

0, 25, 75 ppm Sprague Dawley.
30 day interim kill

- no significant change in body weight,
males, 75 ppm, $\uparrow$ B.W of 4%
females, 75 ppm $\downarrow$ B.W of 7%
- $\downarrow$ SPT, males + females
not dose related - male
"does not appear to be related to VOC toxicity"
- no organ weight change
- Histopathology
minimal vacuolization in cytoplasm of
hepatocytes (0, 1, 2 ♀; 0, 1, 4 ♂)
"all liver changes reversible"

(25, 75 ppm in interim report of long term)

Final Report
Identical as spring issue
Added summary & conclusion

90-DAY REPEATED INHALATION TOXICITY STUDY OF
VINYLIDENE CHLORIDE IN RATS

M. F. Balmer, L. W. Rampy and J. F. Quast

Reviewed by:

J. M. Norris

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Toxicology Research Laboratory
Health and Environmental Research
Dow Chemical U.S.A.
1803 Building
Midland, Michigan 48640

SUMMARY AND CONCLUSIONS

Groups of male and female Sprague-Dawley rats have been repeatedly exposed to vinylidene chloride (VDC) vapors by inhalation 6 hrs/day, 5 days/week. Rats were exposed to 25 or 75 ppm VDC vapors 60 times during 90 days. There was an interim kill after 30 days of the study. Another, parallel, study was carried out in the same chambers. The second study was a two-year study.

No adverse effects were seen with respect to body weight, hematologic parameters, clinical chemistry values, demeanor or mortality in animals of either sex. Minimal microscopic changes in the liver in the form of cytoplasmic vacuolation of the hepatocytes occurred in occasional animals in both levels at the 30-day interim kill. The incidence of hepatic changes was greater in animals of the 75 ppm group which were examined at the end of the 90-day study. At this point in time, it is concluded that repeated exposure of rats to 25 or 75 ppm of VDC vapors results in minimal liver injury.

INTRODUCTION

The toxicity study of rats exposed by inhalation to vinylidene chloride (VDC) vapors, reported herein, is one of a series of studies being conducted in order to evaluate the toxicity and possible tumorigenesis of VDC. This study was financed by member companies of the Manufacturing Chemists Association and was conducted in the Toxicology Research Laboratory, Health and Environmental Research, The Dow Chemical Company.

METHODS

Test Material. Production grade vinylidene chloride from the Midland, Michigan plant of The Dow Chemical Company was used in this study. The inhibitor (hydroquinone monomethyl ether) level present was in the range of 130 to 240 ppm with single determinations of 558 and 1600 ppm for single containers from the last portions of two batches used.

Vapor Generation, Analysis, and Chambers. The VDC vapor was generated by metering the liquid compound into a glass vaporization flask at a controlled rate. The temperature of the flask was maintained at approximately 25°C. The vapor was swept by air into the exposure chamber at an air-flow rate calculated to produce the desired concentration.

Analysis of the chamber atmosphere was normally done 2 to 5 times during the exposure period by infrared spectroscopy. A Perkin-Elmer Model 12A I.R. spectrophotometer was used. A path length of 10 meters and a wavelength of 12.6 μ were used for the analysis. Chamber concentration was determined by interpolating from a standard curve. The standard curve was obtained by preparing known concentrations of VDC in air in the range of concentration. Exposures were carried out in a 3.7 cubic meter stainless steel chamber under dynamic airflow conditions. Control animals were maintained at ambient conditions in an animal holding room.

Animal Exposures. Groups of Sprague-Dawley (Spartan substrain) weanling rats, equally divided by sex, were exposed to 0, 25, or 75 ppm of VDC. Groups of 20 rats/sex were used in each exposure level. Eight rats/sex/exposure level were killed for examination on the 32nd day of the study. The remaining 12 rats/sex/exposure level were killed for examination on day 90 of the study. Male rats were in the body weight range of 275-310 g at the start of the study. Female rats weighed 190-210 g. The duration of exposure was 6 hrs/day 5 days/week. There were 21 exposures in 32 days for rats in the "30" day interim kill and 60 exposures in 90 days for rats in the "90" day group. Food and water were not available to exposed or control animals during the daily exposures. Between exposures food and water were available ad libitum.

Two parallel studies were conducted simultaneously in the same exposure chamber. The second study was a long-term inhalation study which continued after termination of the 90-day study.

Animal Observation. Rats were observed during the exposure period for changes in appearance or demeanor. Special attention was given to observing possible eye or nasal irritation. Body weights were recorded weekly for the first month, twice during the second month, and at termination.

