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TOX/2025/04

Committee on the Toxicity of Chemicals in Food, Consumer Products and the Environment

Deriving a health-based guidance value for antimony to support development of UK Drinking Water Standards – further information

Introduction

1. The UK Health Security Agency (UKHSA) advises the Drinking Water Inspectorate (DWI) on potential health risks from chemicals in drinking water. Post EU exit, the DWI is reviewing the regulatory standards for some chemicals in drinking water, including antimony. UKHSA is seeking advice from the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) with respect to an appropriate health-based guidance value (HBGV) for antimony.

2. In October 2024, the COT considered an initial discussion paper (TOX/2024/38) which outlined a study by (Poon et al. 1998) on antimony potassium tartrate and commentaries of this (Lynch et al. 1999, Valli et al. 2000). The World Health Organization Drinking Water Guidelines (WHO, 2003), the US Agency for Toxic Substances and Disease Registry (ATSDR, 2019) and Health Canada Drinking water Guidelines (Health Canada, 2024) had all used the same study by Poon et al. (1998) to derive health-based guidance values but differed in interpretation of the study and choice of critical No Observed Adverse Effect Level (NOAEL). Health Canada and ATSDR selected a critical NOAEL of 60 micrograms Sb per kilogram bodyweight per day (µg Sb/kg bw/day) while the WHO selected a NOAEL of 6,000 µg Sb/kg bw/day. At the October 2024 meeting, the COT considered that the Poon et al. (1998) study

showed a NOAEL of 6,000 µg Sb/kg bw/day, which is in agreement with the WHO and Lynch et al. (1999) interpretations of the study.

3. The previous discussion paper (TOX/2024/38) briefly summarised available oral toxicity studies and the COT noted that the Rossi et al. (1987) reproductive toxicity study identified a lower Point of Departure (POD) compared to NOAEL that COT selected for the Poon et al. (1998) study. To determine the appropriate POD for a HBGV, the Committee requested more details on the Rossi et al. (1987) study, additional information on other reproductive/developmental toxicity studies, and a table summarising the available oral and reproductive/developmental toxicity studies.

4. Therefore, this paper provides a detailed summary of toxicity studies reporting a NOAEL lower than 6,000 µg Sb/kg bw/day (the NOAEL identified by COT from the Poon et al. (1998) study). Studies with NOAEL above 6,000 µg Sb/kg bw/day are summarized in Annex A and Annex B contains a table presenting the details and findings of all studies (i.e., including those with NOAELs both below and above 6,000 µg Sb/kg bw/day).

5. In addition, this paper summarises the available information on solubility, absorption and bioavailability of different antimony compounds, as well as summarising the NTP intraperitoneal study on antimony, which the COT considered in October 2024 as potentially useful in a weight of evidence consideration with respect to toxicity of antimony.

6. The COT is asked to consider these additional studies and determine an appropriate point of departure, uncertainty factors and HBGV to support an update to the antimony drinking water standard in the UK.

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Background

7. COT has previously reviewed the dietary exposure to antimony in infants and young children aged 4 to 18 months as part of the 2014 survey of metals and other elements in infant foods. COT has also reviewed dietary exposure to antimony in various population subgroups as part of the 2006 UK Total Diet study of metals and other elements. For these reviews, COT used the WHO tolerable daily intake (TDI) of 6 µg/kg bw/day for the evaluation. More recently Health Canada and ATSDR have considered antimony and derived lower HBGVs, these are described in detail in the previous discussion paper TOX/2024/38.

Properties of different antimony compounds

8. Antimony exists in multiple oxidation states, primarily trivalent and pentavalent antimony. The toxicity of antimony is a function of the water solubility and the oxidation state of the antimony species under consideration (Elinder & Friberg, 1986). In general, trivalent antimony is more toxic than pentavalent antimony. The solubility and form of antimony compounds affect their mobility and bioavailability; for example, soluble forms like antimony potassium tartrate have a higher bioavailability than less soluble forms. Table 1 below summarises the chemistry, solubility, absorption and bioavailability of these antimony compounds.

9. Antimony can enter drinking water from various sources, including leaching from natural geological formations and human activities (e.g., mining). Soluble antimony remains mobile, while less soluble forms adhere to soil and sediments by binding with extractable iron and aluminium. Trivalent and pentavalent antimony species can coexist and interconvert in the environment ((WHO, (2003); ATSDR, (2019); Health Canada, (2024)) The most common source of antimony in drinking water is through the dissolution of metal plumbing and fittings, with antimony (V), a less toxic form, considered to be the most frequent form in drinking water (DWI Communication).

10. In drinking water, the prevalence of pentavalent antimony can be explained by the oxidizing nature of the treatment processes generally applied (for example, chlorination or ozonation) which oxidize trivalent to pentavalent antimony, and by the types of plumbing solder and pipes in the distribution systems (Health Canada, 2024).

Table 1 below summarises absorption, bioavailability, solubility, and valency of different antimony compounds.

Antimony Compound	**Valency**	**Solubility**	**Absorption**	**Bioavailability**
Antimony Trioxide (Sb_2O_3)	+3	Slightly soluble in water	Poor gastrointestinal absorption (approx. 1%).	Poor bioavailability.
Antimony Pentoxide (Sb_2O_5)	+5	Very slightly soluble in water.	Generally, poorly absorbed.	Limited bioavailability data.
Antimony Potassium Tartrate (APT) ($KSbOC_4H_4O_6$)	+3	Highly soluble in water.	Higher absorption, up to 10% via gastrointestinal tract.	Higher bioavailability due to higher absorption.
Sodium Hexahydroxo-antimonate ($NaSb(OH)_6$)	+5	Moderately soluble in water.	Limited data on absorption.	Limited data on bioavailability.

Antimony Compound	**Valency**	**Solubility**	**Absorption**	**Bioavailability**
Antimony Trichloride ($SbCl_3$)	+3	Very soluble in water.	Relatively higher absorption compared to other antimony compounds.	Higher bioavailability compared to trioxide.
Stibine (SbH_3)	-3	Slightly soluble in water.	Limited absorption data available.	Limited data.
Elemental Antimony (Sb) or metallic antimony	0	Insoluble in water.	Not absorbed in elemental form.	Not bioavailable in its elemental form.
Meglumine antimoniate ($C_7H_{18}NO_8Sb$)	+5	Highly soluble in water.	Not absorbed orally but absorbed completely intramuscularly and subcutaneously.	Poor oral bioavailability. >90% bioavailable via intramuscular and subcutaneous route.
Sodium stibogluconate ($C_{12}H_{36}Na_3O_{26}Sb_{2+}$)	+5	Highly soluble in water.	Not absorbed orally but higher absorption following intramuscular and subcutaneous administration.	Poor oral bioavailability but higher bioavailability via intramuscular and subcutaneous route.

