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ALLYL CHLORIDE

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Carcinogenesis Testing Program
Division of Cancer Cause and Prevention
National Cancer Institute
National Institutes of Health
Bethesda, Maryland 20014

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REPORT ON THE BIOASSAY OF ALLYL CHLORIDE
FOR POSSIBLE CARCINOGENICITY

CARCINOGENESIS TESTING PROGRAM
DIVISION OF CANCER CAUSE AND PREVENTION
NATIONAL CANCER INSTITUTE, NATIONAL INSTITUTES OF HEALTH

FOREWORD: This report presents the results of the bioassay of allyl chloride conducted for the Carcinogenesis Testing Program, Division of Cancer Cause and Prevention, National Cancer Institute (NCI), National Institutes of Health, Bethesda, Maryland. This is one of a series of experiments designed to determine whether selected chemicals have the capacity to produce cancer in animals. Negative results, in which the test animals do not have a significantly greater incidence of cancer than control animals, do not necessarily mean the test chemical is not a carcinogen because the experiments are conducted under a limited set of circumstances. Positive results demonstrate that the test chemical is carcinogenic for animals under the conditions of the test and indicate a potential risk to man. The actual determination of the risk to man from animal carcinogens requires a wider analysis.

CONTRIBUTORS: This bioassay of allyl chloride was conducted by Hazleton Laboratories America, Inc., Vienna, Virginia, initially under direct contract to the NCI and currently under a subcontract to Tracor Jitco, Inc., prime contractor for the NCI Carcinogenesis Testing Program.

The experimental design was determined by the NCI Project Officers, Dr. J. H. Weisburger (1,2) and Dr. E. K. Weisburger (1). The principal investigators for the contract were Dr. M. B. Powers (3), Dr. R. W. Voelker (3), Dr. W. A. Olson (3,4) and Dr. W. M. Weatherholtz (3). Chemical analysis was performed by Dr. C. L. Guyton (3,5) and the analytical results were reviewed by Dr. N. Zimmerman (6); the technical supervisor of animal treatment and observation was Ms. K. J. Petrovics (3).

Histopathologic examinations were performed by Dr. R. H. Habermann (3) and reviewed by Dr. R. W. Voelker (3) at the Hazleton Laboratories America, Inc., and the diagnoses included in this report represent the interpretation of these pathologists. Histopathology findings and reports were reviewed by Dr. R. L. Schueler (7).

Compilation of individual animal survival, pathology, and summary tables was performed by EG&G Mason Research Institute (8); the statistical analysis was performed by Mr. W. W. Belew (6) and Dr. J. R. Joiner (7), using methods selected for the Carcinogenesis Testing Program by Dr. J. J. Gart (9).

This report was prepared at METREK, a Division of The MITRE Corporation (6) under the direction of the NCI. Those responsible for this report at METREK are the project coordinator, Dr. L. W. Thomas (6), task leader Dr. M. R. Kornreich (6), senior biologist Ms. P. Walker (6), biochemist Dr. B. Fuller (6), and technical editor Ms. P. A. Miller (6). The final report was reviewed by members of the participating organizations.

The following other scientists at the National Cancer Institute were responsible for evaluating the bioassay experiment, interpreting the results, and reporting the findings: Dr. K. C. Chu (1), Dr. C. Cueto, Jr. (1), Dr. J. F. Douglas (1), Dr. D. G. Goodman (1), Dr. R. A. Griesemer (1), Dr. H. A. Milman (1), Dr. T. W. Orme (1), Dr. R. A. Squire (1,10), Dr. J. M. Ward (1), and Dr. C. E. Whitmire (1).

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SUMMARY

A bioassay for possible carcinogenicity of technical-grade allyl chloride (3-chloropropene) was conducted using Osborne-Mendel rats and B6C3F1 mice. At initiation of the study the rats were approximately 6 weeks old and the mice approximately 5 weeks old. Allyl chloride in corn oil was administered by gavage to two groups of each species for 5 days a week for 78 weeks, followed by observation periods of 30 to 33 weeks for the rats and 14 weeks for the mice. The time-weighted average dosages were, respectively, 77 and 57 mg/kg/day for high and low dose male rats; 73 and 55 mg/kg/day for high and low dose female rats; 199 and 172 mg/kg/day for high and low dose male mice; and 258 and 129 mg/kg/day for high and low dose female mice.

For each species, 20 animals of each sex were placed on test as vehicle controls. These animals were intubated with corn oil at the same time that dosed animals were gavaged with allyl chloride in corn oil. Twenty animals of each sex were placed on test as untreated controls for each species. These animals were not intubated.

Survival of high dose male mice and high dose rats of both sexes was extremely poor. Fifty percent of the high dose male mice were dead by week 27; the 10 members of this group that survived past week 48 were sacrificed in week 56. Among the high dose rats, 50 percent of the males had died by week 14 and 50 percent of the females had died by week 38. Because of early mortality in these groups, the number of animals surviving long enough to be at risk from late-developing tumors was not adequate for meaningful statistical analysis.

In this bioassay, squamous-cell carcinomas of the forestomach in male and female mice and squamous-cell papillomas of the forestomach in female mice occurred in incidences that were higher than in historical controls. No other neoplasms occurred in statistically significant increased incidences in dosed rats or mice.

Under the conditions of this bioassay no convincing evidence was presented for the carcinogenicity of allyl chloride in Osborne-Mendel rats of either sex. The results are suggestive that allyl chloride is carcinogenic in male and female B6C3F1 mice since the compound, when administered by gavage, caused a low incidence of neoplastic and nonneoplastic lesions of the forestomach.

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I. INTRODUCTION

Allyl chloride (NCI No. C04615) is one of a group of halogenated chemical intermediates selected for carcinogenesis bioassay by the National Cancer Institute. Chemicals were selected on the basis of large-scale production, extensive use, and lack of adequate chronic toxicity data.

The Chemical Abstracts Service (CAS) Ninth Collective Index (1977) name for this compound is 3-chloro-1-propene.* It is also called 3-chloropropene or chloropropylene.

Allyl chloride is one of the most commercially important allyl compounds. Commercial-scale production of allyl chloride began in 1945 and increased to 295 million pounds annually in 1972 (Stanford Research Institute, 1975). It is an extremely useful chemical intermediate since it can react both as an organic halide and as an olefin (Pilorz, 1964). Most derivatives of allyl chloride do not reach an end-use market themselves, but are part of further syntheses. Important "first generation" derivatives of allyl chloride include glycerol, epichlorohydrin, and allyl alcohol (Pilorz, 1964). Other derivatives include medicinals, such as barbiturates, diuretics (Pilorz, 1964), and herbicides (Kuwahara et al., 1973).

The National Institute for Occupational Safety and Health (1976) estimates that approximately 5000 workers in the United States are

*The CAS registry number is 107-05-1.

potentially exposed to allyl chloride annually. Human exposure to allyl chloride occurs principally by vapor inhalation in the working areas of industrial plants employing this compound for syntheses. Liver damage was reported in employees of the plastics industry after exposure to air concentrations varying from 1 to 113 ppm of allyl chloride for 16 months (Hausler and Lenich, 1968). Vapor exposure also produces eye and lung damage (Pilorz, 1964). Allyl chloride can be absorbed rapidly through the skin (Pilorz, 1964). Observations of industrial exposure indicate that liquid allyl chloride is a skin irritant which can cause dermatitis, damage to underlying tissues of the skin, chemical burns, and deep-seated pain (National Institute for Occupational Safety and Health, 1976).

