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Interim Results of Two-Year Toxicological Studies in Rats of Vinylidene Chloride Incorporated in the Drinking Water or Administered by Repeated Inhalation

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Male and female Sprague-Dawley rats were exposed to vinylidene chloride (VDC) orally or by inhalation in 2-year toxicological studies. Interim results are included in this report. VDC was given in the drinking water at mean ± S.D. concentrations of 0, 68 ± 13, 106 ± 22, and 220 ± 35 ppm which produced mean ± S.D. dosage levels of 0, 5.9 ± 0.6, 10.0 ± 1.2, and 19.3 ± 2.7 mg/kg for male rats and 0, 7.5 ± 0.4, 12.6 ± 1.1, and 25.6 ± 2.4 mg/kg for female rats. Forty-eight rats/sex/VDC level and 80 rats/sex in the control group were used in the 2-year study with an interim kill of an additional 10 rats/sex/level at 90 days. In the inhalation study, rats were exposed to 0, 10, or 40 ppm of VDC vapor 6 hr/day, 5 days/week for 5 weeks, after which the exposure levels were changed to 0, 25, and 75 ppm of VDC. Exposure continued for a total of 18 months and the rats held for observation an additional 6 months. Interim kills occurred at 1, 6 and 12 months. A separate 90-day study using 20 rats/sex/level was conducted at 0, 25, and 75 ppm of VDC vapor. There were 86 rats/sex/level in the 2-year portion of the study. The parameters monitored were: body weight, food and water consumption (drinking water study only), hematology, clinical chemistries, cytogenetics of bone marrow cells (inhalation study only), mortality, terminal organ weights, and gross and histopathology. Based on interim kills and gross pathologic observations, the main conclusions are: increased cytoplasmic vacuolation of hepatocytes was seen in the livers of rats given 200 ppm VDC in drinking water or 25 or 75 ppm VDC vapor by inhalation; based on gross tumor count, tumor incidence in VDC-exposed rats was not greater than controls.

Introduction

Vinylidene chloride (1,1-dichloroethylene, VDC, $H_2C{=}CCl_2$) is widely used in copolymerization with other monomers. The polymers containing VDC are used in many applications including several where contact with food occurs. Thus potential human exposure to VDC could occur by ingestion because of possible residues of unpolymerized VDC in food packaging materials and by inhalation of VDC vapor in air in the work atmosphere.

Currently available pertinent toxicological data on vinylidene chloride are limited. Irish (*1*) reported liver and kidney injury to animals exposed 8 hr/day, 5 days/week by inhalation for several months at concentrations of 100 and 50 ppm. Minimal injury was seen to these organs at 25 ppm. Prendergast, et al. (*2*) reported no mortality of animals exposed for 30 days, 8 hr/day, 5 days/week to 100 ppm of VDC vapor. Mortality was seen in monkeys and guinea pigs exposed 24 hr/day for 90 days to concentrations of 47 and 25 ppm and 47, 25 and 15 ppm of VDC vapor respectively. Liver injury was reported in dogs, monkeys and rats and kidney changes in rats continuously exposed for 90 days to 45 ppm. Gage (*3*) reported that 20 exposures of rats for 6 hr daily to 500 ppm vinylidene chloride produced nasal irritation, decreased body weight gain and liver cell degeneration. Siegel et al. (*4*) re-

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ported that the single-exposure LC_{50} for rats was 6350 ppm. No studies of chronic oral administration of VDC itself have been reported.

Because of the lack of toxicological information available on VDC, additional toxicological studies of VDC in animals were deemed necessary to elucidate more fully the action of VDC after chronic exposures. The studies discussed in this report are a part of the toxicologic investigations on VDC conducted in the Toxicology Research Laboratory of Dow Chemical, U.S.A. under the sponsorship of a number of VDC manufacturers and users through the Manufacturing Chemists Association.

Studies by two routes of exposure, ingestion via inclusion in drinking water and inhalation, were undertaken in rats. The objectives of the two studies were to evaluate toxicity (including carcinogenicity) of VDC by the oral and inhalation routes in rats. Interim results of these studies are reported here—interim in that not all histopathology had been completed at the time of the conference at which this information was presented. Complete results will be published at a later date.

Materials

The composition of typical samples used in the vinylidene chloride (VDC) two-year drinking water and inhalation studies are listed in Tables 1 and 2, respectively. The samples were analyzed by gas chromatography. Samples used for both studies were supplied by Dow Chemical, U.S.A. The samples for the two studies were essentially the same except the material used in the inhalation study had a higher level of the inhibitor, hydroquinone monomethyl ether. Since the method used to generate VDC vapor for the inhalation studies evaporated the sample completely, the maximum concentrations for the various impurities that could occur are shown in Table 2. These represent maximum values calculated from the highest level of impurity found in the liquid VDC samples. The concentrations of all of the structurally related impurities were low. It is unlikely that any of them contributed significantly to any toxicity seen in the studies.

Table 1. Typical sample composition for vinylidene chloride used in two-year drinking water study in rats.

Impurity	Concentration, ppm
Vinyl bromide	4
Vinyl chloride	3–50
Trans-1,2-dichloroethene	138–1700
Cis-1,2-dichloroethene	24–680
1,1,1-Trichloroethane	2–60
1,1,2-Trichoroethane	48
Hydroquinone monomethyl ether (inhibitor)	2

Methods

Animals

Animals used in both studies were Sprague-Dawley SPF (specific pathogen-free) derived rats purchased from Spartan Laboratories, Haslett, Michigan. The rats were 6-7 weeks old when purchased.

