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TOX/2025/23

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

Statement on the derivation of a health-based guidance value for antimony – First Draft

Introduction

1. Post European Union (EU) exit, the Drinking Water Inspectorate (DWI) is reviewing the regulatory standards for some chemicals in drinking water, including antimony. The UK Health Security Agency (UKHSA) sought 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. Two discussion papers on the relevant available evidence of antimony toxicity were presented and discussed at the October 2024 and February 2025 meetings. A first draft statement summarising the Committee's conclusions is attached as Annex 1 to this paper.

Questions for the Committee

3. The Committee is asked to consider:

   i. Does the Committee have any comments on the general structure and content of this draft statement?
   ii. Is the table in Annex A of the statement useful or does the Committee think it should be removed?
   iii. Is the Committee content with its conclusions presented within this draft statement?
   iv. Does the Committee have any other comments on this draft statement?

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Secretariat

April 2025

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Annex 1 to TOX/2025/23

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

Statement on the derivation of a health-based guidance value for antimony First draft statement

Secretariat
April 2025

Executive Summary

1. Post European Union (EU) exit, the Drinking Water Inspectorate (DWI) is reviewing the regulatory standards for some chemicals in drinking water, including antimony. The UK Health Security Agency (UKHSA) sought 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. The World Health Organization (WHO), the US Agency for Toxic Substances and Disease Registry (ATSDR) and Health Canada have used the same study (Poon et al., 1998) 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 agreed that the Poon et al. (1998) study was the most appropriate study to use to derive a HBGV for antimony. The COT determined that the NOAEL of 6,000 micrograms per kilogram of body weight per day (µg/kg bw/day), based on decreased body weight gain and reduced food and water consumption in adult rats, was

the point of departure. An uncertainty factor (UF) of 300 was recommended, resulting in a tolerable daily intake (TDI) of 20 µg Sb/kg bw/day as a HBGV for antimony.

Background and scope of discussion

4. The UKHSA advises the 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 sought advice from the COT with respect to an appropriate HBGV for antimony, which would inform the consideration of an appropriate drinking water regulatory limit for antimony.

5. The 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, 2017). The 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 (COT, 2006). For these reviews, the COT used the WHO TDI of 6 µg/kg bw/day for the evaluation (WHO, 2003).

6. More recently Health Canada (2024) and ATSDR (2019) have considered antimony and derived lower HBGVs. WHO, ATSDR and Health Canada all derived their HBGVs from the same study (Poon et al., 1998), however, they diverge in their interpretation of the study results and the selection of the NOAEL.

7. Two antimony discussion papers (TOX/2024/38 and TOX/2025/04) were presented to the COT at the October 2024 and February 2025 meetings respectively. The COT assessed the Poon et al. (1998) study and its interpretations, as well as other available evidence in order to determine an appropriate HBGV to support an update to the antimony drinking water standard in the UK.

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Properties of antimony and sources in drinking water

8. Antimony (Sb, CAS number: 7440-36-0) is a silvery white metal naturally present in the Earth's crust (Sundar and Chakravarty, 2010). The most common source of antimony in drinking water appears to be dissolution from metal plumbing and fittings (WHO, 2003). Antimony compounds can exist in trivalent (Sb^{3+}) and pentavalent (Sb^{5+}) states, with trivalent antimony being considered more toxic than pentavalent antimony. In drinking water, pentavalent antimony is the more prevalent form of antimony. However, some evidence suggests that both can coexist and cycle between each other under certain conditions (Health Canada, 2024). For further information on the properties of antimony, see TOX/2024/38 and TOX/2025/04.

Oral toxicity data for antimony

Poon et al. 1998 study and interpretation

9. 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 parts per million (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 (0 and 42,170 µg/kg bw/day for males and 45,690 µg/kg bw/day for females) for 13 weeks followed by a 4-week recovery period.

10. A dose-dependent reduction (15–17%) in serum glucose levels in females exposed to doses greater than or equal to 640 µg Sb/kg bw/day was observed. Lower glucose values were also observed in the males; however, these were not statistically different from controls.

