Antimony

Evaluation of health hazards and proposal
of a health based quality criterion for soil

Environmental Project No. 1727, 2015

Contents

Preface

This report has been prepared by Lea Bredsdorff and Elsa Nielsen, Division of Risk Assessment and Nutrition, National Food Institute, Technical University of Denmark.

Antimony has been detected in the soil at a Danish shooting place. The Danish EPA has requested a documentation for a health-based soil quality criterion for antimony. Most of the information on the toxicity of antimony and its inorganic compounds stems from studies with inhalation exposure revealing that the critical effects following inhalation are local effects in the respiratory tract. As the local effects in the respiratory tract following inhalation are not relevant for the setting of a health-based soil quality criterion for antimony, only data from studies with oral and dermal exposure have been included in this document.

The report has been elaborated according to the general practice laid down in the Danish EPA guidance document for the setting of health-based quality criteria for chemical substances in relation to soil, ambient air and drinking water (Vejledning fra Miljøstyrelsen 5/2006).

The report has been subjected to review and discussion and has been endorsed by a steering committee with representatives from the following Danish authorities / institutions:

The National Board of Health
The Danish Nature Agency
The Danish Veterinary and Food Administration
Danish Regions
Danish Environmental Protection Agency

1.   General description

Antimony displays four oxidation states: -3, 0, +3, or +5. The +3 state is the most common and stable one. Antimony is classified as a non-metal or metalloid, although it has metallic characteristics in the trivalent state.

This evaluation will only cover antimony, selected inorganic antimony compounds and antimony potassium tartrate (see Table 1).

1.1   Identity

The identity of the selected antimony compounds evaluated in this document is presented in Table 1.

Table 1 Identity of the selected antimony compounds

Substance	CAS RN	Structural formula	Molecular weight (g/mole)	Synonyms
Metallic antimony	7440-36-0	Sb	121.75	Antimony black; Antimony element; Antimony regulus and Stibium
Antimony trichloride	10025-91-9	$SbCl_3$	228.11	Antimony butter and Trichlorostibine
Antimony trioxide	1309-64-4	Sb_2O_3	291.50	Flowers of antimony; Senarmontite; Valentinite; Antimony white; Diantimony trioxide and Antimony peroxide
Antimony trisulphide	1345-04-6	Sb_2S_3	339.69	Antimony glance; Antimony needles; Antimony orange and Stibnite
Antimony pentoxide	1314-60-9	Sb_2O_5	323.5	Stibic anhydride; Antimony anhydride and Antimonic acid
Antimony pentasulphide	1315-04-4	Sb_2S_5	403.80	Antimonial saffron; Antimony red and Antimony persulfide
Antimony potassium tartrate	28300-74-5	$C_8H_4K_2O_{12}Sb_2 \cdot 3H_2O$	667.85 613.83 (anhydrous)	Antimonyl potassium tartrate; Potassium antimonyl, tartrate; Tartox; Tartrated antimony; Potassium antimony tartrate; Tartar emetic and Antimony potassium tartrate trihydrate.

1.2   Physical / chemical properties

Selected physical / chemical properties of antimony and the selected antimony compounds evaluated in this document are presented in Table 2.

Table 2 Physical / chemical properties of antimony and the selected antimony compounds

Substance	Description	Melting point	Boiling point	Density (g/cm^3) (25°C)	Solubility
Metallic antimony	Silvery white solid	630 °C	1635 °C	6.684	Water: Insoluble
Antimony trichloride	Colourless solid with a sharp, unpleasant odour	73.4 °C	283 °C	3.140	Water: 6 g/l (0°C) Soluble in various organic solvents
Antimony trioxide	White (senarmontite) or colourless (valentinite) solid without odour	656 °C	1550 °C (sublimes)	5.2 (senarmontite) 5.7 (valentinite)	Water: very slightly soluble
Antimony trisulphide	Black (stibnite, the natural form) or yellow-red (amorphous) solid	550 °C	1150 °C	4.64 (stibnite) 4.12 (amorphous)	Water: 1.75 mg/l (18°C) Soluble in alcohol
Antimony pentoxide	Yellow solid	380 °C (decomposes)	_	3.78	Water: very slightly soluble
Antimony pentasulphide	Yellow solid without odour	75 °C (decomposes)	_	4.12	Insoluble in water and in alcohol
Antimony potassium tartrate	Colourless solid without odour	100 °C	_	2.6	Water: 83 g/l (20 °C) Insoluble in alcohol

References: ATSDR (1992), IARC (1989), SciFinder (2014)

1.3   Production and use

Antimony is produced from minerals. The most important mineral source of the metal is stibnite (antimony trisulfide), but it is also found in trace amounts in silver, copper and lead ores (EU-RAR 2008).

Antimony trioxide is obtained by roasting stibnite ores (Sb_2S_3) which are reported to contain 55% antimony (IARC 1989).

Antimony has no significant use in its unalloyed state (ATSDR 1992).

Antimony trioxide is primarily used as a flame retardant in plastics, rubbers, textiles, and in pigments, paints and ceramics. Antimony 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. Antimony trioxide is also used as an additive in glass manufacture. (EU-RAR 2008).

Antimony trisulphide is used as a primer in ammunition and smoke markers, in the production of vermilion or yellow pigment and antimony salts such as antimony oxide and chloride, and in the manufacture of ruby glass (IARC 1989).

Antimony potassium tartrate (tartar emetic) has been used to induce vomiting in poisoning cases (WHO 2003), and in the treatment of parasitic diseases and infections (ATSDR 1992).

1.4 Environmental occurrence and fate

Antimony is naturally present in the earth's crust and occurs in more than 100 minerals. Antimony ores are small and scattered throughout the world. The antimony content of commercial ores ranges from 5 to 60%. (ATSDR 1992).

Antimony trioxide occurs in nature as the minerals valentinite and senarmontite (IARC 1989).

Antimony trisulphide occurs in nature as the mineral stibnite (IARC 1989).

The emission of antimony into the human environment appears to be exclusively the result of human activity. Most emitted antimony is in the form of antimony trioxide, which is released as a result of coal burning or with fly ash when antimony-containing ores are smelted (WHO 2003).

Antimony, being a natural element, cannot be degraded; however, it can be transformed between different binding/speciation forms and oxidation states. Antimony released to the environment will eventually end up in either of the two compartments soil or sediment, depending on the release, form of antimony, meteorological conditions, etc. (EU-RAR 2008).

1.4.1 Air

As a fairly volatile metal, antimony will volatilise during combustion processes (smelting operations, combustion of coal, and refuse incineration) and will subsequently condense on suspended particulate matter that is predominantly less than 1 µm in size. In the atmosphere, the particles tend to settle out slowly and can be transported far from its source. The particles can also be removed by dry and wet deposition. (ATSDR 1992, EU-RAR 2008).

When released into the atmosphere as an aerosol, antimony is believed to be oxidised to antimony trioxide by reaction with atmospheric oxidants. Antimony trioxide particles do not undergo changes in chemical composition, particle size, or morphology after emission. (ATSDR 1992, EU-RAR 2008).

1.4.2 Water

The concentrations of antimony in drinking water appear to be less than 5 µg/l (WHO 2003).

In the EU-RAR, the reasonable worst case ambient antimony concentration in freshwater (dissolved) was reported to be 0.72 µg/l. EU drinking water surveys with measured data on antimony concentrations in drinking water have been compiled and submitted in a report (in 2007). The result from this report showed that the extent of these surveys was highly variable, ranging from only a few data points in most studies to approximately one thousand in one case (Finnish study). As most surveys only reported mean/median and/or total range and individual raw data were not available, reasonable worst case concentrations were not estimated. The Finnish study reported a 98th percentile close to 0.2 µg/l (maximum 1.46 µg/l). (EU-RAR 2008).
The reasonable worst case ambient antimony concentration in freshwater (dissolved) of 0.72 µg/l was taken forward to the risk characterisation in the EU-RAR as this value was supported by measured data of European drinking water with all median and mean values reported from these surveys well below 0.72 µg/l.

As a natural constituent of soil, antimony will be transported into streams and waterways due to weathering and run-off from soils; much of this antimony is associated with particulate matter (ATSDR 1992, EU-RAR 2008).

Soluble forms of antimony tend to be quite mobile in water, whereas less soluble species are adsorbed onto clay or soil particles and sediments, where they are mainly bound to extractable iron and aluminium. The available data regarding speciation of antimony in water, together with thermodynamic predictions indicate that the most favoured form in water will be the pentavalent oxoanion ($Sb(OH)_6^-$) (WHO 2003).

In aerobic waters, antimony occurs in the pentavalent forms whereas trivalent antimony is dominant in anaerobic water. Antimony can be reduced and methylated by microorganisms in the aquatic environment and become mobilized. (ATSDR 1992).

1.4.3   Soil

The average concentration of antimony in the earth's crust has been suggested to be approximately 0.2-0.3 mg/kg, with much higher concentrations in rocks containing antimony minerals, such as stibnite. The average antimony concentration in soils is about 0.5 to 1 mg/kg, but wide ranges have been reported. (EU-RAR 2008).

A Dutch report from 1992 identified the lead containing antimony, spread through hunting, shooting and sport fishing as one of the most important sources of antimony pollution in soil and water in the Netherlands. An emission of 16,000 kg Sb and 4,000 kg Sb was estimated to soil and water in the Netherlands, respectively. The Dutch estimate was considered uncertain in the EU-RAR since it was based on figures that were over 15 years old, and that the use of lead containing antimony may have change considerably since then. A more proper estimate of this source should for instance consider 1) an accumulation has occurred over a number of years, 2) that the lead containing antimony spread to soil includes shooting-ranges as well as other types of soils, 3) bioavailability of the antimony varies with a number of factors such as time, compartment (type of soil or water) it is situated in, etc. (EU-RAR 2008).

A Danish report from 2014 has reported levels of antimony in soil (16 samples) at a shooting place ranging from below the detection limit (< 1 mg Sb/kg dry matter) to 515 mg Sb/kg dry matter (NIRAS 2014).

In general, the knowledge on weathering reactions, mobility and adsorptive behaviour of antimony, its compounds and ions in soil is relatively limited. The sorption and precipitation of $Ca[Sb(OH)_6]_2$ seem to be more important than the dissolution processes of Sb_2O_3 as regards the fate of antimony. The solubility of antimony compounds depends on the soil conditions and the time given to dissolve. The most important soil characteristic as regards the mobility of antimony in soil (and sediments), appears to be the presence of hydrous oxides of iron, manganese, and aluminium, to which antimony may adsorb. In addition, these hydrous oxides seem to oxidise dissolved trivalent antimonite ($Sb(OH)_3$) to the pentavalent antimonate ($Sb(OH)_6^-$). The effect of pH as such is probably less important as compared to the effect of the hydrous oxides. (EU-RAR 2008).

Several studies using bacteria in both aerobic and anaerobic cultures have shown that methylation of antimony may result in the formation of volatile antimony compounds (EU-RAR 2008).