Design of Two-Year Drinking Water Study

This study consisted of three components: the two-year portion, with which this report is mainly concerned; a 90-day study in which the rats were treated simultaneously with those in the two-year study; and a three-generation reproduction study. In the latter portion, the parents for the F_0, or the primary generation, were taken from animals in the two-year study, used to produce the next generation and then returned to the two-year study. The F_0 parent rats were given drinking water containing VDC at all times. Results of the reproduction study are not included in this report. A total of 66 rats per sex per VDC dosage level and 98 rats per sex in the control group were used. There were 48 rats per sex in each of the three VDC dosage levels and 80 rats

Table 2. Typical sample composition of vinylidene chloride and calculated chamber concentrations of impurities in two-year inhalation study in rats.

Impurity	Concentration in liquid sample, ppm	Maximum concentration (calculated) in 75 ppm atmosphere, ppb
Vinyl chloride	2–6[a]	113
Vinyl bromide	0–14	1.1
Cis-1,2-dichloroethene	30–1600	126
Trans-1,2-dichloroethene	100–3000	237
1,1,1-Trichloroethane	0–8	0.5
1,1,2-Trichloroethane	0–0.9	0.05
Hydroquinone monomethyl ether (inhibitor)	130–400	121

[a]One sample contained 1300 ppm of vinyl chloride.

per sex in the control group for the two-year study. Ten rats per sex per dosage level (including the control group) were used in the 90-day study. Two rats per sex per group were sacrificed at 1, 3, 10, and 30 days of the study for determination of nonprotein sulfhydryl levels in liver and kidney.

The nominal concentrations of VDC in the drinking water (tap water was used) were 0, 60, 100, or 200 ppm (w/v). The actual mean ± SD VDC concentrations, determined by gas chromatographic analysis, were 0, 68 ± 13, 106 ± 22, and 220 ± 35 ppm. The mean ± SD daily dosage levels in mg/kg based on the amount of water consumed, were 0, 5.9 ± 0.6, 10.0 ± 1.2, and 19.3 ± 2.7 mg/kg for male rats and 0, 7.5 ± 0.4, 12.6 ± 1.1 and 25.6 ± 2.4 mg/kg for female rats. Drinking water containing VDC was the only source of water throughout the study.

The rats were observed at regular intervals for signs of toxicity. Ground commercial chow and water (containing the appropriate concentration of VDC) were freely available at all times. Food and water consumption were measured throughout the study. Body weights were recorded weekly at first and then monthly throughout the remainder of the study.

Hematologic and clinical chemical measurements and urinalyses were carried out at 30 and 90 days of the 90-day study and at months 6, 12, 18, and 24 of the two-year study. Determinations of nonprotein sulfhydryl levels in liver and kidney (*5*) were carried out on rats killed on days 1, 3, 10, 30, and 90 of the 90-day study and at the end of the two-year study. Hematologic measurements included total erythrocyte count, total and differential leukocyte count, packed cell volume and hemoglobin concentration. Urinalysis included determination of specific gravity, pH, glucose, ketones, bilirubin, occult blood, and protein. Clinical chemical measurements included determination of serum alkaline phosphatase (AP) activity, serum glutamic pyruvic transaminase (SGPT) activity, and levels of urea nitrogen in the blood (BUN).

All rats were subjected to a complete gross pathologic examination by a veterinary pathologist whether killed at a scheduled sacrifice, killed in a moribund state, or after having died spontaneously. Weights of brain, heart, liver, kidney, and testes of rats killed at times of scheduled sacrifice were recorded. Organs and tissues from all rats were preserved in formalin for histopathologic examination. Special attention was given to grossly observed tumors or tumorlike processes in rats in the two-year study, and all such lesions were included in the tissues saved for histopathologic evaluation.

Statistical evaluation of hematology, clinical chemistry, organ weight and body weight data were evaluated using an analysis of variance and Dunnett's test (*6*). When histopathology is complete, tumor incidence will be evaluated by the Fisher exact probability test (*7*). The level of significance chosen for all cases is $p < 0.05$.

Design of Two-Year Repeated Inhalation Study

In this study, 104 male and 104 female rats were used in each of three groups: the control group and two groups exposed to VDC vapor. Exposures were 6 hr/day, 5 days/week for 18 months. For the first 5 weeks of exposure, the exposure levels were 10 or 40 ppm (40 or 159 mg/m^3) of VDC. At the end of 4 weeks of exposure there was an interim kill of four animals per sex per level. As no effects were found at that interim kill, exposure levels were raised to 25 or 75 ppm (99 or 298 mg/m^3) at the end of 5 weeks, one week after the kill. At 6 months into the study, 1 month of exposure to 10 or 40 ppm and 5 months of exposure to 25 or 75 ppm of VDC, an additional five animals per sex per level were killed. After the 30-day sacrifice, four rats per sex per level had been added to the groups specifically for cytogenetic evaluation. At the end of six months of exposure of these animals to 25 or 75 ppm of VDC (seven months into the study), these rats were killed and bone marrow cells collected for cytogenetic evaluation. After 12 months of exposure five rats per sex per level were sacrificed. The group size per sex for the two year portion of the study, after subtracting for interim kills, was 86. Exposure was discontinued at 18 months, and all animals still alive were maintained until 24 months, at which time all rats remaining alive were killed.

An additional 20 rats per sex per level were exposed at 0, 25 or 75 ppm VDC in a separate 90-day study. In this study eight rats per sex per level were killed after 30 days and the remaining 12 per sex per level at 90 days.

Exposures were carried out in 3.7 m^3 stainless steel chambers under dynamic air flow conditions. Control rats were maintained under ambient conditions in an animal holding room. Commercial pelleted chow and water were freely available at all times except during exposure, when food and water were removed from all groups, including controls.

