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

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Introduction and Background

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

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 of 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. This discussion paper examines the interpretation of a 90-day rat drinking water toxicity study on antimony potassium tartrate by Poon et al. (1998). The World Health Organization (WHO), the US Agency for Toxic Substances and Disease Registry (ATSDR) and Health Canada (2024) have used this study to derive different HBGVs. The differences are primarily due to variations in the interpretation of the study findings, particularly in the choice of the No Observed Adverse Effect Level (NOAEL).

3. The COT is asked to consider these interpretations and determine an appropriate HBGV to support an update to the antimony drinking water standard in the UK.

Background

4. 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.

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Properties of antimony

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Properties of antimony

5. Antimony (Sb, CAS number: 7440-36-0) is a silvery white metal with atomic number 51. Antimony and its compounds are naturally present in the Earth's crust and are released into the environment by natural discharges such as windblown dust, volcanic eruptions, sea spray, forest fires and biogenic sources (Sundar, S., & Chakravarty, J., 2010).

6. Antimony compounds can exist in two valency states: trivalent (Sb^{3+}) and pentavalent (Sb^{5+}). Trivalent compounds include antimony trioxide (Sb2O3), antimony trisulfide (Sb2S3) and antimony trichloride (Sb2Cl3), while pentavalent compounds include antimony pentoxide (Sb2O5), antimony pentasulfide (Sb2S5), and antimony potassium tartrate (K2Sb2(C4H2O6)2. The most important antimony compounds from the context of potential exposure to humans are antimony trioxide and antimony pentoxide, due to their widespread use in industrial applications.

7. 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, and the inorganic compounds are more toxic than the organic compounds.

8. Elemental antimony exhibits no solubility in water, while antimony trioxide is slightly soluble, and antimony pentoxide is very slightly soluble. In contrast, antimony potassium tartrate is highly water-soluble, and sodium hexahydroxyantimonate demonstrates moderate solubility (Health Canada (2024), ATSDR (2019)).

9. Occupational exposure to antimony occurs mainly in workers involved in industries producing antimony and antimony trioxide, metal mining, smelting and refining, coal-fired power plants, refuse incineration, or those working in indoor firing ranges. The most common source of antimony in drinking-water appears to be dissolution from metal plumbing and fittings. Antimony is not removed from water by conventional treatment processes and control would therefore be by source selection or dilution (WHO, 2003).

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Toxicokinetics and Toxicity

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Toxicokinetics

10. Antimony is poorly absorbed, and its absorption is largely dependent on the solubility and its oxidation state, of the specific antimony compound. Absorption through the gastrointestinal tract is estimated at approximately 1% for antimony trioxide and 10% for antimony potassium tartrate (ICRP, 1981).

11. The highest concentrations of antimony are found in the gastrointestinal tract, red blood cells, liver, kidney, bone, lung, spleen, and thyroid of laboratory animals exposed via oral exposure (NTP, 1992). In the blood, pentavalent antimony is mainly found in the serum, whereas trivalent antimony is found in the haemoglobin of red blood cells; both forms can enter red blood cells, with pentavalent antimony shown to do so via protein channels. Antimony can also transfer across the placenta and through breast milk, indicating potential exposure to the developing foetus and infants (Miranda et al. 2006).

12. Antimony is not metabolised. However, there are data suggesting the interconversion of pentavalent antimony and trivalent antimony. In mammals, in vitro studies indicate that ingested antimony undergoes intracellular interconversion between its trivalent and pentavalent states (NTP, 2018). The reduction of pentavalent to trivalent antimony occurs in a dose-dependent manner and is facilitated by acidic pH and higher temperatures. Once reduced to trivalent antimony, the compound conjugates with reduced glutathione (GSH), which is then followed by enterohepatic recycling of the trivalent antimony-GSH complex.

13. Antimony is excreted in the urine and faeces. Trivalent antimony is predominantly excreted in the faeces, with smaller amounts in the urine and pentavalent antimony is primarily excreted in the urine (Goodwin and Page, 1943).

