01-VC/PVC-TXG

ENC. WITH: ltr dated 2-11-80
FROM: Don R. Clay, US.E. TO: Cokayne - Shell Chem
ZG Bell + PVC Grp
"et al"

U.S. CONSUMER PRODUCT SAFETY COMMISSION

WASHINGTON, D.C. 20207

February 6, 1980

Dr. Theodore R. Torkelson
Health & Environmental Sciences
Building #1603
Dow Chemical U.S.A.
Midland, Michigan 48640

Dear Ted:

In response to your telephone request of 2/5/80, I am enclosing for your information a copy of the paper entitled: "Toxicology, Carcinogenicity and Reproductive Effects of Single and Multiple Exposures to Vinyl Chloride in Rats and Mice." This paper is now being submitted for publication.

If you or your colleagues have comments or questions, please contact me directly at (301) 492-6504.

Sincerely,

Robert M. Hehir
Technical Director of Laboratories

cc: Dr. J. McLaughlin, CPSC
Dr. B. McNamara, CSL-Edgewood Arsenal
Don R. Clay, DAED/ES, CPSC

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ENC. WITH ltr dated 2-6-80
FROM: US Product Safety Comm R.M. Hehir TO: TL Torkelson Dow Chem U.S.A

See ltr dated 2-11-80 Dow Chem U.S.A. re "dust"

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

by

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DISCLAIMER

The views, opinions and conclusions expressed in this paper are those of the authors and do not necessarily represent the views of the Consumer Product Safety Commission.

Dictated Feb 1980

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ABSTRACT

From a regulatory point of view there is serious concern for the safety of humans exposed to single and intermittent low level concentrations of known carcinogens. Vinyl chloride monomer (VCM), already identified as a human and animal carcinogen, was selected as a model agent to explore this area of interest for two reasons - one, exposure to consumers and industrial workers was wide-spread and secondly, some basic information on its mode of action was available and more was being developed. In the traditional cancer bioassay, animals are repeatedly exposed over their normal life span to small doses of suspect chemical. In the current studies rats and mice were exposed in an inhalation chamber to single one-hour doses of vinyl chloride ranging from 50 to 50,000 ppm. In addition, other groups were given 10 one-hour exposures to 500 ppm or 100 one-hour exposures to 50 ppm of the same chemical. All animals were kept in cages for the remainder of their lives, generally 18-24 months. Moribund animals were euthanized and survivors were sacrificed on schedule and their tissues examined for pathological changes. A multi-generation reproduction study in Sprague-Dawley/Wistar rats, carried out simultaneously, did not demonstrate adverse effects on reproductive performance. Moreover, the original parents from the vinyl chloride reproduction study were also maintained for two years and subsequent examination failed to disclose any carcinogenic effect. Specifically, the oncogenic study demonstrated dose related effects for single one-hour exposure of vinyl chloride at high levels i.e., 5,000 and 50,000 ppm. These concentrations increased the incidence of pulmonary adenomas and carcinomas in mice. Repeated exposures of A/J mice

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to the same chemical at 500 ppm x 10 one-hour exposures also increased the incidence of pulmonary ademonas and carcinomas which are considered highly significant (P=.001) when compared to matched controls. However, at a lower repeated dose of 50 ppm x 100 one-hour exposure no significant increase in tumors was observed. Rats exposed to identical concentrations of vinyl chloride failed to elicit a tumorigenic response. The liver as a target organ received special attention. Electron microscopic (EM) studies of the Fischer rats exposed for one hour to vinyl chloride showed sublethal cytoplasmic injury which subsequently recovered. Examinations of the Sprague-Dawley/Wistar rats which were held for 24 months after the 49th exposure to 2,450 or 24,950 ppm vinyl chloride revealed only age related changes.

