TOXICOLOGY, CARCINOGENICITY, AND REPRODUCTIVE EFFECTS OF SINGLE AND MULTIPLE EXPOSURES TO VINYL CHLORIDE IN RATS AND MICE

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Toxicology, Carcinogenicity and Reproductive Effects of Single and Multiple Exposures to Vinyl Chloride in Rats and Mice

I. INTRODUCTION.

The background information on vinyl chloride monomer (VCM) with technical details is reviewed in "Scientific and Technical Assessment Report on Vinyl Chloride and Polyvinyl Chloride", US Environmental Protection Agency, EPA-600/6-76-004, June 1975.[1]

VCM studies in rats and mice reported herein were conducted at the Chemical Systems Laboratory (CSL) under interagency agreement with Consumer Products Safety Commission (CPSC).

II. EXPERIMENTAL PROCEDURES.

A. Exposure Procedures for Toxicology and Carcinogenicity.

1. Doses.

Male and female rats (Fischer 344) and mice (A/J or ICR) were totally exposed in one of the following ways:

a. One single one-hour exposure at 0, 50, 500, 5,000 or 50,000 ppm. (Fischer 344 rats, ICR Mice) (Appendix, Table I)

b. Ten one-hour exposures at 500 ppm (one-hour per day, five days per week for two weeks). (Fischer 344, A/J Mice) (Appendix, Table II)

c. One-hundred one-hour exposures at 50 ppm (one-hour per day, five days per week for 20 weeks). (Fischer 344 rats, A/J Mice)

2. Exposure and Sampling Techniques.

The exposures were conducted in 1000 liter, stainless steel dynamic flow chambers of the Rochester type. Construction insured laminar flow and uniform exposure of the test animals.

During one-hour exposure periods four 0.5 cc gas samples were collected at selected times for concentration analysis.

A Hewlett-Packard series 5830A Reporting Gas Chromatograph equipped with a dual-flame ionization detector was used for VCM analysis.

The system is sensitive to 60 parts per billion of vinyl chloride.

Following exposure the animals were air-washed in the chamber until less than 1 ppm of VCM was detectable. They were then placed in the animal holding area for the remainder of the observation period (up to 24 months).

3. Observation.

Animals were observed twice daily for indications of their general health. The following signs were noted: mortality, health, external sores, subcutaneous masses, alertness, and activity. All test groups were weighed weekly for the first eight weeks post exposure and monthly thereafter.

No blood chemistry or hematology studies were performed.

4. Pathology.

a. Gross and Light Microscopy.

A complete gross pathological examination was performed on most control and exposed animals which died or were sacrificed. Autolysis precluded such examination in a few cases. Light microscopic examination was made of the following tissues: lung, trachea, heart, liver, stomach, small intestine, large intestine, spleen, kidneys, bladder, bone marrow (sternum), adrenals, pancreas, duodenum, brain (2 sections), pituitary, spinal cord (cervical), skin, thyroid, uterus-ovaries, eye, ear, nose, muscle and bone (femur). Particular emphasis was placed on examination of brain, lung, liver and the Zymbal gland in the rodent ear.

All rodents were to be serially sacrificed at 8, 16, 24 months post exposure. However, the life span of the mice forced some changes in the later times of sacrifice and termination of mouse experiments. For the single exposure the planned 16 and 24 month sacrifices were replaced by

an 18-month sacrifice. The latter is minimum suggested by the National Cancer Institute for cancer bioassays in small rodents. For the multiple dose studies (500 ppm x 10 exposures; 50 ppm x 100 exposures) in mice the final sacrifice was at 20 months rather than 24 months. The change was made in consideration of the risk of animal loss through death and possible cannabolism.

b. Electron Microscopical Studies.

For the electron microscopical studies the following animals were selected at random:

Groups consisting of five males and five females Fischer 344 rats from each of the single one-hour (50, 500, 5000 and 50,000 ppm) exposures with equal numbers of their corresponding control group. The groups were sacrificed at 8, 16 and 24 months, respectively, after the exposure.

Groups consisting of five males and five female Fischer 344 rats from each of the multiple one-hour exposures (10 x 500 oom, 100 x 50 ppm) with equal numbers of their control group. The groups were sacrificed at the end of 16 and 24 months, respectively, after the final exposure.

One group of five male and five female Sprague/Dawley/Wistar rats from the parenteral generation of the reproduction group (49 x 50 ppm, 49 x 500 ppm) with equal numbers of their control group. This group was sacrificed 24 months after the final exposure.

The rats were anesthetized with pentobarbital and their livers were perfused via the vena cava with chilled electron microscopical fixative consisting of 4% formaldehyde, 1% glutaraldehyde in 0.1 M phosphate buffer[2] (E.M. McDowell & B.F. Trump, Histological Fixatives Suitable for Diagnostic Light and Electron Microscopy, Arch, Path. Lab. Med. 100:405-415, 1976).

After mincing, the tissues were post-fixed in 1% phosphate buffered

osmium tetroxide, dehydrated in graded alcohol solutions, cleared in propylene oxide and embedded in Epon[3] (J.H. Luft, Improvements in Epoxy Resin Embedding Methods, J. Biophys. Biochem. Cytol. 9:409-414, 1961).

B. Reproduction Study and Carcinogenicity.

F_0 male and female parents Sprague/Dawley/Wistar Rats were exposed to 50 ppm or 500 ppm of VCM one-hour per day, five days per week for 10 weeks (49 exposures) before they were mated. (Appendix, Table III) This assured exposure of all forms of male germ cells. The females were exposed during all phases of the oogenic cycle. The parents were evaluated for numbers of matings, percentages of pregnancies, fertility and lactation indices. The F_1, F_2 and F_3 off-spring were evaluated for litter-size, percent of stillborn pups, post-natal growth, viability, survivability and reproduction anomalies.

The parenteral generation of Sprague/Dawley/Wistar Rats were maintained for 24 months post exposure for carcinogenic evaluation.

III. RESULTS.

A. Toxicology (single and multiple exposures).

1. Observation During Exposure.

Exposures of rats and mice for one-hour to concentrations of 50, 500, 5,000, and 50,000 ppm produced no remarkable signs of toxicity except for mice exposed to the highest level. Fifty percent of the males were hyperventilating after 45 minutes of exposure; twitching and possible

ataxia were noted. At 59 minutes tremors were seen. Females showed some hyperactivity at 40 minutes and 25% showed respiratory difficulty and ataxia after 55 minutes. No other effects were noted.

There were no remarkable signs of toxicity during the ten repeated exposures of mice and rats at 500 ppm of VCM, nor in rats during the 49 exposures at 500 ppm, nor in either species during the 100 exposures at 50 ppm.

2. Observations After Exposure

There were no consistent or dose-related differences between control and exposed (single or multiple) mice or rats in: death rate, (Appendix, Fig I IX, inclusive) toxic signs, gain in body weight. (Appendix, Figs X-XVIII inclusiv

B. Gross Pathology

There was a suggestion of a higher frequency of masses in the lungs and livers of mice and rats exposed once or repeatedly at the higher dose levels. (500, 5,000, 50,000 ppm)

C. Light Microscopic Pathology

1. Mice (single exposure)

Histological examination at 8 and 18 months in ICR mice exposed once to concentrations of 50, 500, 5000 or 50000 ppm showed the following changes attributable to VCM. (Appendix, Table IV-VI, inclusive) The development of lung adenomas increased with exposure to higher dose levels of vinyl chloride:

control - 12/120 or 10%

50,000 ppm - 45/137 or 32.8%

5,000 ppm - 24/143 or 16.8%

500 ppm - 18/139 or 12.9%

50 ppm - 14/139 or 10.1%

Progression to carcinoma was minimal:

control - 0/120 or 0%

50,000 ppm - 3/137 or 2.2%

5,000 ppm - 1/143 or 0.7%

500 ppm - 1/139 or 0.7%

50 ppm - 0/139 or 0%

Pneumonitis was evident in all animal groups which were exposed to VCM in doses of 500 ppm or more.

2. Mice (10 exposures)

Changes attributable to VCM in A/J mice exposed ten times at 500 ppm and examined at 8,16 and 20 months are as follows (Appendix, Tables VII-X, inclusive)

The induction of pulmonary adenomas:

controls - 31/90 or 34.4%

500 ppm - 124/166 or 74.7%

Progression to malignancy (carcinoma) in the test group was greater than in the controls:

controls - 3/90 or 3.3%

500 ppm - 22/166 or 13.3%

3. Mice (100 exposures)

Marginal increases in the occurrence of adenomas of the lungs were attributable to VCM in A/J mice exposed 100 times at 50 ppm and evaluated at 8, 16 and 20 months. (Appendix, Tables VII-X, inclusive)

controls - 29/84 or 34.5%

50 ppm - 65/158 or 44.1%

Progress to malignancy (carcinoma) was apparent:

controls - 2/84 or 2.4%

50 ppm - 7/158 or 4.4%

4. Rats (single exposures)

Except for aggravation of latent pulmonary changes, particularly bronchopneumonia, changes attributable to VCM were not apparent in any of the tissues evaluated microscopically at 8, 16 or 24 months from Fischer 344 rats exposed to concentrations of 50, 500, 5000 or 50,000 ppm. (Appendix , Tables XI-XIV, inclusive)

5. Rats (multiple exposures)

No changes attributable to VCM were apparent in any of the tissues evaluated microscopically at 8, 16 or 24 months from Fischer 344 rats exposed ten times at 500 ppm or 100 times at 50 ppm. (Appendix, Tables XV-XVII, inclusive)

6. Rats (49 exposures from the reproductive study)

The following histological observations were made 24 months post exposure in Sprague-Dawley/Wistar rats which had been exposed 49 times at 50 ppm or 500 ppm of VCM. (Appendix, Table XVII)

Neoplastic and non-neoplastic lesions were observed in approximately equal frequency in control and test animals.

The only lesions that occurred in higher frequency in the VCM exposed animal than in control rats were eosinophilic cell alterations presented as foci and/or areas. The appearance of these foci was related to dosage. The nature of these lesions is controversial. Some pathologists feel that basophilic lesions have greater significance with respect to neoplasm development than do other cellular alterations. Others feel that all of these cellular alterations may be part of a spectrum capable of progressing to the formation of neoplastic nodules.

7. Summary of Light Microscopy Studies

The carcinogenic, or possible related changes (eosinophilic foci) attributable to exposure of VCM in rats and mice are summarized in Table 1.

TABLE 1. VINYL CHLORIDE STUDIES

Experimental Group*	PPM	DAYS (1 hr/day)	SUMMARY (ppm-hrs)	SPECIES/NUMBER EXPOSED		RESULTS
A	50,000	1	50,000	ICR Mice Fischer Rats	180 178	33% adenomas negative
C	500	49	24,500	Sprague-Dawley/ Wistar Rats	49	eosinophilic changes
A	5,000	1	5,000	ICR Mice Fischer Rats	180 180	16.8% adenomas negative
B	500	10	5,000	AJ Mice Fischer Rats	180 180	74% adenomas negative
B	50	100	5,000	AJ Mice Fischer Rats	179 180	41% adenomas negative
C	50	49	2,450	Sprague-Dawley/ Wistar	47	Eosinophilic changes
A	500	1	500	ICR Mice Fischer Rats	180 190	like controls negative
A	50	1	50	ICR Mice Fischer Rats	180 180	like controls negative
				TOTAL EXPOSED	2263	
				TOTAL CONTROL	776	
				COMBINED TOTAL	3039	

*A - 170 ICR Mice (82 male and 88 female) and 178 Fischer Rats (92 male and 79 female) served as control animals for the single exposure (50,000; 5,000; 500; 50 PPM) studies.

B - 190 AJ Mice (89 male and 101 female) and 200 Fischer Rats (100 male and 100 female) served as control animals for the multiple exposure (10 X 500 PPM and 100 X 50 PPM) studies.

C - 45 Sprague-Dawley/Wistar (20 male and 25 female) served as control animals for the multigeneration reproduction study.

D. Electron Microscopical Results.

1. General.

In general, these studies indicate that exposure to vinyl chloride increased organelle turnover (Fig. XIX) as well as loss of volume control (bleb formation) and increased lysosomal activity in the liver of rats (Figure XIX). These alterations progressively decreased as recovery time after exposure increased.

Hepatocellular carcinoma was seen in one male Fischer rat which had received ten exposures of 500 ppm. Lymphosarcoma was noted in one female Fischer rat which had received a single exposure at 500 ppm. Since these were individual cases, and since no cancers were seen at 50,000 ppm, the lymphosarcoma and the hepatocellular carcinoma are not likely related to the vinyl chloride exposure. Thus, it appears that exposure to vinyl chloride did not produce cancer in rats in any of these single or multiple exposures.

General conclusions concerning these various segments of the electron microscopical results follow.

2. General Conclusion of 8-Month Recovery to Single Exposure 50, 500, 5000, 50,000 ppm-hr) of Vinyl Chloride in Fischer Rats.

a. Alterations from control (Fig. XVIII) occurred in all treated animals at each concentration.

b. Changes were less severe in female animals.

c. Hepatocytic alteration included lipid accumulation (Fig. XIX), increased dense bodies (Fig. XX), lipofuschin granules (Fig. XX) and residual bodies. These are an indication of cytoplasmic sublethal injury.

d. Alteration was incremental with increasing exposure concentration.

e. Most severe changes involved cellular necrosis with subsequent phagocytosis by Kupffer cells. (Fig XXI) seen in single and multiple exposures.

f. Extruded areas of hepatocyte cytoplasm (in bleb formation)(Fig. XIX may indicate a means of removal of altered portions of cells.

3. General Conclusion of 8-Month Recovery to Multiple Exposures (500 ppm X 10 exposures; 50 ppm X 100 exposures) to Vinyl Chloride in Fischer Rats.

a. Changes were seen in male and female treated animals. (Fig. XXI)

b. Less alteration was encountered in female rats.

c. Cellular changes was greater than that seen in single dose animals.

d. Alterations involving hepatocyte nuclei, not seen in single dose animals, were encountered in males of this group.

4. General Conclusion of 16-Month Recovery After Single Exposure (50, 500, 5000, 50,000 ppm x 1 hr) to Vinyl Chloride in Fischer Rats.

a. Normal morphology (Fig. XXII) was noted after 16 months in the lower exposure concentrations. When compared to the above alterations at 8 months the 16 months recovery period appeared to be sufficient for return to control morphology.

b. When changes in controls were subtracted from those in treated animals, the most significant finding was hepatocyte necrosis in high dose males.

5. General Conclusion of 16-Month Recovery to Multiple Exposures (500 ppm X 10 exposures; 50 ppm X 100 exposures in Fischer Rats.

a. Electron microscopic evidence supportive of a diagnosis of hepatocellular carcinoma was seen in one male given 10 doses of 500 ppm vinyl chloride. (Fig. XXIII)

b. Other changes included cleft-like spaces in hepatocytes and Kupffer cells. These were interpreted as age-related changes in hemoglobin/ hemosiderin metabolism.

c. Changes were more severe in males.

6. General Conclusion to 24-Month Recovery from Single Dose (50, 500, 5000, 50,000 ppm) Vinyl Chloride in Fischer Rats.

a. Age-related changes including formation of cleft-like spaces (possibly related to hemoglobin/hemosiderin), inflammatory infiltrate (pericholangitis) and some collagen accumulation were seen in controls (Fig. XXIV) and treated animals in this group.

b. In this group hepatocytic injury - not encountered in controls - was observed. At 5000 ppm one female showed evidence of lymphosarcoma.

7. General Conclusion to 24-Month Recovery After Multiple Doses (50 ppm X 10) of Vinyl Chloride in Fischer Rats.

a. Controls and treated animals showed changes similar to those seen after 24 months recovery to single exposure.

b. These changes were regarded as age-related and non-specific (Fig. XXV

8. General Conclusion to 49 Exposures for 1 Hr at Daily Intervals Followed by 24 Month of Recovery (50 and 500 ppm) (Sprague/Dawley/Wistar Rats).

a. Age-related non-specific change was encountered in all groups.

b. Most advanced changes were related to 500 ppm group of male rats in which cell swelling and platelet aggregation were seen.

E. Multigeneration Study in Rats (Sprague/Dawley/Wistar).

No consistent changes attributable to VCM were found in F_0 parents which were exposed to 50 ppm or 500 ppm of the vinyl chloride monomer one hour per day, five days per week for ten weeks before mating and evaluated for numbers of matings, percentages of pregnancies, fertility and lactation indices. The F_1, F_2, and F_3 offspring were evaluated for litter size, percent of stillborn pups, post-natal growth, viability, survivability and reproduction anomalies. (Appendix, Table XIX - XXV, inclusive)

Electron microscopical examination of the parent rats which were held for 24 months after the 49th exposure revealed age related changes, cell swelling, and platelet aggregation but no tumors, (Fig. XXV).

IV. DISCUSSION.

A. Factors in Carcinogenicity.

Theoretically, a single molecule of a carcinogenic substance may produce a cancer-if it is not destroyed in the body before it reaches a susceptible body cell, if it makes a carcinogenic biochemical combination ("hit") with the cell, if this combination is not repaired, if the cancer cells are not destroyed by the immune system, and if other host factors are favorable to carcinogenicity. On the other hand it may be assumed that not every molecule will make a carcinogenic "hit", that some "hits" will be repaired, and some "hits" may not develop into tumors because of unfavorable host factors, and in some situations the cancer cells may be destroyed by the bodies immune system. The higher the dose rate the greater the number of hits and the greater the freguency of tumor production.

The above considerations suggest the existence of "no effect" doses, threshold doses, and dose response curves which have the hockey stick shape described by Bryan and Shimkin.[4] These considerations have been discussed for radiation[5,6] and chemical carcinogenesis[7,8] by numerous authors.

The Food Protection Committee, Food and Nutrition Board of National Academy of Sciences - National Research Council[9] noted that dose-response relationship applied to carcinogens. The higher the dose, the greater is the incidence of response and the shorter the time required to elicit the response. This relationship has been reported for 1,2,5,6,-dibenzoanthracene (DBA)[4], 20-methylcholanthrone (MC)[12], and DMBA plus croton oil [12], p-dimethylaminoazobenzene[13], and carbon tetrachloride.[14] Dose response curves have been given for ultraviolet light[15] and ionizing radiation.[16,17].

There are non-tumorigenic levels of exposure to carcinogens for given experimental conditions. Carcinogens do not produce cancers in all exposed animals. In bioassays, the lower dose levels sometimes do not produce tumors while higher dose do produce tumors.[11,12,13]

The possibility is recognized that "no effect" doses may exert carcinogenic effects which are too weak to be detected with the numbers of animals used in routine testing.