Hematology. Hematologic parameters including red blood cell count, hemoglobin concentration, packed cell volume, and total and differential white blood cell count were determined on 5 rats/sex/level shortly before the 30 and 90-day sacrifices. Blood for the hematological determinations was taken from the tail vein.

Clinical Chemistry. Clinical chemistry determinations were carried out on serum samples collected from all animals at both the 30 and 90-day sacrifice. Determinations carried out included serum glutamic pyruvic transaminase (SGPT) activity, blood urea nitrogen (BUN) level, and alkaline phosphatase (AP) activity.

Pathology. At the time of sacrifice, each rat was anesthetized with methoxyflurane prior to clamping of the trachea and

decapitation. The lungs and trachea were removed as a unit and expanded with 10% buffered formalin. Animals were fasted overnight prior to sacrifice. The heart, liver, kidneys, brain, and testes (males) were removed and weighed. Representative specimens of the following organs and tissues were taken from all animals and fixed in 10% neutral buffered formalin: adrenal glands, all gross lesions, heart, aorta, bone marrow, brain, ear canal, esophagus, gonads (testes and ovaries), kidneys, large intestine, larynx, liver, lungs, lymph nodes (mediastinal and mesenteric), mammary tissue, pancreas, parathyroid gland, peripheral nerve (sciatic), pituitary gland, prostate, accessory sex glands, epididymides, salivary gland, seminal vesicles, skeletal muscle, skin, small intestine, spinal cord, sternum, spleen, stomach, thymus, thyroid gland, trachea, urinary bladder, uterus and nasal turbinate. Eyes were fixed in Zenker's fixative. The above tissues were processed by conventional methods, stained with hematoxylin and eosin, and evaluated by light microscopy.

Statistical Evaluation. Body weight, clinical chemistry, hematology, and organ weight data have been analyzed using an analysis of variance with comparison of group means by Dunnett's test.

RESULTS AND DISCUSSION

Analysis. Each batch of production grade vinylidene chloride used in the study was checked by gas chromatography to establish identity and levels of impurities. The impurities and ranges of concentrations found are in Table 1. Also in Table 1 are the calculated concentration of impurities that would be found in a 75 ppm atmosphere of vinylidene chloride, assuming total vaporization of the sample.

The mean chamber concentrations, standard deviations and percent of exposures within 10% and 25% of nominal concentration are in Table 2. The mean exposure levels were 26.4 ppm and 72.7 ppm.

Animal Observation. No signs of eye or nasal irritation or other changes in appearance or demeanor were observed in any of the animals.

No significant differences in body weight have been seen between VDC exposed and control groups of either sex in the 90-day study (Figure 1).

Hematology. Mean hematologic values are recorded in Tables 3 and 4. Packed cell volume, red blood cell count, and hemoglobin concentration were statistically significantly lower at 30 days for male rats exposed to 25 ppm of VDC than for control rats.

None of these values remained low at the end of the study, nor were other differences seen. For female rats in the 90-day study, red and white blood cell counts and hemoglobin concentration were statistically significantly lower at 30 days exposure for the 25 ppm group than for controls. Of these values, only the hemoglobin concentration remained low at the end of the study. The mean white blood cell count for the 75 ppm group of females was lower than the control group at the end of the study.

Although statistically significant differences in hematological values appeared between groups, they did not appear consistently in the same exposure group at different times, nor were they dose-related. The mean values are within the range of values normally seen in the Sprague-Dawley rats used in this laboratory. For these reasons it is concluded that exposure to VDC vapors has produced no toxicologically significant changes in hematological parameters.

Clinical Chemistry. Clinical chemistry values for rats exposed to VDC are presented in Tables 5 and 6. Male rats exposed to 25 ppm of VDC had a statistically significantly lower mean alkaline phosphatase activity at 90 days. Female rats at the same exposure level had a statistically significantly increased alkaline phosphatase activity. Since changes in this value were not seen at the higher exposure level and were different in the two sexes, they are not thought to be associated with organ damage.

SGPT activity was statistically significantly lower at 90 days for both VDC-exposed groups of males. This value was also low at 30 and 90 days for females exposed to 75 ppm of VDC. Since there was evidence of liver effects in these experiments (see below), elevated SGPT values would be expected instead of lower values. The significance of reduced SGPT activity, if any, is not known. It does not appear to be associated with toxicological effects in this experiment.

Mortality. No deaths occurred in animals in the 90-day exposure.

PATHOLOGY

Organ Weights. Mean organ weight and organ/body weight ratios are presented in Tables 7 and 8. No significant differences were found in these values at either the 30-day interim kill or the 90-day final kill.

