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The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals

123. Antimony

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Preface

The Nordic Council is an intergovernmental collaborative body for the five countries, Denmark, Finland, Iceland, Norway and Sweden. One of the committees, the Nordic Senior Executive Committee for Occupational Environmental Matters, initiated a project in order to produce criteria documents to be used by the regulatory authorities in the Nordic countries as a scientific basis for the setting of national occupational exposure limits.

The management of the project is given to an expert group. At present the Nordic Expert Group consists of the following member:

Vidir Kristjansson	Administration of Occupational, Safety and Health, Iceland
Petter Kristensen	National Institute of Occupational Health, Norway
Per Lundberg (chairman)	National Institute for Working Life, Sweden
Vesa Riihimäki	Institute of Occupational Health, Finland
Leif Simonsen	National Institute of Occupational Health, Denmark

For each document an author is appointed by the Expert Group and the national member acts as a referent. The author searches for literature in different data bases such as Toxline, Medline, Cancerlit and Nioshtic. Information from other sources such as WHO, NIOSH and the Dutch Expert Committee is also used as are handbooks such as Patty's Industrial Hygiene and Toxicology. Evaluation is made of all relevant scientific original literature found. In exceptional cases information from documents difficult to access are used. The draft document is discussed within the Expert Group and is finally accepted as the Group's document.

Editorial work is performed by the Group's Scientific Secretary, Gregory Moore/Johan Montelius, and technical editing by Ms Karin Sundström, at the National Institute for Working Life in Sweden.

Only literature judged as reliable and relevant for the discussion is referred to in this document. Concentrations in air are given in mg/m^3 and in biological media in mol/l. In case they are otherwise given in the original papers they are if possible recalculated and the original values are given within brackets.

The documents aim at establishing a dose-response / dose-effect relationship and defining a critical effect based only on the scientific literature. The task is not to give a proposal for a numerical occupational exposure limit value.

The evaluation of the literature and the drafting of this document on Antimony was made by Drs John Erik Berg and Knut Skyberg at the Department of Occupational Medicine, National Institute of Occupational Health, Oslo, Norway. The final version was accepted by the Nordic Expert Group November 21, 1997, as its document.

We acknowledge the Nordic Council for its financial support of this project.

Gregory Moore/Johan Montelius
Scientific Secretary

Per Lundberg
Chairman

Abbreviations

AAS	Atomic absorption spectrophotometry
ACGIH	American Conference of Governmental and Industrial Hygienist
AES	Atomic emission spectroscopy
APT	Antimony potassium tartrate
ECG	Electrocardiogram
BW	Body weight
ETAAS	Electrothermal atomic absorption spectrometry
GABA	γ-Aminobutyric acid
GSH	Glutathione
IAEA	International Atomic Energy Association
IARC	International Agency for Research on Cancer
ICP-AES	Inductively coupled plasma atomic emission spectrometry
ILO	International Labour Office
LD_{50}	Dose that is estimated to be lethal to 50% of test animals
LOAEL	Lowest Observable Adverse Effect Level
NAA	Neutron activation analysis
NIOSH	US National Institute for Occupational Safety and Health
NOAEL	No Observable Adverse Effect Level
OEL	Occupational exposure limit
PIXE	Particle-induced X-ray emission analysis
SFC	Supercritical fluid chromatography
TWA	Time-weighted average

Contents

1. Introduction

Antimony is an elementary metal, but mined mostly as antimony sulphide (stibnite). Antimony sulphide is known to be used as a cosmetic, like face painting, since 4000 BC (103). From biblical times up until the 20th century, it has also been used in therapeutic drugs. Because of its high toxicity and lack of efficacy, the medical use in humans was prohibited in the sixteenth century (68). It was reintroduced in 1657 because King Louis XIV appeared to have been successfully treated for typhoid fever with an antimony preparation given by a quack. During the following 200 years, however, antimony had quite widespread use in pharmacology, for the treatment of syphilis, fever and melancholy. James's powder was used against fever and in epilepsy, and contained one part oxide of antimony and two parts phosphate of lime. Hutchinson recommended the external use of potassium antimony tartrate for rheumatism. In the mid 1850s antimony was used to facilitate labour. During the American Civil War antimony became unpopular because of its irritating action on intestinal mucosa. The anthroposophical movement has used antimony mainly due to its founder's (Rudolf Steiner) misinterpretation of Paracelsus' writing. Anthroposophical medicines containing as much as 5% of antimony are still sold in the UK.

The total world reserves of antimony were estimated in 1988 to be 4.35 million metric tons, the half of which in China (72). The leading producers are Bolivia and South Africa (103). Antimony is found in 114 minerals. Pure antimony has few applications, but alloys are used for instance with lead as grid alloy in storage batteries, as tank linings, foil, bullets and in cable sheaths. Non-metal compounds of antimony are used as flame retardant, as pigment in paints and as a glass-forming substance. Antimony still is a component in antiparasitic medicine (Triostam, Pentostam). Antimony has no known essential biological function in living organisms (96).

In an old study of antimony trioxide workers Sir Thomas Oliver reported on 6 workers engaged in the production for a mean of 10 years (73). He observed skin affection only in two men, in spite of handling the antimony trioxide with bare hands. Sickness absence was no problem. His conclusion, thus, was that industrial production of antimony represented no hygienic problem or risk, a statement which today at least would have to be moderated.

The first description of adverse effects of antimony in man, i.e. in a chemist, was reported by Ramazzini in 1713 (103).

2. Substance Identification

Antimony or stibium (atomic symbol Sb) is an element, and belongs to group V. Antimony's atomic number is 51 and has an atomic weight of 121.75. The outer

electron shell contains 5 electrons, and the oxidation states of antimony are 0, +3 and +5.

Antimony occurs in its elemental form and in several compounds and alloys. The most common compounds are oxides, sulphides and hydride (see Table 1). The most common alloys of antimony are in combination with lead, tin and copper but alloys with other metals occur.

3. Physical and Chemical Properties

Pure antimony is a silver white, brittle, hard metal, which is easily pulverised (103). The crystal structure is hexagonal. The density is 6.68 at 25°C. It is soluble in hot concentrated H_2SO_4 and in aqua regia (HCl/HNO_3 in a 3:1 mixture). The physical and chemical properties of some antimony compounds are given in Table 2. Antimony is only slowly oxidised in moist air forming a blackish-grey mixture of antimony and antimony oxide. Antimony metal burns in air or oxygen with a red heat with incandescence forming white vapour of antimony trioxide. This vapour has a garlic-like smell.

Antimony pentaoxide is an oxidising agent which is converted to its trivalent form in acidic media (103).

Antimony-lead alloys have a high corrosion resistance to many chemicals. A lead oxide and carbonate protective coat is formed upon exposure to air rendering the alloy practically inert to further chemical reaction with the atmosphere.

Table 1. Substance identification of antimony and some inorganic compounds.

Chemical abstract name	Molecular formula	CAS registry number	Molecular weight
Antimony	Sb	7440-36-0	121.75
Antimony hydride (stibine)	SbH_3	7803-52-3	124.78
Antimony trifluoride	SbF_3	7783-56-4	178.75
Antimony pentafluoride	SbF_5	7783-70-2	216.75
Antimony trichloride	$SbCl_3$	10025-91-9	228.11
Antimony pentachloride	$SbCl_5$	7647-18-9	299.00
Antimony trioxide	Sb_2O_3	1309-64-4	291.50
Antimony pentoxide	Sb_2O_5	1314-60-9	323.50
Antimony orange	Sb_2S_3	1345-04-6	339.68
Stibnite	Sb_2S_3	7446-32-4	339.68
Antimony pentasulphide	Sb_2S_5	1315-04-4	403.80
Antimony tribromide	$SbBr_3$	7789-61-9	361.48

Stibnite is a naturally occurring form of diantimony trisulphide which is black and has an orthorhombic crystal structure, whereas, for instance, while Sb_2S_3 in the form of antimony orange is yellow red and has an amorphous structure.

Table 2. Physical and chemical properties of some antimony compounds.

Compound	Formula	Crystalline form and properties	Melting point °C	Boiling point °C	Solubility in cold water
Antimony	Sb	Silver white metal hexagonal	630.5	1750	insoluble
bromide, tri-	$SbBr_3$	col., rhomb.	96.6	280	decomposes
chloride, penta-	$SbCl_5$	white liquid or monoclinic	2.8	79	decomposes
chloride, tri-	Butter of antimony $SbCl_3$	col., rhomb., deliq.	73.4	283	very soluble
fluoride, penta-	SbF_5	col. oily liquid	7	149.5	soluble
fluoride, tri-	SbF_3	col., rhomb.	292	subl. 319	very soluble
hydride (=stibine)	SbH_3	inflammable gas	-88	-17.1	slightly soluble
iodide, tri-	SbI_3	ruby-red, hexagonal	170	401	decomposes
oxide, penta-	Sb_2O_5/Sb_4O_{10}	yellow powder	380/930	-	very slightly soluble
oxide, tetra-	Natural cervantite Sb_2O_4	white powder	930	-	very slightly soluble
oxide, tri-	Natural senarmonite Sb_2O_3	white, cub.	656	subl. 1550	very slightly soluble
oxide, tri-	Natural valentinite Sb_2O_3	col., rhomb.	656	1550	very slightly soluble
potassium tartrate	Tartar emetic $K(SbO)C_4H_4O_6 \cdot 1/2H_2O$	col. cry.	100	-	soluble
selenide	Sb_2Se_3	grey cry.	611	-	very slightly soluble
sulfide, penta-	Sb_2S_5	yellow powder, prism	dec. 75	-	insoluble
sulfide, tri-	Natural stibnite Sb_2S_3	black, rhomb.	550	ca 1150	insoluble
sulfide, tri-	Antimony orange Sb_2S_3	yellow-red, amorph.	550	ca 1150	insoluble

amorph. = amorphous, col. = colourless, cry. = crystal, cub. = cubic, dec. = decomposes; deliq. = deliquescent, rhomb. = rhombic/ortho-rhombic, subl. = sublimes. Based on information in ref. (57).

