 6.3 mg/m^3 groups respectively) and type II cell hyperplasia (0/10, 5/10, 4/10 and 5/10 in control, 2.6, 4.4, and 6.3 mg/m^3 groups respectively), were observed. Accumulations of pigmented macrophages and associated inflammation were likely the cause of the increased lung weights of treated animals compared to controls. The microscopic finding of increased numbers of alveolar macrophages containing foreign material noted in the current study is similar to findings observed in previous subacute and chronic inhalation studies of diantimony trioxide in Fischer rats. However, as would be expected, the inflammation and type II cell hyperplasia noted in the current study was generally of acute to subacute duration as opposed to the

granulomatous inflammation and interstitial fibrosis observed in the previous studies by Watt, Groth *et al.* and Newton *et al*. (Watt, 1983; Groth et al., 1986a; Newton and Daly, 1990).

In conclusion, this study showed a dose related increase in lung weight and a diffuse accumulation of pigmented alveolar macrophages, probably reflecting accumulation and phagocytosis of the test article particulate matter in the dams. Also, scattered foci of acute inflammation and type II cell hyperplasia were often observed. It should also be noted that the exposure doses in this study were almost the same in the three dose groups. This is also reflected in the mean level of antimony in RBC, which did not show a dose dependent increase. The concentration of antimony in RBC was almost the same in the two lowest groups and barely twice as high in the highest dose group. This indicates that three different dose groups were not achieved in this study, which is the minimum number of dose groups recommended in The OECD guideline 414.

A LOAEC for local toxicity in the lungs of 2.6 mg/m^3 is suggested from this study based on acute pneumonia with significantly increased lung weight, 24.2 and 20.3% higher than control for absolute and relative weights respectively.

Studies in humans

The human repeated dose studies reported below are case reports on workers employed in industries manufacturing diantimony trioxide. The workers were probably subjected to inhalation, dermal and oral exposure, although it can be assumed that exposure via inhalation was the dominating route.

In a case study, illness among workers of a mining company engaged in the mining, concentrating and smelting of an antimony sulphide ore was reported (Lucian and Renes, 1953). The illness was found among workers engaged in the smelting operations and among maintenance workers who spent a substantial part of their time in the smelter building. During the first five months of operation, there were 78 men who had worked two weeks or longer in the smelter building. Sixty-nine of these workers made 218 visits to the plant physician for reasons of occupational illness. Air samples were collected during the sixth months, when the conditions were substantially the same as during the previous five months, and analysed for the presence of antimony and arsenic. The smelter was divided into two zones, the electric furnace area and the cupel area. The average zone concentration of antimony was 10.07 and 11.81 mg per m^3 of air, respectively for the two zones. The average zone concentration of arsenic was 1.10 and 0.36 mg per m^3 of air, respectively for the two zones.

The frequency of various types of symptoms and illnesses observed each month was relatively constant, however with increasing length of employment in the smelter, there was a progressive increase in the number of severe illnesses, like nasal septal perforations, laryngitis, tracheitis and pneumonitis. The following percenatage distribution of the diagnoses made during the first five months was; bronchitis (7%), conjunctivitis (4%), dermatitis (20%), gastritis (3%), gastroenteritis (5.5%), laryngitis (11%), neuritis (1%), pharyngitis (8%), pneumonotis (5.5%), rhinitis (20%), secondary sinusitis (1.5%), septal perforations (8.5%) and tracheitis (10%). Chest x-rays taken of six men who were acutely ill from heavy exposures to smelter fumes showed definite pneumonitis extending fanwise from each hilus. Among workers who had heavy exposures to smelter fumes seemingly systemic toxic effects, such as abdominal cramps, diarrhea, vomiting, dizziness, nerve tenderness and tingling, severe headaches and prostration. Antimony was detected in urine in seven out of nine

workers and arsenic was found in the urine of one worker (the number of urine samples taken were not stated). Laryngitis, with voice changes among affected workers, ranged from hoarseness to inability of speech. The dermatitis that developed among the workers was observed in sweaty, hairy, friction areas, such as axillae, groin and back of the neck. These were nodular ulcerative lesions. The occurrence of dermatitis was sporadic and most of the cases occurred during one week in the second month of operation, presumably after the workers had been very heavily exposed to fumes.

Of the subjective symptoms reported by the workers, soreness and bleeding of the nose were experienced by more than 70% of the workers. Sore throat, hoarseness, burning or redness of the eyes, metallic taste in the mouth, pain in the chest, headache and shortness of breath were the second most frequent complaints and were noted by about 25% of the workers. About 10% of the workers complained about weight loss, nausea, vomiting, diarrhoea, inability to smell properly and tightness in the chest. Less frequent complaints were spitting of blood, abnormal urination, abdominal cramps, muscle soreness, insomnia and blurred vision.

This case study indicates that occupational exposure to antimony may result in upper respiratory irritations, pulmonary inflammation, skin lesions and systemic reactions. Although exposure to arsenic also occurred, no early signs of arsenic intoxication, such as increased pigmentation of certain skin areas, keratoses of the palms and soles, loss of hair and nails, garlic odour of the breath and perspiration or swelling of ankles were observed. No detailed exposure data were presented, therefore this study cannot be used for quantitative risk assessment.

Examinations, including radiography, were performed at the work place on 101 workers employed for at least 3 years in an antimony sulphide ore smelting plant in Serbia (Karajovic, 1957). The report is in German and an English summary is available. Upon chemical analysis of produced dust it was shown to contain 35-90 % Sb_2O_3, 1-6 % Sb_2O_5, 1-4 % Fe_2O_3 and 0.3-9 % As_2O_3. The working conditions were reported to be “not at all ideal”. Subjective symptoms that were reported were light respiratory difficulty, tiredness, myalgia, light coughing, and light dyspepsia without pain or diarrhoea.

Lung radiography was performed on 62 workers. 31 workers were found to have lung changes. Reported were also 22 cases of emphysema with bronchitis, 51 cases of catarrh in the upper respiratory tract, 16 cases of deviation of the nasal septum, 12 cases of conjunctivitis and 16 cases of antimony dermatosis. The antimony dermatosis was characterised by vesicular or pustular lesions with residual scars and hyperpigmentation, especially during the summer season and 13 of the cases were working near the furnace where temperatures were high.

No effects were observed on the gastrointestinal tracts, the liver, the cardiovascular system or the central or peripheral nervous system, which according to the authors indicated that there were no systemic toxic effects.

20 of the examined workers who had definite or suspected pneumoconiotic symptoms were taken to the clinic for more detailed examinations. The same subjective and objective findings as found during the first examination were also found in the selected group. eight workers were reported to have pneumoconiosis simplex, four of these had lighter lung ventilation insufficiency. No cases of progressive pneumoconiosis were found. There were no effects on the heart and the EKG was normal.

This study indicates that exposure to diantimony trioxide may cause pneumoconiosis, emphysema, irritation to the eye, respiratory tract and the skin. However, data on exposure are lacking and no control group was included in the study. Therefore, this study cannot be used for quantitative risk assessment.

In a briefly reported study, men working at a plant near Newcastle in United Kingdom with the production of antimony oxide and the pure metal from sulphide ore by various smelting processes were radiographed (McCallum, 1963). A number (not further specified) of the workers had radiographic lung changes, resembling the simple pneumoconiosis of coal workers. These changes appeared to be symptomless and were first noticed in men who were radiographed during another investigation. Observation of these men did not show any alteration in the radiological opacities, but two men developed tuberculosis lesions, which responded promptly to chemotherapy. The only man with pneumoconiosis who had respiratory symptoms had chronic bronchitis with respiratory obstruction. Duplicate air samples were taken in different areas of the factory and mean values of antimony in air ranged between 0.53 and 5.3 mg antimony/ m^3 in most of the workplace areas. Concentrations as high as 36.7 mg antimony/ m^3, on an intermittent basis, were recorded in the metal tapping area.

This study supports that lung changes resembling pneumoconiosis occurs in humans occupationally exposed to diantimony trioxide. However, due to lack of specific exposure data this study cannot be used for quantitative risk assessment.

In a more comprehensive radiological investigation of workers from the plant near Newcastle in United Kingdom, 274 men were examined by using macro-radiographs to show magnified areas of the lung fields (McCallum, 1967). 26 new cases of antimony pneumoconiosis were discovered. Another 18 men with antimony pneumoconiosis were already under clinical observation. All the antimony pneumoconiosis was of the simple type. Clinical examination and lung functioning tests (not further specified) did not reveal any other harmful effects of inhalation of diantimony trioxide. Histological examination of the lungs of antimony workers (number not stated, but probably few since it was indicated that such material was scarce) suggested that there was little or no reaction to antimony dust in the lungs. Histological sections of the lungs of an antimony worker who died from carcinoma of the lung showed an accumulation of dust particles and dust laden macrophages lying in alveolar septa and in perivascular tissues without fibrosis or an inflammatory reaction.

This study supports that lung changes resembling pneumoconiosis occurs in humans occupationally exposed to diantimony trioxide. However, no exposure data were reported and no control group was included, therefore this study cannot be used for quantitative risk assessment.

Male workers in Pennsylvania, USA exposed to the dust of antimony ore and diantimony trioxide during their job of converting crude ore into diantimony trioxide were examined (Cooper *et al.*, 1968). The reason for doing the investigation was that fine small opacities was observed throughout both lung fields in a 33 years old, male worker who had worked for 10 years converting crude ore into diantimony trioxide. This worker also reported that the refined powder irritated his nose and caused nosebleeds at times. The number of employees at the

plant since 1960 had been 34 but 6 worked only for a few months and were excluded from the examination. The ages ranged from 25-61 years and the duration of exposure ranged between 1-15 years (not further specified). The antimony concentration in air, measured at different locations was 138 mg/m^3 in the bagging area, 11-75 mg/m^3 in ten other locations, 1.0-9.8 mg/m^3 in thirteen other locations and 0.081-0.95 mg/m^3 in another thirteen locations. Data on antimony in urine are presented for all except one worker and the range is 0-1020 µg antimony/ 1000 ml urine.

Chest x-ray was performed on 13 workers. Three cases with antimony pneumoconiosis and five with suspicious findings were observed. In the group as a whole, very little time had been lost for sickness. No tuberculosis had been observed in the antimony workers. Pulmonary function studies, including vital capacity, lung volumes, minute ventilation, tidal volume, mixing efficiency, maximum-mid expiratory flow rates, forced expiratory volume in one second, maximum breathing capacity and diffusing capacity, were performed on 14 subjects. Arterial blood oxygen, carbon dioxide pH and plasma bicarbonate were determined at rest and after exercise. No consistent pattern of abnormalities in lung function was observed but isolated findings were noted in some (not further specified). Of those with abnormalities of pulmonary function, one had definite small opacities, one had very early changes and two had no changes in the lungs. The remaining three subjects with either suspicious or definite pneumoconiosis all had normal pulmonary function. Electrocardiograms were done on seven workers, three of whom had antimony pneumoconiosis. six workers had normal tracings and one showed a slight bradycardia

This study indicates that occupational exposure to diantimony trioxide may give rise to pneumoconiosis and isolated cases of abnormal lung function. Bradycardia and irritated and nosebleeds was also reported. Due to the lack of individual exposure data the study cannot be used for quantitative risk assessment.

The lung function and radiological characteristics was investigated in 51 male workers employed in an antimony smelting plant in Serbia (Potkonjak and Pavlovich, 1983). This study is also described in the 4.1.2.3. Irritation section. The subjects were aged between 31 to 54 years old with an average age of 45 years and had worked in the plant for 9 to 31 years. All had experienced pneumoconiotic changes. They were exposed to airborne dust containing predominantly antimony oxide [Sb_2O_3 (38.73-88.86%), Sb_2O_5 (2.11-7.82%), SiO_2 (0.82-4.72), Fe_2O_3 (0.90-3.81%) and As_2O_3 (0.21-6.48%)]. No information on antimony air concentration is given. Over a 25-year period they were examined 2-5 times; the evaluation included a physical examination (specialist consultations were obtained when appropriate), laboratory analysis (erythrocyte sedimentation rate, blood differential count, hemoglobin, hematocrit and urin analysis), postero-anterior chest X-ray and pulmonary function studies. Arterial blood gases were measured at rest and after exercise.

The X-rays of the 51 men showed sporadic and singly disseminated small, dense, roundish or polygonal opacities of pinhead type, diameter usually less than 1.0 mm, in 34 workers (67%); numerous small, pinhead type opacities densely distributed in the mid-lung regions of seven workers (14%); a markedly high profusion of pinhead type opacities in the entire lung field of 9 workers (17%) and a markedly high profusion of larger (1-3 mm), often irregular, opacities in the entire lung field of one worker (2%). No case of confluent massive fibrosis was observed. Other findings included enlarged, dense hilar shadows and emphysematous changes in the upper and lower regions (34.5%); active tuberculous lesions (i.e. non-calcified) were seen in one case and their identity was confirmed by laboratory examination; inactive

tuberculosis in 18.2%; peribronchial changes were noted in 17 workers (33%). The pneumoconiotic changes were only seen in smelters who were exposed to the antimony oxide dust for more than 9 years (data not shown).