II. MATERIALS AND METHODS

A. Chemicals

One batch of technical-grade allyl chloride (Figure 1) was purchased by Hazleton Laboratories America, Inc., Vienna, Virginia, from Aldrich Chemical Company, Inc. The purity of the compound was initially determined by gas-liquid chromatography (GLC) total-area analysis and by infrared spectroscopy. Six peaks were revealed; the fourth peak accounted for 98 percent of the total area and was presumed to be allyl chloride. One minor peak accounted for about 1.4 percent of the total area and the other four peaks totaled less than 1 percent of the area. This indication of purity in the range of 98 percent was consistent with the purity noted by the supplier. The infrared spectrum of the allyl chloride was consistent with that expected from the structure of the compound.

Second and third purity determinations were conducted approximately 19 and 26 months, respectively, after the original analysis in order to establish the stability of allyl chloride after storage. The second and third purity determinations, using GLC, showed the major peak to be approximately 98 and 99 percent, respectively, of the total area. The infrared spectra obtained in both of these analyses were consistent with the pattern shown in the first analysis. Therefore it was assumed that this batch of allyl chloride remained stable during the storage period of approximately 2 years.

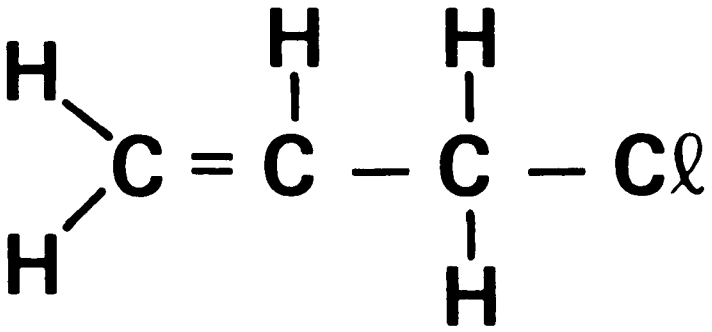


FIGURE 1
CHEMICAL STRUCTURE OF ALLYL CHLORIDE

Throughout this report the term allyl chloride is used to represent this technical-grade material.

B. Dosage Preparation

Fresh solutions of allyl chloride in Duke's® corn oil (S. F. Sauer Company, Richmond, Virginia) were prepared weekly, sealed, and stored in dark bottles at 1°C. The concentration of allyl chloride in corn oil varied from 5.5 to 7.0 percent for the rat chronic bioassay and from 2.0 to 5.0 percent for the mouse chronic bioassay. These allyl chloride solutions were considered generally stable for 10 days under the indicated storage conditions.

C. Animals

Two animal species, rats and mice, were used in the carcinogenicity bioassay. The Osborne-Mendel rat was selected on the basis of a comparative study of the tumorigenic responsiveness to carbon tetrachloride of five different strains of rats (Reuber and Glover, 1970). The B6C3F1 mouse was selected because it has been used by the NCI for carcinogenesis bioassays and has proved satisfactory in this capacity.

Rats and mice of both sexes were obtained through contracts with the Division of Cancer Treatment, National Cancer Institute. The Osborne-Mendel rats were procured from the Battelle Memorial Institute, Columbus, Ohio, and the B6C3F1 mice from the Charles River Breeding Laboratories, Inc., Wilmington, Massachusetts. Upon receipt, animals were quarantined for at least 10 days, observed for visible

signs of disease or parasites, and assigned to the various treated and control groups.

D. Animal Maintenance

All animals were housed by species in temperature- and humidity-controlled rooms. The temperature range was 20° to 24°C and the relative humidity was maintained between 45 and 55 percent. The air conditioning system provided filtered air at a rate of 12 complete changes of room air per hour. Fluorescent lighting was provided on a 12-hour-daily cycle.

The rats were individually housed in suspended galvanized-steel wire-mesh cages with perforated floors. The mice were housed by sex in groups of 10 in solid-bottom polypropylene cages equipped with filter tops. Sanitized cages with fresh bedding (Sanichips®, Pinewood Sawdust Company, Moonachie, New Jersey) were provided once each week for mice. Rats received sanitized cages with no bedding with the same frequency. Food hoppers were changed and heat-sterilized once a week for the first 10 weeks and once a month thereafter. Fresh heat-sterilized glass water bottles and sipper tubes were provided three times a week. Food (Wayne Lab-Blox® meal, Allied Mills, Inc., Chicago, Illinois) and water were available ad libitum.

The rats dosed with allyl chloride and the untreated and vehicle control rats were housed in the same room with rats intubated with* chloroform (67-66-3); carbon tetrachloride (56-23-5); 1,1,2,2-tetrachloroethane (79-34-5); and 1,2-dibromoethane (106-93-4).

*CAS registry numbers are given in parentheses.

The mice dosed with allyl chloride and the untreated and vehicle control mice were housed in the same room as mice intubated with 1,1,2,2-tetrachloroethane (7934-5); chloroform (67-66-3); 3-sulfolene (77-79-2); chloropicrin (76-06-2); trichlorofluoromethane (75-69-4); dibromochloropropane (96-12-8); iodoform (75-47-8); methylchloroform (71-55-6); 1,2-dibromoethane (106-93-4); 1,2-dichloroethane (107-06-2): 1,1-dichloroethane (75-34-3); trichloroethylene (79-01-6); carbon tetrachloride (56-23-5); 1,1,2-trichloroethane (79-00-5); hexachloroethane (67-72-1) carbon disulfide (75-15-0); and tetrachloroethylene (127-18-4).

E. Gastric Intubation

Intubation was performed for five consecutive days per week on a mg/kg body weight basis, utilizing the most recently observed group mean body weight as a guide for determining the dose. Mean body weights for each group were recorded at weekly intervals for the first 10 weeks and at monthly intervals thereafter. All animals of one sex within a treated group received the same dose. Animals were gavaged with allyl chloride solutions under a hood to minimize extraneous exposure of other animals and laboratory personnel to the chemical.

F. Selection of Initial Dose Levels

In order to estimate the maximum tolerated dosages of allyl chloride for administration to treated animals in the chronic studies, subchronic toxicity tests were conducted with both rats and mice.

Animals of each species were distributed among six groups, each consisting of five males and five females. Intubation was performed 5 days per week for 6 weeks, followed by a 2-week observation period to detect any delayed toxicity. Allyl chloride, dissolved in corn oil, was introduced by gavage to five of the six rat groups at dosages of 56, 100, 178, 316, and 562 mg/kg/day and to five of the six mouse groups at dosages of 178, 316, 562, 1000, and 1780 mg/kg/day. The sixth group of each species served as a vehicle control group, receiving only corn oil.

Based on observations during the subchronic toxicity tests, the initial high dosage selected for the chronic bioassay was 110 mg/kg/day for rats of both sexes.