11. Other toxicological endpoints were identified by the study at the highest antimony doses in males and females (42,170 or 45,690 µg Sb/kg bw/day). These included a

decrease in water and food consumption, a decrease in body weight gain (significant in males starting at week 6 and females at week 12), haematological changes which differed between males and females, decreases in serum creatinine levels and alkaline phosphatase levels, and liver effects including changes in activity of some liver enzymes such as ethoxyresorufin-O-deethylase (EROD) and glutathione-S-transferase (GST).

12. Anisokaryosis in the liver was observed in all antimony-exposed groups, with a dose-related increase in the severity observed.

13. Other hepatic effects included an increase in hepatocellular portal density in all antimony-exposed groups, but this was considered mild in males and females at greater than or equal to 560 and 640 µg Sb/kg bw/day respectively. Minimal nuclear hyperchromicity was also observed at these levels but with no consistent dose-response relationship.

14. 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.

15. Spleen effects included 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.

16. The study authors concluded 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.

17. Lynch et al. (1999) reviewed the Poon et al. (1998) study and provided an alternative interpretation of the observed toxicological effects. The authors stated that

the observed effects at lower doses were either adaptive or non-toxicological in nature. They 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. 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 (though they stated that these effects may be due to the nonpalatability of the drinking water).

18. Valli et al. (2000), from the same group as Poon et al. (1998), 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. Valli et al. (2000) stated 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.

Further oral antimony studies with NOAELs less than 6000 µg/kg bw/day

19. Marmo et al. (1987), Rossi et al. (1987) and Angrisani et al. (1988) reported findings from an antimony exposure study in NOS Albino normotensive rats.

20. Rossi et al. (1987) reported a NOAEL in maternal rats of 70 µg Sb/kg bw/day. This was due to a significant dose-dependent decrease in maternal body weight by gestation day 20 following prenatal oral exposure to antimony trichloride. 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 reported 8 to 10% deficit (in the low- and high- dose groups respectively) from controls seen on gestation day 20 represents a relatively small change from the 7% deficit at the start of gestation. The pup lowest observed adverse effect level (LOAEL) was reported as 700 µg Sb/kg bw/day due to decreases in body weight (Rossi et al., 1987).

21. Additional findings reported by Marmo et al. (1987) noted decreased vasomotor reactivity due to both prenatal and postnatal oral exposure to antimony trichloride. Additional findings reported by Angrisani et al. (1988) showed postnatal exposure to antimony trichloride did not affect maternal or pup body weights or systolic arterial blood pressure.

22. In a study conducted by Kanisawa and Schroeder (1969), life term oral exposure to 5 ppm antimony as potassium tartrate (equivalent to 350 µg Sb/kg bw/day) in mice did not result in a significant difference in the incidences of spontaneous tumours or malignant tumours compared to controls. The authors identified 350 µg Sb/kg bw/day as the NOAEL for this study.

23. In a lifetime exposure study conducted by Schroeder et al. (1970), a significant reduction in survival rates and reduced non-fasting glucose levels were identified when rats were exposed to 430 µg Sb/kg bw/day potassium tartrate in their drinking water. The authors reported a LOAEL of 430 µg Sb/kg bw/day based on these effects.

24. Annex A provides further detail on the available antimony toxicity studies with comments on the Committees consideration of the reported NOAELs.

HBGVs established by WHO, ATSDR and Health Canada

25. WHO selected a NOAEL of 6,000 µg Sb/kg bw/day from the Poon et al. (1998) study, as recommended by Lynch et al. (1999), for decreased body weight gain and reduced food and water intake. A UF 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 (WHO 2003).

26. ATSDR selected a NOAEL of 60 µg Sb/kg bw/day for decreases in serum glucose levels in female rats observed in the Poon et al. (1998). A UF of 100 (10 for extrapolation from animals to humans and 10 for human variability) was applied to

derive an intermediate-duration (15 – 365 days) oral Minimal Risk Level (MRL) of 0.6 µg/kg bw/day (ATSDR 2019).

27. Health Canada also 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. A UF of 300 was applied (10 for interspecies variation, 10 for intraspecies variation and 3 for the use of a subchronic study) resulting in a TDI of 0.2 µg/kg bw/day (Health Canada, 2024).