Antimony hydride, stibine, is a colourless gas at room temperature with an unpleasant smell. In the presence of other gases such as hydrogen, stibine decomposes to hydrogen and minute particles of antimony metal suspended in the gaseous phase (22). Eventually a mirror or film of antimony is formed on the walls of the container. If sufficient oxygen is also present, particles of less than 5 μm are formed producing a white deposit. This deposit consists of antimony trioxide with some higher oxides in smaller quantities.

4. Occurrence, Production and Use

Antimony occurs as stibnite (antimony sulphide) and as a common impurity in quartz. Only stibnite is mined to produce antimony. The main producing countries are Bolivia, South Africa and China. Stibnite has also been mined in England but this activity has been discontinued.

Antimony is processed from stibnite by roasting the sulphide ore in gas-fired furnaces to produce an oxide fume (see Fig. 1). In addition to mining, a large amount of the metal is obtained from recycling processes, mostly of batteries.

Antimony-lead is the most common alloy of antimony. Chemically all proportions are possible, however, commercially the lower percentages (1-10% of antimony) are produced.

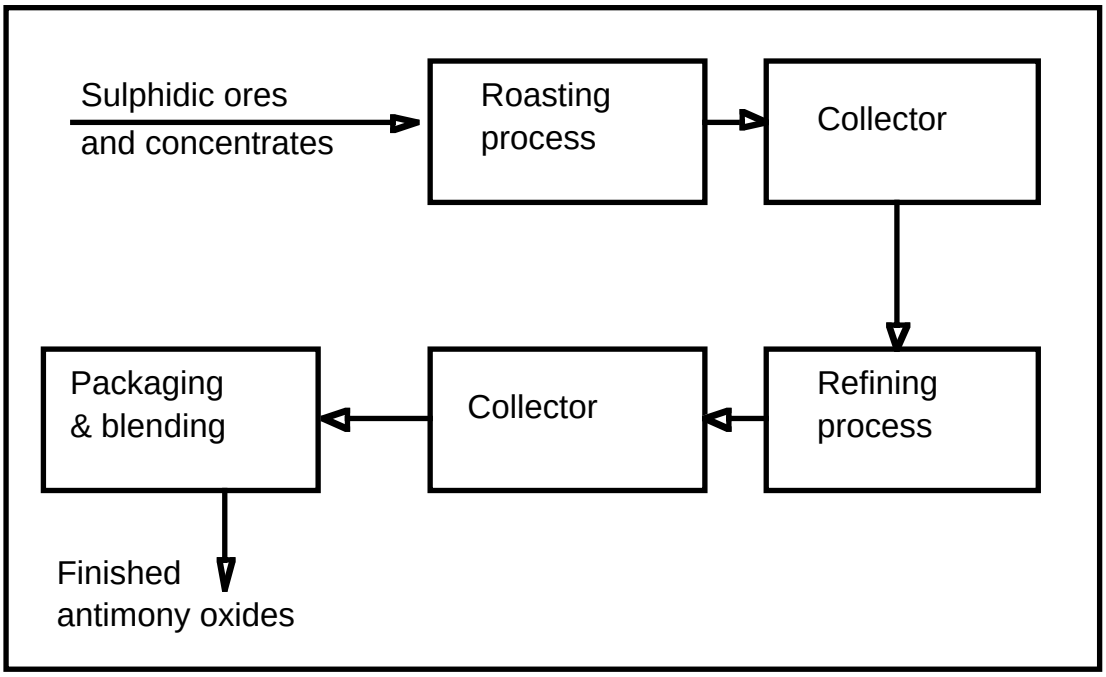

Fig. 1. The production process of antimony oxides. Reproduced from ref. (65).

In industry metals containing antimony are used in storage batteries, solder metal, cable sheathing, electrodes, printing metals and ammunition. High purity antimony is used in semiconductors and thermoelectric devices, and in glass industry. Since early in the 20th century antimony trioxide has been used as a white pigment for paint. Currently antimony oxide combined with a halide such as chlorine has a widespread use as a flame retardant (76), for instance in textiles (54).

Organic antimony salts are still used in pharmacological preparations for schistosomiasis and leishmaniasis. A pentavalent antimony derivative produced by the reaction of stibonic and gluconic acids, is considered the drug of choice in the treatment of leishmaniasis (81). The historic use of trivalent antimony as an emetic or expectorant is now obsolete.

5. Occupational Exposure and Uptake

There are numerous occupations in which exposure to antimony takes place. Miners, smelter and refinery workers have not only been exposed to dust and fumes from metal antimony and antimony sulphide, but often arsenic and lead. Refinery workers are also exposed to antimony trioxide fumes. Workers using antimony-containing metal alloys, such as storage battery workers, may be exposed to dust from antimony and lead, and stibine and arsine. The gas stibine may evolve during charging of lead batteries, and thus present an occupational hazard in closed atmospheres, as the gas is considered poisonous. When textiles, cables and paints are produced which include antimony trioxide based flame retardants, workers may be exposed to antimony trioxide.

Occupational exposure levels of antimony have been well documented during battery production. During smelter work exposure levels of 1-10 mg/m^3 of antimony-containing dust are given in a review article on antimony (103), for further details see Table 3.

Table 3. Stibine and antimony dust concentrations in work room air

	Range (mg/m^3)	n	Ref.
Stibine			
Battery production	<0.01 - 2.5	10	(46)
Battery production	<0.0004 - 0.0068	12	(75)
Battery production	0.04*	150	(41)
Antimony dust			
Smelter	0.4 - 70.7	31	(80)
Smelter	0.081 - 138	28	(17)
Smelter	6.9 - 83**	3	(77)
Smelter	5.9*	not given	(61)

n = number of measurements

* mean value

** recalculated from total dust measurements and chemical analysis

In a study of US refinery workers Renes reported a concentration of antimony in the air of 0.40 - 70.7 mg/m^3, with a mean concentration of 10.07 - 11.81 mg/m^3 (80). One year later, following the improvement of hygienic practices, the levels were decreased to 0.23 - 37.00 mg/m^3 with a mean value of 4.69 - 8.23 mg/m^3. In another study of US refinery workers, Cooper et al. reported levels of 0.081-138 mg/m^3. However, the analytical procedures used were not documented in this study (17). In a study of Yugoslavic smelter workers Potkonjak and Pavlovich summarised the total measured dust concentrations to range from 17 to 86 mg/m^3. The total dust consisted of Sb_20_3 (38.7-88.9%) and to a lesser extent Sb_20_5 (2.1-7.8%) (77, 78). Arsenic oxide was also present.

In a historical overview, McCallum (65) refers to measurements made at a refinery in the UK before and after the adaptation of technical process improvements. Before the improvements the measured levels exceeded the current occupational exposure limit (OEL) of 0.5 mg/m^3 (time-weighted average level), however, after improvements the background levels were around the OEL although personal sampling in some instances gave levels exceeding the OEL.

Data have not been found for the concentration of antimony in human biological fluids after stibine exposure; however, data from a lead-acid battery plant in Norway indicate that levels in the blood are up to 90 µg/l (72).

6. Sampling and Analysis

NIOSH (1978) recommended in the "criteria for a recommended standard - occupational exposure to antimony" that particulate antimony and compounds should be sampled using personal sampling pump equipment (54). Dust should be collected in a filter cassette containing an 0.8 mm cellulose ester membrane filter (Millipore type AA or equivalent) supported by a cellulose backup pad. A sample should be collected for an adequate time period to ensure that at least 2.5 µg Sb is present in the sample. Analysis of the particular matter is done by digesting in a mixture of acids followed by electrothermal atomic absorption spectrometry (ETAAS). For volatile antimony compounds, like stibine, an impinger containing an absorbing solution made of 50 g mercuric chloride dissolved in 1 litre of 6 M hydrochloric acid is recommended. The solutions are analysed directly without pre-treatment. The lowest air concentration of stibine that may be measured using the ETAAS method has been reported to be 0.07 mg/m^3 (19). Using inductively coupled plasma atomic emission spectrometry (ICP-AES) a detection limit of 0.001 mg/m^3 for stibine may be obtained (41).