Toxicity

14. The toxicity of antimony has been reviewed by WHO (2003), ATSDR (2019), and Health Canada (2024). The primary targets of toxicity appear to the heart (alterations in ECG readings), gastrointestinal tract (nausea, abdominal pain, vomiting, diarrhoea, anorexia), musculoskeletal system (myalgia, arthralgia), liver (increases in alanine and aspartate aminotransferases), pancreas (increases in serum amylase levels) and nervous system (headache, dizziness).

15. This section focusses on the Poon et al. (1998) study, and the subsequent commentaries by Lynch et al. (1999) and Valli et al. (2000), as these form the basis of the HBGVs proposed by WHO, ATSDR and Health Canada. A summary of additional toxicity studies identified from ATSDR and Health Canada is also provided.

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Summary of the Poon et al. (1998) study

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Summary of the Poon et al. (1998) study

16. In the study by Poon et al. (1998), groups of 15 male and 15 female Sprague-Dawley rats were exposed to 0, 0.5, 5, 50, or 500 ppm antimony as antimony

potassium tartrate (APT, 99.95% pure) in drinking water for 13 weeks. Based on average water consumption and body weight data, the investigators calculated antimony doses of 0, 60, 560, 5,580 and 42,170 µg/kg bw/day in males and 0, 60, 640, 6,130 and 45,690 µg/kg bw/day in females. An additional group of 10 male and 10 female rats was exposed to 0 or 500 ppm for 13 weeks followed by a 4-week recovery period. The following parameters were used to assess toxicity: weekly body weight, food consumption and water intake measurements; haematological and clinical chemistry indices, serum thyroxin and thyroid hormone binding ratio; organ weights (brain, thymus, heart, kidney, spleen, liver); and histopathological examination (brain, pituitary, thyroid and trachea, salivary glands, thymus, lung, heart, liver, kidneys, adrenals, spleen, pancreas, oesophagus, stomach, small and large intestine, urinary bladder, skin, bone marrow and gonadal tissues).

17. No alterations in survival or overt signs of toxicity were observed. Decreases in water consumption (35% lower than controls) and food consumption (12%) were observed in the high dose (42,170/45,690 µg Sb/kg bw/day) group during the exposure period but not during the recovery period. A decrease in body weight gain, significant in males starting at week 6 and females at week 12, was observed at 42,170/45,690 µg Sb/kg bw/day; the body weights appeared to be within 10% of the controls. A significant increase in relative kidney weights was observed in the 42,170/45,690 µg Sb/kg bw/day group.

18. Haematological changes observed included a decrease in red blood cells and platelet counts, along with increase in mean corpuscular volume in males exposed to 42,170 µg Sb/kg bw/day. In females, the only haematological alteration was an increase in monocytes at 45,690 µg Sb/kg bw/day.

19. The serum chemistry changes included a dose-dependent reduction (15–17%) in serum glucose levels in females exposed to doses ≥640 µg Sb/kg bw/day; lower glucose values were also observed in the males, but were not statistically different from controls. No differences in serum glucose levels were observed at the end of the recovery period. Decreases in serum creatinine levels and alkaline phosphatase levels were noted in both males and females exposed to 42,170/45,690 µg Sb/kg bw/day at the end of the exposure period, but not at the end of the observation period. A decrease (24%) in serum cholesterol level and total protein were observed in females exposed to 45,690 µg Sb/kg bw/day; the toxicological significance of this alteration is not known.

20. In terms of liver effects, significant increases in hepatic ethoxyresorufin-O-deethylase (EROD) and glutathione-S-transferase (GST) activities were observed

in males at 42,170 µg Sb/kg bw/day; glutathione-S-transferase activity was also increased in females at 45,690 µg Sb/kg bw/day. Histological alterations included anisokaryosis in the liver in all antimony-exposed groups, with dose-related increases in the severity observed. Anisokaryosis was also observed at the end of the recovery period. The severity scores for the anisokaryosis were 0.1, 0.6, 1.0, 1.9 and 2.8 in the 0, 60, 560, 5,580 and 42,170 µg Sb/kg bw/day males; a severity score of 1 is considered minimal, 2 is mild and 3 is moderate. In the females, the respective severity scores were 0.9, 1.5, 2.3, 2.3 and 2.6. Bridging fibrosis was observed in one animal of each sex in the highest dose group (42,170/45,690 µg Sb/kg bw/day in males/females).