Clinical respiratory symptoms and signs observed were permanent breathlessness in effort in seven cases (16%), periodical breathlessness in effort in 26 cases (50%), coughing with expectoration (chronic bronchitis) in 19 cases (37%), coughing without expectoration in twelve cases (24%), wheezing in twelve cases (24%), generalised weakness in 13 cases (26%), chest tightness or pains in 13 cases (26%), whistling brhonchi in twelve (24%) and snoring, coarse brhonchi in 14 (27%). According to the authors the prevalence of chronic coughing was markedly high whereas the other pulmonary symptoms and signs showed no particularity - they were found as often in patients with other simple pneumoconioses. Pulmonary function tests showed obstructive changes of the forced expiration volume in 17.6%, light abnormality of airway resistance in 17.2% and moderate to severe airway resistance in 9.1%. Small airway obstruction as manifested by forced expiratory flow rates was recorded in 16.7%, bronchospasms was seen in 4.4% and hyperinflation was noted in 34.5%. Arterial blood gases were normal during rest and after exercise; hypoxia was noted in 2 subjects only. Expired gases had normal O_2 and CO_2 concentrations. Non-homogenous alveolar ventilation was found in 31%. Abnormal CO transfer was observed in two cases.

Conjunctivitis was seen in 14 cases (27.5%) and upper airway inflammation in 18 cases (35.3%). It is not clear from the report if the group with upper airway inflammation was included in the group with chronic bronchitis. “Antimony dermatosis” characterised by vesicular or pustular lesions with residual hyperpigmentation were present in 32 workers (63%), especially during the summer season and when working near the furnace where temperatures were excessively high.

No systemic toxicity with regard to the cardiovascular, hepatic, hematopoietic, renal or central or peripheral nervous system was noted, except for musculo-skeletal complaints which were noted without any objective signs of pathology.

This study shows that pneumoconiotic changes (the frequency was not stated) in smelters can be observed after 9 years of exposure and more frequently after 10 or more years. The pneumoconiosis, which was called antimoniosis, was characterised by numerous small opacities of pinhead type, densely distributed in the middle and lower lungfields. Emphysema was observed in 34.5% but massive fibrosis was not seen in any case. Changes in lung function were observed, however, no consistent pattern could be ascertained. Chronic coughing, chronic bronchitis, conjunctivitis and dermatitis were clinical signs but no systemic toxicity was observed.

Lesions of the respiratory tract and the lungs caused by diantimony trioxide have been reported in workers involved in antimony processing metallurgical works in Slovakia (Klucik *et al.*, 1962). The paper is in Czech but a summary in English is available. The workers were exposed to smoke and diantimony trioxide dust and in a limited degree to a concentration of antimony trisulphide for periods ranging from a few years (not further specified) to 28 years. The number of workers examined and their age was not stated. 99.2% of the diantimony trioxide dust particles and 95% of the antimony trisulphide concentrate particles were smaller than 5μm; the average size of the diantimony trioxide particles was 1.03 μm and that of the antimony trisulphide particles 1.84μm.

Rhinitis (54.3%), perforation of the septa (33.2%), pharyngitis (76.5%), bronchitis (54.3%), pneumoconiosis (20.8%) and symptoms of emphysema (41.9) was observed. The development of pneumoconiosis stopped at the micronodular size, the nodules did not tend to confluence. As analysis of the dust did not show any content of free SiO_2, the authors presumed that pneumoconiosis was caused by diantimony trioxide. Due to unclear exposure conditions of the workers, this study is considered inconclusive and will not be used for risk characterisation.

In a briefly reported study the degree of pneumoconiosis in 72 workers, employed in an antimony plant between 6 months and 43 years, was compared with their mean period of employment and their antimony lung level (McCallum *et al.*, 1971). Data from this study is also presented in the 4.1.2.1. Toxicokinetics section. A postero-anterior radiograph of the lungs, which was categorised according to the international classification from 1958, was available for the men. In category 1 the opacities are sporadic and singly disseminated, category 2 shows opacities in the mid-lung regions and in category 3 a markedly high profusion in the entire lung-field is involved. Antimony lung levels were measured by X-ray spectrophotometry.

An increase in radiographic category of pneumoconiosis was associated with a rise in the mean period of employment, although there was a great deal of variation. An increase in radiograph category was also associated with an increase in antimony lung levels, although there was a wide variation in the amount of antimony in the lungs in each category. No statistical calculations were performed. Due to unclear exposure and lack of statistical calculations this study will not be used for risk assessment.

The mortality and the underlying causes were investigated in workers employed in an antimony plant in England where roasting of antimony ore started in the 1920s (Jones, 1994). This study is also described in more detail in the 4.1.2.8. Carcinogenicity section. Over the year's antimony metal, antimony alloys and diantimony trioxide were produced in the plant. Until the early 1970s considerable quantities of lead alloys were made, containing as much as 80% lead and 10% arsenic. All production of antimony metal and its alloys stopped in 1973 and after that only diantimony trioxide was manufactured. Since the 1960s the bulk of ore used was a sulphide ore containing about 60% of antimony and up to 0.5% of arsenic. Arsenic metal and its trioxide were also brought into the plant to make arsenic alloys.

No exposure data were presented but due to the description of the work place it can be assumed that variable occupational exposure to lead, metallic antimony, metallic arsenic, diantimony trioxide, arsenic trioxide and polycyclic aromatic hydrocarbons did occur. All men employed between 1961-1992 and with at least three months of employment were recruited into the survey. Of the 1452 men that were recruited, 32 were not traced. Of the 1420 men that were traced 357 had died and 29 emigrated by 1992.

The workers were subdivided into four occupational groups: a) antimony workers, b) maintenance workers, c) zircon workers and d) others (including office workers and management staff).

Expected death rates were calculated based on local rates of Tyneside conurbation 1961-73 and Tyne and Wear 1974-83. Man-years at risk were calculated for the population in separate decennial age periods for each year from 1st of January 1961-31st of December 1983.

Appropriate age specific death rates were then applied to calculate the number of deaths expected for each cause of death considered. The cause of deaths were divided as follows; lung cancer, stomach cancer, other neoplasms, circulatory disease, ischaemic heart disease, respiratory disease, genitourinary disease, accident and suicides and others. The observed numbers of deaths for each cause were compared with the expected figures calculated as above.

Except for increase in mortality from lung cancer no effects were observed in mortality from other causes.

No effect on mortality from circulatory disease, ischaemic heart disease, respiratory disease, genitourinary disease, accident and suicides and others was observed in this study. However, there were no exposure data reported and thus this study cannot be used for any quantitative risk assessment.

Summary of repeated dose toxicity

The majority (9 out of 14) of the repeated dose studies in animals cited above are considered inconclusive because they do not comply with current test guidelines, they lack essential information regarding exposure conditions and statistical evaluations of the results or both control and exposed animals showed signs of non-treatment related illness. Still, there are inhalation studies indicating that diantimony trioxide is toxic to lung (Newton *et al.*, 1994; Watt, 1983; Groth et al., 1986a; MPI, 2003). A NOAEC of 0.51 mg/m^3 is derived from the study by (Newton *et al.*, 1994) and brought forward to the risk characterisation. It is based on impaired lung clearance observed at 4.50 mg/m^3. There is some uncertainty regarding the accuracy of the LOAEC and NOAEC numerical values as the study had a high background incidence of lung inflammation in control animals. Furthermore, acute pneumonia has been reported in a reproductive toxicity inhalation study performed by (MPI, 2003) supporting adverse lung effects at exposure levels $\geq$ 2.6 mg/m^3.

In humans, all the data comes from case report studies on workers employed in industries manufacturing diantimony trioxide. The workers were probably subjected to inhalation, dermal and oral exposure, although it can be assumed that exposure via inhalation was the dominating route. Although no detailed data on exposure levels were presented and consequently no NOEC or LOEC values can be derived from these studies they indicate that repeated inhalation exposure to diantimony trioxide may cause pulmonary inflammation, lung emphysema and pneumoconiosis. Only isolated cases of changes in lung function were reported. The irritation observed on skin is considered in the B.5.3 section of Irritation.

B.5.7 Mutagenicity

Not relevant for this proposal.

B.5.8 Carcinogenicity

Inhalation

Studies in animals

Three chronic toxicity/carcinogenicity studies are available where the carcinogenicity of inhaled antimony trioxide in rats has been evaluated (Watt, 1983; Groth et al., 1986a; Newton et al., 1994). The exposure duration in all three studies is 12 months and thus all studies deviates from the OECD guideline on chronic toxicity/carcinogenicity, which suggests an exposure period of 24 months in rats. It should be noted that two of the studies (Groth *et al.*, 1986a; Newton et al., 1994) might reflect sub-chronic disease among the animals, and that one study (Watt, 1983) only included females.

In the first study, a chronic inhalation toxicity study, the carcinogenicity of antimony trioxide was investigated in female CDF Fisher rats (Watt, 1983). This study is also reported in chapter B.5.6 Repeated dose toxicity. 148 female rats from the Charles River Laboratories , 14 weeks of age, were divided into three groups (the number per group was not specified) and exposed to 0, 1.9 ± 1.8 and 5.0 ± 3.8 mg antimony trioxide /m^3 for 6 h/day, 5 days/week for one year in whole body exposure chambers. Since the exposure concentrations were reported as Sb, 1.6 ± 1.5 and 4.2 ± 3.2 mg Sb/m^3, respectively, the corresponding values as Sb_2O_3/m^3 have been calculated by the Rapporteur. Air samples were taken within the exposure chambers at the same level as the suspended rat cages. It should be noted that air samples were not taken in the cages. The antimony trioxide used was 99.4% pure with arsenic (0.02%) and lead (0.2%) as the major contaminants. Only particles with mean aerodynamic diameter of 15 μm or less would pass into the chamber. The particle size (Ferret's diameter) was 0.44 and 0.40 μm for the low and high concentrations (GSD 2.23 and 2.13, respectively). Control animals were moved to other chambers during each exposure session but no more information regarding the conditions of those chambers are given by the author. Surviving animals were kept up to 15 months post-exposure for observation.

Prior to and after approximately 3, 6, 9 and 12 months of exposure, and 2 to 12 and 12 to 15 months post-exposure animals were sacrificed and evaluated for evidence of toxicity. At sacrifice, the heart, lung, liver, spleen and kidney were weighed and fixed in 10% buffered formalin for subsequent light microscopic examination. Blood samples were taken for analyses of differential count, red and white blood cell count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin and mean corpuscular hemoglobin volume, serum enzymes and chemistry. Animals were weighed periodically throughout the exposure period.

No exposure-related effects on survival, hematology, or clinical chemistry were noted. The body weights of the exposed animals were significantly but reversibly higher than the controls; in the low-dose group during most of the exposure period (range of % increase in body weight: 5.5-10.5) but not by the end of the exposure period (% increase in body weight: 3.7) or post-exposure (range of % increase in body weight: 2.5-7.3), whereas high-dose animals had significantly higher body weights pre-exposure (range of % increase in body weight: 2.1-7.8) and during exposure (range of % increase in body weight: 1.9-6.3, but not post-exposure (range of % increase in body weight: 3.9-5.6). Since some of the weight differences occurred before the start of exposure, it cannot be determined to what extent, if any, antimony trioxide contributed to it. The lung weight was significantly but reversibly increased at nine months in the high dose group and at 12 months in both exposure groups, but no significant difference was observed at one year post exposure. A number of neoplastic effects were observed in the lungs of exposed animals (Table 11) and in many animals the neoplasms were multifocal. Scirrhous carcinomas (malignant, poorly-differentiated adenocarcinomas surrounded by dense fibrous tissue) were the most common type of lung

neoplasm, found only in the high dose rats at the end of exposure and during the observation period (Table 11). The increased incidence was statistically significant in animals sacrificed between 2 and 12 months postexposure and between 12 and 15 months postexposure. The scirrhous carcinomas appeared to arise from the alveolar epithelial lining cells and the cells exhibited a variety of morphologic changes; they were hypertrophied, hyperchromatic and exhibited varying degrees of mitotic activity and anaplasia. There was evidence of local invasion but no evidence of metastasis. An abundance of fibrous connective tissue was associated with these carcinomas and considered in excess of what would be expected as a stroma for scirrhous carcinomas and alsounusual for a primary neoplasm of the rat lung.

Two squamous cell carcinomas were observed in the 18 high dose rats killed at one year post exposure, however the incidence was not statistically significant (Table 11). Squamous cell carcinomas also appeared to be originating from the alveolar lining epithelial cells. These cells, in addition to exhibiting varying degrees of anaplasia, had gone through a metaplastic change to a more squamous type cell with evidence of keratin production. A fibrous connective tissue stroma was a prominent part of these neoplasms, however it was less than seen in the scirrhous carcinomas.

Bronchiolar adenomas were found in both exposed and control animals and were not considered as treatment-related but similar to those that occur naturally in the rat lung. The incidence in the high dose group (4 tumours in 45 animals) was not statistically significantly higher than that of the controls (1 tumour in 41 animals). A variety of neoplastic changes were observed in other tissues, most notably mammary glands, but they were not considered treatment-related since their incidence and severity was not significantly different between the exposed and the control rats

This study shows that exposure to diantimony trioxide significantly increase the incidence of pulmonary scirrhous carcinomas in female rats, 2 to 15 months after 12 months inhalation of 5.0 ± 3.8 mg antimony trioxide/m^3. The incidence of scirrhous carcinomas in animals sacrificed between 0 and 15 months post exposure in the highest exposure group was 44% (15/34). The corresponding value for the control was 0/28. A LOAEC of 5.0 mg/m^3 is suggested based on the development of scirrhous carcinomas. The NOAEC is set to 1.9 mg/m^3. There is however some uncertainty regarding this LOAEC of 5.0 mg/m^3 as a re-evaluation 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 may have been above those reported, but the difference could also be due to different particle generation techniques or different strains of rats.