Breathing zone air may be collected during a whole shift through a 0,8 mm Millipore filter, type AAWPO3700 (Molsheim, France) using a personal battery operated pump at a flow rate of 1 l/minute (6). The filter must be mineralised in HNO_3 in the presence of 1 mg nickel. The concentration of Sb may be measured by atomic absorption spectrometry.

The current methods of Sb analysis used are neutron activation analysis (NAA) and electrothermal atomic absorption spectrometry (ETAAS). The latter method

is described as being very sensitive (72), but chemical interference from other metals can occur. NAA is a sensitive technique which can detect several other elements. Results may, however, be inconsistent when the samples are contaminated with quartz. The detection limit for both methods is in the order of 10-100 pg.

NAA is also used by forensic investigators to determine the antimony content present as contaminant in lead bullets (16).

Laintz et al. has described supercritical fluid chromatography (SFC) as a method for simultaneous determination of arsenic and antimony in environmental samples (53). Trivalent antimony is extracted with lithium bis(trifluoroethyl)-dithiocarbamate followed by chromatography. Pentavalent antimony is extracted after reduction with potassium iodide and sodium thiosulphate. A detection limit of 11 pg Sb is possible with this method.

7. Toxicokinetics

Absorption, distribution and elimination of organic salts of antimony has been well documented both in humans and in laboratory animals (33). Studies on inhalation of inorganic antimony in the occupational setting are not well documented. Inconsistent results have been reported by different investigations and may reflect inadequate sampling and sample handling or defective analysis (96). Variation in the control of contamination in the work place studies is probably a major explanation. This inconsistency is, however, not confined to the measurement of antimony, but is a general problem when analysing trace elements in human body fluids (86). Levels of antimony found in the plasma or serum analysed by NAA are given in Table 4. This information concerns occupational studies to mixed exposures, and therefore provides only limited and indirect information on toxicokinetics of the different forms of antimony in humans.

Table 4. Plasma or serum antimony concentrations found by neutron activation analysis of human blood in occupational studies

Mean(SD) µg/l	Number of subjects	Reference*
0.52(0.19)	7	(47)
0.75(0.51)	8	(99)
2.50(1.37)	149	(48)
3.30(2.70)	4	(8)
5.20**	9	(32)

*Partly reproduced from (96).

**Range 1.0-15 µg/ml.

7.1 Uptake

7.1.1 Oral

In animals organic salts of antimony are slowly absorbed via the gastrointestinal tract (21). The slow intestinal absorption of organic salts may be due to their strong irritant effect on the mucosa (91). Metal antimony is poorly absorbed from the gastrointestinal tract (15).

7.1.2 Inhalation

Bulmer and Johnston (15) refer a study with guinea pigs (unspecified number and sex)(20) which were exposed to an atmosphere containing 45.4 mg/m^3 antimony trioxide for several weeks. Detailed lenght of exposure period was not given, but total exposure times of 33-609 hours were calculated, and daily exposure time was 2 hours during the first two weeks and later 3 hours a day. The amount entering the body by the respiratory tract varied from 13 to 424 mg. In a more recent inhalation study on antimony trioxide, rats were exposed at levels of 0.25 - 23.46 mg/m^3 for 13 weeks, Sb_2O_3 accumulated in the lungs, not reaching a steady state during the exposure period (71).

7.2 Distribution

7.2.1 Human

The background levels of antimony in human organs vary greatly, dependent on the method of analysis used (Table 5). Some of the variations may depend on the amount of oxides, sulphides or hydrides of antimony present in the human organ samples. In an in vitro study, trivalent antimony was found to be bound to red blood cells to a greater extent than pentavalent antimony (97). More than 10% of an initial dose of trivalent antimony was still bound to red blood cells incubated in vitro after 24 hours, whereas pentavalent antimony, the active agent of some antiparasitic drugs, was hardly bound to red blood cells. It has been suggested that trivalent antimony may be exchanged with trivalent iron of haemoglobin, or that it becomes attached to the globin moiety of haemoglobin. At present, the mode of binding remains unknown.

Antimony trioxide dust has in vivo been detected in lungs by X-ray spectrophotometry in 113 antimony process workers (67).

Analysis conducted on the autopsied femurs of smelter and refinery workers in Northern Sweden revealed several metals (59). The analytical techniques employed were atomic absorption spectrophotometry (AAS), NAA, and particle-induced X-ray emission analysis (PIXE) in a proton microprobe. The median level of bone Sb among 7-8 workers was 0.015 (range <0.02 - 0.58) ppm, and 0.007 (range 0.007 - 0.1) ppm in a control group of 3-5 nonexposed workers. The values suggest some deposition of antimony in human bones.

Table 5. Background levels of antimony in human biological material (wet weight) from non occupational exposed individuals.

Organ or tissue	Values in several studies	
	range	mean value(s) *
Blood (µg/l)	ND - 33 000	0,7 - 85
Urine (µg/l)	ND - 11	<1.0 - 6.2
Serum (µg/l)	ND - 15	<0.6 - 5.2
Liver (mg/kg)	<0.01 - 0.07	0.006 - 0.023
Lung (mg/kg)	<0.01 - 0.20	0.017 - 0.095
Hair (mg/kg)	ND - 2.64	0.041
Teeth (mg/kg)	0.005 - 0.67	not given

* mean values not given for all studies included in the range column

ND = not detectable

Based on information in ref. (72)

The deposition of antimony in the enamel of teeth has been studied in humans (79). Teeth examined from persons who lived at different periods in time, from Neolithic age, Roman iron age, Viking age and up to present time have been examined. Antimony levels below 0.032 µg/g enamel were detected in teeth from Neolithic man, increasing to 1.59 µg/g in the middle age man, and decreasing to less than 0.006 µg/g at present time.

In a study of workers at a copper mine and of children living in the vicinity, the content of antimony in hair was not significantly different between the two groups (44).

Liebich et al. measured Sb in the hair of welders by NAA, but did not report their findings, may be due to low levels of antimony compounds in welding materials (58).

7.2.2 Animal

A single sub-lethal unlabelled dose of approximately 0.035 mg Sb/g tissue as the pentavalent organic antimony compound di-ethylamine paraamino-phenyl stibiate was given intravenously to a monkey. The animal was sacrificed 20 minutes after. The following distribution of antimony was found: spleen (0.12 mg Sb/g tissue), heart (0.4 mg/g), liver (1.5 mg/g), lungs (2.4 mg/g) and kidneys (7.5 mg/g). Brain content was not given for this experiment, but either trace or non-detectable amounts were found in the other monkey experiments with pentavalent organic antimony (11).

The distribution of 2% Sb_2O_3 (unlabelled) fed to rats for eight months was highest in the thyroid glad (mean = 156 µg/g) followed by the liver (mean = 16 µg/g) and spleen (mean =8 µg/g) (34). The amount of antimony in lungs, heart and kidney was lower.

The effect of antimony on cardiac muscle has been a concern. A progressive decrease in the contractile force of the heart after perfusion with 10-15 mg per kg heart weight was observed in a study on dogs. The decrease was not reversible following perfusion with antimony-free oxygenated blood. This effect may be explained if some antimony had been irreversibly bound to the myocardium during perfusion (14).

7.3 Biotransformation

Inorganic trivalent antimony is not methylated in vivo. A considerable proportion of the antimony enters the enterohepatic circulation.

The hepatobiliary transport of trivalent antimony is gluthatione dependent in the same manner as the transport of trivalent arsenic (6). Administration of trivalent antimony thus increases biliary excretion of gluthatione, indicating that antimony may compromise conjugation of xenobiotics.

Studies in rats indicate that antimony potassium tartrate (25-100 μmol/kg) given intravenously, as also bismuth and arsenic compounds, increases the biliary excretion of non-protein thiols up to 50-fold (39). This was a result of increased hepatobiliary transport of gluthatione. Administration of antimony decreased hepatic gluthatione levels by 30%, and also reduced gluthatione conjugation. Probably antimony is transported as unstable gluthatione complexes.

7.4 Elimination

7.4.1 Excretion in the urine and faeces

Inorganic trivalent antimony is excreted in the urine and via the bile as a GSH conjugate to the faeces (Table 6). Trivalent antimony is equally excreted by the faeces, and in the urine, whereas pentavalent antimony is mainly excreted by the renal route (6). Antimony in urine in workers producing two inorganic penta-valent antimony compounds was measured in pre and post shift urine samples. The regression equation for Sb in air and post-preshift Sb in urine was highly significant ($r = 0.86$, $p < 0.0001$). This indicated that, on the average, an airborne concentration of Sb in the order of 500 $\mu g/m^3$ leads to an increase in urinary Sb concentration of 35 μg Sb per g creatinine during the shift.

Following acute intoxication to antimony trichloride by inhalation of fumes, 7 workers were followed for symptoms and excretion of antimony. After 10 days no antimony was detected in the urine (93).

Treatment with antimony as tartar emetic, in schistosomiasis thus may cause the continued detection of antimony in urine 100 days after the final injection (60).