28. More information on the derivation of the HBGVs for WHO, ATSDR and Health Canada is available in the COT discussion paper TOX/2024/38.

Discussion

29. The COT determined that the effects on serum glucose levels in female rats observed in Poon et al. (1998), which informed the NOAELs selected by ATSDR and Health Canada, showed limited dose-response. The Committee also noted that an intraperitoneal study by the National Toxicology Program (NTP) which examined antimony at higher doses and with greater bioavailability did not observe these effects (NTP 1992).

30. The Committee further agreed that the liver changes observed in Poon et al. (1998), which also informed the NOAEL selected by Health Canada, were minor and not indicative of adverse effects as there was no evidence of increase in liver weight across a large range of doses. The changes in the levels of liver enzymes were deemed to be minor and inconsistent with a hepatotoxic effect. The Poon et al. (1998) study showed no clear evidence of changes in thyroid hormone effects and there was also difficulty in interpreting spleen findings due to high background variation and the findings were not considered to be of toxicological significance.

31. The Committee agreed with the Lynch et al. (1999) interpretation that the significant body weight changes observed at the highest dose in Poon et al. (1998) was critical effect. Therefore, the COT determined a NOAEL of 6,000 µg/kg bw/day for this study.

32. With respect to other oral studies with doses less than the NOAEL determined by COT for the Poon et al. (1998) study, the COT noted that the baseline maternal body weight in the study by Rossi et al. (1987) at gestation day 0 was approximately 7% lower in treated groups compared to controls. Consequently, the observed 8–10% reduction in maternal body weight at gestation day 20 used as the basis for the maternal NOAEL was considered a relatively small change, given the pre-existing baseline differences. The Committee noted that the NTP intraperitoneal study observed body weight effects only at the highest dose (9,600 µg Sb/kg bw/day).

33. The COT further observed that while decreased pup body weight was reported in the Rossi et al. (1987) study in the high dose group, the investigation by Angrisani et al. (1998) antimony exposure found no significant changes in pup body weight. With the lower initial maternal body weights in the treated groups reported in the Rossi et al. (1987) study, it was suggested that the observed lower body weight in prenatally exposed pups could be secondary to the lower maternal body weights of this group rather than a direct effect of antimony on pups. For these reasons, the lower NOAEL and LOAEL (when compared to the 6,000 µg Sb/kg bw/day NOAEL from the Poon et al. (1998) study) relating to maternal and pup body weight reported in the Rossi et al. (1987) study were discounted.

34. There were concerns regarding the reliability of the studies by Kanisawa and Schroeder (1969) and Schroeder (1970) and challenges interpreting their data. Furthermore, the nature of these studies does not allow for the demonstration of a dose-response, therefore the NOAELs and LOAELs reported in these studies were also discounted.

Overall Conclusion

35. Overall, the COT concluded that the NOAEL of 6,000 µg Sb/kg bw/day, from the Poon et al. (1998) study based on decreased body weight gain and reduced food and water consumption in adult rats, was the appropriate point of departure to use as the basis of a HBGV for antimony.

36. The Committee also highlighted that the pentavalent form of antimony, which is predominant in drinking water, exhibits lower toxicity compared to the trivalent form. As Poon et al. (1998) utilized the trivalent form of antimony (antimony potassium tartrate) in their study, a HBGV derived from the NOAEL of 6,000 µg Sb/kg bw/day was considered a sufficiently protective for antimony in drinking water.

37. The Committee recommended a UF of 300, comprising a factor of 10 for interspecies variation, 10 for intraspecies variation, and 3 for subchronic to chronic extrapolation. This results in a TDI of 20 µg Sb/kg bw/day.

