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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

maternal effects observed in a lower-dose group were among the mice exposed to 50 ppm VC plus ethanol; these animals had decreased food consumption, gestational weight gain, and liver weight. No effects were seen among the mice exposed to 50 ppm VC without ethanol.

Exposure to VC alone did not appear to be embryotoxic in any of the three species. The frequency of resorptions in mice exposed to 500 ppm VC was significantly higher than among the control group (13% vs. 7%), but this control frequency was unexpectedly low for the laboratory. Some decrease in fetal body weight or crown-rump length was observed in rats exposed to 500 ppm, but not in the group exposed to 2500 ppm. No effects on resorption frequency or fetal size was observed in either group of exposed rabbits.

There was also no clear evidence of teratogenicity after exposure to VC alone in any of the three species at either high or low exposure concentration. No gross external or skeletal anomalies were observed among any of the three species tested. The only soft-tissue anomaly observed at greater frequency was dilated ureter among the rats exposed to 2500 ppm VC alone. The significance of this finding was regarded as uncertain, however, because the frequency of dilated ureter was significantly lower among rats exposed to 2500 ppm of VC plus ethanol.

The strength of this study lies in its conclusion that "exposure of pregnant mice, rats, or rabbits to vinyl chloride by inhalation at concentrations sufficiently high to cause maternal toxicity was not teratogenic in any of the three species." This result suggests that developmental toxicity, as defined in this study, is very unlikely to occur at exposure levels not leading to frank maternal toxicity. The study is limited by the absence of microscopic tissue examination of the offspring, which may have revealed more subtle effects of exposure is any had occurred.

A teratogenicity study in rats was conducted by the State Institute of Occupational Health, Budapest, Hungary, and reported by Ungvary et al. in 1978. (2) Bred female CFY rats were exposed for 24 hours per day to either 0 or 1500 ppm of VC in air, during the 1st, 2nd, or 3rd trimester of gestation. The

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 different from control offspring in mean body weight. No gross or soft-tissue malformations were observed more frequently among the offspring of exposed dams.

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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 exposures were administered throughout the period of gestation, rather than only part of it. A substantial weakness of the report, on the other hand, is its lack of statistical analysis of the findings.

Last 24 h/day for only 1st or 2nd trimester

A study conducted by Mirkova et al. at the Institute of Hygiene and Occupational Diseases, Sofia, Bulgaria, was reported in 1978. (3) Pregnant Wistar rats were exposed to approximately 2.4 ppm of VC for 24 hours per day throughout the period of gestation. Control "values" were referred to in the report of the study, but their source was not explicitly described.

Total embryonic mortality was stated to be twice as great in exposed animals as in the control values. The overall increase was attributed to an 8-fold increase in early post-implantation mortality. Overall reduced fetal weight was reported in the exposed group, but it was suggested that this was secondary to maternal liver damage. The data supporting this suggestion of maternal toxicity were not described.

Teratogenic effects, consisting of blood vessel damage manifesting as microscopic hemorrhages, encephalocele, hydrocephalus, and ossification defects, were reported among the exposed offspring. In addition, postnatal development was reported to be affected in second and third generation offspring; the effects reported were liver and nervous system dysfunction.

The value of this report is seriously limited by the inadequate description of the conditions of the experiment, the absence of clear maternal toxicity evaluation, and the lack of numerical or statistical data. Moreover, the results reported must be considered of questionable plausibility because of the extremely low VC air concentration to which the animals were exposed.

Finally, another teratogenicity study was reported by Salnikova & Kitovskaya of the Institute of Hygiene and Occupational Diseases, U.S.S.R. Academy of Medical Sciences, in 1980. (4) In the experiment, pregnant Wistar rats were exposed for 4 hours per day throughout the period of gestation to 0, 1.9, or 13.9 ppm of VC in air. Outcomes evaluated in the study were maternal toxicity, embryotoxicity, teratogenicity, and post-natal development.

The dams exposed to the higher VC level were reported to have significantly decreased erythrocyte counts and urinary hippuric acid levels than control dams. No effects were observed in the dams exposed to the lower level of VC. No other evidence of maternal toxicity was described in the report.

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

air concentrations
the levels and duration of
exposure of the animals to VC.

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 and the quality of the data. 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.

References

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