21. Other hepatic effects included an increase in hepatocellular portal density in all antimony-exposed groups and minimal nuclear hyperchromicity at ≥560/640 µg Sb/kg bw/day, but there was not a consistent dose-response relationship for this endpoint. Similarly, the increase in portal density in the hepatocellular cytoplasm was graded as minimal at the two lowest doses in the males and females and mild at the two highest doses.

22. In terms of skeletal effects, an increase in myeloid hyperplasia in the bone marrow was observed at ≥5,580 µg Sb/kg bw/day in males and ≥640 µg Sb/kg bw/day in females.

23. Spleen effects include sinus congestion at ≥560 µg Sb/kg bw/day in males, sinus hyperplasia at 42,170 µg Sb/kg bw/day in males and ≥640 µg Sb/kg bw/day in females and arterial cuff atrophy at 42,170 µg Sb/kg bw/day in males. In the recovery period, increases in incidence of sinus congestion (males only), arterial cuff atrophy, periarteriolar lymphocyte sheath cell density and sinus haematopoiesis were observed.

24. Statistically significant increases in thyroid hormone binding ratio were observed in females at 6,130 and 45,690 µg Sb/kg bw/day. Thyroid histological alterations included an increase in epithelial height, reduced follicle size and nuclear vesiculation in antimony rats; an increased occurrence of collapsed follicles was observed in the antimony recovery group. These thyroid effects did not show a strong dose-response relationship and did not appear to affect thyroid function; the study authors did not consider these effects to be adverse.

25. The study authors concluded that 0.5 ppm antimony in drinking water, equivalent to an average intake of 60 µg Sb/kg bw/day, as the NOAEL for this study, primarily based on the statistically significant dose-dependent decrease in serum glucose levels in females at ≥640 µg Sb/kg bw/day.

Lynch et al. (1999) interpretation

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Lynch et al. (1999) interpretation

26. Lynch et al. (1999) reviewed the Poon et al. (1998) study and provided an alternative interpretation of the observed toxicological effects. These authors considered that some of the histological findings, particularly in the liver, spleen and thyroid, should not be considered toxicologically relevant and proposed a higher NOAEL.

27. Lynch et al. (1999) concluded that several of the findings in the Poon et al. (1998) study was likely to represent normal physiological variations or adaptive changes rather than adverse effects directly attributable to antimony exposure:

i. **Haematology**: Decreased red blood cell count in high-dose males and the observation of hematuria in the bladders of three high-dose males at necropsy are considered of less certain relationship to treatment.

ii. **Serum Biochemistry**: Several of the changes in the serum biochemistry parameters at the high dose, in particular the report of decreased non fasting glucose, serum cholesterol and alkaline phosphatase levels, are potentially due to the drastic decrease in water intake (about 35%) and moderate decrease in food intake (about 12%) noted in these animals. These changes are concluded to be of no biological or toxicological significance and, therefore, inappropriate on which to establish a NOAEL value.

iii. **Liver Findings**: The observed increased severity and/or incidence of anisokaryosis and nuclear hyperchromicity in the liver, although present in the treated animals, are common features in young adult rats as the ploidy state of hepatocytes increases from exclusively mononuclear diploid at birth to 50 to 70% mononuclear tetraploid by adulthood. They argued that these changes were adaptive rather than adverse and therefore should not be used as the basis for establishing the NOAEL. The bridging fibrosis in the liver observed in the highest dose tested is considered of uncertain relationship to treatment considering very limited (one animal of each sex) incidence.