1.4.4   Foodstuffs

Antimony does not bio-accumulate so exposure to naturally occurring antimony through food is very low. Antimony is present in food, including vegetables grown on antimony-contaminated soils, mostly in the low μg/kg wet weight range or less. (WHO 2003).

In food or beverages antimony is present in trace amounts; the main contributors to antimony intake are cereals, sweeteners, fish and crustaceans, fruits and vegetables, and alcoholic beverages (EU-RAR 2008).

1.4.5 Bioaccumulation

Antimony has been considered to have a low to moderate bioaccumulation potential in both marine and freshwater species. Measured data from different aquatic organisms have been used to calculate tentative bio-concentration factor values (BCFs). For marine fish the BCFs vary between 40 and 15000 whereas for freshwater fish the BCF values are lower, the highest being 14. For invertebrates tentative BCFs in the range of 4000-5000 have been calculated. (EU-RAR 2008).

Bio-magnification of antimony is not likely to occur considering the finding of low antimony levels in higher animals (EU-RAR 2008).

1.5 Human exposure

Daily oral uptake of antimony ranges from 10 to 70 µg and therefore appears to be significantly higher than uptake via inhalation. Total exposure from environmental sources (air, soil) and food/drinking-water is very low compared with exposure in the workplace. (WHO 2003).

In the EU-RAR, the exposure assessment of antimony via the diet is based on a duplicate diet study among nursing mothers from Germany, Poland and the Czech Republic. Data reported from total diet studies in UK and France were slightly lower, but in the same order of magnitude. The typical exposure via food was estimated to 3.7 µg/day (median), which was similar to that reported in UK (median 3 µg/day) but somewhat higher than that reported in France (median 0.9 µg/day). The reasonable worst case exposure was estimated to 4.8 µg/day (90th percentile), which also was similar to that reported in UK (97.5[th] percentile 4 µg/day) but somewhat higher than that reported in France (97.5[th] percentile 2 µg/day). (EU-RAR 2008).

In the EU-RAR, the reasonable worst case exposure of antimony from drinking water was estimated to 1.44 µg/day, based on the reasonable worst case ambient antimony concentration in freshwater (dissolved) of 0.72 µg/l (see section 1.4.2) and assuming a daily intake of 2 litres of drinking water (EU-RAR 2008).

2. Toxicokinetics

2.1.1   Oral intake

Examination of four persons after involuntary acute intoxication with <u>antimony potassium tartrate</u> revealed an absorption rate of 5 % (Iffland & Bösche 1987 and Lauwers et al. 1990 – quoted from WHO 2003).

In rats orally exposed to (^{124}Sb) <u>antimony potassium tartrate</u> estimates of absorption from the GI tract was about 5 % (Moskalev 1964 – quoted from EU-RAR 2008).

Sprague-Dawley rats (15-25 animals/sex/group, 127-136 g) were given <u>antimony potassium tartrate</u> in the drinking water in concentrations of 0 (control), 0.5, 5, 50 or 500 mg/l for 90 days. Antimony was determined in abdominal fat, liver, spleen, kidneys, brain, red blood cells and serum. Antimony was found in abdominal fat (50 and 500 mg/l groups), brain (50 and 500 mg/l groups), kidney (5, 50 and 500 mg/l groups), liver (5, 50 and 500 mg/l groups), spleen (all treatment groups) and red blood cells (all treatment groups). Tissue concentrations were dose related and followed the order red blood cells > > spleen, liver > kidney > brain, fat > serum (Poon et al 1998). This study is described in more detail in section 4.4.2.

Charles River CD mice (53-55 animals/sex, approximately 3-4 weeks old) were given <u>antimony potassium tartrate</u> in the drinking water in a concentration of 5 mg/l for their entire lifespan Hearts, lungs, kidneys, livers and spleens from dead animals (381 to 751 days of age) were analysed for antimony. Mean antimony levels in kidney, liver, heart, lung and spleen were 25, 51.3, 17.1, 60.5 and 19.2 %, respectively (Schroeder et al 1968).

Mice were given (^{124}Sb) <u>antimony potassium tartrate</u> in single oral doses of 8, 16 or 32 mg/kg bw. Antimony was measured in urine after 25 hours. The excretion in the respective dose groups was 7.9, 5.3, and 4.6 %. Total antimony from urine, carcass and tissues in mice given 16 mg/kg bw was 16 %. An additional group of mice was exposed to (^{124}Sb) antimony potassium tartrate in a concentration of 16 mg/kg bw/day by gavage for 10 consecutive days. Urinary excretion varied from 0.15 to 7.9 % (mean 5 %) during the treatment period (Waitz et al 1965 – quoted from EU-RAR 2008).

The oral bioavailability and the rate and route of excretion of <u>antimony trioxide</u> were determined in rats in a study performed according to OECD Guideline 417. Sprague Dawley Crl:CD (SD) rats (4 animals/sex/group) were given antimony trioxide in single doses of 0 (control), 100 or 1000 mg/kg bw, or repeated doses of 1000 mg/kg bw for 14 days (TNO 2005 - quoted from EU-RAR 2008). Absorption from the gastrointestinal tract into the vascular system was slow with a Cmax at approximately 24 hours after single administration for both dose groups. Cmax was only two times higher in the 1000 mg/kg dose group compared to the 100 mg/kg dose group. The difference between both dose groups for the calculated area under the curve (AUC)$_{(0-72h)}$ was similar with a ratio between the low and the high dose of 2.09 and 1.37 in males and females, respectively. The elimination from blood was slow and a decrease in blood concentration was only observed after 72 hours. The oral bioavailability in the low dose and the high dose groups was 0.3 and 0.05 %, respectively. Steady state was not obtained after repeated dose exposure for 14 days 417.
The presence of antimony was confirmed in whole blood, plasma, bone marrow, femur, liver, kidney, lung, heart, spleen, brain, thyroid, testes, prostate, uterus, ovaries, muscle and skin.

Antimony was also found in whole blood, bone marrow and thyroid from the control group in concentrations similar to those found in the low single dose group.

The recovery of antimony after single exposure of 100 mg/kg was 0.05 and 0.034 % in urine and 79.23 and 83.33 % in faeces in males and females, respectively. The recovery of antimony after single exposure of 1000 mg/kg was 0.0079 and 0.008 % in urine and 100.07 and 98.74 % in faeces in males and females, respectively.

Male Wistar rats (number not reported) were given antimony trioxide in dietary levels of 0 (control) and 1 % (w/w) for 12 weeks (treatment period) followed by an antimony free diet for additional 12 weeks (recovery period). Blood and organs were sampled at 0, 4 and 12 weeks after cessation of antimony trioxide administration. Antimony was detected in all examined organs. The highest concentrations of antimony were found in the blood, spleen, lungs, kidney, hair and bone at the end of the treatment period. Four weeks into the recovery period, the antimony concentrations in the organs were generally unchanged from those measured at the end of the treatment period, while after a further 8 weeks they had decreased by about 50%. (Hiraoka 1986 – quoted from EU-RAR 2008). This study is also described in section 4.4.2.

Male Wistar rats (5 animals/group) were given antimony trioxide in the diet in concentrations of 1 or 2 % (corresponding approximately to 500 and 1000 mg/kg bw/day, respectively) for 24 weeks. Antimony was detected in liver, kidney, spleen, heart, brain, lung, stomach, testes and blood. The highest contents were found in blood (1%: 148.11±25.91 mg/l; 2%: 114.87±35.94 mg/l), spleen (1%: 61.88±6.78 mg/kg; 2%: 55.71±14.81 mg/kg), lung (1%: 28.84±4.67 mg/kg; 2%: 27.26±8.12 mg/kg), kidney (1%: 19.99±2.81 mg/kg; 2%: 16.64±5.6 mg/kg), liver (1%: 19±9.07 mg/kg; 2%: 17.74±4.31 mg/kg) and stomach (1%: 16.56±9.56 mg/kg; 2%: 24.09±10.01 mg/kg) (Sunagawa 1981 – quoted from EU-RAR 2008). This study is also described in section 4.4.2.

In rats fed a diet containing 2% antimony trioxide for eight months, the highest concentrations of antimony were found in the thyroid and adrenals (88.9 and 67.8 mg/kg, respectively, wet or dry weight not stated). Spleen, liver, lung, heart, and kidney had concentrations between 6.7 and 18.9 mg/kg. (Gross et al. 1955 - quoted from IARC 1989).

The retention of antimony in rat pups given (^{125}Sb) antimony chloride was 40 and 20 % of the dose for suckling and 15-day-old suckling rat pups, respectively, 5 days after administration (Inaba et al. 1983 – quoted from EU-RAR 2008).

In hamsters, estimates of the absorption of antimony trichloride from the GI tract ranged from 2 to 7 % (Felicetti et al. 1974 - quoted from ATSDR 1992).

Castrated male juvenile swine (9.5±1.2 kg bw) were exposed to antimony by oral administration of soil containing lead, cadmium, arsenic and antimony for 14 days. Antimony was detected in kidney, liver and bones (Denys et al. 2012).

The oral bioaccessibility of antimony (total Sb) as measured in an *in vitro* simplified bioaccessibility extraction test has been reported to be less than 3 % from floodplain soils and between 1.5 and 12 % from mine contaminated soil (Wilson et al. 2014), and between 10 and 50 % from shooting range soils (Sanderson et al. 2012). In the study of antimony bioaccessibility from shooting range soil it was noted that the bioaccessibility in some samples approached 100 % and that it from two out of four sites was correlated with total antimony concentration in the soil.

2.1.2 Dermal contact

Antimony trioxide is absorbed dermally in rabbits (NRC 2000 – quoted from NTP 2005).

An *in vitro* study with human skin has been performed in accordance with OECD Test Guideline 428 to establish the likely dermal penetration of antimony resulting from topical exposure. Antimony trioxide was applied to human skin in concentrations of 100 or 300 µg/cm² for 6 hours. The total dermal absorption of antimony trioxide was estimated to be 0.26 % at 100 µg/cm², and 0.135 % at 300 µg/cm² (Roper and Stupart, 2006 – quoted from EU-RAR 2008).

2.2 Elimination

Antimony and its inorganic compounds are not metabolised. No data on interconversion of trivalent and pentavalent antimony have been found. Antimony is excreted via the urine and faeces. The rate and route of excretion are dependent on the valency of the compound. In general, pentavalent antimony is mainly excreted in the urine and trivalent mainly in the faeces. Pentavalent antimony is excreted more rapidly in the urine than trivalent antimony. Species differences are observed with rats having longer clearance (from the blood) than mice and dogs. (ATSDR 1992).

3. Human toxicity

3.1 Single dose toxicity

3.1.1 Oral intake
The minimal lethal dose for oral intoxication by antimony potassium tartrate is 300 mg for a child and 1200 mg for an adult (WHO 2003).