Table 11. Lung tumour incidence in Fisher rats after inhalation exposure to antimony trioxide. Only females were included in this study.

		Any lung neoplasm			Scirrhous carcinoma			Squamous cell carcinoma			Bronchioalveolar adenoma		
Group	Death or Sacrifice	Control	Low	High	Control	Low	High	Control	Low	High	Control	Low	High
A	Pre-exposure	0/3	0/1	0/0	0/3	0/1	0/0	0/3	0/1	0/0	0/3	0/1	0/0
B	From start through 5 months	0/2	0/4	0/3	0/2	0/4	0/3	0/2	0/4	0/3	0/2	0/4	0/3

	of exposure												
C	From 6 through 9 months of exposure	0/4	0/3	0/3	0/4	0/3	0/3	0/4	0/3	0/3	0/4	0/3	0/3
D	From 9 through 12 months of exposure	0/4	0/5	0/5	0/4	0/5	0/5	0/4	0/5	0/5	0/4	0/5	1/5
E	At the end of exposure (12 months)	0/9	0/9	2/9	0/9	0/9	1/9	0/9	0/9	0/9	0/9	0/9	0/9
F	Between 2 and 12 months post-exposure	1/6	0/5	5/7	0/6	0/5	5/7 *	0/6	0/5	0/7	1/6	0/5	0/7
G	12 to 15 months post-exposure	1/13	1/17	14/18	0/13	0/17	9/18 **	0/13	0/17	2/18	0/13	1/17	3/18
Total A-G		2/41	1/44	21/45	0/41	0/44	15/45	0/41	0/44	2/45	1/41	1/44	4/45
Total E-G		2/28	1/31	21/34	0/28	0/31	15/34	0/28	0/31	2/34	1/28	1/31	3/34

Statistically different from control: $*p < 0.05$; $** p < 0.01$

The same study also included eight female Sinclair S-1 miniature swine that were exposed under similar conditions as the rats and housed in the same exposure chambers. The animals were divided into high dose (n=3), low dose (n=3) and control (n=2) groups. No exposure-related histopathological changes were observed in the swine. No real conclusions can be drawn on the carcinogenicity of antimony trioxide from this limited study.

In the second study, the carcinogenic effects of antimony trioxide and antimony ore (Sb_2S_3) were evaluated in Wistar rats, 90 males and 90 females per group (Groth *et al.*, 1986a). This study is also described in section 4.1.2.6. Repeated dose toxicity. The animals, 8 months of age, were exposed by inhalation to antimony trioxide [time-weighted average (TWA) 45 mg/m^3 (range = 0-191.1)], antimony ore [TWA 36-40 mg/m^3 (range = 0-91.1)] or filtered air (controls) in exposure chambers, 7 h/day, 5 days/week for up to 52 weeks. The MMADs for antimony trioxide and antimony ore were 2.80 and 4.78 µm, respectively (GSD not reported). The antimony content in the antimony trioxide was 80% and in the antimony ore it was 46%. Major contaminants in the antimony trioxide were lead (0.23%), tin (0.21%) and arsenic (0.004%) and in the antimony ore they were aluminium (0.48%), iron (0.33%), lead (0.25%), tin (0.16%) and arsenic (0.079%). At 6, 9, and 12 months after initiating exposures 5 animals/sex/group were sacrificed and autopsied, the remainder of the animals were sacrificed 18-20 weeks post-exposure. In addition, all animals that died or were sacrificed due to ill

health were autopsied. At autopsy all organs were examined grossly and tissue sections from the lungs, liver, kidneys, pancreas, spleen, adrenal, thyroid, pituitary, bladder, brain, eye, bone marrow, skin, lymph nodes (mesenteric and tracheobronchial), stomach and colon (ascending and descending) from each rat were fixed in buffered 10% formalin, embedded, sectioned and stained with hematoxylin and eosin for examination by light microscopy. Samples from the testicle and prostate from males and mammary gland, ovary, uterus and cervix from females were also examined as well as any abnormal tissue. In addition, at the final sacrifice heart tissue was sampled and examined by light microscopy. At sacrifices, portions of liver, lungs, kidneys, brains, spleens and blood from 5 animals/sex/group were sampled for antimony concentration analysis.

The data indicate that there was no treatment related mortality. However, for each of the groups, the female survival rate was significantly greater than the male counterparts. The mean body weight of the males exposed to antimony trioxide and the females exposed to antimony ore was slightly but statistically significantly reduced (6.2% and 6.4%, respectively). Sporadic bleeding from eyes and hematuria occurred in all groups, but appeared to occur more frequently in the antimony trioxide and antimony ore groups (data not shown). Although, according to the authors, no significant pathological alterations were seen in any of the control lungs, occasional foci containing lymphocytes, typical of chronic pneumonia, were seen in a few rats.

No lung tumours were seen in the control rats of either sex or in the male rats exposed to either compound. In contrast, both the antimony trioxide and antimony ore exposed female rats developed lung tumours, including squamous-cell carcinomas, bronchoalveolar adenomas and carcinomas and scirrhous carcinomas (Table 12 and Table 13). The first lung tumour was observed in a female rat that died after 41 weeks of antimony ore-exposure. The first lung tumour in the antimony trioxide group was seen at 12 months of exposure. If only the animals at risk (those alive at the first lung tumour was found) and subsequently examined are used in the calculations, then the incidence of lung tumours for antimony trioxide-exposed rats was 27% and that for antimony ore-exposed rats was 25%. These incidences were significantly ($p < 0.001$) greater than in the control group, which had no lung tumours.

Different types of tumours that are typical for this strain of rats were observed in thyroid, skin (subcutis), mammary gland, pituitary and adrenal tissue in all groups; however, no exposure-related differences in the incidence of these neoplasms were observed.

Table0-12. Lung tumour incidence in female rats after inhalation exposure to antimony trioxide and antimony ore.

Weeks on experiment	Controls	antimony trioxide	antimony ore
53 (serial sacrifice)	0/5	2/5	2/5
54-71 (died)	0/15	5/23	3/21
71-73 (serial sacrifice)	0/39	12/31	11/33
Total (18-73 weeks)	0/89	19/89	17/87
41-72 “animals at risk”	0/69	19/70 ***	17/68 ***

Statistically different from control: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

Table0-13 Tumour type frequency in female rats after inhalation exposure to antimony trioxide or antimony ore

Compound	Scirrhous carcinomas	Squamous cell carcinomas	Bronchoalveolar adenomas and carcinomas	Multiple lung tumours (2-4/rat)

Sb_2O_3	5/19	9/19	11/19	6/19
Sb ore	4/17	9/17	6/17	3/19

This study shows that the incidence of various lung neoplasms significantly increased in female rats exposed to 45 mg antimony trioxide/m^3 for 12 months via inhalation. In general the lung tumours occurred after 12 months of exposure with an incidence of 32% (19/59) in animals examined after 12 months of exposure (including animals from weeks on experiment 53, 54-71 and 71-73; Table 12). No lung tumours were found in males despite higher antimony concentrations found in male lungs than in female lungs, suggesting that female rats are more susceptible to the induction of lung cancer by antimony trioxide and antimony ore and also indicating that the tumour response was not only a function of lung tissue concentration of antimony. It is noted that only one dose per compound was investigated, which does not allow a dose-response assessment. Moreover, all animals including controls showed signs (further described in the Repeated dose toxicity section B.5.6) which might reflect sub-chronic disease of unknown aetiology among the animals.

In conclusion, antimony trioxide caused a statistically significant increase in lung cancer in female rats under the present test conditions. However, the underlying mechanism of the tumour formation is unclear. The authors state that interstitial fibrosis is a frequent precursor to the induction of lung tumours in rats exposed to particulates containing beryllium compounds (Groth *et al.*, 1980) and quartz (Groth *et al.*, 1986b). However, in the present study on antimony a high incidence of lung neoplasms in female rats and a lack of neoplasms in male rats were observed although pulmonary interstitial fibrosis was seen in both males and females. A LOAEC of 45 mg/m^3 is suggested based on observed lung cancer in females.

The oncogenicity of antimony trioxide was also evaluated in a whole-body inhalation study, performed by Bio/dynamics Inc. and published by Newton and co-workers, (Newton and Daly, 1990; Newton *et al.*, 1994). This study, which is also described in section B.5.6, Repeated dose toxicity, is based on the results from both the Watt and Groth studies. Fisher 344 rats, 65 males and 65 females per dose group, 8 weeks of age, were exposed to antimony trioxide at 0, 0.06, 0.51 or 4.50 mg/m^3 for 6h/d, 5d/wk for 12 months followed by a 12-month observation period. Control animals were exposed to clean air only. The flow rate was 18-25 complete air changes per hour (the recommended flow rate in OECD guideline 412, 413 and 453 is 12-15 air changes per hour, Rapporteur comment). Five animals per sex per group were sacrificed at 6 and 12 months of exposure and at 6 months postexposure. All surviving animals were sacrificed at 24 months (12 months postexposure). The purity of the antimony trioxide was 99.68% and the particle MMAD was 3.76 ± 0.84 μm with a geometric standard deviation of 1.79±0.32 for all concentrations.

Animals were observed twice daily for viability and overt signs of toxicity. Detailed observations were conducted weekly and body weights were measured twice pretest, weekly for the first 13 weeks, monthly thereafter and at termination. Ophtalmoscopic examinations were performed on all animals pretest and on the day before their scheduled sacrifice. Hematological effects were evaluated at 12, 18 and 24 months. Complete gross postmortem examinations of all major organs were performed in all animals. Histological examinations were performed on hematoxylin-eosin-stained tissue sections of heart, nasal turbinates, larynx, trachea, lung and peribronchial lymph node. At each sacrifice, the left lung lobe was

frozen for later antimony analyses and blood samples were collected. Fecal samples were collected at the 18- and 24-month sacrifices.

Survival was not affected by the exposures to antimony trioxide. At termination at 24 months, there was 56% survival of the males and 48% survival of the females.

Pulmonary carcinomas were seen in only three animals, two males (one each from the control and high dose groups) and in one female (from the medium dose group). These carcinomas were not considered to be antimony trioxide exposure related. No other primary lung neoplasms were seen. Elevated total leukocyte counts and atypical lymphocytes in some animals in all groups at the terminal euthanization indicated the presence of leukemia. However, leukemia is a common finding in aged Fischer 344 rats. Other postmortem neoplastic findings (not further specified) occurred mostly with comparable incidence and severity in the treated and control animals or they occurred sporadically. None of these findings were considered to be of either oncological or toxicological significance with respect to antimony trioxide.

In conclusion, no evidence of antimony trioxide-induced carcinogenicity was found under the exposure conditions of this study. The chronic interstitial pneumonia and the chromodacryorrhea (shedding of bloody tears) observed without dose-response in both control and antimony trioxide exposed animals suggest that the animals suffered from sub-chronic disease of unknown etiology. These non-neoplastic findings are further described in the B.5.6, Repeated dose toxicity section.

Studies in humans

The mortality and the underlying causes were investigated in workers employed in an antimony plant where roasting of antimony ore started in the 1920s (Jones, 1994). This study is also described in the B.5.6 Repeated dose toxicity section.

Over the years, antimony metal, antimony alloys and antimony trioxide were produced in the plant. Until the early 1970s considerable quantities of lead alloys were made, containing as much as 80% lead and 10% arsenic. All production of antimony metal and its alloys stopped in 1973 and after that only antimony trioxide was manufactured. Since the 1960s the bulk of ore used was a sulphide ore containing about 60 % antimony and up to 0.5% of arsenic. Arsenic metal and its trioxide were also brought into the plant to make arsenic alloys.

Since 1950 another non-antimony process, the milling of zircon sand, has also been carried out at the site. The process is purely physical, with no chemical change involved. The zircon and antimony workers have worked separately, except for a few cases where temporary transfers of workers between the processes have been necessary.

No exposure data were presented but variable occupational exposure to lead, metallic antimony, metallic arsenic, antimony trioxide and arsenic trioxide was assumed by the author. It was also assumed that there was exposure to polycyclic aromatic hydrocarbons due to the combustion in the furnaces used.

All men employed between 1961 and 1992, and with at least three months of employment were recruited into the survey. Of the 1452 men that were recruited, 32 were not traced. Of the 1420 men that were traced, 357 had died and 29 emigrated by December 1992.

The workers were subdivided into four occupational groups: a) antimony workers, b) maintenance workers, c) zircon workers and d) others (including office workers and management staff).

Two sets of expected death rates were worked out: the first based on national rates for England and Wales and the second based on local rates (Tyneside conurbation 1961-83, Tyne and Wear 1974-83). Man-years at risk were calculated for the population in separate decennial age periods for each year from January 1961 to December 1983. Appropriate age specific death rates were then applied to calculate the number of deaths expected for each cause of death considered. The causes of death were divided as follows; lung cancer, stomach cancer, other neoplasms, circulatory disease, ischemic heart disease, respiratory disease, genitourinary disease, accident and suicides and others. The observed numbers of deaths for each cause were compared with the expected figures calculated as above.

