Annex A

In this guide

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

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 the NOAEL

			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.	
Species: Sprague-Dawley rats. **Route of exposure:** Oral-Drinking water.	**Initial Study Original Dose:** 0, 0.5, 5, 50, or 500 ppm antimony potassium		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 to liver enzyme activity all observed at the highest antimony dose (42,170/45,690 µg Sb/kg bw/day in males and females	**Poon et al. (1998) recommend** **NOAEL:** NOA is based on decreased in serum glucos levels in females at ≥640 µg Sb/ bw/day. However, the Committee determined t these effects showed limit dose-respons The Committ noted that ar

			Prenatal and Postnatal exposure: Decreased antihypotensive response to norepinephrine and hypotensive response to isoprenaline at both dose levels in 60-day old rats. The hypotensive response to acetylcholine was decreased at the highest dose of antimony trichloride in 60-day old rats. No change in antihypotensive or hypotensive responses was seen in 30-day old rats.		
Marmo et al. (1987)	**Species:** NOS Albino normotensive rats. **Route of exposure:** Oral-Drinking water. **Study duration:** Maternal exposure: - 1st day of pregnancy until weaning (22nd day after delivery) or from PND1 to PND 22. Pups: - From weaning until 30 or 60 days of age. **No/Sex:** 30	**Original Dose:** 1 and 10 mg/L antimony trichloride. **Recalculated Dose Levels:** 70 and 700 µg Sb/kg bw/day.	**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	70 µg Sb/kg bw/day. Pup LOAEL: 700 µg Sb/kg bw/day.	See Rossi et (1987)

Rossi et al. (1987)	**Species:** NOS Albino normotensive rats. **Route of exposure:** Oral-Drinking water. **Study duration:** Prenatal: 1st day of pregnancy until weaning (22nd day	**Original Dose**: 1 and 10 mg/L antimony trichloride. **Recalculated**	**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	Maternal NOAEL: 70 µg Sb/kg bw/day. Pup LOAEL: 700	NOAEL is bas on dose-dependent decrease in maternal boc weight by gestation da 20 following prenatal oral antimony exposure. Th COT noted th the baseline maternal boc weight in the study by Ros et al. (1987) gestation da was approximate 7% lower in treated grou compared to controls. Consequentl the observed 8–10% reduction in maternal boc weight at gestation da 20 used as th basis for the maternal NO was consider a relatively small change given the pre existing baseline differences. With the lowe maternal boc

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 Rat offspring: - 10 pups/ group, equal sex ratio.	**Original Dose:** 1 and 10 mg/L antimony trichloride. **Recalculated Dose Levels:** 70 and 700 µg Sb/kg bw/day	Postnatal exposure to antimony trichloride did not affect maternal or pup body weights or systolic arterial blood pressure. No macroscopic teratogenic effects have been observed. Antimony exposure did not significantly affect the length of gestation, and number of newborns per litter.	Maternal NOAEL: 70 µg Sb/kg bw/day. Pup LOAEL: 700 µg Sb/kg bw/day.	See Rossi et (1987)

Kanisawa and Schroeder (1969)	**Species:** Mice (White Swiss, Charles River CD-1). **Route of exposure:** Oral-Drinking water. **Study duration:** Lifetime exposure. **No/Sex:** Control mice – 71; Antimony treatment – 76.	**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 rais concerns regarding th reliability of t data and challenges interpreting t data. Furthermore the nature of this study do not allow for demonstratio of a dose-response, therefore the NOAEL was discounted.

			Negligible effects on growth and mature weight. Antimony was not tumorigenic.		
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.	Decrease in survival rate. Antimony, however, was innately toxic, males surviving 106 days and females 107 days less than the controls at median life spans, and 70 and 165 days less when 90% were dead; Hearts of males fed antimony weighed 18.9% less than their respective controls, whereas the hearts of females weighed 3.5% more. Decreased non-fasting serum glucose levels. Non fasting glucose levels were lower than fasting ones in the antimony group. Glycosuria was found in 23% of 90 controls, 43%	LOAEL: 430 µg Sb/kg bw/day.	The COT rais concerns regarding th reliability of t data and challenges interpreting t data. Furthermore the nature of this study do not allow for demonstratio of a dose-response, therefore the LOAEL was discounted.

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 wa given intraperitone therefore thi study was nc used for the determinatio of the appropriate NOAEL for or antimony consumption

			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.		
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.	Relative liver weight was increased in male and female rats from all dose groups (maximum increase of 20% for males and 40% for females at 9600 µg Sb/kg bw/day). Dose-related increases in serum alanine aminotransferase and sorbitol dehydrogenase were also observed in male and female rats. Hepatocellular degeneration and necrosis were observed in male rats and in female rats. Kidney	1,200 µg Sb/kg bw/day.	The dose wa given intraperitone therefore thi study was nc used for the determinatio of the appropriate NOAEL for or antimony consumption

Sunagawa (1981)	**Species:** Wistar rats. **Route of exposure:** Oral-Feeding. **Study duration:** 24 weeks. **No/Sex:** 5 per dose.	**Original Dose**: Metallic Antimony: 0, 0.5, 1.0, 2.0%. Antimony Trioxide: 0, 1.0, 2.0%. **Recalculated Dose Levels:** Metallic Antimony: 0, 500,000, 1,000,000, 2,000,000 µg Sb/kg bw/day. Antimony Trioxide: 0, 418,000, 836,000 µg Sb/kg bw/day.	Metallic antimony high dose: decreased body weight gain. Metallic antimony high dose: decreased hematocrit and hemoglobin. Antimony trioxide all dose: decreased erythrocyte levels. Metallic antimony mid and high dose: slight cloudy swelling in hepatic cords. Antimony trioxide all dose: slight cloudy swelling in hepatic cords.	LOAEL: 418,000 µg Sb/kg bw/day.	The LOAEL is higher than t NOAEL from Poon et al. (1998) that t COT determi was the appropriate point of departure to use as the ba of a HBGV fo antimony.