Running Title: Biological Effects of Short-Term Exposures to VCM

INTRODUCTION

The responsibility for regulating vinyl chloride fell between the overlapping jurisdiction of several federal agencies. Federal proposals to control vinyl chloride's use as an aerosol propellant, to limit occupational exposure and emission from chemical and fabricating plants as well as to regulate its shipment were initiated by the Food and Drug Administration, the Environmental Protection Agency, the Consumer Product Safety Commission, the Department of Transportation and the Occupational Health and Safety Administration in (1974). These actions followed reports of long-term chronic toxicity studies by Viola et.al., (1971) and Maltoni(1974), which demonstrated vinyl chloride's carcinogenic activity in experimental animals. The need for immediate action was further heightened by the epidemiological studies of Creech and Johnson (1974). Their report uncovered four cases of hepatic angiosarcoma in chemical plant workers associated with polyvinyl chloride production. Further industrial investigations by Tabershaw et al., (1974) identified additional cases. The relationship between vinyl chloride and angiosarcoma in man and animal has been substantiated by a number of American and European scientists. For the most part, the government's primary attention was focused on reducing occupational exposures, in addition, basic research projects were also being initiated by other federal agencies. Considering the scope of the federal research programs and proposed rulemaking which would eliminate unnecessary exposure to vinyl chloride it appeared that the potential problem was well under control. However, vinyl chloride has bean referred to by medical

researchers as a "potent carcinogen." What did we know about the potential hazards to consumers dealing with a host of everyday products containing vinyl chloride in such items as aerosol hairsprays, pestiides, paints, etc.? Vinyl chloride is a base ingredient in one of the most commonly used plastics, polyvinyl chloride (PVC), which was omnipresent in their everyday life i.e., food wrappings, pipes, home and auto upholstery and hundreds of other sundry products. The fact was we could find no relevant information on the long-term biological effects of acute or intermittent inhalation exposures to any known carcinogen. Preliminary studies by FDA and EPA demonstrated that the use of certain aerosol hairsprays or pesticides could result in exposures of vinyl chloride of 200 and 400 ppm respectively for short duration. Bearing in mind that Maltoni and Lefemine (1974) and Keplinger et al., (1975), implicated even low level repeated doses of vinyl chloride i.e., 50 ppm as being capable of inducing angiosarcoma in laboratory rodents there was genuine concern for single high level and intermittent lower level exposures of vinyl chloride in humans. Therefore, the CPSC had two primary objectives in mind in sponsoring this research: (1) to study the long term effects of graded single and short-term intermittent exposures to vinyl chloride and (2) to study the effects of vinyl chloride on reproduction.

Furthermore, we felt that this program would complement other ongoing research efforts to determine the pharmacokinetics and mechanism of action for this chemical. Quite apart from the objectives just mentioned, there was a secondary objective, to look at the question of a "threshold effect" or "safety factor" for low dose exposures for a well defined carcinogenic substance like vinyl chloride. There is a

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natural scientific curiosity about the question of a "threshold effect" and while we did not hope to resolve the debate on this highly controversial issue we did expect to develop sufficient scientific data to help formulate regulatory policy and to sustain future decisions to control low level human exposures to chemical carcinogens.

The experimental protocols were jointly developed by the staff of Chemical Systems Laboratory (formerly Edgewood Arsenal) and by the Health Science staff at the Consumer Product Safety Commission. The protocols were reviewed and critiqued by both governmental and private sector experts and their suggestions were considered and incorporated into the final experimental design.

MATERIALS AND METHODS

Vinyl Chloride Monomer

The vinyl chloride monomer gas (99.9% minimum purity), used in these inhalation studies, was obtained from Matheson Gas Products in size 1F cylinders containing 200 lbs. of the monomer under 34 psi at 70°F.

Animals

Rats: Fischer 344, male and female (Charles River Laboratory, Wilmington, Mass.).

Sprague-Dawley/Wistar, male and female (Chemical Systems Laboratory Colony, Edgewood, Maryland).

Mice: AJ Strain, male and female (Jackson Laboratory, Bar Harbor, Maine).

ICR Strain, male and female (Charles River Laboratory, Wilmington, Mass.)

Exposure and Sampling Techniques

The exposures were conducted in 100 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 ml 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).

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Exposure Procedures for Toxicology and Carcinogenicity

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, exposure shown in Table 1.

b. Ten one-hour exposures at 500 ppm (one-hour per day, five days per week for two weeks). Fischer 344, A/J mice, exposure schedule shown in Table 2.

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, exposure schedule shown in Table 2.

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.

Pathology

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.

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 cannibalism.

Electron Microscopic Studies

For the electron microscopic studies the following animals were selected at random.

Groups consisting of five male and five female Fischer 344 rats from each of the single one-hour (50-500-5,000 and 50,000 ppm) exposures with equal numbers of their corresponding control group were sacrificed at 8, 16, and 24 months.