At a level of 562 mg/kg/day or less only one mouse died during the 8-week study (a female treated with 562 mg/kg/day). No retardation in body weight gain was observed in either sex at 562 mg/kg/day or less. The initial high dosages selected for the mouse chronic bioassay were 400 mg/kg/day for males and 300 mg/kg/day for females.

G. Experimental Design

The experimental design parameters for this chronic study (species, sex, group size, dosages administered, duration of treated and untreated observation periods, and the time-weighted average dosages) are summarized in Tables 1 and 2.

A chronic bioassay was initiated using dosages of 110 and 55 mg/kg/day for rats. Due to lack of toxicity, dosage levels were raised

TABLE 1

DESIGN SUMMARY FOR OSBORNE-MENDEL RATS
ALLYL CHLORIDE GAVAGE EXPERIMENT

	INITIAL GROUP SIZE	ALLYL CHLORIDE DOSAGE[a]	OBSERVATION PERIOD TREATED (WEEKS)	OBSERVATION PERIOD UNTREATED (WEEKS)	TIME-WEIGHTED AVERAGE DOSAGE[b]
MALE					
UNTREATED CONTROL	20	0	0	110	0
VEHICLE CONTROL	20	0	78	32	0
LOW DOSE	50	70 55 0	10 68	 32	57
HIGH DOSE	50	140 110 55 0	10 16 52	 30	77
FEMALE					
UNTREATED CONTROL	20	0	0	110	0
VEHICLE CONTROL	20	0	78	33	0
LOW DOSE	50	55 0	78	 32	55
HIGH DOSE	50	110 55 0	26 52	 32	73

[a] Dosages, given in mg/kg body weight, were administered by gavage 5 consecutive days per week.

[b] Time-weighted average dosage = $\frac{\Sigma(\text{dosage X weeks received})}{\Sigma(\text{weeks receiving chemical})}$

TABLE 2

DESIGN SUMMARY FOR B6C3F1 MICE
ALLYL CHLORIDE GAVAGE EXPERIMENT

	INITIAL GROUP SIZE	ALLYL CHLORIDE DOSAGE[a]	OBSERVATION PERIOD TREATED (WEEKS)	OBSERVATION PERIOD UNTREATED (WEEKS)	TIME-WEIGHTED AVERAGE DOSAGE OVER A 78-WEEK PERIOD[b]
MALE					
UNTREATED CONTROL	20	0	0	90	0
VEHICLE CONTROL	20	0	78	13	0
LOW DOSE	50	200	15		172
		250	1		
		200	9		
		200[c]	42	11	
		0		13	
HIGH DOSE[d]	50	400	15		199
		500	1		
		400	9		
		400[c]	3	1	
		200[c]	21	6	
FEMALE					
UNTREATED CONTROL	20	0	0	90	0
VEHICLE CONTROL	20	0	78	13	0
LOW DOSE	50	150	25		129
		150[c]	42	11	
		0		14	
HIGH DOSE	50	300	25		258
	50	300[c]	42	11	
		0		14	

[a] Dosages, given in mg/kg body weight, were administered by gavage 5 consecutive days per week.

[b] Time-weighted average dosage = $\frac{\Sigma(\text{dosage X weeks received})}{78 \text{ weeks}}$

[c] These dosages were cyclically administered with a pattern of 1 dose-free week followed by 4 weeks (5 days per week) of chemical administration at the dosage level indicated.

[d] Terminated in week 56.

twice. Effective week 6, the dosages were raised to 140 and 70 mg/kg/day for both sexes and in week 12, the dosage levels for male rats were raised again, this time to 180 and 90 mg/kg/day. Because of excessive mortality after week 12, this bioassay was terminated during week 31 and the animals were discarded. Based on observations during this bioassay, a new bioassay of allyl chloride was initiated at the following levels: 140 and 70 mg/kg/day for male rats and 110 and 55 mg/kg/day for female rats.

At initiation of this study the treated and untreated control rats were approximately 6 weeks old. The vehicle control rats were approximately 7 weeks old when they were started on test; however, they were placed on test approximately 3 months before the untreated controls and the dosed groups.

Gavage was performed five consecutive days per week. The initial dosages utilized for male rats were 140 and 70 mg/kg/day. Throughout this report the male rats initially receiving the former dosage are referred to as the high dose group and those initially receiving the latter dosage are referred to as the low dose group. In week 11 the high and low dosages were reduced to 110 and 55 mg/kg/day, respectively. After 16 weeks the dosage administered to the high dose males was decreased to 55 mg/kg/day, the same dosage received by the low dose group. This dosage was maintained for the remainder of the compound administration period. Initially, the female rats received dosages of 110 and 55 mg/kg/day. Throughout this report the female

rats initially receiving the former dosage are referred to as the high dose group and those initially receiving the latter dosage are referred to as the low dose group. In week 27, because of toxic effects, the dosage level for high dose females was lowered to 55 mg/kg/day. The vehicle control rats received corn oil in volumes equal to those administered to the high dose groups. Untreated control rats received no intubations. After the 78-week dosing period, rats were observed for 30 to 33 weeks.

At the initiation of the study the vehicle control and treated mice were approximately 5 weeks old. The untreated control mice had a median birth date approximately 2 weeks later than the other mice, and were placed on test a corresponding 2 weeks later.

Throughout this report the male mice receiving initial dosages of 400 mg/kg/day are referred to as the high dose and those receiving initial dosages of 200 mg/kg/day are referred to as the low dose. The female mice intubated with 300 and 150 mg/kg/day are referred to, respectively, as the high and low dose groups.

The dosages utilized for high dose male mice were 400 mg/kg/day for the first 15 weeks, 500 mg/kg/day the next week, 400 mg/kg/day from week 17 through week 29, and 200 mg/kg/day from week 30 until week 56 when all surviving animals in this group were sacrificed. The dosage utilized for low dose males was 200 mg/kg/day except during week 16, when they received 250 mg/kg/day. The dosages used for high and low dose female mice were 300 and 150 mg/kg/day,

respectively, throughout the 78 weeks of the experiment. In order to decrease total intake of allyl chloride, in week 26 intubation ceased for all mice for 1 week and was followed by 4 weeks of intubation at the previous dose levels. This pattern of cyclic administration continued for the remainder of the dosing period.

After the 78-week dosing period the surviving groups were observed for up to 14 weeks.

H. Clinical and Histopathologic Examinations

Animals were weighed immediately prior to initiation of the experiment. Body weights, food consumption, and data concerning appearance, behavior, signs of toxic effects, and incidence, size, and location of tissue masses were recorded at weekly intervals for the first 10 weeks and at monthly intervals thereafter. From the first day, all animals were inspected daily for mortality. The presence of tissue masses was determined by observation and palpation of each animal.

A necropsy was performed on each animal regardless of whether it died, was killed when moribund, or was sacrificed at the end of the bioassay. The animals were euthanized by exsanguination under sodium pentobarbital anesthesia, and were immediately necropsied. The histopathologic examination consisted of gross and microscopic examination of major tissues, organs, and gross lesions taken from sacrificed animals and, whenever possible, from animals found dead.