90-Day Exposure - 30-Day Interim Kill. Gross pathologic findings in male and female rats killed at 30 days of the 90-day exposure are presented in Table 9. There were no gross pathologic changes present in either male or female rats considered treatment-related. Histopathologic findings in male and female rats are presented in Tables 10 and 11, respectively. Treatment-related histopathologic changes in the liver were found in both male and female exposed rats. The microscopic changes were characterized

by occasional individual hepatocytes having a vacuolated cytoplasm. This was very minimal in amount at both exposure levels. Histopathologic changes in the kidneys of female control and exposed rats show a very minimal degree of focal chronic progressive nephrosis. This is a spontaneously occurring lesion in these rats and is qualitatively identical in the control and exposed rats. All other pathologic observations were interpreted to be spontaneous in occurrence and comparable in the exposed and control rats. The pathologic changes observed in the livers of treated rats are interpreted to be of a reversible nature.

90-Day Exposure - Final Kill. Gross pathologic findings in male and female rats killed at the end of the 90-day exposure are presented in Table 12. There were no gross pathologic changes present in either male or female rats considered treatment-related. Histopathologic findings in male and female rats are presented in Tables 13 and 14, respectively. Treatment-related histopathologic changes in the liver were found in both male and female exposed rats. The microscopic liver changes are characterized by a minimal increased degree of vacuolation in the cytoplasm of the hepatocytes. These minimal changes were seen in rats at both exposure levels. Histopathologic changes in the kidneys of exposed or control rats do not show a qualitative or quantitative difference. The remaining microscopic alterations listed in the tables are considered spontaneous in occurrence and of comparable degree in control and exposed rats. The character

of the hepatic changes at this time are comparable to those observed after 30 days exposure; however, a greater number of exposed rats show a microscopic change after 90 days exposure.

Microscopic examination of the 1 mm sized circumscribed white foci in the epididymis of two rats in the top exposure group revealed the presence of an intratubular sperm granuloma. In view of the unilateral location and localized confinement in the epididymis it is not considered treatment-related. The pathologic changes observed in the livers of treated rats are interpreted to be of a reversible nature.