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Summary of findings from toxicity studies

11. At the COT meeting in October 2024, the Committee noted that the Rossi et al. (1987), had a lower point of departure than that identified by the COT from the Poon et al. (1998) paper. The COT therefore requested further information on this study and other reproductive/developmental toxicity studies to allow consideration of whether the POD should be based on the Poon et al. (1998) paper or another study.

12. This section summarises the available studies reporting a NOAEL lower than 6,000 µg Sb/kg bw/day identified by COT from the Poon et al. (1998) study. The summaries of Marmo et al. (1987), Rossi et al. (1987) and Angrisani et al. (1988), are based on the US EPA (2008) review as it was not possible to obtain the original papers. The other studies Kanisawa and Schroeder (1969), Schroder et al. (1970) and NTP (1992) were identified from the ATSDR (2019) and Health Canada (2024) reviews.

Reproductive and developmental toxicity studies

13. Marmo et al. (1987) studied the effects of prenatal and/or postnatal exposure to antimony trichloride on vasomotor reactivity in the developing NOS albino rat. Briefly, pregnant rats (30/group) were exposed to 0, 1 or 10 mg/L antimony trichloride (equivalent to 0, 70 and 700 µg Sb/kg bw/day, respectively) in drinking water from the first day of pregnancy until weaning of the offspring (22 days old) or during the postnatal period only (birth to 22 days old). Pups were randomised within 12 hours of birth and distributed to lactating dams with a litter size culled to 10 (equal numbers of male and female pups, if possible). Rat offspring were exposed to antimony trichloride in their drinking water (0, 1 or 10 mg/L) from weaning until 30 or 60 days of age. Rat offspring (10/group, 30 or 60 days old) were anaesthetized, and the right femoral vein was cannulated for injection of drugs.

14. Arterial blood pressure was measured using a catheter connected to the right common carotid artery. This study measured systolic blood pressure and the response

to either antihypotensive or hypotensive agents or conditions in 30 or 60-day old offspring. The antihypotensive response was evaluated using a 40-second occlusion of the left common carotid artery or intravenous (i.v.) injection of noradrenaline (0.1, 1, or 5 µg/kg for 5 seconds). The hypotensive response was measured after injection of isoprenaline (0.01, 0.1, or 1 µg/kg i.v. for 5 seconds) or acetylcholine (0.01, 0.1, or 1 µg/kg i.v. for 5 seconds).

15. Exposure to antimony trichloride (prenatal/postnatal or postnatal only) did not affect offspring arterial blood pressure, measured at 30 or 60 days after birth. Combined prenatal and postnatal exposure to antimony trichloride did not affect the antihypotensive response to carotid artery occlusion. Antimony trichloride decreased the antihypotensive response to noradrenaline and the hypotensive response to isoprenaline at both dose levels in 60-day old rats. The hypotensive response to acetylcholine was decreased at the highest dose of antimony trichloride in 60-day old rats, while the response of the low dose group was similar to controls. No change in antihypotensive or hypotensive responses was seen in 30-day old rats treated with antimony trichloride during the prenatal and postnatal exposure periods.

16. In rats exposed only during the lactation period (postnatal dosing in dams) and in the drinking water after weaning, 60-day old offspring from the high-dose group showed a decrease in antihypotensive responses to carotid artery occlusion and noradrenaline injection and a decrease in hypotensive response to isoprenaline and acetylcholine. A decreased hypotensive response to isoprenaline and acetylcholine was also seen in 30-day old offspring exposed to the highest dose of antimony trichloride. In the low- dose group (postnatal exposure), a decreased response to noradrenaline and isoprenaline was observed in 60-day old rats, while 30-day old rats were similar to controls. This study suggests that vasomotor reactivity was affected by both prenatal and postnatal exposure to antimony trichloride. However, blood pressure responses were only measured in 10 pups/dose group and the report did not indicate whether each pup

came from a different litter within that dose group or whether some pups came from the same litter.

17. Rossi et al. (1987) reported additional findings (i.e., maternal blood pressure and maternal and pup body weights) for the combined prenatal and postnatal exposure to antimony trichloride. Pregnant female NOS albino rats (30 rats/group) received antimony trichloride in their drinking water (0, 1 or 10 mg/L) from gestational day 1 through weaning. Rat offspring (randomized, distributed to lactating dams and culled to 10/litter with equal sex ratio) were exposed prenatally and postnatally (through lactation until weaning and in their drinking water from 22 to 60 days old at concentrations of 0, 1 or 10 mg/L). Maternal body weights were recorded on days 10 and 20 of gestation and pup body weights were measured on postnatal days 5, 10, 22, 30, and 60. The length of gestation and the number of pups/litter was recorded.

18. No significant alterations in litter size or macroscopic effects were observed in the offspring of dams exposed to antimony trichloride during gestation and lactation. Maternal body weight was decreased by 8% (low-dose group) to 10% (high-dose group) on the 20th day of gestation as compared to controls (statistically significant at both doses). It should be noted, however, that basal maternal body weights for each treatment group on day 0 of gestation prior to exposure were approximately 7% lower than the control group. Thus, the 8 to 10% deficit from controls seen on gestation day 20 represents a relatively small change from the 7% deficit at the start of gestation.

19. Pup body weights were similar to controls at birth and at 5 days of age but were decreased in the high-dose group from the 10th (24% decrease from controls) to the 60th (11% decrease from controls) day of age. Exposure to antimony trichloride did not affect maternal or pup systolic arterial blood pressure. The results of the vasomotor reactivity studies in offspring were reported by Marmo et al. (1987) and are described above.

20. Angrisani et al. (1988) reported additional findings (i.e., maternal blood pressure and maternal and pup body weights) for postnatal (only) exposure to antimony trichloride (0, 1 or 10 mg/L) in pregnant female NOS albino rats (30 rats/group, exposed from delivery through weaning) and in rat offspring (randomized, distributed to lactating dams and culled to 10/litter with equal sex ratio) exposed postnatally (through lactation until weaning and in the drinking water from 22 to 60 days old at concentrations of 0, 1, or 10 mg/L).

21. Maternal body weights were recorded daily until 60 days after birth and pup body weights were measured daily between postnatal days 5 and 60. Postnatal exposure to antimony trichloride did not affect maternal or pup body weights or systolic arterial blood pressure. The results of the vasomotor reactivity studies in offspring were reported by Marmo et al. (1987).