The concept of lifetime accumulative, non-tumorigenic and tumorigenic doses of radiation has been adopted. The Federal Radiation Council[18] stated that for occupationally exposed personnel the accumulated dose of radiation to the whole body, head, trunk, active blood forming organs, gonads or lens of the eye shall not exceed:

1. In any calendar quarter, 1.25 roentgen equivalent mammal (rem)
2. Total lifetime dose of 5 (N-18) rem where N equals the present age in years.

B. Vinyl Chloride and Carcinogenicity.

Maltoni described a dose-response relationship for the carcinogenic effect of vinyl chloride in animals. The neoplastic response was related to the length of exposure.[19,20]

Lee et al.,[21] noted that the incidence and severity of tumors increased with the concentration of VC and the length of exposure.

The above statments indicated that the total dose (concentration X exposure time) may be of importance in the carcinogenicity of vinyl chloride. Total inhaled dose can be approximated by the Haber concept.[22] In its simplest form this concept states that the total inhaled dose, Ct (mg min/cu m) is the product of C (concentration in mg/cu m) X t (time in minutes).

The concentration can be expressed also in part per million (ppm) and the time can be expressed in hours producing Ct in ppm-hr. Factors for breathing rate and detoxication can be included when these data are available. However, the simplified Ct approximation of total inhaled dosage is sometimes useful.

A rough calculation of total dosages has been made for some of the data of Maltoni [19,20]; Lee et al.,[21] Viola et al.,[23] Caputo et al.,[24] and Keplinger et al.[25]

These Ct calculations are summarized in Tables 2 and 3.

In the studies of P.L. Viola, A. Bigotti and A. Caputo[23] tumors were seen in rats which had been exposed to 30,000 ppm of vinyl chloride four hours per day, five days per week for 12 months. Positive effects were obtained at the total dose (CT) of 28,800,000 ppm-hrs.

A. Caputo, P.L. Viola and A. Bigotti[24] exposed rats to vinyl chloride four hours per day, five days per week for 12 months. The concentrations were 20,000; 10,000; 5,000; 2,000; 500; or 50 ppm. The total dose (Ct) for the 50 ppm was 48,000 ppm-hrs. No tumors were produced at this level. The total dose for 500 ppm was 480,000 ppm-hrs. Tumors did occur at the latter dose appearing as early as eight months was 320,000 ppm-hrs.

Tumors appeared in the rabbits after nine months at 10,000 ppm. Thus the lowest total dose was 7,200,000 ppm-hrs.

M.L. Keplinger et al.,[25] exposed rats, hamsters and mice to vinyl chloride. Only the data on mice was sufficiently complete for examination of total dose effects. The animals were exposed seven hours per day, five days per week for eight months. The lowest Ct was 56,000 ppm-hrs. This Ct and all higher ones did produce tumors in mice.

TABLE 2

MALTONI VINYL CHLORIDE STUDIES [19,20]
Calculations based on reference 19

TEST	SPECIES	RESULTS (CARCINOGENESIS) - PPM-HRS
BT1	RATS	QUESTIONABLE AT 52K*
BT3	RATS	NEGATIVE AT 17K QUESTIONABLE AT 85K POSITIVE AT 170K, 850K, 2000K, 3000K
BT6	RATS	POSITIVE AT 24,600K
BT7	RATS	NEGATIVE AT 52K, 260K QUESTIONABLE AT 520K POSITIVE AT 2600K, 6200K, and 10,400K
BT4	MICE	POSITIVE AT 30K, 150K, 300K, 600K, 1500K and 3600K

K* = thousand (000)

TABLE 3

OTHER VINYL CHLORIDE STUDIES

AUTHORS	SPECIES	RESULTS (CARCINOGENESIS) - PPM-HRS
VIOLA, BIGOTTI,[23] CAPUTO	RATS	POSITIVE AT 28, 800K
CAPUTO, VIOLA,[24] BIGOTTI	RATS	NEGATIVE AT 48K
		POSITIVE AT 320K, 1280K, 3200K 6400K, 12,800K
	RABBITS	POSITIVE AT 7200K
KEPLINGER et al.,[25]	MICE (RATS & HAMSTERS)	POSITIVE AT 56K
LEE [21]	MICE	ALL TESTS ESSENTIALLY NEGATIVE BELOW AND POSITIVE ABOVE 48K
CONSUMER PRODUCTS SAFETY COMMISSION	ICR MICE	50 AND 500 - NEGATIVE 5000 - BORDERLINE POSITIVE 50,000 - POSITIVE
	A/J MICE	5000 - POSITIVE
	FISCHER RATS	50, 500, 5000 AND 50,000 - NEGATIVE
		24,500 - EOSINOPHILIC LOCI, NO CANCERS

Calculations (Tables 1 and 2 Appendix) on the Consumer Products Safety Commission studies indicate that strongly positive carcinogenic effects may not appear in rats until the total dose (Ct) of VCM reaches or exceeds 50,000 ppm-hrs. The maximum response in the rats was the appearance of eosinophilic cells which might suggest a pre-cancerous change.

The CPSC VCM tests in mice indicate that increased frequencies of adenoma may appear in this species at Ct's of 5,000 ppm-hr and above. This total dose for carcinogenicity is in general agreement with Lee et al.,[21] (48,000 ppm-hrs) and Maltoni[19,20] (between 30,000 ppm-hrs and 150,000 ppm-hrs), and the other investigators.[23,24,25] In general, in orders of magnitude, carcinogenic tendencies are seen in some species at Ct's of 5,000 to 50,000 ppm-hrs. Definite carcinogenicity appears in both rats and mice at Ct's of 50,000 to 500,000 ppm-hrs, and high incidences of carcinogensis are noted in mice and rats at Ct's of greater than 500,000 ppm-hrs.

The previous studies[19,20,21,23,24,25] and present CPSC study are in agreement as to the dose-time relationship for carcinogenesis related to vinyl chloride exposure. All of these studies considered collectively may indicate that there may be a life-time total dose for vinyl chloride below which carcinogenicity is not likely to occur. This "no cancer" Ct seems to be below 5000 ppm-hr for mice. For histological confirmed carcinogenesis the "no cancer" Ct in rats appears to be greater than 50,000 ppm/hrs. The results of the light or the electron microscopical study did not reveal carcinogenic responses in rats at Cts from 50-50,000 ppm-hrs. However, Ct's of 2450 ppm-hr produced eosinophilic loci but no

tumors in rats in the CPSC tests.

As an additional consideration in the total dose concept, Ct's of 5000 ppm-hr produced increased incidence of adenomas in mice when the exposures were at 5000 ppm for one day, 500 ppm for 10 days or 50 ppm for 100 days. The increased incidence of adenomas produced by the single exposure of mice at 5000 ppm is of borderline significance. However, there is the indication that even single exposure of sufficient magnitude may be carcinogenic in sensitive species.

The dose-response relationship and the "no effect" dose concept have been described for other carcinogens.

It is difficult to relate these animal studies to man. Data on vinyl chloride exposure in plants have been limited. However, acute dizzyness, headache, nausea and chronic liver damage have been seen in vinyl chloride workers. It is assumed that peak exposure levels of several thousand parts per million were experienced at times. Air monitoring of one group of plants during 1950-59 indicate that time-weighted (8-hr) average exposure were 120-385 ppm. (This would give daily Cts of 960-3080 ppm-hrs). Peak exposures possibly exceeded 1000 ppm. This may not have been typical of all polyvinyl chloride plants.(1)

Data on vinyl chloride in ambient air are limited also. Atmospheric measurements in the vicinity of production plants indicate that concentrations are below 1 ppm. One peak grab sample of 33 ppm has been reported at 0.5 kilometer from the center of one plant.(1)

The time-weighted threshold limit value of the American Conference of Government Industrial Hygienest for 1977 was 200 ppm. There is a notice of intended change.[26] The Environmental Protection Agency[27] has established

the following emission limits for vinyl chloride: (1) formation and purification processes is 10 pmm, (2) emissions from equipment preceding and including the stripper in the plant process flow is 10 ppm, (3) emissions from equipment following the stripper are to be controlled by stripping · dispersion resins to 2000 ppm and other resins to 400 ppm.

Assuming that man is as sensitive as the mouse or rat the carcinogenic effects of vinyl chloride might be expected after an accumulated Ct of about 5000 ppm-hrs or approximately 150,000 ppm-hr;(Maltoni BT3) respecti... Based on the high pollution values given above (1000 ppm-hr per day) carcinogenic doses could have been accrued in one week (mouse) or 30 weeks (rat). At the TLV of 200 ppm (daily Ct of 1600 ppm-hr) the time to accumulate a carcinogenic dose would be 3 days (mouse) or about 19 weeks (rat). Comparable accumulation times at 10 ppm (80 ppm-hrs per day) would be about 12 weeks (mouse) or 375 weeks (rats). The calculations are based upon a five day working week.

IV. CONCLUSIONS.

A. Except at the highest concentration, 50,000 ppm, where possibly anesthetic-type effects were seen vinyl chloride produced no pharmacotoxic (excluding pathology) signs in mice or rats during or after exposure.

B. No reproductive or teratogenic changes attributable to vinyl chloride were found. Mating; % pregnancies; fertility, lactation indices, % still-borns; litter size; post-natal growth; viability, survivability, anomalies.

C. Vinyl chloride seemed to produce pneumonitis in mice and to aggravate bronchopneumonic in rats.

D. Vinyl chloride produced eosinophilic changes in rats but no

frank (light microscopy) carcinogenesis.

E. Vinyl chloride produced increased in frequency of tumors in mice.

F. Electron microscopical studies revealed some hepatocellular changes but no carcinogenesis related to the vinyl chloride exposures at Ct's of 50,000 ppm-hrs or less.

1. The carcinogenic effectiveness of VCM depends upon concentration and exposure time, Ct.[4,5,6]

2. There were VCM doses which were not carcinogenic and there appeared to be a total accumulated dose above which tumors were produced.[13,15-17] Similar effects have been noted with other chemicals.

3. Tumors were not seen in mice at Ct's of 500 ppm-hrs nor in rats at 50,000 ppm-hrs or less.[4,5,6,9,10,11]

4. Carcinogenic effects of VCM were seen in mice at total doses (Cts) of 5,000 ppm-hrs and above.[6,11]

168
50
8400
10
84.00

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APPENDIX

Table I. Single Exposure Schedule of Animals To VCM

Species	Sex	Dose	Exposure date AM	Exposure date PM	Exposure group size(s)	Age at time of exposure
		ppm				weeks
Fischer Rat	M	50	3/4/75		90	15
		500	3/11/75		90	16
		5000	3/18/75		85	17
		50000	3/25/75		90	18
	F	50		3/4/75	90	15
		500		3/11/75	100	16
		5000		3/18/75	95	17
		50000		3/25/75	88	18
ICR Mouse	M	50	3/4/75		90	15
		500	3/11/75		90	16
		5000	3/18/75		90	17
		50000	3/25/75		90	18
	F	50		3/4/75	90	15
		500		3/11/75	90	16
		5000		3/18/75	90	17
		50000		3/25/75	90	18
Rat	M	Neg/Cont.			92	15-18
	F	Neg/Cont/			79	15-18
Mouse	M	Neg/Cont.			82	15-18
	F	Neg/Cont.			88	15-18

APPENDIX

Table II. Exposure Schedule for Animals Exposed Repeatedly to VCM

Species	Sex	Dose	Exposure periods	Exposure dates		Exposure Group size(s)		Age	
				From	To	Start	End	Start	End
		ppm	days						wks
Fischer Rat	M	50	100	8/27/75	1/26/76	90	86	21	41
		500	10	7/7/75	7/18/75	90	90	14	16
	F	50	100	8/27/75	1/26/76	90	87	21	41
		500	10	7/7/75	7/18/75	90	90	14	16
A/J Mouse	M	50	100	7/7/75	7/18/75	90	87	15	35
		500	10	8/27/75	1/26/76	90	90	8	10
	F	50	100	7/7/75	7/18/75	90	88	15	35
		500	10	8/27/75	1/26/76	90	90	8	10
Fischer Rat	M	Neg. control	100(c)	-		50	50	21	41
			10(c)	-		50	50	14	16
	F	Neg. control	100(c)	-		50	47	21	41
			10(c)	-		50	50	14	16
A/J Mouse	M	Neg. control	100(c)	-		40	39	15	35
			10(c)	-		50	50	8	10
	F	Neg. control	100(c)	-		50	50	15	35
			10(c)	-		50	50	8	10

NOTE: (c) control for corresponding dose above.

APPENDIX

Table III. VCM Multigeneration Study F_0 Parents

Group	Compound	Dose	Number of Males	Number of Females
I	Air	Control	25	25
II	VCM	Low Dose (50 ppm)	25	25
III	VCM	High Dose (500 ppm)	25	25

