

A DOMINANT LETHAL STUDY IN MALE RATS AFTER REPEATED EXPOSURES TO VINYL CHLORIDE OR VINYLIDENE CHLORIDE

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Male CD rats were exposed 6 hr/day for 5 days/wk to 0, 50, 250, or 1,000 ppm of vinyl chloride or 55 ppm of vinylidene chloride. Starting on week 11 of exposure, these males were mated with untreated females. There was no evidence of either preimplantation loss or postimplantation loss in pregnant females that resulted from these matings. Consequently, it was concluded that these exposures did not produce germinal mutation, as manifested by a dominant lethal effect, in male rats.

INTRODUCTION

Vinyl chloride (VC) and vinylidene chloride (VDC) are structurally related monomers used in the synthesis of plastics. VC is carcinogenic in both humans (Creech and Johnson, 1974) and animals (Viola et al., 1971; Maltoni and Lefemine, 1975; Lee et al., 1977). In addition, both VC and VDC are mutagenic in a variety of microbial systems (Loprieno et al., 1976; Bartsch et al., 1975). Epidemiological studies suggest that VC produces germinal mutations, as manifested by increased fetal loss, in humans (Infante et al., 1976). However, there was no evidence of a dominant lethal mutation in male mice exposed to VC for 5 days and sequentially mated with untreated females (Anderson et al., 1976). The purpose of this study was to determine whether repeated exposures to VC or VDC, for 11 wk, produced germinal mutations of the dominant lethal type in male rats.

METHODS

CD rats (Charles River Breeding Laboratories, North Wilmington, Massachusetts) were used in this study. Adult males weighing 180-200 g were exposed 6 hr/day for 5 days/wk to 0, 50, 250, or 1,000 ppm of VC or 55 ppm of VDC (Lee et al., 1977). All rats were given free access to

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feed and water except during the daily exposure period, when feed was withheld.

Since potential effects of these compounds on specific stages of the spermatogenic cycle were not of immediate concern, we employed a modification of the dominant lethal study described by Green et al. (1977). During week 11 of exposure, each male was housed with two unexposed virgin females for at least seven successive evenings or until the male mated with two females. During the day, the males continued to be exposed to VC or VDC. The females were examined in the morning for evidence of mating as demonstrated by the presence of sperm in vaginal smears or the presence of a vaginal plug. On gestational day 13, females were sacrificed and the number of corpora lutea and implants (viable and dead) was determined.

RESULTS

Although VC exposure did not significantly reduce the ratio of fertile to exposed males, there was a reduced number of males, in the group exposed to 1,000 ppm of VC, that mated with two females (Table 1). In addition, there was a reduced ratio of pregnant to mated females in the

TABLE 1. Number and Classification of Rats in Study with Vinyl Chloride (VC) and Vinylidene Chloride (VDC)

Classification	No. of rats at chamber concentration (ppm)				
	VC				VDC
	0	50	250	1,000	55
Exposed male rats					
Tested	12	12	12	12	11
Mated with two females	12	10	11	8 ^a	9
Mated with one female	0	2	1	2	2
Mated with no females	0	0	0	2	0
Fertile ^b	12	11	10	10	10
Unexposed female rats					
Mated	24	22	23	18	20
Pregnant	24	20	16 ^a	14 ^a	13 ^a
With one dead implant	7	5	7	5	3
With two dead implants	3	2	0	1	1
With ≥ three dead implants	2	2	1	0	2

^aSignificantly different from control (Fisher's exact probability test, $p < 0.05$).

^bFathered at least one litter with one or more viable implants.

TABLE 2. Mating Results in Study with Vinyl Chloride (VC) and Vinylidene Chloride (VDC)

Measurement	Chamber concentration (ppm)				
	VC				VDC
	0	50	250	1,000	55
Corpora lutea per dam	15.8 ± 0.6 ^a	14.3 ± 0.8	15.2 ± 0.3	15.1 ± 0.6	15.1 ± 0.5
Implants per dam	13.7 ± 0.8	12.0 ± 0.9	13.4 ± 0.5	11.9 ± 0.9	14.2 ± 0.5
Implants per corpora lutea X 100	86 ± 3	83 ± 5	88 ± 4	81 ± 6	94 ± 2
(Viable/total implants) X 100	92 ± 2	92 ± 3	93 ± 3	95 ± 2	93 ± 3

^aMean ± SE calculated on a per dam basis for the number of pregnant rats indicated in Table 1.

groups mated with males exposed to 250 or 1,000 ppm of VC or 55 ppm of VDC. The mating period ranged from 7 days for the control group to 8-9 days for the treated groups.

Pregnancies that resulted from the mating of exposed males with unexposed females were normal in terms of the number of corpora lutea and implants (Table 2). In these females, there was no evidence of preimplantation loss, as measured by the ratio of implants to corpora lutea, or postimplantation loss, as measured by the ratio of viable implants to total implants.

DISCUSSION

The present study was incorporated into an ongoing carcinogenic study with VC and VDC to evaluate the potential of these compounds for producing dominant lethal effects. In the carcinogenic study, hemangiosarcoma of the liver and lung occurred in CD rats exposed for 9-12 months to 250 or 1,000 ppm of VC (Lee et al., 1977). In addition, there were no lesions in the testes or accessory organs indicative of a treatment-related effect on reproductive performance.

In the present study, neither preimplantation nor postimplantation losses were observed in pregnancies that resulted from the mating of VC- or VDC-exposed males (Table 2). However, the occurrence of a preimplantation loss was suggested by the increased number of nonpregnant females in the groups mated with males exposed to 250 or 1,000 ppm of VC or 55 ppm of VDC (Table 1). The relevance of this latter observation to the detection of a dominant lethal effect is questionable for two reasons. First, there was no indication of a preimplantation loss in pregnant rats. Second, a postimplantation loss is more indicative of dominant lethality than a preimplantation loss. Since neither preimplantation nor postimplantation losses were observed in pregnant rats, it was concluded that the VC and VDC exposures used in this study did not produce dominant lethal mutations in the germinal cells of male rats.

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