			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.		
Hiraoka (1986)	**Species:** Wistar rats. **Route of exposure:** Oral-Feeding. **Study duration:** 12 weeks. 12 weeks recovery. **No/Sex**: 12 males per group.	**Original Dose:** Metallic Antimony: 0.1% (w/w), 1.0% (w/w) o. Antimony Trioxide: 1.0% (w/w). **Recalculated Dose Levels:** Metallic Antimony: 85,000, 850,000 µg Sb/kg bw/day. Antimony Trioxide: 700,000 µg Sb/kg bw/day.	Recovery animal-increased in weight up to the normal level. Some significant changes of the organ weight and the ratio between organ weight and body weight of the rats, after the administration of Sb and Sb2O3; 1.0%-Sb: decreased haemtocrit. 0.1%-Sb: no changes in Hb, AST and albumin to globulin ratio. 0.1%-Sb: increased ALT. 1.0%-Sb: decreased total protein levels; High concentrations of antimony were found in liver,	700,000 µg Sb/kg bw/day.	The NOAEL is higher than t NOAEL from Poon et al. (1998) that t COT determi was the appropriate point of departure to use as the ba of a HBGV fo antimony.

			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).		
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.	The frequency of dilated ureter was increased in fetuses from the 150,000 and 300,000 µg Sb/kg/day dose groups. Skeletal variations were also seen in the mid- and high-dose groups (misaligned sternebrae, supernumerary ribs, misshapened basiooccipital bone). Transplacental transfer of antimony was confirmed by	75,000 µg Sb/kg/day.	The LOAEL is higher than t NOAEL from Poon et al. (1998) that t COT determi was the appropriate point of departure to use as the ba of a HBGV fo antimony.

Hext et al. (1999)	**Species:** Wistar rats. **Route of exposure:** Oral-Feeding. **Study duration:** 90 days. **No/Sex:** 12 Males per group.	**Original Dose:** 0, 1,000, 5,000, 20,000 ppm antimony trioxide. **Recalculated Dose Levels:** Males: 0, 70,000, 353,000, 1,408,000 µg Sb/kg bw/day. Females: 0,	Absolute and relative liver weights were increased by approximately 10% in female rats fed 20,000 ppm antimony trioxide; Elevated red cell count in high-dose male rats (+4%) and a decreased mean cell volume in high-dose female rats (-2%); Triglyceride content was increased (+30%) and alkaline phosphatase activity was decreased (-12%) in high-dose male rats. High-dose female rats exhibited an increase in plasma cholesterol (+13%), a decrease in alkaline phosphatase activity (-36%) and an increase in aspartate aminotransferase activity (+52%). Alkaline phosphatase	1,408,000 µg Sb/kg bw/day (male rats) and 1,570,000 µg Sb/kg bw/day (female rats).	The NOAELs higher than t NOAEL from Poon et al. (1998) that t COT determi was the appropriate point of departure to use as the ba of a HBGV fo

Coelho et al. (2014)	**Species:** Pregnant female Wistar rats. Route of exposure: Subcutaneous injection. **Study duration:** Gestation Day 0-PND 21. No/Sex: Control - 14; Treatment - 16 per dose.	Original Dose: 0, 75, 150, 300 mg SbV/kg bw/day of meglumine antimoniate. **Recalculated Dose Levels:** 0, 75,000, 150,000, 300,000 µg SbV/kg bw/day.	At the highest dose, MA reduced the birth weight and the number of viable newborns. In the male offspring, MA did not impair development (somatic, reflex maturation, weight gain, puberty onset, open field test), sperm count, or reproductive performance. Except for a minor effect on body weight gain and vertical exploration in the open field, MA also did not affect the development of female offspring. Measurements of the Sb levels in the blood of MA-treated female rats and their offspring demonstrated that Sb is transferred to the fetuses via the placenta and to the suckling pups via milk.	150,000 µg SbV/kg bw/day.	The dose wa given via subcutaneou injection therefore thi study was no used for the determinatio of the appropriate NOAEL for or antimony consumption

		Reduction (P0.05) in foetal birth weight and litter size was observed as compared to the control. High dose of SSG & MA: - Death of all animals before 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	
Species: Sprague	**Original Dose Levels:** 1. Sodium Stibogluconate (SSG): 30,000, 100,000,		The dose wa

Omura et al. (2002)	**Species:** Wistar rats, CD-1 mice. **Route of exposure:** Oral-gavage feeding. **Study duration:** 4 weeks. **No/Sex:** Rats: 7 to 8 per group. Mice: 8-10 per group.	Original dose: 1.Antimony Potassium Tartrate group: 27.4 mg/kg body weight. 2.Low-Antimony trioxide group: 12 mg/kg body weight 3.High-Antimony trioxide group: 1,200 mg/kg body weight. 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.	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 t NOAEL from Poon et al. (1998) that t COT determi was the appropriate point of departure to use as the ba of a HBGV fo antimony.

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 mg Sb/m^3 of antimony trioxide before conception and during gestation.	209,000 µg Sb/m^3.	The dose wa given via inhalation therefore thi study was nc used for the determinatio of the appropriate NOAEL for or antimony consumption

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 t NOAEL from Poon et al. (1998) that t COT determi was the appropriate point of departure to use as the ba of a HBGV fo antimony.