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

One group of five males and five female Sprague-Dawley/Wistar rats from the parental generation of the reproduction group (49 x 50 ppm, 49 x 500 ppm) along with equal numbers of their control group were 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 microscopic fixative consisting of 4% formaldehyde, 1% glutaraldehyde in 0.1 M phosphate buffer as described by E.M. McDowell and B.F. Trump (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 by the modified techniques of J.H. Luft (1961).

Reproduction Study and Carcinogenicity

F_o male and female parents or Sprague-Dawley/Wistar rats were exposed as outlined in Table 3 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. This assured exposure of all forms of male germ cells. The females were exposed during all phases of the oogenic cycle. Each parental generation was evaluated for fertility, litter size, number stillborn and ability to lactate. The F_1, and F_2, and F_3 off-spring were evaluated for post-natal growth, viability, survivability and reproduction anomalies.

The parental generation of Sprague-Dawley/Wistar rats were maintained for 24 months post exposure for carcinogenic evaluation.

RESULTS

Toxicology (single and multiple exposures)

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 ataxia were noted. At 59 minutes tremors were seen. Females showed some hyperactivity at 50 minutes and 25 percent 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.

Observation After Exposure

There were no significant differences in mortalities at P=.05 level between exposed and control animals using Student - T or Chi-Squared analysis at any level. However, when the KOLMOGOROV - SMIRNOV two sample test is used to analyze the VCM mortality data there is a significant difference at P=.05 level between 50,000 ppm and control male single exposure ICR mice and between 50,000 ppm and 50 ppm single dose ICR mice. No other dose level or species showed significance.

Gross Pathology

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

Light Microscopic Pathology

Mice (single exposure)

Histological examination at 8 and 18 months in ICR mice exposed once to concentrations of 50, 500, 5000 or 50,000 ppm showed the following changes attributable to VCM. Summary of histologically identified changes in the liver and lung are shown in Table 4.

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The development of lung adenomas increased with exposure to higher dose levels of vinyl chloride but the progression to carcinoma was minimal as summarized in Table 5. Pneumonitis was evident in all animal groups which were exposed to VCM in doses of 500 ppm or more.

Mice(10 x 1hr x 500 ppm and 100 x 1hr x 50 ppm exposures)

A summary of the histopathologic changes observed in the liver and/or lung of A/J mice at 8, 16 and 20 months following their multiple exposures to VCM are presented in Tables 6 and 7. The increased incidence of pulmonary adenomas and carcinomas was attributed to the VCM exposure. The pulmonary findings are presented for comparative purposes in Table 8. The effects of multiple exposures of VCM on A/J mice in Table 8 were compared by the z test for difference of means and proportions. Accordingly, there is a highly significant difference in the number of pulmonary adenomas ($P < .001$) and carcinomas ($P \simeq .001$) in the A/J mice exposed to 500 ppm VCM for 10 x one hour exposures when compared to their matched controls. By the same token, there is no significant difference in pulmonary adenomas and carcinomas in test versus control animals at the 50 ppm x 100 x one hour exposure level.

Rats (single exposures)

Except for aggravation of latent pulmonary changes, particularly bronchopneumonia as shown in Table 9, 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.

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 10 times at 500 ppm or 100 times at 50 ppm as shown in Table 10.

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.

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 as shown in Table 10. The appearance of these foci was related to dosage. The nature of these lesions is controversial.

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 11. The significance of these histologic changes will be discussed later in the paper.

Electron Microscopic Results

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

Hepatocellular carcinoma was seen in one male Fischer rat which had received 10 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 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 of 8-Month Recovery to Single Exposure to 50, 500, 5000, and 50,000 ppm-hr of Vinyl Chloride in Fischer Rats

a. Alterations from control occurred in all treated animals at each concentration.

b. Changes were less severe in female animals.

c. Hepatocytic alteration included lipid accumulation, increased dense bodies, lipofuschin granules 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 seen in single and multiple exposures.

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

General Conclusions of 16-Month Recovery After Single Exposures to 50, 500, 5000, and 50,000 ppm x 1 hr to Vinyl Chloride in Fischer Rats

a. Normal morphology 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.

General Conclusions to 24-Month Recovery from Single Dose Exposures of 50, 500, 5000, and 50,000 ppm Vinyl Chloride in Fischer Rats

a. Age-related changes including formation of cleft-like spaces

(possible related-to hemoglobin/hemosiderin), inflammatory infiltrate (pericholangitis) and some collagen accumulation were seen in controls 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.