In the antimony workers there was a significant increase in mortality from lung cancer (37 v. 23.9, $p = 0.016$) but no difference in mortality from stomach cancer or other neoplasms. For maintenance men there was also a significant increase in mortality from lung cancer (15 v. 8.1, $p = 0.038$) but not from stomach cancer or other neoplasms. No increased death rates were observed in the groups of zircon workers or others. When the employees were divided into those employed before and after 1st of January 1961 it was shown that for the antimony workers employed before January 1961 there was a significant excess of mortality from lung cancer (32 v. 14.7, $p = 0.001$). Significant excess was also seen in the maintenance workers before 1961 (12 v. 5.3, $p = 0.016$). No evidence of an excess of mortality from lung cancer was found in the zircon and other groups, or in any of the groups employed after 1st of January 1961. When deaths from lung cancer in antimony workers were divided into calendar year of first exposure (from 1940-1990) an excess of mortality from lung cancer for all five-year periods of first exposure up to 31st of December 1960 was found. People who started work before 1955 showed an excess of three to four times the lung cancer expected, the group who started work from 1955 to 1960 showed less than a doubling of lung cancer, whereas people who started work after 1960 showed no such excess.

Analysis of deaths from lung cancer in antimony workers by years since their first exposure to antimony showed that < 20 years after the first exposure there is no excess of lung cancer but after that time a significant twofold excess emerges. However there was no trend of greater risk with increased years of exposure.

This study shows a significant excess of mortality from lung cancer among antimony smelter workers and maintenance workers. The excess of deaths from lung cancer in smelter workers was confined to those joining before 1961 and did not appear until 20 years after their first exposure to the antimony process. There was an excess of lung cancer for workers first exposed in all the five-year calendar periods before 1960. This suggests that antimony workers were occupationally exposed to some carcinogen before 1960. Because at the stage of follow up, very few of the men employed after 1960 were first exposed to the antimony process > 20 years previously and because the lung cancer excess was not obvious until 20 years after first exposure it is not possible to be certain whether the carcinogenic effect persisted after 1960. Considering the variable exposure (including in addition to antimony compounds also arsenic compounds, lead and polycyclic aromatic hydrocarbons) and the lack of exposure data it is not possible to determine what factors that have been responsible for the lung cancer.

Summary of carcinogenicity

Three chronic inhalation studies in rats are available for carcinogenicity assessment of diantimony trioxide (Watt, 1983; Groth et al., 1986a; Newton et al., 1994). Two animal studies indicate neoplastic properties of diantimony trioxide, whereas one animal study showed negative results. There is also one human study available (Jones, 1994). However, due to lack of exposure data the human study is regarded inconclusive. The exposure duration in all three animal studies is 12 months and thus all studies deviates from the OECD guideline on chronic toxicity/carcinogenicity, which prescribes an exposure period of 24 months for rats. In the first animal study (Watt, 1983) inhalation of 5.0 mg Sb_2O_3/m^3 for 12 months produced lung neoplasms in 44% of the animals tested (only females were exposed). In the second study, (Groth et al., 1986a) a 9 times higher dose (45 mg Sb_2O_3/m^3) produced pulmonary neoplasms in 32% of the female rats exposed under similar conditions, but none in male rats. It is noted that the female survival rate was significantly higher than the male counterparts in the study by Groth et al., (1986a). The differences in incidence between the studies might be explained by a longer observation period (12 months vs 20 weeks) and by the use of older animals (8 months vs 14 weeks) in the study by Watt (1983). The study by Newton et al., (1994) showed no diantimony trioxide-related lung tumours, neither in males nor females, at any dose level up to 4.5 mg/m^3. This is in contrast with the data reported by Watt and Groth and the cause to the difference is not entirely clear. However, the histopathology slides from the negative Newton study was re-evaluated by the pathologist who evaluated the slides from the Groth and of the Watt studies. The re-examination confirmed a lack of antimony trioxide-related neoplastic changes in the Newton study. In addition, the comparison of the Watt and the Newton studies, which were conducted at similar exposure levels, showed that the exposed rats had more lung damage and appeared to have considerably more antimony deposited in the lungs in the Watt study than in the Newton study. This may suggest that the exposure levels in the Watt study may have been above those reported. Given that the dose level in the study by Groth is 10 times higher and also the dose levels in the study by Watt were likely higher than 1.9 and 5.0 mg/m^3 the dose levels in the Newton study most probably fit in the dose range where no tumours were observed. However, the difference could also be due to different particle generation techniques or different strains of rats. The particle size, which will affect lung deposition, clearance and retention and hence target organ dose, was similar among the studies although they were all measured using different techniques.

In the study by Newton and co-workers it was shown that diantimony trioxide reduced the pulmonary clearance rate in a dose dependent manner, interpreted by the authors as a toxic effect of diantimony trioxide rather than a general effect due to pulmonary overload. However, it is wellknown that reduced lung clearance rate at chronic exposure of rats to poorly soluble particles (PSPs) can result in pulmonary overload, subsequently followed by an inflammatory response, epithelial cell hypertrophy and/or hyperplasia and squamous metaplasia. The persistence of these tissue responses over chronic time periods can lead to secondary development of lung tumours (Hext, 1994). Thus, it could be speculated that the neoplastic effects seen in the Watt and Groth studies is a result of pulmonary overload and an inflammatory response to particulate diantimony trioxide. The tumour development as a consequence of pulmonary overload is an inflammatory-driven process which usually takes over a year (15-18 months) of PSP exposure via inhalation (Driscoll *et al.*, 1997). In the present studies on antimony trioxide, development of lung tumours occurred earlier – already at 12 months of antimony inhalation.

PSPs have several common characteristics such as low solubility, low order of toxicity and they are generally non-genotoxic (Miller, 2000; ILSI Risk Science Institute Workshop Participants., 2000). PSPs include among others, titanium dioxide, carbon black, diesel soot, shale, talc and coal mine dust. *In vitro* studies on titanium dioxide and carbon black have not shown these materials to be genotoxic (Kanematsu *et al.*, 1980; Kirwin et al., 1981; Tennant et al., 1987). In contrast, diantimony trioxide is generally negative for gene mutations but has the potential to induce structural chromosome aberrations in vitro (see section 4.1.2.7 Mutagenicity). Whether or not diantimony trioxide should be regarded as a PSP can thus be discussed.

The inflammatory response to inhalatory PSP exposure includes macrophage breakdown, neutrophil accumulation in alveolar airspaces and bronchioalveolar epithelial cell proliferation. At pulmonary overload, the particle clearance function of the macrophages is impaired resulting in persisting lung burden. Extended impairment of clearance leads to development of pulmonary tumors in rats but not in mice or hamsters (Heinrich *et al.*, 1986; Muhle et al., 1990). Accumulation of particles starts and inflammatory cell influx increases sharply (ILSI Risk Science Institute Workshop Participants., 2000), (Oberdorster, 1995). The surface dose is considered the best indicator for developing pulmonary overload and a surface dose to cause lung cancer in rats has been identified between 2 000 and 3 000 cm^2 particle surface/lung (Borm et al., 2004). The surface dose needed to cause neutrophilic inflammation by PSPs is 10-fold lower, 200-300 cm^2 (Tran et al., 1999), (ILSI Risk Science Institute Workshop Participants., 2000).

Experimental evidence thus supports the hypothesis that there are links between chronic inflammation and epithelial changes leading to pulmonary cancer in rats (Donaldson, 2000), although the causal mechanisms to explain this association are still unclear (Coussens and Werb, 2002; Schottenfeld and Beebe-Dimmer, 2006). Particles generate reactive oxygen species (ROS) and reactive nitrogen species (RNS), which are thought to be involved in genotoxic as well as proliferative effects (Mossman and Churg, 1998; Schins, 2002; Fubini and Hubbard, 2003).

In the majority of studies with particle exposure it appears that females develop the higher incidences of lung tumors (Lee *et al.*, 1985). This may be attributable to a more potent response to the particle in females or to the fact that in a number of studies the females had a greater survival rate. Even a relatively small increase in longevity in one sex may result in an apparent disproportion increase in tumour incidence as the tumours develop towards the end of the life span of the rat (Hext, 1994). In the present animal studies, diantimony trioxide produced lung cancer in female rats. A higher concentration of diantimony trioxide was however found in lungs from male rats and there appeared to be more inflammatory cells in the male rat lung than in the female rat lung (Groth *et al.*, 1986a) indicating that the tumour response was not only a function of lung tissue concentration of diantimony trioxide. In this study, a 32% incidence of lung neoplasms in female rats and a lack of neoplasms in male rats exposed to diantimony trioxide were observed although pulmonary interstitial fibrosis was seen in both males and females.

The issue whether genotoxicity or particle overload may be the reason for diantimony trioxide-induced lung tumors is still not entirely clear. Despite the lack of conclusive data on local genotoxicity in the lung, the overall expert judgement by TC NES is that the most likely mechanism for carcinogenicity appears to be 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 as a starting point for a quantitative risk characterisation the NOAEC of 0.51 mg/m^3 derived for local repeated dose toxicity is

also used for carcinogenicity. There may be some uncertainty regarding the accuracy of the NOAEC numerical value as the study had a high background incidence of lung inflammation in control animals. In addition, the exposure duration was 12 months and thus deviates from the OECD guideline on chronic toxicity/carcinogenicity, which prescribes an exposure period of 24 months for rats. It could be discussed whether effects caused by pulmonary overload in the rat is also relevant for humans. Positive (Hext, 1994), (Oberdorster, 1995) and negative (Tran and Buchanan, 2000; Kuempel et al., 2001) findings of particle overload in human lungs are reported. Macrophage transport of particles into the alveolar interstitium is the major clearance mechanism in humans but of minor importance to the rat. These species differences are related to morphological features of the lung, i.e. to the relative short pathway length from the alveoli to the ciliated terminal bronchioles in rats (Bailey et al., 1989; Kreyling, 1990; Kreyling et al., 1991). In the absence of mechanistic data to the contrary, it must be assumed that the rat model of tumorigenicity can identify potential carcinogenic hazards to humans and the rat presently remains the appropriate model for both neoplastic and non-neoplastic responses to PSP exposure (ILSI Risk Science Institute Workshop Participants., 2000).

Antimony trioxide is currently classified in Annex 1, Directive 67/548/EEC as “Carcinogenic Category 3”.

B.5.9 Toxicity for reproduction

Not relevant for this proposal.

B.5.10 Other effects

Not relevant for this proposal.

B.5.11 Derivation of DNEL(s)/DMEL(s) or other quantitative or qualitative measure for dose response

Repeated inhalation exposure to diantimony trioxide gives local toxic effects in the lung and a NOAEC of 0.51 mg/m^3 is derived from a 12 month inhalation exposure study in rat. This experimental NOAEC, adapted by a factor of 6/8 to account for differences between the experimental inhalation duration of 6 h per day and the average working day of 8 h per day and then multiplied by a factor of 6.7/10 for activity driven differences of respiratory volumes in workers, results in a corrected NOAEC of 0.26 mg/m^3 (0.51 mg/m^3 · 6/8 · 6.7/10). The following assessment factors are applied in calculating the DNEL for a local effect in the lung;

- a factor of 2.5 for interspecies differences
- a factor of 5 for intraspecies differences; this covers the variation in sensitivity expected between workers

Accordingly, the DNEL for a local effect in the lung is 0.021 mg/m^3 [0.26 mg/m^3/(2.5 · 5)].

Diantimony trioxide is considered to be a carcinogenic substance and is classified for carcinogenicity. Although the mechanism for pulmonary tumour formation is still unclear it may be assumed that particle deposition followed by macrophage infiltration, pulmonary inflammation and impaired clearance are pivotal initial steps in the process. Consequently, diantimony trioxide can be regarded as a threshold carcinogen and as a starting point for a quantitative risk characterisation the NOAEC of 0.51 mg/m^3 derived for local repeated dose toxicity is also used for carcinogenicity. This results in a DNEL of 0.021 mg/m^3 calculated as described above.

B.6 Human health hazard assessment of physico-chemical properties

B.6.1 Explosivity

Not relevant for this proposal.

B.6.2 Flammability

Not relevant for this proposal.

B.6.3 Oxidising properties

Not relevant for this proposal.

B.7 Environmental hazard assessment

B.7.1 Aquatic compartment (including sediment)

Toxicity test results for sediment organisms

Fresh water

Three reliable and relevant chronic sediment toxicity tests with different single species are available. The test species all have different exposure routes, feeding habits and ecological niches: (1) the bottom-dwelling *Hyalella azteca* (crustacean) is a surface deposit and filter feeder, (2) *Chironomus riparius* (insect) burrows within the sediment with a combined surface and subsurface feeding behaviour, and (3) *Lumbriculus variegatus* (oligochaete) is a head-down deposit feeder that feeds well below the sediment-water interface.