Figure I

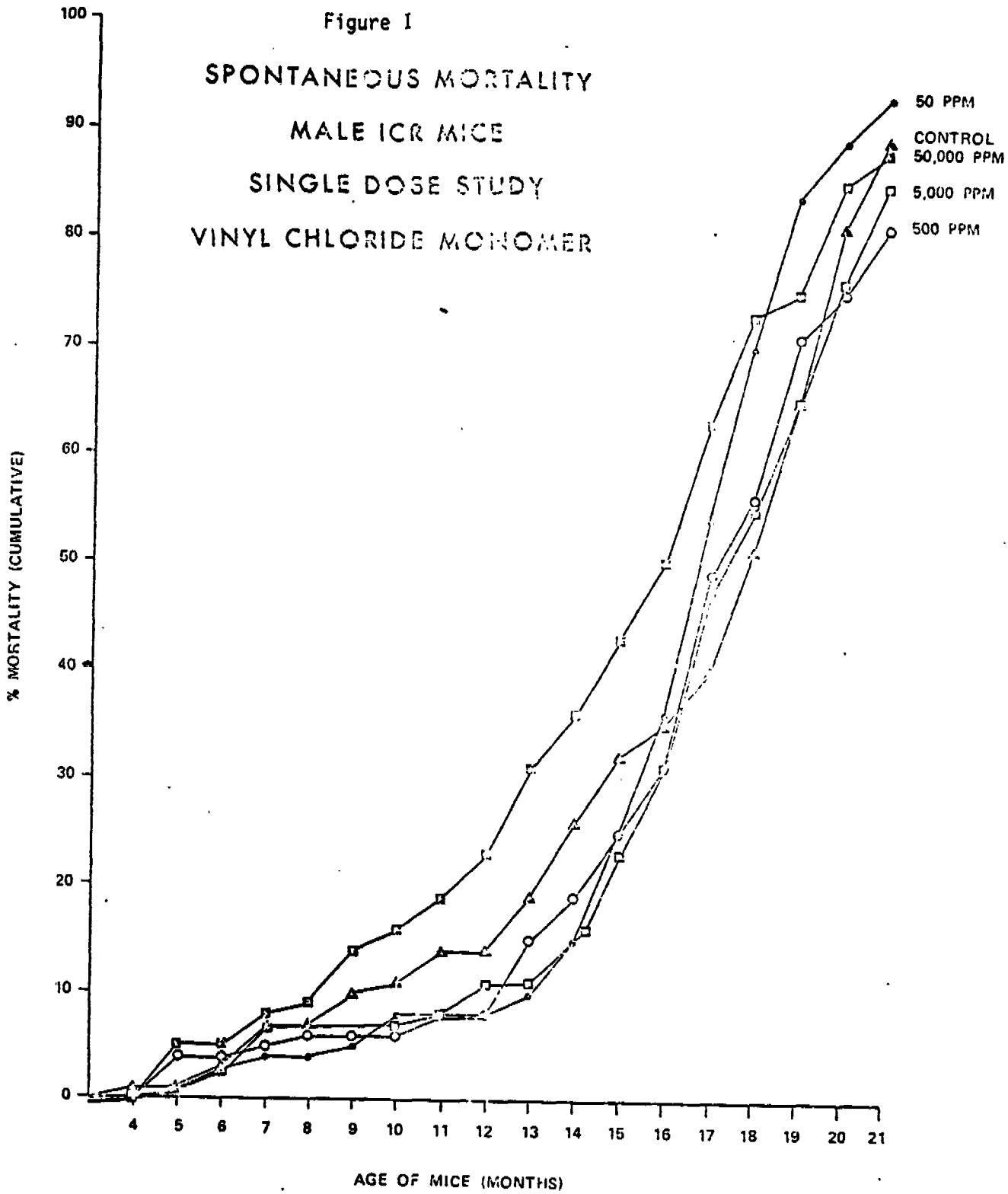

Figure II

SPONTANEOUS MORTALITY

FEMALE ICR MICE

SINGLE DOSE STUDY

VINYL CHLORIDE MONOMER

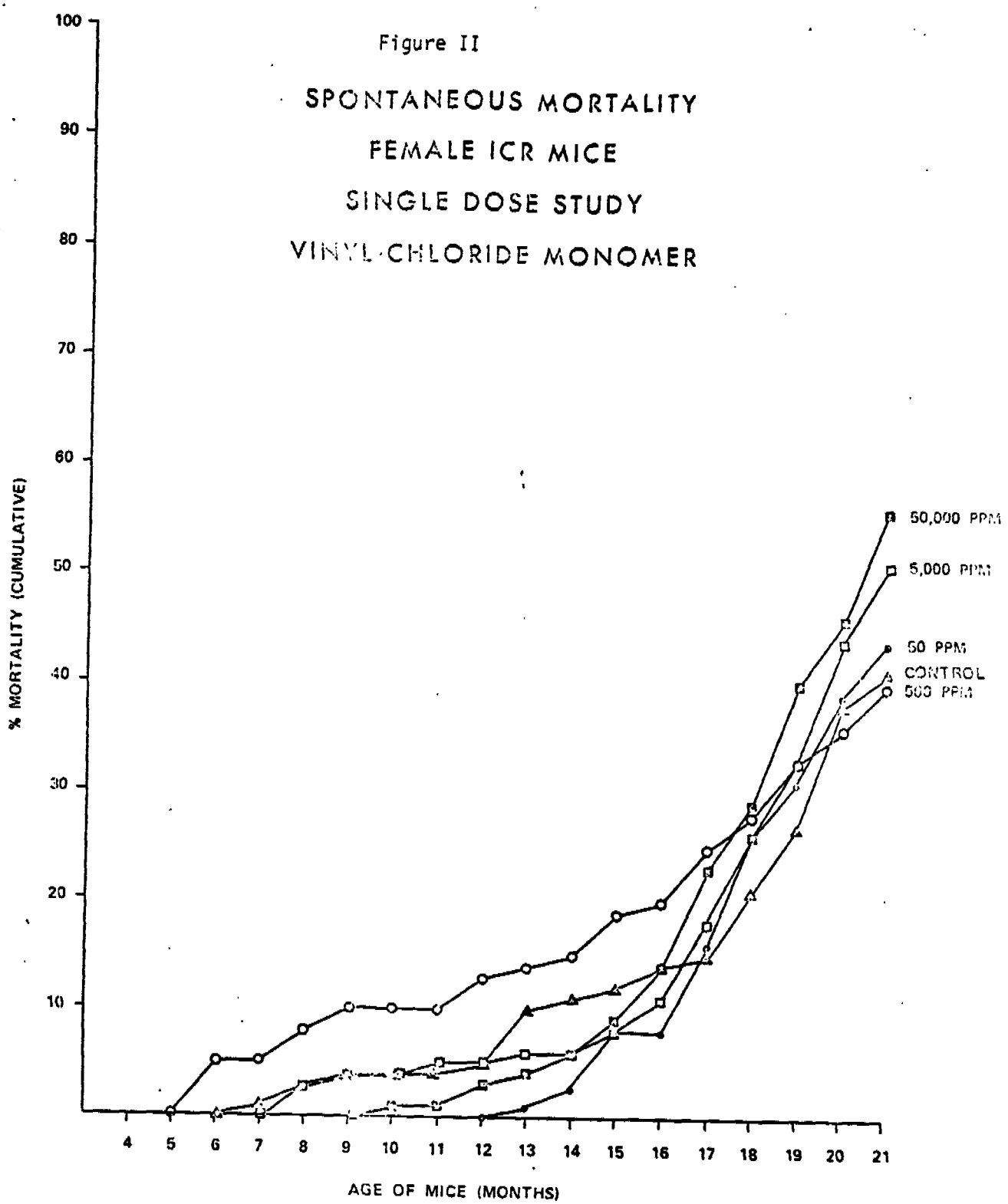

Figure III

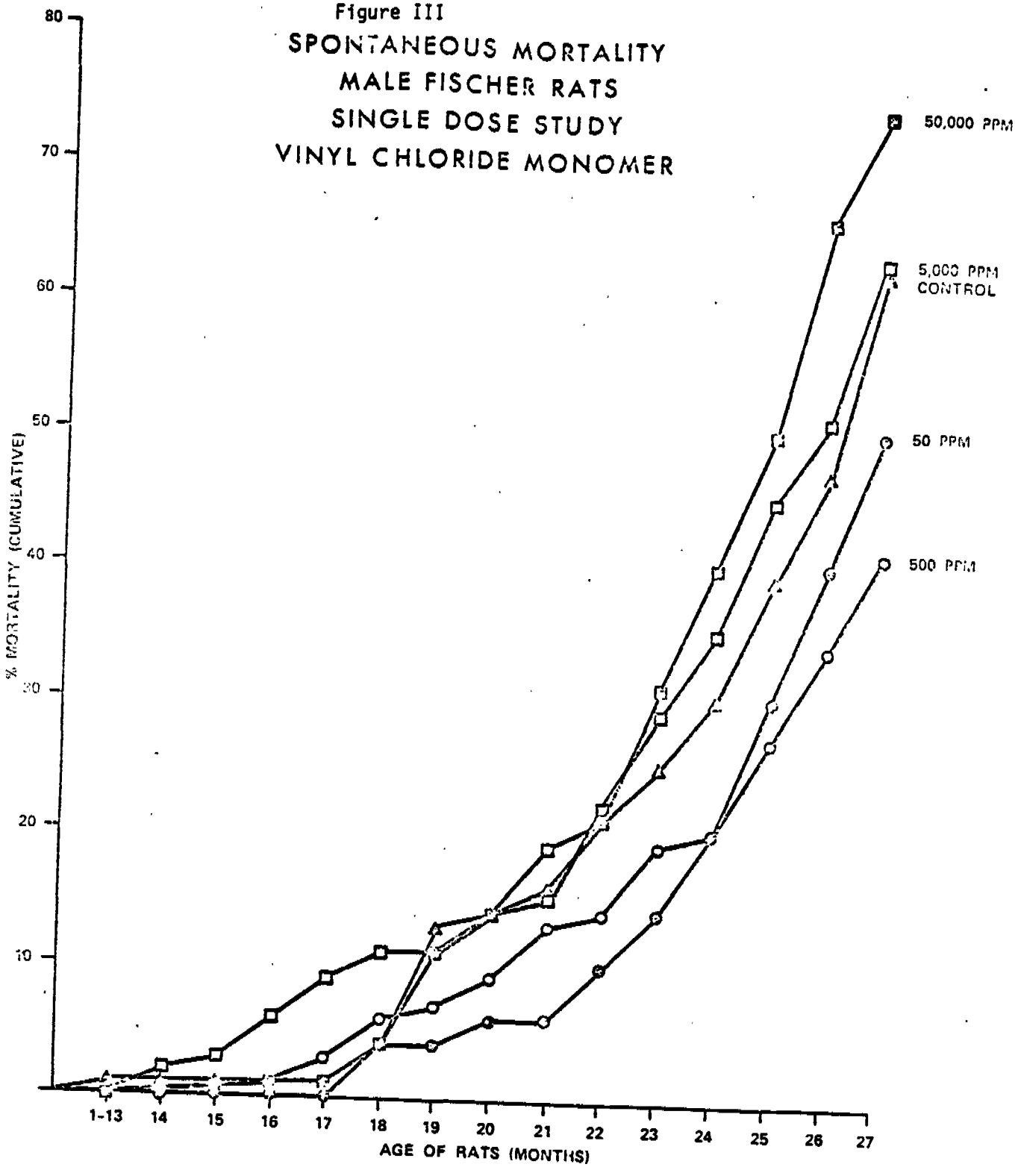

Figure IV

SPONTANEOUS MORTALITY
FEMALE FISCHER RATS
SINGLE DOSE STUDY
VINYL CHLORIDE MONOMER

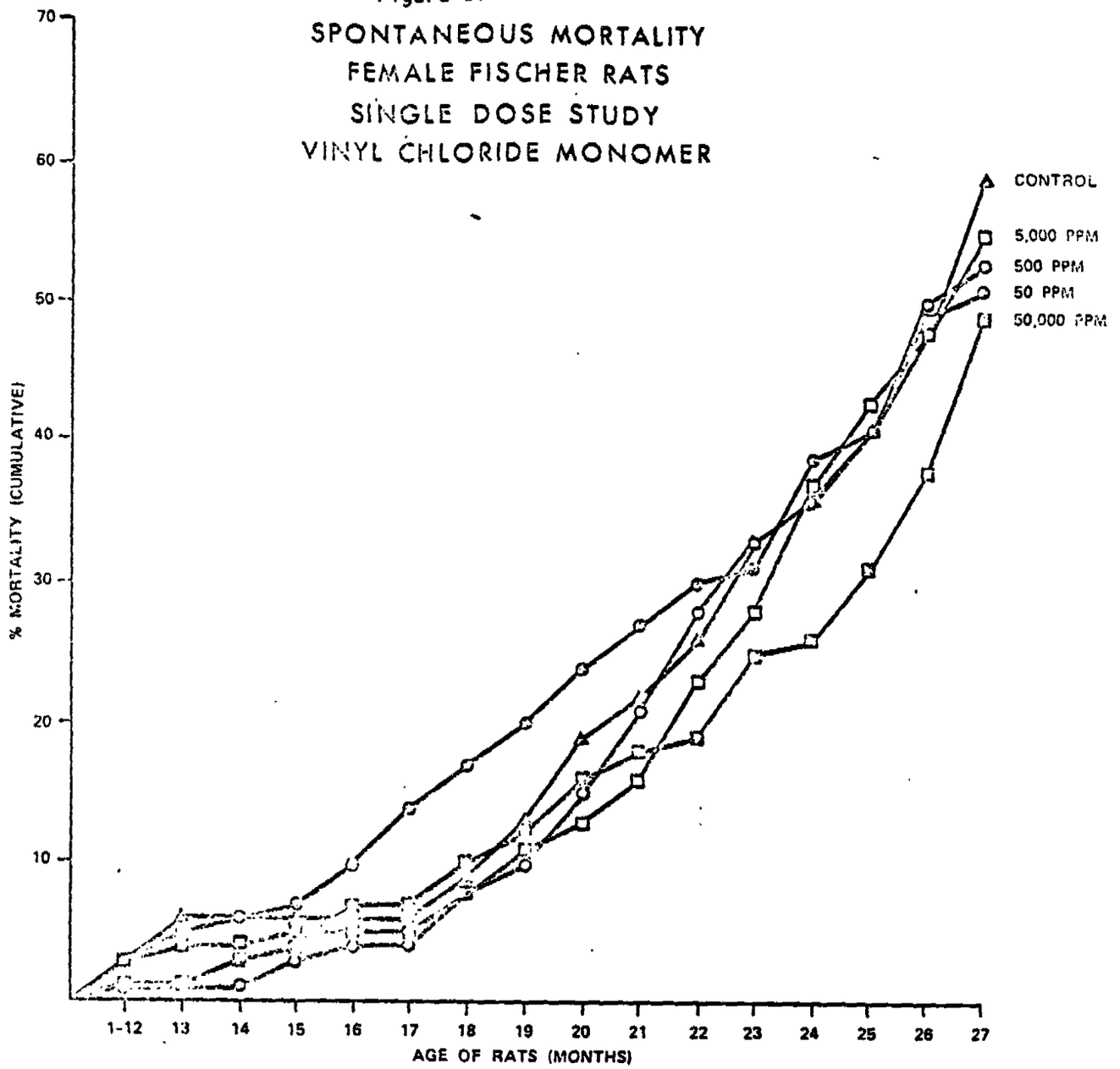

Figure V

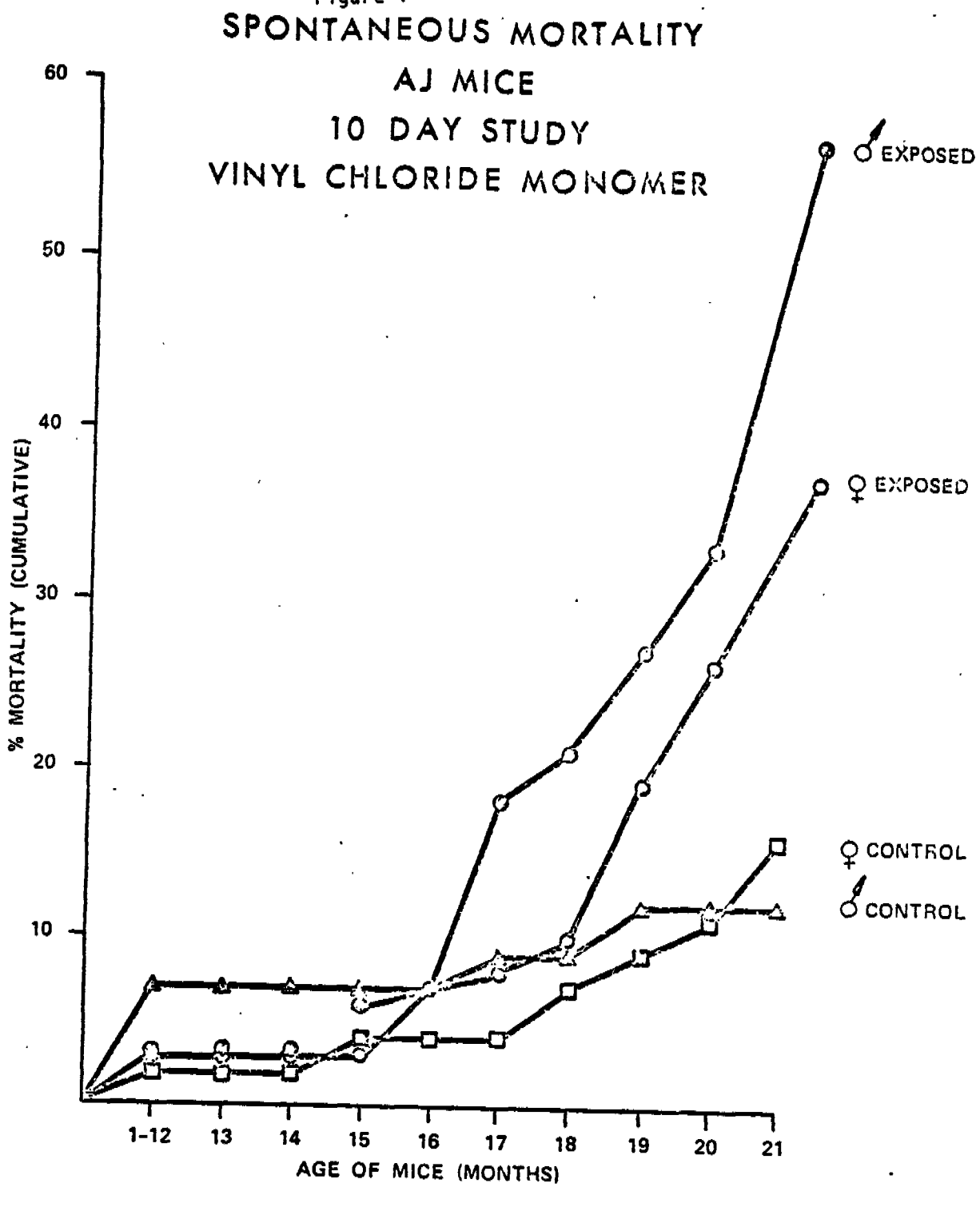

Figure VI

SPONTANEOUS MORTALITY
FISCHER RATS
10 DAY STUDY
VINYL CHLORIDE MONOMER

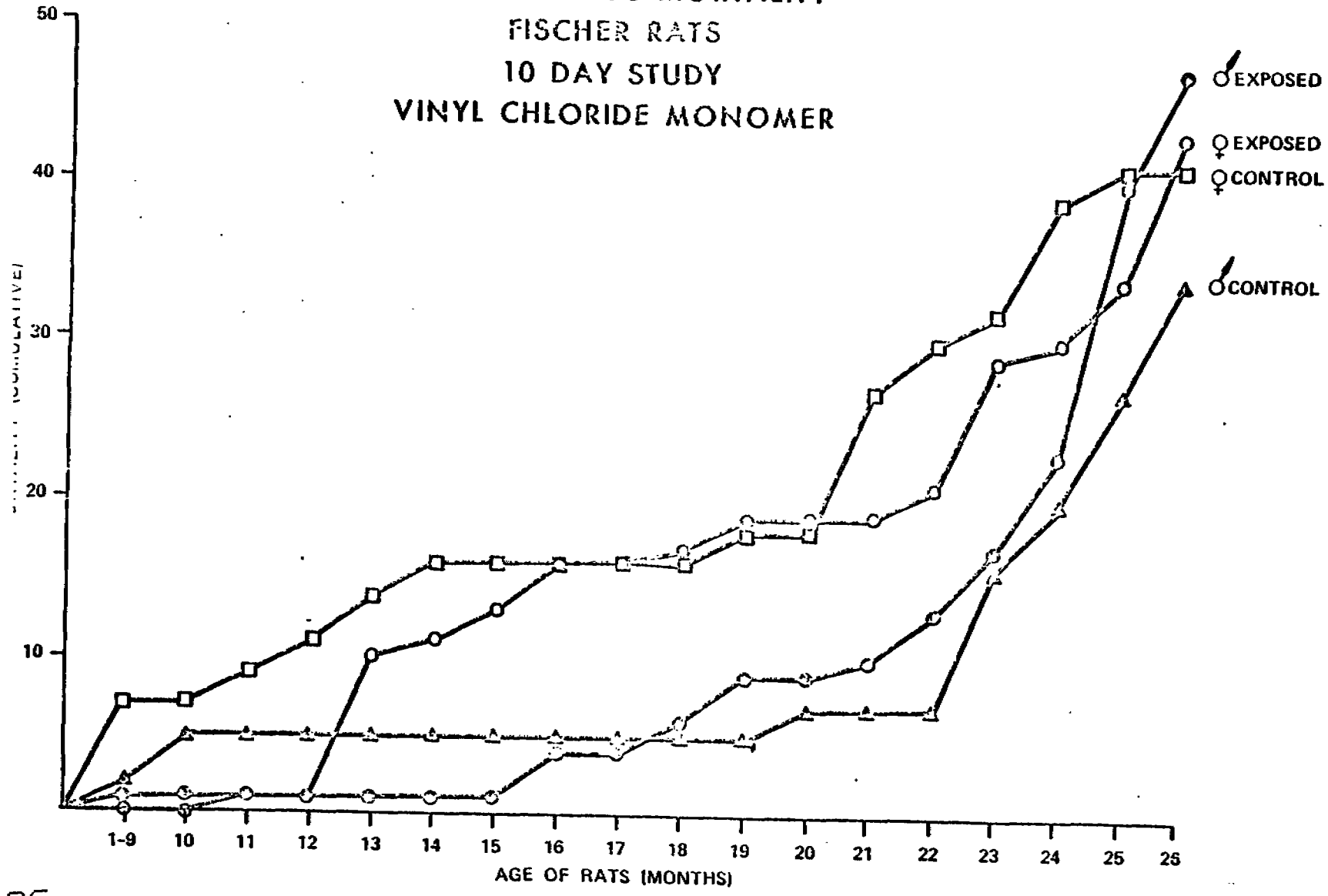

Figure VII

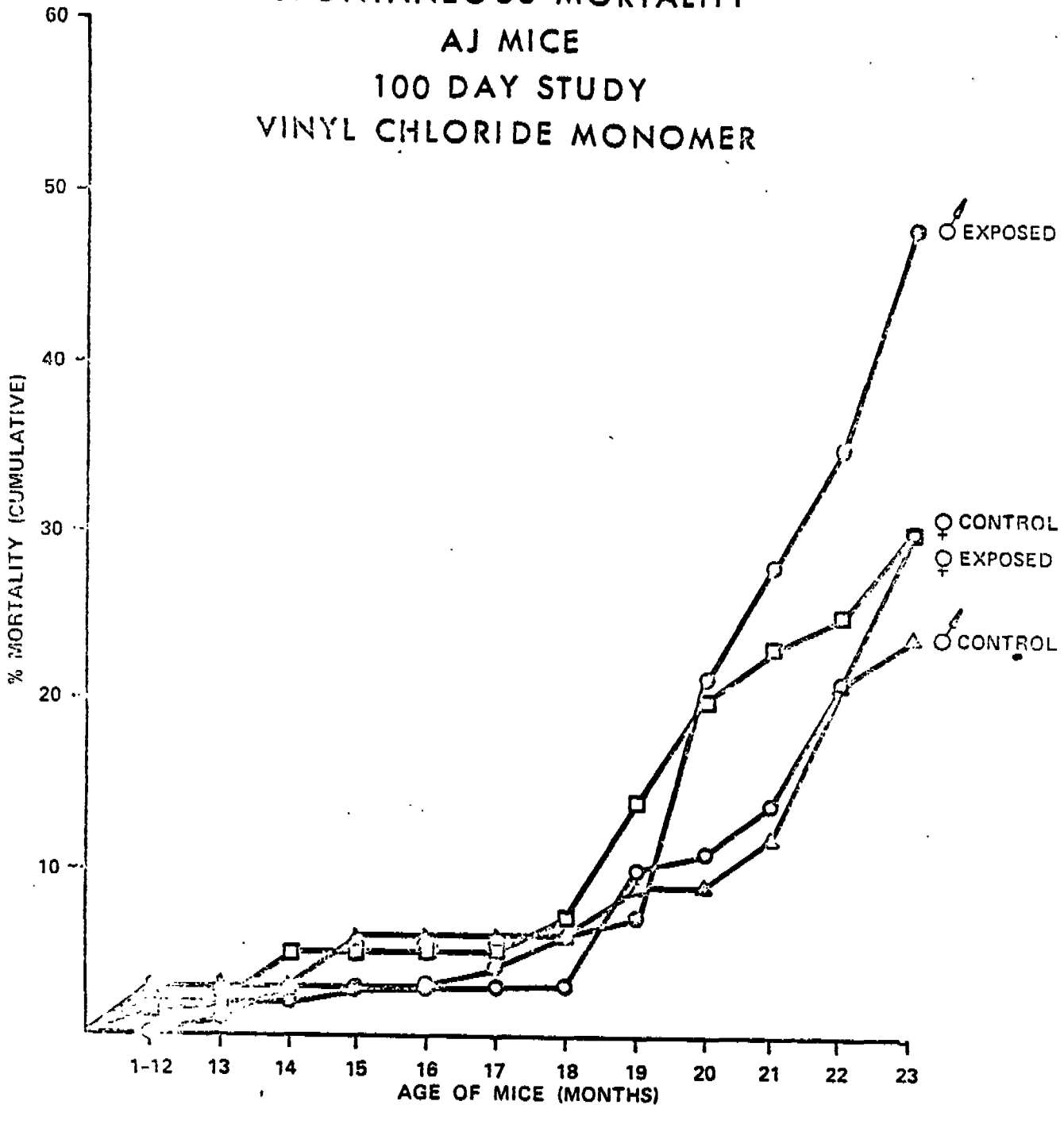

Figure VIII

SPONTANEOUS MORTALITY
FISCHER RATS
100 DAY STUDY
VINYL CHLORIDE MONOMER

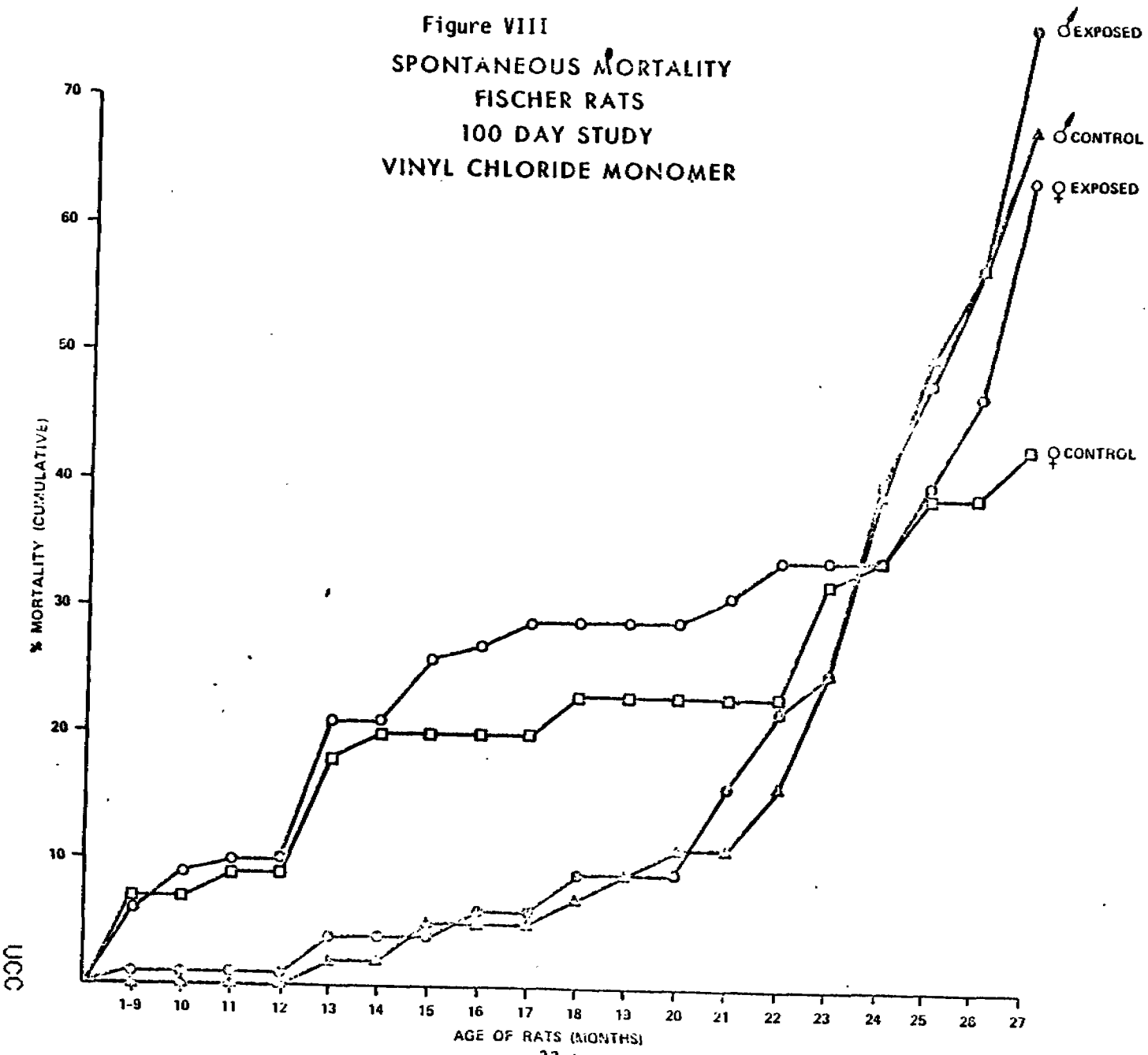

Figure IX

SPONTANEOUS MORTALITY
FISCHER RATS
100 DAY STUDY
VINYL CHLORIDE MONOMER

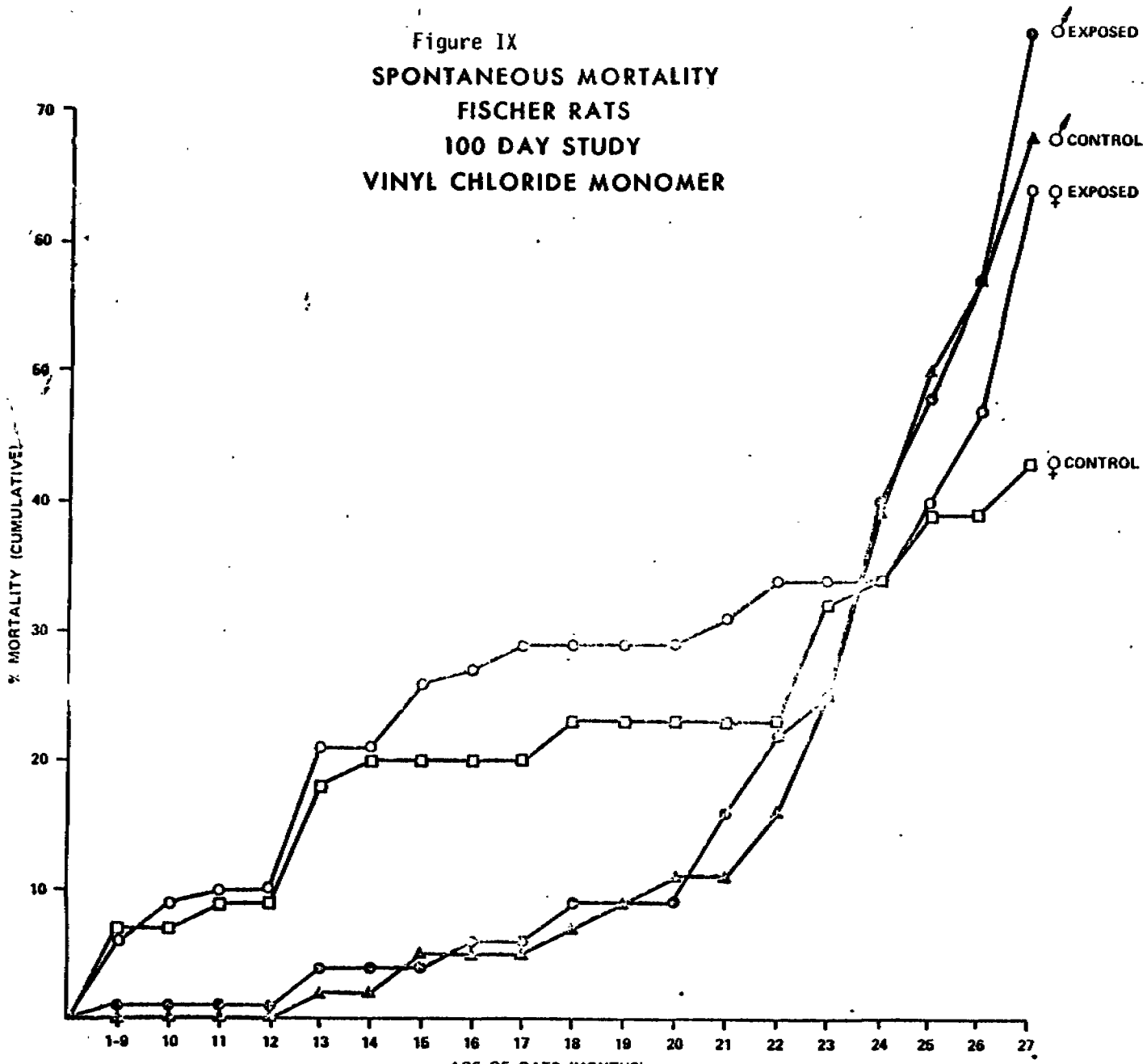

Figure X

GROWTH CURVES OF MALE ICR MICE EXPOSED ONCE TO VCM

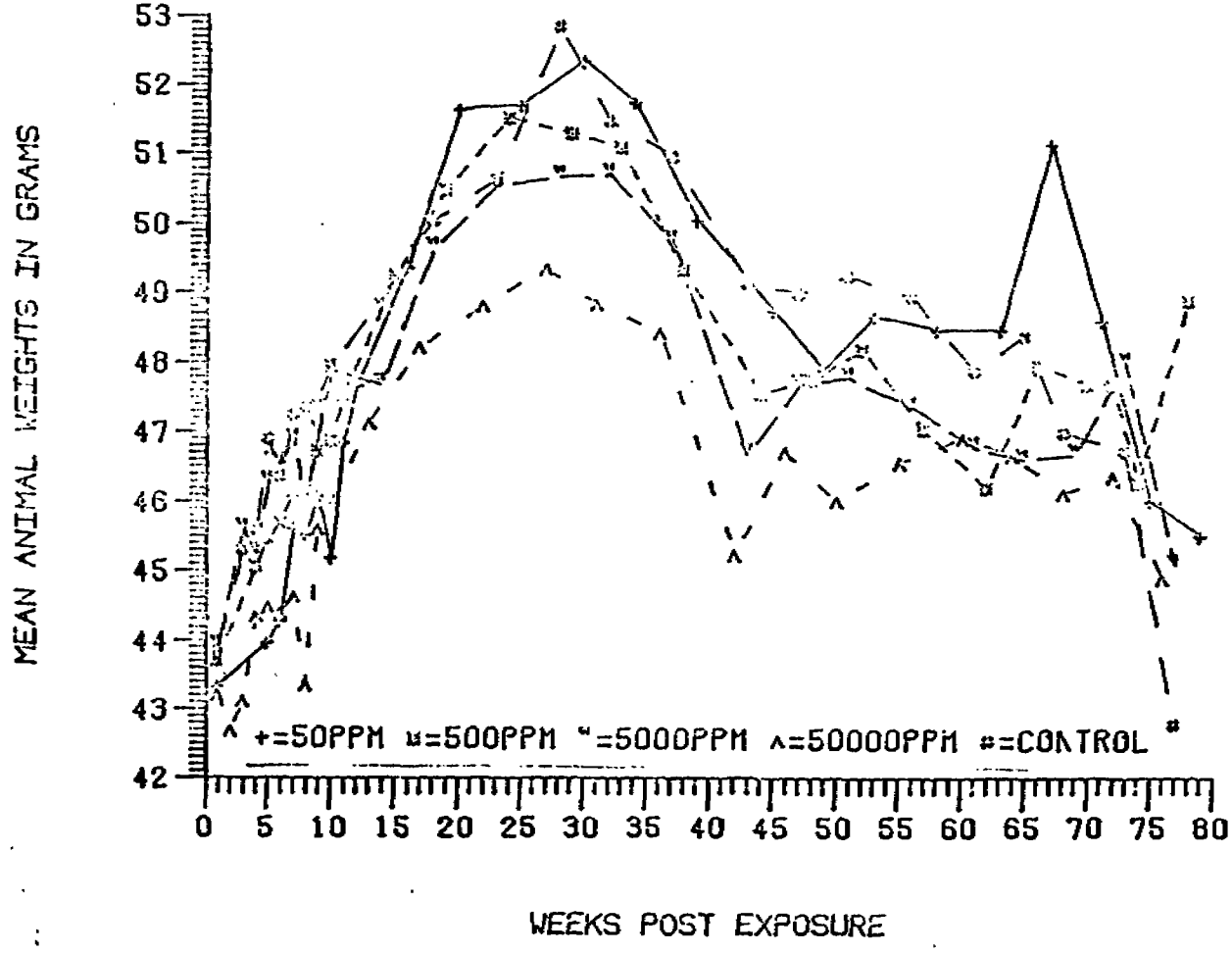

Figure XI

GROWTH CURVES OF FEMALE ICR MICE EXPOSED ONCE TO VCM

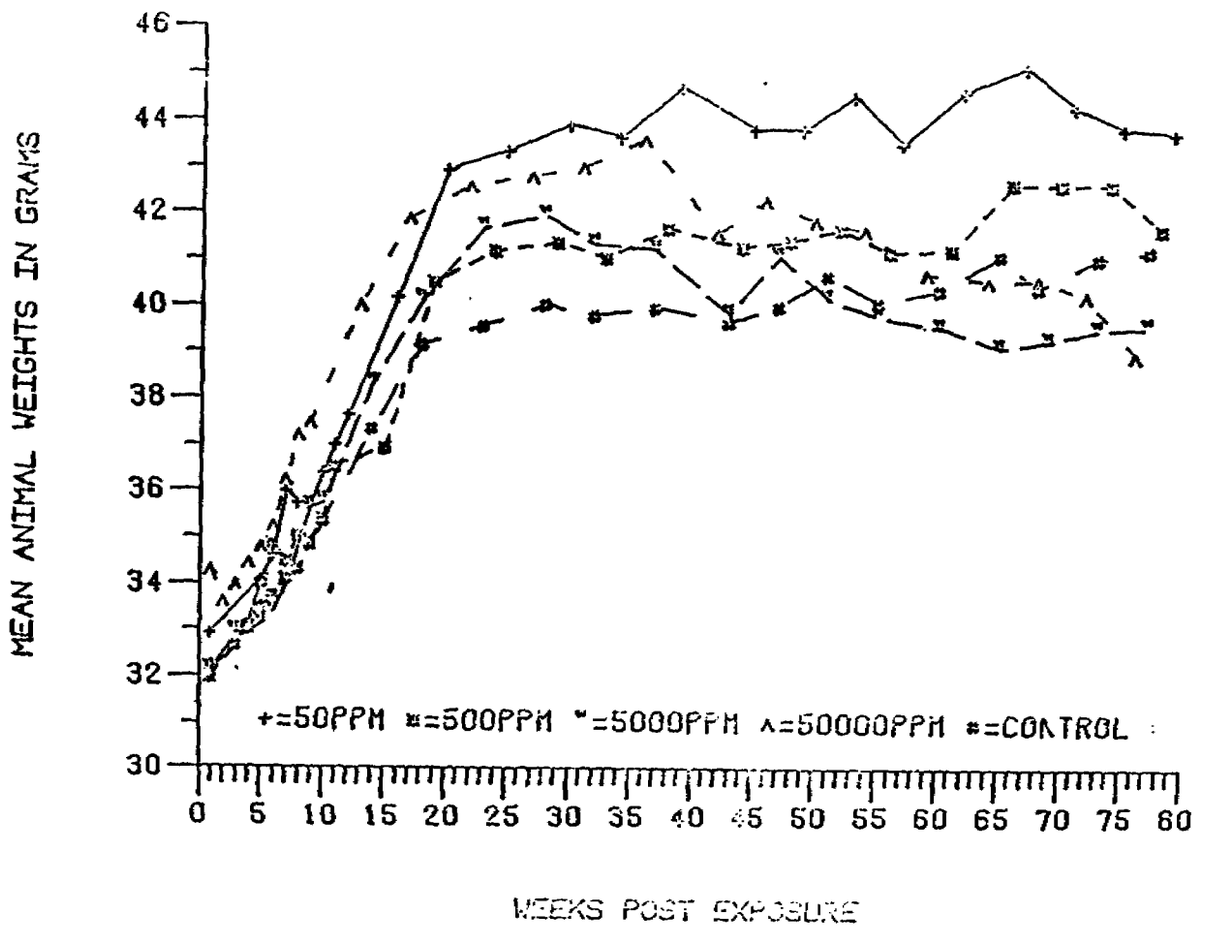

Figure XII

GROWTH CURVES OF MALE FISCHER RATS EXPOSED ONCE TO VCM

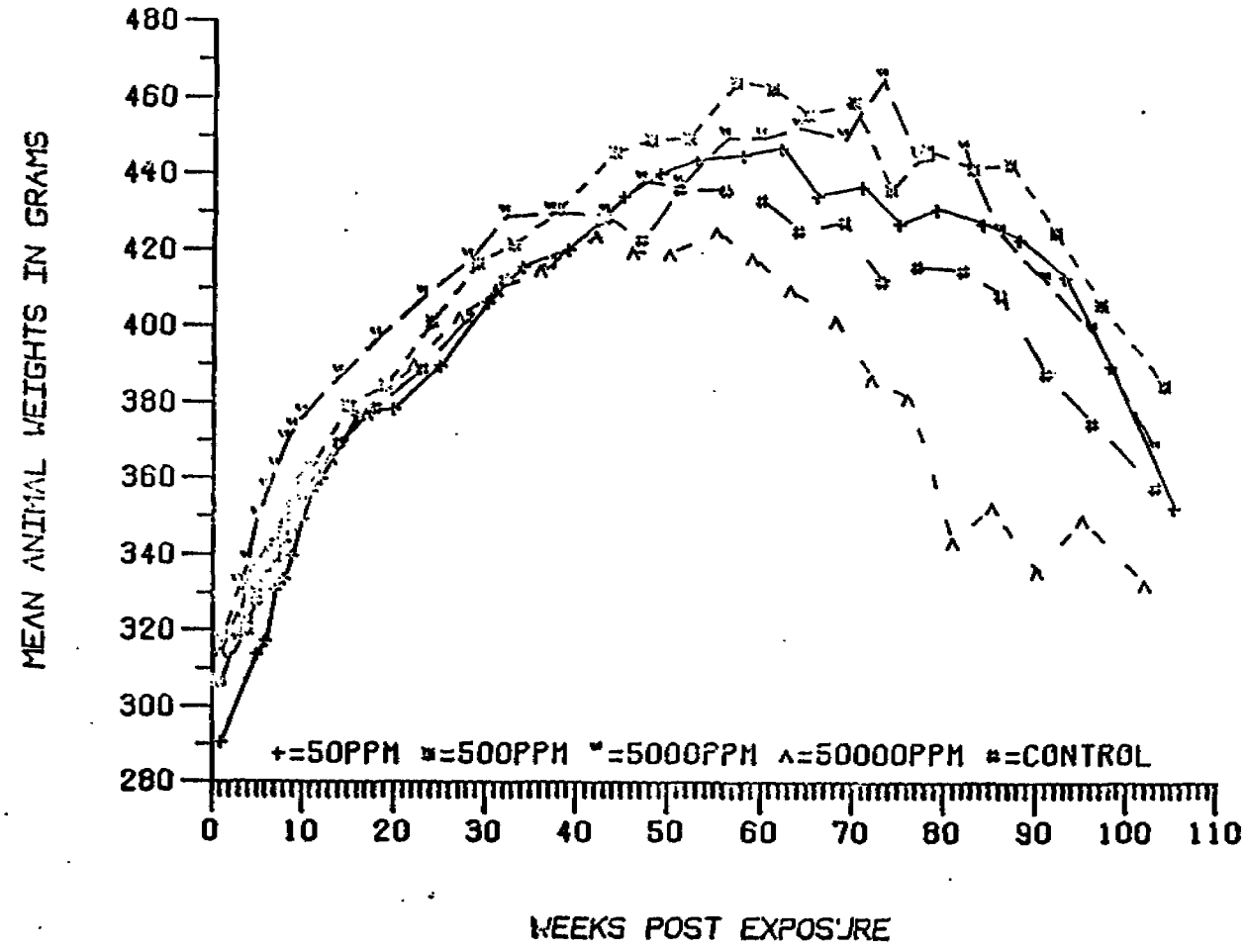

Figure XIII

GROWTH CURVES OF FEMALE FISCHER RATS EXPOSED ONCE TO VCM

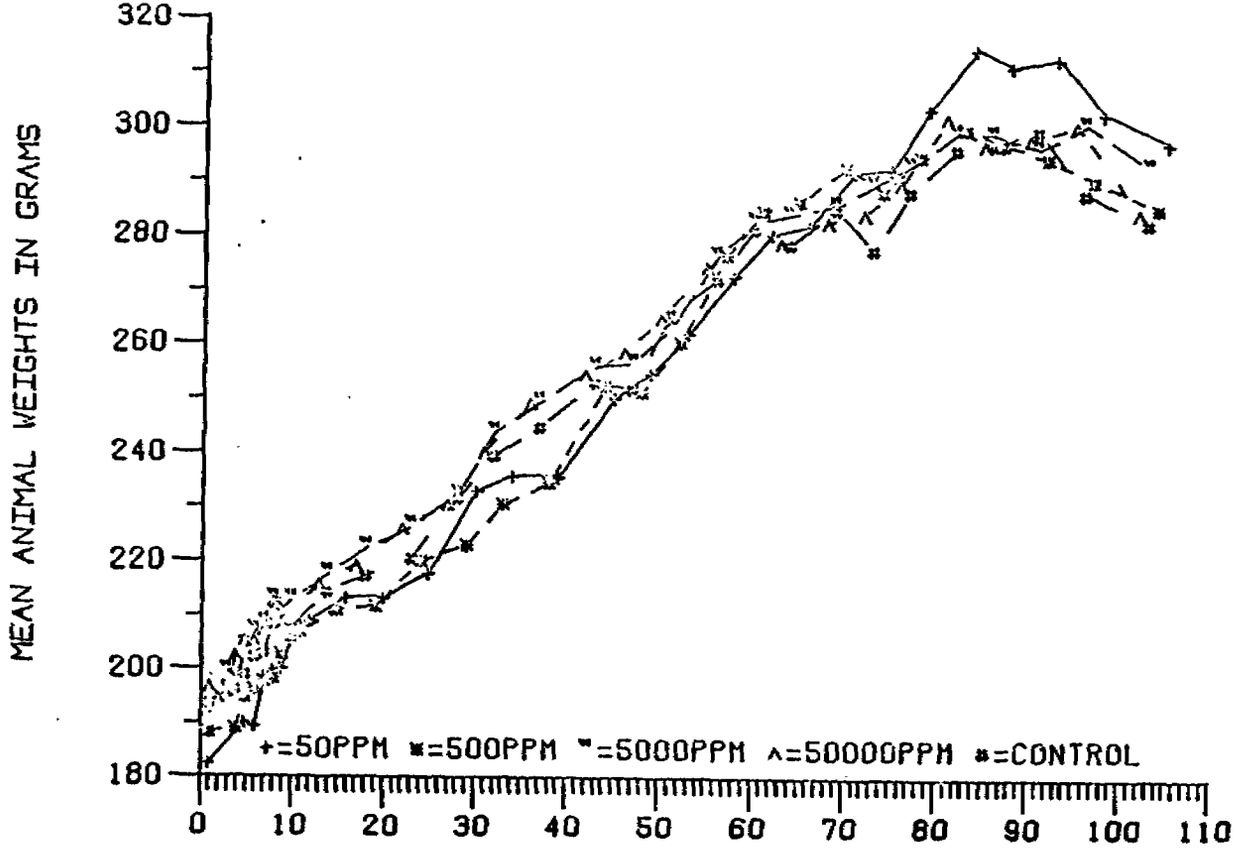

Figure XIV

GROWTH CURVES OF A/J MICE EXPOSED TO VCM IN 10 DAY STUDY

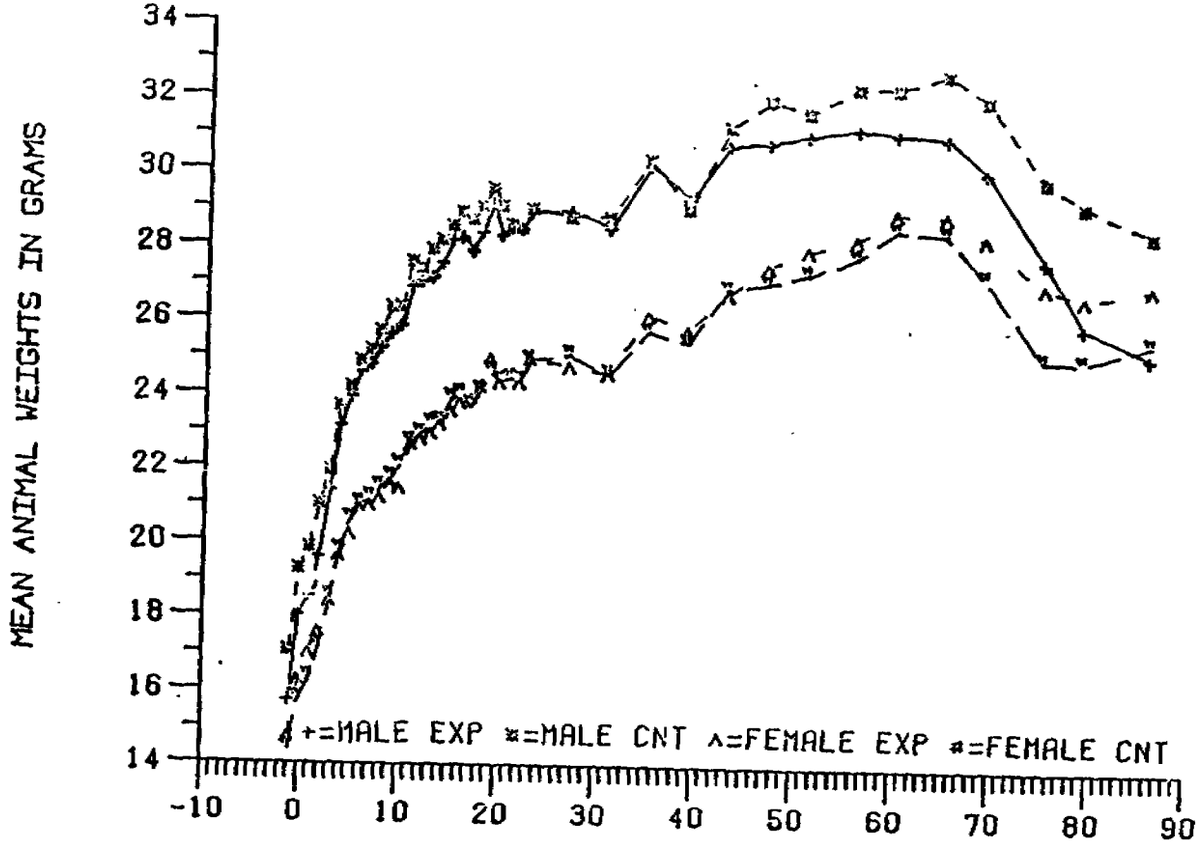

Figure XV

GROWTH CURVES OF A/J MICE EXPOSED TO VCM IN 100 DAY STUDY

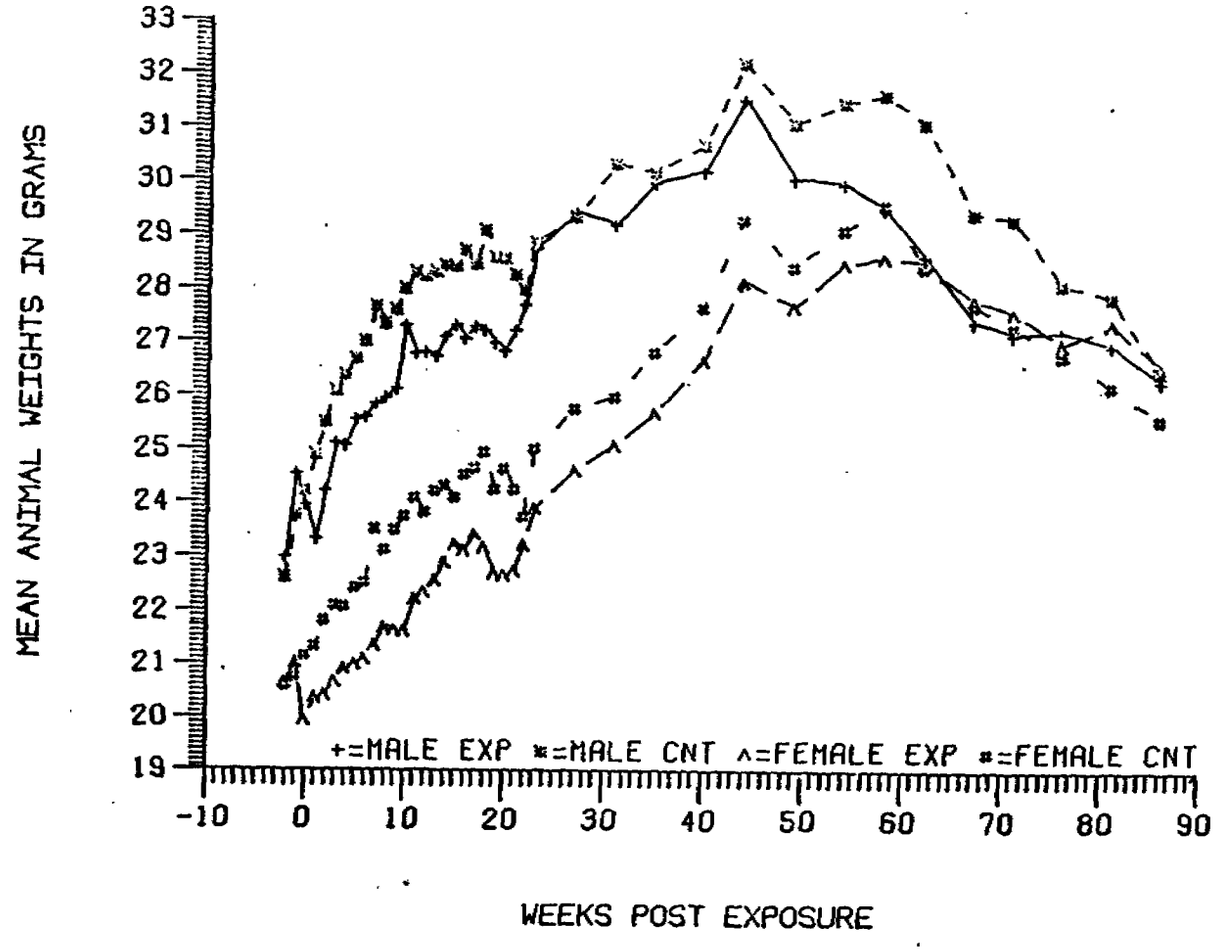

Figure XVI

GROWTH CURVES OF FISCHER RATS EXPOSED TO VCM IN 10 DAY STUDY

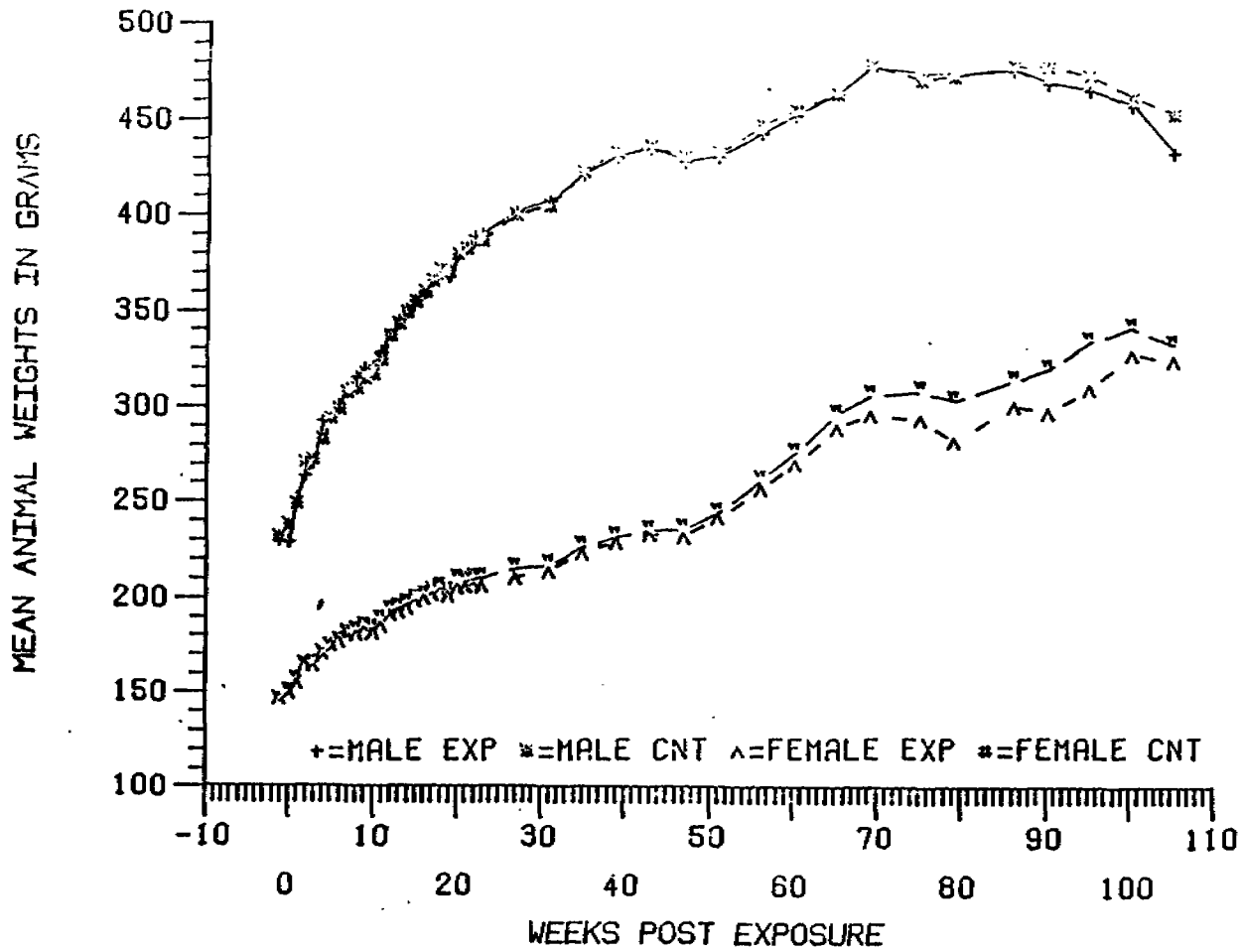

Figure XVII

GROWTH CURVES OF FISCHER RATS EXPOSED TO VCM IN 100 DAY STUDY

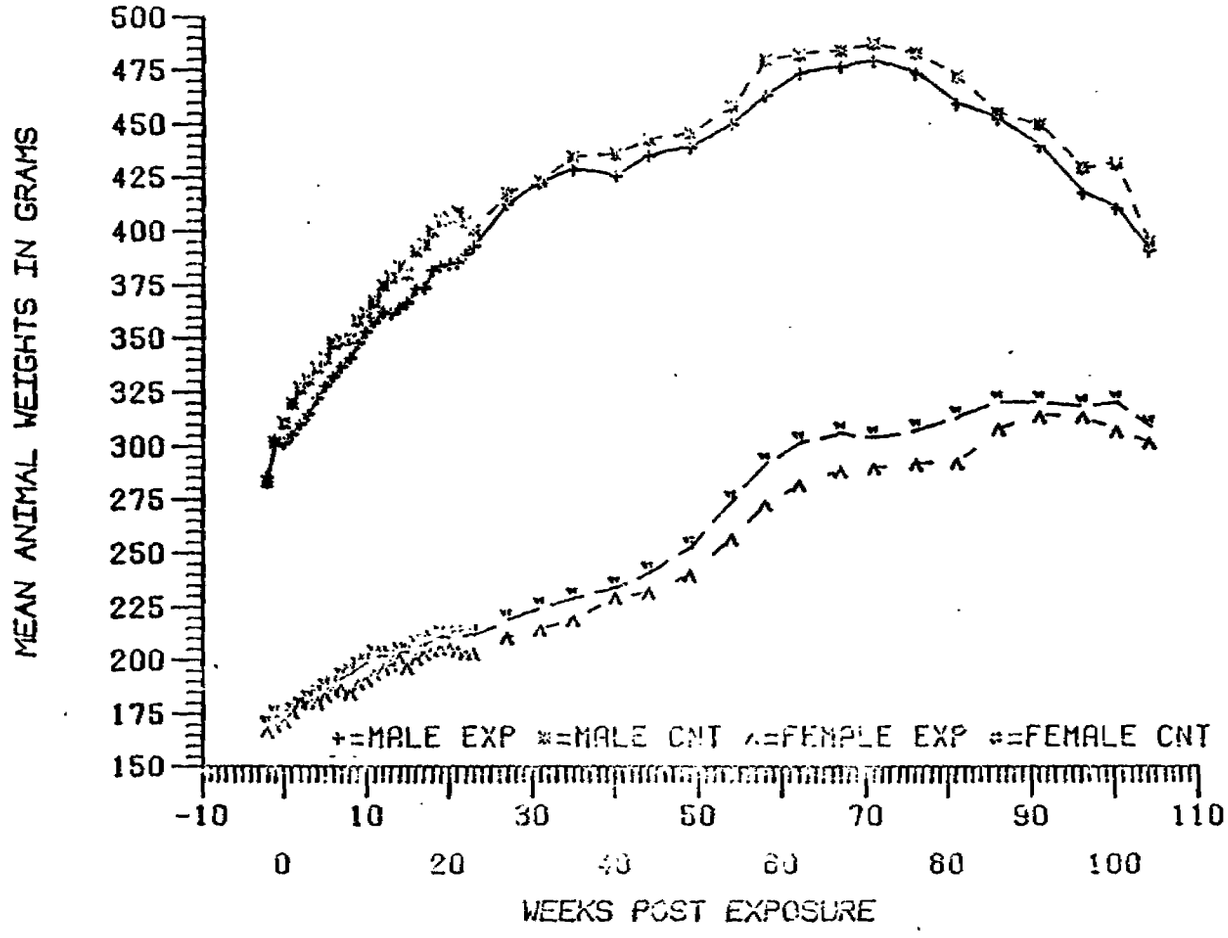

Table IV. Over-all Summary Incidence of Non-neoplastic Changes and Histologically-Proven Neoplasms Within The Liver and Lungs of ICR Swiss Mice Exposed to Vinyl Chloride.

Single Inhalation Exposure

Tissue/Response	Exposure	Incidence of Response									
		Control		Vinyl chloride							
	Dose Level (PPM)	0		50,000		5,000		500		50	
	Sex of Animals	M	F	M	F	M	F	M	F	M	F
	Animals Per Group*	62	77	74	82	76	82	72	75	81	80
Liver	Number Evaluated	50	75	63	78	68	76	67	72	64	68
- hepatic cell necrosis		2	10	3	5	5	7	4	6	2	3
- hepatic cell vacuolation (lipidosis)		2	11		4	2	12	3	5	1	4
- hepatic cell hypertrophy		1		2	8		8	4	13	1	
- hepatic cell hyperplasia						4	4				
- angiectasis					1		4				
- sinusoidal reticulosis					5						
- hepatic cell adenoma		2		1			1			2	
- hepatic cell carcinoma		2		4	1	6	1	9		2	
- hemangioma									2		1