22. In summary, exposure of dams and pups to antimony trichloride (prenatal and/or postnatal) did not change the systolic arterial blood pressure in dams during gestation or after birth, or in pups at 30 and 60 days of age (Marmo et al. 1987; Rossi et al. 1987; Angrisani et al. 1988). The vasomotor response to injection of antihypotensive or hypotensive agents was decreased at both concentrations in 60-day old rats exposed prenatally and/or postnatally; however, the clinical significance of the reported changes is unclear and was not discussed by the study authors (Marmo et al. 1987; Rossi et al. 1987; Angrisani et al. 1988). Combined prenatal and postnatal exposure to antimony trichloride produced a small decrease in maternal body weight during gestation (Rossi et al. 1987), while postnatal exposure during lactation did not affect maternal body weight (Angrisani et al. 1988).

23. Pup body weights were significantly lower than controls starting at 10 days of age (24% decrease) and continuing through 60 days of age (11% decrease) following combined prenatal and postnatal exposure to 10 mg/L antimony trichoride (Rossi et al. 1987) but were not decreased by postnatal exposure only (Angrisani et al. 1988). The relationship between decreased pup and dam body weights is unclear. Both maternal

and pup body weights were decreased in rats treated pre- and postnatally, but not in rats treated only postnatally. This suggests that the effect in pups may be secondary to the effect in dams even though pup body weights did not differ from controls until 10 days after birth.

24. Maternal doses for the gestational exposure period can be calculated using the average maternal body weight during gestation (298 g; Rossi et al. 1987) and the drinking water ingestion rate, calculated using the allometric relationship between drinking water ingestion and body weight (0.041 L/day) (U.S. EPA, 1988). The gestational maternal doses were estimated to be 0, 140, or 1,400 µg/kg bw/day antimony trichloride, or 0, 70, or 700 µg Sb/kg bw/day. The maternal dose of 700 µg Sb/kg bw/day was considered the LOAEL for this study, based on decreased maternal and pup body weights. The low dose of 70 µg Sb/kg bw/day was considered a NOAEL due to the very slight effect on maternal body weight and absence of effect on pup body weight at this dose.

Other oral toxicity studies with a NOAEL or LOAEL below 6,000 µg Sb/kg bw/day

25. In a study conducted by Kanisawa and Schroeder (1969), White Swiss mice of the Charles River Strain (CD-1) were exposed to 5 ppm antimony as potassium tartrate (equivalent to 350 µg Sb/kg bw/day) in drinking water for life term. Compared to controls, no significant differences in the incidences of spontaneous tumours and malignant tumours were observed in the antimony treated group. Based on these observations, 350 µg Sb/kg bw per day was identified as the NOAEL in this study (ATSDR, 2019).

26. In a lifetime exposure study conducted by Schroeder et al. (1970) on Long-Evans rats, animals were administered antimony potassium tartrate in drinking water at a dose of 430 µg Sb/kg bw/day. The study found a significant reduction in survival rates, with reduced non-fasting serum glucose levels. A Low observed adverse effect level

(LOAEL) of 430 µg Sb/kg bw/day was identified based on these effects (ATSDR, 2019).

Antimony intraperitoneal injection studies by NTP

27. The Committee requested a summary of the NTP intraperitoneal study at the October meeting 2024, as it was potentially useful in a weight of evidence consideration with respect to toxicity of antimony.

28. Intraperitoneal injection studies using antimony potassium tartrate (purity>99.4%) were conducted in F344 rats and $B6C3F_1$ mice (10/sex/group) (NTP, 1992). A 16-day range finding study used doses of 0, 1,500, 3,000, 6,000, 11,000 or 22,000 µg/kg bw/day in rats and 0, 6,000, 13,000, 25,000, 50,000, or 100,000 µg/kg bw/day in mice, administered as 12 injections given on consecutive weekdays. These correspond to doses of 0, 600, 1,200, 2,400, 4,400, or 8,800 µg Sb/kg bw/day in rats and 0, 2,400, 5,200, 10,000, 20,000, or 40,000 µg Sb/kg bw/day in mice. Mortality was observed in the high dose groups for both rats (3/20) and mice (20/20).

29. Liver lesions, characterised as necrosis and inflammation of the liver capsule, were observed in 7 of 10 mice given 20,000 µg Sb/kg bw/day (both sexes). These lesions were not observed in mice from the highest dose group that died prior to the end of the study. Liver necrosis and kidney degeneration were observed in the high dose male rats that died prior to the end of the study.

30. A 13-week intraperitoneal injection studies using antimony potassium tartrate doses of 0, 1,500, 3,000, 6,000, 12,000, or 24,000 µg/kg bw/day given 3 times per week, resulting in daily antimony doses of 0, 600, 1,200, 2,400, 4,800, or 9,600 µg Sb/kg bw/day. Mortality was observed in 4 of 10 male rats in the highest dose groups. A reduction in body weight was seen in both male (18%) and female (11%) rats from these groups. Relative liver weight was increased in male and female rats from all dose groups (maximum increase of 20% for males and 40% for females at 9600 µg Sb/kg bw/day). Dose-related increases in serum alanine aminotransferase and sorbitol dehydrogenase were also observed in male and female rats. Liver degeneration and

necrosis were observed in male rats and in female rats. Kidney degeneration was also observed in the highest dose group in female rats (3/10). No clinical signs of toxicity or gross or microscopic changes were observed in mice exposed to antimony potassium tartrate in this study.

Summary of information from TOX/2024/38 and TOX/2025/04

31. Absorption of antimony is low. Absorption through the gastrointestinal tract is estimated at approximately 1% for antimony trioxide and 10% for antimony potassium tartrate.

32. A number of studies on antimony are available, with a wide range of NOAELs reported. The toxicity of antimony has been reviewed by WHO (2003), ATSDR (2019) and Health Canada (2024).

33. Though WHO, ATSDR and Health Canada have used the findings from Poon et al. (1998) study, they diverge significantly in their interpretation of the study results and the selection of NOAEL. Table 2 below summarises the values and the uncertainty factors used.

Table 2: Comparison of NOAELs, uncertainty factors and TDI/MRL values from different authoritative bodies.

Authority	**NOAEL (µg/kg bw/day)**	**Uncertainty factor**	**TDI/MRL (µg/kg bw/day)**
WHO (2003)	6000	1000 (100 for interspecies and intraspecies differences and 10 for the use of subchronic study).	6
Health Canada (2024)	60	300 (100 for interspecies and intraspecies differences and 3 for the use of subchronic study).	0.2

ATSDR (2019)	60	100 (10 for interspecies and 10 for intraspecies differences).	0.6 (Intermediate MRL for 14-365 days).