The VDC vapor concentration was generated by metering liquid VDC into a temperature controlled vaporization flask. The vapor was swept by air into the exposure chamber. Chamber concentrations of VDC were monitored by infrared spectrophotometry. The nominal and mean analytical concentrations are shown in Table 3. Also shown is the

percent of exposure days on which the analytical concentration was within 25% of nominal concentration. The range of analytically determined concentrations recorded is shown in the last line of Table 3, demonstrating that there was no overlap of concentrations between levels.

Gross and histopathologic evaluation of all animals and terminal organ weights at the interim and final sacrifices were carried out on rats in the inhalation study in the same manner as described for the drinking water study. Statistical evaluation of data was also the same as described for the drinking water study.

Table 3. Chamber concentrations of vinylidene chloride vapor in inhalation studies.

	First 35 days of 2-yr study		Balance of 2-yr study		90-day study	
Nominal concentration, ppm	10	40	25	75	25	75
Nominal concentration, mg/m^3	40	159	99	298	99	298
Mean analytical concentration ± S D , ppm	9.5±2.5	35.8±6.2	25.4±4.6	72.6±7.5	26.4±4.8	72.7±9.8
Exposure days within 25% of nominal concentration, %	68	86	81	96	82	98
Range of concentration, ppm	5.0–13.7	20.0–45.1	12.0–39.5	52.1–96.0		

The rats were observed frequently for signs of toxicity. Food and water consumption were not measured in the inhalation studies. Body weights were recorded weekly at first and then once per month.

Hematologic measurements including the same parameters as in the drinking water study, were made at the 30 and 90 day sacrifices of the 90-day study and at the 6, 12, and 24 month sacrifices of the two-year study. Clinical chemistry determinations of SGPT and AP activity and BUN levels were made at the time of each interim kill. Blood glucose levels were carried out at the 12 and 24 month kills only. Additional determinations of SGPT activity were made at 2 and 7 weeks of the two-year study.

Results and Discussion

Drinking Water Study

Mean body weights of rats included in the two year drinking water study of VDC are shown graphically in Figure 1. There were occasional statistically significant differences between one or more exposure groups and controls, but there were no consistent overall differences in mean body weight between VDC-exposed and control groups.

There were sporadic statistically significant differences between VDC-treated and control rats in food and water consumption and in clinical chemistry, hematology, and urinalysis determinations.

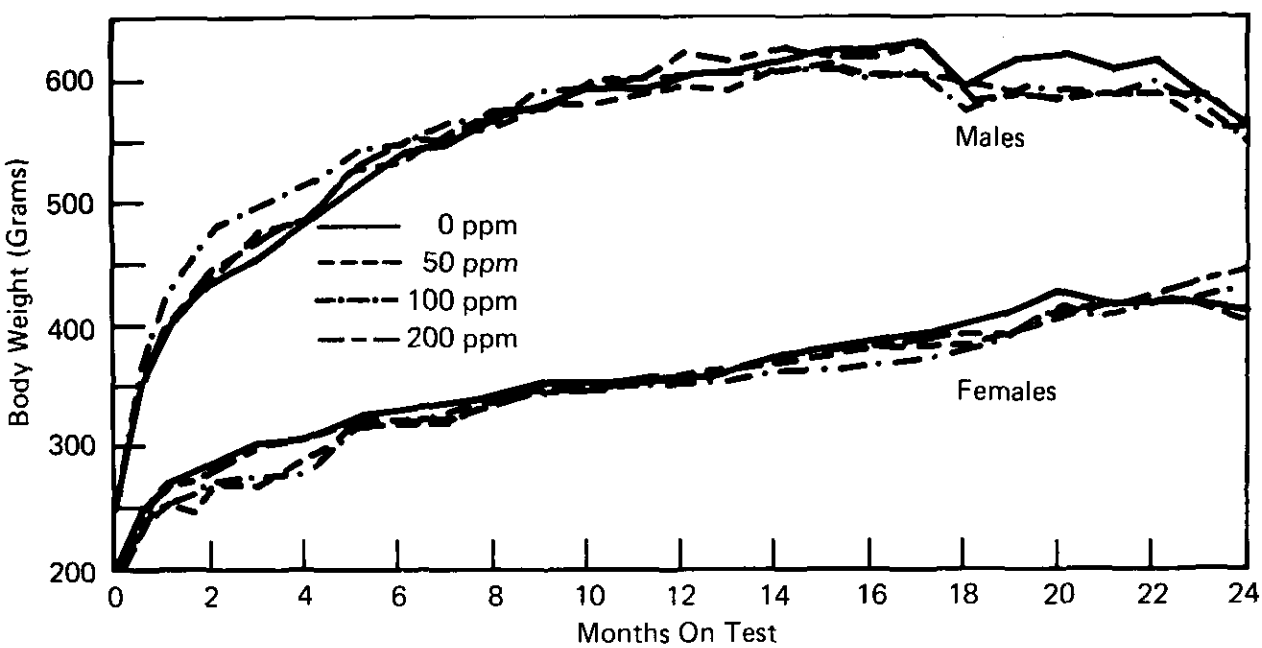

FIGURE 1. Mean body weight of male and female rats given vinylidene chloride in their drinking water for two years.

These differences did not occur in a dose-related fashion; they were not seen consistently from one determination to another and were not considered to be related to treatment with VDC. The determination of nonprotein sulfhydryl levels in liver and kidney showed no differences between VDC-treated and control rats.