- hemangiosarcoma		1				1					
Lung	Number Evaluated	50	70	61	76	65	78	66	73	71	68
- pneumonitis		1	6	21	10	13	17	19	15	4	7
- bronchio-alveolar adenoma		4	8	31	14	14	10	8	10	8	6
- bronchio-alveolar carcinoma				1	2	1			1		

* Total includes animals from scheduled sacrificed (8 and 18 month periods) and spontaneous deaths.

Table V. Summary of Incidence of Histologically-Proven Neoplasms Within Tissues ICR Mice Exposed to Vinyl Chloride Monomer (Single Inhalation Exposure)

1-hr Inhalation Exposure in ppm	Spontaneous Deaths									Schedule Sacrifice						Totals	
	0-6 Months			7-12 Months			13-18 Months			8 Months			18 Months				
	M	F	Total	M	F	Total	M	F	Total	M	F	Total	M	F	Total	Male	Female
50,000	0	0	0	5	11	16	33	32	65	4	1	5	7	17	24	49	61
5,000	0	2	2	4	2	6	22	27	49	2	1	3	5	13	18	33	45
500	0	5	5	6	8	14	19	14	33	1	0	1	5	24	29	31	51
50	0	0	0	4	15	19	9	18	27	0	0	0	2	14	16	15	47
0 (Control)	2	0	2	0	1	1	14	41	55	0	0	0	2	12	14	18	54
TOTALS VCM	0	7	7	19	36	55	83	91	174	7	2	9	19	68	87		

Table VI. Incidence of Histologically-Proven Neoplasms Within Tissues From ICR Mice Exposed to Vinyl Chloride Monomer (Single Inhalation Exposure)

Sacrifice Period	Organ Tissue	50,000 ppm			5,000 ppm			500 ppm			50 ppm			0 ppm (Control)		
		M	F	Total	M	F	Total	M	F	Total	M	F	Total	M	F	Total
Scheduled	Lung	4	1	5	1	1	2	0	0	0	0	0	0	0	0	0
8 months	Liver	0	0	0	1	0	1	1	0	1	0	0	0	0	0	0
	Kidney	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Stomach	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Other*	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Totals	4	1	5	2	1	3	1	0	1	0	0	0	0	0	0
18 months	Lung	5	6	11	3	7	10	4	12	16	1	4	5	1	7	8
	Liver	2	3	5	2	0	2	1	1	2	0	1	1	1	2	3
	Kidney	0	0	0	0	1	1	0	3	3	0	2	2	0	0	0
	Stomach	0	0	0	0	0	0	0	1	1	1	0	1	0	0	0
	Other*	0	8	8	0	5	5	0	7	7	0	7	7	0	3	3
	Totals	7	14	24	5	13	18	5	24	29	2	14	16	2	12	14
Spontaneous Deaths	Lung	0	0	0	0	1	1	0	1	1	0	0	0	0	0	0
	Liver	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0
	Kidney	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0
0-6 mon	Stomach	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Other*	0	0	0	0	1	1	0	2	2	0	0	0	2	0	2
	Totals	0	0	0	0	2	2	0	5	5	0	0	0	2	0	2
7-12 mon	Lung	3	3	6	3	1	4	1	2	3	2	2	4	0	0	0
	Liver	0	2	2	0	0	0	2	1	3	1	0	1	0	0	0
	Kidney	1	2	3	1	0	1	1	1	2	0	2	2	0	0	0
	Stomach	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0
	Other*	1	4	5	0	1	1	2	4	6	1	10	11	0	1	1
	Totals	5	11	16	4	2	6	6	8	14	4	15	19	0	1	1
13-18 mon	Lung	22	16	38	12	5	17	5	2	7	5	5	10	4	9	13
	Liver	5	5	10	5	5	10	8	4	12	4	2	6	5	7	12
	Kidney	4	0	4	1	3	4	1	2	3	0	1	1	1	5	6