Tissues were preserved in 10 percent buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin prior to microscopic examination. An occasional section was subjected to special staining techniques for more definitive diagnosis.

Slides were prepared from the following tissues: subcutaneous tissue, lungs and bronchi, trachea, bone marrow, spleen, lymph nodes, thymus, heart, salivary gland, liver, gallbladder (mice), pancreas, esophagus, stomach, small intestine, large intestine, kidney, urinary bladder, pituitary, adrenal, thyroid, parathyroid, testis, prostate, brain, uterus, mammary gland, and ovary.

A few tissues were not examined for some animals, particularly for those that died early. Also, some animals were missing, cannibalized, or judged to be in such an advanced state of autolysis as to preclude histopathologic interpretation. Thus, the number of animals for which particular organs, tissues, or lesions were examined microscopically varies and does not necessarily represent the number of animals that were placed on experiment in each group.

I. Data Recording and Statistical Analyses

Pertinent data on this experiment have been recorded in an automatic data processing system, the Carcinogenesis Bioassay Data System (Linhart et al., 1974). The data elements include descriptive information on the chemicals, animals, experimental design, clinical observations, survival, body weight, and individual pathologic results, as recommended by the International Union Against Cancer (Berenblum,

1969). Data tables were generated for verification of data transcription and for statistical review.

These data were analyzed using the statistical techniques described in this section. Those analyses of the experimental results that bear on the possibility of carcinogenicity are discussed in the statistical narrative sections.

Probabilities of survival were estimated by the product-limit procedure of Kaplan and Meier (1958) and are presented in this report in the form of graphs. Animals were statistically censored as of the time that they died of other than natural causes or were found to be missing; animals dying from natural causes were not statistically censored. Statistical analyses for a possible dose-related effect on survival used the method of Cox (1972) when testing two groups for equality and used Tarone's (1975) extensions of Cox's methods when testing a dose-related trend. One-tailed P-values have been reported for all tests except the departure from linearity test, which is only reported when its two-tailed P-value is less than 0.05.

The incidence of neoplastic or nonneoplastic lesions has been given as the ratio of the number of animals bearing such lesions at a specific anatomic site (numerator) to the number of animals in which that site was examined (denominator). In most instances, the denominators included only those animals for which that site was examined histologically. However, when macroscopic examination was required to detect lesions prior to histologic sampling (e.g., skin or mammary

tumors), or when lesions could have appeared at multiple sites (e.g., lymphomas), the denominators consist of the numbers of animals necropsied.

The purpose of the statistical analyses of tumor incidence is to determine whether animals receiving the test chemical developed a significantly higher proportion of tumors than did the control animals. As a part of these analyses, the one-tailed Fisher exact test (Cox, 1970, pp. 48-52) was used to compare the tumor incidence of a control group to that of a group of treated animals at each dose level. When results for a number of treated groups, k, are compared simultaneously with those for a control group, a correction to ensure an overall significance level of 0.05 may be made. The Bonferroni inequality (Miller, 1966, pp. 6-10) requires that the P-value for any comparison be less than or equal to 0.05/k. In cases where this correction was used, it is discussed in the narrative section. It is not, however, presented in the tables, where the Fisher exact P-values are shown.

The Cochran-Armitage test for linear trend in proportions, with continuity correction (Armitage, 1971, pp. 362-365), was also used when appropriate. Under the assumption of a linear trend, this test determined if the slope of the dose-response curve is different from zero at the one-tailed 0.05 level of significance. Unless otherwise noted, the direction of the significant trend was a positive dose relationship. This method also provides a two-tailed test of departure from linear trend.

A time-adjusted analysis was applied when numerous early deaths resulted from causes that were not associated with the formation of tumors. In this analysis, deaths that occurred before the first tumor was observed were excluded by basing the statistical tests on animals that survived at least 52 weeks, unless a tumor was found at the anatomic site of interest before week 52. When such an early tumor was found, comparisons were based exclusively on animals that survived at least as long as the animal in which the first tumor was found. Once this reduced set of data was obtained, the standard procedures for analyses of the incidence of tumors (Fisher exact tests, Cochran-Armitage tests, etc.) were followed.

When appropriate, life-table methods were used to analyze the incidence of tumors. Curves of the proportions surviving without an observed tumor were computed as in Saffiotti et al. (1972). The week during which animals died naturally or were sacrificed was entered as the time point of tumor observation. Cox's methods of comparing these curves were used for two groups; Tarone's extension to testing for linear trend was used for three groups. The statistical tests for the incidence of tumors which used life-table methods were one-tailed and, unless otherwise noted, in the direction of a positive dose relationship. Significant departures from linearity ($P < 0.05$, two-tailed test) were also noted.

The approximate 95 percent confidence interval for the relative risk of each dosed group compared to its control was calculated from

the exact interval on the odds ratio (Gart, 1971). The relative risk is defined as p_t/p_c where p_t is the true binomial probability of the incidence of a specific type of tumor in a treated group of animals and p_c is the true probability of the spontaneous incidence of the same type of tumor in a control group. The hypothesis of equality between the true proportion of a specific tumor in a treated group and the proportion in a control group corresponds to a relative risk of unity. Values in excess of unity represent the condition of a larger proportion in the treated group than in the control.

The lower and upper limits of the confidence interval of the relative risk have been included in the tables of statistical analyses. The interpretation of the limits is that in approximately 95 percent of a large number of identical experiments, the true ratio of the risk in a treated group of animals to that in a control group would be within the interval calculated from the experiment. When the lower limit of the confidence interval is greater than one, it can be inferred that a statistically significant result (a $P < 0.025$ one-tailed test when the control incidence is not zero, $P < 0.050$ when the control incidence is zero) has occurred. When the lower limit is less than unity but the upper limit is greater than unity, the lower limit indicates the absence of a significant result while the upper limit indicates that there is a theoretical possibility of the induction of tumors by the test chemical which could not be detected under the conditions of this test.

III. CHRONIC TESTING RESULTS: RATS

A. Body Weights and Clinical Observations

All groups of rats gained weight consistently during the first 46 weeks of the experiment (Figure 2). Between week 46 and week 50, the mean body weight of high dose male rats decreased from 557 grams to 528 grams. The high dose male rats continued to lose weight so that at the end of the dosing period the mean body weight of animals in this group had dropped to 487 grams. Low dose male rats experienced no appreciable mean body weight depression relative to controls. Throughout the bioassay, male and female rats treated with allyl chloride experienced consistent mean body weight depression relative to controls. Fluctuations in the growth curve may be due to mortality; as the size of the group diminishes, the mean body weight may be subject to wide variations.

Hunched appearance and abdominal urine stains were the predominant clinical signs observed during the study. Abdominal urine stains were noted in an increasing number of treated rats as the experiment progressed. By week 42 approximately 40 percent of the high dose males and high and low dose females had this condition. Abdominal urine stains were infrequently noted in the controls until the last 6 months of the study when the observation was noted in approximately 30 percent of the control rats.

A few rats showed hunched posture during the first few weeks of the study, but their appearance and behavior were otherwise normal.