Cumulative percent mortality for male rats in the two-year drinking water study is graphed in Figure 2. All three treatment groups exhibited slightly higher mortality than the control group. The differences between the treatment groups and the control values were not dose-related except that there were a few more deaths in the 200 ppm group early in the study.

For female rats (Fig. 3), the two lower level treatment groups had lower mortality than the control group. The 200 ppm VDC-treatment group had higher mortality than the control group during part of the second year of the study, but not at the termination of the study. Overall, the difference in mortality for male or female rats given VDC were too small to be of toxicological significance.

Except for a decreased kidney to body weight ratio in male rats at the lowest VDC level compared to controls at the 90-day sacrifice, there were no statistically significant differences in organ weights or organ to body weight ratios at either the 90-day or two-year sacrifice.

With respect to nontumor pathology, the only treatment related effect seen was increased cytoplasmic vacuolation of hepatocytes in both sexes of rats given 200 ppm of VDC in their drinking water. This was a minimal change which was judged to be reversible if the animals had been removed from treatment. The liver effect described was seen in rats sacrificed after 90 days of treatment. At the time of this interim report, histopathology had not been completed on animals which died spontaneously or were killed after two years of treatment to verify whether the liver effect continues to be seen at later stages of the study.

Data on tumor pathology are shown in Table 4. These data are based on gross pathologic observations only. As in other long-term studies in rats, many kinds of spontaneous tumors were seen in the control population. Rather than list all of these, the types of tumors most pertinent to a VDC study have been included. No tumor categories have been omitted for which incidence in the VDC-treated rats is significantly higher than in control rats.

Data for male rats are listed first in Table 4. The incidence of subcutaneous tumors in the mammary and midcervical region in the VDC-treated rats was slightly higher than in the control rats but was not outside the range which has been experienced with control rats of the same strain in other studies in our laboratory. Thus, the slightly higher incidence is

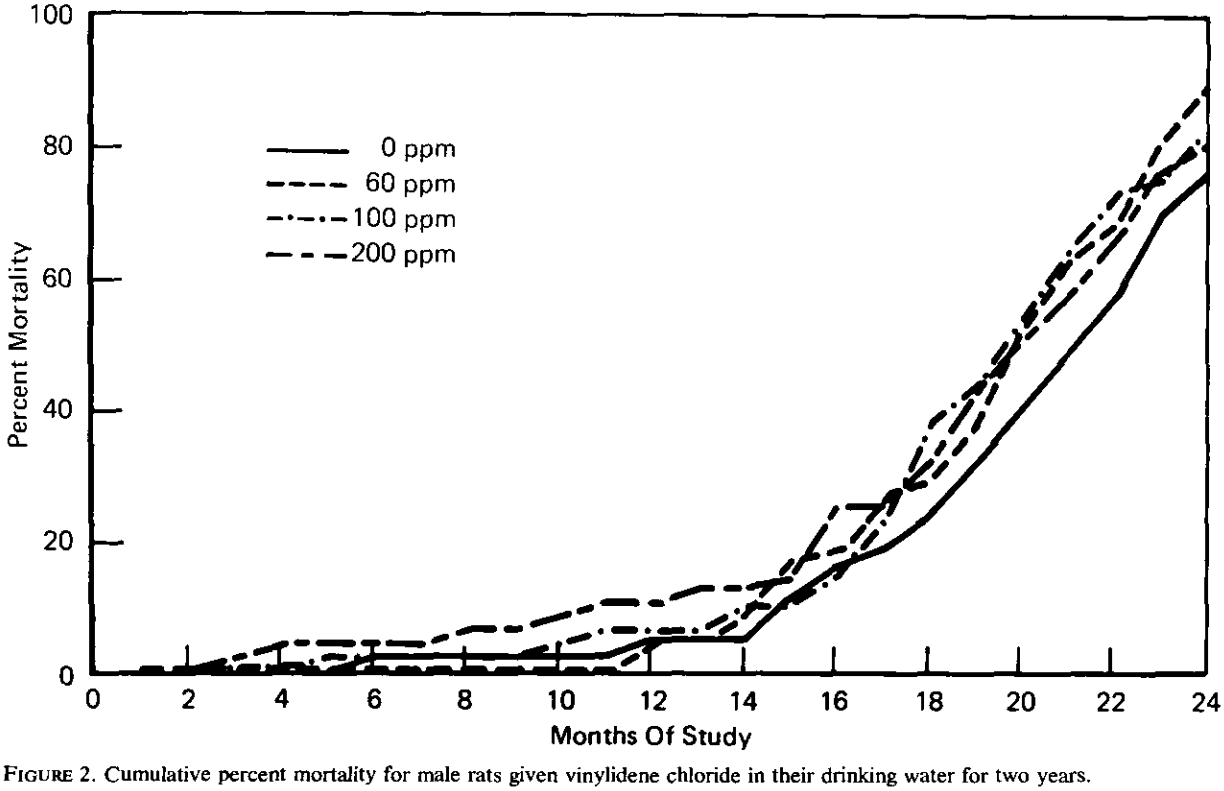

FIGURE 2. Cumulative percent mortality for male rats given vinylidene chloride in their drinking water for two years.