In a human volunteer, labelled antimony (^{117}Sb) was administered intravenously as the chloride. At least two clearance components were found (90), with half-times of 4 and 58 minutes.

Table 6. Urinary and faecal excretion of Sb by rats given a single intravenous dose of 800µg Sb/kg BW.

Hours after exposure		Urine		Faeces	
		µgSb	% of dose	µgSb	% of dose
	0-24	39.61	19.2	34.51	16.8
	24-48	5.21	2.5	10.58	5.1
	48-72	1.30	0.6	4.62	2.2
	72-96	0.14	0.1	1.02	0.5
Sum	0-96	46.26	22.4	50.73	24.6

As given in ref. (6).

7.4.2 Clearance from the lungs

Inhalation of inorganic antimony Sb_2Cl_3 has been studied in rats. Twenty percent of the body burden of Sb_2C1_3 was retained in the lungs 4 days after exposure (23). In Syrian hamsters antimony-tartrate-aerosols were rapidly cleared from the lungs. Less than 1% of tri- and pentavalent antimony were observed 2 hours after exposure (27).

7.4.3 Clearance from other organs

Pregnant BALB/c mice strain were fed arsenic or antimony (18.5 mega Bq/k ^{125}Sb). After delivery, the offspring were transferred to normal mothers not fed antimony or arsenic. The new-born mice then rapidly lost arsenic, but seemed to retain antimony (29). Antimony was found in the new-born mice in the following organs in decreasing order: Bone, skeletal muscle, spleen, heart, kidney, and lung. After 50 days, ^{125}Sb activity could only be demonstrated in muscle, skin and spleen. Antimony seems to cross the placenta as readily as arsenic after injection, but does so to a lesser extent if given in the diet. The content of radioactive isotopes of arsenic and antimony both increased markedly in new-born mice during nursing.

7.5 Relevant kinetic interactions

To date not documented in the literature.

8. Methods of Biological Monitoring

In general, uptake of a given chemical may be proportional to the exposure concentration (25). This is, however, not necessarily the case with metal aerosols, where two parameters make the situation different:

1) Aerosols, of the same metal, can be of different aerodynamic diameters, depending on the industrial process and hence deposition may vary in different lung regions.
2) As opposed to organic volatile substances, solubility of antimony in the lungs is limited, by change from one form of compound to the other. Several considerations must be taken into account when conducting/selecting methods for biological monitoring. For example it is important to consider: routes of uptake; if excreted both in the urine and bile/faeces; difficulty to determine the contribution of different routes to total uptake (air or food); if uptake is dependent on the chemical form and differs between species.

The total body burden is often of special interest, and different biological exposure indicators may reflect the body burden differently.

Neutron activation analysis (NAA) and atomic absorption spectrophotometry (AAS) are the most important analytical methods currently used (see Section 6). The detection limits expressed as mg/m^3 are for airborne hydride stibine 0.001 by inductively coupled plasma atomic emission spectroscopy (ICP-AES) and 0.00001 by ETAAS (41). The current method of choice for concentrations of interest in industry is ICP-AES. This method has the advantage that several other airborne hydrides, such as arsine, can be measured. Although ETAAS has a higher degree of sensitivity only a single element can be determined per analysis.

X-ray spectrophotometry

Antimony trioxide dust in human lungs may be measured in vivo by X-ray spectrophotometry (66, 67). The method depends on the absorption by dust particles in the lungs of monochromatic X-rays having two alternative wavelengths which lie on either side of the K critical wavelength of antimony. A scintillation counter is mounted with the X-ray source giving in vivo measurements of antimony dust exposure. The total X-ray dose that the worker receives upon examination is one hundredth of the area dose of a normal chest X-ray.

Human hair and lung tissue analysis by neutron activation analysis

Human hair may be used as a pollutant dosimeter for antimony exposure (2). Neutron activation analysis (NAA) is the basis for analysis of hair from workers exposed to many heavy metals. Hair samples are washed with acetone and water according to IAEA procedures (International Atomic Energy Association). Scalp hair is a rather strong adsorbent for heavy metals. NAA is especially suitable to detect small quantities of other metals such as cadmium and mercury in hair.

A detection limit of 1.8 mg per kg lung tissue and concentrations of antimony of 0.2 mg per kg in 0.5 g of dried biological samples have been reported with these methods (103).

Atomic-absorption-spectrophotometry (AAS)
Antimony levels in blood may be determined by hydride and electrothermal AAS technique (63). Before measurements, blood and plasma samples were digested in nitric acid. As antimony is mainly bound to erythrocytes, whole blood analysis is recommended. The relatively low detection limit of 0.2-1.0 μg/1 indicates that the method may also be used with non-exposed persons (103).

Another application of this method is for wet-oxidation of urine, followed by extraction of metal chelates into an organic phase (89). The resulting phase is then analysed by AAS. It is emphasised that nitric acid must be eliminated from the wet-oxidation mixture because it results in incomplete recovery of antimony. There is also a possibility of directly extracting antimony from urine followed by AAS with carbon-rod atomisation. Smith and Griffiths (89) recommend this as the preferred method for the analysis of urine samples from non-exposed individuals. Both methods give reliable results up to 200 μg/1.

Cerumen analysis by atomic emission spectroscopy (AES)
Cerumen consists of the secretions of the sebaceous and ceruminous glands as well as cell debris, which are similar material as found in sweat (49). Cerumen may readily be harvested from workers with Q-tips, which are then treated with nitric acid, heated and further processed for analysis. By contrast, non-exposed individuals have antimony ranges of 13-72 μg/g in the cerumen. The plasma levels were 0.0032 mg/1 - 0.054 mg/1 and the skin contained 0.03-0.22 μg/g.

9. Mechanisms of Toxicity

The effect of industrial dusts on activated alveolar macrophages has been studied in rabbits (36). Macrophages were incubated with airborne dusts containing different metals or Fe_2O_3. Hydrogen peroxide and superoxide anion radical release from the macrophages were decreased by antimony dusts and other metal dusts but not by Fe_2O_3. Phagocytising macrophages are important in pulmonary host defence. Production and release of superoxide anion radicals are required for this function. Decrease of superoxide anion radical production is associated with decreased pulmonary host defence. Lung toxicity of antimony may be due to a suppression of macrophage activity.

10. Effects in Animals and in Vitro Studies

10.1 Irritation and sensitisation

Antimony potassium tartrate, often called tartar emetic, is slowly absorbed by the gastrointestinal tract, where it causes local irritation, resulting in vomiting (21).

Dermatological reactions to antimony trioxide on intact and non-intact skin have not been observed in rats (strain information not given) (34). Inhalation of

inorganic antimony compounds apparently does not cause irritation of the pulmonary tissue, and is rapidly cleared from lung in rats (nose only exposure of female albino rats - strain information not given) (23). Lipid pneumonia has been observed in rats and rabbits after exposure to antimony trioxide. The mechanism is not understood but is thought to be due to the accumulation of highly irritating lipids from successive disintegrating alveolar macrophages (possibly low-density lipoprotein which can give rise to foam cells).

10.2 Acute toxicity

Antimony potassium tartrate, was estimated by Bradley and Frederick (12) to have a minimum lethal oral dose for rats of 300 mg/kg BW (15).

Potassium antimony tartrate, given intraperitoneally as single doses of 2 mg or 20 mg/kg BW to adult male albino rats infected with Schistosoma mansoni significantly increased the cerebral hemisphere acetylcholine content and reduced the GABA content compared to controls (84). This effect may be the reason why convulsions are observed in some patients on high doses of anti-parasitic medication containing antimony.

Acute toxicity of different antimony compounds are shown in Table 7 expressed as LD_{50}. The table indicates that antimony in the metal form is more toxic than the tri- or pentavalent inorganic compounds. The tartrate, an organic form of antimony, is highly toxic.

10.3 Short-term toxicity

Organic salts of antimony given to test animals (dog, rat) in therapeutic doses may inhibit the contractility of the myocard, induce bradycardia and ST-segment depression on the electrocardiogram (ECG). A dose of 30 mg of potassium antimony tartrate per kilogram of heart weight, which corresponded to 10-15 mg Sb/kg BW, was administered via the coronary circulation to isolated canine heart. The dose given was comparable to the total dose given to humans as a cure for schistosomiasis over 20 days. The ECG-changes may not be permanent, as other studies have shown regression of the effects one month after exposure had ended. The progressive decrease in contractile force was not reversible despite perfusion with antimony-free oxygenated blood. Thus, some antimony may have been bound to the myocardium after perfusion. A slight reduction in blood pressure was also observed (14).

In a study where guinea pigs were exposed to 45.4 mg diantimonytrioxide/m^3 for 33 - 609 hours, no morphological changes in the heart muscle were found on microscopic or gross examination at autopsy (20). Neither did the authors observe any ECG changes.

Mice given potassium antimony tartrate (5 ppm) in drinking water showed about the same prevalence of fatty degeneration of the liver compared to control mice fed drinking water without antimony (88).

Table 7. Mortality (LD_{50}) from acute oral exposure to different compounds of antimony (mg of antimony per kg BW).