COT Month 2025

Statement 2025/XX

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List of abbreviations and their full meanings

µg Sb/kg bw/day	Micrograms of antimony per kilogram of body weight per day
APT	Antimony Potassium Tartrate
ATSDR	Agency for Toxic Substances and Disease Registry
bw	Body Weight
COT	Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment
DWI	Drinking Water Inspectorate
EROD	Ethoxyresorufin-O-deethylase
EU	European Union
GST	Glutathione-S-transferase
HBGV	Health-based guidance value
LOAEL	Lowest Observed Adverse Effect Level - the lowest dose in a study at which adverse 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
POD	Point of Departure
ppm	Parts per million
Sb	Antimony

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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.
UF	Uncertainty factor
UKHSA	United Kingdom Health Security Agency
WHO	World Health Organization

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References

Angrisani, M., Lampa, E., Lisa, M., Matera, C., Marrazzo, R. and Scafuro, M., 1988. Vasomotor reactivity and postnatal exposure to antimony trichloride. Current therapeutic research, 43(1), pp.153-159.

Agency for Toxic Substances and Disease Registry (ATSDR) (2019) Toxicological profile for antimony. U.S. Department of Health and Human Services, Public Health Service, Atlanta, GA. ATSDR Antimony Tox Profile

Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) (2017) Statement on the results of the 2014 survey of metals and other elements in infant foods. 2014infantmetalssurveystatement.pdf (cot.food.gov.uk)

Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) (2006) Statement on the results of the 2006 UK Total Diet Study of metals and other elements. [ARCHIVED CONTENT] COT statement on the 2006 UK total diet study of metals and other elements | Food Standards Agency (nationalarchives.gov.uk)

Health Canada (2024) Antimony: Environmental and health assessment. Health Canada, Ottawa. Guidelines for Canadian Drinking Water Quality: Guideline Technical Document – Antimony - Canada.ca

Kanisawa, M. and Schroeder, H.A., 1969. Life term studies on the effect of trace elements on spontaneous tumours in mice and rats. Cancer Research, 29(4), pp.892-895.

Lynch, B.S., Capen, C.C., Nestmann, E.R., Veenstra, G. and Deyo, J.A., 1999. Review of subchronic/chronic toxicity of antimony potassium tartrate. Regulatory Toxicology and Pharmacology, 30(1), pp.9-17. https://doi.org/10.1006/rtph.1999.1312

Marmo, E., Matera, M.G., CUPARENCU, B., ROSSI, F., ACAMPORA, R. and VACCA, C., 1987. Prenatal and postnatal metal exposure: effect on vasomotor reactivity

development of pups: experimental research with antimony trichloride, thallium sulfate, and sodium metavanadate. Current therapeutic research, 42(5), pp.823-838.

NTP 1992. NTP report on the toxicity studies of antimony potassium tartrate in F344/N rats and B6C3F1 mice (drinking water and intraperitoneal injection studies). Research Triangle Park, NC: NTP Tox 11. NIH Publication No. 92-3130.

Poon, R., Chu, I., Lecavalier, P., Valli, V.E., Foster, W., Gupta, S. and Thomas, B., 1998. Effects of antimony on rats following 90-day exposure via drinking water. Food and Chemical Toxicology, 36(1), pp.21-35. https://doi.org/10.1016/S0278-6915(97)80120-2

Rossi, F., Acampora, R., Vacca, C., Maione, S., Matera, M.G., Servodio, R. and Marmo, E., 1987. Prenatal and postnatal antimony exposure in rats: effect on vasomotor reactivity development of pups. Teratogenesis, carcinogenesis and mutagenesis, 7(5), pp.491-496. https://doi.org/10.1002/tcm.1770070507

Schroeder, H.A., Mitchener, M. and Nason, A.P., 1970. Zirconium, niobium, antimony, vanadium and lead in rats: life term studies. The Journal of nutrition, 100(1), pp.59-68. . https://doi.org/10.1093/jn/100.1.59

Sundar, Shyam and Jaya Chakravarty. “Antimony toxicity.” International journal of environmental research and public health vol. 7,12 (2010): 4267-77. doi:10.3390/ijerph7124267. https://doi.org/10.3390/ijerph7124267

Valli, V.E., Poon, R., Chu, I., Gupta, S. and Thomas, B.H., 2000. Subchronic/chronic toxicity of antimony potassium tartrate. Regulatory Toxicology and Pharmacology: RTP, 32(3), pp.337-8. https://doi.org/10.1006/rtph.2000.1414

WHO (2003) Antimony in drinking-water: Background document for development of WHO Guidelines for Drinking-water Quality. World Health Organization, Geneva. Antimony in Drinking water – WHO

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Annex A

Statement on the derivation of a health-based guidance value for antimony to support development of UK Drinking Water Standards

Table 1. Summary of antimony toxicity studies and comments on the derived NOAELs.