General Conclusions of 8-Month Recovery to Multiple Exposures to 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.

b. Less alteration was encountered in female rats.

c. Cellular changes were 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.

General Conclusions of 16-Month Recovery to Multiple Exposures of 500 ppm x 10 exposures and 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.

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

General Conclusions to 24-Month Recovery After Multiple Doses of 500 ppm x 10 and 50 ppm x 100 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.

General Conclusions to 49 Exposures for 1 Hr at Daily Intervals Followed by 24 Months 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.

Multigeneration Study in Rats (Sprague-Dawley/Wistar)

No consistent changes attributable to VCM were found in F_o 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 effect on fertility, viability and survival of offspring and ability to lactate. 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 as shown in Tables 12-18.

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

DISCUSSION AND CONCLUSIONS

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 also 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 frequency of tumor production.

The second set of considerations above suggest the existence of "no effect" doses, threshold doses, and dose response curves which have the hockey stick shape described by Bryan and Shimkin (1943). These considerations have been discussed for radiation by Storer (1975) and Lipton et al., (1970) and for chemical carcinogenesis by Saffiotti and Maugh (1978).

The Food Protection Committee, Food and Nutrition Board of National Academy of Sciences - National Research Council in (1959) noted that a dose response relationship could be applied to carcinogens. The higher the dose, the greater the response and the shorter the time required to elicit that response. This relationship has been reported for 1, 2, 5, 6-dibenzoanthracene (DBA) by Bryan and Shimkin (1943) for 20-methylcholanthrone (MC) and for 9, 10-dimethyl-1, 2-benzanthracene (DMBA) plus croton oil by Graffi (1953) for p-dimethylaminoazobenzene by Druckery (1959) and for carbon tetrachloride by Eschenbrenner and Miller (1944). Dose response curves have been given for ultraviolet light by Blum (1950) and for ionizing radiation by Finkel (1958) and Mole (1958).

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 levels sometimes do produce tumors. This remark is supported by experimental observations of such researchers as Poel (1959), Graffi (1953) and Druckery (1959).

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

The concept of lifetime accumulative, non-tumorigenic and tumorigenic doses of radiation has been adopted. The Federal Radiation Council (1960) 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.

Vinyl Chloride and Carcinogenicity

Maltoni (1975) and Maltoni and Lefemine (1975), described a dose-response relationship for the carcinogenic effect of vinyl chloride in animals. The neoplastic response was related to the length of exposure.

Lee et al., (1978) noted that the incidence and severity to tumors increased with the concentration of VCM and the length of exposure.

The statements above indicate that the total dose (concentration X exposure time) may be of importance in the carcinogenicity of vinyl chloride. The total inhaled dose can be approximated utilizing concepts developed by Haber in (1924). 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 parts 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 (1975) and Maltoni and Lefemine (1975); Lee et al., (1978); Viola et al., (1971); Caputo et al.,(1974) and Keplinger et al., (1975).

These Ct calculations are summarized in Tables 19 and 20.

In the studies of P. L. Viola, A. Bigotti and A. Caputo (1971) 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 (1974) exposed rats and rabbits 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 in rats at this dose 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 or at 320,000 ppm-hrs. Tumors appeared in the rabbits after nine months following similar treatment at a concentration of 10,000 ppm VCM. Thus the lowest total dose demonstrating carcinogenosis in rabbits was 7,200,000 ppm-hrs.

M. L. Keplinger et al., (1975) 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.

Calculations from the data of the Consumer Product Safety Commission studies (Tables 5 and 11) 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., (1978) 78,000 ppm-hrs and Maltoni (1975) and Maltoni and Lefemine (1975) between 30,000 ppm-hrs and 150,000 ppm-hrs, and other investigators. 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 carcinogencity appears in both mice and rats at Ct;s of 50,000 to 500,000 ppm-hrs, and high incidences of carcinogenesis are noted in mice and rats at Ct's of greater than 500,000 ppm-hrs.

