

Annex A

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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
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		<p>Dose-dependent decrease in serum glucose levels in females at $\geq 640 \mu\text{g Sb/kg bw/day}$.</p> <p>Decrease also noted in males but not statistically significant.</p> <p>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 $\mu\text{g Sb/kg bw/day}$ in males and females).</p>	
<p>Species: Sprague-Dawley rats.</p> <p>Route of exposure: Oral-Drinking water.</p>	<p>Initial Study Original Dose: 0, 0.5, 5, 50, or 500 ppm antimony potassium</p>		<p>Poon et al. (1998) recommended NOAEL: NOAEL is based on decreased in serum glucose levels in females at $\geq 640 \mu\text{g Sb/kg bw/day}$. However, the Committee determined that these effects showed limited dose-response. The Committee noted that an</p>

Marmo et al. (1987)	<p>Species: NOS Albino normotensive rats.</p> <p>Route of exposure: Oral-Drinking water.</p> <p>Study duration: Maternal exposure: - 1st day of pregnancy until weaning (22nd day after delivery) or from PND1 to PND 22.</p> <p>Pups: - From weaning until 30 or 60 days of age.</p> <p>No/Sex: 30</p>	<p>Original Dose: 1 and 10 mg/L antimony trichloride.</p> <p>Recalculated Dose Levels: 70 and 700 µg Sb/kg bw/day.</p>	<p>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.</p> <p>No change in antihypotensive or hypotensive responses was seen in 30-day old rats.</p> <p>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</p>	<p>70 µg Sb/kg bw/day.</p> <p>Pup LOAEL: 700 µg Sb/kg bw/day.</p> <p>See Rossi et al. (1987)</p>
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				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) gestation day 20 was approximately 7% lower in treated group 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. With the low maternal body
Rossi et al. (1987)	<p>Species: NOS Albino normotensive rats.</p> <p>Route of exposure: Oral-Drinking water.</p> <p>Study duration: Prenatal: 1st day of pregnancy until weaning (22nd day</p>	<p>Original Dose : 1 and 10 mg/L antimony trichloride.</p> <p>Recalculated</p>	<p>Both doses: Maternal body weight decreased significantly in a dose-dependent manner by the 20th day of gestation.</p> <p>High dose: Pups had decreased BW; No macroscopic teratogenic effects have</p>	<p>Maternal NOAEL: 70 µg Sb/kg bw/day.</p> <p>Pup LOAEL: 700</p>

Angrisani et al. (1987)	Species: NOS Albino normotensive rats.		Postnatal exposure to antimony trichloride did not affect maternal or pup body weights or systolic arterial blood pressure.	
	Route of exposure: Oral-Drinking water.	Original Dose: 1 and 10 mg/L antimony trichloride.	No macroscopic teratogenic effects have been observed.	Maternal NOAEL: 70 µg Sb/kg bw/day. See Rossi et al. (1987)
	Study duration: Postnatal: From PND1 to PND60. No/Sex: 30 per group Rat offspring: - 10 pups/ group, equal sex ratio.	Recalculated Dose Levels: 70 and 700 µg Sb/kg bw/day	Antimony exposure did not significantly affect the length of gestation, and number of newborns per litter.	Pup LOAEL: 700 µg Sb/kg bw/day.

Kanisawa and Schroeder (1969)	Species: Mice (White Swiss, Charles River CD-1).		Compared to control, significant differences in the incidences of spontaneous tumors and malignant tumors did not appear.	The COT raises concerns regarding the reliability of the data and challenges interpreting the data. Furthermore, the nature of this study does not allow for a demonstration of a dose-response, therefore the NOAEL was discounted.
	Route of exposure: Oral-Drinking water.	Original Dose : 5 ppm Antimony Potassium Tartrate.	Female mice had 350 µg Sb/kg shorter life spans bw/day. when given antimony than their controls.	
	Study duration: Lifetime exposure.	Recalculated Dose Level: 350 µg Sb/kg bw/day.		
	No/Sex: Control mice – 71; Antimony treatment – 76.			
			Fatty degeneration of liver noticed in both control (22.2%) and antimony fed groups (15.9 %).	

Schroeder et al. (1970)	<p>Species: Long Evan Rats.</p> <p>Route of exposure: Oral-Drinking water.</p> <p>Study duration: 2 years.</p> <p>No/Sex: Not reported.</p>	<p>Original Dose: 5 ppm - Antimony Potassium Tartrate (APT).</p> <p>Recalculated Dose Level: 430 µg Sb/kg bw/day.</p>	<p>Negligible effects on growth and mature weight. Antimony was not tumorigenic.</p>	<p>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.</p> <p>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%</p>	<p>LOAEL: 430 µg Sb/kg bw/day.</p>	<p>The COT raises concerns regarding the reliability of the data and challenges interpreting the data. Furthermore, the nature of this study does not allow for demonstration of a dose- response, therefore the LOAEL was discounted.</p>
			<p>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;</p>			

NTP (1992)	Species: B6C3F1 Mice	Original Dose: 0, 1.5, 3, 6, 12 and 24 mg/kg antimony potassium tartrate; 3 times per week.	High dose: Body weights were reduced by about 10% compared to controls (not statistically significant).	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.
	Route of exposure: Intraperitoneal injection.		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.		
	Study duration: 13 weeks.				
	No/Sex: 10 Males per group. 10 Females per group.	Recalculated Dose Levels: 0, 600, 1,200, 2,400, 4,800 and 9,600 µg Sb/kg bw/day.	In association with these changes was increased absolute and relative spleen weight.		