Moderate bradyrhythmic dysfunctions following acute antimony ingestion and phlebitis (inflammation of veins) were reported in two patients accidentally ingesting antimony potassium tartrate (IPCS INTOX Databank 2005 – quoted from NTP 2005).

According to the EU-RAR, no reliable human information regarding the acute toxicity after single oral intake of antimony trioxide is available (EU-RAR 2008).

No data on other inorganic antimony compounds have been located.

3.1.2 Dermal contact
According to the EU-RAR, no human data regarding the acute toxicity after single dermal exposure to antimony trioxide could be located. (EU-RAR 2008).

No data on other inorganic antimony compounds have been located.

3.2 Skin irritation
Several human case reports indicate that antimony trioxide may cause dermatitis on skin damp with perspiration. Lesions arise on body parts exposed to fumes from melted antimony and heat and appear to be closely associated with sweat ducts (White et al 1993, Stevenson 1965, McCallum 1963, Potkonjak & Pavlovich 1983 – all quoted from EU-RAR 2008). According to the EU-RAR, antimony trioxide should be regarded as a skin irritant in humans under conditions that evoke sweating (EU-RAR 2008).

In workers handling antimony materials, effects on the skin, called antimony spots or "antimony dermatitis", have been reported; the spots are transient and mainly affect skin areas exposed to heat and those areas where sweating occurs (several authors quoted in IARC 1989, and in ATSDR 1992).

No data on other inorganic antimony compounds have been located.

3.3 Skin sensitisation
A number of human studies on skin sensitisation is described in the EU-RAR; according to the EU-RAR, there are no human studies of adequate quality that can be used for assessing the sensitising potential of antimony trioxide (EU-RAR 2008).

No data on other inorganic antimony compounds have been located.

3.4 Repeated dose toxicity

3.4.1 Oral intake

Repeated oral exposure to therapeutic doses of trivalent antimony has been associated with optic nerve destruction, inflammation of the uvea and retinal bleeding. Symptoms of intoxication reported were headache, coughing, anorexia, troubled sleep and vertigo (Stemmer 1976 – quoted from WHO 2003).

According to the EU-RAR, no human data on repeated oral exposure with antimony trioxide have been located (EU-RAR 2008).

No data on other inorganic antimony compounds have been located.

3.4.2 Dermal contact

According to the EU-RAR, no human data on repeated dermal exposure with antimony trioxide have been located (EU-RAR 2008).

No data on other inorganic antimony compounds have been located.

3.5 Toxicity to reproduction

No human data regarding toxicity to reproduction after oral intake of or dermal contact to antimony compounds have been located.

3.6 Mutagenic and genotoxic effects

In humans no induction of micronuclei or sister chromatid exchanges could be seen in lymphocytes from workers occupationally exposed to antimony trioxide, but a higher proportion of the workers in the "high exposure group" showed oxidative DNA damage in their lymphocytes (Cavallo et al. 2002 – quoted from EU-RAR 2008). The "high exposure" was less than 0.001 mg/m^3, the workers were exposed to diverse chemicals and no monitoring was performed on the control group, therefore a correlation between the oxidative DNA damage and air concentration of antimony trioxide is, according to the EU-RAR, uncertain (EU-RAR 2008).

Significant inductions of chromosomal aberrations and micronuclei were observed in patients (n=15) after administration of therapeutic doses of antimony potassium tartrate (route of administration not specified) (Hashem & Shawki 1976 – quoted from WHO 2003).

No data on other inorganic antimony compounds have been located.

3.7 Carcinogenic effects

No human data regarding carcinogenic effects after oral intake of or dermal contact to antimony compounds have been located.

4. Animal toxicity

4.1 Single dose toxicity

4.1.1 Oral intake

Studies on oral acute toxicity are presented in the following table:

Compound	Species	Animals/group	Sex	LD$_{50}$	Reference
Antimony trisulphide	Rat	10	_	>2000 mg/kg bw	Ball et al 1996 – quoted from NTP 2002
Antimony trioxide	Rat	6	_	>20000 mg/kg bw	Smyth & Carpenter 1948 – quoted from IARC 1989
Antimony trioxide	Rat	10	_	>600 mg/kg bw	Fleming 1938 – quoted from EU RAR 2008
Antimony trioxide	Rat	5	_	>20000 mg/kg bw	Carnegie-Mellon Institute of Research 1978 – quoted from EU RAR 2008
Antimony trichloride	Rat	_	_	360 mg Sb/kg bw	Arzamastev 1964 quoted from EU-RAR 2008
Antimony trichloride	Guinea pig	_	_	305 mg Sb/kg bw	Arzamastev 1964 quoted from EU-RAR 2008
Antimony potassium tartrate	Rabbit	_	_	115 mg/kg bw	Gebel 1999 – quoted from WHO 2003
Antimony potassium tartrate	Rat	_	_	115 mg/kg bw	Christensen & Fairchild 1976 – quoted from Omura et al 2002
Antimony potassium tartrate	Mouse	_	_	600 mg/kg bw	Christensen & Fairchild 1976 – quoted from Omura et al 2002

Reduced growth and other nonspecific effects were seen in rats after 1000 mg/kg bw antimony trioxide (Smyth & Carpenter 1948 - quoted from IARC 1989). However, in rats given 16000 mg/kg bw of antimony trioxide by stomach tube, no apparent ill effects were observed within a 30-day observation period (Gross et al., 1955 - quoted from IARC 1989 and EU-RAR 2008) and only pilo-erection, diarrhoea and wet fur were reported after 20000 mg/kg of antimony trioxide administered by stomach tube (Carnigie-Mellon Institute of Research 1978 – quoted from EU-RAR 2008).

No treatment-related adverse effects were observed in Sprague Dawley Crl:CD (SD) (4 animals/sex/group) given antimony trioxide in single doses of 100 or 1000 mg/kg bw. (TNO 2005 - quoted from EU-RAR 2008). This study is described in more detail in section 2.1.2.

4.1.2   Dermal contact

No mortality or other clinical symptoms were observed in rabbits after dermal application of antimony trioxide in a concentration of 8300 mg/kg bw (Gross et al 1955 – quoted from EU-RAR 2008). An LD50 > 8300 mg/kg bw can, according to the EU-RAR be derived for dermal exposure of rabbit (EU-RAR 2008).

Death was reported in rabbits (1/6 animals) after a single dermal application of antimony trioxide at 8000 mg/kg in corn oil and one rabbit was observed 24 hours post-application with unsteady gait (Carnegie-Mellon Institute of Research 1978 – quoted from EU-RAR 2008).

A dose of 2000 mg/kg antimony trisulphide (1440 mg Sb/kg) applied to the intact skin of 10 Wistar rats for 24 hours under an occlusive dressing caused no deaths or signs of toxicity during a 15-day observation period (Ball et al., 1996 – quoted from NTP 2002).

4.2   Skin irritation

No significant local irritation was observed in albino rabbits (n=8) after dermal application of antimony trioxide (8300 mg/kg bw) for one week (Gross et al 1955 – quoted from EU-RAR 2008). According to the EU-RAR, this is the only study that can be used for risk assessment of the skin irritation potential of antimony oxide and showed that antimony oxide is not irritating to rabbit skin.

No data on other inorganic antimony compounds have been located.

4.3   Skin sensitisation

No skin sensitisation potential of antimony trioxide was observed in a skin sensitisation test in guinea pigs according to the Magnusson and Kligman method and performed according to OECD Test Guideline No 406 (LPT and IAOIA 2005 – quoted from EU-RAR 2008). Antimony trioxide was administered in concentrations up to 10 % by intradermal injections and up to 50 % for topical applications.

No data on other inorganic antimony compounds have been located.

4.4   Repeated dose toxicity

4.4.1   Oral intake

4.4.1.1   Rats

F344/N rats (5 animals/sex/group) were given antimony potassium tartrate in the drinking water in concentrations of 0 (control), 150, 300, 650, 1250 or 2500 mg/l for 14 days (NTP 1992). Water consumption was measured on day 7 or 8 and 15. Histopathology was performed on all animals at the end of the study. The daily mg/kg dosages, calculated using the water consumption data and the body weight averages, were 0 (control), 16, 28, 59, 94 and 168 mg/kg bw/day. In males, water consumption was lower in the 94 and 168 mg/kg bw/day groups; in females, water consumption was proportionally lower in the 28, 59, 94 and 168 mg/kg bw/day groups. Higher relative liver weight was observed in both males and females in the highest dose group and relative kidney weights were higher in females from the highest dose group. All antimony treated male rats had protein droplets normally present in the cytoplasm of the renal tubular epithelium that stained more prominently than control rats.

Sprague-Dawley rats (15-25 animals/sex/group, 127-136 g) were given antimony potassium tartrate in the drinking water in concentrations of 0 (control), 0.5, 5, 50 or 500 mg Sb/l for 90 days (Poon et al. 1998). Body weight, water consumption and food intake were measured weekly and clinical observations were made daily. All animals were sacrificed after 90 days, except for 10 animals/sex from the control and the highest dose groups. These remaining rats (recovery groups) were given water free of antimony for an additional 4 weeks before termination. Blood and urine were collected at the end of the study. Blood was analysed for erythrocyte counts, haematocrit, mean corpuscular volume, mean haemoglobin concentration, platelet count and total and differential counts of leucocytes. Serum albumin, alkaline phosphatase, aspartate aminotransferase, creatine kinase, sorbitol dehydrogenase, bilirubin, calcium, cholesterol, creatinine, glucose, inorganic phosphate, lactic dehydrogenase, total protein, urea nitrogen, uric acid, thiobarbituric acid reactive substances, thyroxin (T_4) and thyroid hormone binding ratio. The brain, thymus, heart, kidney, spleen and liver were weighed. Livers were analysed for the activity of aniline hydroxylase, aminopyrine N-demethylase, ethoxyresorufin-*O*-deethylase and UDP-glucuronosyltransferase. Brain, pituitary, thyroid, trachea, salivary glands, thymus, lung, heart, liver, kidneys, adrenals, spleen, pancreas, oesophagus, gastric cardia, fundus, pylorus, duodenum, jejunum, ileum, caecum, colon, urinary bladder, skin, bone marrow and gonadal tissues were removed for histopathological examinations. Calculated antimony intakes by rats given 0.5, 5, 50 or 500 mg Sb/l were 0.06, 0.56, 5.58 and 42.17 mg Sb/kg bw/day for males and 0.06, 0.64, 6.13 and 45.69 mg Sb/kg bw/day for females. Animals in the highest dose group consumed about 35 % less water compared to the other dose groups and control. No difference in water consumption was observed in the recovery group. Food consumption was lower by 12 % in the highest dose group by the end of the treatment period and statistically significantly lower weight gain was observed in group from week 6 (males) and week 12 (females) compared to control (p<0.05). The difference disappeared during the recovery period. Relative kidney weights were statistically significantly higher the highest dose group compared to control. Serum glucose was significantly lower in females from the three highest dose groups and thyroid hormone binding ratio was significantly higher in females from the two highest dose groups compared to control (p<0.05). Total protein and cholesterol was significantly lower in females from the highest dose group compared to control (p<0.05). Creatinine and alkaline phosphatase was significantly lower in both sexes from the highest dose group compared to control (p<0.05). No differences in serum chemistry values were observed in the recovery group. Significant changes in red blood cell count (lower), mean corpuscular volume (higher) and platelets (lower) were observed in males from the highest dose group compared to control (p<0.05). Monocytes were significantly higher in females from the highest dose group compared to control (p<0.05). No differences in haematological values were observed in the recovery group. Ethoxyresorufin-*O*-deethylase was higher in males (500 mg/l group) and females (50 mg/l group) and glutathione-S-transferase was higher in both sexes from the highest dose group compared to control (p<0.05). Treatment-related histological changes were observed in the thyroid gland (reduced follicle size, increased epithelial height and nuclear vesiculation) and liver (anisokaryosis, nuclear hyperchromicity, increased portal density in the cytoplasm of hepatocytes, increased peri-venous homogeneity and bridging fibrosis). Mild treatment related changes were observed in thymus (reduced cortical volume and increased medullary volume), spleen (sinus congestion) and pituitary (cytoplasmic vacuolation and inclusions). According to the authors the histological changes were predominantly reversible. A NOAEL for antimony of 0.5 mg Sb/l (equivalent to a calculated intake of 0.06 mg Sb/kg bw/day) was suggested by the authors based on biochemical and histological changes and retention of antimony in red blood cells and spleen (see Poon et al 1998 in section 2.2.2).
Based on this study, Lynch et al. (1999) concluded that the NOAEL is 6 mg Sb/kg bw/day based on decreased body weight gain and reduced food and water intake; this NOAEL forms the basis for the WHO drinking water guideline (WHO 2003).