In this study (Heijerick and Vangheluwe, 2003c), the amphipod *Hyalella azteca* was exposed to various concentrations of trivalent antimony ($SbCl_3$) in a sediment-water system (see Table 14 below). The amphipods were exposed for 28 days. After this period, the amphipods were separated from the sediment and placed in sediment-free chambers for another 14 days. During this period, survival (day 28, 35, 42), growth (day 28, 42) and reproduction (number of young per female produced from day 28 to 42) were measured. This study was performed with 13 replicates, five concentrations (range: 30.8 - 249 mg Sb/kg ww; 44 - 355 mg Sb/kg dw) and a control, with each replicate consisting of 10 amphipods (for more information on the study, see table 3.2.11 below). The 13 replicates were used as follows: four replicates were used for the 28-day growth and survival endpoints and eight for the measurements of survival and reproduction on day 35 and 42 (incl. growth). The remaining replicate was used for the performance of chemical measurements. The overlying water was renewed at least three times a week (±75%). The most sensitive endpoint was growth (both weight and length) after 28 days of exposure, which resulted in a NOEC of 87 mg Sb/kg ww (124 mg Sb/kg dw).

Larvae of the midge *Chironomus riparius* were exposed to a concentration range of $SbCl_3$ in a sediment-water system (Heijerick and Vangheluwe, 2005a; Table 14). The test procedure was based on the OECD draft proposal for a new guideline 218 “Sediment-Water Chironomid Toxicity Test Using Spiked Sediment” (Draft February 2001, adopted April 2004). Two-day old larvae were exposed to spiked sediment until the larvae transformed to the adult phase. Mortality and growth of the larvae, and emergence to midges were determined after 14 and 28 days of exposure. The study was performed with six concentrations (23 - 445 mg Sb/kg ww; 33 - 636 mg Sb/kg dw) and a control (<1.4 mg Sb/kg ww; <2.0 mg Sb/kg dw), and 11 replicates per concentration of which five replicates were used to determine survival and growth after 14 days of exposure, five to determine emergence after 28 days of exposure, and

the remaining replicate to perform chemical analyses. The overlying water was renewed at least three times a week (±75% renewal). The most sensitive endpoint was growth (weight), which resulted in a NOEC of 78 mg Sb/kg ww (112 mg Sb/kg dw).

Adults of the oligochaete *Lumbriculus variegatus* were exposed to a concentration range of $SbCl_3$ in a sediment-water system (Heijerick and Vangheluwe, 2005b; Table 14). The test procedure was based on the OECD draft "Bioaccumulation; Sediment test using benthic oligochaetes" (January 2000; 3rd revised draft) and the EPA Guideline 600/R-99/064 "Methods for measuring the toxicity and bioaccumulation of sediment-associated contaminants with freshwater invertebrates", Section 13, Test Method 100.3 "*Lumbriculus variegatus* bioaccumulation test for sediments". The test organisms were exposed for 28 days to the spiked sediment. At the end of the exposure period survival, reproduction and growth were monitored. The study was performed with six concentrations (23 - 445 mg Sb/kg ww; 33 – 636 mg Sb/kg dw) and a control (<1.4 mg Sb/kg ww), and 7 replicates per concentration of which six replicates were used to determine survival, reproduction and growth after 28 days of exposure and the remaining replicate to perform chemical analyses. The overlying water was renewed at least three times a week (±75% renewal). The most sensitive endpoint was growth (weight), which resulted in a NOEC of 78 mg Sb/kg ww (112 mg Sb/kg dw).

Table 14 presenting toxicity tests for sediment-living organisms in freshwater.

Organism	Compound	Valency	Medium	Test conditions	Nominal/ Measured	Exposure period (d)	Endpoint	NOEC (mg Sb/kg ww.)	NOEC (mg Sb/kg dw.)	LOEC (mg Sb/kg ww.; % effect)	LOEC (mg Sb/kg dw.; % effect)	Reference	Reliable & Relevant
Chironomus riparius Age = 2 days	$SbCl_3$	Sb(III)	Artificial sediment (in % of sediment dry weight): peat 5%, quartz sand 75%, kaolinite clay 20%, pH 7.0 ± 0.5, organic carbon 2±0.5%, calcium carbonate 0.05-0.1%, water 30%. EPA medium as overlying water H=234-252 pH=7.52-7.79 DO=4.90-5.45	Semi-static T=20 ± 1	M	14 28	Survival Growth (weight) Emergence	≥ 445 <u>78</u> ≥ 445	≥ 636 112 ≥ 636	> 445 120 > 445	> 636 172 > 636	Heijerick and Vangheluwe, 2005a	R
Hyalella azteca Age = 6-7 d	$SbCl_3$	Sb(III)	Artificial sediment (in % of sediment dry weight): peat 5%, quartz sand 75%, kaolinite clay 20%, organic	Semi-static T=23	M	28 42	Growth (weight) Growth (length) Survival Growth (weight) Growth (length) Reproduction	86.8 86.8 190.4 190.4 190.4 190.4	124 124 272 272 272 272	190.4 (29%) 190.4 (8%) 248.5 (21%) 248.5 (34%) 248.5 (17%) 248.5 (89%)	272 (29%) 272 (8%) 355 (21%) 355 (34%) 355 (17%) 355 (89%)	Heijerick and Vangheluwe, 2003c	R

Organism	Compound	Valency	Medium	Test conditions	Nominal/ Measured	Exposure period (d)	Endpoint	NOEC (mg Sb/kg ww.)	NOEC (mg Sb/kg dw.)	LOEC (mg Sb/kg ww.; % effect)	LOEC (mg Sb/kg dw.; % effect)	Reference	Reliable & Relevant
			carbon 2±0.5%, calcium carbonate 0.05-0.1%, water 30-50%. Borgman medium as overlying water H=148±21.6 pH=7.92-7.95 DO=5.52-5.92				(number of young per female)						
Lumbriculus variegatus Age = 7 days	$SbCl_3$	Sb(III)	Artificial sediment (in % of sediment dry weight): peat 5%, quartz sand 75%, kaolinite clay 20%, pH 7.0 ± 0.5, organic carbon 2±0.5%, calcium carbonate 0.05-0.1%, water 30%. EPA medium as overlying water H=222-267	Semi-static T=25 ± 1	M	28	Survival / reproduction Growth (weight)	120 <u>78</u>	172 112	244 120	348 172	Heijerick and Vangheluwe, 2005b	R

Organism	Compound	Valency	Medium	Test conditions	Nominal/ Measured	Exposure period (d)	Endpoint	NOEC (mg Sb/kg ww.)	NOEC (mg Sb/kg dw.)	LOEC (mg Sb/kg ww.; % effect)	LOEC (mg Sb/kg dw.; % effect)	Reference	Reliable & Relevant
			pH=7.73-7.94 DO=5.0-5.9										

DO = dissolved oxygen (mg O_2/l); T = temperature (ºC)

Calculation of Predicted No Effect Concentration (PNEC) for sediment organisms

Reliable and relevant chronic NOEC values are available for three species with different living and feeding conditions. According to the TGD (2003) the $PNEC_{sediment}$ shall be derived from the lowest NOEC divided by an assessment factor of 10. The lowest NOEC (78 mg Sb/kg ww or 112 mg Sb/kg dw) has been derived for the midge *Chironomus riparius* and the oligochaete *Lumbriculus variegatus*.

This results in the following $PNEC_{sediment}$:

$PNEC_{sediment}$ = 11.2 mg Sb/kg dw (7.8 mgSb/kg ww).

B.7.2 Terrestrial compartment

Not relevant for this proposal.

B.7.3 Atmospheric compartment

Not relevant for this proposal.

B.7.4 Microbiological activity in sewage treatment systems

Not relevant for this proposal.

B.7.5 Non compartment specific effects relevant for the food chain (secondary poisoning)

Not relevant for this proposal.

B.8 PBT and vPvB assessment

B.8.1 Assessment of PBT/vPvB properties – Comparison with criteria of Annex XIII

Not relevant for this proposal.

B.8.2 Emission characterisation

Not relevant for this proposal.

B.9 Exposure assessment

Information on exposure has only been included for the scenarios where need for further measures to reduce risks has been identified. For the risk assessment of other scenarios and further details we refer to the EU Risk Assessment Report.

B.9.1 General discussion on releases and exposure

B.9.1.1 Summary of existing legal requirements

Chemical Agents at Work 98/24/EEC

The directive lays down general provisions for safety and health relating to workplace chemicals, including procedures for setting Community level occupational exposure limit (OEL) values.

To ensure that risks from hazardous chemical agents are eliminated or reduced to a minimum, employers are requested to conduct a risk assessment of such substances. The risk assessment must be documented. The employers, applying a set of general principles, should take action to reduce or remove identified risks. The effectiveness of the preventive measures should be monitored and the assessment should be reviewed. The Directive sets a hierarchy for exposure controls to be applied if a risk assessment reveals risks.

The general principles are substitution, prevention, protection and control. If it is not possible to substitute the chemical agent or process that poses a risk, the next steps to be taken are engineering controls, use of adequate equipment or general protection measures such as ventilation. The last option should be to use individual personal protective equipment.

The directive also gives provision for the Commission to draw up practical guidelines to assist compliance with the directive. These guidelines will be non-binding but should relate to development of standardised methods for measuring and evaluating air concentration at workplace, determination and assessment of risk and preventative and protective measures to control risk.

Member States were to implement the Chemical Agents Directive by the 5th of May 2001. Thereafter a report should be given to the Commission every five years on its practical implementation.

The Water Framework Directive (2000/60/EC)[3]

The Water Framework Directive (WFD) establishes a wide framework for Community action in the field of water policy. The aim of the directive is to maintain and improve the aquatic environment. The directive covers inland surface waters, transitional waters, coastal waters and groundwater. The aquatic environment of surface waters includes the water column, its sediments and biota.

The WFD recognises that individual substances or groups of substances may present a significant risk to or via the aquatic environment and require action against pollution caused by these substances. Substances that present a significant risk to, or via the aquatic environment, will be prioritised for action on the basis of risk ("priority substances"). It is not proposed to add diantimony trioxide to the list of priority substances.

[3] Directive 2000/60/EC of the European Parliament and of the Council of 23 October 2000 establishing a framework for Community action in the field of water policy

The Directive on Integrated Pollution Prevention and Control (2008/1/EC)[4]

The aim of the IPPC directive is to lay down measures designed to prevent or control emissions in order to achieve a high level of protection of the environment. The instruments for risk reduction in the directive are permit requirements, including emission limit values (ELV) and the creation of reference documents on best available techniques, BREFs.

BREFs are the result of an exchange of information between member states and industry on best available techniques (BAT), organized by the commission. The results are published as IPPC BAT Reference Documents (BREFs). The means to reduce emissions as well as achievable emission limit values have to be described in the BREFs. BREFs must be taken into account when the competent authorities of Member States determine conditions for IPPC permits. New medium-sized and large industrial installations, covered by the IPPC Directive, have to obtain a permit from the competent national authority before they are put into operation. Existing installations of the same kind should obtain a permit at the latest 2007.

Installations for industrial production of chemicals such as diantimony trioxide are within the scope of the IPPC directive. No measures other than those already foreseen under the current legislation will be added.

B.9.1.2 Summary of effectiveness of the implemented risk management measures

Relevant parts of the above legislation had not entered into force when the information for the risk assessment was collected. Currently, the entry into force has either already happened (for example the requirement for permits under the IPPC directive) or is foreseen within a reasonable time-frame (for example registrations under Reach). Measures under these legislations are considered to be effective once the relevant regulations have been implemented. The proposed measures to reduce the risks are based on the conclusions from the risk assessment but takes into account risk management measures coming into force.

B.9.2 Occupational exposure

There are several industries in which diantimony trioxide is produced or used, and the life cycle stages where occupational exposure may occur are; production, formulation, i.e. industrial use of diantimony trioxide as an additive and processing, i.e. industrial and professional use, of semi- or end-products containing diantimony trioxide. At some sites, both formulation and processing may take place. In addition, exposure might occur during recycling and disposal of articles containing diantimony trioxide, but there is no available information about this. It is assumed that exposure during recycling and disposal is limited compared to the exposure from production, formulation and industrial and professional use, and therefore these scenarios are not considered further in this exposure assessment.

[4] Council Directive 2008/1/EC of 24 September 1996 concerning integrated pollution prevention and control

The following data were used for the occupational exposure assessments of diantimony trioxide:

- Measured workplace data from production and uses of diantimony trioxide
- Physico-chemical data of diantimony trioxide
- Qualitative data, such as process descriptions and use pattern of the product, and quantitative data regarding frequency and duration of handling of diantimony trioxide
- Concentrations of diantimony trioxide used in the different products

Industry exposure data

A number of "tailor-made" questionnaires were developed by Industry (International Antimony Oxide Industry Association (IAOIA) specifically for the collection of data relevant for occupational exposure at the producer and downstream users of diantimony trioxide.

The questionnaires were distributed within Europe to previously identified companies. A total coverage of 100 % for producers and 63 % for downstream users, respectively, of the annual consumption of diantimony trioxide was obtained. Process descriptions are based on visits conducted in each sector on representative sites. These visits were conducted by the authors of the reports. Occupational exposure data were gathered from each of the sectors, where available. Relevant exposure descriptors were collected by a questionnaire in order to provide for a sector-wide analysis of:

– Frequency/duration of handling and amount of handled diantimony trioxide powder
– Process and exposure controls, and details of protective measures
– Similarity of relevant process conditions
– Used forms of diantimony trioxide
– Laboratory particle size determinations - and dustiness (not sector specific)

The following diantimony trioxide downstream user markets were identified;

– PET resin
– PET fibre and films
– Flame retarded plastics – PVC
– Flame retarded plastics – non PVC
– Flame retarded textiles
– Pigments/paints/coatings and ceramics
– Rubber manufacturing
– Crystal glass

Analogous and surrogate data

Analogous or surrogate data was used for some life cycle stages when the collected data was not considered to be sufficient and/or representative and data from other uses with similar handling of the substance were available.