34. In their evaluations of metals in the diet, e.g., in 2006 and 2017, COT used the WHO TDI as a basis for its assessment.

35. The COT agreed at the October 2024 meeting with the NOAEL of 6,000 µg/kg bw/day used by the WHO (recommended by Lynch et al. (1999)) for the Poon et al. (1998) study. Some lower LOAELs and NOAELs have been reported in some of the studies summarised above and there is a need to consider the most suitable critical PoD for oral exposure to antimony.

Questions for the Committee

36. Members are invited to consider the following questions:

i) Can the Committee identify a Point of Departure (PoD) on which the assessment of antimony should be based?

ii) Is the Committee able to derive a health-based guidance value for antimony and if so, what uncertainty factors does the Committee propose to use with the NOAEL?

iii) Are there any other uncertainties or considerations the Committee would like to highlight in evaluating antimony?

iv) Does the Committee have any other comments?

Secretariat
February 2025

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List of abbreviations and their full meanings

AST	Aspartate Aminotransferase
ATSDR	Agency for Toxic Substances and Disease Registry
bw	Body Weight
CAS	Chemical Abstracts Service
COT	Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment
GSH	Glutathione
HBGV	Health-based guidance value
ICP-MS	Inductively Coupled Plasma – Mass Spectrometry
i.m.	Intramuscular
i.p.	Intraperitoneal
i.v.	Intravenous
LOAEL	Lowest Observed Adverse Effect Level - the lowest dose in a study at which adverse effect(s) are observed.
MA	Meglumine Antimoniate
mg	Milligram
µg	Microgram
MRL	Minimal Risk Level - an estimate of the daily human exposure to a substance that is likely to be without appreciable risk of adverse non-cancer health effects over a specified duration of exposure.
NOAEL	No Observed Adverse Effect Level - the highest administered dose at which no adverse effect has been observed.

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NTP	National Toxicology Program
ppm	Parts per million
PVA	Pentavalent Antimony
Sb	Antimony
SSG	Sodium Stibogluconate
TDI	Tolerable Daily Intake - an estimate of the amount of a contaminant, expressed on a body weight basis (e.g., mg/kg body weight) that can be ingested over a lifetime without appreciable health risk.
WHO	World Health Organization

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TOX/2025/04 Annex A

Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment

Deriving a health-based guidance value for antimony to support development of UK Drinking Water Standards – further information

Summary of studies with NOAEL values above 6,000 µg Sb/kg bw/day

Secretariat

February 2025

Other oral toxicity and reproductive/developmental toxicity study summaries with a NOAEL or LOAEL above 6,000 µg Sb/kg bw/day

1. This section summarises the additional available oral toxicity and reproductive/developmental toxicity studies. The summaries of these studies were identified from ATSDR (2019) and Health Canada (2024).

2. In the study conducted by Sunagawa (1981), groups of 5 Wistar rats were exposed to 0, 0.5, 1.0 or 2.0% metallic antimony in the diet (estimated doses of 0, 500,000, 1,000,000 and 2,000,000 µg Sb/kg bw/day) or 0, 1.0 or 2.0% antimony trioxide in the diet (0, 1,000,000 or 2,000,000 µg/kg bw/day corresponding to 0, 418,000, 836,000 µg Sb/kg bw/day) for 24 weeks. The description of this study from the Japanese literature is taken from the English language abstract. In the rats exposed to metallic antimony, significant adverse effects included dose-related decreases in body-weight gain, decreases in haematocrit and haemoglobin levels in the high-dose group and slight cloudy swelling in hepatic cords in the mid- and high-dose groups. Decreased erythrocyte levels and slight cloudy swelling of hepatic cords were observed in both groups of rats exposed to antimony trioxide. 418,000 µg Sb/kg bw/day was concluded as Low observed effect level (LOEL) dose from this study. The English abstract provided no further details on this study.

3. In a 12-week study conducted by Hiraoka (1986), groups of male Wistar rats (no information on number of animals per group) were treated with diets containing either 0.1% (w/w) of metal antimony (0.1%-Sb group, equivalent to 85,000 µg Sb/kg bw/day), 1.0% (w/w) of metal antimony (1.0%-Sb group, equivalent to 850,000 µg Sb/kg bw/day) or 1.0% (w/w) of antimony trioxide (1.0%-Sb_2O_3 group, equivalent to 700,000 µg Sb/kg bw/day). All the rats were allowed antimony-free diet for the following 12 weeks. Blood and organs were taken from the rats at the time of removal of the antimony-containing diet, 4 or 12 weeks after the removal of the antimony-containing diet. The results obtained were:

i. Neither abnormal behaviour nor unusual general appearance of the rats was observed in this experiment.

ii. The metal antimony and antimony trioxide inhibited the weight gain of rats. The weight of the rats of each 1.0%-Sb and 1.0%-Sb2O3 groups was lighter than that of 0.1%-Sb group. During recovery, the rats increased in weight up to the normal level at 12 weeks after removal of the antimony-containing diet.

iii. The haematocrit in blood from 1.0%-Sb group rats was significantly decreased at 4 weeks after the removal of the antimony-containing diet. The total protein levels in blood from 1.0%-Sb group rats was significantly decreased at the time of removal of the antimony-containing diet. A significant increase of alanine transaminase (ALT - reported as Glutamate Pyruvate Transaminase (GPT)) level was seen in the blood from 0.1%-Sb group rats at 4 weeks after the supply of the antimony-free diet began. No significant changes of Hb and aspartate transaminase (AST – reported as glutamic-oxaloacetic transaminase (GOT)) levels and albumin to globulin (A/G) ratio were found in the blood samples from all rats.

iv. Some significant changes of the organ weight and the ratio between organ weight and body weight of the rats, after the administration of Sb and Sb_2O_3 containing diet, were found.

v. High concentrations of antimony were found in liver, spleen, lungs, hairs and bone and the highest concentration was detected in the blood of the rats. A NOAEL of 700,000 µg Sb/kg bw/day was identified for antimony trioxide.