	Stomach	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Other*	2	11	13	4	14	18	5	6	11	0	10	10	4	20	24
	Total	33	32	65	22	27	49	19	14	33	9	18	27	14	41	55

Table VII . Over-all Summary Incidence of Non-neoplastic Ghanges and Histologically-Proven Neoplasms Within The Liver and Lungs of AJ Mice Exposed to Vinyl Chloride (Multiple Inhalation Exposure)

Tissue/Response	Exposure	Incidence of Response: Control		Vinyl chloride	
	Dose Level (PPM)	0		500	
	Hours Exposure	10 x 1		10 x 1	
	Sex of Animal	M	F	M	F
	Animals Per Group*	46	48	78	92
Liver	**Number Evaluated**	**45**	**48**	**78**	**89**
- hepatic cell necrosis		4	6	6	13
- lymphoid cell infiltrate		1		1	
- hepatic cell lipidosis		2		2	
- neutrophil infiltrate		2			1
- bile duct hyperplasia		1			
- granulomatous foci				1	
- sinusoidal reticulosis				1	
- hepatocyst					1
- amyloidosis				1	
- angiectasis					1
- hepatic cell adenoma		1			
- cholangiocarcinoma				1	
		11	6	13	16
Lung	**Number Evaluated**	**43**	**47**	**76**	**90**
- edema					1
- pneumonitis			2		
- bronchio-alveolar hyperplasia		2	1		2
- bronchio-alveolar adenoma		15	16	56	68
- bronchio-alveolar carcinoma			3	12	10
		17	22	68	81

* Total includes animals from scheduled sacrificed (8, 16, 20 month periods) and spontaneous deaths

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Table VIII. Over-all Summary Incidence of Non-neoplastic Changes and Histologically-Proven Neoplasms Within The Lungs of AJ Mice Exposed to Vinyl Chloride.

Multiple Inhalation Exposure

Tissue/Response	Exposure	Incidence of Response: Control		Vinyl chloride	
	Dose Level (PPM)	0		50	
	Hours Exposure	100 x 1		100 x 1	
	Sex of Animal	M	F	M	F
	Animals Per Group*	39	47	81	83
Lung	Number Evaluated	39	45	77	81
- edema		2			
- congestion		4	1	1	
- focal hemorrhage		2		2	
- pneumonitis		5	3	4	5
- bronchio-alveolar hyperplasia			3		3
- osseous metaplasia					1
- bronchio-alveolar adenoma		11	18	27	38
- bronchio-alveolar carcinoma		2		3	4
- reticulum cell sarcoma					1
		13	18	30	43

* Total includes animals from scheduled sacrifice (8, 16, 20 month periods) and spontaneous deaths.

Table IX. Summary of Incidence of Histologically-Proven Neoplasms Within Tissues From AJ Mice Exposed to Vinyl Chloride Monomer (Multiple Inhalation Exposures)

Sacrifice Period	1-hr Inhalation Exposures to Vinyl Chloride Monomer												TOTALS			
	50 ppm x 100			CONTROL			500 ppm x 10			CONTROL			V C M		CONTROLS	
	M	F	TOTAL	M	F	TOTAL	M	F	TOTAL	M	F	TOTAL	M	F	M	F
Spontaneous Deaths 0-6 Months	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0
7-12 Months	8	3	11	0	0	0	2	1	3	0	0	0	10	4	0	0
13-20 Months	23	20	43	3	5	8	36	27	63	2	3	5	59	47	5	8
