Summary of findings from toxicity studies

In this guide

11. At the COT meeting in October 2024, the Committee noted that the Rossi et al. (1987), had a lower point of departure than that identified by the COT from the Poon et al. (1998) paper. The COT therefore requested further information on this study and other reproductive/developmental toxicity studies to allow consideration of whether the POD should be based on the Poon et al. (1998) paper or another study.

12. This section summarises the available studies reporting a NOAEL lower than 6,000 µg Sb/kg bw/day identified by COT from the Poon et al. (1998) study. The summaries of Marmo et al. (1987), Rossi et al. (1987) and Angrisani et al. (1988), are based on the US EPA (2008) review as it was not possible to obtain the original papers. The other studies Kanisawa and Schroeder (1969), Schroder et al. (1970) and NTP (1992) were identified from the ATSDR (2019) and Health

Canada (2024) reviews.

Reproductive and developmental toxicity studies

13. Marmo et al. (1987) studied the effects of prenatal and/or postnatal exposure to antimony trichloride on vasomotor reactivity in the developing NOS albino rat. Briefly, pregnant rats (30/group) were exposed to 0, 1 or 10 mg/L antimony trichloride (equivalent to 0, 70 and 700 µg Sb/kg bw/day, respectively) in drinking water from the first day of pregnancy until weaning of the offspring (22 days old) or during the postnatal period only (birth to 22 days old). Pups were randomised within 12 hours of birth and distributed to lactating dams with a litter size culled to 10 (equal numbers of male and female pups, if possible). Rat offspring were exposed to antimony trichloride in their drinking water (0, 1 or 10 mg/L) from weaning until 30 or 60 days of age. Rat offspring (10/group, 30 or 60 days old) were anaesthetized, and the right femoral vein was cannulated for injection of drugs.

14. Arterial blood pressure was measured using a catheter connected to the right common carotid artery. This study measured systolic blood pressure and the response to either antihypotensive or hypotensive agents or conditions in 30 or 60-day old offspring. The antihypotensive response was evaluated using a 40-second occlusion of the left common carotid artery or intravenous (i.v.) injection of noradrenaline (0.1, 1, or 5 µg/kg for 5 seconds). The hypotensive response was measured after injection of isoprenaline (0.01, 0.1, or 1 µg/kg i.v. for 5 seconds) or acetylcholine (0.01, 0.1, or 1 µg/kg i.v. for 5 seconds).

15. Exposure to antimony trichloride (prenatal/postnatal or postnatal only) did not affect offspring arterial blood pressure, measured at 30 or 60 days after birth. Combined prenatal and postnatal exposure to antimony trichloride did not affect the antihypotensive response to carotid artery occlusion. Antimony trichloride decreased the antihypotensive response to noradrenaline and the 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, while the response of the low dose group was similar to controls. No change in antihypotensive or hypotensive responses was seen in 30-day old rats treated with antimony trichloride during the prenatal and postnatal exposure periods.

16. In rats exposed only during the lactation period (postnatal dosing in dams) and in the drinking water after weaning, 60-day old offspring from the high-dose group showed a decrease in antihypotensive responses to carotid artery occlusion and noradrenaline injection and a decrease in hypotensive response to isoprenaline and acetylcholine. A decreased hypotensive response to isoprenaline and acetylcholine was also seen in 30- day old offspring exposed to the highest dose of antimony trichloride. In the low- dose group (postnatal exposure), a decreased response to noradrenaline and isoprenaline was observed in 60-day old rats, while 30-day old rats were similar to controls. This study suggests that vasomotor reactivity was affected by both prenatal and postnatal exposure to antimony trichloride. However, blood pressure responses were only measured in 10 pups/dose group and the report did not indicate whether each pup came from a different litter within that dose group or whether some pups came from the same litter.

17. Rossi et al. (1987) reported additional findings (i.e., maternal blood pressure and maternal and pup body weights) for the combined prenatal and postnatal exposure to antimony trichloride. Pregnant female NOS albino rats (30 rats/group) received antimony trichloride in their drinking water (0, 1 or 10 mg/L) from gestational day 1 through weaning. Rat offspring (randomized, distributed to lactating dams and culled to 10/litter with equal sex ratio) were exposed prenatally and postnatally (through lactation until weaning and in their drinking water from 22 to 60 days old at concentrations of 0, 1 or 10 mg/L). Maternal body weights were recorded on days 10 and 20 of gestation and pup body weights were measured on postnatal days 5, 10, 22, 30, and 60. The length of gestation and the number of pups/litter was recorded.