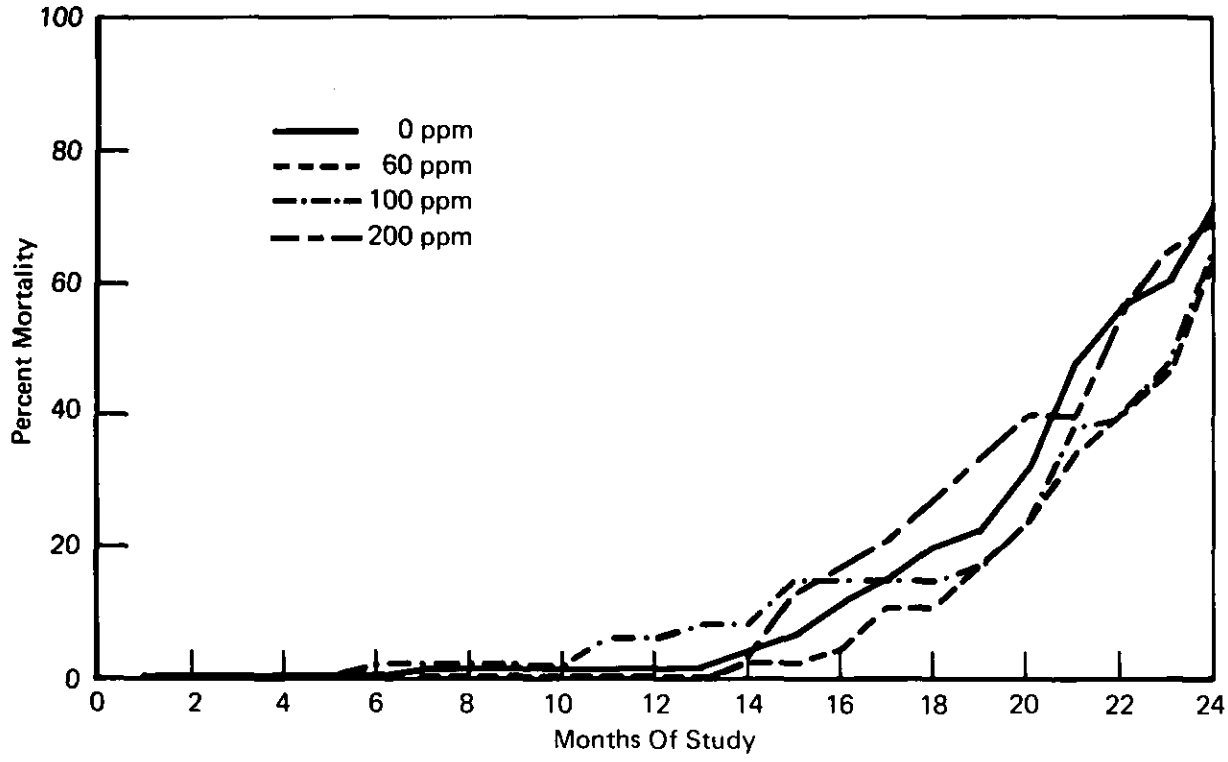

FIGURE 3. Cumulative percent mortality for female rats given vinylidene chloride in their drinking water for two years.

not indicative of a treatment related effect. Subcutaneous tumors in the eye, ear, and head region are the next category indicated. If tumors of Zymbal gland were grossly visible at necropsy, they would be recorded here. Tumors of the Zymbal gland in rats have been reported by Maltoni (*8*) to result from exposure to vinyl chloride. However, the incidence of subcutaneous tumors in this region as well as the body or limb region is clearly not significantly higher in VDC-treated rats than in the control group of the present study. Nodular proliferation in the liver as a primary site did not occur at higher incidence in VDC-treated rats than in control rats. The incidence of other types of tumors in the liver were also so low as to be of no toxicological concern. In the kidney, an organ which Maltoni had verbally reported to be affected in mice by VDC, a primary site tumor was seen in two control rats and only one VDC-treated rat, and that at the lowest dose level.

In female Sprague-Dawley rats, mammary tumors, classified here as tumors in the mammary and midcervical region, occurred spontaneously at very high incidence as illustrated by the incidence in the control group. In this case, the percentage incidence of mammary tumors was higher in VDC-treated rats than in control rats, but the incidence in control animals was so high that the slightly higher incidence in VDC-treated rats is not statistically or toxicologically significant. Subcutaneous tumors in the eye, ear, and head region, site of Zymbal gland tumors if they were to be found, occurred with similar incidence among the groups. A subcutaneous tumor in the body or limb region occurred in only one rat, not a meaningful incidence. Nodular proliferation in the liver as a primary site occurred in the high and low treatment groups at somewhat higher incidence than in the control group but not at high enough incidence to be of toxicological significance. The other types of liver tumors occurred only in the control rats. In the kidney, only two tumors were found as primary site tumors, one in a VDC-treated rat and one in a control rat.

Repeated Inhalation Study

No clinical signs of toxicity were seen at any time in rats in the inhalation study. Mean body weights of rats in the two-year repeated inhalation study are shown graphically in Figure 4. Male rats exposed to VDC vapor gained weight at a slightly lower rate than control rats during most of the study. The mean body weights for male rats were statistically significantly lower for both exposure groups only during the period of 8–12 or 13 months of the study. At other times the mean body weights of VDC-exposed male rats were not significantly lower than

Table 4. Grossly observed tumors in rats given vinylidene chloride in drinking water for two years.