Route of exposure

The main routes of occupational exposure to diantimony trioxide are by inhalation of airborne solid dust and dermal exposure to solid diantimony trioxide. Dermal exposure may occur during direct handling, either by contamination of skin surfaces or by dermal deposition of airborne dust.

A summary of the exposure values used in the risk assessment for workers are presented in table 15.

Table 15 Summary of values taken forward to risk characterisation.

Inhalation exposure	Typical (mg/m³)	RWC (mg/m³)	Remarks
1. Production of diantimony trioxide			
- Conversion	0.027 with RPE	2.9 without RPE 0.15 with RPE	Measured data
- Refuming	0.012 with RPE	0.94 without RPE 0.047 with RPE	Measured data
- Final handing	0.040 with RPE	2.1 without RPE 0.11 with RPE	Measured data
2. Use as a catalyst in production of PET			
- Powder handling	0.002	0.026	Measured data
3. Use as a flame-retardant in production of plastics			
- Raw material handling	0.13	0.57	Measured data
4. Use as a flame-retardant in treated textiles			
- Formulation	0.13	0.57	Analogous data
- Processing	<0.001	0.001	Measured data
- Further handling	negl	negl	Industry info
5. Use in pigments, paints, coatings and ceramics			
- Loading and mixing	0.036	0.16	Analogous data
6. Use as a flame-retardant in production of rubber			
- Formulation	0.051	0.22	Analogous data
- Processing	0.064	0.14	Analogous data
7. Use in production of crystal glass			
- Cutting	0.003	0.015	Analogous data

B.9.3 environmental exposure assessment – sediment compartment

IAOIA (International Antimony Oxide Industry Association) has, in cooperation with consultants, gathered data on environmental exposure (EURAS, 2006a; EURAS

2007). This shows that there are around 550 industrial users of diantimony trioxide in EU15.

A number of environmental scenarios have been assessed in the risk assessment. Need for further measures to reduce the risks has been identified for the fresh water sediment compartment in the following three scenarios:

- One production site, P1
- Use as flame-retardant in textiles – formulation, generic site
- Use as flame-retardant in textiles – industrial use (application to textiles), generic site

Production site – P1

Information on releases from diantimony trioxide production have been reported from all four sites currently (2006) producing diantimony trioxide in EU15.

Reported local emissions are summarised in Table 16.

Table 16 Local emissions from diantimony trioxide producing plants.

Site	Water		Notes
	kg Sb_2O_3/y	kg Sb/day	
P-1	5.6 to surface water	0.06	2005 values
P-3	0	0	Water stated 2005
P-4	0	0	Water stated 2005
P-5	1.7 (min 1.2, max 2.1) to municipal STP	0.01	Water 90P of values for 2003 – 2005

The local PEC (Predicted Environmental Concentration) for the sediment compartment is calculated from the ambient background concentration and the reported emissions from production site P1. (PECs for the other production sites were also calculated but did not result in PEC/PNEC ratios above 1.) The sediment PEC value for site P1 taken forward to the risk characterisation is 38.3 mg Sb/kg ww.

Use as flame-retardant in textiles – formulation, generic site

The total usage of diantimony trioxide for flame-retardants backcoating formulations in the textile industry in the EU15 is reported to be 1 757 t/y (EURAS, 2007).

Emissions to surface water

The reported emissions cover a large part of the use in this sector (80 % of tonnage and 55 % of sites). The reported values are deemed to be representative for the industry sector based on this coverage together with information on processes

collected and presented by industry and the regional distribution (replies from 7 countries in EU15) (EURAS, 2007).

The reporting sites were deemed to be representative for sites in this use pattern and therefore default values for emissions were not used. A realistic worst case scenario (generic scenario) was created representing the sites for which no information was available. The generic formulation scenario was based on the highest reported release factor, which was 1 064 g/t to surface water. The reported emission factor to water represents emission after waste water treatment on site. It has been assumed, as a realistic worst case, that waste water will be treated either on site or in an off-site (municipal) STP, not both. The 90-percentile of tonnage used per formulation site (192 t/year) as reported by Industry has been used to dimension the generic site. The resulting emission to water was 201 kg Sb_2O_3 / y (equivalent to 0.59 kg Sb / day).

The local PEC (Predicted Environmental Concentration) for the sediment compartment is calculated from the ambient background concentration and the calculated emissions for the generic formulation site. The sediment PEC value for the generic formulation site taken forward to the risk characterisation is 27.7 mg Sb/kg ww.

Use as flame-retardant in textiles – industrial use (application to textiles), generic site

Emissions to surface water

Because of the limited information on releases from industrial use the emission factor from the OECD Emission Scenario Document (ESD) on Textile Finishing has been used to calculate the releases from a generic local scenario for application to textiles. For coating the default emission factor in the ESD is 0.01, this factor is in the same range as the highest reported emission factor for a site with formulation and processing (7 689 g/t).

The site is assumed to use approximately 105 tonnes diantimony trioxide per year which gives an emission of 1050 kg Sb_2O_3 / y (equivalent to 2.92 kg Sb / day).

The local PEC (Predicted Environmental Concentration) for the sediment compartment is calculated from the ambient background concentration and the calculated emissions for the generic application site. The sediment PEC value taken forward to the risk characterisation is 67.4 mg Sb/kg ww.

B.10 Risk characterisation

We have only included those scenarios where a need for further measures to reduce risks has been identified. For the risk assessment of other scenarios we refer to the EU Risk Assessment Report.

B.10.1 Human health

General Introduction

Irritation

The only animal study which can be used for risk assessment of the skin irritation potential of antimony oxide shows that antimony oxide is not irritating to rabbit skin. However, several human case report studies indicate that diantimony trioxide may cause dermatitis on skin damp with perspiration and the lesions appear to be closely associated with sweat ducts. Thus the lack of dermal irritation in rabbits may be explained by the fact that rabbits lack sweat glands. There are five human case report studies on workers, occupationally exposed to diantimony trioxide, where conjunctivitis and irritation to the eyes and/ or irritation in the respiratory tract have been described. However, there is little exposure data in these studies and therefore it is unclear whether or not diantimony trioxide was the causative agent. Two animal studies indicate that diantimony trioxide is mildly irritating when applied to the eyes of rabbits. One of the studies also shows that diantimony trioxide may cause necrosis of the lower conjunctivae and the nictitating membrane. However, neither of these effects fulfils the EU criteria for classification as irritating to eyes. There is one acute inhalation toxicity animal study available, which has also assessed the irritation potential of diantimony trioxide to the respiratory tract, indicating that diantimony trioxide is not irritating to the respiratory system. In conclusion, based on available animal data diantimony trioxide is not irritating to eyes or to the respiratory system. Based on practical experience in humans, diantimony trioxide should be classified as irritating to skin (R38).

Repeated dose toxicity

The majority of the repeated dose studies in animals are considered inconclusive, either because they do not comply with current test guidelines or because both control and exposed animals showed signs of non-treatment related illness. Still, there are studies that indicate that diantimony trioxide is toxic to lung (Newton et al., 1994; Watt, 1983; Groth et al., 1986a; MPI, 2003). A NOAEC of 0.51 mg/m^3 is derived from the study by (Newton et al., 1994) based on impaired lung clearance observed at 4.50 mg/m^3 Although there might be some uncertainty regarding the accuracy of the NOAEC numerical value, as the study had a high background incidence of lung inflammation in control animals, the NOAEC of 0.51 mg/m^3 is used in the risk characterisation. Furthermore, acute pneumonia has been reported in a reproductive toxicity inhalation study performed by (MPI, 2003), supporting adverse lung effects at exposure levels $\geq$ 2.6 mg/m3. In this context, it could be discussed whether effects caused by pulmonary overload in the rat is also relevant for humans. Positive (Hext, 1994; Oberdorster, 1995) and negative (Tran and Buchanan, 2000; Kuempel et al., 2001) findings of particle overload in human lungs are reported. Macrophage transport of particles into the alveolar interstitium is the major clearance mechanism in humans but of minor importance to the rat. These species differences are related to morphological features of the lung, i.e. to the relative short pathway length from the alveoli to the ciliated terminal bronchioles in rats (Bailey et al., 1989; Kreyling, 1990; Kreyling et al., 1991). In the absence of mechanistic data to the contrary, it must be assumed that the rat model can identify potential hazards to humans and the rat presently remains the appropriate model for both neoplastic and non-neoplastic responses to PSP exposure (ILSI Risk Science Institute Workshop Participants., 2000).

In humans, all the data comes from case report studies on workers employed in industries manufacturing diantimony trioxide. These studies indicate that repeated inhalation exposure to diantimony trioxide may cause pulmonary inflammation, lung emphysema and pneumoconiosis. Only isolated cases of changes in lung function were reported.

Carcinogenicity

Three chronic toxicity/ carcinogenicity studies in rats with inhalation exposure to antimony trioxide are available. Two of these studies indicate neoplastic properties of antimony trioxide, whereas one animal study showed negative results. There is also one human study available (Jones, 1994). However, due to lack of exposure data, the human study is regarded inconclusive. The exposure duration in all three animal studies is 12 months and thus all studies deviates from the OECD guideline on chronic toxicity/carcinogenicity, which prescribes an exposure period of 24 months for rats. In the first animal study (Watt, 1983) inhalation of 5.0 mg Sb_2O_3/m^3 for 12 months produced lung neoplasms in 44% of the animals tested (only females were exposed). In the second study, (Groth et al., 1986a)a 9 times higher dose (45 mg Sb_2O_3/m^3) produced pulmonary neoplasms in 32% of the female rats exposed under similar conditions, but none in male rats. It is noted that the female survival rate was significantly higher than the male counterparts in the study by Groth et al., (1986a). The differences in incidence between the studies might be explained by a longer observation period (12 months vs 20 weeks) and by the use of older animals (8 months vs 14 weeks) in the study by (Watt, 1983). The study by Newton et al., (1994) showed no diantimony trioxide-related lung tumours, neither in males nor females, at any dose level up to 4.5 mg/m^3. This is in contrast with the data reported by Watt and Groth and the cause to the difference is not entirely clear. However, a comparison of the Watt and the Newton studies, which were conducted at similar exposure levels, showed that the exposed rats had more lung damage and appeared to have considerably more antimony deposited in the lungs in the Watt study than in the Newton study. This may suggest that the exposure levels in the Watt study may have been above those reported. Given that the dose level in the study by Groth is 10 times higher and also the dose levels in the study by Watt were likely higher than 1.9 and 5.0 mg/m^3 the dose levels in the Newton study most probably fit in the dose range where no tumous were observed. The particle size, which will affect lung deposition, clearance and retention and hence target organ dose, was similar among the studies although they were all measured using different techniques. The three studies together also show a picture of impaired pulmonary clearance, pulmonary overload, macrophage infiltration, chronic interstitial pneumonia and fibrosis. Based on the data from all three studies it can be argued that the tumours found are due to pulmonary overload and subsequently to inflammation and neoplastic transformation of epithelial cells. In this context, it could be discussed whether effects caused by pulmonary overload in the rat is also relevant for humans. Positive (Hext, 1994; Oberdorster, 1995) and negative (Tran and Buchanan, 2000; Kuempel et al., 2001) findings of particle overload in human lungs are reported. However, in the absence of mechanistic data to the contrary, it must be assumed that the rat model can identify potential carcinogenic hazards to humans and the rat presently remains the appropriate model for both neoplastic and non-neoplastic responses to PSP exposure (ILSI Risk Science Institute Workshop Participants., 2000). Consequently, diantimony trioxide can be regarded as a threshold carcinogen and as a starting point for a quantitative risk

characterisation the NOAEC of 0.51 mg/m^3 derived for local repeated dose toxicity is also used for carcinogenicity (Newton et al., 1994) and is used in the risk characterisation. It is based on impaired lung clearance observed at 4.50 mg/m^3. There may be some uncertainty regarding the accuracy of the NOAEC numerical value as the study had a high background incidence of lung inflammation in control animals. In addition, the exposure duration was 12 months and thus deviates from the OECD guideline on chronic toxicity/carcinogenicity, which prescribes an exposure period of 24 months for rats. Based on the present data it is concluded that diantimony trioxide induces lung tumours in experimental animals and therefore antimony trioxide is currently classified in Annex 1, Directive 67/548/EEC as Carc. Cat. 3: R40 (Limited evidence of a carcinogenic effect).

Calculation of MOS- and reference MOS values

For risk assessment the MOS approach as outlined in the TGD (Human Health Risk Characterisation, Final draft) is applied.

Table 17 Summary of critical effect measures. NOAEL/ NOAEC value is given for repeated dose toxicity. The skin irritating properties are indicated by a + sign.