The previous studies of Maltoni (1975), Maltoni and Lefemine (1975), Lee et al., (1978), Viola et al., (1971), Caputo et al., (1974), Keplinger et al.,(1975) and the 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-hrs 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

electron microscopic study did not reveal carcinogenic responses in rats at Cts from 50 to 50,000 ppm-hrs. However, Ct's of 2450 ppm-hrs produced eosinophilic foci but no overt tumors in rats in the CPSC tests.

As an additional consideration in the total dose concept, CT's of 5000 ppm-hrs 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 a single exposure of sufficient magnitude may be carcinogenic in sensitive species.

Under the conditions of exposure, VCM produced pneumonitis in all mice above 500 ppm. The high level of pneumonitis among test mice was a result of test exposure, not a prior condition of spontaneous disease. Furthermore, the pneumonitis was recognized and evaluated as an inherent response, not as an undesirable variable of exposure. The idea that viral infection of the lungs (i.e., influenza) might lead to cancer is not new. For example, Steiner and Loosli (1950) studied the effects of human influenza virus (Type A) on the incidence of lung tumors in mice . The supposition was that infection might, under certain conditions, cause cancers but more specifically from the proliferative changes that occurred in the lung following recovery. The Steiner-Loosli (1950) experiment was a test of that supposition. In their experiment the hyperplasia which developed as a result of infection did not go on to tumors. On the contrary these investigators noted possible inhibitory or anticarcinogenic effects which they felt deserved further study. Under

the conditions of this toxicologic study, pneumonitis and pulmonary adenomas were induced in mice. This is a conclusion strictly limited by the available data. Relationships, synergistically or otherwise, between pneumonitis and pulmonary adenomas or carcinomas are neither explicit nor ascribable. There is a real possibility that vinyl chloride could induce pneumonitis in man. However, this does not mean that pulmonary cancer may or may not be the inevitable consequences. It is, therefore, 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-weighed (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.

Data on vinyl chloride in ambient air are limited also. Atmospheric measurements in the vicinity of production plants indicate that concentrations are frequently below 1 ppm. One peak grab sample of 33 ppm has been reported in an EPA Scientific and Technical Assessment Report (1975) at 0.5 kilometer from the center of one plant.

The time-weighted threshold limit value of the American Conference of Government Industrial Hygienist for (1977) was 200 ppm. There is a notice of intended change. The Environmental Protection Agency in (1976) established the following emission limits for vinyl chloride; (1)formation and purification processes is 10 ppm, (2) emissions from equipment preceding and including the stripper in the plant process flow is 10 ppm, and (3) emissions from equipment following the stripper are to be controlled by stripping dispersion resins to 2000 ppm and other resins to 400 ppm. The Code of Federal Regulation 40, Protection of Environment, (1978) states that fugitive emissions from loading and unloading of lines, rotating pumps, reciprocating pumps, rotating compressors, agitators, manual venting of gases, and opening of equipment must be ducted through control systems so that the concentration of vinyl chloride in the exhaust does not exceed 10 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, Table 19), respectively. 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 (rats). At the TLV of 200 ppm (daily Ct of 1600 ppm-hr) as postulated in Table 21 the time to accumulate a carcinogenic would be three 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.

There are a number of methods which could be used to obtain risk estimates for low doses of this carcinogenic agent. Aside from the fact

that none of the current extra-polation procedures can be justified on a biological basis, the exercise permits one to compare theoretical risk levels for various chemicals. Whereas the Armitage and Doll (1961) multi-stage model assumes the risk is approximately linear even in the low dose range; the probit model of Mantel and Bryan (1961), has a hockey stick appearance. That is to say, as the dose approaches zero, the response function in this region is extremely flat (zero slope).

By comparison, the log probit model for high levels of risk and high tumor rates gives a lower predicted dose than the linear extrapolation model. Realizing that any low dose extrapolation method is arbitrary and subject to biological and mathematical criticism, we never-the-less selected a model developed by Guess and Crump (1976) to analyze our data. Instead of assuming the shape of the dose response function we allowed the program to fit the experimental data to the best model by using a Monte-Carlo goodness - of-fit test. We used a computer program (GLOBAL) which has been described in a paper by Crump, Guess, and Deal (1977). The procedure is based upon a dose response function of the form:

$$P(d) = 1 - \exp^{-Q(d)} \qquad (1)$$

$$Q(d) = \sum_{i=0}^{\infty} q_i d^1 \qquad (2)$$

where Q(d) is a polynomial with non-negative coefficients q_i of unknown degree, where $q_i \geq o$ for all i events and $q_i = o$ for all but finitely many i. P(d) is the probability that an animal will develop a particular response which is linear in d dose rate for small d if $q_i > o$. Moreover, P(d) can be arbitrarily flattened by taking enough of the low order coefficients equal to zero, since at very low doses $P(d) - P(0) \sim \exp(-q_o)\ q_i d^1$ where 1 is the smallest positive integer for which $q_i > 0$. Accordingly, Crump, Guess and Deal (1977), interpret P(d) as the probability that an animal will

develop a particular type of tumor during the duration of the experiment while under continuous exposure to a dose rate d of the chemical being tested.