iv. **Spleen Findings**: The sinus congestion represents a normal physiological function of the spleen and hyperplasia of the sinus is a common finding in female rats. Considering reduced severity of sinus congestion in male rats and its absence in female rats, lack of dose response (either incidence or severity) in the occurrence of sinus hyperplasia in female rats, no clear signs of toxicity to the hematopoietic system, the authors concluded that the observed histopathological findings in the spleens were of no clinical or toxicological significance.

v. **Thyroid Findings**: The decreased thyroid follicular size and increased epithelial height in males, were of a subtle nature and were not dose related. Additionally, weights of thyroid were not available to support the histopathological findings. The authors suggested that histopathological changes represent normal physiological variation considering the highly dynamic nature of rat thyroids and not to be considered of toxicological significance.

28. Based on these considerations, Lynch et al. (1999) proposed that the NOAEL for the study should be set at 50 ppm, equivalent to an average intake of 6,000 Sb µg/kg bw/day, based on the finding of decreased body weight gain and decreased food and water consumption at the 500 ppm dose level, even though

these effects may be due to the nonpalatability of the drinking water. The observed effects at lower doses were considered by Lynch et al. (1999) to be either adaptive or non-toxicological in nature.

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Response from Valli et al. (2000)

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Response from Valli et al. (2000)

29. In response to Lynch et al. (1999), Valli et al. (2000), which is the same group as Poon et al. (1998), re-affirmed the NOAEL of 60 µg/kg bw/day and emphasized the need to consider the full range of toxicological findings in the Poon et al. (1998) study. They responded that the histological changes have been observed, analysed and interpreted in conjunction with the serum biochemistry, haematology, tissue residue data and other changes in a fully appropriate

manner.

i. **Changes in the serum biochemical parameters**: Lynch et al. (1999) interpreted that lowering of serum glucose, cholesterol and alkaline phosphatase were likely secondary to reduced caloric and water intake. Valli et al. (2000) responded that no clinical dehydration was observed in the antimony treated animals and no increase in serum albumin and haematocrit were observed in treated animals which might have been expected in clinical dehydration. Valli et al. (2000) did not respond to the comments by Lynch et al. (1999) that serum glucose estimation was conducted in non-fasted rats and potential confounding effect of reduced food intake on some of the observed serum biochemical changes.

ii. **Liver Findings**: Valli et al. (2000) acknowledged that anisokaryosis and hyperchromicity are commonly seen in young adult rats. However, they emphasized that these findings should not be dismissed, particularly given the concurrent significant decreases in alkaline phosphatase, serum creatinine and glucose as well as decreased serum cholesterol and total protein in high-dose females. They argued that the combination of histological changes and biochemical alterations suggested a functional impairment in the liver, warranting a more conservative NOAEL.

iii. **Spleen Findings**: Valli et al. (2000) acknowledged that spleen variations can occur under different circumstances, but they stressed that the changes noted were evaluated against spleens of concurrent vehicle controls and handled in exactly the same manner as far as anaesthesia and collection methods were concerned. They further emphasized that the interpretation of changes in the spleen is crucial, that antimony accumulates in red blood cells and because of the normal function of the spleen in removing senescent and injured blood cells, their accumulation might well be the basis for alterations in splenic histology as a result of exposure to APT.

iv. **Thyroid Findings**: Valli et al. (2000) agreed that there is normally much more variation in thyroid morphology in male rats as compared to females and as a result, females tend to be more reliable indicators of thyroid toxic effects at low levels of exposure. Further, since the thyroid gland is both a storage and an endocrine organ, it was not surprising that there was a considerable level of reserve thyroid globulin which is the reason that thyroxine levels may not change in the face of mild injury to the thyroid gland.

30. Valli et al. (2000) maintained that the NOAEL of 60 µg/kg bw/day, as identified by Poon et al. (1998) was appropriate given the observed liver and spleen

histology and serum biochemistry alterations. They argued that the higher NOAEL of 6,000 µg/kg bw/day proposed by Lynch et al. (1999) underestimated the potential for early signs of toxicity and was not sufficiently protective.