FIGURE 1

Mean Body Weights of Rats on 90 Day Exposure
to Vinylidene Chloride Vapors

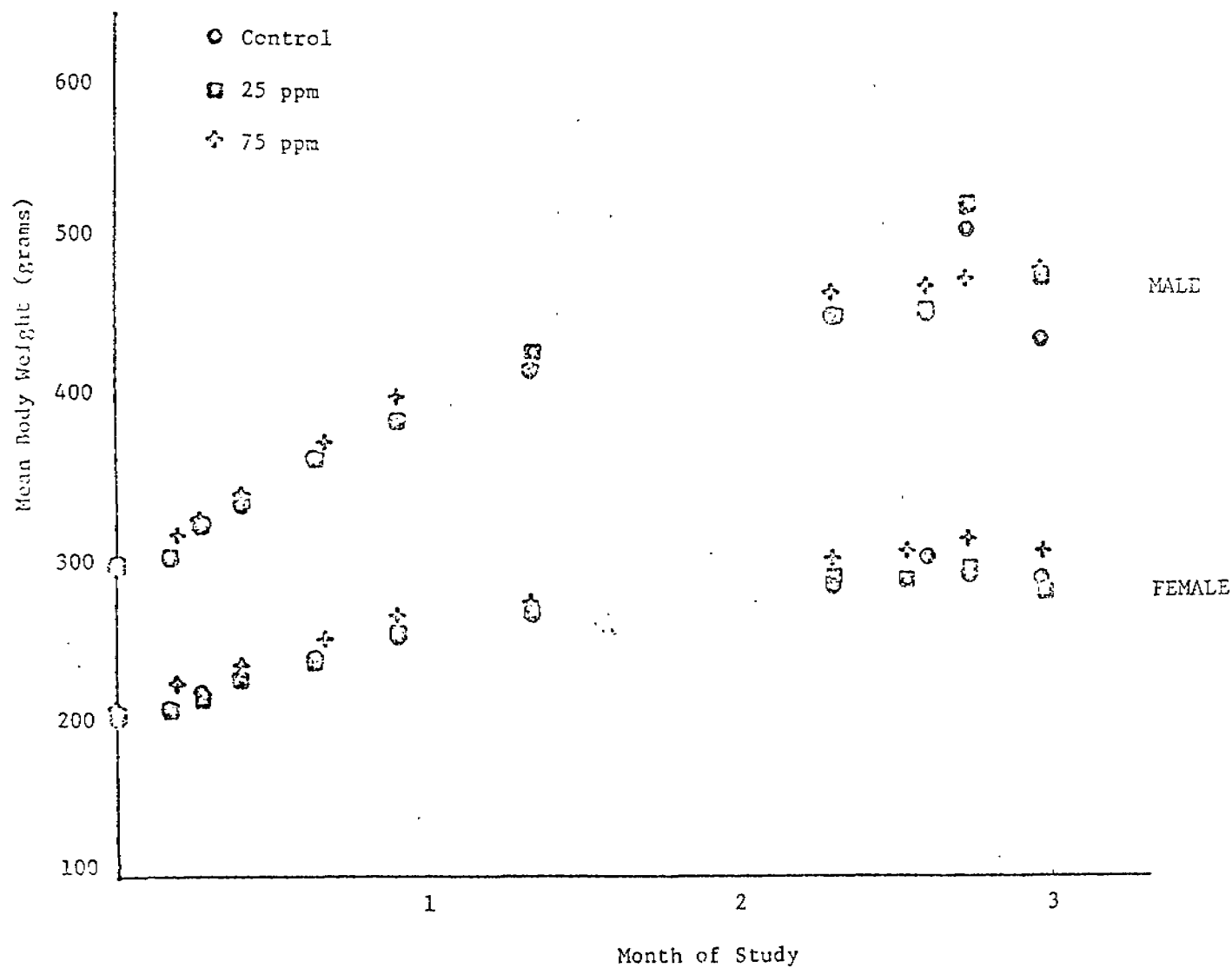


TABLE 1

Typical Analysis of Vinylidene Chloride and Calculated
Chamber Concentrations of Impurities

<u>Impurities</u>	<u>Analysis*</u>	Maximum Concentration (Calculated) in 75 ppm Atmosphere
Vinyl chloride	0-0.12%**	104 ppb
Vinyl bromide	0-14 ppm	1.1 ppb
cis 1,2-dichloroethylene	0.003-0.15%	126 ppb
trans 1,2-dichloroethylene	0.02-0.3%	237 ppb
1,1,1 trichloroethane	0-3 ppm	0.2 ppb
1,1,2 trichloroethane	0.0-9 ppm	0.05 ppb
<u>Inhibitors</u>		
Hydroquinone monomethyl ether	130-240 ppm***	119 ppb
<u>Vinylidene Chloride</u>		74.41 ppm

* Gas chromatographic analysis

** Analysis from 4 batches

1200 ppm, 50 ppm, 2 ppm, 3 ppm

*** There were single determinations of 558 and 1600 ppm for single containers from the last portions of two batches used.

TABLE 2

Chamber Concentrations of Vinylidene Chloride Vapor

Nominal Concentration (ppm)	25	75
Analytical Concentration ±S.D. (ppm)	26.4 ±4.8	72.7 ±9.8
% of Exposure Days Within 10% of Nominal Concentration	45	63
% of Exposure Days Within 25% of Nominal Concentration	82	98

TABLE 3

Mean ($\pm$ S.D.) Hematologic Values for Male Rats on 90 Day
Exposure to Vinylidene Chloride Vapors

Exposure Level (ppm)	Time	N	PCV %	RBC $\times 10^6/\text{mm}^3$	Hgb g/100ml	WBC $\times 10^3/\text{mm}^3$	Differential Count					
							Neut		Lym	Mon.	Eos.	Bas.
							Seg.	B/J				
0	30 days	5	58.6 $\pm$ 2.0	8.72 $\pm$ 0.71	18.4 $\pm$ 0.7	16.3 $\pm$ 1.8	10	0	88	1	1	0
25	30 days	5	52.4 $\pm$ 5.0*	7.54 $\pm$ 0.67*	17.3 $\pm$ 1.3*	18.9 $\pm$ 4.4	14	0	85	1	0	0
75	30 days	5	55.6 $\pm$ 2.9	8.45 $\pm$ 0.53	18.0 $\pm$ 0.7	17.9 $\pm$ 3.1	13	0	86	1	0	0
0	81 days	5	53.8 $\pm$ 1.6	7.69 $\pm$ 0.78	17.9 $\pm$ 1.0	13.9 $\pm$ 1.1	15	0	77	6	1	0
25	81 days	5	54.2 $\pm$ 3.8	7.45 $\pm$ 0.20	18.0 $\pm$ 0.9	11.9 $\pm$ 1.1	16	0	77	6	1	0
75	81 days	5	53.9 $\pm$ 1.3	7.39 $\pm$ 0.39	17.9 $\pm$ 0.6	14.6 $\pm$ 1.7	17	0	72	6	3	0

*Significantly lower than control group by Analysis of Variance and Dunnett's test ($p < 0.05$).