Author and year	**Study details**	**Dose level**	**Findings**	**No observed adverse effect level (NOAEL)**	**Comments on the NOAEL**
Poon et al. (1998)	**Species:** Sprague-Dawley rats. **Route of exposure:** Oral-Drinking water. **Initial study duration:** 13 weeks.	**Initial Study Original Dose:** 0, 0.5, 5, 50, or 500 ppm antimony potassium tartrate. **Initial Study Recalculated Dose Levels:**	Dose-dependent decrease in serum glucose levels in females at ≥640 µg Sb/kg bw/day. Decrease also noted in males but not statistically significant. decrease in water and food consumption, a decrease in body weight gain (significant in males starting at week 6	**Poon et al. (1998) recommended NOAEL**: 60 µg Sb/kg bw/day. **Lynch et al. (1999) recommended NOAEL:**	**Poon et al. (1998) recommended NOAEL:** NOAEL is based on decreased in serum glucose levels in females at ≥640 µg Sb/kg bw/day. However, the Committee determined that these effects showed limited dose-response. The Committee noted that an NTP intraperitoneal study did not

	Initial No/Sex: 15 male and 15 female. **Follow up study duration:** 13 weeks followed by a 4-week recovery period. **Follow up No/Sex**: 10 male and 10 female.	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. Follow up Study Original Dose: 0 or 500 ppm.	and females at week 12), haematological changes which differed between males and females, decreases in serum creatinine levels and alkaline phosphatase levels, and liver effects including changes to liver enzyme activity all observed at the highest antimony dose (42,170/45,690 µg Sb/kg bw/day in males and females respectively). Dose-related increase in the severity of anisokaryosis observed in all antimony-exposed groups. Increased hepatocellular portal density in all	6,000 Sb µg/kg bw/day.	observe these effects despite higher concentrations and greater bioavailability of antimony. **Lynch et al. (1999) recommended NOAEL:** NOAEL is based on decreased body weight gain and decreased food and water consumption at the 500 ppm dose level. The COT agrees that this is an appropriate NOAEL for this study and is the appropriate point of departure to use as the basis of a HBGV for antimony.

			antimony-exposed groups and minimal nuclear hyperchromicity at ≥560/640 µg Sb/kg. increased 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. Sinus congestion at ≥640 µg Sb/kg bw/day observed in females. Sinus congestion at ≥560 µg Sb/kg bw/day and sinus hyperplasia and arterial cuff atrophy at 42,170 µg Sb/kg bw/day observed 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.		
Marmo et al. (1987)	**Species:** NOS Albino normotensive rats. **Route of exposure:** Oral-Drinking water. **Study duration:** Maternal exposure: - 1st day of pregnancy	**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	70 µg Sb/kg bw/day. Pup LOAEL: 700 µg Sb/kg bw/day.	See Rossi et al. (1987)

	until weaning (22nd day after delivery) or from PND1 to PND 22. Pups: - From weaning until 30 or 60 days of age. **No/Sex:** 30 per group. Rat offspring: - 10 pups/ group, equal sex ratio.		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 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)	**Species:** NOS Albino normotensive rats. **Route of exposure:** Oral-Drinking water. **Study duration:** Prenatal: 1st day of pregnancy until weaning	**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	NOAEL is based on dose-dependent decrease in maternal body weight by gestation day 20 following prenatal oral antimony exposure. The COT noted that the baseline maternal body weight in the study by Rossi et al. (1987) at gestation day 0 was approximately 7% lower in treated groups compared to controls. Consequently, the observed 8–10% reduction in maternal body weight at gestation day 20 used as the basis for the maternal NOAEL

