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Evaluation of the Potential Carcinogenicity of Lead and Lead Compounds:

Review Draft

In Support of Reportable Quantity Adjustments Pursuant to CERCLA Section 102

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NOTICE

This document is a preliminary draft. It has not been formally released by EPA and should not at this stage be construed to represent Agency policy. It is being circulated for comment on its technical accuracy and policy implications.

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the value placed on this study (which shows that lead induces tumors at multiple sites at doses lower than those reported in other studies) for evaluating the carcinogenicity of lead. The number of animals used in each exposure group is small; thus, meaningful results requires pooling data from the various groups.

1.2.1.1.4. American Petroleum Institute, 1971. Chronic toxicity studies were conducted for 22 months in rats. Male and female Charles River CD rats (50 per group per sex) were exposed to lead acetate in their diets at concentrations of 0, 10, 50, 100, or 1000 ppm. The rats were killed at the end of the exposure period.

Intranuclear inclusion bodies and cytomegaly were found in most animals. Atypical nodular or adenomatous renal epithelial hyperplasia was observed in one male receiving 50 ppm (number examined not reported), 4/14 males receiving 100 ppm, and 7/15 males and 3/15 females receiving 1000 ppm. According to the report, renal neoplasia of the cortical epithelium was observed, but incidence data were not presented.

1.2.1.1.5. Azar et al., 1973. Lead acetate was fed to rats (strain not specified) at concentrations of lead measured at 5 (basal diet), 18, 62, 141, 548, 1130, or 2102 ppm for 2 years. There were 100 rats of each sex in the control group and 50 rats of each sex in each exposure group receiving the four lowest doses. The two highest doses were started at a different time and consisted of 20 rats of each sex in the control and exposed groups. Body weights, food consumption, and lead content in the blood, urine, feces, and tissues were measured; clinical appearance and behavioral changes were observed. All animals were examined for gross and microscopic lesions.

No clinical toxicity or behavioral changes were observed in rats, even at the highest concentration of lead. Body weight gain was reported to be reduced in animals receiving the two highest concentrations. Mortality was increased in male rats receiving 548 or 2102 ppm, compared with their respective controls. An unexplained high mortality rate was observed in the second group of control rats; consequently, the mortality rate in males receiving 1130 ppm was not increased significantly. The mortality rate was not increased in any of the female groups. Kidney tumors, most of them adenomas arising from the tubular epithelium, were induced in male rats receiving the three highest doses and in female rats receiving the highest dose only. The tumor incidence was 10, 50, and 80 percent in males receiving 548, 1130, and 2102 ppm, respectively, and 35 percent in females receiving 2102 ppm. No tumors were observed in controls. The lead content in the kidney increased with dose up to 13.2 and 13.37 ug/g of tissue in rats fed 548 and 1130 ppm, respectively, with a slight decrease to 11.60 ug/g of tissue at 2102 ppm at the end of 24 months. Thus, the increase in the tumor incidence at the higher doses did not correlate with a similar increase in lead content in the kidney. However, other measurements, specifically, urine, liver, and bone lead content, continued to increase with dose. Lead content was highest in bone, which had levels more than 10 times that of other tissues, and its level increased throughout all dietary concentrations. The number of stippled red blood cells increased at the 18-ppm dose and the ALA-D was decreased at 62 ppm; the hemoglobin and hematocrit, however, were not depressed in the rats until they received a dose of 1130 ppm. At 1130 and 2120 ppm lead, 21-day-old weanling rats showed no tumors but did show histological changes in the kidney comparable to those seen in adult rats receiving 548 ppm or more lead in their diet.

There were several weaknesses in this study. The description of methodology was very scanty. Body weights and food consumption data were not presented. Only the terminal mortality rate was presented, and time to first tumor was not given; tumor incidence could not be related to numbers of animals at risk (number of survivors at latency). Furthermore, the data were not analyzed statistically. The report of the study comes from the proceedings of the International Symposium on the Environmental Health Effects of Lead convened in Amsterdam in October 1972. The proceedings were published 7 months later in May 1973. A telephone call to the Haskell Laboratory in Newark, Delaware, revealed that the raw data from the study could not be located and thus was not available for review. There is no evidence that this study has undergone a peer review in the conventional sense of being published in a peer-reviewed journal. The strengths of the study include the use of multiple dose levels, the 2-year duration of exposure, and the numbers of animals per dose at the lower dose levels.

1.2.1.1.6. Tanner and Lipsky, 1984. Male Fischer 344 rats were exposed to lead acetate in their diets at a concentration of 10,000 ppm for up to 52 weeks; controls were fed a basal diet without added lead acetate. Survivors were killed at 16, 24, 36, or 52 weeks from the start of exposure. Although 50 animals per group were exposed at the start of the study, as a result of scheduled deaths and early mortality, only 5 rats remained after 52 weeks. None of the controls developed tumors.

No tumors were found in animals (5 to 10 rats for each time period) killed at 16, 24, or 36 weeks. One exposed animal, of five surviving, developed an adenocarcinoma of the kidney at 52 weeks. Nonneoplastic renal lesions were also observed. Karyomegaly (enlarged nuclei) was the first morphologic change