Scheduled Sacrifice 8 Months	3	1	4	0	1	1	6	6	12	0	0	0	9	7	0	1
16 Months	10	6	16	2	3	5	14	8	22	1	1	2	24	14	3	4
20 Months	19	44	63	16	11	27	29	41	70	17	21	38	48	85	33	32
Totals	63	74	137	21	20	41	87	85	172	20	25	45	150	159	41	45

Table X. Incidence of Histologically-Proven Neoplasms Within Tissues From AJ Mice Exposed to Vinyl Chloride Monomer (Multiple Inhalation Exposure)

Sacrifice Period	Organ Tissue	Scheduled Sacrifice and Spontaneous Deaths											
		50 ppm x 100			Control			500 ppm x 100			Control		
		M	F	Total	M	F	Total	M	F	Total	M	F	Total
Scheduled	Lung	1	1	2	0	1	1	6	6	12	0	0	0
8 Months	Liver	0	0	0	0	0	0	0	0	0	0	0	0
	Kidney	0	0	0	0	0	0	0	0	0	0	0	0
	Stomach	0	0	0	0	0	0	0	0	0	0	0	0
	Other*	0	0	0	0	0	0	0	0	0	0	0	0
	Totals	3	1	4	0	1	1	6	6	12	0	0	0
16 Months	Lung	4	5	9	2	3	5	9	8	17	1	1	2
	Liver	6	0	6	0	0	0	0	0	0	0	0	0
	Kidney	0	0	0	0	0	0	0	0	0	0	0	0
	Stomach	0	1	1	0	0	0	0	0	0	0	0	0
	Other*	0	0	0	0	0	0	5	0	5	0	0	0
	Totals	10	6	16	2	3	5	14	8	22	1	1	2
20 Months	Lung	16	28	44	10	11	21	25	40	65	14	17	31
	Liver	2	3	5	2	0	2	0	0	0	1	0	1
	Kidney	0	3	3	0	0	0	1	0	1	0	0	0
	Stomach	0	0	0	0	0	0	0	0	0	0	0	0
	Other*	1	10	11	4	0	4	3	1	4	2	4	6
	Totals	19	44	63	16	11	27	29	41	70	17	21	38
Spontaneous Deaths	Lung	0	0	0	0	0	0	0	1	1	0	0	0
	Liver	0	0	0	0	0	0	0	0	0	0	0	0
0-6 Months	Kidney	0	0	0	0	0	0	0	0	0	0	0	0
	Stomach	0	0	0	0	0	0	0	0	0	0	0	0
	Other*	0	0	0	0	0	0	0	1	1	0	0	0
	Totals	0	0	0	0	0	0	0	2	2	0	0	0
7-12 Month	Lung	2	1	3	0	0	0	1	0	1	0	0	0
	Liver	2	0	2	0	0	0	0	0	0	0	0	0
	Kidney	1	0	1	0	0	0	0	0	0	0	0	0
	Stomach	0	0	0	0	0	0	0	0	0	0	0	0
	Other*	3	2	5	0	0	0	1	1	2	0	0	0
	Totals	8	3	11	0	0	0	2	1	3	0	0	0
13-20 Months	Lung	13	10	23	2	3	5	28	23	51	0	1	1
	Liver	2	3	5	0	1	1	2	0	2	0	1	1
	Kidney	4	0	4	0	0	0	0	0	0	0	1	1
	Stomach	0	0	0	0	0	0	0	0	0	0	0	0
	Other*	4	7	11	1	1	2	6	4	10	1	1	2
	Total	23	20	43	3	5	8	36	27	63	2	3	5

Table XI. Over-all Summary Incidence of Non-neoplastic Changes Within The Lungs of Fischer Rats Exposed To Vinyl Chloride.

Single Inhalation Exposure

Tissue/Response	Exposure / Dose Level (PPM) / Sex of Animal / Animals Per Group*	Incidence of Response: Control 0 M	Control 0 F	Vinyl chloride 50,000 M	Vinyl chloride 50,000 F	Vinyl chloride 5,000 M	Vinyl chloride 5,000 F	Vinyl chloride 500 M	Vinyl chloride 500 F	Vinyl chloride 50 M	Vinyl chloride 50 F
	Animals Per Group*	89	74	86	87	83	93	87	100	90	91
Lung	Number Evaluated	85	67	80	77	80	87	85	95	80	74
- bronchopneumonia		26	10	45	13	13	10	15	3	28	3
	% incidence	30.6	14.9	56.2	16.9	16.3	11.5	17.6	3	35.0	4.1

* Total includes animals from scheduled sacrifice (8, 16, and 24 month periods) and spontaneous deaths.

