

Lynch et al. (1999) interpretation

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Lynch et al. (1999) interpretation

26. Lynch et al. (1999) reviewed the Poon et al. (1998) study and provided an alternative interpretation of the observed toxicological effects. These authors 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.

27. Lynch et al. (1999) concluded that several of the findings in the Poon et al. (1998) study was likely to represent normal physiological variations or adaptive changes rather than adverse effects directly attributable to antimony exposure:

- i. **Haematology:** Decreased red blood cell count in high-dose males and the observation of hematuria in the bladders of three high-dose males at necropsy are considered of less certain relationship to treatment.
- ii. **Serum Biochemistry:** Several of the changes in the serum biochemistry parameters at the high dose, in particular the report of decreased non fasting glucose, serum cholesterol and alkaline phosphatase levels, are potentially due to the drastic decrease in water intake (about 35%) and moderate decrease in food intake (about 12%) noted in these animals. These changes are concluded to be of no biological or toxicological significance and, therefore, inappropriate on which to establish a NOAEL value.
- iii. **Liver Findings:** The observed increased severity and/or incidence of anisokaryosis and nuclear hyperchromicity in the liver, although present in the treated animals, are common features in young adult rats as the ploidy state of hepatocytes increases from exclusively mononuclear diploid at birth to 50 to 70% mononuclear tetraploid by adulthood. They argued that these changes were adaptive rather than adverse and therefore should not be used as the basis for establishing the NOAEL. The bridging fibrosis in the liver observed in the highest dose tested is considered of uncertain relationship to treatment considering very limited (one animal of each sex) incidence.
- iv. **Spleen Findings:** The sinus congestion represents a normal physiological function of the spleen and hyperplasia of the sinus is a common finding in female rats. Considering reduced severity of sinus congestion in male rats and its absence in female rats, lack of dose response (either incidence or severity) in the occurrence of sinus hyperplasia in female rats, no clear signs of toxicity to the hematopoietic system, the authors concluded that the observed histopathological findings in the spleens were of no clinical or toxicological significance.
- v. **Thyroid Findings:** The decreased thyroid follicular size and increased epithelial height in males, were of a subtle nature and were not dose related. Additionally, weights of thyroid were not available to support the histopathological findings. The authors suggested that histopathological changes represent normal physiological variation considering the highly dynamic nature of rat thyroids and not to be considered of toxicological significance.

28. Based on these considerations, 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, even though

these effects may be due to the nonpalatability of the drinking water. The observed effects at lower doses were considered by Lynch et al. (1999) to be either adaptive or non-toxicological in nature.