4. Miranda et al. (2006) evaluated the developmental toxicity and transplacental transfer of meglumine antimoniate (pentavalent compound) following subcutaneous injection in pregnant female Wistar rats (19-21/group). Antimony doses of 0, 75,000, 150,000 or 300,000 µg Sb/kg/day were administered on GD 1-20. Rats were sacrificed by CO_2 inhalation on GD21 and the number of implantation sites, live/dead foetuses,

resorptions and corpora lutea were counted. Living foetuses were weighed, measured, examined for gross abnormalities and processed for evaluation of skeletal (staining with Alizarin Red) and visceral abnormalities (micro-sectioning after fixation in Bouin's solution). Maternal blood samples were collected each day from a separate group of rats given 300,000 µg Sb/kg/day. Foetal blood samples were obtained from the offspring of this group on GD21. Maternal and foetal body weights were reduced in the high-dose group (18% and 10%, respectively, at 300,000 µg Sb/kg/day). Embryolethality was also observed in this dose group (decreased number of live foetuses). The frequency of dilated ureter was increased in foetuses from the 150,000 and 300,000 µg Sb/kg/day dose groups. Skeletal variations were also seen in the mid- and high-dose groups (misaligned sternebrae, supernumerary ribs, misshapened basiooccipital bone). Transplacental transfer of antimony was confirmed by foetal blood analysis with foetal blood concentrations measured to be roughly one-third of the concentrations found in maternal blood.

5. A 90-day dietary study of antimony trioxide was conducted in male and female Wistar rats (Alpk:APSD strain) by Hext et al. (1999). Rats (12/sex/group) were fed diets containing 0, 1,000, 5,000 or 20,000 ppm antimony trioxide (99% purity) resulting in doses for the male rats of 0, 70,000, 353,000, 1,408,000 µg Sb/kg/day and for female rats of 0, 81,000, 413,000, 1,570,000 µg Sb/kg/day. Food consumption was measured continuously and calculated as a weekly mean. Body weights were measured weekly. Doses were calculated for each week, based on feed consumption and body weight. Cage-side observations were made daily and detailed clinical observations were made weekly. During the last week of the study, control and high-dose rats received an eye examination using an indirect ophthalmoscope and a mydriatic substance to dilate the pupil. Urine samples were collected (16-hour collection) from rats housed in metabolic cages during the last week of the study. Urine volume was measured, and samples were analysed for appearance, specific gravity, pH, glucose, ketones, bilirubin, protein and blood. Urine was centrifuged and the sediment was stained and examined. Blood samples were obtained for haematology and clinical chemistry by cardiac puncture

following sacrifice by halothane overdose. Adrenal glands, brain, kidneys, liver, epididymides and testes were removed, weighed and prepared for histopathological examination. All tissues from the control and high dose rats were examined, as well as any abnormal tissue from the intermediate dose groups.

6. Food consumption and body weight gain were similar to controls for all treatment groups. No significant clinical signs or ocular changes were associated with exposure to antimony trioxide. In high-dose female rats, urine volume was increased (+79%) and specific gravity was decreased (-1%). Urinary pH was increased in male rats given 1,000 ppm (+5%) or 20,000 ppm (+5%) but was similar to the control value in the 5,000 ppm group. Changes in urinary parameters were not dose-related and were considered by the study authors to be incidental.

7. Minor changes were noted in some haematological parameters, with an elevated red cell count in high-dose male rats (+4%) and a decreased mean cell volume in high-dose female rats (-2%). The study authors considered the haematological changes to be too small to be of toxicological significance. Triglyceride content was increased (+30%) and alkaline phosphatase activity was decreased (-12%) in high-dose male rats. High-dose female rats exhibited an increase in plasma cholesterol (+13%), a decrease in alkaline phosphatase activity (-36%) and an increase in aspartate aminotransferase activity (+52%). Alkaline phosphatase activity was also decreased (-23%) in female rats given 5,000 ppm of antimony trioxide in the diet. No other treatment related changes in plasma biochemistry were observed. Absolute and relative liver weights were increased by approximately 10% in female rats fed 20,000 ppm antimony trioxide. No gross findings indicative of toxicity was seen at necropsy. The incidence of pituitary cysts was higher in the 20,000 ppm dose groups of both male and female rats (4/12 treated males, 3/12 treated females, 1/12 control males and females). The study authors considered pituitary cysts to be a common spontaneous lesion with reported incidence values within the historical control range (i.e., not treatment-related). Three male rats in the high dose group had slight to moderate plasma cell infiltration in the cervical lymph node. This

change has also been previously seen in historical controls from the same laboratory and was therefore not considered treatment related. No other histopathological lesions were observed.

8. Considering small increase in liver weight, small decrease in plasma alkaline phosphatase activity and small increase in plasma aspartate and alanine aminotransferase levels in the high dose group without any histological correlate in the liver. The high dose was concluded to be the NOAEL equivalent to 1,408,000 µg Sb/kg bw/day (male rats) and 1,570,000 µg Sb/kg bw/day (female rats).

9. Coelho et al. (2014) investigated the neurobehavioral development, sexual maturation and fertility of the offspring of meglumine antimoniate (MA) treated rats. Dams were administered MA (0, 75,000, 150,000 and 300,000 µg SbV/kg body wt/d, sc) from gestation day 0, throughout parturition and lactation, until weaning. At the highest dose, MA reduced the birth weight and the number of viable newborns. In the male offspring, MA did not impair development (somatic, reflex maturation, weight gain, puberty onset, open field test), sperm count, or reproductive performance. Except for a minor effect on body weight gain and vertical exploration in the open field, MA also did not affect the development of female offspring. Measurements of the Sb levels in the blood of MA-treated female rats and their offspring demonstrated that Sb is transferred to the foetuses via the placenta and to the suckling pups via milk.

10. In a study by Alkhawajah et al. (1996), the possible teratogenic potential of the pentavalent compounds (PVA), sodium stibogluconate (SSG) and meglumine antimoniate (MA) when they are used during pregnancy in rats were studied. Animals were divided into 10 treatment groups of 10 rats each. Rats in Group 1 were injected with saline (control). Groups 2-5 were injected with SSG i.m. for 10 successive days (days 6-15 of pregnancy) with doses of 30,000, 100,000, 300,000 and 900,000 µg Sb/kg. Groups 6-9 were injected with MA for the same period and at the same dose levels. Those in Group 10 were injected with 100,000 µg/kg of $SbCl_3$, using the same protocol. On day 20 of gestation foetuses were removed by C-section and examined for

any teratogenic abnormality. Rats injected with SSG (30,000 µg Sb/kg) exhibited a 5.9% foetal resorption rate. This effect seems to be dose dependent as doses of 100,000 and 300,000 µg Sb/kg caused 14% and 21.4% foetal resorption, respectively. Injection of MA at the same dose levels of 30,000, 100,000 and 300,000 µg Sb/kg also caused dose dependent increase in foetal resorption of 1.2 %, 26.7% and 3396, respectively. Most resorptions with either SSG or MA appeared to occur in early gestation. The mean weight of the viable foetuses from mothers treated with PVA'S was significantly lower than that of the control mice ($P<0.05$). Some skeletal and visceral deformities were also observed in many foetuses. Antimony trichloride also caused 36% foetal resorption when it was injected at a dose of 100,000 µg/kg. It can be concluded that the teratogenic effects of PVA'S may be related to their antimony content.