TABLE 4

Mean ($\pm$ S.D.) Hematologic Values for Female Rats on 90 Day
Exposure to Vinylidene Chloride Vapors

Exposure Level (ppm)	Time	N	PCV %	RBC $\times 10^6/\text{mm}^3$	Hgb g/100ml	WBC $\times 10^3/\text{mm}^3$	Differential Count					
							Neut		Lym	Mon.	Eos.	Bas.
							Seg.	B/J				
0	30 days	5	52.0 $\pm$ 3.6	8.21 $\pm$ 0.31	17.5 $\pm$ 0.8	15.2 $\pm$ 1.6	8	0	90	1	1	0
25	30 days	5	49.0 $\pm$ 1.8	7.07 $\pm$ 0.53*	15.9 $\pm$ 0.6*	12.1 $\pm$ 3.8*	14	0	84	0	2	0
75	30 days	5	49.8 $\pm$ 3.7	7.42 $\pm$ 0.85	16.5 $\pm$ 1.3	13.4 $\pm$ 2.9	11	0	87	1	1	0
0	81 days	5	46.8 $\pm$ 1.7	6.15 $\pm$ 0.44	16.4 $\pm$ 0.05	12.0 $\pm$ 2.3	12	0	81	5	2	0
25	81 days	5	44.5 $\pm$ 2.2	5.92 $\pm$ 0.30	15.2 $\pm$ 0.4*	10.9 $\pm$ 2.9	11	0	84	3	2	0
75	81 days	5	48.0 $\pm$ 3.1	6.13 $\pm$ 0.69	16.1 $\pm$ 0.9	8.0 $\pm$ 1.5*	11	0	84	4	1	0

*Significantly lower than control group by Analysis of Variance and Dunnett's test ($p < 0.05$).

TABLE 5

Mean ($\pm$ S.D.) Clinical Chemistry Values for Male Rats on
90 Day Exposure to Vinylidene Chloride Vapors

<u>Exposure Level (ppm)</u>	<u>Time</u>	<u>N</u>	<u>SGPT mU/ml</u>	<u>BUN mg/100ml</u>	<u>Alk. Phos. mU/ml</u>
0	30 days	8	33 $\pm$ 6	22.2 $\pm$ 4.3	232 $\pm$ 52
25	30 days	8	32 $\pm$ 3	25.4 $\pm$ 2.9	212 $\pm$ 39
75	30 days	8	34 $\pm$ 5	23.8 $\pm$ 4.6	199 $\pm$ 28
0	90 days	12	52 $\pm$ 7	19.7 $\pm$ 2.7	224 $\pm$ 79
25	90 days	12	38 $\pm$ 7*	21.8 $\pm$ 2.5	128 $\pm$ 27*
75	90 days	12	41 $\pm$ 9*	21.0 $\pm$ 3.2	179 $\pm$ 40

*Significantly different from control group by Analysis of
Variance and Dunnett's test, $p < 0.05$.

TABLE 6

Mean ($\pm$ S.D.) Clinical Chemistry Values for Female Rats on
90 Day Exposure to Vinylidene Chloride Vapors

<u>Exposure Level (ppm)</u>	<u>Time</u>	<u>N</u>	<u>SGPT mU/ml</u>	<u>BUN mg/100ml</u>	<u>Alk. Phos. mU/ml</u>
0	30 days	8	28 $\pm$ 5	26.2 $\pm$ 7.4	154 $\pm$ 28
25	30 days	8	25 $\pm$ 3	25.2 $\pm$ 3.8	162 $\pm$ 36
75	30 days	8	22 $\pm$ 4*	24.8 $\pm$ 7.2	145 $\pm$ 32
0	90 days	12	35 $\pm$ 6	21.5 $\pm$ 4.9	88 $\pm$ 11
25	90 days	12	31 $\pm$ 4	22.8 $\pm$ 3.4	109 $\pm$ 33*
75	90 days	12	30 $\pm$ 4*	24.0 $\pm$ 3.1	76 $\pm$ 15

*Significantly different from control group by Analysis of
Variance and Dunnett's test, $p < 0.05$.