Table XII. Summary of Incidence of Histologically-Proven Neoplasms Within Tissues From Fischer Rats Exposed to Vinyl Chloride Monomer (Sinlge Inhalation Exposure)

1-hr Inhalation Exposure in ppm	Spontaneous Deaths												Schedule Sacrifice									Totals	
	0-6 Months			7-12 Months			13-18 Months			19-24 Months			8 Months			16 Months			24 Months				
	M	F	T*	M	F	T*	M	F	T*	M	F	T*	M	F	T*	M	F	T*	M	F	T*	Male	Female
50,000	0	0	0	0	4	4	16	20	36	86	47	133	2	0	2	4	2	6	21	34	55	129	107
5,000	0	0	0	2	2	4	20	9	29	71	37	108	0	0	0	5	1	6	37	52	89	135	101
500	0	0	0	0	2	2	18	18	36	57	64	121	0	0	0	13	0	13	82	37	119	170	121
50	0	0	0	0	2	2	18	15	33	89	28	117	0	0	0	7	0	7	64	27	91	178	72
0 (Control)	0	0	0	0	0	0	13	3	16	102	56	158	0	0	0	11	3	14	60	27	87	186	89
Totals VCM	0	0	0	2	10	12	72	62	134	303	176	479	2	0	2	29	3	32	204	150	354		

Table XIII. Incidence of Histologically-Proven Neoplasms Within Tissues From Fischer Rats Exposed to Vinyl Chloride Monomer (Single Inhalation Exposure)

Sacrifice Period	Organ Tissue	50,000 ppm			5,000 ppm			500 ppm			50 ppm			0 ppm (control)		
		M	F	Total	M	F	Total	M	F	Total	M	F	Total	M	F	Total
Scheduled	Lung	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
8 months	Liver	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Kidney	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Stomach	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Other*	2	0	2	0	0	0	0	0	0	0	0	0	0	0	0
	Total	2	0	2	0	0	0	0	0	0	0	0	0	0	0	0
16 months	Lung	2	0	2	0	0	0	1	0	1	1	0	1	0	0	0
	Liver	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Kidney	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Stomach	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Other*	2	2	4	5	1	6	12	0	12	6	0	6	11	3	14
	Total	4	2	6	5	1	6	13	0	13	7	0	7	11	3	14
24 months	Lung	0	2	2	0	0	0	3	3	6	1	2	3	3	2	5
	Liver	1	3	4	3	2	5	8	4	12	9	3	12	9	1	10
	Kidney	0	0	0	0	0	0	1	0	1	0	0	0	1	0	1
	Stomach	0	1	1	0	1	1	0	0	0	0	0	0	0	1	1
	Other*	20	28	48	34	49	83	70	30	100	54	22	76	47	23	70
	Total	21	34	55	37	52	89	82	37	119	64	27	91	60	27	87

Table XIV. Incidence of Histologically-Proven Neoplasms Within Tissues From Fischer Rats Exposed to Vinyl Chloride Monomer (Single Inhalation Exposure)

Sacrifice Period	Organ Tissue	50,000 ppm			5,000 ppm			500 ppm			50 ppm			0 ppm (control)		
		M	F	Total	M	F	Total	M	F	Total	M	F	Total	M	F	Total
Spontaneous Deaths 0-6 Months	Lung	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Liver	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Kidney	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Stomach	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Other*	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Totals	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7-12 Months	Lung	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Liver	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0
	Kideny	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Stomach	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Other*	0	4	4	2	2	4	0	1	1	0	2	2	0	0	0
	Totals	0	4	4	2	2	4	0	1	1	0	2	2	0	0	0
13-18 Months	Lung	1	4	5	5	1	6	3	5	8	3	1	2	0	0	0
	Liver	2	3	5	4	2	6	2	4	6	2	0	4	0	0	0
	Kidney	0	1	1	0	1	1	0	0	0	2	0	2	0	0	0
	Stomach	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0
	Other*	13	12	25	11	5	16	13	9	22	11	13	24	13	3	16
	Totals	16	20	36	20	9	29	18	18	36	18	15	33	13	3	16
19-24 Months	Lung	4	4	8	11	5	16	4	8	12	11	0	11	8	0	8
	Liver	12	6	18	9	4	13	6	10	16	9	0	9	14	8	22
	Kidney	2	1	3	3	1	4	0	1	1	3	0	3	3	1	4
	Stomach	0	2	2	0	0	0	0	3	3	0	0	0	3	1	4
	Other*	68	34	102	48	27	75	47	42	89	26	28	54	74	46	120
	Totals	86	47	133	71	37	108	57	64	121	69	28	117	102	56	158

Table XV. Summary of Incidence of Histologically-Proven Neoplasms Within Tissues From Fischer Rats Exposed to Vinyl Chloride Monomer (Multiple Inhalation Exposures)

Sacrifice Period	1-hr Inhalation Exposures to Vinyl Chloride Monomer												Totals			
	50 ppm x 100			Control			500 ppm x 100			Control			VCM		Control	
	M	F	Total	M	F	Total	M	F	Total	M	F	Total	M	F	M	F
Spontaneous Deaths 0-6 Months	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7-12 Months	0	0	0	3	0	3	0	0	0	0	0	0	0	0	3	0
13-18 Month	14	6	20	5	0	5	10	6	16	3	0	3	24	12	8	0
19-24 Month	111	51	162	52	29	81	52	29	81	33	34	67	163	80	85	63
Scheduled Sacrifice 8 Months	0	0	0	0	0	0	0	1	1	0	0	0	0	1	0	0
16 Months	8	10	18	4	1	5	10	1	11	0	0	0	18	11	4	1
24 Months	43	43	86	32	29	61	42	71	113	69	27	96	85	114	101	56
Totals	176	110	166	96	59	145	114	108	222	105	61	166	290	218	201	120

Table XVI. Incidence of Histologically-Proven Neoplasm Within Tissues From Fischer Rats Exposed to Vinyl Chloride Monomer (Multiple Inhalation Exposure)

Sacrifice Period	Organ Tissue	Spontaneous Deaths											
		50 ppm x 100			Control			500 ppm x 100			Control		
		M	F	Total	M	F	Total	M	F	Total	M	F	Total
0-6 Months	Lung	0	0	0	0	0	0	0	0	0	0	0	0
	Liver	0	0	0	0	0	0	0	0	0	0	0	0
	Kidney	0	0	0	0	0	0	0	0	0	0	0	0
	Stomach	0	0	0	0	0	0	0	0	0	0	0	0
	Other*	0	0	0	0	0	0	0	0	0	0	0	0
	Totals	0	0	0	0	0	0	0	0	0	0	0	0
7-12 Months	Lung	0	0	0	0	0	0	0	0	0	0	0	0
	Liver	0	0	0	0	0	0	0	0	0	0	0	0
	Kidney	0	0	0	0	0	0	0	0	0	0	0	0
	Stomach	0	0	0	0	0	0	0	0	0	0	0	0
	Other*	0	0	0	3	0	3	0	0	0	0	0	0
	Totals	0	0	0	3	0	3	0	0	0	0	0	0
13-18 Months	Lung	3	0	3	2	0	2	4	0	4	1	0	1
	Liver	3	0	3	0	0	0	2	0	2	1	0	1
	Kidney	0	0	0	0	0	0	0	0	0	0	0	0
	Stomach	0	0	0	0	0	0	0	0	0	0	0	0
	Other*	8	6	14	3	0	3	4	6	10	1	0	1
	Totals	14	6	20	5	0	5	10	6	16	3	0	3
19-24 Months	Lung	11	5	16	9	4	13	9	4	13	8	5	13
	Liver	15	7	22	9	4	13	9	4	13	5	8	13
	Kidney	1	1	2	2	2	4	2	2	4	1	2	3
	Stomach	1	1	2	0	2	2	0	2	2	1	2	3
	Other*	83	37	120	32	17	49	32	17	49	18	17	35
	Totals	111	51	162	52	29	81	52	29	81	33	34	67

Table XVII. Incidence of Histologically-Proven Neoplasms Within Tissues From Fischer Rats Exposed to Vinyl Chloride Monomer (Multiple Inhalation Exposures)

Sacrifice Period	Organ Tissue	Scheduled Sacrifice											
		50 ppm x 100			Control			500 ppm x 100			Control		
		M	F	Total	M	F	Total	M	F	Total	M	F	Total
8 Months	Lung	0	0	0	0	0	0	0	0	0	0	0	0
	Liver	0	0	0	0	0	0	0	0	0	0	0	0
	Kidney	0	0	0	0	0	0	0	0	0	0	0	0
	Stomach	0	0	0	0	0	0	0	0	0	0	0	0
	Other*	0	0	0	0	0	0	0	1	1	0	0	0
	Total	0	0	0	0	0	0	0	1	1	0	0	0
16 Months	Lung	0	0	0	0	0	0	0	0	0	0	0	0
	Liver	0	0	0	0	0	0	0	0	0	0	0	0
	Kidney	0	0	0	0	0	0	2	0	2	0	0	0
	Stomach	0	0	0	0	0	0	0	0	0	0	0	0
	Other*	8	10	18	4	1	5	8	1	9	0	0	0
	Total	8	10	18	4	1	5	10	1	11	0	0	0
24 Months	Lung	1	0	1	1	1	2	4	2	6	3	0	3
	Liver	7	2	9	2	3	5	10	1	11	5	4	9
	Kidney	0	0	0	0	0	0	2	0	2	0	0	0
	Stomach	0	0	0	0	0	0	0	0	0	1	0	1
	Other*	35	41	76	29	25	54	26	68	94	66	23	83
	Total	43	43	86	32	29	61	42	71	113	69	27	96

Table XVIII. Incidence of Eosinophilic Changes Within Livers of EWA Colony (Sprague-Dawley) Rats-Multiple Inhalation Exposures to Vinyl Chloride (VC)

Exposure	Control			VC			VC		
Dose Level (PPM)	0			500			50		
Hours Exposure	49			49			49		
Group+	A	B	T	A	B	T	A	B	T
Males: Animals per group	9	16	25	13	12	25	11	14	25
Eosinophilic Focus/Foci	1/9	1/13	2/22	10/13***	3/11	13/24***	4/10	4/11*	8/21**
%	11.1	7.7	9.1	76.9	27.3	54.2	40.0	36.4	38.1
Eosinophilic Area/Areas	0/9	1/13	1/22	1/13	1/11	2/24	0/10	3/11	3/21
%	0.0	7.7	4.5	7.7	9.1	8.3	0.0	27.3	14.3
Eosinophilic Alterations++	1/9	1/13	2/22	10/13	4/11	14/24****	4/10	5/11**	9/21**
%	11.1	7.7	9.1	76.9	36.4	58.3	40.0	45.4	42.8
Females: Animal per group	18	7	25	11	14	25	19	6	25
Eosinophilic Focus/Foci	0/18	0/7	0/25	4/11	1/13	5/24**	2/19	1/6	3/25*
%	0.0	0.0	0.0	36.4	7.7	20.8	10.5	16.7	12.0
Eosinophilic Area/Areas	4/18	0/7	4/25	2/11	0/13	2/24	1/9	1/6	2/25
%	22.2	0.0	16.0	18.2	0.0	8.3	5.3	16.7	8.0
Eosinlphilic Alterations++	4/18	0/7	4/25	5/11	1/13	6/24	3/19	1/6	4/25
%	22.2	0.0	16.0	45.4	7.7	25.0	15.8	16.7	16.0

+ Group: A = Scheduled sacrifice, B = Spontaneous deaths, T = Total
++ Eosinophilic fee: and/or areas in the same animal are tabulated one time as an eosinophilic alteration
* = Different from control at 5.0 - >2.5% level (P = .05 - .025)
** = Different from control at 2.5 - >0.5% level (P = 0.25 - .005)
*** = Different from control at 0.5 - >0.05% level (P = .005 - .0005)
**** = Different from control at 0.05% level (P = .0005)

Table XIX. Summary of Matings and Percentage Pregnancy Observed in the VCM Three-Generation Study.

	Control*			50 ppm*			500 ppm*		
	Total Females Mated	Total Females Pregnant	% Pregnant Females	Total Females Mated	Total Females Pregnant	% Pregnant Females	Total Females Mated	Total Females Pregnant	% Pregnant Females
F_0 Gen.	25	22	88	25	21	84	25	23	92
F_1 Gen.	20	19	95	19	18	94.7	21	21	100
F_2 Gen.	19	19	100	18	18	100	21	21	100

Here and in all similar tables, the exposure level refers to that of the F_0 generation.

Table XXI. Summary of Average Litter Size for Each Treatment Group and Generation.

	Average Litter Size	STD DEV
Control	11.10	0.38
50 ppm VCM	11.32	0.39
500 ppm VCM	10.92	0.36
F_1 Generation	8.83*	0.36
F_2 Generation	12.57	0.39
F_3 Generation	11.93	0.39

* Significantly different, p = 0.05

Table XX. Average Litter Size for the Three-Generation VCM Study.

	Control				50 ppm				500 ppm			
	Total Pups Born	Total Number Litters	Average Litter Size	STD Dev	Total Pups Born	Total Number Litters	Average Litter Size	STD Dev	Total Pups Born	Total Number Litters	Average Litter Size	STD Dev
F_1 Generation	195	22	8.9	0.63	202	21	9.6	0.64	184	23	8.0	0.61
F_2 Generation	239	19	12.6	0.67	234	18	13.0	0.69	255	21	12.1	0.64
F_3 Generation	225	19	11.8	0.67	204	18	11.3	0.69	285	21	12.6	0.64

Table XXII. Percentage of Stillborn Pups in the VCM Three-Generation Study

	Control			50 ppm			500 ppm		
	Total Pups Born	Total Stillborn	% Stillborn	Total Pups Born	Total Stillborn	% Stillborn	Total Pups Born	Total Stillborn	% Stillborn
F_1 Generation	195	1	0.51	202	5	2.48	184	3	1.63
F_2 Generation	239	0	0.00	234	2	0.85	255	2	0.78
F_3 Generation	225	2	0.89	204	5	2.45	265	3	1.13

Table XXIII. Numbers, Sex, and Weights of F_1 Generation

Age of Pups Days	Total Number of Pups						Average Weight (Grams)					
	Control		50 ppm		500 ppm		Control		50 ppm		500 ppm	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
1	102	92	105	93	93	88	6.88	6.60	6.98	6.69	7.05	6.76
4	102	92	105	93	92	88	10.50	10.03	10.50	10.15	10.72	10.37
7	102	89	105	93	92	88	15.29	14.71	15.30	14.87	15.76	15.41
14	102	89	105	92	92	88	27.8	26.8	28.6	27.2	28.6	23.4
21	102	89	105	92	92	88	44.5	42.4	44.3	42.8	45.4	44.1

Table XXIV. Numbers, Sex, and Weights of F_2 Generation

Age of Pups Days	Total Number of Pups						Average Weight (Grams)					
	Control		50 ppm		500 ppm		Control		50 ppm		500 ppm	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
1	120	119	114	118	123	130	6.38	6.13	6.55	6.16	6.52	6.18
4	118	119	114	117	122	130	9.70	9.13	9.82	9.21	10.00	9.27
7	118	119	113	116	122	130	14.38	13.85	14.57	13.45	14.72	13.97
14	118	119	113	116	122	130	27.77	27.26	28.10	26.15	28.80	27.44
21	118	119	113	116	122	130	40.89	40.57	41.54	38.67	42.93	41.20

Table XXV. Numbers, Sex, and Weights of F_3 Generation

Age of Pups Days	Total Number of Pups						Average Weight (Grams)					
	Control		50 ppm		500 ppm		Control		50 ppm		500 ppm	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
1	112	111	91	108	139	123	6.82	6.38	6.84	6.61	6.66	6.30
4	112	111	91	108	139	123	10.18	9.47	10.35	9.76	9.87	9.07
7	111	111	91	108	139	123	14.63	13.90	14.81	14.18	13.89	13.25
14	111	111	90	108	135	121	25.41	25.39	27.46	25.81	25.53	23.95
21	111	111	90	108	134	121	34.77	33.85	36.75	35.14	35.11	33.40

Table XXVI. Viability, Survival, and Lactation Indexes in a Three-Generation Study of Reproductive Performance After Exposure of the F_0 Parents to VCM Gas.

	Generation	Control	Low Dose 50 ppm	High Dose 500 ppm
Viability Index	F_1	100	100	99.4
	F_2	99.2	99.7	99.6
	F_3	100	100	100
Survival Index Day 21	F_1	98.5	99.5	99.4
	F_2	99.2	98.7	99.6
	F_3	99.6	99.5	97.3
Lactation Index	F_1	98.5	99.5	99.4
	F_2	100	99.1	100
	F_3	99.6	99.5	97.3

$$\text{Viability Index} = \frac{\text{No. of pups alive at Day 4}}{\text{No. of pups born alive}} \times 100$$

$$\text{Day 21 Survival Index} = \frac{\text{No. of pups alive at Day 21}}{\text{No. of pups born alive}} \times 100$$

$$\text{Lactation Index} = \frac{\text{No. of pups alive at Day 21}}{\text{No. of pups alive at Day 4}} \times 100$$

Banerjee, B.N., Course Director, Teratology-Principles and Procedures Related to Fetal Development. The Center for Professional Advancement, Sommerville, New Jersey. September 1974. Course Notes.

Figure XVIII
Control - 8 months

FIGURE LEGEND

Control hepatocyte morphology with normal appearing endothelium adjacent. X5,000.

Negative #198,063

Figure XVIII'
Control - 8 months

Figure XIX
Single Exposure - 8 months post-exposure

FIGURE LEGEND

Hepatocytes show lipid droplet accumulation. At center of field, cytoplasm devoid of recognizable organelles is in shape of bleb. Adjacent belb is apparently free in space of Disse. This may represent a means whereby cytoplasmic material may be shed. X5,000.

Negative #A52381

UCC
002316

Ptgure XIX, Single Exposure - 8 months post-exposure

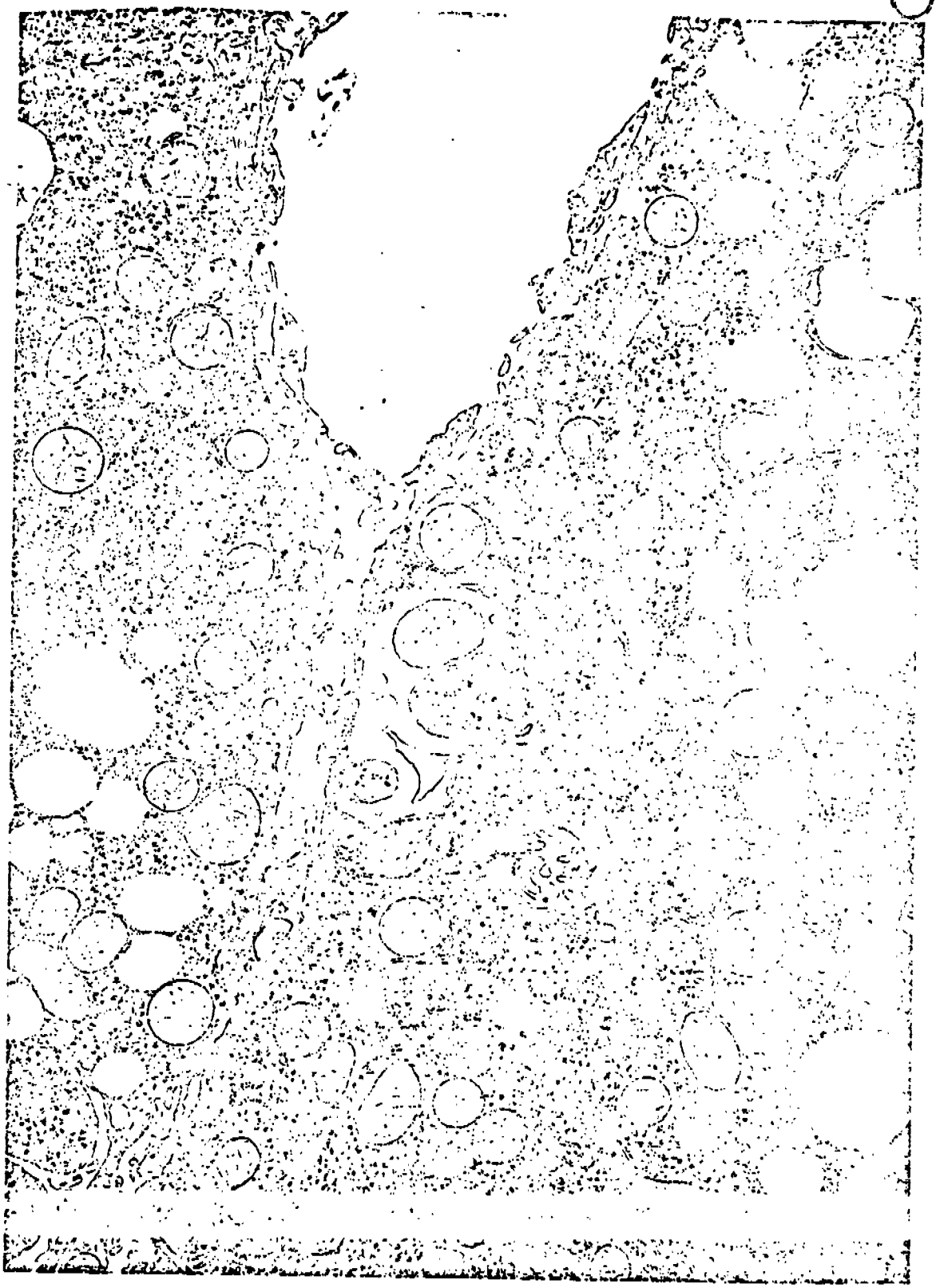


Figure XX
Single Exposure - 8 months post-exposure

FIGURE LEGEND

Figure shows portion of two hepatocytes. Note numbers of small dense bodies with one or more electron-lucent regions. These are lipofuchsin granules. X4,000.