	(22nd day after delivery). Postnatal: 22nd to 60 days in drinking water. **No/Sex:** 30 per group. Rat offspring: - 10 pups/ group, equal sex ratio.				was considered a relatively small change, given the pre-existing baseline differences. With the lower maternal body weights in the treated groups reported in the Rossi et al. (1987) study, it was suggested that the observed lower pup body weight could be secondary to the lower maternal body weights seen in this group rather than direct effect of antimony on pups. The Committee also noted that the NTP intraperitoneal study observed body weight effects only at the highest dose (9,600 µg Sb/kg bw/day). For these reasons, the lower NOAEL and LOAEL relating to maternal and pup body weight

					reported in the Rossi et al. (1987) study were discounted.
Angrisani et al. (1987)	**Species:** NOS Albino normotensive rats. **Route of exposure:** Oral-Drinking water. **Study duration:** Postnatal: From PND1 to PND60. **No/Sex:** 30 per group	**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.	See Rossi et al. (1987)

	Rat offspring: - 10 pups/ group, equal sex ratio.				
Kanisawa and Schroeder (1969)	**Species:** Mice (White Swiss, Charles River CD-1). **Route of exposure:** Oral-Drinking water. **Study duration:** Lifetime exposure.	**Original Dose**: 5 ppm Antimony Potassium Tartrate. **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.	The COT raised concerns regarding the reliability of the data and challenges interpreting the data. Furthermore, the nature of this study does not allow for the demonstration of a dose-response, therefore the NOAEL was discounted.

	No/Sex: Control mice – 71; Antimony treatment – 76.				
Schroeder et al. (1970)	**Species:** Long Evan Rats. **Route of exposure:** Oral-Drinking water. **Study duration:** 2 years. **No/Sex**: 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%	LOAEL: 430 µg Sb/kg bw/day.	The COT raised concerns regarding the reliability of the data and challenges interpreting the data. Furthermore, the nature of this study does not allow for the demonstration of a dose-response, therefore the LOAEL was discounted.

			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 significant increases in concentration over time.		
NTP (1992)	**Species:** B6C3F1 Mice **Route of exposure:** Intraperitoneal injection. **Study duration**: 13 weeks. **No/Sex:** 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.	The dose was given intraperitoneally therefore this study was not used for the determination of the appropriate NOAEL for oral antimony consumption.

NTP (1992)	**Species:** F344/N rats. **Route of exposure:** Intraperitoneal injection. **Study duration:** 13 weeks. **No/Sex:** 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.	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	1,200 µg Sb/kg bw/day.	The dose was given intraperitoneally therefore this study was not used for the determination of the appropriate NOAEL for oral antimony consumption.

			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)	**Species:** Wistar rats. **Route of exposure:** Oral-Feeding. **Study duration:** 24 weeks.	**Original Dose**: Metallic Antimony: 0, 0.5, 1.0, 2.0%. Antimony Trioxide: 0, 1.0, 2.0%. **Recalculated Dose Levels:**	Metallic antimony high dose: decreased body weight gain. Metallic antimony high dose: decreased hematocrit and hemoglobin. Antimony trioxide all dose: decreased erythrocyte levels.	LOAEL: 418,000 µg Sb/kg bw/day.	The LOAEL is higher than the NOAEL from Poon et al. (1998) that the COT determined was the appropriate point of departure to use as the basis of a HBGV for antimony.

	No/Sex: 5 per dose.	Metallic Antimony: 0, 500,000, 1,000,000, 2,000,000 µg Sb/kg bw/day. Antimony Trioxide: 0, 418,000, 836,000 µg Sb/kg bw/day.	Metallic antimony mid and high dose: slight cloudy swelling in hepatic cords. Antimony trioxide all dose: slight cloudy swelling in hepatic cords.		
Hiraoka (1986)	**Species:** Wistar rats. **Route of exposure:** Oral-Feeding. **Study duration:** 12 weeks.	**Original Dose:** Metallic Antimony: 0.1% (w/w), 1.0% (w/w) o. Antimony Trioxide: 1.0% (w/w).	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	700,000 µg Sb/kg bw/day.	The NOAEL is higher than the NOAEL from Poon et al. (1998) that the COT determined was the appropriate point of departure to use as the basis of a HBGV for antimony.