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HBGV’s established by the WHO, ATSDR and Health Canada

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HBGV’s established by the WHO, ATSDR and Health Canada

World Health Organization (WHO)

31. In 2003, WHO derived a tolerable daily intake (TDI) for antimony of 6.0 µg/kg bw/day (WHO, 2003). This was based on the findings of Poon et al., 1998 with a

modified approach in interpreting the NOAEL of the study as suggested by Lynch et al., (1999).

32. WHO selected a NOAEL of 6,000 µg Sb/kg bw/day for decreased body weight gain and reduced food and water intake. An uncertainty factor of 1,000 (100 for interspecies and intraspecies differences and 10 for the short duration of the study) was applied to the NOAEL resulting in the TDI of 6.0 µg/kg bw/day.

33. The TDI of 6.0 µg Sb/kg bw/day was used to derive the WHO drinking water guideline value by, allowing an allocation to water of 10% of the TDI and assuming a 60 kg adult consumes 2L of water per day. The resultant drinking water guideline value of 20 µg/L and is derived to be protective for lifetime exposure. The WHO states that this could be highly conservative, due to the nature of the endpoints selected and the large uncertainty factor applied in the derivation of this TDI (WHO, 2022).

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Agency for Toxic Substances and Disease Registry (ATSDR)

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Agency for Toxic Substances and Disease Registry (ATSDR)

34. While ATSDR has not derived drinking water guidelines, it has derived an intermediate-duration oral Minimal Risk Level (MRL). An MRL is 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; the intermediate duration used in this instance covers exposures between 15 and 365 days. Oral intermediate duration MRL for antimony of 0.6 µg/kg bw/day was derived based on the findings and NOAEL interpretation by Poon et al., 1998. This is based on a NOAEL of 60 µg Sb/kg bw/day for decreases in serum glucose levels in female rats observed in the Poon et al., with an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability) (ATSDR, 2019).

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Health Canada

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35. In 2024, Health Canada selected a NOAEL of 60 µg Sb /kg bw/day from the study by Poon et al., (1998), based on observed histopathological changes in the liver (anisokaryosis) and alterations in serum biochemistry indicative of liver effects. Using this NOAEL, a tolerable daily intake (TDI) was derived by applying an uncertainty factor (UF) of 300 to account for interspecies variation (×10), intraspecies variation (×10) and the use of a subchronic study (×3), resulting in a TDI of 0.2 µg/kg body weight per day (Health Canada,2024).

36. The Health Canada health-based drinking water value of 3 µg/L for total antimony in drinking water was then derived from this TDI using an average adult body weight of 74 kg, a drinking water allocation factor of 0.3 (based on the upper bound of estimated intake for drinking water) and a drinking water intake rate of 1.53 L/day (Health Canada,2024).

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Differences between WHO, ATSDR and Health Canada

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Differences between WHO, ATSDR and Health Canada

37. 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 NOAEL selected:

- WHO chose a NOAEL of 6,000 µg Sb/kg bw/day, viewing liver effects at lower doses as adaptive changes with no toxicological significance (as suggested by Lynch et al., 1999).
- Health Canada and ATSDR selected a NOAEL of 60 µg Sb/kg bw/day, based on liver anisokaryosis and serum biochemistry changes, viewing these effects as indicative of altered liver function (as suggested by Poon et al., 1998).

38. There are also some differences in the uncertainty factors applied in the derivation of the TDI/MRL values, this mainly relates to study duration, with WHO using a factor of 10 for study duration, Health Canada using a factor of 3 for study duration, and ATSDR do not include a factor for study duration, but the MRL is for intermediate term exposure (15-365 days).

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Additional Toxicology Studies

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Additional Toxicology Studies

39. Several other studies have contributed to the understanding of the toxic effects of antimony across species and exposure durations.

40. In a study conducted by Kanisawa and Schroeder (1969), White Swiss mice of the Charles River Strain (CD-1) were exposed to 5 µg/ml 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. 350 µg Sb/kg bw per day was concluded as NOAEL from this study.

41. 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.