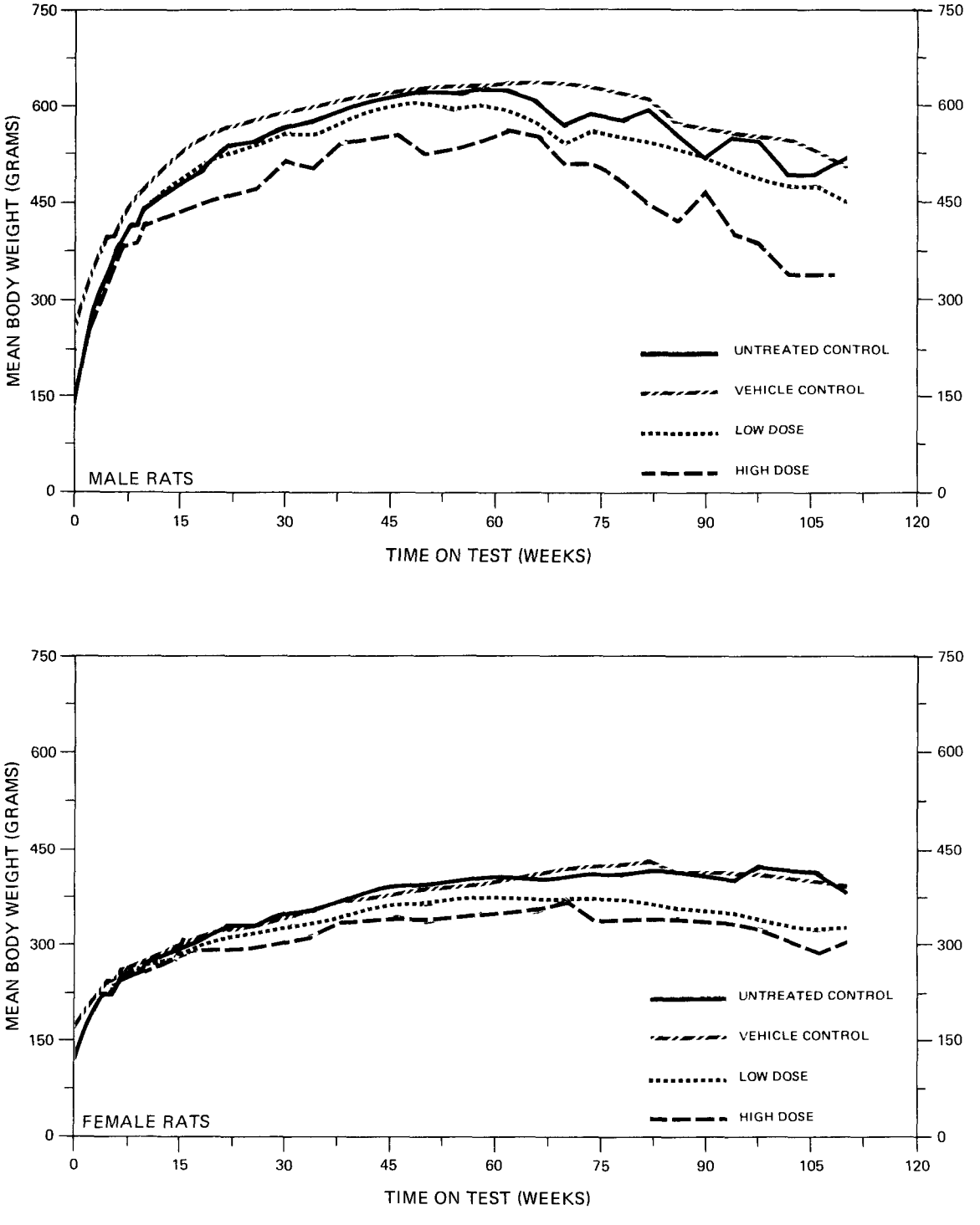


FIGURE 2
GROWTH CURVES FOR ALLYL CHLORIDE CHRONIC STUDY RATS

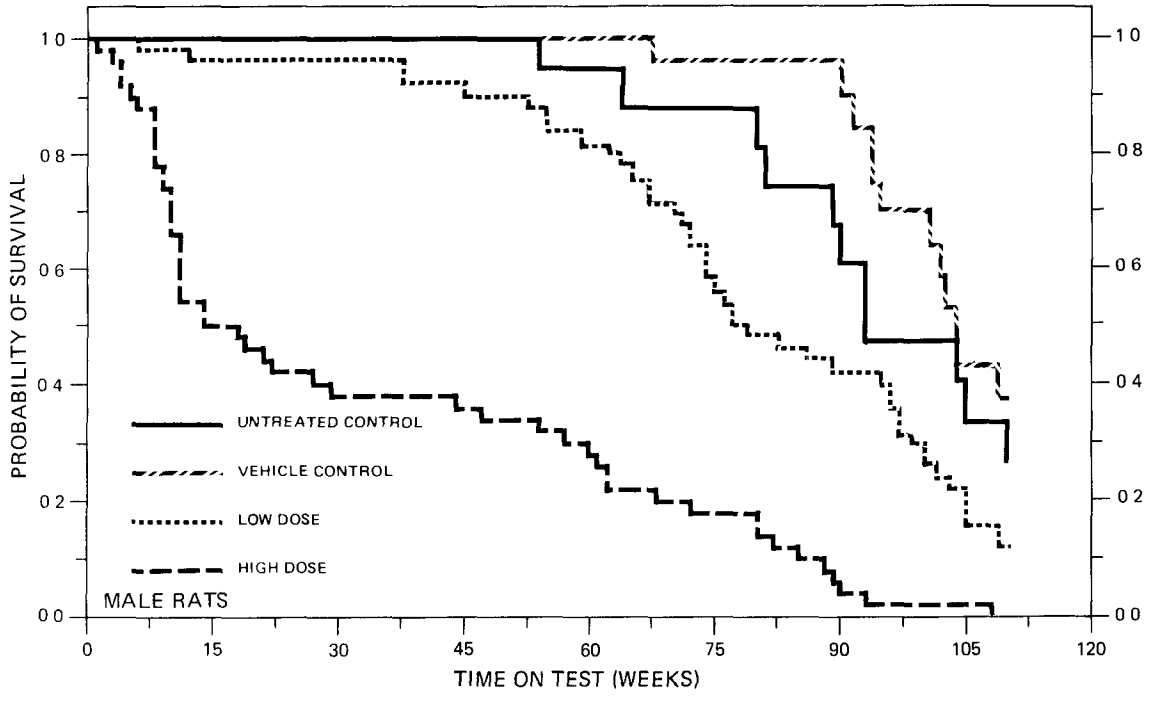
By week 10 more rats, particularly the females, exhibited a hunched appearance. By week 26, 30 percent of the treated males and 50 percent of the treated females had a hunched appearance. As the study progressed more animals in all groups including the controls showed hunched appearance and at the end of the study (in week 110), most or all survivors had a hunched appearance.