11. In a study conducted by Omura et al. (2002), the testicular toxicity of antimony trioxide was evaluated in Crj:Wistar rats (7-8/group) and Cjr:CD-1 mice (8-10/group). Antimony trioxide (purity >99.9%) (10,000 or 1,000,000 µg Sb/kg-day) was administered by oral gavage to rats (3 days/week for 4 weeks) and mice (5 days/week for 4 weeks). Animals were sacrificed by carbon dioxide inhalation 24 hours after the final gavage dose was administered. The testes, epididymides, ventral prostate and seminal vesicle (without fluid) were removed and weighed. Histopathological changes were evaluated in the testes and the number, motility and morphology of sperm from the cauda epididymides were assessed. Three mice (1 control, 2 given 1,000,000 µg Sb/kg-day) died due to gavage error. No significant effect on body weight or organ weight of reproductive tissues was observed. Sperm parameters were not affected by antimony trioxide treatment and histopathology results were essentially negative. A NOAEL of 1,000,000 µg Sb/kg/day (highest dose tested) was concluded for male reproductive effects of antimony trioxide in this study.

12. In a study conducted by Belyaeva (1967), female rats were exposed to either 0 or 209 mg/m³ of antimony trioxide by inhalation for 4 hours per day over 1.5-2 months. After this period, they were mated, and exposure continued until 3-5 days before

expected delivery. Pregnancy was achieved in 16 of 24 treated females and all 10 controls. No changes in body weight gain were noted. Foetal body weights remained unchanged. Unspecified lesions were reported in the lungs, liver, kidneys, and pancreas. Reproductive effects, including failure to conceive and uterine metaplasia, were observed. However, a decrease in fertility and reduced number of offspring was found in rats exposed to 209 mg Sb/m³ of antimony trioxide before conception and during gestation (Belyaeva, 1967). The original article was published in Russian language, which we were not able to retrieve. The summary of this study was taken from the Toxicological profile provided by ATSDR, 2019.

13. In a REACH registration dossier submitted to ECHA, pregnant female Sprague-Dawley rats received sodium hexahydroxoantimonate via gavage at the dose levels of 0, 49,000, 148,000, 493,000 µg Sb/kg bw per day between gestation day 6-19. Increased (non-significant) incidence in delayed skeletal development were observed in the mid and high dose groups. Most values were only slightly above historical control data. When considering skeletal malformations overall, incidence was observed in 99.3% to 100% of foetuses and 100% of litters including controls. 49,000 µg Sb/kg bw per day was concluded as NOAEL from this study.

This is a paper for discussion. This does not represent the views of the Committee and should not be cited.

TOX/2025/04 Annex A

Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment

Deriving a health-based guidance value for antimony to support development of UK Drinking Water Standards – further information

Tabulated summary of antimony studies

Secretariat

February 2025

Table 3: Summary of toxicity studies of antimony

Author and year	Species / Route of exposure	Study details	Dose level	Findings	No observed adverse effect level (NOAEL)
Marmo et al. (1987)	NOS Albino normotensive rats; Oral: Drinking water.	**Study duration:** Maternal exposure: - 1st day of pregnancy until weaning (22nd day after delivery) or from PND1 to PND 22. Pups: - From weaning until 30 or 60 days of age. **No/Sex/Dose:** 30 per group.	**Original Dose:** 1 and 10 mg/L antimony trichloride. **Recalculated Dose Levels:** 70 and 700 µg Sb/kg bw/day.	**Prenatal and Postnatal exposure:** - Decreased antihypotensive response to norepinephrine and hypotensive response to isoprenaline at both dose levels in 60-day old rats. The hypotensive response to acetylcholine was decreased at the highest dose of antimony trichloride in 60-day old rats. No change in antihypotensive or hypotensive responses was seen in 30-day old rats. **Postnatal exposure:** - 60-day-old offspring in the high-dose group showed reduced antihypotensive responses to carotid artery occlusion and norepinephrine injection, as well as reduced hypotensive responses to isoprenaline and acetylcholine. In 30-day-old offspring in the high-dose group, reduced hypotensive	70 µg Sb/kg bw/day.

		Rat offspring: - 10 pups/ group, equal sex ratio.		responses to isoprenaline and acetylcholine were also observed. In the low-dose group, 60-day-old rats had reduced responses to norepinephrine and isoprenaline, while 30-day-old rats showed responses similar to controls.	
Rossi et al. (1987)	NOS Albino normotensive rats; Oral: Drinking water.	**Study duration:** Prenatal: 1st day of pregnancy until weaning (22nd day after delivery). Postnatal: 22nd to 60 days in drinking water. **No/Sex/Dose:** 30 per group	**Original Dose:** 1 and 10 mg/L antimony trichloride. **Recalculated Dose Levels:** 70 and 700 µg Sb/kg bw/day.	**Both doses:** Maternal body weight decreased significantly in a dose-dependent manner by the 20th day of gestation. **High dose:** Pups had decreased BW; No macroscopic teratogenic effects have been observed. Antimony exposure did not significantly affect maternal and pup systolic arterial blood pressure, length of gestation, and number of newborns per litter.	Maternal NOAEL: 70 µg Sb/kg bw/day. Pup LOAEL: 700 µg Sb/kg bw/day.

		Rat offspring: - 10 pups/ group, equal sex ratio.			
Angrisani et al. (1987)	NOS Albino normotensive rats; Oral: Drinking water.	**Study duration:** Postnatal: From PND1 to PND60. **No/Sex/Dose:** 30 per group. Rat offspring: - 10 pups/ group, equal sex ratio.	**Original Dose:** 1 and 10 mg/L antimony trichloride. **Recalculated Dose Levels:** 70 and 700 µg Sb/kg bw/day.	Postnatal exposure to antimony trichloride did not affect maternal or pup body weights or systolic arterial blood pressure. No macroscopic teratogenic effects have been observed. Antimony exposure did not significantly affect the length of gestation, and number of newborns per litter.	Maternal NOAEL: 70 µg Sb/kg bw/day. Pup LOAEL: 700 µg Sb/kg bw/day.
Kanisawa and Schroeder (1969)	Mice (White Swiss, Charles River CD-1); Oral: Drinking water.	**Study duration:** Lifetime exposure. **No/Sex/Dose:** Control mice – 71; Antimony treatment – 76.	**Original Dose:** Antimony Potassium Tartrate (APT) – 5 ppm. **Recalculated Dose Level:** 350 µg Sb/kg bw/day.	Compared to control, significant differences in the incidences of spontaneous tumors and malignant tumors did not appear. Female mice had shorter life spans when given antimony than their controls. Fatty degeneration of liver noticed in both control (22.2%) and antimony fed groups (15.9 %).	350 µg Sb/kg bw/day.