Endpoint	Inhalation measure	Dermal measure
Irritation / corrosivity	-	+
Repeated dose toxicity	0.51 mg/m^3	-
Carcinogenicity	0.51 mg/m^3	-

Workers

There are several industries in which diantimony trioxide is produced or used, and the life cycle stages where occupational exposure may occur are; production, formulation, i.e. industrial use of diantimony trioxide as an additive, and processing, i.e. industrial and professional use of semi- or end-products containing diantimony trioxide. At some sites, both formulation and processing may take place. In addition, exposure might occur during recycling and disposal of articles containing diantimony trioxide, but there is no available information about this. It is assumed that exposure during recycling and disposal is limited compared to the exposure from production, formulation and industrial and professional use, and therefore this scenario is not considered further in this exposure assessment.

In addition to production of diantimony trioxide, the following uses have been identified:

- Use as catalyst in production of PET
- Use as flame-retardant in production of plastics
- Use as flame-retardant in treated textiles
- Use in pigments, paints, coatings and ceramics
- Use as flame-retardant in production of rubber
- Use in production of crystal glass

The following data were used for the occupational exposure assessments of diantimony trioxide:

- measured workplace data from production and uses of diantimony trioxide
- physico-chemical data of diantimony trioxide
- qualitative data, such as process description and use pattern of the product, and quantitative data regarding frequency and duration of handling of diantimony trioxide
- concentrations of diantimony trioxide used in the different products

For all scenarios of occupational exposure, a respiratory volume of 10 m^3/work day is used.

The main routes of occupational exposure to diantimony trioxide are inhalation of airborne solid dust and dermal exposure to solid diantimony trioxide. Dermal exposure may occur during direct handling, either by contamination of skin surfaces or by dermal deposition of airborne dust. However, due to negligible dermal absorbtion of antimony, dermal exposure is not calculated in the quantitative risk characterisation.

Irritation

Diantimony trioxide is considered irritating to skin. Given the skin irritating potential of diantimony trioxide it is concluded that the substance is of concern for workers with regard to skin irritation and, hence, there is a need for classification. Once classified the, the risk is regarded to be adequately controlled.

Repeated dose toxicity

Repeated inhalation exposure to diantimony trioxide gives local toxic effects in the lung and a NOAEC of 0.51 mg/m^3 is derived from a 12 month inhalation exposure study in rat, supported by observations of acute pneumonia in a 19 days inhalation developmental toxicity study. No systemic toxicity is observed after repeated exposure, therefore no quantitative risk characterisation is performed for systemic repeated dose toxicity.

Inhalation (local)

To calculate MOS-values for local pulmonary toxicity the exposure levels should be compared with a corrected NOAEC of 0.26 mg/m^3 calculated as follows (see Table 18): The experimental NOAEC of 0.51 mg/m^3 adapted by a factor of 6/8 to account for differences between the experimental inhalation duration of 6 h per day and the average working day of 8 h per day and then multiplied by a factor of 6.7/10 for activity driven differences of respiratory volumes in workers (0.51 mg/m^3 · 6/8 · 6.7/10). The achieved MOS-values are then compared with a reference MOS of 12.5 (see below).

The following assessment factors are applied in the setting of a reference MOS to a local effect in the lung;

- a factor of 2.5 for interspecies differences

- a factor of 5 for intraspecies differences; this covers the variation in sensitivity expected between workers

Table 18 Occupational risk assessment for repeated dose toxicity (local effects). The NOAEC-value is compared with typical and reasonable worst-case (RWC) exposures to calculate MOS-values.

	Inhalation (local effects)							
	Typical exposure* (mg/m^3)	Corrected NOAEC (mg/m^3)	MOS	Conclu-sion	RWC exposure* (mg/m^3)	Corrected NOAEC (mg/m^3)	MOS	Conclu-sion
Production of Diantimony Trioxide								
Conversion, with RPE	0.027	0.26	9.6	(iii)	0.15	0.26	1.7	(iii)
Refuming, with RPE	0.012	0.26	22	(ii)	0.047	0.26	5.5	(iii)
Final handling, with RPE	0.040	0.26	6.5	(iii)	0.11	0. 26	2.4	(iii)
Conversion, without RPE					2.9	0.26	0.09	(iii)
Refuming, without RPE					0.94	0.26	0.28	(iii)
Final handling, without RPE					2.1	0.26	0.12	(iii)
Use as a catalyst in production of PET								
Powder handling	0.002	0.26	130	(ii)	0.026	0. 26	10	(iii)
Use as flame-retardant in production of plastics								
Raw material handling	0.13	0. 26	2	(iii)	0.57	0. 26	0.46	(iii)
Use as flame-retardant in treated textiles								
Formulation	0.13	0. 26	2	(iii)	0.57	0. 26	0.46	(iii)
Processing	<0.001	0. 26	-		0.001	0. 26	260	(ii)
Further handling	negl.	0. 26	-		negl.	0. 26	-	
Use in pigments, paints, coatings and ceramics								
Loading and mixing	0.036	0. 26	7.2	(iii)	0.16	0. 26	1.6	(iii)
Use as flame-retardant in production of rubber								
Formulation	0.051	0. 26	5.1	(iii)	0.22	0. 26	1.2	(iii)
Processing	0.064	0. 26	4	(iii)	0.14	0. 26	1.9	(iii)
Use in production of crystal glass								
Cutting	0.003	0. 26	87	(ii)	0.015	0. 26	17	(ii)

*Exposure values from sections 4.1.1.2.2-8

It can be seen that there is a need for limiting the risks for a number of occupational exposure scenarios.

Carcinogenicity

Diantimony trioxide is considered to be a carcinogenic substance and is classified for carcinogenicity. Although the mechanism for pulmonary tumour formation is still unclear it may be assumed that particle deposition followed by macrophage infiltration, pulmonary inflammation and impaired clearance are pivotal initial steps in the process. Consequently, diantimony trioxide can be regarded as a threshold carcinogen and as a starting point for a quantitative risk characterisation the NOAEC of 0.51 mg/m^3 derived for local repeated dose toxicity is also used for carcinogenicity.

Inhalation

To calculate MOS-values for pulmonary carcinogenicity the exposure levels should be compared with a corrected NOAEC of 0.26 mg/m^3 calculated as follows (see Table): The experimental NOAEC of 0.51 mg/m^3 adapted by a factor of 6/8 to account for differences between the experimental inhalation duration of 6 h per day and the average working day of 8 h per day and then multiplied by a factor of 6.7/10 for activity driven differences of respiratory volumes in workers (0.51 mg/m^3 · 6/8 · 6.7/10). The achieved MOS-values are then compared with a reference MOS of 12.5 (see below).

The following assessment factors are applied in the setting of a reference MOS to a local effect in the lung;

- a factor of 2.5 for interspecies differences
- a factor of 5 for intraspecies differences; this covers the variation in sensitivity expected between workers

Table 19 Occupational risk assessment for pulmonary carcinogenicity. The NOAEC-value is compared with typical and reasonable worst-case (RWC) exposures to calculate MOS-values.

	Inhalation (pulmonary carcinigenicity)							
	Typical exposure* (mg/m^3)	Corrected NOAEC (mg/m^3)	MOS	Conclu-sion	RWC exposure* (mg/m^3)	Corrected NOAEC (mg/m^3)	MOS	Conclu-sion
Production of Diantimony Trioxide								
Conversion, with RPE	0.027	0.26	9.6	(iii)	0.15	0.26	1.7	(iii)
Refuming, with RPE	0.012	0.26	22	(ii)	0.047	0.26	5.5	(iii)
Final handling, with RPE	0.040	0.26	6.5	(iii)	0.11	0. 26	2.4	(iii)
Conversion, without RPE					2.9	0. 26	0.09	(iii)
Refuming, without RPE					0.94	0. 26	0.28	(iii)
Final handling, without RPE					2.1	0. 26	0.12	(iii)
Use as a catalyst in								

production of PET								
Powder handling	0.002	0.26	130	(ii)	0.026	0. 26	10	(iii)
Use as flame-retardant in production of plastics								
Raw material handling	0.13	0. 26	2	(iii)	0.57	0. 26	0.46	(iii)
Use as flame-retardant in treated textiles								
Formulation	0.13	0. 26	2	(iii)	0.57	0. 26	0.46	(iii)
Processing	<0.001	0. 26	-		0.001	0. 26	260	(ii)
Further handling	negl.	0. 26	-		negl.	0. 26	-	
Use in pigments, paints, coatings and ceramics								
Loading and mixing	0.036	0. 26	7.2	(iii)	0.16	0. 26	1.6	(iii)
Use as flame-retardant in production of rubber								
Formulation	0.051	0. 26	5.1	(iii)	0.22	0. 26	1.2	(iii)
Processing	0.064	0. 26	4	(iii)	0.14	0. 26	1.9	(iii)
Use in production of crystal glass								
Cutting	0.003	0. 26	87	(ii)	0.015	0. 26	17	(ii)

*Exposure values from sections 4.1.1.2.2-8

It can be seen that there is a need for limiting the risks for a number of occupational exposure scenarios.

B.10.2 Environment

Sediment

$PNEC_{sediment}$ = 7.8 mg Sb/kg ww was derived by dividing the lowest NOEC (midge *Chironomus riparius* or oligochaete *Lumbriculus variegates*) with an assessment factor of 10, since NOECs from three species with different living and feeding conditions are available.

The risk characterisation ratios for sediment are shown in Table . Predicted PEC:s have only been included for the realistic worst cases and if these give PEC/PNEC ratio > 1.

Table 20 PEC/PNEC ratios for sediment

	$PEC_{local, sediment}$ (mg Sb/kg wet weight)	RCR (PEC/PNEC)
Production, site P1	38.3	*4.9*
Formulation as flame-retardant in textiles, generic site	27.7	*3.5*

	$PEC_{local,\ sediment}$ (mg Sb/kg wet weight)	RCR (PEC/PNEC)
Application of textile back-coating, generic site	67.4	*8.6*

Four sites producing diantimony trioxide have reported information on releases making it possible to make a completely site-specific prediction of PEC. Of these one (site P1) had a PEC/PNEC ratio >1 which is also supported by measured concentrations of antimony in sediment near the site.

For the use areas formulation and industrial processing of flame-retardant textile back-coatings, the PEC/PNEC ratios are above 1 only for the generic (formulation and processing) sites. The PEC calculation for the generic textile formulation site is performed assuming no municipal STP treatment. The reason for this is that the emission factor used represents emissions after on-site treatment and it is not assumed to be a realistic worst case to assume both on site and off site sewage treatment. However, even if it was assumed that the waste water from the generic site was treated off site the PEC would be 14.2 mg/kg ww giving a PEC/PNEC ratio of 1.82.

Conclusions to the risk assessment for the sediment compartment:

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

This conclusion applies to the generic scenarios for formulation and application of flame-retardant textile back-coating and to one production site (site P1).

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those that are already being applied.

This conclusion applies to all other scenarios, including nineteen sites using diantimony trioxide in textile applications and three production sites, that all report releases.

B.11 Summary on hazard and risk

Introduction

Diantimony trioxide is a solid substance at room temperature and is mostly handled as solid powder; dry or in wetted form, pellets, paste, or granules. The particle size of diantimony trioxide differs between different technical products. The vapour pressure of solid diantimony trioxide is low and it has a low solubility in most solvents.

The major use of diantimony trioxide is as a flame-retardant. However, it does not itself have flame-retarding properties; instead it is a synergist for halogenated flame-retardants in plastics, paints, adhesives, sealants, rubber, and textile back coatings.

Other uses of diantimony trioxide include: as polymerisation catalyst used in PET resin manufacture and as a clarifying aid in certain glasses, and in pigments. Approximately 25 000 tonnes per year are used in EU, mainly (>70%) in the production of flame-retarded plastics (PVC and non-PVC). Diantimony trioxide is presently produced in four plants in EU.

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.

The human population may be exposed to diantimony trioxide at the workplace, from use of consumer products containing diantimony trioxide and indirectly via the environment through contact with contaminated air. In the environment,t diantimony trioxide will dissolve to the trivalent and pentavalent forms of antimony. Consequently, humans may also be exposed indirectly via the environment to the antimony ion through consumption of food, water and soil.

Environment

The compartments of concern are: fresh water sediment (generic scenarios for formulation and application of flame-retardant textile back-coating and one production site).

Sediment

There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

This applies to the generic scenarios for formulation and application of flame-retardant textile back-coating and to one production site (site P1).

There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

This conclusion applies to all other scenarios, including nineteen sites using diantimony trioxide in textile applications and three production sites, that all report releases.

Human health

Human health (toxicity)

Human populations exposed to diantimony trioxide include workers, consumers and humans exposed via the environment. Indirect exposure via the environment to the antimony ion may also occur as diantimony trioxide is readily dissolved to the trivalent and pentavalent antimony ions in the environment. However, the risk characterisation has shown that only exposure of workers is of concern. For exposure assessment, both measured data, analogues data, calculations and modelling have been used.

The endpoints of concern are: skin irritation, local pulmonary toxicity and carcinogenicity.

Repeated inhalation exposure to diantimony trioxide gives local toxic effects in the lung and a NOAEC of 0.51 mg/m^3 is derived from a 12 month inhalation exposure study in rat, supported by observations of acute pneumonia in a 19 days inhalation developmental toxicity study. No systemic toxicity was observed after repeated exposure. There may be some uncertainty regarding the accuracy of the NOAEC numerical value as the study had a high background incidence of lung inflammation in control animals.

