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

In this guide

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

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

2. In the study conducted by Sunagawa (1981), groups of 5 Wistar rats were exposed to 0, 0.5, 1.0 or 2.0% metallic antimony in the diet (estimated

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

3. In a 12-week study conducted by Hiraoka (1986), groups of male Wistar rats (no information on number of animals per group) were treated with diets containing either 0.1% (w/w) of metal antimony (0.1%-Sb group, equivalent to 85,000 µg Sb/kg bw/day), 1.0% (w/w) of metal antimony (1.0%-Sb group, equivalent to 850,000 µg Sb/kg bw/day) or 1.0% (w/w) of antimony trioxide (1.0%-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.

4. Miranda et al. (2006) evaluated the developmental toxicity and transplacental transfer of meglumine antimoniate (pentavalent compound) following subcutaneous injection in pregnant female Wistar rats (19-21/group). Antimony doses of 0, 75,000, 150,000 or 300,000 µg Sb/kg/day were administered on GD 1-20. Rats were sacrificed by CO_2 inhalation on GD21 and the number of implantation sites, live/dead foetuses, resorptions and corpora lutea were counted. Living foetuses were weighed, measured, examined for gross abnormalities and processed for evaluation of skeletal (staining with Alizarin Red) and visceral abnormalities (micro-sectioning after fixation in Bouin's solution). Maternal blood samples were collected each day from a separate group of rats given 300,000 µg Sb/kg/day. Foetal blood samples were obtained from the offspring of this group on GD21. Maternal and foetal body weights were reduced in the high-dose group (18% and 10%, respectively, at 300,000 µg Sb/kg/day). Embryolethality was also observed in this dose group (decreased number of live foetuses). The frequency of dilated ureter was increased in foetuses from the 150,000 and 300,000 µg Sb/kg/day dose groups. Skeletal variations were also seen in the mid- and high-dose groups (misaligned sternebrae, supernumerary ribs, misshapened basiooccipital bone). Transplacental transfer of antimony was confirmed by foetal blood analysis with foetal blood concentrations measured to be roughly one-third of the concentrations found in maternal blood.

5. A 90-day dietary study of antimony trioxide was conducted in male and female Wistar rats (Alpk:APSD strain) by Hext et al. (1999). Rats (12/sex/group) were fed diets containing 0, 1,000, 5,000 or 20,000 ppm antimony trioxide (99% purity) resulting in doses for the male rats of 0, 70,000, 353,000, 1,408,000 µg Sb/kg/day and for female rats of 0, 81,000, 413,000, 1,570,000 µg Sb/kg/day. Food consumption was measured continuously and calculated as a weekly mean. Body weights were measured weekly. Doses were calculated for each week, based on feed consumption and body weight. Cage-side observations were made daily and detailed clinical observations were made weekly. During the last week of the study, control and high-dose rats received an eye examination using an

indirect ophthalmoscope and a mydriatic substance to dilate the pupil. Urine samples were collected (16-hour collection) from rats housed in metabolic cages during the last week of the study. Urine volume was measured, and samples were analysed for appearance, specific gravity, pH, glucose, ketones, bilirubin, protein and blood. Urine was centrifuged and the sediment was stained and examined. Blood samples were obtained for haematology and clinical chemistry by cardiac puncture following sacrifice by halothane overdose. Adrenal glands, brain, kidneys, liver, epididymides and testes were removed, weighed and prepared for histopathological examination. All tissues from the control and high dose rats were examined, as well as any abnormal tissue from the intermediate dose groups.

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

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

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

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

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

10. In a study by Alkhawajah et al. (1996), the possible teratogenic potential of the pentavalent compounds (PVA), sodium stibogluconate (SSG) and meglumine antimoniate (MA) when they are used during pregnancy in rats were studied. Animals were divided into 10 treatment groups of 10 rats each. Rats in Group 1 were injected with saline (control). Groups 2-5 were injected with SSG i.m. for 10 successive days (days 6-15 of pregnancy) with doses of 30,000, 100,000, 300,000 and 900,000 µg Sb/kg. Groups 6-9 were injected with MA for the same period and at the same dose levels. Those in Group 10 were injected with 100,000 µg/kg of $SbCl_3$, using the same protocol. On day 20 of gestation foetuses were removed by C-section and examined for any teratogenic abnormality. Rats injected with SSG (30,000 µg Sb/kg) exhibited a 5.9% foetal resorption rate. This effect seems to be dose dependent as doses of 100,000 and 300,000 µg Sb/kg caused 14% and 21.4% foetal resorption, respectively. Injection of MA at the same dose levels of 30,000, 100,000 and 300,000 µg Sb/kg also caused dose dependent increase in foetal resorption of 1.2 %, 26.7% and 3396, respectively. Most resorptions with either SSG or MA appeared to occur in early

gestation. The mean weight of the viable foetuses from mothers treated with PVA'S was significantly lower than that of the control mice ($P<0.05$). Some skeletal and visceral deformities were also observed in many foetuses. Antimony trichloride also caused 36% foetal resorption when it was injected at a dose of 100,000 µg/kg. It can be concluded that the teratogenic effects of PVA'S may be related to their antimony content.

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

12. In a study conducted by Belyaeva (1967), female rats were exposed to either 0 or 209 mg/m³ of antimony trioxide by inhalation for 4 hours per day over 1.5-2 months. After this period, they were mated, and exposure continued until 3-5 days before expected delivery. Pregnancy was achieved in 16 of 24 treated females and all 10 controls. No changes in body weight gain were noted. Foetal body weights remained unchanged. Unspecified lesions were reported in the lungs, liver, kidneys, and pancreas. Reproductive effects, including failure to conceive and uterine metaplasia, were observed. However, a decrease in fertility and reduced number of offspring was found in rats exposed to 209 mg Sb/m³ of antimony trioxide before conception and during gestation (Belyaeva, 1967). The original article was published in Russian language, which we were not able to retrieve. The summary of this study was taken from the Toxicological profile provided by ATSDR, 2019.

13. In a REACH registration dossier submitted to ECHA, pregnant female Sprague- Dawley rats received sodium hexahydroxoantimonate via gavage at the dose levels of 0, 49,000, 148,000, 493,000 µg Sb/kg bw per day between gestation day 6-19. Increased (non-significant) incidence in delayed skeletal

development were observed in the mid and high dose groups. Most values were only slightly above historical control data. When considering skeletal malformations overall, incidence was observed in 99.3% to 100% of foetuses and 100% of litters including controls. 49,000 µg Sb/kg bw per day was concluded as NOAEL from this study.