TABLE 7

Mean ($\pm$ S.D.) Organ Weights and Organ to Body Weight Ratios for Male Rats on
90 Day Exposure to Vinylidene Chloride Vapors

Exposure Level (ppm)	Time	N	Body Weight (g)	Brain		Heart		Liver		Kidney		Testes	
				g	g/100g	g	g/100g	g	g/100g	g	g/100g	g	g/100g
0	30 days	8	383 $\pm$ 14.3	1.86 $\pm$ 0.04	0.49 $\pm$ 0.01	1.20 $\pm$ 0.08	0.32 $\pm$ 0.03	11.36 $\pm$ 0.98	2.97 $\pm$ 0.18	2.74 $\pm$ 0.16	0.72 $\pm$ 0.04	3.62 $\pm$ 0.27	0.93 $\pm$ 0.07
25	30 days	8	378 $\pm$ 19.5	1.85 $\pm$ 0.06	0.49 $\pm$ 0.02	1.17 $\pm$ 0.07	0.31 $\pm$ 0.01	11.20 $\pm$ 0.95	2.96 $\pm$ 0.17	2.78 $\pm$ 0.16	0.74 $\pm$ 0.03	3.86 $\pm$ 0.13	1.03 $\pm$ 0.07
75	30 days	8	390 $\pm$ 11.4	1.87 $\pm$ 0.05	0.48 $\pm$ 0.02	1.22 $\pm$ 0.08	0.31 $\pm$ 0.02	11.39 $\pm$ 0.97	2.93 $\pm$ 0.24	2.87 $\pm$ 0.25	0.74 $\pm$ 0.07	3.79 $\pm$ 0.24	0.97 $\pm$ 0.08
0	90 days	12	449.1 $\pm$ 48.7	1.84 $\pm$ 0.12	0.42 $\pm$ 0.06	1.25 $\pm$ 0.15	0.28 $\pm$ 0.02	13.40 $\pm$ 2.55	2.96 $\pm$ 0.35	2.85 $\pm$ 0.42	0.63 $\pm$ 0.05	3.80 $\pm$ 0.27	0.85 $\pm$ 0.10
25	90 days	12	468.7 $\pm$ 20.3	1.91 $\pm$ 0.06	0.41 $\pm$ 0.02	1.29 $\pm$ 0.05	0.27 $\pm$ 0.01	12.22 $\pm$ 1.02	2.61 $\pm$ 0.21	2.96 $\pm$ 0.10	0.63 $\pm$ 0.03	3.96 $\pm$ 0.18	0.85 $\pm$ 0.04
75	90 days	12	467.4 $\pm$ 27.0	1.91 $\pm$ 0.06	0.41 $\pm$ 0.02	1.35 $\pm$ 0.09	0.29 $\pm$ 0.02	12.79 $\pm$ 0.78	2.74 $\pm$ 0.14	3.00 $\pm$ 0.26	0.64 $\pm$ 0.03	3.86 $\pm$ 0.41	0.83 $\pm$ 0.10

No significant differences between exposed and control groups by Analysis of Variance and Dunnett's test, $p < 0.05$.

TABLE 8

Mean ($\pm$ S.D.) Organ Weights and Organ to Body Weight Ratios for Female Rats
on 90 Day Exposure to Vinylidene Chloride Vapors

Exposure Level (ppm)	Time	N	Body Weight (g)	Brain		Heart		Liver		Kidney	
				g	g/100g	g	g/100g	g	g/100g	g	g/100g
0	30 days	8	244 $\pm$ 11.3	1.70 $\pm$ 0.04	0.70 $\pm$ 0.04	0.86 $\pm$ 0.05	0.35 $\pm$ 0.02	6.95 $\pm$ 0.52	2.85 $\pm$ 0.18	1.71 $\pm$ 0.13	0.70 $\pm$ 0.05
25	30 days	8	246 $\pm$ 8.7	1.77 $\pm$ 0.72	0.72 $\pm$ 0.03	0.86 $\pm$ 0.04	0.35 $\pm$ 0.02	7.08 $\pm$ 0.48	2.88 $\pm$ 0.14	1.81 $\pm$ 0.12	0.73 $\pm$ 0.04
75	30 days	8	243 $\pm$ 10.0	1.71 $\pm$ 0.05	0.71 $\pm$ 0.03	0.89 $\pm$ 0.07	0.37 $\pm$ 0.03	7.02 $\pm$ 0.48	2.89 $\pm$ 0.12	1.76 $\pm$ 0.10	0.73 $\pm$ 0.03
0	90 days	12	281.7 $\pm$ 19.9	1.74 $\pm$ 0.08	0.62 $\pm$ 0.05	0.92 $\pm$ 0.03	0.33 $\pm$ 0.02	6.78 $\pm$ 0.70	2.41 $\pm$ 0.14	1.74 $\pm$ 0.15	0.62 $\pm$ 0.04
25	90 days	12	271.5 $\pm$ 27.2	1.78 $\pm$ 0.08	0.66 $\pm$ 0.07	0.91 $\pm$ 0.06	0.34 $\pm$ 0.03	6.58 $\pm$ 0.38	2.44 $\pm$ 0.24	1.80 $\pm$ 0.16	0.67 $\pm$ 0.07
75	90 days	12	262.4 $\pm$ 17.9	1.74 $\pm$ 0.10	0.67 $\pm$ 0.06	0.96 $\pm$ 0.07	0.37 $\pm$ 0.03	6.83 $\pm$ 0.67	2.61 $\pm$ 0.25	1.89 $\pm$ 0.13	0.72 $\pm$ 0.08