Diantimony trioxide is considered to be a carcinogenic substance and is classified for carcinogenicity. Although the mechanism for pulmonary tumour formation is still unclear it may be assumed that particle deposition followed by macrophage infiltration, pulmonary inflammation and impaired clearance are pivotal initial steps in the process. Consequently, diantimony trioxide can be regarded as a threshold carcinogen and as a starting point for a quantitative risk characterisation the NOAEC of 0.51 mg/m^3 derived for local repeated dose toxicity is also used for carcinogenicity.

Workers

There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

This applies to skin irritation for all scenarios to indicate the need for classification. Once classified, the risk is regarded to be adequately controlled.

The need for limiting the risks also applies to repeated dose toxicity (local pulmonary toxicity after inhalation) and carcinogenicity (pulmonary carcinogenicity) for the following scenarios: **Production of diantimony trioxide:** Conversion, Refuming and Final handling with and without RPE, **Use as a catalyst in production of PET**: Powder handling, **Use as flame-retardant in production of plastics**: Raw material handling, **Use as flame-retardant in treated textiles**: Formulation, **Use in pigments, paints, coatings and ceramics:** Loading and mixing, **Use as flame-retardant in production of rubber:** Formulation and Processing.

C. AVAILABLE INFORMATION ON ALTERNATIVES

The proposed measures do not mean that diantimony trioxide or current techniques must be substituted. Risk management measures, for the reduction of exposure to dusty materials in the work-place and to reduce emissions of material from industrial sites are well known. Examples of such measures could be organisational changes and engineering controls. No discussion on alternatives has therefore been included.

C.1 Identification of possible alternative substances and techniques

C.2 Availability of alternatives

C.3 Human health risks related to alternatives

C.4 Environment risks related to alternatives

C.5 Technical and economical feasibility of alternatives

C.6 Other information on alternatives

D. JUSTIFICATION FOR ACTION ON A COMMUNITY-WIDE BASIS

D.1 Considerations related to human health and environmental risks

Risks for workers have been identified in several industry sectors and the potential effects give cause for concern. This justifies community-wide action within the existing legal framework.

Risks for the environment have been identified near some industrial sites and the potential effects give cause for concern. This justifies community-wide action within the existing legal framework. Using the information from the risk assessment in actions already required under current legislation (now or at a later stage as specific provisions come into force) is however considered to be sufficient to adequately control the risks to the environment.

D.2 Considerations related to internal market

The proposed community-wide actions will not be obstacles to the free movement in the inner market.

D.3 Other considerations

The outcome of the risk assessment under Regulation (EEC) 793/93 is that there is a need for further measures to reduce risks other than those already in place.

D.4 Summary

Community-wide measures are considered to be justified based on the extent and nature of the identified needs to reduce risks.

E. JUSTIFICATION WHY THE PROPOSED MEASURES ARE THE MOST APPROPRIATE COMMUNITY-WIDE MEASURE

E.1 Identification and description of risk management options

E.1.1 Risk to be addressed – the baseline

A need for further measures to reduce the risks for workers has been identified (according to the criteria of Regulation (EEC) 793/93) in several industry sectors and the potential effects give cause for concern. Using the information from the risk assessment in actions already required under Reach will help to control those risks.

A need for further measures to reduce the risks to the local environment has been identified (according to the criteria of Regulation (EEC) 793/93) near some industrial sites and the potential effects give cause for concern. Using the information from the risk assessment in actions already required under current legislation (now or at a later stage as specific provisions come into force) is however considered to be sufficient to adequately control the risks to the environment.

Industry has already taken action to reduce risks, see section H.

E.1.2 Other Community-wide risk management options than the proposed measures

One option is to propose no measures apart from those already in place.
Other possible community-wide measures include restrictions in manufacturing, placing on the market and use under Reach (to protect workers and/or the local environment).

E.1.3 Options for restrictions

Not relevant since no restrictions are proposed.

E.2 Comparison of instruments: proposed measures vs. other Community-wide risk management options

E.2.1 Effectiveness

E.2.1.1 Risk reduction capacity

For the ***protection of workers*** the proposed community-wide OEL, the proposed inclusion of information in the Chemical Safety Assessment under Reach together with the existing legal framework is considered sufficient to give an adequate control of the risks.

For the ***protection of the local environment*** the proposed inclusion of information in the setting of permit under Directive 2008/1/EC, establishing EQS under Directive 2000/60/EC and in the Chemical Safety Assessment under Reach, together with the existing legal framework is considered sufficient to give an adequate control of the risks.

Restrictions in manufacture, placing on the market and use of diantimony trioxide under Regulation 1907/2006 (Reach) could also be formulated to adequately control the risks to workers and/or the local environment.

E.2.1.2 Proportionality

Both the proposed measures and restrictions are considered sufficient to achieve the objective - adequate control of the identified risks. The proposed measures lay, in net total and compared to restrictions, less financial and administrative burden upon the Union, national governments, regional or local authorities, economic operators and citizens, thereby fulfilling the requirement of minimising the burden whilst being commensurate to the objective to be achieved.

E.2.2 Practicality: implementability, enforceability, manageability

The proposed measures are all under a current legislative framework and follows normal practice in the respective frameworks. They are therefore considered possible to implement, enforce and manage within the current system.

E.2.3 Monitorability

The proposed measures are all under a current legislative framework and follows normal practice in the respective frameworks. This is considered to give a sufficient basis for monitoring.

E.2.4 Overall assessment against the three criteria

The proposed measures are considered to fulfil the criteria of effectivenss, practicality and monitorability.

E.3 Comparison of proposed options

The proposed measures have been evaluated under section E.2 above. No further options have been considered.

E.3.1 Effectiveness

E.3.1.1 Risk reduction capacity

E.3.1.1.1 Effect on human health

E.3.1.1.2 Effect on the environment

E.3.1.1.3 Other effects

E.3.1.2 Proportionality

E.3.1.2.1 Economic feasibility

E.3.1.2.2 Technical feasibility

E.3.1.2.3 Other issue relating to proportionality

E.3.2 Practicality

E.3.2.1 Implementability

E.3.2.2 Enforceability

E.3.3 Monitorability

E.3.4 Overall assessment against the three criteria

E.4 Main assumptions used and decisions made during analysis

Existing community-wide legal frameworks has been considered to function.

E.5 The proposed measures and summary of the justifications

Workers

The legislation for workers' protection currently into force at Community level is generally considered to give an adequate framework to limit the risks of the substance to the extent needed and shall apply.

Within this framework it is recommended:

- to establish at community level occupational exposure limit values for Antimony trioxide according to Directive 98/24/EEC[5].

Measures foreseen as a consequence of regulations already in place

Regulation (EC) 1907/2006 (Reach)

Diantimony trioxide is classified as dangerous in accordance with directive 67/548/EEC. An importer or producer that imports or produces more than 10 tons of diantimony trioxide should therefore include an exposure assessment and a risk characterisation in the chemical safety assessment that is part of the required registration under Reach. Exposure scenarios are sets of conditions that describe how substances are manufactured or used during their life-cycle and how the manufacturer or importer controls, or recommends to control, exposures of humans and the environment. The exposure scenarios must include the appropriate risk management measures and operational conditions that, when properly implemented, ensure that the risks from the uses of the substance are adequately controlled. Exposure scenarios need to be developed to cover all "identified uses" which are the manufacturers' or importers' own uses, and uses which are made known to the manufacturer or importer by his downstream users and which the manufacturer or importer includes in his assessment. Relevant exposure scenarios will need to be annexed to the safety data sheets that will be supplied to downstream users and distributors. The chemical safety assessment should show that the risks to the human population are adequately controlled, if necessary by describing how the manufacturer or importer controls or recommends downstream users to control exposure to humans and the environment. The description of how to control the risks will be included in the exposure scenario annexed to the safety data sheet (SDS). The downstream users will have to check that their use(s) are "covered" by the SDS, i.e. that they use a substance within the conditions described in the exposure scenarios in the Annex to the SDS, and apply these conditions.

Within this framework it is recommended:

- that any importer, producer or downstream user takes into account relevant information in the EU RAR when performing the chemical safety assessment.
- that ECHA takes into account relevant information in the EU RAR in the compliance check of registrations.
- that national authorities take into account relevant information in the EU RAR when enforcing Reach.

Directive 2000/60/EC (WFD)

[5] OJ L 131, 05.05.1998, p. 11

For the river basins where emissions of diantimony trioxide may cause a risk, the relevant Member State should establish Environmental Quality Standards (EQS) and the national pollution reduction measures to achieve those EQS in 2015 should be included in the river basin management plans in line with the provisions of Directive 2000/60/EC.

Directive 2008/1/EC (IPPC)
The competent authorities in the Member States concerned should lay down, in the permits issued under Directive 96/61/EC, conditions, emission limit values or equivalent parameters or technical measures regarding diantimony trioxide in order for the installations concerned to operate by the end of October 2007 according to BAT and taking into account the technical characteristic of the installations concerned, their geographical location and the local environmental conditions.

Member States should carefully monitor the implementation of BAT regarding diantimony trioxide and report any important developments to the Commission in the framework of the exchange of information on BAT.

The proposed measures are considered to be effective, practical, monitorable and proportionate to the objective to be achieved – adequate control of risks.

F. SOCIO-ECONOMIC ASSESSMENT OF PROPOSED MEASURES

No restrictions on marketing and use of antimony trioxide have been proposed. This section is therefore not elaborated.

Measures already foreseen under relevant existing legislation is seen as the reference level (baseline). For diantimony trioxide and the identified needs to reduce risks Directive 2000/60/EC; Directive 96/61/EC and Regulation (EC) 1907/2006 are all relevant. The discussion below only considers the consequences of further measures.

F.1 Human health and environmental impacts

F.1.1 Human health impacts

The proposed measures are considered to be effective and will therefore lead to improved health for workers exposed to diantimony trioxide. No quantification has been made.

F.1.2 Environmental impacts

The proposed measures are considered to be effective and will therefore lead to improved environmental status near the sites that gave cause for concern. No quantification has been made.

F.2 Economic impacts

The establishment of a community-wide OEL leads to costs in relation to:
- developing and maintaining the OEL at community-level
- handling and enforcing the community-wide OEL in the member states (the OEL would only be indicative), several countries have national OELs and in these cases

and where a member state would have introduced an OEL anyway, costs may be reduced by having access to a community-wide OEL
- implementing controls to reach the OEL and follow-up in industry

The regulations regarding OELs vary considerably among the member states. For this reason and for lack of information no quantification has been done. The costs are however likely to be limited.

F.3 Social impacts

No significant social impacts are foreseen.

F.4 Wider economic impacts

No significant wider economic impacts are foreseen.

F.5 Distributional impacts

No significant distributional impacts are foreseen.

F.6 Main assumptions used and decisions made during analysis

F.7 Uncertainties

The number of workers exposed to diantimony trioxide has not been quantified.
The costs of the proposed measures are uncertain and have therefore only been described in qualitative terms.

F.8 Summary of the benefits and costs

No quantification of benefits and costs has been made, but the costs have been assessed to be limited and there are clear benefits in terms of workers health and the status of the local environment near certain industrial sites.

G. STAKEHOLDER CONSULTATION

Extensive consultations with industry and member states experts took place during the risk assessment (up to spring 2008) under regulation (EEC) 793/93, including written communications, bilateral meetings with representatives of industry producing diantimony trioxide and discussions in meetings (meetings of Technical Committee of New and Existing Substances, TCNES). The results from these consultations have been incorporated in the Risk Assessment Report.

H. OTHER INFORMATION

Voluntary actions by industry

This section provides a summary of information submitted by industry after the risk assessment was finalised.

Sediment risk for Producer P-1

According to Industry, a number of measures have been taken by producer P-1 to reduce the identified risks for the local aquatic compartment (sediment) by reducing emissions and removing historical contamination. Monitoring of antimony concentrations in the local environment shows a clear decreasing trend. This information was received after the risk assessment was concluded and is therefore not included in the exposure assessment and risk characterisation. (i2a, 2008a)

For the risk for the generic textile scenario:
According to industry, all companies that provided data were found to be clear from risk. Only for those companies that did not provide information and for which the calculations were done consequently with default values, a risk was identified. Industry therefore has no further actions to propose for these sites.

For the risks identified to workers:
Industry has voluntarily committed itself to monitor workers occupationally exposed to diantimony trioxide. The emphasis will be placed on measures of primary prevention in order to maintain the levels of diantimony trioxide as low as reasonably possible. The efficacy of these measures can be controlled by monitoring the exposed workers and start building up a harmonised database. The current occupational health and industrial hygiene programs will be evaluated by an expert group and an advice will be given on additional indicators to complete these programs. This can be done in a joint effort of the independent expert, SCOEL and the International Antimony Association toxicologists by spring 2009.

In addition, written guidance will provide all stakeholders involved in the diantimony trioxide workplace risk management with accurate information on how to best monitor diantimony trioxide exposure at the workplace (also by spring 2009). Finally, determining the correlation between diantimony trioxide exposure and possible adverse health effects would help establish more accurate occupational exposure limits. This step will start once the monitoring has been harmonised and will take 1.5 to 2 years to complete (i2a, 2008b).

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ANNEXES