Schroeder et al. (1970)	Long Evan Rats; Oral: Drinking water.	**Study duration:** 2 years. **No/Sex/Dose:** Not reported.	**Original Dose:** 5 ppm - Antimony Potassium Tartrate (APT). **Recalculated Dose Level:** 430 µg Sb/kg bw/day.	Negligible effects on growth and mature weight. Antimony was not tumorigenic. Decrease in survival rate. Antimony, however, was innately toxic, males surviving 106 days and females 107 days less than the controls at median life spans, and 70 and 165 days less when 90% were dead; Hearts of males fed antimony weighed 18.9% less than their respective controls, whereas the hearts of females weighed 3.5% more. Decreased non-fasting serum glucose levels. Non fasting glucose levels were lower than fasting ones in the antimony group. Glycosuria was found in 23% of 90 controls, 43% of 23 in the antimony group. In both sexes, significant differences in the serum cholesterol levels occurred when compared to their controls. Antimony was found to accumulate in various tissues like kidney, liver, heart, lung and spleen, with	LOAEL: 430 µg Sb/kg bw/day.

				significant increases in concentration over time.	
NTP (1992)	B6C3F1 Mice; Intraperitoneal injection.	**Study duration:** 13 weeks. **No/Sex/Dose:** 10 Males per group. 10 Females per group.	**Original Dose:** 0, 1.5, 3, 6, 12 and 24 mg/kg antimony potassium tartrate; 3 times per week. **Recalculated Dose Levels:** 0, 600, 1,200, 2,400, 4,800 and 9,600 µg Sb/kg bw/day.	High dose: Body weights were reduced by about 10% compared to controls (not statistically significant). Hematological analyses revealed decreases in red blood cell counts and hemoglobin of both sexes of high-dose mice at week 7 and again at week 13 for the red blood cell counts. In association with these changes was increased absolute and relative spleen weight.	4,800 µg Sb/kg bw/day.
NTP (1992)	F344/N Rats; Intraperitoneal injection.	**Study duration:** 13 weeks. **No/Sex/Dose:** 10 Males per group	**Original Dose:** 0, 1.5, 3, 6, 12 and 24 mg/kg antimony potassium tartrate; 3 times per week. **Recalculated Dose Levels:**	Mortality was observed in 4 of 10 male rats in the highest dose groups. A reduction in body weight was seen in both male (18%) and female (11%) rats from these groups. Relative liver weight was increased in male and female rats from all dose groups (maximum increase of 20% for males and	1,200 µg Sb/kg bw/day.

		10 Females per group.	0, 600, 1,200, 2,400, 4,800 and 9,600 µg Sb/kg bw/day.	40% for females at 9600 µg Sb/kg bw/day). Dose-related increases in serum alanine aminotransferase and sorbitol dehydrogenase were also observed in male and female rats. Hepatocellular degeneration and necrosis were observed in male rats and in female rats. Kidney degeneration was also observed in the highest dose group in female rats (3/10).	
Sunagawa (1981)	Wistar rats; Oral: Feeding.	**Study duration:** 24 weeks. **No/Sex/Dose:** 5 per dose.	**Original Dose:** Metallic Antimony: 0, 0.5, 1.0, 2.0%. Antimony Trioxide: 0, 1.0, 2.0%. **Recalculated Dose Levels:** Metallic Antimony: 0, 500,000, 1,000,000,	Metallic antimony high dose: decreased body weight gain. Metallic antimony high dose: decreased hematocrit and hemoglobin. Antimony trioxide all dose: decreased erythrocyte levels. Metallic antimony mid and high dose: slight cloudy swelling in hepatic cords. Antimony trioxide all dose: slight cloudy swelling in hepatic cords.	LOEL: 418,000 µg Sb/kg bw/day.

			2,000,000 µg Sb/kg bw/day. Antimony Trioxide: 0, 418,000, 836,000 µg Sb/kg bw/day.		
Hiraoka (1986)	Wistar rats; Oral: Feeding.	**Study duration:** 12 weeks. 12 weeks recovery. **No/Sex/Dose:** 12 males per group.	**Original Dose**: Metallic Antimony: 0.1% (w/w), 1.0% (w/w) o Antimony Trioxide: 1.0% (w/w) **Recalculated Dose Levels:** Metallic Antimony: 85,000, 850,000 µg Sb/kg bw/day. Antimony Trioxide:	BW gain decreased for all. The weight of the rats of each 1.0%-Sb and 1.0%-Sb2O3 groups was lighter than that of 0.1%-Sb group. Recovery animal- increased in weight up to the normal level. Some significant changes of the organ weight and the ratio between organ weight and body weight of the rats, after the administration of Sb and Sb2O3; 1.0%-Sb: decreased haemtocrit 0.1%-Sb: no changes in Hb, AST and albumin to globulin ratio. 0.1%-Sb: increased ALT. 1.0%-Sb: decreased total protein levels; High concentrations of antimony were found in liver, spleen, lungs, hairs and bone and	700,000 µg Sb/kg bw/day.

			700,000 µg Sb/kg bw/day.	the highest concentration was detected in the blood of the rats.	
Miranda et al. (2006)	Wistar rats; Subcutaneous Injection.	**Study duration:** GD1 – 20. **No/Sex/Dose** : 19-21/group.	**Original Dose:** 0, 75, 150, 300 mg SbV/kg bw/day Meglumine antimoniate. **Recalculated Dose Levels:** 0, 75,000, 150,000 or 300,000 µg Sb/kg/day.	Maternal and fetal body weights were reduced in the high-dose group (18% and 10%, respectively, at 300,000 µg Sb/kg/day). Embryo lethality was also observed in this dose group (decreased number of live fetuses). The frequency of dilated ureter was increased in fetuses from the 150,000 and 300,000 µg Sb/kg/day dose groups. Skeletal variations were also seen in the mid- and high-dose groups (misaligned sternebrae, supernumerary ribs, misshapened basiooccipital bone). Transplacental transfer of antimony was confirmed by fetal blood analysis with fetal blood concentrations measured to be roughly one-third of the concentrations found in maternal blood.	75,000