Long-Evans rats (≥50 animals/sex/group) were administered 5 mg/l antimony potassium tartrate in the drinking water for up to 4 years (Schroeder et al. 1970). Weights, blood samples and blood pressure were obtained weekly until 6 weeks of age and then at monthly intervals. Blood was

analysed for cholesterol and serum glucose (both fasting and non-fasting). Dead animals were weighed and dissected. Male rats survived 106 and females 107 days less than the controls at median lifespan, and 70 and 165 days less when 90% were dead. Longevity (defined as the mean age of the last surviving 10%) was statistically significantly reduced compared to controls ($p<0.001$). Non-fasting serum glucose levels were statistically significantly lower than fasting serum glucose levels in males ($p<0.05$). Cholesterol levels were statistically significantly higher in males and statistically significantly lower in females compared to control ($p<0.005$). Although not precisely stated, the concentration of 5 mg/l in the drinking water was expressed as corresponding to 0.35 mg/kg bw by the authors (Schroeder et al. 1970).

The oral reference dose (RfD) for antimony set by the US-EPA is based on this study (IRIS 2015a).

Male Crj: Wistar rats (8 animals/group; 6 weeks old) or male Crj: CD-1 mice (10 animals/group; 7 weeks old) were gavaged with antimony trioxide in concentrations of 0 (control), 12 and 1200 mg/kg bw/day or antimony potassium tartrate in a concentration of 27.4 mg/kg bw/day for 3 days/week for 4 weeks (rats) or for 5 days/week for 4 weeks (mice). At the end of the study testes, epididymidis, ventral prostate and seminal vesicles were weighed and the testes were histopathological examined for disorganisation and exfoliation of the seminiferous epithelium, degeneration of germ cells, vacuolisation of the epithelium, sperm retention in the epithelium and delayed spermiation. Number, motility and morphology of sperm in the cauda epididymidis were also evaluated. No statistically significant treatment-related adverse effects were observed (Omura et al. 2002 – quoted from EU-RAR 2008). According to the EU-RAR, an oral NOAEL of 1200 mg/kg bw for testicular toxicity is suggested (EU-RAR 2008).

Sprague Dawley Crl:CD (SD) (4 animals/sex/group) were given antimony trioxide in a concentration of 0 or 1000 mg/kg for 14 days. No treatment related adverse effects were observed (TNO 2005 – quoted from EU-RAR 2008). This study is described in more detail in section 2.1.2.

Male albino rats (number not reported) were given antimony trioxide in dietary levels of 0 (control), 60, 270 and 1070 mg/kg bw/day for 30 days. Animals from the high-dose group were reported to eat significantly less, grow significantly less and have significantly higher red blood cell count compared to controls (p values not reported). One rat in the high-dose group had minor cloudy swelling in the kidneys (Carnegie-Mellon Institute of Industrial Research 1945 – quoted from EU-RAR 2008).

Sherman rats (10 animals/sex/group) were given antimony trioxide in dietary levels ranging from 60 to 1070 mg/kg bw/day (3-4 unspecified dose levels) for 30 days. Body weight, appetite, death and micropathology of adrenal, upper intestine, kidneys, liver and spleen were studied. Reduced growth and appetite and unspecified micropatological effects were observed in the highest-dose group (1070 mg/kg bw/day). The maximum dose level having no effect was reported to be 270 mg/kg bw/day (Smyth and Carpenter 1948 – quoted from EU-RAR 2008).

Wistar-derived Alpk:ApfSD rats (8 animals/sex/group) were given dietary antimony trioxide in concentrations of 0 (control), 1000, 5000 or 20000 mg/kg for 28 days in a dose range-finding study. According to the authors the dietary concentration of antimony in the highest dose group was equal to a dose of 1000 mg/kg bw/day. Lesions were observed in liver, kidney and adrenal capsules in two females from the highest dose group (Central Toxicology Laboratory 1996 – quoted from WHO 2003).

Wistar-derived Alpk:APSD rats (12 animals/sex/group) were given dietary antimony trioxide in concentrations of 0 (control), 1000, 5000 or 20000 mg/kg for 90 days. Clinical condition and behaviour were observed daily. Body weights were recorded before exposure started and then once a week until termination. Blood was sampled and analysed for haematology and clinical chemistry parameters at the end of the study. Complete necropsies were performed on all rats. All organs and

tissues were examined for macroscopic lesions and adrenal glands, brain, kidneys, liver, epididymides and testes were weighed. Tissues from an extensive range of organs from the controls and the highest dose group were examined under the light microscope, together with any macroscopically abnormal tissue from the intermediate groups. The authors calculated the mean doses of antimony trioxide to be 84, 421 and 1686 mg/kg bw/day in males and 97, 494 and 1879 mg/kg bw/day in females. Urinary volume was higher (p<0.05) and specific gravity was lower (p<0.01) in females from the highest dose groups compared to control. Triglycerides were higher and alkaline phosphatase was lower in males from the highest dose groups compared to control. Alkaline phosphatase was also higher in female animals at 5000 and 20000 mg/kg (p<0.01) compared to control and in a dose-dependent manner. Cholesterol (p<0.05) and aspartate aminotransferase levels (p<0.01) were higher in females in the highest dose group compared to control. Relative liver weights were 10 % higher in both sexes from the highest dose group compared to control. No other treatment related effects were observed (Hext et al. 1999). According to the EU-RAR, a NOAEL corresponding to 1686 mg/kg bw/day (males) and 1879 mg/kg bw/day (females) can be derived from this study. It was also noted in the EU-RAR that "*Diantimony trioxide, supplied as a white solid with a purity of 99 %, was mixed in the diet and the homogeneity of the mixture was > 95%. No information is provided on the size of the diantimony trioxide particles in the diet, which is likely to affect the gastrointestinal uptake of the substance.*" (EU-RAR 2008).

According to NTP, the NOAEL is 494 mg/kg bw/day and the LOAEL is 1879 mg/kg/day (NTP 2005).

According to WHO, the NOAEC of 20000 mg/kg in the diet was equivalent to a NOAEL of 1685.9 mg/kg bw/day (or 1407.7 mg Sb/kg bw/day).

Male Wistar rats (number not reported) were given antimony trioxide in dietary levels of 0 (control) and 1 % (w/w) for 12 weeks followed by an antimony free diet for additional 12 weeks. Blood and organs were sampled at 0, 4 and 12 weeks after cessation of antimony trioxide administration. No effects on behaviour, general appearance, body weight, haematology or blood biochemistry were observed (Hiraoka 1986 – quoted from EU-RAR 2008).

Male Wistar rats (12-15 animals/group) were given antimony trioxide in a dietary concentration of 0 (control), 1 or 2 % for 24 weeks. Haematological and biochemical parameters were analysed in 5 animals/group except for haematocrit and haemoglobin values which were measured in 11 animals/group. Total body weight and organ weights were registered and histopathological examinations of the liver was performed. A small but significant lower red blood cell count was observed in both exposure groups compared to control. Serum biochemical parameters showed significantly higher aspartate aminotransferase values in both exposure groups and alkaline phosphatase was significantly elevated in the high-dose group. The histopathological examinations of the livers showed slight disorder and cloudy swelling in hepatic cords in 3 out of 5 rats in the low-dose group and 2 out of 5 rats in the high-dose group (Sunagawa 1981 – quoted from EU-RAR 2008).

Wistar rats (sex and number not reported) were given dietary antimony trioxide in concentrations of 420-490 mg/kg bw/day for 24 weeks. Hepatic cord swelling, decreased red blood cell counts, lower weight gain and minor changes in relative organ weights were observed. A LOAEL of 420 mg/kg bw/day was established based on mild liver toxicity and decreased red blood cell counts (USCPSC 2004 – quoted from NTP 2005).

Rats (20 animals/group, sex not reported) were given antimony trioxide in dietary levels of 0 (control) or 2 % for 8 months. Lower body weight was observed in the group given antimony trioxide compared to control (Gross et al. 1955 – quoted from EU-RAR 2008).

In a study investigating the histopathological and functional effects of antimony trisulphide on the renal cortex, male Sprague Dawley rats (20 animals/group, 43-57 g corresponding to ca. 3 weeks old (http://www.sageresearchlabs.com/research-models/outbred-rats/sprague-dawley-outbred-rat)) were given antimony trisulphide in a concentration of 0 or 6 mg/kg bw/day for 8 or 12 weeks (Rashedy et al. 2013). Blood was sampled at the end of the study and serum was analysed for blood urea, creatinine, potassium and sodium. Histological examinations of the kidneys were performed after termination. Treatment related higher blood urea, creatinine, potassium and sodium were observed in rats given antimony trisulphide for 6 ($p<0.05$) and 8 weeks ($p<0.01$). The authors did not use statistical methods for evaluating the results from the histological examinations but reports on several changes in the renal cortex in the groups given antimony trisulphide including (but not limited to) glomerular changes in the form of distortion, destruction and shrinkage of glomerular tufts; congested glomeruli; periglomerular haemorrhage; obliteration of Bowmans's space; marked damage of the tubular brush border; congestion of blood vessels and haemorrhage in the renal cortex and cellular oedema in tubular cells. The authors referred to several (n>25) other studies on the toxic effects of antimony, however, these references are either cited wrongly or non-existing.