NTP (1992)			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	
	Species: F344/N rats.	Original Dose: 0, 1.5, 3, 6, 12 and 24 mg/kg antimony potassium tartrate; 3 times per week.	(maximum increase of 20% for males and 40% for females at 9600 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
	Route of exposure: Intraperitoneal injection.		1,200 µg Sb/kg bw/day.	
	Study duration: 13 weeks.			
	No/Sex: 10 Males per group. 10 Females per group.	Recalculated Dose Levels: 0, 600, 1,200, 2,400, 4,800 and 9,600 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	

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%. 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 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.

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

			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.	
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.	75,000 µg Sb/kg/day. Skeletal variations were also seen in the mid- and high-dose groups (misaligned sternebrae, supernumerary ribs, misshapened basiooccipital bone). Transplacental transfer of antimony was confirmed by fetal blood	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.

Hext et al. (1999)	<p>Absolute and relative liver weights were increased by approximately 10% in female rats fed 20,000 ppm antimony trioxide;</p> <p>Elevated red cell count in high-dose male rats (+4%) and a decreased mean cell volume in high-dose female rats (-2%);</p> <p>Triglyceride content was increased (+30%) and alkaline phosphatase activity was decreased (-12%) in high-dose male rats.</p> <p>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%).</p> <p>Alkaline phosphatase</p>		<p>The NOAELs 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</p>
	<p>Species: Wistar rats.</p> <p>Route of exposure: Oral-Feeding.</p> <p>Study duration: 90 days.</p> <p>No/Sex: 12 Males per group.</p>	<p>Original Dose: 0, 1,000, 5,000, 20,000 ppm antimony trioxide.</p> <p>Recalculated Dose Levels:</p> <p>Males: 0, 70,000, 353,000, 1,408,000 µg Sb/kg bw/day.</p> <p>Females: 0,</p>	

Coelho et al. (2014)	<p>At the highest dose, MA reduced the birth weight and the number of viable newborns.</p> <p>In the male offspring, MA did not impair development (somatic, reflex maturation, weight gain, puberty onset, open field test), sperm count, or reproductive performance.</p> <p>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.</p> <p>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.</p>		<p>The dose was given via subcutaneous injection therefore this study was not used for the determination of the appropriate NOAEL for oral antimony consumption.</p>
	<p>Species: Pregnant female Wistar rats.</p> <p>Route of exposure: Subcutaneous injection.</p> <p>Study duration: Gestation Day 0-PND 21.</p> <p>No/Sex: Control - 14; Treatment - 16 per dose.</p>	<p>Original Dose: 0, 75, 150, 300 mg SbV/kg bw/day of meglumine antimoniate.</p> <p>Recalculated Dose Levels: 0, 75,000, 150,000, 300,000 µg SbV/kg bw/day.</p>	

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

**Original Dose
Levels:**

1. Sodium
Stibogluconate
(SSG): 30,000,
100,000.

Species:
Sprague
Dawley

The dose wa
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Omura et al. (2002)		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.
	Species: Wistar rats, CD-1 mice.			
	Route of exposure: Oral-gavage feeding.	3.High- Antimony trioxide group: 1,200 mg/kg body weight.		
	Study duration: 4 weeks.	Recalculated dose levels:		
	No/Sex: Rats: 7 to 8 per group. Mice: 8-10 per group.	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.		

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.

Belyaeva (1967)			No changes in body weight gain were noted. Fetal body weights remained unchanged.	
	Species: Rats (not specified).	Original Dose: 0 and 209,000 $\mu\text{g Sb/m}^3$ antimony trioxide.	Unspecified lesions were reported in the lungs, liver, kidneys, and pancreas.	The dose was given via inhalation therefore this study was not used for the determination of the appropriate NOAEL for oral antimony consumption.
	Route of exposure: Inhalation.		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.	
	Study duration: 1.5-2 months, 4 hours/day.	Recalculated Dose Levels: 0 and 209,000 $\mu\text{g Sb/m}^3$.		
	No/Sex: 10-24/group.			

REACH registration dossier submitted to ECHA (2014)	Species: Sprague-Dawley rats.	Original Dose: 0, 100, 300 and 1000 mg/kg bw/day sodium hexahydroxo-antimonate.	Increased (non-significant) incidence in delayed skeletal development were observed in the mid and high dose groups.		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.
	Route of exposure: Oral-Drinking water.	Recalculated Dose Levels: 0, 49,000, 148,000, 493,000 µg Sb/kg bw/day.	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.	
	Study duration: Gestation days 6-19.				
	No/Sex: 2 females per dose.				