IV.1.c. Although C8 is the major organofluorine compound found in humans, little information is available concerning human responses to C8 exposure. Therefore, a study was conducted among 115 workers exposed to C8 occupationally (serum fluorine levels varied between 0 and 26 ppm, with a mean of 3.3). In an examination of the cross-sectional associations between C8 and hepatic enzymes, lipoproteins, and cholesterol, there was no significant clinical hepatic toxicity of the C8 levels observed in this study (Gilliland and Mandel, 1996). Serum C8 levels were positively associated with estradiol and negatively associated with free testosterone and not associated with luteinizing hormone. The negative association between testosterone and C8 was stronger in older men. Thyroid stimulating hormone and C8 were positively associated. Prolactin and C8 were positively associated in moderate drinkers. The effect of adiposity on serum glutamyl oxaloacetic acid and glutamyl pyruvic transaminase decreased as C8 increased. The induction of gamma glutamyl transferase by alcohol was decreased as C8 increased. The effect of alcohol on HDL was reduced as C8 increased. A positive association

between hemoglobin, mean cellular volume, and leukocyte counts with C8 was observed. These results suggest that C8 affects male reproductive hormones and that the liver is not a significant site of toxicity in humans at the C8 levels observed in this study. However, C8 appears to modify hepatic and immune responses to xenobiotics (Gilliland and Mandel, 1993).

V. EPIDEMIOLOGY

V.1.a. A retrospective cohort mortality study was made of employees at a 3M plant where C8 and other fluorocompounds are manufactured. Records on 4218 employees were reviewed. Only those who worked for 6 months or more (3688 workers) were included in the mortality follow-up. Of the 180 known deaths, 177 death certificates were obtained. Overall the number of deaths was significantly less than expected. The observed-to-expected ratio for cancer deaths was 1.0 (Ubel, et al., 1980).

V.1.b. In a retrospective cohort mortality study, a relationship between mortality and employment at a plant where C8 and other fluorocompounds are manufactured were investigated (Gilliland and Mandel, 1993). The cohort consisted of 2788 male and 749 female workers employed between 1947 and 1983. The all-causes standardized mortality rate (SMR) was 0.75 for males and 0.77 for females. There was no significantly increased cause-specific SMR for men or women. The SMRs for prostate cancer were 2.03 in the exposed group and 0.58 in the not-exposed group. In the exposed group there were 4 observed and 2 expected deaths from prostate cancer. Among men, 10 years of employment in C8 production was associated with a significant 3-fold increase in prostate cancer mortality when compared to no employment in production. Given the small number of prostate cancer deaths and the natural history of the disease, the association between production work and prostate cancer must be viewed as hypothesis generating and not over interpreted. If the prostate cancer mortality excess is related to C8, the results of this study and other clinical studies suggest that C8 may increase prostate cancer mortality through endocrine alterations.

VI. DISCUSSION OF ENDPOINTS

VI.1. Discussion of Target Organs

The primary target organ for C8-induced toxicity is the liver in mice, rats, and dogs, regardless of route of exposure. The hepatotoxicity manifests as increased liver weights, hepatocellular hypertrophy, liver degeneration, increases in liver enzymes, necrosis of the liver, and induction of peroxisomes (rats and mice only). Many of these effects were demonstrated to be reversible when animals were provided with a recovery period. Evidence of hepatotoxicity was not evident in studies in monkeys or humans.

In contrast with the rodent, the target organs in the monkey were the