18. No significant alterations in litter size or macroscopic effects were observed in the offspring of dams exposed to antimony trichloride during gestation and lactation. Maternal body weight was decreased by 8% (low-dose group) to 10% (high-dose group) on the 20th day of gestation as compared to controls (statistically significant at both doses). 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 8 to 10% deficit from controls seen on gestation day 20 represents a relatively small change from the 7% deficit at the start of gestation.

19. Pup body weights were similar to controls at birth and at 5 days of age but were decreased in the high-dose group from the 10th (24% decrease from controls) to the 60th (11% decrease from controls) day of age. Exposure to

antimony trichloride did not affect maternal or pup systolic arterial blood pressure. The results of the vasomotor reactivity studies in offspring were reported by Marmo et al. (1987) and are described above.

20. Angrisani et al. (1988) reported additional findings (i.e., maternal blood pressure and maternal and pup body weights) for postnatal (only) exposure to antimony trichloride (0, 1 or 10 mg/L) in pregnant female NOS albino rats (30 rats/group, exposed from delivery through weaning) and in rat offspring (randomized, distributed to lactating dams and culled to 10/litter with equal sex ratio) exposed postnatally (through lactation until weaning and in the drinking water from 22 to 60 days old at concentrations of 0, 1, or 10 mg/L).

21. Maternal body weights were recorded daily until 60 days after birth and pup body weights were measured daily between postnatal days 5 and 60. Postnatal exposure to antimony trichloride did not affect maternal or pup body weights or systolic arterial blood pressure. The results of the vasomotor reactivity studies in offspring were reported by Marmo et al. (1987).

22. In summary, exposure of dams and pups to antimony trichloride (prenatal and/or postnatal) did not change the systolic arterial blood pressure in dams during gestation or after birth, or in pups at 30 and 60 days of age (Marmo et al. 1987; Rossi et al. 1987; Angrisani et al. 1988). The vasomotor response to injection of antihypotensive or hypotensive agents was decreased at both concentrations in 60-day old rats exposed prenatally and/or postnatally; however, the clinical significance of the reported changes is unclear and was not discussed by the study authors (Marmo et al. 1987; Rossi et al. 1987; Angrisani et al. 1988). Combined prenatal and postnatal exposure to antimony trichloride produced a small decrease in maternal body weight during gestation (Rossi et al. 1987), while postnatal exposure during lactation did not affect maternal body weight (Angrisani et al. 1988).

23. Pup body weights were significantly lower than controls starting at 10 days of age (24% decrease) and continuing through 60 days of age (11% decrease) following combined prenatal and postnatal exposure to 10 mg/L antimony trichoride (Rossi et al. 1987) but were not decreased by postnatal exposure only (Angrisani et al. 1988). The relationship between decreased pup and dam body weights is unclear. Both maternal and pup body weights were decreased in rats treated pre- and postnatally, but not in rats treated only postnatally. This suggests that the effect in pups may be secondary to the effect in dams even though pup body weights did not differ from controls until 10 days after birth.

24. Maternal doses for the gestational exposure period can be calculated using the average maternal body weight during gestation (298 g; Rossi et al. 1987) and the drinking water ingestion rate, calculated using the allometric relationship between drinking water ingestion and body weight (0.041 L/day) (U.S. EPA, 1988). The gestational maternal doses were estimated to be 0, 140, or 1,400 µg/kg bw/day antimony trichloride, or 0, 70, or 700 µg Sb/kg bw/day. The maternal dose of 700 µg Sb/kg bw/day was considered the LOAEL for this study, based on decreased maternal and pup body weights. The low dose of 70 µg Sb/kg bw/day was considered a NOAEL due to the very slight effect on maternal body weight and absence of effect on pup body weight at this dose.

Other oral toxicity studies with a NOAEL or LOAEL below 6,000 µg Sb/kg bw/day

25. In a study conducted by Kanisawa and Schroeder (1969), White Swiss mice of the Charles River Strain (CD-1) were exposed to 5 ppm antimony as potassium tartrate (equivalent to 350 µg Sb/kg bw/day) in drinking water for life term. Compared to controls, no significant differences in the incidences of spontaneous tumours and malignant tumours were observed in the antimony treated group. Based on these observations, 350 µg Sb/kg bw per day was identified as the NOAEL in this study (ATSDR, 2019).

26. In a lifetime exposure study conducted by Schroeder et al. (1970) on Long-Evans rats, animals were administered antimony potassium tartrate in drinking water at a dose of 430 µg Sb/kg bw/day. The study found a significant reduction in survival rates, with reduced non-fasting serum glucose levels. A Low observed adverse effect level (LOAEL) of 430 µg Sb/kg bw/day was identified based on these effects (ATSDR, 2019).