No significant differences between exposed and control groups by Analysis of Variance and Dunnett's test, $p < 0.05$

TABLE 9

GROSS PATHOLOGIC FINDINGS IN RATS ON 90 DAY EXPOSURE
TO VINYLIDENE CHLORIDE VAPORS - 30 DAY INTERIM KILL

<u>Pathologic Findings</u>	<u>Vapor Concentration (ppm)</u>		
	<u>0</u>	<u>25</u>	<u>75</u>
<u>Males</u>			
No visible lesions	3/8	1/8	3/8
Dilated renal pelvis, unilateral, right	0/8	1/8	0/8
Focal corneal cloudiness	0/8	1/8	1/8
Subpleural 1 to 2 mm sized pale gray foci in the lungs	5/8	5/8	4/8
Caudate lobe of the liver appears strangulated and pale colored	0/8	1/8	0/8
Intestinal nematodiasis	1/8	3/8	0/8
<u>Females</u>			
No visible lesions	3/8	2/8	6/8
Clear fluid in the uterine horns	3/8	0/8	0/8
Subpleural 1 to 2 mm sized pale gray foci in the lungs	4/8	6/8	2/8
Intestinal nematodiasis	1/8	0/8	0/8

Data listed as number of rats affected/number of rats examined.

TABLE 10

HISTOPATHOLOGIC FINDINGS IN MALE RATS ON 90 DAY EXPOSURE
VAPORS - 30 DAY INTERIM KILL

<u>Microscopic Examination</u>	<u>Vapor Concentration (ppm)</u>		
	<u>0</u>	<u>25*</u>	<u>75</u>
Focal chronic interstitial nephritis	1/8	1/8	2/8
Focal renal tubular collapse and atrophy	4/8	1/8	1/8
Focal granular casts within the renal tubules	6/8	2/8	3/8
Focal dilated renal tubules with eosinophilic staining casts	4/8	3/8	3/8
Focal chronic hepatitis	6/8	4/8	6/8
Minimal increase in cytoplasmic vacuolation of the hepatocytes	0/8	1/8	1/8
Focal subacute to chronic interstitial pneumonia	6/8	7/8	7/8
Chronic peribronchial lymphoid cellular infiltrate	8/8	8/8	8/8
Focal chronic tracheitis	3/8	0/0	4/8
Focal chronic interstitial prostatitis	6/8	0/0	3/8
Intestinal nematodiasis	2/8	0/0	2/8
Chronic focal myocarditis	0/8	0/0	2/8
Focal subacute pancreatitis	1/8	0/0	2/8

Data listed as number of rats affected/number of rats examined.

*Microscopic examination only of kidneys, liver, and lung in this group.

TABLE 11

HISTOPATHOLOGIC FINDINGS IN FEMALE RATS ON 90 DAY EXPOSURE
TO VINYLIDENE CHLORIDE VAPORS - 30 DAY INTERIM KILL

<u>Microscopic Examination</u>	<u>Vapor Concentration (ppm)</u>		
	<u>0</u>	<u>25*</u>	<u>75</u>
Focal renal tubular collapse and atrophy	2/8	2/8	4/8
Focal chronic interstitial nephritis	3/8	0/8	2/8
Focal granular casts within the renal tubules	5/8	5/8	5/8
Focal dilated renal tubules with eosinophilic staining casts	3/8	4/8	5/8
Focal chronic hepatitis	8/8	6/8	8/8
Minimal increase in cytoplasmic vacuolation of the hepatocytes	0/8	1/8	2/8
Focal subacute to chronic interstitial pneumonia	5/8	8/8	4/8
Focal peribronchial lymphoid cellular infiltrate	8/8	8/8	8/8
Focal chronic tracheitis	3/8	0/0	4/8
Intestinal nematodiasis	3/8	0/0	1/8
Focal subacute pancreatitis	1/8	0/0	1/8
Focal chronic myocarditis	1/8	0/0	1/8
Pituitary gland microcyst in the pars distalis	2/8	0/0	0/8

Data listed as number of rats affected/number of rats examined.