4.4.1.2 Mice

B6C3F$_1$ mice (5 animals/sex/group) were given antimony potassium tartrate in the drinking water in concentrations of 0 (control), 150, 300, 650, 1250 or 2500 mg/l for 14 days (NTP 1992). Water consumption was measured on day 7 or 8 and 15. Histopathology was performed on all animals at the end of the study. The daily mg/kg dosages, calculated using the water consumption data and the body weight averages, were 0 (control), 59, 98, 174, 273 and 407 mg/kg bw/day. Body weight gain was significantly lower in males dosed with 273 or 407 mg/kg bw/day and in females dosed with 407 mg/kg bw/day for 8 days, but only in high-dose males by day 16. Clinical signs of toxicity included rough hair-coat, emaciation, abnormal posture, hypoactivity and decreased faecal material. According to the authors this was consistent with avoidance of the antimony-treated water in all treatment groups in proportion to dosage; however, due to "*extreme variability*" in measurement of water consumption this was not documented. Dose related higher relative liver weights were observed (sex or dosage not reported). Treatment related lesions were observed in the liver (a minimal to moderate cytoplasmic vacuolization of hepatocytes in all male and female mice in the highest dose-group only; the changes were generally more severe in males than females) and forestomach (round, white nodules consisting of focal areas of ulceration with necrosis and inflammation of the squamous mucosa which extended into the underlying muscularis of the forestomach in both sexes in the highest dose group).

Charles River CD mice (53-55 animals/sex/group, approximately 3-4 weeks old) were given antimony potassium tartrate in the drinking water in concentrations of 0 (control) or 5 mg/l (Schroeder et al. 1968). Animals were weighed weekly for the first 8 weeks and then at monthly intervals for their entire lifespan. Dead animals were dissected and abnormal tissues were prepared for microscopic examination. There was no statistically significant difference in survival rate between treated and control animals. Body weights were statistically significantly lower in male and female mice given antimony potassium tartrate after 90, 150 and 540 days ($p<0.025$) and 150, 360 and 540 days ($p<0.005$), respectively, compared to control. No other statistically significant treatment-related effects were observed.

4.4.2 Dermal contact

According to the EU-RAR, no data on repeated dose toxicity following dermal contact to antimony trioxide have been located (EU-RAR 2008).

No data on other inorganic antimony compounds have been located.

4.5 Toxicity to reproduction

4.5.1 Oral intake

Pregnant female NOS albino normotensive rats were given 0 (control), 0.1 or 1 mg/dl antimony trichloride in the drinking water from the first day of pregnancy until weaning (day 22 after delivery) (equivalent to 0.12 and 1.2 mg/kg bw/day, respectively using EFSA default value 0.12 for sub-acute studies (EFSA 2012)). Pups were similarly exposed to antimony trichloride from day 22 to 60. Body weight and systolic arterial blood pressure were measured in dams from gestational day (GD) 1 to 20. Length of gestation and number of new-borns per litter ware determined. Body weights of the pups were measured from postnatal day (PD) 1 to 60. Statistically significantly lower body weights were observed in antimony trichloride treated dams on GD 20 compared to controls ($p<0.05$) and statistically significantly lower body weight were observed in high-dose pups from PD 10 to 60. No developmental effects (differences in the number of new-born pups per litter and macroscopic teratogenic effects) were observed in the offspring (Rossi et al. 1987).

No data on other inorganic antimony compounds have been located.

4.5.2 Dermal contact

According to the EU-RAR, no data on reproductive toxicity following dermal contact to antimony trioxide have been located (EU-RAR 2008).

No data on other inorganic antimony compounds have been located.

4.6 Mutagenic and genotoxic effects

4.6.1 *In vitro* studies

Antimony trichloride (>99.9 % pure) was tested for mutagenicity in an *in vitro umu* test in *Salmonella typhimurium* strain TA1535/pS1002 with or without metabolic activation in concentrations ranging between $1.6*10^{-6}$ and $8.2*10^{-4}$ M. Antimony trichloride was negative under all test conditions. (Yamamoto et al. 2002).

Antimony trichloride was tested for mutagenicity in an Ames test using *Salmonella typhimurium* strains TA 98 and TA 100 in a concentration of 1 mM with or without metabolic activation. Antimony trichloride was negative under all test conditions. (Kubo et al. 2002).

Antimony trichloride was tested for mutagenicity in the SOS chromotest using *Escherichia coli* strain PQ37 in doses ranging from 11 – 707 μM. Antimony trichloride was negative for mutagenicity but cytotoxic in doses above 354 μM (Lantzsch & Gebel 1997).

Antimony trioxide (99.9 % pure in DMSO) was tested for mutagenicity in a *Salmonella typhimurium* microsome assay in strains TA 1535, TA 1537, TA 98 and TA 100 and in *Escherichia coli* strains WP2P and WP2P*uvr*A using both the pre-incubation (60 min) and plate incorporations protocol. The concentrations tested were 100, 200, 500, 1000, 2500 and 5000 μg/plate, with and without metabolic activation. No increases in revertant numbers were observed (Elliott et al. 1998 – quoted from EU-RAR 2008).

Antimony trichloride and antimony trioxide were tested in a spot test (reversion assay) using *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537 and TA 1538 and in *Escherichia coli* strains B/r WP2 try⁻ and WP2 hcr⁻ try⁻ in concentrations of 0.01 and 0.05 M, respectively. No mutagenicity was observed. (Kanematsu et al. 1980 – quoted from EU-RAR 2008).

Antimony trichloride and antimony trioxide were tested in the *Bacillus subtilis* Rec assay using strains M45(rec-) and H17(rec+) in concentrations of 0.01 and 0.05 M, respectively. Antimony trichloride and antimony trioxide were classified as strong positive (more than 6 mm difference in the diameter of the killing zones in the M45 and H17 plates) and mild positive (less than 6 mm and more than 4 mm of difference in the diameter of the killing zones in the M45 and H17 plates), respectively (Kanematsu et al. 1980).

Antimony trichloride, antimony trioxide and antimony pentoxide were tested in a *Salmonella typhimurium* mutation assay using strains TA 100 and TA 98 with and without metabolic activation in concentrations of 625, 1250, 2500 and 5000; 0.43, 0.86 and 1.71 and 50, 100 and 200 60 µg/plate, respectively . No mutagenicity weas observed (Kuroda et al. 1991 – quoted from EU-RAR 2008).

Antimony trichloride, antimony trioxide and antimony pentoxide were tested in the *Bacillus subtilis* Rec assay using strains M45(rec-) and H17(rec+) in concentrations of 6.3, 12.5 and 23; 0.3, 0.6 and 1.1 and 60 µg/disk, respectively. A strong positive rec effect, defined as a difference in the diameter of the killing zones in the M45 and H17 plates larger than 4 mm, was observed for antimony trichloride and antimony trioxide (Kuroda et al. 1991 – quoted from EU-RAR 2008).

Antimony trioxide (99.9 % pure in DMSO) was tested in the mouse lymphoma L5178Y mutation assay in concentrations of 6, 13, 25 and 50 µg/ml with and without metabolic activation. No increases in mutant frequency were observed (Elliott et al. 1998 – quoted from EU-RAR 2008).

Antimony trichloride tested for DNA damage potential and apoptosis in Chinese hamster ovary (CHO-K1) cells (0-400 µM for 4 hours), human bronchial epithelial (BES-6) cells (0-200 µM for 4 hours) and human fibroblasts (HF) (0-400 µM for 4 hours). Antimony trichloride induced micronuclei in all cell types at concentrations > 50 µM. Delayed apoptosis was observed in all cell types following a post-incubation period of 16-24 hours at concentrations > 50 µM (Huang et al 1998).

Antimony trioxide (99.9 % pure in DMSO) was tested in an *in vitro* cytogenetic assay in human lymphocytes in concentrations of 10, 50 and 100 µg/ml with and without metabolic activation. Mitotic activity was not affected. According to the authors, statistically and biologically significant, concentration-related increases in mean percent aberrant cells (excluding cells with only gap-type aberrations) were seen at the 68-h sampling time in cultures from both donors in the presence of S9-mix (50 and 100 µg/ml), and in cultures from one of the donors in the absence of S9-mix (100 µg/ml). No increase in the number of polyploidy and endo-reduplicated cells was observed (Elliott et al. 1998 – quoted from EU-RAR 2008).

Antimony trioxide (99.9 % pure in DMSO) was tested in an *in vitro* SCE assay in human lymphocytes in concentrations of 0, 0.1, 0.5, 1, 2 and 5 µM for 24 hours. A significant dose-dependent increase in the number of SCEs in lymphocytes from a minimum dose of 0.5 µM was induced. Antimony trioxide was cytotoxic at 5 µM (Gebel 1997 – quoted from EU-RAR 2008).

Antimony trichloride, antimony trioxide and antimony pentoxide were tested in a sister chromatid exchange (SCE) assay using V79 Chinese hamster cells in concentrations of 1.3, 2.5, 5, 10 and 20; 0.09, 0.17 and 0.34 and 10, 20 and 40 µg/ml, respectively. Antimony trichloride and antimony trioxide significantly induced SCEs at concentrations equal to and higher than 2.5 and 0.09 µg/ml, respectively (p<0.05) (Kuroda et al. 1991 – quoted from EU-RAR 2008).

Antimony trichloride was tested in an *in vitro* single cell gel test (Comet assay) in whole blood and human lymphocytes in the presence or absence of proteinase K in concentrations of 0 (control), 1, 5, 10, 25 and 50 µM. Significant increases in DNA fragments were seen from 5 to 50 µM (1.1 and 11

µg/ml, respectively) of antimony trichloride in lymphocytes. Loss of DNA-protein cross-links were observed in the presence of proteinase K. (Schaumlöffel & Gebel 1998 – quoted from EU-RAR 2008).

Antimony trichloride was tested in an *in vitro* micronucleus test in human peripheral lymphocytes in concentrations of 0 (control), 0.1, 0.5, 1, 2, 5, 10, 25 and 50 µM with or without supplementation with superoxide dismutase or catalase. A significantly elevated frequency of micronuclei was observed at concentrations ≥ 5 µM. The number of micronuclei formed was not suppressed by co-incubation with superoxide dismutase or catalase. (Schaumlöffel & Gebel 1998 – quoted from EU-RAR 2008).

Antimony trichloride was tested for genotoxicity in a micronucleus test and a single cell gel assay (Comet assay) in the presence or absence of proteinase K using V79 Chinese hamster cells in concentrations up to 50 and 10 µM, respectively. Significantly higher frequencies of micronuclei were observed at concentrations of 25 µM and above in the micronucleus test (p<0.05). Tail movement (indicating DMA damage) increased dose-dependently and was significantly elevated at 1 and 10 µM (p<0.001). DNA-protein cross-links were not observed (Gebel et al. 1998).