Compound	Rats	Guinea pigs
Potassium antimony-trioxidetartrate	11	15
Antimony (metal)	100	150
Antimony trisulfide	1000	NG*
Antimony pentasulfide	1500	NG
Antimony trioxide	3250	NG
Antimony pentoxide	4000	NG

*NG = Not given in study.
From ref. (62).

Different pentavalent antimony salts each given in the amount of 0.3 g/kg BW to Wistar rats intraperitoneally each day for 30 days interfered with urine osmo–lality. This suggests that there may be an effect on the action of the antidiuretic hormone. The disturbance regressed after cessation of treatment. If a higher dose was given, 2 g/kg of BW, signs of acute tubular necrosis were observed (95).

Pentavalent organic Sb, as sodium stibogluconate or meglumine antimoniate, containing 300 or 900 mg Sb/kg/day, were given to albino rats of both sexes intramuscularly for 30 days (3). The former dose is comparable to the daily dose given to humans in the treatment of Leishmaniasis. A dose related reduction in weight gain, haemoglobin and haematocrit, and raised white cell counts were observed for both substances. Also biochemical signs of hepatotoxicity and nephrotoxicity were observed.

Mice ($B6C3F_1$) and rats (F344) were given antimony potassium tartrate (APT) intraperitoneally (1.5 - 22 mg/kg BW in rats; 6 -100 mg/kg BW in mice) or in drinking water (16-168 mg/kg BW in rats; 59 - 407 mg/kg BW in mice) in a 14 days study (21). APT was poorly absorbed and relatively non toxic orally, but intraperitoneal administration increased mortality, reduced body weight, and produced lesions in liver and kidney.

10.4 Long-term toxicity/carcinogenicity

In an inhalation study on guinea pigs the animals were exposed to fume of antimony trioxide. The air concentration of antimony trioxide was 45.4 mg/m^3. Daily exposure of 2-3 hours per day for more than 2 months gave rise to interstitial pneumonitis and fibrosis of the lungs. Increases in absolute liver weight occurred after exposure for more than 4 weeks, due to fatty degeneration (20).

Long-term pulmonary effects of antimony trioxide were also examined in a study on rats and rabbits using inhalation and intratracheal instillation. In the inhalation experiment average Sb_2O_3 dust concentration 89 mg/m^3 (rabbit) and 100-125 mg/m^3 (rat), particle size was 0.6 μm, and exposure period was 14,5 and 10 months. In the intratracheal experiments Sb_2O_3 doses were 12-125 mg and

particle sizes <1.0 - 1.5 μm. Many animals died from pneumonia, and autopsy showed alveolar macrophage reaction and interstitial fibrosis of the lungs. The antimony content of the lungs was related to the length of exposure. The authors argued that doses were so high that pulmonary overload occurred, and should not be interpreted as indication of fibrogenic property (34).

Mice were given antimony potassium tartrate in drinking water at a dose of 5 ppm during their whole life (88). Survival and the tumour frequency were not affected in treated mice compared with controls. There was no increase in the number of benign or malignant tumours.

In a more recent study aimed at investigating vasomotor reactivity pregnant rats were given antimony trichloride in drinking water (0.1 and 1 mg/dl) until 22 days after delivery. Maternal rats had a smaller weight gain than controls (83). No macroscopic teratogenic effects were observed in the offspring.

NIOSH raised concern in their criteria document from 1978 (54) due to an alleged increase in the incidence of lung cancer in antimony smelter workers in England. This concern was later investigated by Groth et al. in a carcinogenesis assay in rats (Wistar derived, 90 males and 90 females per group) (35). The rats were given Sb_2O_3 (time-weighted average 45 and 46 mg/m^3) or antimony ore concentrate (mainly antimony trisulphide: time-weighted average 36 and 40 mg/m^3) with particle sizes of 1.23 or 2.22 (mass median diameter). They were exposed for 7 hours/day, 5 days/week for up to 52 weeks. Interstitial fibrosis was observed in both exposure groups at the end of the exposure period, both among males and females. Lung neoplasms were found in 19/70 (27%) of female rats exposed to Sb_2O_3 and 17/68 (25%) of female rats exposed to Sb ore as compared to zero in the control group ($p<0.001$ for both comparisons). Lung neoplasms were not seen in male rats. The lungs of the treated male rats were found to contain higher concentrations of antimony than female lungs. Thus the tumour response does not appear to be a function of lung tissue concentration of antimony alone. Arsenic was also found in the lungs, which was higher in rats exposed to Sb_2O_3 than to Sb ore.

In a review of existing data on animal carcinogenicity from 1986 (26) only a single thesis study by Watt (98) is reported. In this study female CDF-rats were exposed to antimony trioxide at concentrations of 1.6 and 4.2 mg/m^3 of Sb for 6h/day, 5days/week for one year, with a follow-up period for another year. There was a higher than expected frequency of lung neoplasms after the cessation of exposure, i.e. in 14 out of 18 rats in the high dose group compared with one in the low dose group, and none in the control group.

IARC concluded in 1988 (42) that: There is sufficient evidence for the carcinogenicity of antimony trioxide in experimental animals. There is limited evidence for the carcinogenicity of antimony trisulphide in experimental animals.
Since then a paper describing two animal inhalation studies of antimony trioxide has been published (71). Male and female Fisher rats, 50 animals per sex per exposure group, were exposed to levels of 0, 0.25, 1.08, 4.92 and 23.46 mg/m^3 for 6hr/day, 5 days/week for 13 weeks, followed by a 27 week observation period in

the subchronic study. In the carcinogenicity study the exposure levels were 0.06, 0.51 and 4.50 mg/m^3 for 12 months, with a 12-months follow-up period. The group size was 65 animals. The mass median aerodynamic diameter was 3.05 and 3.76 μm , respectively. In the subchronic study corneal irregularities were observed in about 30% of the animals. This effect was not dose related, and was not confirmed in the chronic study, as the effect was also present among control animals. In the subchronic study, alveolar macrophages, chronic interstitial inflammation and interstitial fibrosis were seen more frequent in the group with highest exposure. In the chronic study, these effects were also observed, and most pronounced in the group with highest exposure. There was no difference in survival or tumour frequency between exposed and controls. The authors discuss possible explanations for the discrepancy between their study and the previous two experimental carcinogenicity studies on antimony trioxide. Considering the lung burden data available, the most likely explanation is said to be that the exposure levels were in fact higher in the studies of Groth et al. (35) and Watt (98). It is referred to the fact that lung burden overload may produce pulmonary tumours, even from exposure to biologically relatively inactive chemicals, like titanium oxide. In addition it may be argued that the number of animals was rather small in Watt's study. However, this can not be stated about the study of Groth et al.

10.5 Mutagenicity and genotoxicity

Gurnani et al. found that 1/50 to 1/20 of LD_{50} of antimony trioxide fed to male white Swiss mice, induced chromosomal aberrations in bone marrow and sperm head (37, 38). (For the calculations an LD_{50} of antimony trioxide >20.000 mg/kg of body weight was used.) The frequency of chromosomal abnormalities induced, in bone marrow preparations, was dependent of the dose given and the duration of exposure (Table 8). The highest dose, given for the longest period, was lethal. Effects on germ cells, indicated by sperm head abnormalities, were possible, but differences did not reach the level of statistical significance.

Tri- and pentavalent oxides and chlorides of antimony were not mutagenic in the Salmonella assay. In the short-term SCE assay the trivalent forms of antimony were positive. In a DNA-damage test ("rec assay") all but trivalent chloride was strongly positive (52).

Swiss mice were given different concentrations (0.5 g to 1.5 g per kg BW) of antimony trichloride orally in vivo (5). DNA fragments were observed in spleen cells in the high dose group, only.

Cultured human leucocytes were incubated with antimony sodium tartrate ($2.3 \cdot 10^{-9}$ M) for 48 hours to determine toxicity as decreased mitotic index (74). The tartrate salt caused a statistically significant increased ($p<0.05$) number of chromosome breaks (12% of the cells compared with 2% among controls).

Table 8. Bone marrow chromosomal aberrations (CA) observed in male mice exposed to antimony trioxide.

Days administrated	No. of animals	Dose (mg/kg BW/d)	Percentage of CA (gaps excluded)	Breaks/cell
7	5	Control	1.4	0.010
	5	400	2.2	0.018
	5	666.67	3.4	0.022
	5	1000	9.6	0.074
			(p <0.001*)	(p<0.001*)
14	5	Control	1.6	0.010
	5	400	3.2	0.022
	5	666.67	4.0	0.026
	5	1000	10.2	0.086
			(p <0.001*)	(p<0.001*)
21	5	Control	1.6	0.010
	5	400	4.6	0.026
	5	666.67	4.8	0.040
	5	1000	#	#
			NS	NS

*Values determined by a one-tailed trend test. NS = not statistical significant

#Dose was lethal.

As given in ref. (37).

10.6 Reproductive and developmental toxicity

Pregnant ewes given trivalent antimony potassium tartrate (2 mg/kg BW) throughout pregnancy gave birth to lambs without any sign of disease (43).