By using the experimental values in table 5, comparing the single VCM inhalation exposures of ICR mice and the progression of pulmonary lung lesions to carcinoma over an 18 month period in the GLOBAL computer program one can theoretically determine an approprate (dose-response) mathematical model and also the risk given the dose or conversely the dose given excess risk. These values along with the upper and lower 95 and 99 percent confidence limits are presented in Table 22 for the multi-stage polynomial model.

By interpolation of the data presented in Table 22 we estimate an approximate two-fold increase in the risk of developing a pulmonary carcinoma in the experimental animal when exposed to 5000 ppm VCM compared to the spontaneous background level. At the highest exposure level, i.e., 50,000 ppm, the theoretical risk of developing the same pulmonary tumor is increased about nine fold. Examining the dose given excess risk, the model predicts that a continuous exposure to 2.4 ppm VCM would induce one excess cancer case in a million.

CONCLUSIONS

An overall summary of the biological effects of VCM on the laboratory animals studies is presented in Table 23.

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

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B. No reproductive changes attributable to VCM were found. These include mating, percent pregnancies, fertility, lactation, percent still-borns, litter size, post-natal growth, neonatal viability, neonatal survivability, and fetal anomalies.

C. VCM seemed to produce pneumonitis in mice and to aggravate bronchopneumonia in rats.

D. VCM produced eosinophilic changes in rats but no frank (light microscopy) carcinogenesis.

E. VCM produced an increase in frequency of lung tumors in mice.

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

G. The carcinogenic effects of VCM in mice seem to depend upon concentration and exposure time, Ct. There were VCM doses which were not carcinogenic and there appeared to be a total accumulated dose above which tumors were produced. Tumors were not seen in mice at Ct's of 500 ppm-hrs, however, carcinogenic effects of VCM were seen in mice at total doses (Cts) of 5,000 ppm-hrs and above.

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Table 1. 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 344 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

Table 2. 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.

Table 3. VCM Multigeneration Study F_0 Parents [a/]

Group	Compound	Dose[b/]	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

a/ Sprague-Dawley/Wistar rats.

b/ Exposed to 50 or 500 PPM of VCM one-hour per day, five days per week for 10 weeks (49 exposures) before mating.

Table 4. 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

		Incidence of Response									
	Exposure	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
Tissue/Response	Animals Per Group[a]	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						1					
- hemangiosarcoma		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		

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

Table 5:

HISTOLOGICAL EXAMINATION OF ICR MICE AT 8 AND 18 MONTHS FOLLOWING A SINGLE (1-HOUR) EXPOSURE TO VINYL CHLORIDE MONOMER

VINYL CHLORIDE CONCENTRATION	HISTOLOGICAL CHANGES ATTRIBUTABLE TO VINYL CHLORIDE	
	INDUCTION OF PULMONARY ADENOMAS	PROGRESSION TO CARCINOMA
50,000 PPM*	45/137 OR 33.3%	3/137 OR 2.2%
5,000 PPM*	24/143 OR 16.8%	1/143 OR 0.7%
500 PPM*	18/139 OR 12.9%	1/139 OR 0.7%
50 PPM	14/139 OR 10.1%	0/139 OR 0%
0 (CONTROL)	12/120 OR 10.0%	0/120 OR 0%

*PNEUMONITIS WAS EVIDENT IN ALL ANIMAL GROUPS WHICH WERE EXPOSED TO VCM AT DOSES OF 500 PPM OR MORE.