Respiratory signs, characterized by labored respiration, wheezing, and/or nasal discharge, were observed at a low or moderate incidence in all groups including controls during the latter part of the first year, increasing gradually as the rats aged. Other signs commonly associated with aging in the laboratory rat were observed at a comparable rate in control and treated animals during the second year of the study. These common signs included alopecia, sores on the body and/or extremities, reddish discharge or crust around the body orifices, and palpable subcutaneous masses or nodules.

B. Survival

The estimated probabilities of survival for male and female rats in the control and allyl chloride-dosed groups are shown in Figure 3.

For both male and female rats the Tarone test indicated a significant association ($P < 0.001$) between increased dosage and accelerated mortality. For both sexes the departure from linearity was significant ($P < 0.001$), primarily because of the extremely poor survival among the high dose groups.



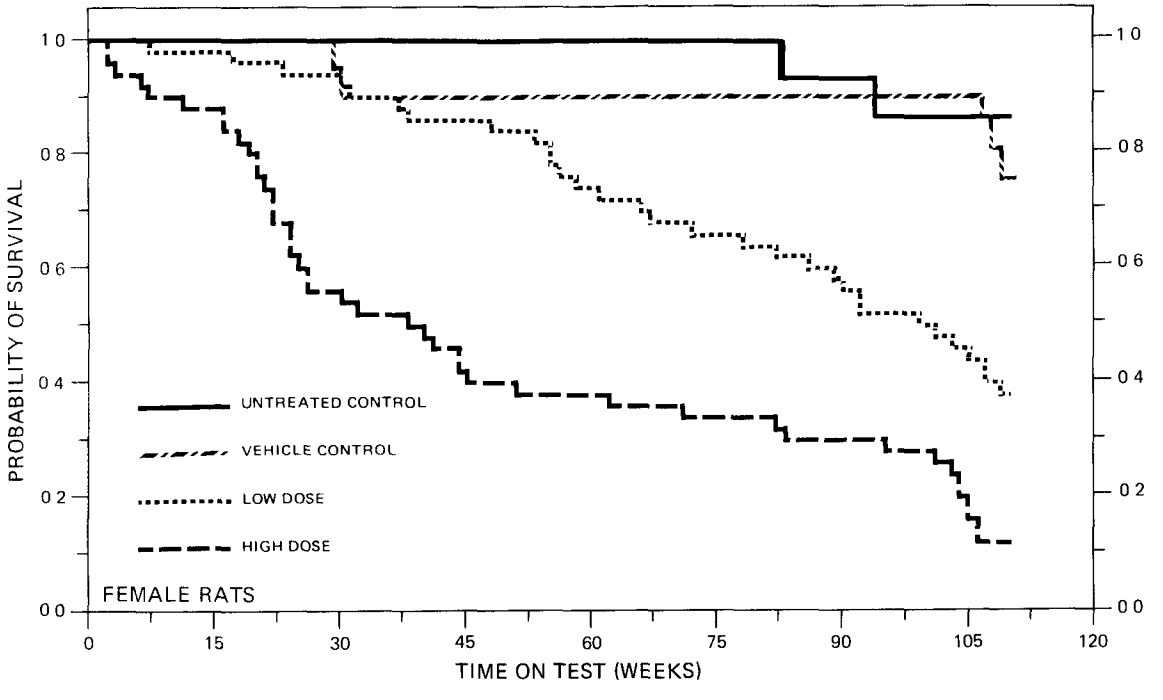


FIGURE 3
SURVIVAL COMPARISONS OF ALLYL CHLORIDE CHRONIC STUDY RATS

Fifty percent (25/50) of the low dose males survived until week 77 and 50 percent (25/50) of the low dose females survived until week 99. As a result, adequate numbers of low dose rats were at risk from late-developing tumors.

For the high dose groups, however, 50 percent (25/50) of the males had died by week 14 and 50 percent (25/50) of the females had died by week 38. Only 34 percent (17/50) of the high dose males survived one year; none survived until the end of the study. Only 12 percent (6/50) of the high dose females survived until the end of the study. These unusually early deaths were not associated with observed tumors. The small numbers of high dose males and females that survived long enough to be at risk from late-developing tumors precluded meaningful analysis of the incidence of these types of tumors for these groups.

C. Pathology

Histopathologic findings on neoplasms in rats are tabulated in Appendix A (Tables A1 and A2); findings on nonneoplastic lesions are tabulated in Appendix C (Tables C1 and C2).

A variety of neoplasms were observed among both treated and control rats. Each of the types of tumors observed had been encountered historically as a spontaneous lesion in the Osborne-Mendel rat. No difference in the frequency of neoplasms or nonneoplastic lesions were noted in this test between the control and treated animals.

Results of this histopathologic examination present no evidence that allyl chloride is carcinogenic in Osborne-Mendel rats of either sex.

D. Statistical Analyses of Results

The results of the statistical analyses of tumor incidence in rats are summarized in Tables 3 and 4. Due to the high early mortality in both male and female high dose rats, many rats may have died before they were at risk from late-developing tumors. To partially compensate for this, these analyses were performed based solely upon those rats that survived at least 52 weeks or, if the tumor of interest was observed earlier than 52 weeks, at least until the first tumor of that type was observed. The analysis for every type of tumor that was observed in more than 5 percent of any of the allyl chloride-dosed groups of either sex is included.

For all analyses neither the Cochran-Armitage tests nor the Fisher exact tests indicated any statistically significant increase in the proportion of tumors found in dosed rats over that found in control rats for any tumor type for either sex. These results, therefore, provided no conclusive evidence of the carcinogencity of allyl chloride. In the high dose groups of both sexes these results must be considered statistically inconclusive due to elevated mortality. In the low dose groups, however, adequate numbers of rats were at risk for meaningful statistical analyses.

TABLE 3

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT
SPECIFIC SITES IN MALE RATS TREATED WITH ALLYL CHLORIDE[a] AND SURVIVING AT LEAST 52 WEEKS

TOPOGRAPHY: MORPHOLOGY	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
Subcutaneous Tissue: Fibroma[b]	0/20(0.00)	0/19(0.00)	3/45(0.07)	0/17(0.00)
P Values[c]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Untreated Control)[d]	---	---	Infinite	---
Lower Limit	---	---	0.283	---
Upper Limit	---	---	Infinite	---
Relative Risk (Vehicle Control)[d]	---	---	Infinite	---
Lower Limit	---	---	0.272	---
Upper Limit	---	---	Infinite	---
Weeks to First Observed Tumor	---	---	77	---
Subcutaneous Tissue: Fibrosarcoma[b]	1/20(0.05)	0/19(0.00)	1/45(0.02)	0/17(0.00)
P Values[c]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Untreated Control)[d]	---	---	0.444	0.000
Lower Limit	---	---	0.006	0.000
Upper Limit	---	---	34.903	21.164
Relative Risk (Vehicle Control)[d]	---	---	Infinite	---
Lower Limit	---	---	0.024	---
Upper Limit	---	---	Infinite	---
Weeks to First Observed Tumor	54	---	105	---

TABLE 3 (Continued)

