REVIEW OF LITERATURE CONCERNING THE POTENTIAL DEVELOPMENTAL TOXICITY OF VINYL CHLORIDE

Introduction

A number of experimental studies of the possible developmental toxicity of vinyl chloride (VC) were reported in the 1970's, after VC had been shown to be a human and animal hepatocarcinogen. The number of such studies available for review in the open literature is small, and some are of questionable quality. On balance, however, the literature suggests that *in utero* exposure to VC does not lead to developmental toxicity in experimental animals.

Summary of studies

The largest teratology study of VC exposure was performed in the Toxicology Research Laboratory of The Dow Chemical Company, under the sponsorship of the Manufacturing Chemists Association. The results were reported by John et al. in 1977. (1) In this experiment, bred female Sprague-Dawley rats and New Zealand rabbits were exposed to air concentrations of 0, 500, or 2500 parts per million (ppm) of VC for 7 hours per day during gestation. Bred female CF-1 mice were exposed to air concentrations of 0, 50, or 500 ppm of VC for 7 hours per day. Additional groups of all three species, along with corresponding levels of VC exposure, were given drinking water containing 15% ethanol (which was suspected at the time of being a potentiating agent for VC toxicity). The dams were examined for signs of maternal toxicity (decreased food consumption, decreased gestational weight gain, or change in absolute liver weight). Fetal offspring were examined for gross external, soft tissue, or skeletal anomalies.

Signs of maternal toxicity were observed in all three species at the high level of VC exposure. In the mice, maternal toxicity appeared at 500 ppm VC with and without concomitant ethanol exposure. Rats exposed to 2500 ppm with and without ethanol experienced increased liver weight. Rats and rabbits exposed to 2500 ppm plus ethanol experienced decreased gestational weight gain, while those exposed to 2500 ppm without ethanol did not. The only

rats exposed to VC during the 1st trimester were also administered subcutaneous injections of trypan blue, a known teratogenic agent.

Only one group of exposed dams, those exposed during the 3rd week of gestation, showed evidence of decreased weight gain. This group did not experience a change in absolute or relative liver weight, however, while the rats exposed during the 1st or 2nd week did show changes in liver weight. No maternal mortality was observed.

There was some increase in resorptions among the rats exposed during the 1st or 2nd week of pregnancy. A higher implantation and birth rate was suggested as an explanation for the increase seen in the group exposed during the 2nd week, but VC toxicity was considered a probable cause of increased resorption in the group exposed during the 1st week.

A small increase in the frequency of skeletal retardation was reported among the offspring exposed to VC alone during the 1st week of gestation and among the offspring of control and exposed dams also given trypan blue injections. The offspring observed to have skeletal retardation did not differ from control offspring in mean body weight. No gross or soft-tissue malformations were observed more frequently among the offspring of exposed dams.

The authors concluded that "VC exposure in itself has no teratogenic effect in CFY rats, but an embryotoxic effect of VC exposure during the early stages of pregnancy at high atmospheric concentrations should be taken into consideration." It should be noted that this study's observation of a possible early embryotoxic effect occurred in the absence of clear maternal toxicity. A strength of this study is that the animals were exposed for 24 hours per day. A potential weakness was that while the intent of the investigators may have been to study the effects of exposure over the entire period of gestation, the design employed did not expose any individual animals over the entire period. A substantial weakness of the report, on the other hand, is its lack of statistical analysis of the findings.

A study conducted by Mirkova et al. at the Institute of Hygiene and Occupational Diseases, Sofia, Bulgaria, was reported in 1978. (3) Pregnant

There was no evidence of effect on pre- or post-implantation embryonic mortality in either exposure group. There did appear to be increased frequency of hemorrhage in the microscopic examinations of the fetuses in both exposure groups compared to the controls, and of intumescence in the offspring in the higher exposure group.

Exposure was not observed to have any effect on lactation in the dams allowed to give birth, nor on survival of offspring from these dams. The live pups from both exposure groups were reported to show adverse behavioral and physiological effects, such as blood count changes, differences in selected organ weights, and urinary hippuric acid levels.

In this study, maternal exposure at the then-current allowable occupational level in the U.S.S.R. (about 14 ppm) was compared with exposure nearly 1 order of magnitude less (about 2 ppm). The authors concluded that significant embryotropic effects were observed at the allowable level and recommended that this level be re-evaluated. The strengths of this study were in the highly detailed examinations performed on both dams and pups. The study's significance is limited by the apparently subtle nature of the effects reported, the limited description of the experimental methods, and the cursory discussion of the clinical significance of the effects observed.

Conclusion

This brief review of the literature demonstrates that the database concerning developmental effects of *in utero* VC exposure is not large and is quite inconsistent in terms of the experimental methods used, air concentrations of VC, durations of exposure of animals to VC, and data quality. Nevertheless, the largest and best reported of these studies, conducted with three species of experimental animals and high air concentrations, supports a conclusion that inhalation exposure of VC does not produce significant embryotoxic or teratogenic effects at levels which do not also induce significant maternal toxicity.