4.6.2   *In vivo* studies

A bone marrow micronucleus assay was performed with antimony trioxide (99.9 % pure) after both single and repeated dose exposure of CD-1 mice (5 animals/sex/group; 5-11 weeks old). In the single dose study an oral dose of 5000 mg/kg bw was given by gavage and bone marrow was sampled 24 and 48 hours after dosing. In the repeated dose study daily doses of 400, 667 or 1000 mg/kg bw were given by gavage and bone marrow was sampled after 8, 15 or 22 days of dosing. A statistically significant decrease in the mean percent polychromatic erythrocytes was seen in females at the 24 h sampling time (p<0.01). No toxicity was observed and the incidence of micronuclei was not increased (Elliot et al. 1998 – quoted from EU-RAR 2008).

A chromosomal aberrations test in mouse bone marrow was performed with antimony trioxide after both single and repeated dose exposure of Swiss albino mice (5 animals/sex/group; 25-30 g). In the single dose study oral doses of 400, 666.67 and 1000 mg/kg bw were given by gavage and bone marrow was sampled 6, 12, 18 and 24 hours after dosing. In the repeated dose study the same doses were administered to male mice only (5 animals/group) and bone marrow was sampled on days 7, 14 and 21. All animals in the highest dose group in the repeated dose study died on day 20, hence chromosomal aberrations were only analysed in the low and middle dose group on day 21. In the repeated dose study the frequency of aberrations including gaps, without gaps and break/cell increased proportionally with the dose to a significance of p ≤ 0.001 in the trend test for the first 14 days. In the single dose study, no statistically significant differences in the number of chromosomal aberrations were observed (Gurnani et al. 1992 – quoted from EU-RAR 2008).

Micronuclei and chromosome aberrations were evaluated in the bone marrow of Sprague-Dawley Crl:CD (SD) rats (6 animals/sex/group; 6-8 weeks old) given antimony trioxide (purity 99.93 %) in doses of 250, 500 and 1000 mg/kg bw for 21 days by gavage. No increase in chromosome aberrations or micronuclei in the bone marrow cells were observed (Kirkland et al. 2007 – quoted from EU-RAR 2008).

A liver DNA repair assay was performed with antimony trioxide (99.9 % pure) in male Alderley Park Alpk: APfSD rats (5 animals/sex/group; 200-300 g) given a single oral dose of 3200 or 5000 mg/kg bw by gavage. Hepatocytes were sampled after 2 or 16 hours. The treated animals showed no signs of toxicity and there was no increase in net nuclear grains or percentage of cells in repair at either sampling time (Elliot et al 1998 – quoted from EU-RAR 2008).

4.7 Carcinogenic effects

4.7.1 Oral intake

No tumours were observed in rats or mice administered antimony at 5 mg/l as potassium antimony tartrate in the drinking water for a lifetime (Schroeder et al 1968; Schroeder et al. 1970, Kanisawa & Schroeder 1969 - quoted from ATSDR 1992, and from IRIS 1995).

According to the EU-RAR, no data on carcinogenic potential following oral exposure to antimony trioxide have been located (EU-RAR 2008).

No data on other inorganic antimony compounds have been located.

4.7.2 Dermal contact

According to the EU-RAR, no data on carcinogenic potential following dermal contact to antimony trioxide have been located (EU-RAR 2008).

No data on other inorganic antimony compounds have been located.

5. Regulations

5.1 Ambient air

Denmark (C-value):   0.001 mg Sb/m^3, antimony compounds in inorganic dust (MST 2008).

5.2 Drinking water

Denmark: 2 µg Sb/l (entrance to the property) (MM 2014)

5 µg Sb/l (tap) (MM 2014)

WHO: 20 µg/l (WHO 2003)

The background for the guideline value is as follows (WHO 2003):

"*The most common source of antimony in drinking-water appears to be dissolution from metal plumbing and fittings. The form of antimony in drinking-water is a key determinant of its toxicity, and it would appear that antimony leached from antimony-containing materials would be in the form of the antimony(V) oxo-anion, which is the less toxic form. It is therefore critical that the study selected for guideline derivation be a drinking-water study.*
The suggested NOAEL (Lynch et al., 1999) in the sub-chronic drinking-water study in rats conducted by Poon et al. (1998) was 6.0 mg/kg of body weight per day based on decreased body weight gain and reduced food and water intake. A TDI of 6 µg/kg of body weight can be determined by applying an uncertainty factor of 1000 (100 for intra- and interspecies variation and 10 for the use of a sub-chronic study). A guideline value of 20 µg/litre (rounded figure) can be derived from this TDI by assuming a 60-kg adult drinking 2 litres of water per day and allocating 10% of the TDI to drinking-water. It should be noted that this value could be highly conservative because of the nature of the end-points and the large uncertainty factor; further data could result in a lower uncertainty factor."

US-EPA: 6 µg/l (MCLG / MCL) (US-EPA 1992)

The maximum contaminant level goal (MCLG) is set at a concentration level at which no known or anticipated adverse health effects occur, allowing for an adequate margin of safety. The MCLG for antimony is derived based on an oral reference dose (RfD) of 0.0004 mg/kg bw/day (see section 5.7) and assumes that a 70 kg adult ingests 2 litres/day of drinking water. The MCLG assumes a relative source contribution factor of 40%. (US-EPA 1992).
Based on the MCLG, US-EPA has set an enforceable standard for antimony, called a maximum contaminant level (MCL), at 0.006 mg/l. MCLs are set as close to the MCLGs as possible, considering cost, benefits and the ability of public water systems to detect and remove contaminants using suitable treatment technologies. For antimony, the MCL equals the MCLG, because analytical methods or treatment technology do not pose any limitation. (US-EPA 2013).

5.3   Soil
Denmark: -

5.4   Occupational Exposure Limits
Denmark: 0.5 mg Sb/m³, antimony and its compounds except stibine (At 2007).

5.5   Classification
Antimony tri- and pentachloride:
Skin Corr. 1B H314 (causes severe skin burns and eye damage), Aquatic Chronic 2 H411 (toxic to aquatic life with long lasting effects).

Antimony trioxide:
Carc. 2 H351 (suspected of causing cancer).

Antimony compounds, with the exception of the tetroxide (Sb2O4), pentoxide (Sb2O5), trisulphide (Sb2S3), pentasulphide (Sb2S5) and those specified elsewhere in Annex VI of Regulation (EC) No 1272/2008 (CLP Regulation):
Acute Tox. 4 H302 (harmful if swallowed), Acute Tox. 4 H332 (harmful if inhaled), Aquatic Chronic 2 H411 (toxic to aquatic life with long lasting effects).

5.6   IARC
Antimony trioxide is possibly carcinogenic to humans (Group 2B). There is inadequate evidence for the carcinogenicity in humans. There is sufficient evidence for the carcinogenicity in experimental animals. (IARC 1989).

Antimony trisulphide is not classifiable as to its carcinogenicity to humans (Group 3). There is inadequate evidence for the carcinogenicity in humans. There is limited evidence for the carcinogenicity in experimental animals. (IARC 1989).

5.7   US-EPA
Oral reference dose (RfD): 0.0004 mg/kg bw/day (last revised: 02/01/1991).
The oral RfD is based on a LOAEL of 0.35 mg/kg bw/day for decreased longevity, blood glucose and cholesterol in rats (Schroeder et al. 1970 - see section 4.2). An uncertainty factor of 1000 (10 for interspecies conversion, 10 to protect sensitive individuals, and 10 because the effect level was a LOAEL and no NOEL was established) was applied. (IRIS 2015a).

Antimony has not undergone an evaluation and determination under US-EPA's IRIS program for evidence of human carcinogenic potential (IRIS 2015a).

Antimony trioxide has not undergone an evaluation and determination under US-EPA's IRIS program for evidence of human carcinogenic potential. No oral reference dose (RfD) has been established (IRIS 2015b).

5.8   WHO / JECFA
WHO/JECFA has not evaluated the safety of antimony and/or antimony compounds.

5.9 EFSA

EFSA has evaluated antimony trioxide used as an additive in food contact materials (EFSA 2004). A Restriction of 0.04 mg/kg of food (as Sb) is applied. The Restriction is based on the TDI of 0.006 mg Sb/kg bw/day derived by WHO in relation to the drinking water guideline (see section 5.2).

6. Summary and evaluation

6.1   Description

Antimony is a non-metal or metalloid. It forms stable tri- and pentavalent compounds.

6.2   Environment

Antimony is naturally present in the earth's crust in low concentrations (approximately 0.2-0.3 mg/kg). Antimony trioxide occurs in nature as the minerals valentinite and senarmontite, and antimony trisulphide as the mineral.

The emission of antimony into the human environment appears to be exclusively the result of human activity. Most emitted antimony is in the form of antimony trioxide, which is released as a result of coal burning or with fly ash when antimony-containing ores are smelted.

The average antimony concentration in soils has been reported to be about 0.5 to 1 mg/kg, but wide ranges have been reported.

A Danish report from 2014 has reported levels of antimony in soil at a shooting place ranging from below the detection limit (< 1 mg Sb/kg dry matter) to 515 mg Sb/kg dry matter.

In the EU-RAR, the reasonable worst case ambient antimony concentration in freshwater (dissolved) was reported to be 0.72 µg/l. EU drinking water surveys (reported in the EU-RAR) with measured data on antimony concentrations in drinking water compiled and submitted in 2007 showed that all median and mean values were well below 0.72 µg/l.

Antimony, being a natural element, cannot be degraded; however, it can be transformed between different binding/speciation forms and oxidation states. Antimony released to the environment will eventually end up in either of the two compartments soil or sediment, depending on the release, form of antimony, meteorological conditions, etc. As a constituent of soil, antimony will also be transported into streams and waterways due to weathering and run-off from soils; much of this antimony is associated with particulate matter.

In general, the knowledge on weathering reactions, mobility and adsorptive behaviour of antimony, its compounds and ions in soil is relatively limited. The sorption and precipitation of $Ca[Sb(OH)_6]_2$ seem to be more important than the dissolution processes of Sb_2O_3 as regards the fate of antimony. Several studies using bacteria in both aerobic and anaerobic cultures have shown that methylation of antimony may result in the formation of volatile antimony compounds.

6.3   Human exposure

The general population is exposed to low levels of antimony in ambient air (low compared to food), drinking water and food.

In the EU-RAR, the typical exposure of antimony via food was estimated to 3.7 µg/day (median) and the reasonable worst case exposure to 4.8 µg/day (90th percentile); the reasonable worst case exposure from drinking water was estimated to 1.44 µg/day.

6.4   Toxicokinetics

The absorption of the water soluble compound antimony potassium tartrate following oral intake is approximately 5% in humans and in experimental animals.