TOPOGRAPHY: MORPHOLOGY	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
Pituitary: Chromophobe Adenoma[b]	2/20(0.10)	0/16(0.00)	1/45(0.02)	0/17(0.00)
P Values[c]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Untreated Control)[d]	---	---	0.222	0.000
Lower Limit	---	---	0.004	0.000
Upper Limit	---	---	4.167	3.778
Relative Risk (Vehicle Control)[d]	---	---	Infinite	---
Lower Limit	---	---	0.020	---
Upper Limit	---	---	Infinite	---
Weeks to First Observed Tumor	90	---	110	---
Thyroid: Follicular-Cell Carcinoma[b]	1/19(0.05)	2/19(0.10)	5/44(0.11)	1/17(0.06)
P Values[c]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Untreated Control)[d]	---	---	2.159	1.118
Lower Limit	---	---	0.277	0.015
Upper Limit	---	---	101.862	82.445
Relative Risk (Vehicle Control)[d]	---	---	1.080	0.559
Lower Limit	---	---	0.205	0.010
Upper Limit	---	---	10.982	9.702
Weeks to First Observed Tumor	90	104	76	88

TABLE 3 (Continued)

TOPOGRAPHY: MORPHOLOGY	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
Thyroid: Follicular-Cell Adenoma or Follicular-Cell Carcinoma[b]	1/19(0.05)	3/19(0.16)	6/44(0.14)	1/17(0.06)
P Values[c]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Untreated Control)[d]	---	---	2.651	1.118
Lower Limit	---	---	0.361	0.015
Upper Limit	---	---	118.816	82.445
Relative Risk (Vehicle Control)[d]	---	---	0.884	0.373
Lower Limit	---	---	0.218	0.008
Upper Limit	---	---	5.055	4.101
Weeks to First Observed Tumor	90	103	65	88
Thyroid: C-Cell Adenoma[b]	0/19(0.00)	1/19(0.05)	0/44(0.00)	0/17(0.00)
P Values[c]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Untreated Control)[d]	---	---	---	---
Lower Limit	---	---	---	---
Upper Limit	---	---	---	---
Relative Risk (Vehicle Control)[d]	---	---	0.000	0.000
Lower Limit	---	---	0.000	0.000
Upper Limit	---	---	7.800	19.052
Weeks to First Observed Tumor	---	110	---	---

TABLE 3 (Concluded)

[a]Treated groups received time-weighted average doses of 57 and 77 mg/kg by gavage.

[b]Number of tumor-bearing animals/number of animals examined at site (proportion).

[c]The probability level for the Cochran-Armitage test is given beneath the incidence of tumors in the corresponding control group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. The probability level for the Fisher exact test for the comparison of a treated group with the untreated control group (*) or the vehicle control group (**) is given beneath the incidence of tumors in that treated group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. For both Cochran-Armitage and Fisher exact tests a negative designation (N) indicates a lower incidence in the treated group(s) than in the control group.

[d]The 95% confidence interval on the relative risk of the treated group to the control group.

TABLE 4

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT
SPECIFIC SITES IN FEMALE RATS TREATED WITH ALLYL CHLORIDE[a] AND SURVIVING AT LEAST 52 WEEKS

TOPOGRAPHY: MORPHOLOGY	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
Subcutaneous Tissue: Fibroma[b]	0/20(0.00)	0/18(0.00)	1/42(0.02)	2/19(0.011)
P Values[c]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Untreated Control)[d]	---	---	Infinite	Infinite
Lower Limit	---	---	0.027	0.326
Upper Limit	---	---	Infinite	Infinite
Relative Risk (Vehicle Control)[d]	---	---	Infinite	Infinite
Lower Limit	---	---	0.024	0.295
Upper Limit	---	---	Infinite	Infinite
Weeks to First Observed Tumor	---	---	78	101
Subcutaneous Tissue: Fibrosarcoma[b]	0/20(0.00)	0/18(0.00)	2/42(0.05)	1/19(0.05)
P Values[c]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Untreated Control)[d]	---	---	Infinite	Infinite
Lower Limit	---	---	0.149	0.058
Upper Limit	---	---	Infinite	Infinite
Relative Risk (Vehicle Control)[d]	---	---	Infinite	Infinite
Lower Limit	---	---	0.136	0.052
Upper Limit	---	---	Infinite	Infinite
Weeks to First Observed Tumor	---	---	92	95

TABLE 4 (Continued)

TOPOGRAPHY: MORPHOLOGY	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
Pituitary: Chromophobe Adenoma[b]	6/19(0.32)	6/18(0.33)	6/42(0.14)	1/19(0.05)
P Values[c]	P = 0.027(N)	P = 0.021(N)	N.S.	P = 0.045*(N) P = 0.037**(N)
Relative Risk (Untreated Control)[d]	---	---	0.452	0.167
Lower Limit	---	---	0.145	0.004
Upper Limit	---	---	1.502	1.189
Relative Risk (Vehicle Control)[d]	---	---	0.429	0.158
Lower Limit	---	---	0.139	0.004
Upper Limit	---	---	1.418	1.124
Weeks to First Observed Tumor	110	108	89	103
Thyroid: Follicular-Cell Carcinoma[b]	0/20(0.00)	0/17(0.00)	1/42(0.02)	1/19(0.05)
P Values[c]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Untreated Control)[d]	---	---	Infinite	Infinite
Lower Limit	---	---	0.026	0.058
Upper Limit	---	---	Infinite	Infinite
Relative Risk (Vehicle Control)[d]	---	---	Infinite	Infinite
Lower Limit	---	---	0.023	0.050
Upper Limit	---	---	Infinite	Infinite
Weeks to First Observed Tumor	---	---	92	110

TABLE 4 (Continued)

TOPOGRAPHY: MORPHOLOGY	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
Thyroid: Follicular-Cell Adenoma or Follicular-Cell Carcinoma[b]	0/20(0.00)	1/17(0.05)	1/42(0.02)	1/19(0.05)
P Values[c]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Untreated Control)[d]	---	---	Infinite	Infinite
Lower Limit	---	---	0.026	0.058
Upper Limit	---	---	Infinite	Infinite
Relative Risk (Vehicle Control)[d]	---	---	0.405	0.895
Lower Limit	---	---	0.006	0.012
Upper Limit	---	---	31.046	66.483
Weeks to First Observed Tumor	---	110	92	110
Thyroid: C-Cell Carcinoma[b]	2/20(0.10)	0/17(0.00)	1/42(0.02)	0/19(0.00)
P Values[c]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Untreated Control)[d]	---	---	0.238	0.000
Lower Limit	---	---	0.004	0.000
Upper Limit	---	---	4.359	3.408
Relative Risk (Vehicle Control)[d]	---	---	Infinite	---
Lower Limit	---	---	0.023	---
Upper Limit	---	---	Infinite	---
Weeks to First Observed Tumor	110	---	103	---

TABLE 4 (Continued)