*Microscopic examination only of kidneys, liver, and lung in this group.

TABLE 12

GROSS PATHOLOGIC FINDINGS IN RATS ON 90 DAY EXPOSURE
TO VINYLIDENE CHLORIDE VAPORS - FINAL KILL

<u>Pathologic Findings</u>	<u>Vapor Concentration (ppm)</u>		
	<u>0</u>	<u>25</u>	<u>75</u>
<u>Males</u>			
No visible lesions	4/12	6/12	5/12
Carcass shows a decreased amount of adipose tissue in the abdominal cavity	1/12	0/12	0/12
Epididymis contains a 1 mm sized circumscribed white foci in the tunic, unilateral	0/12	0/12	2/12
Intestinal nematodiasis	8/12	6/12	6/12
<u>Females</u>			
No visible lesions	8/12	5/12	6/16
Clear fluid in the uterine horns	2/12	4/12	2/12
Intestinal nematodiasis	3/12	1/12	4/12
Focal pneumonia in the apical lobe of the lung	0/12	1/12	0/12
Strangulated piece of adipose tissue in the right mesovarium	0/12	1/12	0/12

Data listed as number of rats affected/number of rats examined.

TABLE 13

HISTOPATHOLOGIC FINDINGS IN MALE RATS ON 90 DAY EXPOSURE
TO VINYLIDENE CHLORIDE VAPORS - FINAL KILL

<u>Microscopic Examination</u>	<u>Vapor Concentration (ppm)</u>		
	<u>0</u>	<u>25</u>	<u>75</u>
Focal chronic interstitial nephritis	1/5	1/5	0/5
Focal renal tubular collapse and atrophy	5/5	3/5	4/5
Focal granular casts within the renal tubules	1/5	1/5	1/5
Focal dilated renal tubules with eosinophilic staining casts	4/5	4/5	5/5
Focal chronic hepatitis	5/5	5/5	4/5
Minimal increase in cytoplasmic vacuolation of the hepatocytes	0/5	1/5	2/5
Focal subacute to chronic interstitial pneumonia	3/5	2/5	2/5
Chronic peribronchial lymphoid cellular infiltrate	5/5	5/5	5/5
Focal chronic tracheitis	2/5	3/5	2/5
Focal chronic interstitial prostatitis	3/5	2/5	4/5
Intestinal nematodiasis	3/5	0/5	0/5
Chronic focal myocarditis	1/5	0/5	0/5

Data listed as number of rats affected/number of rats examined.

TABLE 14

HISTOPATHOLOGIC FINDINGS IN FEMALE RATS ON 90 DAY EXPOSURE
TO VINYLIDENE CHLORIDE VAPORS - FINAL KILL

<u>Microscopic Examination</u>	<u>Vapor Concentration (ppm)</u>		
	<u>0</u>	<u>25</u>	<u>75</u>
Focal renal tubular collapse and atrophy	4/5	1/5	3/5
Focal chronic interstitial nephritis	1/5	1/5	0/5
Focal granular casts within the renal tubules	0/5	1/5	0/5
Focal dilated renal tubules with eosinophilic staining casts	4/5	1/5	4/5
Focal chronic hepatitis	5/5	5/5	5/5
Minimal increase in cytoplasmic vacuolation of the hepatocytes	0/5	1/5	4/5
Focal subacute to chronic interstitial pneumonia	2/5	0/5	0/5
Focal peribronchial lymphoid cellular infiltrate	5/5	4/5	4/5
Focal chronic tracheitis	3/5	2/5	1/5
Intestinal nematodiasis	2/5	1/5	2/5
Chronic focal myocarditis	1/5	1/5	0/5

Data listed as number of rats affected/number of rats examined.

90 day, drinking water

Sprague-Dawley: Spartan Suckling

0, 60, 100, 200 ppm in H₂O

- no deaths
 - no significant clinical (coagulation) observation
 - no dose-related weight difference
 - no treatment related hematology difference
 - no difference in Urine samples (S.G., pH, sugar, protein, ketones, occult blood, bilirubin)
 - no organ weight difference
 - Histopathology
 - 1/5 male, 3/5 female at 200 ppm - cytoplasmic vacuolation of occasional individual hepatocytes - reversible
- Chronic: 50, 100, 200 ppm

Treatment related

- fatty changes / fatty degeneration in liver.

- only Treatment related

lesion

See point 2 in MTD article under

Histopathology