Sex	Tumor	Dose, ppm	No. animals with tumor[a]	No. animals in group	Tumors, %
		Control	6/6	80	7.5
M	Subcutaneous tumor (mammary and mid-cervical region)	200	6/4	47[b]	8.5
		100	6/6	48	12.5
		60	6/6	48	12.5
M	Subcutaneous tumor (eye, ear, and head region)	Control	4	80	5.0
		200	2	47	4.3
		100	0	48	0
		60	1	48	2.1
M	Subcutaneous tumor (body or limb region)	Control	2	80	2.5
		200	0	47	0
		100	0	48	0
		60	2	48	4.2
M	Nodular proliferation in liver (primary site)	Control	5	80	6.3
		200	0	47	0
		100	1	48	2.1
		60	1	48	2.1
M	Liver (metastatic foci)	Control	0	80	0
		200	0	47	0
		100	0	48	0
		60	1	48	2.1
M	Liver (diffuse tumor infiltrate and enlarged, associated with lymphoid)	Control	0	80	0
		200	0	47	0
		100	1	48	2.1
		60	2	48	4.2
M	Kidney (primary site)	Control	2	80	2.5
		200	0	47	0
		100	0	48	0
		60	1	48	2.1
F	Subcutaneous tumor (mammary and mid-cervical region)	Control	104/59	80	73.7
		200	64/36	48	75.0
		100	68/27	48	77.1
		60	71/40	48	83.3
F	Subcutaneous tumor (eye, ear, and head region)	Control	1	80	1.3
		200	1	48	2.1
		100	2	48	4.2
		60	1	48	2.1
F	Subcutaneous tumor (body or limb region)	Control	0	80	0
		200	0	48	0
		100	1	48	2.1
		60	0	48	0
F	Nodular proliferation in liver (primary site)	Control	2	80	2.5
		200	3	48	6.3
		100	0	48	0
		60	2	48	4.2
F	Liver (metastatic foci)	Control	1	80	1.3
		200	0	48	0
		100	0	48	0
		60	0	48	0
F	Liver (diffuse tumor infiltrate and enlarged, associated with lymphoid)	Control	2	80	2.5
		200	0	48	0
		100	0	48	0
		60	0	48	0
F	Kidney (primary site)	Control	1	80	1.3
		200	0	48	0
		100	1	48	2.1
		60	0	48	0

[a]Where two numbers appear, data represent number of tumors over number of animals with tumors. Percentage is based on number of animals with tumors.
[b]One rat was unaccounted for in the 200 ppm group.

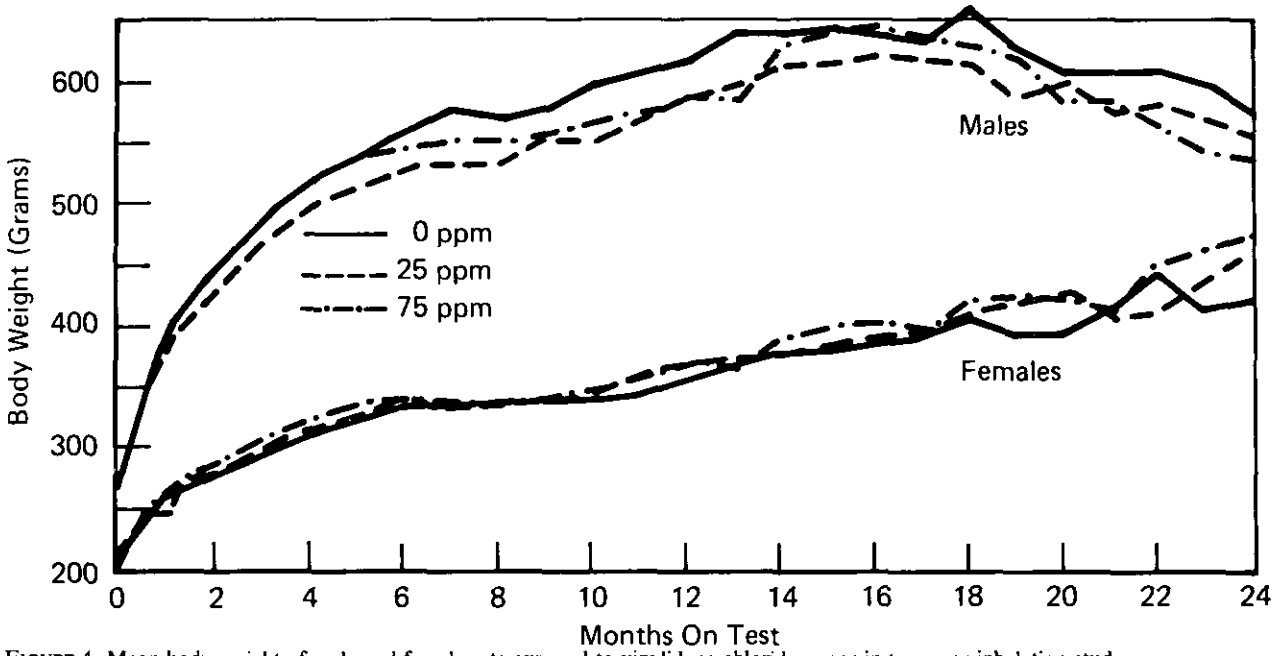

FIGURE 4. Mean body weight of male and female rats exposed to vinylidene chloride vapor in two-year inhalation study.

control rats. The mean body weights of VDC-exposed female rats were comparable to controls or slightly higher.

In the hematologic measurements, there were sporadic statistically significant differences between VDC-exposed and control rats but no effects were seen consistently enough to be deemed related to VDC exposure. There were sporadic differences in clinical chemistry values between VDC-exposed and control rats. None of these differences were seen consistently at the various kills. There were no signs of cytogenetic aberrations in the examination of bone marrow cells collected after 6 months.