Hext et al. (1999)	Wistar rats; Oral: Feeding.	**Study duration:** 90 days. **No/Sex/Dose:** 12 Males per group. 12 Females per group.	**Original Dose:** 0, 1,000, 5,000, 20,000 ppm antimony trioxide. **Recalculated Dose Levels:** Males: 0, 70,000, 353,000, 1,408,000 µg Sb/kg bw/day. Females: 0, 81,000, 413,000, 1,570,000 µg Sb/kg bw/day.	Absolute and relative liver weights were increased by approximately 10% in female rats fed 20,000 ppm antimony trioxide; Elevated red cell count in high-dose male rats (+4%) and a decreased mean cell volume in high-dose female rats (-2%); Triglyceride content was increased (+30%) and alkaline phosphatase activity was decreased (-12%) in high-dose male rats. High-dose female rats exhibited an increase in plasma cholesterol (+13%), a decrease in alkaline phosphatase activity (-36%) and an increase in aspartate aminotransferase activity (+52%). Alkaline phosphatase activity was also decreased (-23%) in female rats given 5,000 ppm of antimony trioxide in the diet. In high-dose female rats, urine volume was increased (+79%) and specific gravity was decreased (-1%). Urinary pH was increased in male rats given 1,000 ppm (+5%) or 20,000 ppm (+5%) but was similar to the control value in the 5,000-ppm group. Changes in urinary parameters were not dose-	1,408,000 µg Sb/kg bw/day (male rats) and 1,570,000 µg Sb/kg bw/day (female rats).

				related and were considered by the study authors to be incidental.	
Coelho et al. (2014)	Pregnant female Wistar rats; Subcutaneous injection.	**Study duration:** Gestation Day 0-PND 21. **No/Sex/Dose:** Control - 14; Treatment - 16 per dose.	**Original Dose:** 0, 75, 150, 300 mg SbV/kg bw/day of meglumine antimoniate. **Recalculated Dose Levels:** 0, 75,000, 150,000, 300,000 µg SbV/kg bw/day.	At the highest dose, MA reduced the birth weight and the number of viable newborns. In the male offspring, MA did not impair development (somatic, reflex maturation, weight gain, puberty onset, open field test), sperm count, or reproductive performance. Except for a minor effect on body weight gain and vertical exploration in the open field, MA also did not affect the development of female offspring. Measurements of the Sb levels in the blood of MA-treated female rats and their offspring demonstrated that Sb is transferred to the fetuses via the placenta and to the suckling pups via milk.	150,000 µg SbV/kg bw/day.
Alkhawajah et al. (1995)	Sprague Dawley rats; Intramuscular injection.	**Study duration:** Gestation Day 6-15.	**Original Dose Levels:** 1. Sodium Stibogluconate	Reduction ($P<0.05$) in foetal birth weight and litter size was observed as compared to the control.	-

		No/Sex/Dose: 10 per dose.	(SSG): 30,000, 100,000, 300,000, 900,000 µg Sb/kg bw/day 2. Meglumine Antimoniate (MA): 30,000, 100,000, 300,000, 900,000 µg Sb/kg bw/day 3. Antimony Trichloride (SbCl3): 100,000 µg Sb/kg bw/day	High dose of SSG & MA: - Death of all animals before completion of the treatment; Skeletal anomalies were restricted to the formation of a rudimentary 14th rib. Haematoma was only seen in the extremities of foetuses born to antimony treated animals. Treatment of pregnant rats with SSG (30,000 µg Sb/kg) daily for 10 successive days, starting on day 6 of gestation, exhibited a 5.9% foetal resorption rate. This effect seems to be dose dependent as doses of 100,000 and 300,000 µg Sb/kg caused 14% and 21.4% foetal resorption, respectively. Injection of MA at the same dose levels of 30,000, 100,000 and 300,000 µg Sb/kg also caused dose dependent increase in foetal resorption rates of 1.2%, 26.7% and 33%, respectively. It was also observed that antimony trichloride caused 36% foetal resorption when it was injected at a dose of 100000 µg/kg.; Visceral anomalies observed in the antimony-treated animals consisted of platal, ocular	

				(undeveloped eyes) and asymmetrical brain hemispheres. All tissues that were analysed (placenta and tissue of dead foetuses) in this study contained antimony in concentrations ranging from 53.4±0.2 to 1.61±0.1 µg Sb/g and the effects were dose dependent.	
Omura et al. (2002)	Wistar rats and CD-1 Mice; Oral: gavage feeding.	**Study duration:** 4 weeks. **No/Sex/Dose:** Rats: 7 to 8 per group. Mice: 8-10 per group.	**Original dose:** 1.Antimony Potassium Tartrate group: 27.4 mg/kg body weight. 2.Low-Antimony trioxide group: 12 mg/kg body weight. 3.High-Antimony trioxide group: 1,200 mg/kg body weight.	1. Three mice (1 control, 2 given 1,200,000 µg/kg-day) died due to gavage error; Sperm parameters were not affected by neither compounds and histopathology results were essentially negative.	1,000,000 µg Sb/kg bw/day.

			Recalculated dose levels: 1. Antimony Potassium Tartrate group: 10,000 µg Sb/kg bw/day. 2. Low-Antimony trioxide group: 10,000 µg Sb/kg bw/day. 3. High-Antimony trioxide group: 1,000,000 µg Sb/kg bw/day.		
Belyaeva (1967)	Rats (NS); Inhalation.	**Study duration:** 1.5-2 months,4 hours/day. **No/Sex/Dose:** 10-24/group.	**Original Dose:** 0 and 209,000 µg Sb/m^3 antimony trioxide. **Recalculated Dose Levels:** 0 and 209,000 µg Sb/m^3.	No changes in body weight gain were noted. Fetal body weights remained unchanged. Unspecified lesions were reported in the lungs, liver, kidneys, and pancreas. Reproductive effects, including failure to conceive and uterine metaplasia, were observed. However, a decrease in fertility and reduced number of offspring	209,000 µg Sb/m^3.

				was found in rats exposed to 209 mg Sb/m³ of antimony trioxide before conception and during gestation.	
REACH registration dossier submitted to ECHA (2014)	Sprague- Dawley rats; Oral: Drinking water.	**Study duration:** Gestation days 6-19. **No/Sex/Dose:** 2 females per dose.	**Original Dose:** 0, 100, 300 and 1000 mg/kg bw/day sodium hexahydroxoantimonate. **Recalculated Dose Levels:** 0, 49,000, 148,000, 493,000 µg Sb/kg bw/day.	Increased (non-significant) incidence in delayed skeletal development were observed in the mid and high dose groups. When considering skeletal malformations overall, incidence was observed in 99.3% to 100% of fetuses and 100% of litters including controls.	49,000 µg Sb/kg bw per day.

This is a paper for discussion. This does not represent the views of the Committee and should not be cited.

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