Appendix F

National Toxicology Program, Memo by Study Director regarding the decision not to conduct chronic studies on acetone, June 8, 1989.

Carcinogenesis & Toxicologic Evaluation Branch
National Toxicology Program
NIEHS, RTP, NC

June 8, 1989
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Summary of Information on Acetone

Acetone was selected for toxicologic evaluation by the NTP as part of an interagency agreement between the NTP and the Agency for Toxic Substances and Disease Registry.

According to a review by the Mitre Co. of the National Priorities List of chemical waste sites, acetone is the 22nd most frequently found organic component of chemical waste sites. Because of its miscibility with water , it is easily carried into ground and surface waters and, ultimately, drinking water. Very limited information concerning the oral short-term toxicity of acetone is available. A study by Sollmann (1921), who exposed rats to 25,000 ppm acetone in drinking water, is inadequate because of the small number (three) of rats tested and the lack of concurrent controls. Furner et al. (1972) also exposed rats to 10,000 ppm acetone in drinking water. Their study, however, was limited by the short duration (5 days of exposure) and by the small number of relevant indices evaluated (body weight, liver weight, free fatty acids, and liver metabolism). In addition, the EPA in 1985 sponsored 13-week gavage toxicity studies of acetone in which Sprague Dawley rats were administered 0, 100, 500, or 2,500 mg/kg per day (Sonawane et al., 1986). The usefulness of the data from these studies, however, is limited because of the pharmacokinetic considerations of a bolus administration and the consequent need to more closely mimic human exposure. Dose selection for the short-term studies described in this report was based on a review of the results from the two drinking water studies mentioned herein and from other animal toxicity studies described in the literature.

14-Day Studies

All rats and mice receiving concentrations as high as 100,000 ppm acetone in drinking water lived to the end of the 14-day studies. The mean body weights of male rats receiving 50,000 or 100,000 ppm and female rats given 100,000 ppm were lower than those of controls. Body weights of all groups of mice were comparable. Kidney and liver weight to body weight ratios for exposed rats and mice were greater than those for controls. Histopathologic changes were not seen in these organs in rats or in the kidney in mice. Centrilobular hepatocellular hypertrophy was noted in male and female mice at 20,000 and 50,000 ppm acetone, respectively.

13-Week Studies

All rats lived to the end of the 13-week studies (drinking water concentrations as high as 50,000 ppm). The final mean body weights of rats at 50,000 ppm were 19% lower than that of controls for males and 7% lower for females. Water consumption by all rats that received 50,000 ppm acetone and females that received 20,000 ppm or more was notably lower than that by controls. Liver and kidney weight to body weight ratios were increased for male and female rats exposed at 20,000 ppm or greater. Caudal and right epididymal weights and sperm motility were decreased for male rats given 50,000 ppm, and the percentage of abnormal

sperm was increased. Leukocytosis and thrombocytopenia were observed at 20,000 ppm and above (males and females), and reticulocytopenia and erythrocytopenia were seen at 5,000 ppm and above (males). These changes, in addition to increase in erythrocyte size (MCV), are consistent with macrocytic anemia. Splenic pigmentation (hemosiderosis) noted in dosed male rats was apparently related to these changes. The increased incidence and severity of nephropathy observed in dosed male rats were considered the most prominent chemically related findings in this study.

All mice lived to the end of the 13-week studies (drinking water concentrations up to 20,000 ppm for males and up to 50,000 ppm for females). The final mean body weights of dosed and control mice were similar. Water consumption by female mice that received 50,000 ppm acetone was notably lower than that by controls. The absolute liver weight and the liver weight to body weight ratio were significantly increased for females exposed at 50,000 ppm, and the absolute spleen weight and the spleen weight to body weight ratio were significantly decreased. Results from the hematologic analyses did not show any biologically significant effects. Centrilobular hepatocellular hypertrophy of minimal severity was seen in 2/10 female mice exposed at 50,000 ppm. No compound-related lesions were found in male mice.

Summary

The results from these studies show that acetone is mildly toxic to rats and mice when administered in drinking water for 13 weeks. Minimal toxic doses were estimated to be 20,000 ppm acetone for male rats and male mice and 50,000 ppm acetone for female mice. No toxic effects were identified for female rats. The testis, kidney, and hematopoietic system were identified as target organs in male rats, and the liver was the target organ for male and female mice.

Recommendations

We do not recommend that chronic toxicity or carcinogenicity studies of acetone be conducted for the following reasons:

- the prechronic studies only demonstrated a very mild toxic response at very high doses in rodents
- the absence of any evidence supporting the carcinogenic potential of acetone

References

Furner, R.L., Neville, E.D., Talarico, K.S., and Feller, D.D. (1972). A common modality of action of simulated space stresses on the oxidative metabolism of ethylmorphine, aniline, and p-nitroanisole by male rat liver. Toxicol. Appl. Pharmacol. 21:569-581.

Sollmann, T. (1921). Studies of chronic intoxications on albino rats. II. Alcohols (ethyl, methyl, and "wood") and acetone. J. Pharmacol. Exp. Ther. 16:291-309.

Sonawane, B., de Rosa, C., Rubenstein, R., Mayhew, D., Becker, S.V., and Dietz, D. (1986). Estimation of reference dose (RfD) for oral exposure of acetone. 7th Annual Meeting, American College of Toxicology, November 16-19, 1986, p. 21 (Abstract).