The less soluble inorganic antimony compounds are only absorbed to a little extent oral intake. Based on an oral bioavailability study (performed according to OECD Test Guideline 417) in rats with antimony trioxide, an oral absorption of 1% was considered and taken forward to the risk characterisation in the EU-RAR. Both the absorption of antimony trioxide and the elimination of antimony from blood is a slow process. Antimony is distributed to most tissues with the highest concentrations found in bone marrow and thyroidea, followed by, spleen, lung, liver, ovaries heart, kidney, femur and skin. Antimony can also be detected in testes and brain. After oral exposure the elimination occurs in two phases; a rapid elimination of antimony primarily via faeces but also via urine lasting for about a week followed by a slower decrease lasting for more than 30 days.

Based on the low dermal absorption value of 0.26 % calculated for antimony trioxide from an *in vitro* percutaneous study with human skin, dermal absorption of antimony trioxide is considered negligible.

6.5   Human toxicity

6.5.1   Single dose toxicity
The minimal lethal dose for oral intoxication by antimony potassium tartrate has been reported to be 300 mg for a child and 1200 mg for an adult.

According to the EU-RAR, no reliable human information regarding the acute toxicity after single oral intake of antimony trioxide is available, and no human data after single dermal exposure to antimony trioxide could be located.

No data on other inorganic antimony compounds have been located.

6.5.2   Skin irritation
According to the EU-RAR, antimony trioxide should be regarded as a skin irritant in humans under conditions that evoke sweating.

No data on other inorganic antimony compounds have been located.

6.5.3   Skin sensitisation
According to the EU-RAR, none of the human studies are of adequate quality for assessing the sensitising potential of antimony trioxide.

No data on other inorganic antimony compounds have been located.

6.5.4   Repeated dose toxicity
No relevant human data regarding repeated dose toxicity following oral intake of antimony compounds have been located, and no human data following dermal exposure to antimony compounds have been located.

6.5.5   Toxicity to reproduction
No human data regarding toxicity to reproduction after oral intake of or dermal contact to antimony compounds have been located.

6.5.6 Mutagenic and genotoxic effects

No relevant human data regarding mutagenic and genotoxic effects have been located.

6.5.7 Carcinogenic effects

No human data regarding carcinogenic effects after oral intake of or dermal contact to antimony compounds have been located.

6.6 Animal toxicity

6.6.1 Single dose toxicity

The acute oral toxicity of the water soluble antimony compounds, i.e. antimony trichloride and antimony potassium tartrate is moderate with LD_{50} values in the of 115 to 600 mg/kg bw.

The acute oral and dermal toxicity studies indicate that the less water soluble antimony compounds, i.e. antimony trioxide and antimony trisulphide are of low acute oral and dermal toxicity in rats.

6.6.2 Skin irritation

According to the EU-RAR, antimony trioxide is not irritating to rabbit skin.

No data on other inorganic antimony compounds have been located.

6.6.3 Skin sensitisation

According to the EU-RAR, there is one reliable animal study, performed according to OECD TG 406 and GLP, which shows that antimony trioxide has no skin sensitising properties.

No data on other inorganic antimony compounds have been located.

6.6.4 Repeated dose toxicity

For the water soluble antimony compound, antimony potassium tartrate, a NOAEL for antimony of 0.5 mg Sb/l (equivalent to a calculated intake of 0.06 mg Sb/kg bw/day) was suggested by the authors (Poon et al. 1998) based on biochemical and histological changes and retention of antimony in red blood cells and spleen. Based on this study, Lynch et al. (1999) concluded that the NOAEL is 6 mg Sb/kg bw/day based on decreased body weight gain and reduced food and water intake; this NOAEL forms the basis for the WHO drinking water guideline (WHO 2003).

In an older study, a LOAEL of 0.35 mg/kg bw/day was observed for decreased longevity, blood glucose and cholesterol in rats (Schroeder et al. 1970). The oral reference dose (RfD) for antimony set by the US-EPA is based on this study (IRIS 2015a).

According to the EU-RAR, two repeated dose oral studies suggest that antimony trioxide may be toxic to the liver. This is based on a 10 % increase in liver weight and significantly elevated aspartate aminotransferase values in one study (Hext et al. 1999), supported by significantly elevated aspartate aminotransferase levels observed in another study (Sunagawa 1981). However, in the absence of histological change or any clinical signs of antimony intoxication to support that the liver findings are adverse, the findings were regarded, according to the EU-RAR as adaptive or incidental to treatment with antimony trioxide. A NOAEL of 1686 mg/kg bw/day for liver toxicity was suggested in the EU-RAR.

According to the EU-RAR, a NOAEL of 1686 mg/kg bw/day for liver toxicity can be derived from the Hext et al. (1999) study. It was also noted in the EU-RAR that "*Diantimony trioxide, supplied as a white solid with a purity of 99 %, was mixed in the diet and the homogeneity of the mixture was > 95%. No information is provided on the size of the diantimony trioxide particles in the diet, which is likely to affect the gastrointestinal uptake of the substance.*" (EU-RAR 2008).

According to NTP, the NOAEL in the Hext et al. (1999) study is 494 mg/kg bw/day and the LOAEL is 1879 mg/kg/day (NTP 2005).
According to WHO, the NOAEC of 20000 mg/kg in the diet the Hext et al. (1999) study was equivalent to a NOAEL of 1685.9 mg/kg bw/day (or 1407.7 mg Sb/kg bw/day).

In a study investigating the histopathological and functional effects of antimony trisulphide on the renal cortex in male Sprague Dawley rats, the authors reported on several changes in the renal cortex in the groups given antimony trisulphide.

No data on other inorganic antimony compounds have been located.

6.6.5 Toxicity to reproduction
No relevant data regarding reproductive toxicity following oral intake of antimony compounds have been located, and no data following dermal exposure to antimony compounds have been located.

6.6.6 Mutagenic and genotoxic effects
Considering the available genotoxicity data, antimony trichloride antimony trioxide do not induce gene mutations *in vitro*, but induces structural chromosome aberrations in cultured mammalian cells *in vitro*. *In vivo* studies on the induction of chromosome aberrations and micronuclei in the bone marrow and unscheduled DNA synthesis in the liver have produced negative results for antimony trioxide; no *in vivo* data for antimony trichloride have been located.

No data on the water soluble antimony potassium tartrate have been located.

6.6.7 Carcinogenic effects
No tumours were observed in rats or mice administered antimony at 5 mg/l (as potassium antimony tartrate) in the drinking water for a lifetime.

No data on other inorganic antimony compounds have been located.

6.7 Evaluation
Antimony trisulphide is used as a primer in ammunition. Antimony has been detected in the soil at a Danish shooting place indicating that antimony can leach from the antimony trisulphide containing ammunition.

In a study investigating the histopathological and functional effects of antimony trisulphide on the renal cortex in male Sprague Dawley rats, the authors reported on several changes in the renal cortex in the groups given antimony trisulphide. The authors referred to several (n>25) other studies on the toxic effects of antimony, however, these references are either cited wrongly or non-existing. Therefore, this study is considered as being of no relevance for the setting of a health-based quality criterion for antimony trisulphide or antimony in soil.
In conclusion, no relevant toxicity data on antimony trisulphide have been located.

Therefore, data on the very slightly soluble inorganic antimony compound, antimony trioxide (the compound for which most toxicity data are available), as well as data on the more water soluble antimony compound, antimony potassium tartrate (which have formed the basis for health-based guidance values set by the WHO and the US-EPA) have also been addressed in this document in order to propose a health-based quality criterion for antimony in soil. Only data on repeated oral and dermal exposure are considered relevant for the setting of a health-based quality criterion for antimony in soil and therefore, addressed in this document.

The data on health effects of antimony compounds in humans following oral intake or dermal contact for these antimony compounds are extremely limited and considered to be of no relevance for the setting of a health-based quality criterion for antimony in soil.

For <u>antimony trioxide</u>, two repeated dose oral studies suggest, according to the EU-RAR that antimony trioxide may be toxic to the liver. This is based on a 10 % increase in liver weight and significantly elevated aspartate aminotransferase values in one study (Hext et al. 1999), supported by significantly elevated aspartate aminotransferase levels observed in another study (Sunagawa 1981). However, in the absence of histological change or any clinical signs of antimony intoxication to support that the liver findings are adverse, the findings were regarded, according to the EU-RAR as adaptive or incidental to treatment with antimony trioxide. A NOAEL of 1686 mg/kg bw/day for liver toxicity was suggested in the EU-RAR. The authors of the present document agree with the evaluation in the EU-RAR, including the NOAEL as presented in the EU-RAR, although realising that the comments presented in the EU-RAR regarding this study ("*Diantimony trioxide, supplied as a white solid with a purity of 99 %, was mixed in the diet and the homogeneity of the mixture was > 95%. No information is provided on the size of the diantimony trioxide particles in the diet, which is likely to affect the gastrointestinal uptake of the substance.*") indicates that this NOAEL is somewhat uncertain, but likely on the conservative side. The authors of the present document also noted that the WHO considered the NOAEL of the Hext et al. (1999) study to be 1686 mg/kg bw/day (or 1408 mg Sb/kg bw/day) supporting the conclusion taken by the EU (as presented in the EU-RAR)..

For the water soluble antimony compound, antimony potassium tartrate, a NOAEL for antimony of 0.5 mg Sb/l (equivalent to a calculated intake of 0.06 mg Sb/kg bw/day) was suggested by the authors of a well-performed 90-day study (Poon et al. 1998) based on biochemical and histological changes and retention of antimony in red blood cells and spleen. However, Lynch et al. (1999) concluded that the NOAEL is 6 mg Sb/kg bw/day based on decreased body weight gain and reduced food and water intake in this study. The authors of the present document agree with the evaluation in the Lynch et al. (1999) review. The NOAEL in the Lynch et al. (1999) review, i.e. 6 mg Sb/kg bw/day also forms the basis for the WHO drinking water guideline (WHO 2003).

In an older study, a LOAEL of 0.35 mg/kg bw/day was reported for decreased longevity, blood glucose and cholesterol in rats (Schroeder et al. 1970). The oral reference dose (RfD) for antimony set by the US-EPA (IRIS 2015a), as well as the former provisional guideline value for antimony in drinking water (WHO 1993) is based on this study. At the only concentration level used, decreased survival and longevity were observed. Although not precisely stated, the concentration of 5 ppm in the drinking water was expressed as corresponding to 0.35 mg/kg bw by the authors. However, it remains still uncertain whether the concentration is expressed as antimony potassium tartrate or as antimony. Thus, this study is considered as inadequate for the estimation of a TDI and a quality criterion for antimony / antimony sulphide in soil.

In general, the knowledge on weathering reactions, mobility and adsorptive behaviour of antimony, its compounds and ions in soil is relatively limited. Therefore, the most relevant species of antimony in the soil at shooting places contaminated with antimony trisulphide remain uncertain. Thus, the proposed health-based soil quality criterion for antimony will be based on the most conservative approach, i.e. that all of the antimony in antimony trisulphide containing ammunition will be released to the soil. Consequently, the proposed health-based soil quality criterion for antimony will be based on the NOAEL of 6 mg Sb/kg bw/day for antimony potassium tartrate as considered by Lynch et al. (1999) and by WHO for the setting of the drinking water guideline (WHO 2003).