Cumulative percent mortality for male rats is graphed in Figure 5. There was very little difference in mortality between the various groups, although

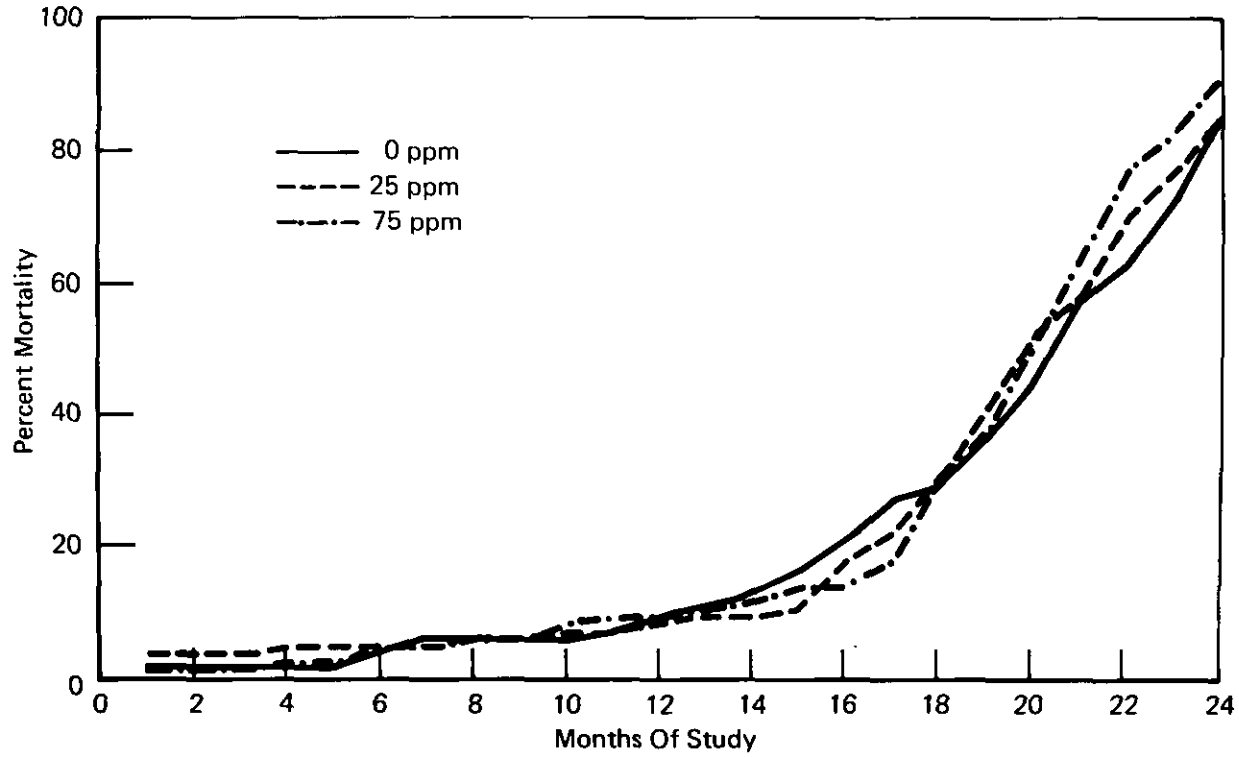

FIGURE 5. Cumulative percent mortality for male rats exposed to vinylidene chloride vapor in two-year inhalation study.

mortality was slightly higher in the 75 ppm group in the very last months of the study. For female rats (Fig. 6), there was slightly increased mortality at both exposure levels from the 12th month on. In both sexes, the mortality differences between groups were small.

In organ weights of animals sacrificed at the interim kills, there was a lower testes to body weight ratio in male rats exposed to 40 ppm VDC for 30 days than in control rats. There was no associated pathology in the testes of these animals and this effect was not seen at any of the other interim kills; therefore it is not attributable to treatment. Lower liver weights were seen in male rats from both VDC-exposed groups killed at one year of the long-term study. The lower liver weights were associated with lower body weights in these groups, and there was also a minimal pathologic change in the liver (see below). The same pathologic change in the liver was seen in females without decrease in liver weight. Higher kidney weights were seen in female rats exposed to both levels of VDC for one year. There was no associated pathology in this organ, however. There were no differences in organ weights between VDC-exposed and control rats at the kills at 30 and 90 days of the 90-day study or at 6 or 24 months of the long-term study. Thus, all the organ weight changes discussed for each organ were seen only at the one kill indicated and were not seen at the times of other interim kills.

In terms of nontumor pathology, the same liver effect was seen in the rats in the inhalation studies as was seen at the high level of the drinking water study. Increased cytoplasmic vacuolation of hepatocytes was seen at both the 25 and 75 ppm exposure levels after 30 days of exposure or longer. It was not seen in rats exposed to 10 or 40 ppm for 30 days, however.