In a more recent study aimed at investigating vasomotor reactivity pregnant rats were given antimony trichloride in drinking water (0.1 and 1 mg/dl) until 22 days after delivery (83). No macroscopic teratogenic effects were observed.

Le Blanc and Dean concluded in a study from 1984 that fathead minnow embryos hatched normally in the presence of solutions saturated with antimony trioxide at concentrations as high as 7.4 μg/l (56).

In a review article written by Winship in 1987, he concluded that animal studies on teratogenicity of antimony were not positive (103).

10.7 Other studies

No data found.

11. Observations in Man

11.1 Acute effects

The symptoms of acute oral antimony poisoning are similar to those of arsenic poisoning, i.e. abdominal pain, vomiting, diarrhoea, dehydration and muscular pain (91). Shock may be a striking feature of acute intoxication. Trivalent antimony is more toxic than the pentavalent form. Haemoglobinuria occurs and may lead to anuria and also uraemia. Hepato- and splenomegaly have also been reported.

Five of seven men accidentally exposed to fume of antimony chloride developed gastrointestinal disturbances. Urinary antimony estimations revealed concentrations of more than 1.0 mg/l (93). Environmental measurements suggested that they were briefly exposed to 73 mg/m^3 antimony expressed as the metal.

Cordasco et al. reported that pulmonary oedema occurred due to antimony exposure from the work environment (18). They observed three cases of antimony pentachloride reactions which induced varying degrees of bronchopulmonary damage subsequent to a malfunction of reactors. Two of the patients subsequently died. Further data on the dose of exposure were not given.

At an antimony plant in Little Rock, USA, X-ray examination of the lungs conducted on six workers who were acutely ill after heavy exposures (2-12 hours) to smelter fumes, all showed definite pneumonitis extending fanwise from each hilus (80). A subsequent survey of exposure was done. The measurements probably did not reflect the level occurring under heavy exposure conditions producing acute pulmonary illness. The concentration range of air-borne antimony in the breathing room samples from the electric furnace area was 0.92 - 70.7 mg/m^3 with a mean of 10.1 mg/m^3.

A case of acute antimony intoxication in a woman has been reported (6). The 24 year old woman was admitted to hospital one hour after the voluntary ingestion of an unknown quantity of a powder containing antimony trisulphide meant for veterinary use. At admission clinical examination showed not abnormalities, except for complaints of slight epigastralgia and dysphagia combined with a metallic taste in the mouth. No clinical signs of intoxication were observed. Blood levels of antimony rapidly reached 5.1 µg/1. After less than a day, the level was decreased to 2.0 µg/l. Levels in the bile were initially measured to be l4 mg/1 and thereafter decreased gradually.

Another case report describes four persons who ate a cake prepared with potassium antimony tartrate instead of cream of tartar (sic!). It was recalculated that about 6 g was used in preparing the cake. One person died of severe gastric bleeding, cardiogenic shock and anuria (55).

In 1774, a doctor requested ”James powder” from his apothecary. The drug consisted of antimony oxide and potassium tartrate, and was usually given as an emetic (69). The doctor persuaded the apothecary to give him three doses of this powder, purportedly to alleviate the "headache, kidney trouble and fever" of the doctor. Each dose of the powder contained 66 mg of antimony. The medical

doctor subsequently died of the severe gastrointestinal effects due to the antimony compound.

The use of old porcelain has caused accidental poisoning. The mechanism has been thought to be release of antimony from porcelain through the action of acidic drinks (4).

11.2 Effects of repeated exposure on organ systems

Except for data on the determination of concentration of antimony in different tissues after industrial exposure, human data on the effects of antimony are few (91). For instance, data on the effects of antimony gas (stibine) are few, and even in the lead-battery industries where stibine exposure may be found, only acute effects on the pulmonary system are observed (19, 22, 41, 46).

Subacute or chronic poisoning causes headache, vomiting, coughing, joint and muscular pain, sleeplessness, vertigo, and loss of appetite. Antimony produces intestinal irritation more rapidly than arsenic (12, 85). Emesis is also more prominent. Metallic antimony is considered most toxic, followed by trivalent and then pentavalent antimony. Antimony sulphide is the least toxic of the antimony salts.

Data on sensitisation by antimony compounds in humans has not been found.

11.2.1 Skin

Papular eruptions have been described on the skin of antimony exposed workers. The changes are termed "antimony spots". They may be preceded by an intense itch. Later the skin changes become vesicular and pustular, and are considered as a form of an occupational contact eczema. Such spots are found among persons who have been exposed to antimony and its salts. The time to the appearance of visible skin eruptions may vary considerably, between two days and three months (92).

There are, however, also reports that antimony spots are not caused by antimony but by arsenic trioxide (94).

The breaking of antimony ingots, and melting the pieces in a crucible in a brazing rod manufacturing plant may cause dermatitis (101). An eruption of follicular papules and pustules may be observed. The cause of the eruption is probably due to the trioxide fumes from the melting of antimony.

Motolese et al. found contact dermatitis in enamellers and decorators in the ceramics industry, some of whom had been exposed to antimony trioxide (70).

Painless ulcerations and perforation of the nasal septum have been reported in antimony workers (65). One of the workers had worked only nine months in the metal furnace. Arsenic in the antimony material was considered the causative agent, as antimony probably does not have such a profound effect on the nasal mucosa.

11.2.2. Eye

Optic atrophy with visual disturbances was described in two persons treated for schistosomiasis after a course of injections with trivalent antimony compounds

(28). The author discusses that the reaction may be due to the infection, and not the treatment.

11.2.3 Respiratory system

Lobanova et al. found that 11% of workers in an antimony ore in Yakutia in Russia had developed dust bronchitis, stage I within 4-10 year after the start of exposure (61). A clinical diagnosis of bronchitis was recorded. However, pneumoconiosis was not detected by X-ray examination of the chest. They investigated 160 workers directly exposed to antimony dust and fumes and 67 control subjects (office clerks at the same factory). Eighty-one per cent of the workers were men, and 58% were from 20-40 years of age. The amount of dust in the working atmosphere was between 51.3 and 2280 mg/m^3 (mean 500.3 mg/m^3). The content of antimony was 4.2±0.8 mg/m^3, and the contamination with arsenic was 0.57±0.05 mg/m^3. The degree to what the reported bronchitis is related to the effects of arsenic and not antimony exposure alone, remains unsettled. Measurements of lung function as FEV_1 were not documented.

Antimony pneumoconiosis is similar in radiological appearance to other forms of simple pneumoconiosis, siderosis or coal worker pneumoconiosis (67). Laryngitis, tracheitis and pneumonitis have been reported in a group of 78 US smelter workers exposed to trivalent antimony oxide with a work area mean concentrations of antimony between 10 and 12 mg/m^3 (80). The observations have not been verified in more recent studies. Progressive massive fibrosis has not been described in antimony workers. Respiratory disability is probably not caused by exposure, although in a Yugoslavian study of 51 smelter workers 18% had obstructive changes and 10% mixed restrictive-obstructive changes (77, 78). Classification of the pneumoconiosis of the 51 workers was as follows: 67% as lp, 14% as 2p, 18% as 3p and 1% as 3pq (according to ILO classification). The confounding effect on the obstructive changes from smoking is unsettled.

A study of antimony process workers at a plant near Newcastle, UK, showed that 44 of 262 men examined had signs of simple pneumoconiosis on X-ray of the lungs. There was a tendency towards a higher average lung antimony content in workers with a longer period of employment in the industry (64). Among 113 antimony process workers from the same plant X-ray spectrophotometry of the lungs were performed, to measure the lung burden of antimony. Chest radiographs were available for 72 subjects. The amount of antimony in the lungs ranged from nil to just over 11 mg/cm^2. There was a significant association between employment duration and lung antimony content. There was an increase in the radiographic category (according to the ILO classification) with increasing length of employment, and also a linear relationship between lung antimony measurements and radiographic category. McCallum later reported (65) that work environment measurements in the 1980's were around the OEL of 0.5 mg/m^3, but in personal samples the concentrations might exceed the OEL. The hygienic standards had been greatly improved over the last 20 years.

11.2.4 Gastrointestinal tract

Pentavalent antimony has been implicated in the development of gastrointestinal symptoms, including diarrhoea, occurring 15-20 days or longer after exposure (80). There was also a detectable concentration of arsenic in the work room atmosphere in this study.

Loss of appetite was the primary complaint after long term exposure of miners (82).

11.2.5 Cardiovascular system

Antimony is considered to be cardiotoxic. This was one of the reasons why antimony emetics (antimony sodium tartrate) were abolished. Sodium antimonyl gluconate used for the treatment of schistosomiasis, was given for 6 days at 300 mg daily caused ECG changes in a ten year-old boy (85). The ECG changes were accompanied by Stokes-Adams attacks, convulsions and runs of ventricular extrasystoles.

In a review article it was suggested that the use of antimony in industry may cause cardiovascular disease (10). In an old study of workers involved in the industry manufacturing grinding wheels, it was reported that 6 out of 125 workers, exposed for eight months to two years, died due to sudden cardiac arrest, whereas during 16 years before the use of antimony in the same plant only one worker had died (13). A cohort age effect cannot be ruled out, thus, any estimation of coronary heart risk from antimony exposure is not possible.