Table 6. Over-all Summary Incidence of Non-neoplastic Changes and Histologically-Proven Neoplasms within the Liver and Lungs of AJ Mice Exposed to Vinyl Chloride

(Multiple Inhalation Exposure)

Tissue/Response	Exposure / Dose Level (PPM) / House Exposure / Sex of Animal / Animals Per Group[a]	Incidence of Response: Control 0 10 x 1 M 46	Control 0 10 x 1 F 48	Vinyl Chloride 500 10 x 1 M 78	Vinyl Chloride 500 10 x 1 F 92
Liver	Number Evaluated	45	48	78	89
- hepatic cell necrosis		4	6	6	13
- lumphoid 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

a/ Total includes animals from scheduled sacrified (8, 16, 20 month periods) and spontaneous deaths.

Table 7. 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 [a]	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

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

Table 8:

HISTOLOGICAL EXAMINATION OF A/J MICE AT 8, 16, AND 20 MONTHS FOLLOWING MULTIPLE (1-HOUR) EXPOSURES TO VINYL CHLORIDE MONOMER

NUMBER OF EXPOSURES & CONCENTRATION OF VCM	HISTOLOGICAL CHANGES ATTRIBUTABLE TO VINYL CHLORIDE MONOMER	
	INDUCTION OF PULMONARY ADENOMAS	PROGRESSION TO CARCINOMA
0 (CONTROLS)	31/90 OR 34.4%	3/90 OR 3.3%
10 X 500 PPM a/	124/166 OR 74.7%	22/166 OR 13.3%
0 (CONTROLS	29/84 OR 34.5%	2/84 OR 2.4%
100 X 50 PPM b/	65/158 OR 44.1%	7/158 OR 4.4%

a/ Highly significant difference in the number of pulmonary adenomas ($P < .001$) and carcinomas ($P \leq .001$) observed at the 500 ppm X 10 one hr exposure level versus control by Z test (Spiegel 1961).

b/ No significant difference for pulmonary adenomas ($P < 0.14$) and carcinomas ($P \leq 0.19$ observed at the lower multiple exposure level.

Table 10. 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/	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 b/	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: Animals 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
Eosiniphilic Alterations b/	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

a/ Group: A = Scheduled sacrifice, B = Spontaneous deaths, T = Total

b/ Eosinophilic foci 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 11. SUMMARY - VINYL CHLORIDE LIFETIME CANCER STUDIES

Experimental Group	PPM	DAYS (1 hr/day)	(ppm-hrs)	SPECIES	NUMBER EXPOSED	RESULTS
A	50,000	1	50,000	ICR Mice Fischer Rats	180 178	2.2% Carcinoma/33% adenoma negative
A	5,000	1	5,000	ICR Mice Fischer Rats	180 180	0.7% Carcinoma/16.8%adenoma negative
A	500	1	500	ICR Mice Fischer Rats	180 190	0.7% Carcinoma negative
A	50	1	50	ICR Mice Fischer Rats	180 180	negative negative
B	500	49	24,500	Sprague-Dawley/ Wistar Rats	49	Eosinophilic changes
B	50	49	2,450	Sprague-Dawley/ Wistar Rats	47	Eosinophilic changes
C	500	10	5,000	AJ Mice Fischer Rats	180 180	74% Adenoma negative
C	50	100	5,000	AJ Mice Fischer Rats	179 180	41% Adenoma negative
				TOTAL EXPOSED	2263	
				TOTAL CONTROL	776	
				COMBINED TOTAL	3039	

A - 170 ICR Mice (82 male and 88 female) and 171 Fischer Rats (92 male and 79 female) served as control animals for the single exposure (50,000; 5,000; 500; 50 PPM) studies.

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

C - 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.

Table 12. Summary of Matings and Percentage Pregnancy Observed in the VCM Three-Generation Study.

	Control[a]			50 ppm[a]			500 ppm[a]		
Gen.[b]	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	25	22	88	25	21	84	25	23	92
F_1	20	19	95	19	18	94.7	21	21	100
F_2	19	19	100	18	18	100	21	21	100

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

[b] Generation

Average Litter Size for the Three-Generation VCM Study.