	12 weeks recovery. **No/Sex**: 12 males per group.	**Recalculated Dose Levels:** Metallic Antimony: 85,000, 850,000 µg Sb/kg bw/day. Antimony Trioxide: 700,000 µg Sb/kg bw/day.	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 the highest concentration was detected in the blood of the rats.		

Miranda et al. (2006)	**Species:** Wistar rats. **Route of exposure:** Subcutaneous injection. **Study duration**: GD1 – 20. **No/Sex:** 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	75,000 µg Sb/kg/day.	The LOAEL is higher than the NOAEL from Poon et al. (1998) that the COT determined was the appropriate point of departure to use as the basis of a HBGV for antimony.

			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.		
Hext et al. (1999)	**Species:** Wistar rats. **Route of exposure:** Oral-Feeding. **Study duration:** 90 days.	**Original Dose:** 0, 1,000, 5,000, 20,000 ppm antimony trioxide. **Recalculated Dose Levels:** Males: 0, 70,000, 353,000,	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	1,408,000 µg Sb/kg bw/day (male rats) and 1,570,000 µg Sb/kg bw/day (female rats).	The NOAELs are higher than the NOAEL from Poon et al. (1998) that the COT determined was the appropriate point of departure to use as the basis of a HBGV for antimony.

	No/Sex: 12 Males per group. 12 Females per group.	1,408,000 µg Sb/kg bw/day. Females: 0, 81,000, 413,000, 1,570,000 µg Sb/kg bw/day.	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-related and were considered by the study authors to be incidental.		
Coelho et al. (2014)	**Species:** Pregnant female Wistar rats. Route of exposure: Subcutaneous injection. **Study duration:**	Original Dose: 0, 75, 150, 300 mg SbV/kg bw/day of meglumine antimoniate. **Recalculated Dose Levels:** 0, 75,000, 150,000,	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.	150,000 µg SbV/kg bw/day.	The dose was given via subcutaneous injection therefore this study was not used for the determination of the appropriate NOAEL for oral antimony consumption.

	Gestation Day 0-PND 21. No/Sex: Control - 14; Treatment - 16 per dose.	300,000 µg SbV/kg bw/day.	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.		
Alkhawajah et al. (1995)	**Species:** Sprague Dawley rats. **Route of exposure:**	**Original Dose Levels:** 1. Sodium Stibogluconate (SSG): 30,000, 100,000,	Reduction ($P<0.05$) in foetal birth weight and litter size was observed as compared to the control. High dose of SSG & MA: - Death of all animals before	-	The dose was given via intramuscular injection therefore this study was not used for the determination of the appropriate NOAEL for oral antimony consumption.

	Intramuscular injection. Study duration: Gestation Day 6-15. No/Sex: 10 per dose.	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 ($SbCl_3$): 100,000 µg Sb/kg bw/da.y	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)	**Species:** Wistar rats, CD-1 mice. **Route of exposure:** Oral-gavage feeding. **Study duration:** 4 weeks.	Original dose: 1.Antimony Potassium Tartrate group: 27.4 mg/kg body weight. 2.Low-Antimony trioxide group: 12 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.	The NOAEL is higher than the NOAEL from Poon et al. (1998) that the COT determined was the appropriate point of departure to use as the basis of a HBGV for antimony.

	No/Sex: Rats: 7 to 8 per group. Mice: 8-10 per group.	3.High-Antimony trioxide group: 1,200 mg/kg body weight. 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)	**Species:** Rats (not specified). **Route of exposure:** Inhalation. **Study duration:** 1.5-2 months, 4 hours/day. **No/Sex:** 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 was found in rats exposed to	209,000 µg Sb/$m^{3.}$	The dose was given via inhalation therefore this study was not used for the determination of the appropriate NOAEL for oral antimony consumption.

			209 mg Sb/m³ of antimony trioxide before conception and during gestation.		
REACH registration dossier submitted to ECHA (2014)	**Species:** Sprague-Dawley rats. **Route of exposure:** Oral-Drinking water. **Study duration:** Gestation days 6-19. **No/Sex:** 2 females per dose.	**Original Dose:** 0, 100, 300 and 1000 mg/kg bw/day sodium hexahydroxo-antimonate. **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.	The NOAEL is higher than the NOAEL from Poon et al. (1998) that the COT determined was the appropriate point of departure to use as the basis of a HBGV for antimony.