On the contrary, McCallum reported that male antimony workers in the Newcastle factory had lower or equally observed levels of deaths from heart disease compared to expected values in the region. The values in the age-groups 0-44, 45-64, and 65+. were found to be 2.0 (obs.) versus 1.99 (exp.), 7.0 versus 10.73, and 5.0 versus 5.15, respectively (65).

A study (87) of 1014 workers from an antimony smelter in Texas, USA, employed between 1937 and 1971, reported mortality from ischaemic heart disease. Using different comparison populations, no differences reached statistical significance.

In an epidemiological review of the relationship between the work place and cardiovascular disease and mortality, antimony was listed as a probable causative agent for arrhythmias and direct myocardial injury (50, 51).

11.2.6 Musculoskeletal system

Pains in the joints of patients treated with sodium antimony tartrate occurring near the end of a two-week long treatment is common. These pains may also be felt after chronic exposure to antimony-containing dusts. Acute arthritis has been reported in wrist, knee and ankle joints, but these are less common than pain in joints (103).

11.3 Genotoxic effects

Data have not been found.

11.4 Carcinogenic effects

Mortality data of the workers at the factory in Newcastle have been reported in various forms. Without giving any numbers, McCallum states that there was a statistically significant increase among antimony process workers up until 1960, but no increase for men first employed after this year (65). Doll reported preliminary data from the same study. Thirty-one deaths of lung cancer vs. 16.7 expected occurred among men exposed before 1961(24). In a later paper 32 deaths from lung cancer vs. 14.7 expected were reported for workers exposed before 1961, and followed up for the period 1961 - 1992 (45). The increased incidence of lung cancer reported was so large that the confounding effect of smoking was ruled out as explaining the large risk increase. For workers exposed after 1960, 5 vs. 9.2 expected cases were observed. The fall in risk has been attributed to improved working conditions. Arsenic, however, an accepted cause of lung cancer, was present in the work atmosphere up until 1960.

Wester et al. concluded multifactorial causes are responsible for the observed excess mortality from lung cancer in smelter workers (100).

A mortality study of 1014 workers from an antimony smelter in Texas, USA, employed between 1937 and 1971 (87) reported lung cancer and heart disease data. Smoking, but no other confounders for exposure data were reported. A standardised mortality ratio (SMR) of 1.39 (90% CI 1.01-1.88) for lung cancer was reported, and there was a significant positive trend with increasing duration of employment.

Gerhardsson et al. conclude after further studies of smelter workers in 1993 that the excess of lung cancer is not exclusively caused by antimony exposure but confounded by the presence of other metals and smoking (31). The results from the US smelter workers study (87) strengthen this conclusion.

In a recent review on the incidence of cancer among workers involved in the glass industry a clear increasing trend of the development of colon cancer was observed, though the exposure also included other trace elements (102). The exposure was divided into three categories of no, small amounts, or large amounts of the metal. The odds ratio related to colon cancer for antimony increased from 1.4 through 1.8 to 5.0, respectively, the last values being statistically significant at the 0.05 level. A more detailed documentation of the exposure level was not given.

In 1989, before the two recent studies mentioned above were published, an evaluation made by IARC (42) concluded as follows: ”There is inadequate evidence for the carcinogenicity of antimony trioxide and antimony trisulphide in humans. There is sufficient evidence for the carcinogenicity of antimony trioxide in experimental animals. There is limited evidence for the carcinogenicity of antimony trisulphide in experimental animals. Antimony trioxide is possibly carcinogenic to humans (group 2B). Antimony trisulphide is not classifiable as to its carcinogenicity to humans (group 3)”.

11.5 Reproductive and developmental effects

In a metallurgical plant 318 female workers (compared to 115 controls) had a higher incidence of menstrual disorders and abortions than females without exposure to antimony (9). The control population consisted of female employees not engaged in antimony production and handling, i.e. office workers. Women exposed to antimony dusts had 3.4% premature births (1.2% in controls) and 12.5% spontaneous abortions (4.1% in controls).

The mean levels of antimony compounds in their blood were reported to be 53 mg/l versus 3 mg/l in controls. Urine levels among the exposed were 29 mg/l (not detectable in controls). The investigators also followed up new-born children of these women. The groups consisted of 70 children from exposed mothers and 20 children from controls. The birth weights for these two groups did not differ (3360 g of 3350 g). At 3, 6 and 12 months the children of exposed mothers (6300 g, 7460 g and 8960 g) had lower body weights than the children of non-exposed mothers (6410 g, 7950 g and 10050 g) (t-tests of difference at 2.6, 3.3 and 5.7, i.e. with $p<<0.05$, respectively). The quality of this paper has seriously been questioned (7). The number of birth effects among controls seems too low, information bias is to be expected, and also confounding due to different socio-economic status.

12. Dose-Effect and Dose-Response Relationship

12.1 Single/short-term exposure

Pentavalent organic antimony, as sodium stibogluconate and meglumine antimoniate given intramuscularly, were both shown to retard the growth rate and cause hepatic enzyme elevations in rats. The range and severity of the toxic reactions increased with dose, and there was adverse effects at the lowest dose of 300 mg Sb per kg per day (3).

In contrast, antimony potassium tartrate was shown to be non-toxic in mice, whereas a dose-related toxicity occurred in rats, measured as mortality, retarded growth rate and increased hepatotoxicity (21). Male rats showed increased mortality at a daily dose of 24 mg per kg for 90 days. Lowered body weight was also observed at the same exposure level. The liver effects were observed for both sexes at a daily level of 6 mg per kg.

The chromosome study of Gurnani et al. (37) gives a no observable effect level of less than 400 mg/kg antimony trioxide per day. The outcome is chromosomal breaks, which may be of some relevance to the carcinogenic risk.

12.2 Long-term exposures

Table 9 shows adverse health effects after inhalation exposure to antimony dust. Acute pulmonary effects were reviewed in paragraph 11.1 (80), while chronic effects were reviewed in paragraph 11.2. At levels of exposure to antimony from

Table 9. Reported level of inhalation exposure of antimony producing adverse health effects in workers.

Response	Exposure level in air (mg/m^3)	Ref
Acute pneumonitis	0.9 - 70.7	(80)
ECG-changes	0.58 - 5.5 (most>3.0)	(13)
Pneumoconiosis	>0.5	(64, 65)

0.58 to 5.5 mg/m^3, with a mean greater than 3.0 mg/m^3, 37 of 75 workers had altered ECG´s and seven deaths due to cardiac disease was suspected (13). The effects observed may in part have been caused by presence of arsenic in the dust, and other exposures are poorly documented. Consequently, this study cannot be used to set a NOAEL.

There are indications of a dose-effect relationship between quantity of antimony and the degree of pneumoconiosis found on chest X-rays (64). However, the lack of exposure data from the smelter industry does not allow a relevant dose-effect relationship estimation. The exposure levels probably may have been well above the OEL in the UK of 0.5 mg/m^3, as McCallum states in 1989 that ”until recently it has been impossible to maintain this TWA consistently throughout the process”. At this level, however, antimony spots are rare, and routine chest radiography has shown a fall in the prevalence of simple pneumoconiosis to less than 4% (65). Pulmonary fibrosis has also been studied in the animal model. The number of alveolar macrophages was increased after 1 year of inhalation exposure to 0.06 mg/m^3 antimony trioxide, but there were no cases of interstitial fibrosis, not even in the higher exposure groups (0.51 and 4.5 mg/m^3) . Signs of chronic pulmonary inflammation were observed both in the exposure and control groups (71).

The problem of combined exposures to antimony and arsenic is present when carcinogenic risk is to be evaluated from epidemiological studies. Although an increased risk of lung cancer has been reported both in the mining and smelting of antimony, exposure data are insufficient to establish a dose-effect relationship from human studies concerning a carcinogenic effect. Earlier animal experiments in rats gave an indication of a carcinogenic risk (35), however this was not confirmed in later experiments (71).

13. Previous Evaluations by (Inter)National Bodies

The US Department of Health, Education, and Welfare issues a series of occupational criteria documents through the National Institute for Occupational Safety and Health (NIOSH). The first American maximum allowable concentration for antimony dust and fumes was recommended by ACGIH in 1947 to be 0.1 mg/m^3 without any justification in scientific studies. An occupational exposure limit of 0.5 mg/m^3 was later set based on animal studies. and a NIOSH report

covering antimony was published in 1978 (54). It was concluded that ”based on data which indicate that exposure to antimony may cause cardiac and respiratory changes and irritation of the skin and mucous membranes” an OEL of 0.5 mg/m^3 is proposed. It is further summarised that ”some data on antimony workers raise the possibilities of respiratory and carcinogenic effects; however these hazards ascribed to antimony have not been confirmed”.

The International Agency for Research on Cancer, IARC, has reviewed the evidence for carcinogenicity of trace elements. The study on antimony and antimony compounds from 1989 concludes that antimony trioxide is carcinogenic in animals, and possibly carcinogenic in humans, whereas antimony trisulfide is not classifiable as to carcinogenicity in humans (42).