GEN.		Control			50 ppm				500 ppm			
		tal 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	195	22	8.9	0.63	202	21	9.6	0.64	184	23	8.0	0.61
F_2	239	19	12.6	0.67	234	18	13.0	0.69	255	21	12.1	0.64
F_3	225	19	11.8	0.67	204	18	11.3	0.69	285	21	12.6	0.64

Table 14. Percentage of Stillborn Pups in the VCM Three-Generation Study

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

Table 15. 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 16. 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 17. 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	26.41	25.39	27.46	25.81	25.53	23.95
21	111	111	90	108	135	121	34.77	33.85	36.75	35.14	35.11	33.40

Table 18. 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	F_1	100	100	99.4
	F_2	99.2	99.7	99.6
	F_3	100	100	100
Survival Index	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

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

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

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

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

Table 19. MALTONI VINYL CHLORIDE STUDIES[a/], [b/]
Calculations based on reference [a/]

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)

a/ C. Maltoni 1975

b/ C. Maltoni and G. Lefemine 1975

TABLE 20. OTHER VINYL CHLORIDE STUDIES

AUTHORS	SPECIES	RESULTS (CARCINOGENESIS) - PPM-HRS
VIOLA, BIGOTTI, CAPUTO 1971	RATS	POSITIVE AT 28,800K
CAPUTO, VIOLA BIGOTTI 1974	RATS	NEGATIVE AT 48K POSITIVE AT 320K, 1280K, 3200K 6400K, 12,800K
	RABBITS	POSITIVE AT 7200K
KEPLINGER et al., 1975	MICE (RATS & HAMSTERS)	POSITIVE AT 56K
LEE 1978	MICE	ALL TESTS ESSENTIALLY NEGATIVE BELOW AND POSITIVE ABOVE 78K.
CONSUMER PRODUCTS SAFETY COMMISSION 1979	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

Table 21:

TLV VS ACCUMULATED PPM/HRS

	TIME* TO ACCUMULATE CARCINOGENIC DOSE	
	MOUSE	RAT
TLV	5000 PPM/HR	150,000 PPM/HR
200 PPM	3 DAYS	19 WEEKS
10 PPM	12 WEEKS	375 WEEKS

*FIVE DAY WORK WEEK

Table 22: VINYL CHLORIDE INHALATION - PULMONARY RISK

Single Exposure (ICR mice)

Risk Given Dose

d[a]	Carcinoma[b]	P(d)[c]	95 Percent		99 Percent	
			L[d]	U	L	U
0	0/120	.002723	-.002118	.007563	-.003639	.009085
50	0/139	.002744	-.002090	.002744	-.003609	.008096
500	1/139	.002931	-.001842	.007703	-.003341	.009203
5000	1/143	.004803	-.000001	.009604	-.001507	.001113
50000	3/137	.023329	-.001435	.048093	-.009218	.055876

Dose Given Excess Risk

P(d) - P (o)[e]	d[a]	95 Percent		99 Percent	
		L	U	L	U
.1	50,000	22063	113312	18767	133209
.01	24,134	10675	54561	9084	64122
.001	2,403	1063	5431	904	6383
.0001	240	106	543	90	638
.00001	24	11	54	9	64
.000001	2.4	1.1	5	1	6
.0000001	.24	.11	.54	.09	.64
.00000001	.024	.011	.054	.009	.064

a/ Vinyl chloride exposure in ppm.

b/ Number of mice with carcinoma/number of mice total.

c/ Risk or probability that animal will develop a particular tumor (Method: Crump, Guess, Deal 1977).

d/ Upper and lower confidence limits of 95 and 99 percent.

e/ Risk of excess cancers at various dose levels.

Table 23:

SUMMARY OF EFFECTS OF VINYL CHLORIDE

TOXICOLOGY

ANESTHETIC EFFECTS AT 50,000 PPM DURING EXPOSURE

NO EFFECTS AFTER EXPOSURE:

- TOXICOLOGICAL SIGNS
- WEIGHT GAIN
- MORTALITY
- REPRODUCTION (PARENTS)
  - MATINGS, PERCENTAGE OF PREGNANCIES
    LACTATION INDEX, FERTILITY INDEX
- REPRODUCTION (F_1, F_2, F_3)
  - PERCENT STILL-BORN, LITTER SIZE, POST NATAL GROWTH, VIABILITY, SURVIVABILITY, ANOMALIES

PATHOLOGY

PNEUMONITIS IN MICE

AGGRAVATION OF BRONCHOPNEUMONIA IN RATS

EOSINOPHILIC CHANGES IN RATS (NO TUMORS)

CARCINOGENESIS

NEGATIVE IN RATS

INCREASE IN FREQUENCY OF TUMORS IN MICE