Negative #A54,048

Figure XX
Single Exposure - 8 months post-exposure

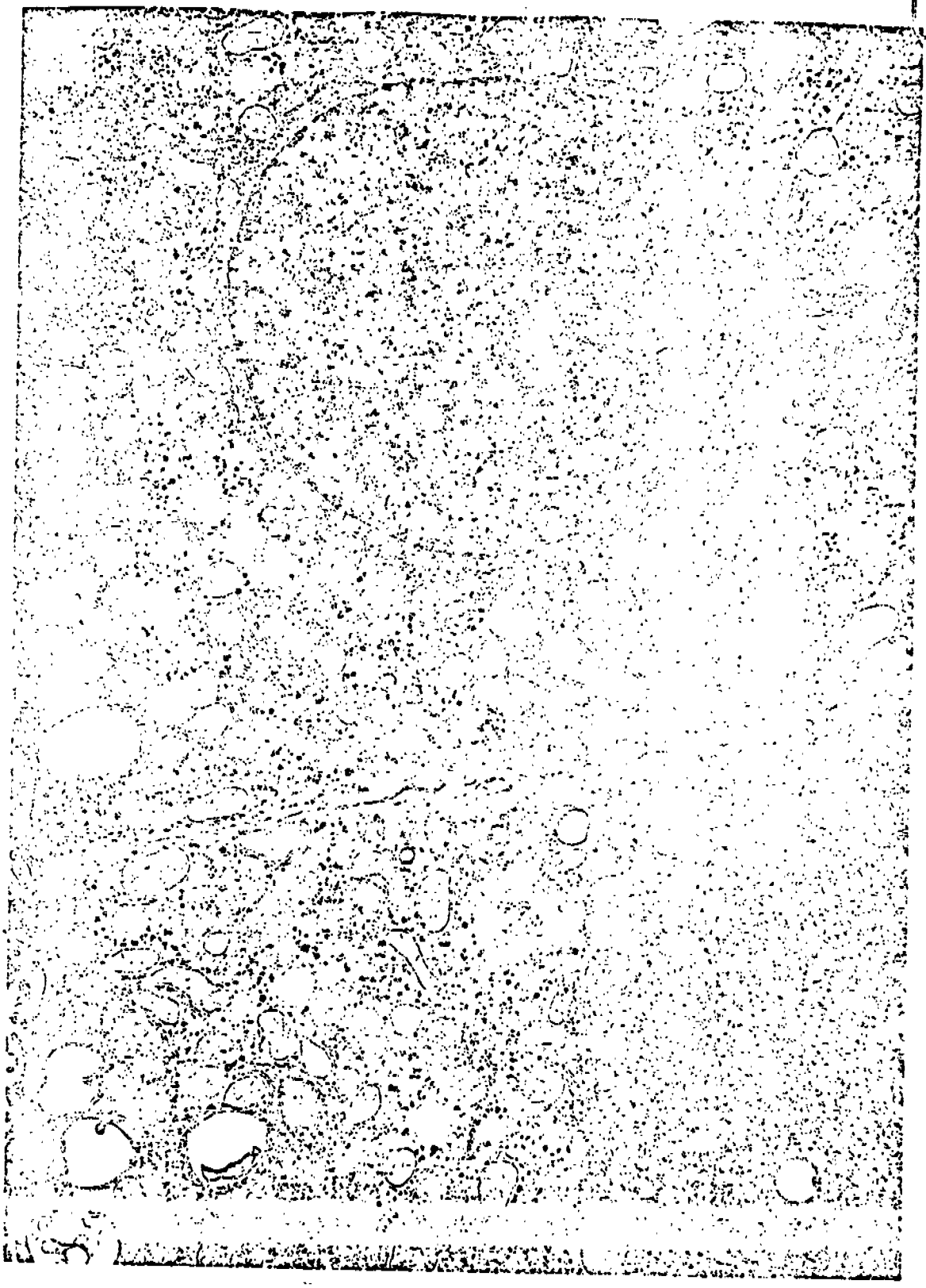


Figure XXI
Multiple Exposure - 8 months post-exposure

FIGURE LEGEND

Kupffer cell shows evidence of active phagocytic function. Large residual body suggests prior engulfment of entire cell (perhaps a white blood cell). X5,000.

Negative #198,066

Figure XXI
Multiple Exposure - 8 months post-exposure

Figure XXII

VINYL CHLORIDE/MULTIPLE DOSE

16 MONTHS POST EXPOSURE CONTROLS

Females VP76 136-138

Changes were encountered in this control group. In hepatocytes, cleft-like spaces were seen in dense bodies. These were suggestive of a crystalline material extracted during processing. Kupffer cells were large and contained large residual bodies. Vesicular endoplasmic reticulum and bizarre shaped mitochondria were occasional findings.

Figure XXII
Controls - Multiple Exposure - 16 months post-exposure

FIGURE LEGEND

Hepatocyte contains numerous dense bodies and lipofuchsin granules. Cleft-like white spaces in dense bodies may represent crystalline material extracted during processing. X5,000.

Negative #197,157

Figure XXII
Control - Multiple Exposure - 16 month post-exposure

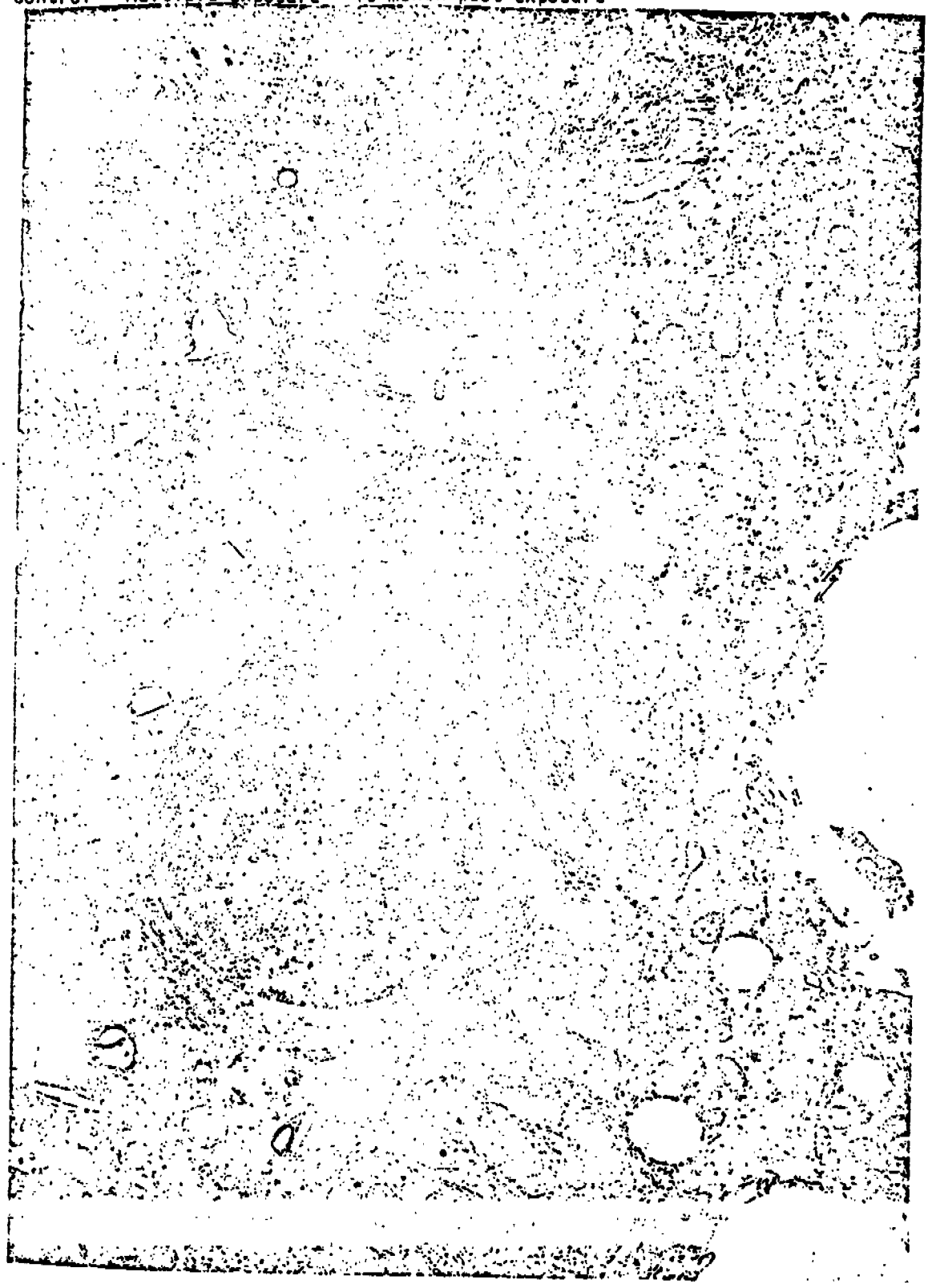


Figure XXIII
Multiple Exposure - 16 months post exposure

FIGURE LEGEND

Indented nucleus at center of field consistent with adenocarcinoma. Cell at upper left is necrotic and shows mitochondria with high amplitude swelling and flocculent densities. X5,000.

Negative #197,434

Figure XXIII
Multiple Exposure - 16 month post-exposure

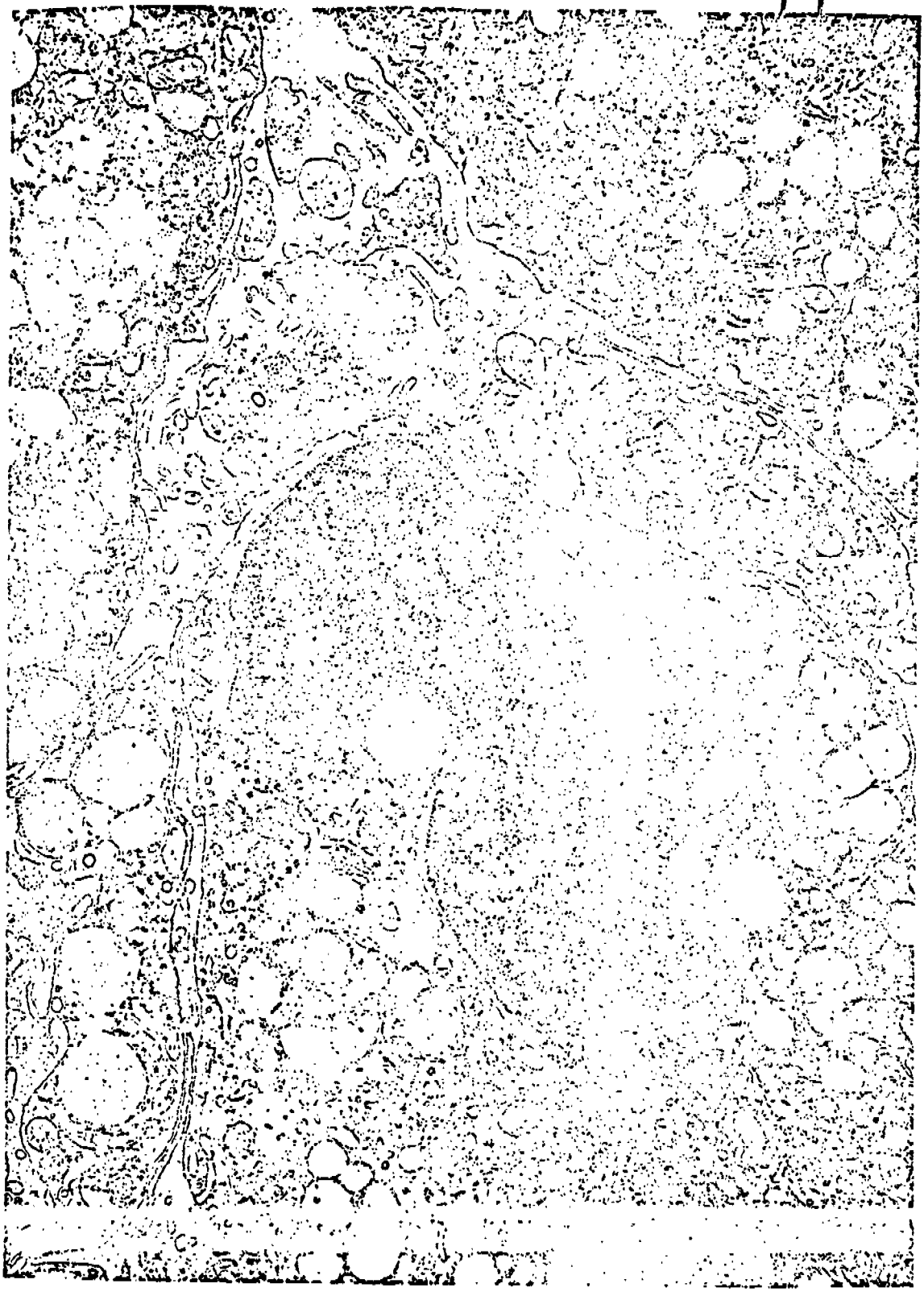


Figure XXIV
Controls - 24 months

FIGURE LEGEND

Normal appearance of hepatocyte in this control group. X5,000.

Negative #209,293

Figure XXIV
Controls - 24 months

Figure XXV

VP77 67-71

MALES

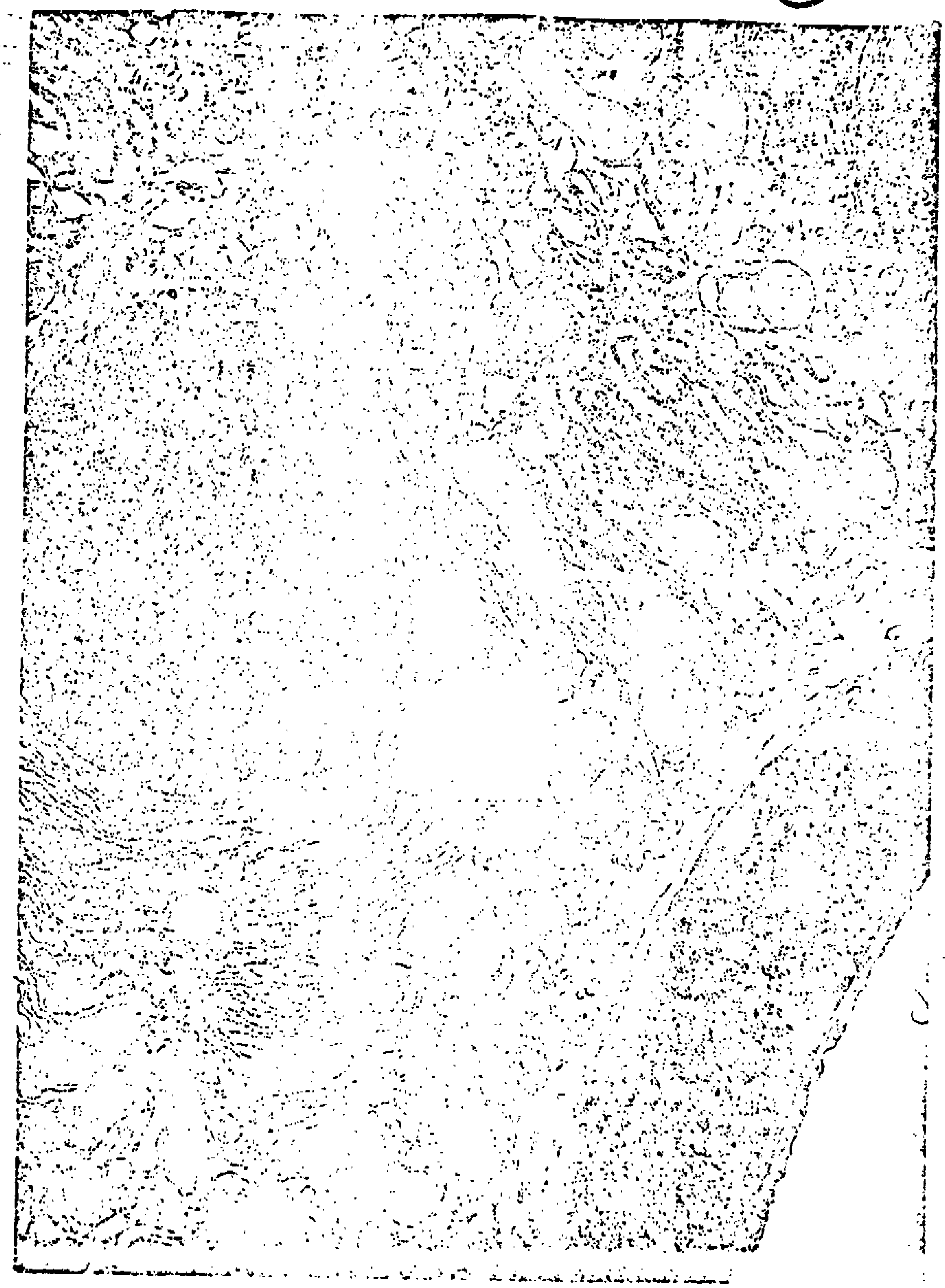
10 WEEKLY EXPOSURES TO PPM VINYL CHLORIDE

POST EXPOSURE 106 WEEKS

General Summary of Findings:

Changes within hepatocytes included increased lipofuchsin granules and endoplasmic reticulum dilatation with a material of low electron density filling endoplasmic reticulum cisternae. In addition, bile canaliculi frequently showed distended lumens with the simplication of the plasma membrane at this site. Non-hepatocytic changes included enlarged Kupffer cells with abundant lysosomes and dense bodies and a mononuclear infiltrate into hepatic parenchyma.

Figure XXV



UCC
002330