7. TDI and quality criterion in soil

7.1 TDI

The TDI is calculated based on a NOAEL of 6 mg Sb/kg bw/day based on decreased body weight gain and reduced food and water intake observed for the water soluble antimony compound, antimony potassium tartrate in the well-performed 90-day study by Poon et al. (1998), as considered by Lynch et al. (1999) and by WHO for the setting of the drinking water guideline (WHO 2003), and agreed by the authors of the present document:

$$TDI = \frac{NOAEL}{UF_I * UF_{II} * UF_{III}} = \frac{6 \text{ mg Sb/kg b.w./day}}{10 * 10 * 10} = 0.006 \text{ mg Sb/kg bw/day}$$

The uncertainty factor UF_I accounting for interspecies variability is set to 10 assuming that humans are more sensitive than animals. The UF_{II} accounting for intraspecies variability is set to 10 reflecting the range in biological sensitivity within the human population. The UF_{III} is set to 10, a factor of 2 because the study is a 90-day study and not a chronic study (in accordance with the REACH guidance document) and a factor of 5 because no relevant data are available on reproductive toxicity and carcinogenic effects following oral intake or dermal contact to antimony compounds.

7.2 Allocation

The general population is predominantly exposed to antimony from other sources than soil. Therefore, only 10% of the TDI is allocated to ingestion of soil.

7.3 Quality criterion in soil

The quality criterion in soil QC_{soil} is calculated based on the TDI of 0.006 mg Sb/kg bw per day and assuming a daily ingestion of 0.1 g soil for a child weighing 13 kg (w_{child}):

$$QC_{soil} = \frac{TDI * f * w_{child}}{ingestion_{soil}} = \frac{0.006 \text{ mg Sb/kg bw/day} * 0.1 * 13 \text{ kg}}{0.0001 \text{ kg/day}}$$

$$= 78 \text{ mg/kg soil}$$

7.3.1 Quality criterion in soil

Quality criterion: 80 mg Sb/kg soil (rounded figure).

7.4   Cut-off criterion in soil

The cut-off criterion in soil is generally set at 10 times the health-based quality criterion in soil for substances where the health-based quality criterion in soil is based on effects observed following repeated exposure for a prolonged period of time (MST 2000).

As the health-based quality criterion in soil is based on a NOAEL for decreased body weight gain and reduced food and water intake for the water soluble antimony compound, antimony potassium tartrate in a 90-day rat study, the cut-off criterion in soil for antimony is set at 10 times the health-based quality criterion in soil of 80 mg Sb/kg soil (rounded figure), i.e. 800 mg Sb/kg soil (rounded figure).

7.4.1   Cut-off criterion in soil

Cut-off criterion: 800 mg Sb/kg soil (rounded figure).

References

At (2007). Grænseværdier for stoffer og materialer. Arbejdstilsynets At-vejledning C.0.1, august 2007.

ATSDR (1992). Toxicological Profile for Antimony. ATSDR/TP-91/02, U.S. Department of Health & Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry.

Denys S, Caboche J, Tack K, Rychen G, Wragg J, Cave M, Jondrreville C and Feidt C (2012). *In vivo* validation of the Unified BARGE Method to assess the bioaccessibility of arsenic, antimony, cadmium and lead in soils. Environ Sci Technol 46, 6252-6260.

EFSA (2004). Opinion of the Scientific Panel on food additives, flavourings, processing aids and materials in contact with food (AFC) on a request from the Commission related to a 2nd list of substances for food contact materials. The EFSA Journal (2004) 24, 1-13.

EFSA (2012). EFSA Scientific Committee; Guidance on selected default values to be used by the EFSA Scientific Committee, Scientific Panels and Units in the absence of actual measured data. The EFSA Journal (2012) 10(3):2579. [32 pp.]

EU-RAR (2008). European Union Risk Assessment Report. Diantimony trioxide Risk assessment.

FFI (2010). Veileder for undersøkelse, risikovurdering, opprydning og avhending av skytebaner og øvingsfelt. FFI-rapport 2010/00116.

Finnish ME (2007). Government decree on the assessment of soil contamination and remediation needs 214/2007. Ministry of the Environment, Finland.

Gebel T, Birkenkamp P, Luthin S and Dunkelberg H (1998). Arsenic(III), but not antimony(III), induces DNA-Protein crosslinks. Anticancer research 18,4253-5258.

Hext PM, Pinto PJ and Rimmel BA (1999). Subchronic feeding study of antimony trioxide in rats. J Appl Toxicol 19, 205-209.

Huang H, Shu SC, Shih JH, Juo CJ and Chiu ID (1998). Antimony trichloride induces DNA damage and apoptosis in mammalian cells. Toxicology 129,113-123.

IARC (1989). Antimony trioxide and antimony trisulfide. In: IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Vol 47, Some organic solvents, resin monomers and related compounds, pigments and occupational exposures in paint manufacture and painting, Lyon, 291-305.

IRIS (2015a). Antimony (CASRN 7440-36-0). In: Integrated Risk Information System. Database quest, last revised: Oral RfD 02/01/1991. US-EPA. http://www.epa.gov/iris/subst/0006.htm

IRIS (2015b). Antimony trioxide (CASRN 1309-64-4). In: Integrated Risk Information System. Database quest. US-EPA. http://www.epa.gov/iris/subst/0676.htm

Kanematsu N, Hara M and Kada T (1980). Rec assay and mutagenicity studies on metal compounds. Mut Res 77, 109-116.

Kubo T, Urano K and Utsumi H (2002). Mutagenicity characteristics of 255 environmental chemicals. J Health Sci 46, 545-554.

Lantzsch H and Gebel T (1997). Genotoxicity of selected metal compounds in the SOS chromotest. Mut Res 389, 191-197.

Lynch BS, Capen CC, Nestmann ER, Veenstra G and Deyo JA (1999) Review of subchronic/chronic toxicity of antimony potassium tartrate. Regul Toxicol Pharmacol 30, 9-17.

MM (2014). Bekendtgørelse om vandkvalitet og tilsyn med vandforsyningsanlæg. Miljøministeriets bekendtgørelse nr. 948 af 22. august 2014.

MST (2000). Rådgivning af beboere i lettere forurenede områder. Vejledning fra Miljøstyrelsen Nr. 7 2000, Miljøstyrelsen, Miljøministeriet.

MST (2008). Supplement til B-værdivejledningen 2008. Miljøprojekt Nr. 1252 2008, Miljøstyrelsen, Miljøministeriet.

NIRAS (2014). 557 Hedeplantage – Viborg skydebaner: Risikovurdering over for grundvand på baggrund af jordforurening med antimony. Forsvarets Bygnings- og Etablissementstjeneste, September 2014. Internal report.

NTP (1992). NTP report on the toxicity studies of antimony potassium tartrate in F344/N rats and B6C3F1 mice (drinking water and intraperitoneal injection studies). National Toxicological Program. NIH Publication No. 92-3130.

NTP (2002). Antimony trioxide [CAS No. 1309-64-4]. Summary of data for chemical selection. National Toxicology Program, National Institute of Environmental Health Sciences.

NTP (2005). Antimony trisulfide [CAS No. 1345-04-6]. Brief review of toxicological literature. National Toxicology Program, National Institute of Environmental Health Sciences.

Omura M, Tanaka A, Hirata M and Inoue N (2002). Testicular toxicity evaluation of two antimony compounds, antimony trioxide and antimony potassium tartrate, in rats and mice. Environ Health Prevent Med 7, 15-18.

Poon R, Chu I, Lecavalier P, Valli VE, Foster W, Gupta S and Thomas B (1998). Effects of antimony on rats following 90-day exposure via drinking water. Food Chem Toxicol 36, 21-35.

Rashedy AH, Solimany AA, Ismail AK, Wahdan MH and Saban KA (2013). Histopathological and functional effects of antimony on the renal cortex of growing albino rats. Int J Clin Exp Pathol 6, 1467-1480.

Rossi F, Acampora R, Vacca C, Maione S, Matera MG, Servodio R and Marmo E (1987). Prenatal and postnatal antimony exposure in rats: effect on vasomotor reactivity development of pups. Teratogen Carcinogen Mutagen 7, 491-496.

Sanderson P, Naidu R, Bolan N, Bowman M and Mclure S (2012). Effect of soil type on distribution and bioaccessibility of metal contaminants in shooting range soils. Sci Total Environ 438, 452-462.

Schroeder HA, Mitchener M, Balassa JJ, Kanisawa M and Nason AP (1968). Zirconium, niobium, antimony and fluorine in mice: Effects on growth, survival and tissue levels. J Nutr 100, 59-68.

Schroeder HA, Mitchener M and Nason AP (1970). Zirconium, niobium, antimony, vanadium and lead in rats: life term studies. J Nutr 95, 95-101.

SciFinder 2014. https://scifinder.cas.org/. CAS RN 7440-36-0; 10025-91-9; 1309-64-4; 1345-04-6; 1314-60-9; 1315-04-4 and 28300-74-5.

STCRT (2013). Circulaire bodemsanering per 1 juli 2013. Staatscourant nr. 16675 27 juni 2013, Holland.

Swedish EPA (2009). Riktvärden för förorenad mark. Modellbeskrivning och vägledning. Naturvårdsverket, Rapport 5976, September 2009.

US-EPA (1992). Antimony. In: Federal Register. July 17, 1992. Part III. Environmental Protection Agency. 40 CFR Parts 141 and 142. National Primary Drinking Water Regulations; Synthetic Organic Chemicals and Inorganic Chemicals; Final Rule.

US-EPA (2015). Basic information about antimony in drinking water. http://water.epa.gov/drink/contaminants/basicinformation/antimony.cfm

VROM (2009). NOBO: Normstelling en bodemkwaliteitsbeoordeling. Onderbouwing en beleidsmatige keuzes voor de bodemnormen in 2005, 2006 en 2007. Ministerie van VROM, Holland.

WHO (1993). Antimony. In: Guidelines for drinking-water quality. World Health Organization, Geneva, Vol. 1 Recommendations, sec. ed., 40-41.

WHO (2003). Anatimony in Drinking-water. Background document for development of WHO *Guidelines for Drinking-water Quality*. World Health Organization, Geneva, WHO/SDE/WSH/03.04/74.

Wilson SC, Tighe M, Paterson E and Ashely PM (2014). Food crop accumulation and bioavailability assessment for antimony (Sb) compared with arsenic (As) in contaminated soils. Environ Sci Pollut Res 21,11671-11681.

Yamamoto A, Kohyama Y and Hanawa T (2002). Mutagenicity evaluation of forty-one metal salts by the umu test. J Biomed Mater Res 59, 176-183.

Antimony

The Danish Environmental Protection Agency has requested an evaluation of health hazards by exposure to antimony. This resulted in the present report which includes estimation of a quality criterion in soil for antimony.