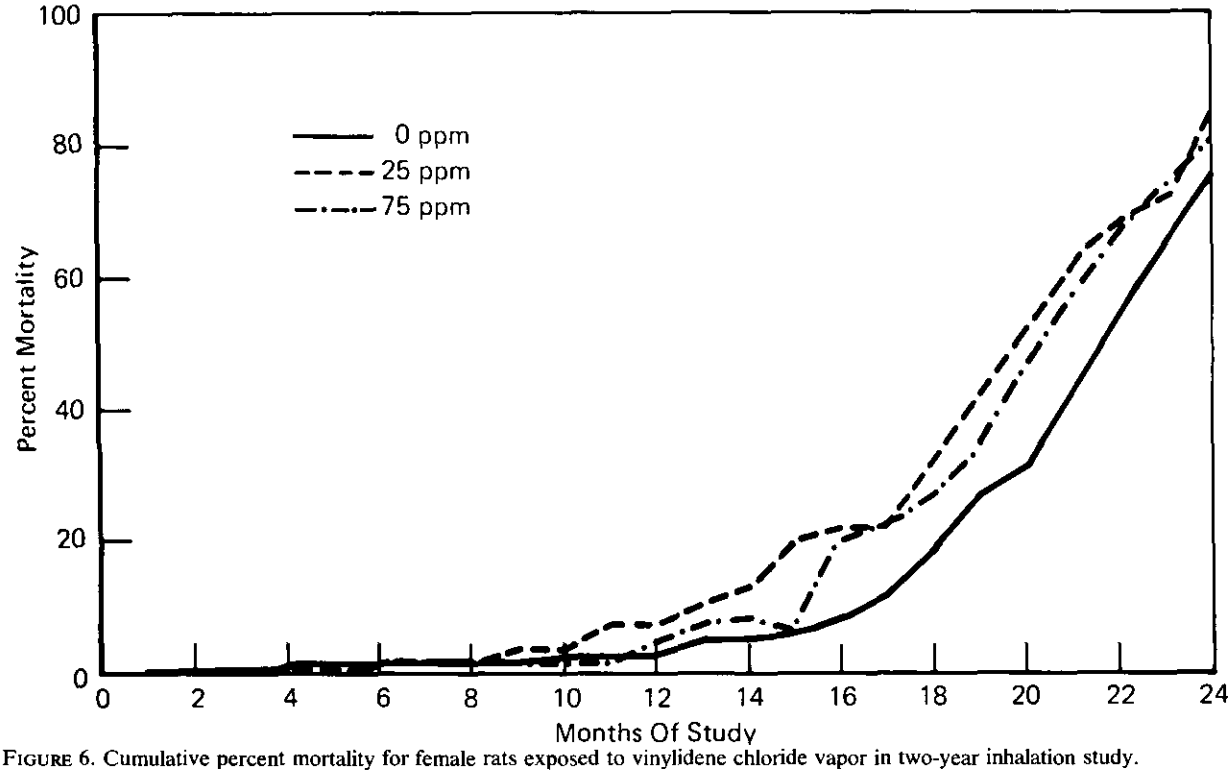

FIGURE 6. Cumulative percent mortality for female rats exposed to vinylidene chloride vapor in two-year inhalation study.

Tumor pathology data are listed in Table 5. Data are presented for the same types of tumors as for the drinking water study. These data are tabulated for the gross observations only. In males, the incidence of subcutaneous tumors of the mammary or midcervical region was similar in the three groups and well within the range of historical controls in our laboratory. The incidence of subcutaneous tumors of the eye, ear, or head region, the region where Zymbal gland tumors would be seen, was very similar among the groups. Subcutaneous tumors in the body or limb region occurred with a similar frequency, slightly higher in the treated animals but not enough to be suggestive of a treatment effect. There were nodules in the liver classified as a tumor or mass in one control rat and two rats at the 75 ppm level, not a significant difference in frequency. Primary tumors in the kidney of male

Table 5. Grossly observed tumors in rats exposed to vinylidene chloride vapor in two-year inhalation study.

Sex	Tumors	Exposure Level (ppm)	No. animals with tumor[a]	No. animals in group	Tumors, %
M	Subcutaneous tumor (mammary or midcervical region)	Control	8/6	86	7.0
		75	9/8	85[b]	9.4
		25	8/7	86	8.1
M	Subcutaneous tumor (eye, ear, or head region)	Control	2	86	2.3
		75	2	85	2.4
		25	5	86	5.8
M	Subcutaneous tumor (body or limb region)	Control	1	86	1.2
		75	4	85	4.7
		25	3	86	3.5
M	Liver nodule (tumor or mass)	Control	1	86	1.2
		75	2	85	2.4
		25	0	86	0
M	Kidney (primary site)	Control	3	86	3.5
		75	0	85	0
		25	0	86	0
F	Subcutaneous tumor (mammary or midcervical region)	Control	138/68	86	79.1
		75	159/74	84[c]	88.1
		25	149/73	88	82.9
F	Subcutaneous tumor (eye, ear, or head region)	Control	1	86	1.2
		75	1	84	1.2
		25	0	88	0
F	Subcutaneous tumor (body or limb region)	Control	2	86	2.3
		75	1	84	1.2
		25	2	88	2.3
F	Liver nodule (tumor or mass)	Control	2	86	2.3
		75	1	84	1.2
		25	0	88	0
F	Kidney (primary site)	Control	1	86	1.2
		75	1	84	1.2
		25	1	88	1.1

[a]Where two numbers appear, data represent number of tumors over number of animals with tumors. Percentage is based on number of animals with tumors.
[b]One male rat was unaccounted for in the 75 ppm exposure group.
[c]Two female rats from the 75 ppm exposure group were mistakenly caged with 25 ppm rats.

rats were seen in three controls but in none of the VDC-exposed animals.

In female rats, as seen in data from the drinking water study, the incidence of mammary tumors was very high. Although the incidence in the VDC-exposed rats was slightly higher than in control rats, it was not of significance in the face of the high background incidence. Only two subcutaneous tumors in the eye, ear or head region were seen, one in the control group and one in the 75 ppm exposure group. The number of subcutaneous tumors of the body or limb region in the various groups was quite comparable. Liver nodules classified as a tumor or mass were found in only two control rats and one rat at the 75 ppm level. In the kidney, there was one kidney tumor recognized grossly in each of the groups of the experiment.

Conclusions

The primary conclusions from the vinylidene chloride toxicity studies for which interim results are reported here are: (1) the exposure of rats to VDC in drinking water or by inhalation resulted in minimal liver changes at 200 ppm in the drinking water study and at both 75 and 25 ppm in the inhalation study; and (2) based on gross tumor count, these studies did not reveal increased numbers of tumors in rats exposed to VDC.

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