The British Health and Safety Executive recently published a thorough criteria document, concluding that cancer is the critical health effect, proposing a maximum exposure limit of 0.5 mg/m^3 (7).

14. Evaluation of Human Health Risks

14.1 Groups at extra risk

From the available information no groups extra vulnerable to antimony exposure can be identified.

14.2 Assessment of health risks

Industrial exposure to antimony compounds may give rise to the following health hazards:

- Lung oedema as acute effects of exposure to pentavalent antimony (18). However, data on the doses were not given in the two fatal cases of antimony pentachloride intoxication.
- Respiratory symptoms; tracheitis, laryngitis and pneumonitis, may develop after exposure to Sb_2O_3 (80). The concentrations found in the breathing zone in the smelter building ranged from 0.9 to 70.7 mg/m^3, with a mean of 10.8 mg/m^3, i.e. giving little information on threshold values for this exposure related irritative respiratory effects. There was also substantial amounts of arsenic in the air.
- Pneumoconiosis following chronic exposure to trivalent antimony oxide dust (65).
- Cutaneous reactions after exposure to antimony, antimony salts (70) or antimony trioxide (92).
- Lung cancer has been suspected after prolonged exposure to antimony containing dust (103). The contamination with arsenic compounds may be a confounder, especially in the less well documented Russian studies on high exposure levels of workers. This suggests that caution must be exercised regarding the potential carcinogenicity of antimony. The general dust levels in the Russian factories were extremely high and would alone cause respiratory problems (61). Carcinogenicity studies in animals have given differing results

(35, 71). A recent study of lung cancer in smelter workers suggests a multi-factorial mechanism for lung cancer development in the smelter worker environment, rather than a direct effect of antimony (31). This may in part settle the disputes over the suspected cancer risk proposed by NIOSH and British experts concerning observations in smelter workers up to 1970.

Clinical assessment of antimony compounds employed in the treatment of parasitic diseases has provided toxicity information pertinent for other antimony compounds used in industry. The case reports on adverse effects of anti-parasitic drugs do not, however, yield dose-response data relevant for the occupationally observed quantities of antimony. Further assessment of the health risks of occupational use of antimony compounds, including the gaseous form stibine, has to be collected from controlled animal studies together with continued emphasis on follow-up of cohorts of antimony smelter workers as in the studies by Gerhardsson et al. (30, 31).

14.3 Scientific basis for an occupational exposure limit

The critical doses given in Table 10 are based on effects documented in the literature. These effects are not always of a very precise nature, partly because the effects are common in all work environments, as mucosal irritation, and partly because antimony compounds are often accompanied by other potentially noxious agents, as arsenic.

Table 10. Reported LOAEL and critical effect in humans of some antimony compounds as documented in the literature*.

Compound	LOAEL	Critical Effect	Ref
Antimony trioxide	>>0.5 mg/m^3	Transitory lung X-ray deposits	(80)
Antimony pentoxide	ND	Pain in muscles and joints during therapeutic use	(80)
Antimony trisulfide	0.6 mg/m^3	T-wave changes in ECG and gastric bleeding	(13)
Antimony smelter dust	**	Pneumoconiosis	(17)
Antimony smelter dust	0.5 mg/m^3	Pneumoconiosis, lung cancer	(45, 65)

*The level of other metals in the work environment of the studies cited, among others arsenic and zirconium, may have contributed in an unknown manner to the levels given here as critical. A work environment without these confounders is, however, hardly seen in industry. Brieger et al's observations (13) should be interpreted with special caution.

ND = not documented.

**Several measurements reported: 0.081 - 0.95, 1.0-9.8, 11-75 and 138 mg/m^3. No relation to cases given.

Antimony trioxide exposure below 0.5 mg/m^3 has not been shown to give rise to pulmonary changes observed on lung X-rays, whereas transitory skin ulcerations may be observed where Sb_2O_3 dust penetrates sweat ducts (92) (94). This level thus may not exclude such skin reactions.

Antimony pentoxide is still in therapeutic use in the treatment of schistosomiasis, and in pharmacological doses gives rise to acceptable and reversible adverse effects.

The data on exposure in industry of antimony trisulphide on humans are few and not sufficient to set a critical dose (40). There are reports on acute, severe toxicity at concentrations of 5 mg/m^3, but the importance of particle size is not yet resolved.

The currently recommended occupational exposure limit according to different national bodies is 0.5 mg/m^3 in the working atmosphere. This level has some support from the old study of Renes (80) and the accidental poisoning study of Taylor (93). At this level it is suggested that, at most, only a very small permanent accumulation of antimony would occur in the body, and it is believed that this level as a time-weighted average concentration limit, should protect against the pneumoconiosis, dermatitis, mucous membrane irritation, and ECG changes reported at higher doses of antimony compounds in work air.

At a level of 0.5 mg/m^3 or lower there is apparently no increased risk of pneumoconiosis or lung cancer (45, 65).

15. Research Needs

There is at present a lack of studies concerning the genotoxicity and also the carcinogenic potential of antimony. The exclusion of or interaction with common contaminants in antimony ore, such as arsenic, which in combination with antimony may be carcinogenic, would be of great concern in the evaluation of such studies (1). Experimental studies should address possible mechanisms of genotoxic effects.

It would be advantageous to establish working co-operation with the occupational health services of Russian factories concerned with the use of antimony. Studies on these cohorts of both men and women workers would probably give important, more reliable, and purportedly, new information (9, 61).

16. Summary

Berg JA, Skyberg K. 123. Antimony. The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals. *Arbete och Hälsa*, 1998;11:1-37.

Antimony is an elementary metal mined mostly as antimony sulphide, and has two valencies, 3+ and 5+. Antimony in the trivalent form is used as grid alloy in storage batteries, cable sheaths in soldering flux and as pigment in paints. Modern use is especially based on the properties as a flame retardant and semi-conductor. Pentavalent antimony is still used as an anti-parasitic medication.

Industrial exposure may give rise to irritation of the respiratory tract, and cause pneumoconiosis after long term exposure. This development may be unfavourably influenced by smoking. The development of lung cancer in antimony smelter workers is multi-factorial, but seems well documented in workers exposed prior to 1960. Animal studies on cancer risk have been contradictory.

Cardiovascular effects have been demonstrated in workers after high exposure. Even some fatalities are documented for humans.

Contact dermatitis may develop in workers in contact with antimony containing dusts.

Acute parenteral symptoms include gastrointestinal pain with vomiting and diarrhoea.

Key words: Antimony, carcinogenicity, dermatitis, genotoxicity, lung cancer, occupational exposure, pneumoconiosis, toxicity.

17. Summary in Norwegian

Berg JA, Skyberg K. 123. Antimony. The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals. *Arbete och Hälsa*, 1998;11:1-37.

Antimon er et metallisk grunnstoff, som utvinnes mest i form av antimon sulfid. Det har to valenser, +3 og +5. Metallet brukes i blybatterier, kabelforinger, i loddefluks og som malingpigment. Moderne bruk baserer seg særlig på antimons flammehindrende og halvleder-egenskaper. Pentavalent antimon brukes som middel mot parasittsykdommer.

Industriell eksponering kan gi irritasjon i luftveiene, som kan føre til en sideroselignende pneumokoniose etter langtids eksponering. Denne utviklingen fremmes av samtidig røyking. Utviklingen av lungekreft hos antimon produksjonsarbeidere er sannsynligvis multifaktoriell, men synes nå vel dokumentert hos arbeidere eksponert før 1960. Arbeidere som har startet sin eksponering seinere, og hatt bedre arbeidsmiljøforhold, ser ikke ut til å ha økt risiko. Kreftrisiko vurdert ved dyreforsøk har gitt motstridende resultater.

Effekter på hjerte-karsystemet av høy eksponering er vist hos arbeidere, med noen dødsfall forårsaket av antimon trioksid.

Kontaktdermatitt var vanlig hos antimonarbeidere tidligere.

Akuttsymptomer ved forgiftning inkluderer gastrointestinale plager som diaré, oppkast og buksmerter.

Nøkkelord: Antimon, dermatitt, genotoksisk effekt, karsinogen effekt, lungekreft, pneumokoniose, toksisitet, yrkesmessig eksponering.

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19. Data bases used in search for literature

In the search for literature the following data bases were used:
- Analytical abstracts
- Cancerline
- Chemical abstracts
- Medline
- NIOSHTIC
- Toxline

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Appendix 1.

Permitted or recommended maximum levels of antimony (Sb)

Country	ppm	mg/m^3	Comments	Year	Ref.
Denmark	-	0.5		1994	1
Finland	-	0.5		1996	2
Germany		0.5		1997	3
	-	5	30 min short-term		
Iceland	-	0.5		1989	4
Netherlands	-	0.5		1997-1998	5
Norway	-	0.5		1995	6
Sweden	-	0.5		1996	7
USA (ACGIH)	-	0.5		1997	8
(NIOSH)	-	0.5		1997	9
(OSHA)	-	0.5		1997	9

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