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

Annex References

Alkhawajah, A.M., Jain, S. and Larbi, E.B., 1996. Effects of antimony compounds on foetal development in rats. Journal of Applied Animal Research, 10(1), pp.15-24. https://doi.org/10.1080/09712119.1996.9706126

Angrisani, M., Lampa, E., Lisa, M., Matera, C., Marrazzo, R. and Scafuro, M., 1988. Vasomotor reactivity and postnatal exposure to antimony trichloride. Current therapeutic research, 43(1), pp.153-159.

Belyaeva, A.P., 1967. The effect produced by antimony on the generative function. doi/full/10.5555/19672702376

Coelho, D.R., De-Carvalho, R.R., Rocha, R.C., Saint'Pierre, T.D. and Paumgartten, F.J., 2014. Effects of in utero and lactational exposure to SbV on rat neurobehavioral development and fertility. Reproductive Toxicology, 50, pp.98-107. https://doi.org/10.1016/j.reprotox.2014.10.016

ECHA: REACH registration dossier submitted to ECHA. Registration Dossier - ECHA

Hext PM, Pinto PJ, Rimmel BA. 1999. Subchronic feeding study of antimony trioxide in rats. J Appl Toxicol 19(3):205-209. https://doi.org/10.1002/(SICI)

Hiraoka, N., 1986. The toxicity and organ-distribution of antimony after.

Kanisawa, M. and Schroeder, H.A., 1969. Life term studies on the effect of trace elements on spontaneous tumours in mice and rats. Cancer Research, 29(4), pp.892-895.

Marmo, E., Matera, M.G., CUPARENCU, B., ROSSI, F., ACAMPORA, R. and VACCA, C., 1987. Prenatal and postnatal metal exposure: effect on vasomotor reactivity

development of pups: experimental research with antimony trichloride, thallium sulfate, and sodium metavanadate. Current therapeutic research, 42(5), pp.823-838.

Miranda, E.S., Miekeley, N., De-Carvalho, R.R. and Paumgartten, F.J. (2006). Developmental toxicity of meglumine antimoniate and transplacental transfer of antimony in the rat. Reprod. Toxicol., 21(3): 292–300. https://doi.org/10.1016/j.reprotox.2005.09.010

NTP. 1992. NTP report on the toxicity studies of antimony potassium tartrate in F344/N rats and B6C3F1 mice (drinking water and intraperitoneal injection studies). Research Triangle Park, NC: NTP Tox 11. NIH Publication No. 92-3130.

Omura M, Tanaka A, Hirata M, et al. 2002. Testicular toxicity evaluation of two antimony compounds, antimony trioxide and antimony potassium tartrate, in rats and mice. Environ Health Prev Med 7(1):15-18. http://doi.org/10.1007/bf02898061

Poon, R., Chu, I., Lecavalier, P., Valli, V.E., Foster, W., Gupta, S. and Thomas, B., 1998. Effects of antimony on rats following 90-day exposure via drinking water. Food and Chemical Toxicology, 36(1), pp.21-35. https://doi.org/10.1016/S0278-6915(97)80120-2

Rossi, F., Acampora, R., Vacca, C., Maione, S., Matera, M.G., Servodio, R. and Marmo, E., 1987. Prenatal and postnatal antimony exposure in rats: effect on vasomotor reactivity development of pups. Teratogenesis, carcinogenesis and mutagenesis, 7(5), pp.491-496. https://doi.org/10.1002/tcm.1770070507

Schroeder, H.A., Mitchener, M. and Nason, A.P., 1970. Zirconium, niobium, antimony, vanadium and lead in rats: life term studies. The Journal of nutrition, 100(1), pp.59-68. https://doi.org/10.1093/jn/100.1.59

Sunagawa, S., 1981. Experimental studies on antimony poisoning (author's transl). Igaku kenkyu. Acta Medica, 51(3), pp.129-142.