42. 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 hematocrit and hemoglobin 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.

43. 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%-Sb2O3 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.

44. In a study by Rossi et al. (1987), pregnant female rats were exposed to antimony trichloride (1 and 10 mg/L in their drinking water ad libitum equivalent to 70 µg Sb/kg bw/day and 700 µg Sb/kg bw/day, respectively) from the first day of pregnancy until weaning (22^{nd} day after delivery). Pups were exposed to antimony trichloride (1 and 10 mg/L in their drinking water ad libitum) from 22^{nd} until 60^{th} day of age. Antimony exposure did not significantly affect maternal and pup systolic arterial blood pressure, length of gestation or number of newborns per litter. Maternal body weight decreased significantly in a dose-dependent manner by the 20th day of gestation at both 0.1 and 1 mg/dl doses. Pups at high dose showed significantly reduced body weight from the 10th to the 60th day after birth. A NOAEL of 70 µg Sb/kg bw/day and a LOAEL of 700 µg Sb/kg bw/day were concluded based on decreased maternal body weight gain (11%) and decreased pup growth on postnatal days (PNDs) 10–60.

45. In a 14-day study conducted by NTP (1992), groups of 10 male and 10 female B6C3F1 mice were exposed to 0, 300, 650, 1,250, 2,500, 5,000 mg/L antimony potassium tartrate (99–100% purity) in drinking water. The investigators used water consumption data and body weight averages to calculate doses of 0, 59,000, 98,000, 174,000, 273,000 and 407,000 µg/kg bw/day antimony potassium tartrate (0, 21,000, 36,000, 63,000, 99,000 and 150,000 µg Sb/kg bw/day).

46. The following parameters were evaluated to assess toxicity: twice daily observations, body weight measurements (days 1 and 8 and at termination), water consumption (days 7 or 8 and day 15), organ weights, histopathology of major tissues and organs in control and high-dose groups (five mice/sex/group) and all early deaths and histopathological examination of the liver and forestomach of mice in all groups (five mice/sex/group). One female mouse in the 150,000 µg Sb/kg bw/day group died prior to the end of the study. On day 8, decreases in body weight gain were observed in males exposed to 99,000 µg Sb/kg bw/day and in males and females exposed to 150,000 µg Sb/kg bw/day. However, by the end of the study, the final weights of all antimony groups were

within 93% of the controls. Decreases in water consumption were observed at all antimony levels.

47. The investigators noted that overt signs of toxicity (rough haircoat, emaciation, abnormal posture, hypoactivity and decreased faecal material, consistent with avoidance of the antimony potassium tartrate containing water) were observed, but did not specify if this was observed in all groups. Histological alterations were observed in the forestomach and liver of mice in the 150,000 µg/kg bw/day group. In the forestomach, focal areas of ulceration with necrosis and inflammation of the squamous mucosa were observed; the incidence was not reported, although the investigators noted that gross forestomach lesions were observed in one male and three females. In the liver, minimal to moderate cytoplasmic vacuolization was observed in all mice in the 150,000 µg Sb/kg bw/day group; the vacuolization had a centrilobular distribution with some extension into portal areas. The NOAEL for liver toxicity was determined to be 99,000 µg Sb/kg bw/day.

48. As part of NTP (1992) study, groups of F344/N rats were administered APT in drinking water for 14 days. The animals were assigned to dose groups of 10 rats/sex. Drinking water doses, estimated by water consumption, were 0, 16,000, 28,000, 59,000, 94,000, or 168,000 µg/kg (0, 5,800, 10,000, 21,000, 34,000, 61,000 µg Sb/kg bw/day). APT was poorly absorbed and relatively nontoxic when given orally. There was no mortality or histopathological lesions in rats receiving doses of APT as high as 168,000 µg/kg. 61,000 µg Sb/kg bw/day was concluded as NOAEL dose from this study.

49. 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.

50. 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.

51. 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.

52. 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).

53. 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%) (12,000 or 1,200,000 µg/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 1,200,000 µg/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 1,200,000 µg/kg/day (highest dose tested) was concluded for male reproductive effects of antimony trioxide in this study.

54. 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 fetuses and 100% of litters including controls. 49,000 µg Sb/kg bw per day was concluded as NOAEL from this study.

55. Table 1 below summarises all the NOAEL values concluded from the available studies, as well as those concluded by authoritative bodies.

Table 1 NOAELs from studies and concluded by authoritative bodies

Authority or Authors	NOAEL (µg Sb/kg bw/day)	Critical effects	Study Reference
World Health Organization (WHO)	6,000	Observed effects at lower doses considered adaptive and not of toxicological significance.	Poon et al. (1998) Lynch et al. (1999)
ATSDR	60	Decreases in serum glucose levels.	Poon et al. (1998)
Health Canada	60	Histological liver changes, alterations in serum biochemistr.	Poon et al. (1998)
Kanisawa & Schroeder (1969)	350	No significant differences in spontaneous and malignant tumour incidence in mice.	Kanisawa & Schroeder, 1969
Schroeder et al. (1970)	430 (LOAEL)	Reduced survival rate in males and females; at the median life spans, survival was reduced by 106 and 107 days for males and females, respectively, compared to controls. Non-fasting serum glucose levels were reduced by 28%–30% in the dosed animals.	Schroeder et al. (1970)
Sunagawa (1981)	418,000	Liver histopathological changes and increased aspartate transaminase (AST) activity.	Sunagawa, 1981

Authority or Authors	NOAEL (µg Sb/kg bw/day)	Critical effects	Study Reference
Hiraoka (1986)	700,000	Inhibited weight gain, changes in hematocrit and protein levels, high antimony concentrations in organs	Hiraoka, 1986
Rossi et al. (1987)	70	Decreased maternal body weight gain and decreased pup growth on PNDs 10–60.	Rossi et al. (1987)
NTP (1992)	99,000	Forestomach lesions in the high dose group. Dose-related increases in relative liver weight; lesions in the liver of most mice in the high dose group.	NTP (1992)
NTP (1992)	61,000	Increase in relative liver weight in the high dose group	NTP (1992)
Hext et al. (1999)	1,408,000 males), 1,570,000 (females)	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. No histological effects on liver.	Hext et al. (1999)
Omura et al. (2002)	1,200,000	No significant effect on reproductive organs or sperm parameters.	Omura et al. (2002)

Authority or Authors	NOAEL (µg Sb/kg bw/day)	Critical effects	Study Reference
ECHA (2014)	49,000	Increased (non-significant) incidence in delayed skeletal development 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 fetuses and 100% of litters including controls. No reproductive toxicity, embryotoxicity or fetotoxicity.	Dossier submitted to ECHA (2014)

Summary and Questions for the Committee

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Summary

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

57. 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).

58. 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	6
Health Canada (2024)	60	300	0.2
ATSDR (2019)	60	100	0.6 (MRL)

59. 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.

60. The COT has not yet seen or commented on the full ATSDR, 2019 and Health Canada's 2024 evaluation. The HBGVs by ATSDR and Health Canada are not aligned with WHO's HBGV from 2003.

Questions for the Committee

61. Members are invited to consider the following questions:

i) What is the Committee's opinion on the interpretation and conclusion of the 90-day drinking water toxicity study of antimony in rats by Poon *et al.,* (1998)?

ii) From the studies presented, is the Committee able to identify a NOAEL on which the assessment of antimony should be based?

iii) 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?

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

v) Does the Committee have any other comments?

Secretariat

October 2024

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

List of abbreviations and their full meanings.

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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
ECG	Electrocardiogram
GSH	Glutathione
HBGV	Health-based guidance value

LOAEL	Lowest Observed Adverse Effect Level - the lowest dose in a study at which adverse effect(s) are observed.
LOEL	Lowest Observed Effect Level - the lowest dose in a study at which effect(s) are observed.
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.
NTP	National Toxicology Program
ppm	Parts per million
Sb	Antimony
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

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

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