TOPOGRAPHY:MORPHOLOGY	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
Thyroid: C-Cell Adenoma or C-Cell Carcinoma[b]	4/20(0.20)	0/17(0.00)	1/42(0.02)	0/19(0.00)
P Values[c]	P = 0.007(N)	N.S.	P = 0.034*(N)	N.S.
Relative Risk (Untreated Control)[d]	---	---	0.119	0.000
Lower Limit	---	---	0.003	0.000
Upper Limit	---	---	1.117	1.077
Relative Risk (Vehicle Control)[d]	---	---	Infinite	---
Lower Limit	---	---	0.023	---
Upper Limit	---	---	Infinite	---
Weeks to First Observed Tumor	61	---	103	---
Mammary Gland: Adenocarcinoma NOS[b]	2/20(0.10)	0/18(0.00)	0/42(0.00)	1/19(0.05)
P Values[c]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Untreated Control)[d]	---	---	0.000	0.526
Lower Limit	---	---	0.000	0.009
Upper Limit	---	---	1.595	9.234
Relative Risk (Vehicle Control)[d]	---	---	---	Infinite
Lower Limit	---	---	---	0.052
Upper Limit	---	---	---	Infinite
Weeks to First Observed Tumor	110	---	---	83

TABLE 4 (Continued)

TOPOGRAPHY:MORPHOLOGY	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
Mammary Gland: Fibroadenoma[b]	2/20(0.10)	7/18(0.39)	13/42(0.31)	4/19(0.21)
P Values[c]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Untreated Control)[d]	---	---	3.095	2.105
Lower Limit	---	---	0.809	0.344
Upper Limit	---	---	26.440	20.839
Relative Risk (Vehicle Control)[d]	---	---	0.796	0.541
Lower Limit	---	---	0.373	0.142
Upper Limit	---	---	2.018	1.750
Weeks to First Observed Tumor	61	109	82	83
Uterus: Endometrial Stromal Polyp[b]	0/20(0.00)	0/18(0.00)	3/42(0.07)	0/19(0.00)
P Values[c]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Untreated Control)[d]	---	---	Infinite	---
Lower Limit	---	---	0.297	---
Upper Limit	---	---	Infinite	---
Relative Risk (Vehicle Control)[d]	---	---	Infinite	---
Lower Limit	---	---	0.269	---
Upper Limit	---	---	Infinite	---
Weeks to First Observed Tumor	---	---	110	---

TABLE 4 (Concluded)

[a]Treated groups received time-weighted average doses of 55 or 73 mg/kg by gavage.

[b]Number of tumor-bearing animals/number of animals examined at site (proportion).

[c]The probability level for the Cochran-Armitage test is given beneath the incidence of tumors in the corresponding control group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. The probability level for the Fisher exact test for the comparison of a treated group with the untreated control group (*) or the vehicle control group (**) is given beneath the incidence of tumors in that treated group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. For both Cochran-Armitage and Fisher exact tests a negative designation (N) indicates a lower incidence in the treated group(s) than in the control group.

[d]The 95% confidence interval on the relative risk of the treated group to the control group.

[e]For sites where the first tumor of interest was observed earlier than 52 weeks, the analyses were based upon all animals that survived until or past the date that the first tumor was observed.

The possibility of negative associations between administration of the chemical and the incidence of pituitary chromophobe adenomas and thyroid C-cell neoplasms was observed in female rats. Mortality, however, was greater in the high dose group as only 6/50 (12 percent) high dose females survived until the end of the study compared to 15/50 (30 percent) vehicle control and 13/20 (65 percent) untreated control rats.

To provide additional insight into the possible carcinogenicity of this compound, 95 percent confidence intervals on the relative risk have been estimated and entered in the tables based upon the observed tumor incidence rates. In all of the intervals shown in Tables 3 and 4 the value one is included; this indicates the absence of statistically significant results. It should also be noted that all of the confidence intervals have an upper limit greater than one, indicating the theoretical possibility of tumor induction in rats by allyl chloride that could not be established under the conditions of this test.

IV. CHRONIC TESTING RESULTS: MICE

A. Body Weights and Clinical Observations

No significant depression in mean body weight was observed for allyl chloride-treated male mice (Figure 4). Among female mice a slight but consistent mean body weight depression was observed after week 10 for the high dose group and after week 20 for the low dose group.

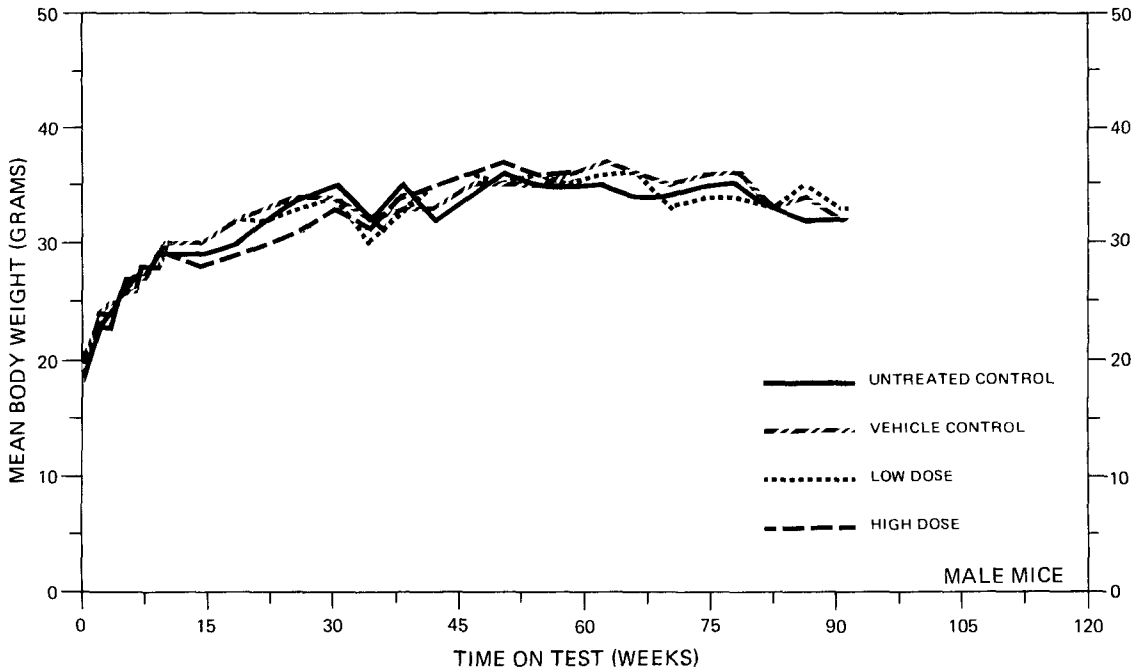
Throughout the study, signs often observed in group-housed laboratory mice were noted at a comparable rate among control and treated mice. These signs included: sores on the body (more prevalent in males because of fighting), penile, anal, or vulvar irritation, anal prolapse, reddened or squinted eyes, hunched posture, soft feces, palpable nodules, and alopecia. The incidence of these signs generally increased in all groups during the last 6 months of the study.

The only symptoms likely to be attributable to allyl chloride toxicity were observed in the 10 high dose male mice surviving beyond week 48. An apparent loss of equilibrium was observed in 8 of the 10, and abdominal distension was observed in all 10 of these animals. These signs were not noted in any of the other groups.

B. Survival

The estimated probabilities of survival for male and female mice in the control and allyl chloride-dosed groups are shown in Figure 5.

In male mice the Tarone test for a positive dose-related trend in mortality was significant ($P < 0.001$). There was a significant



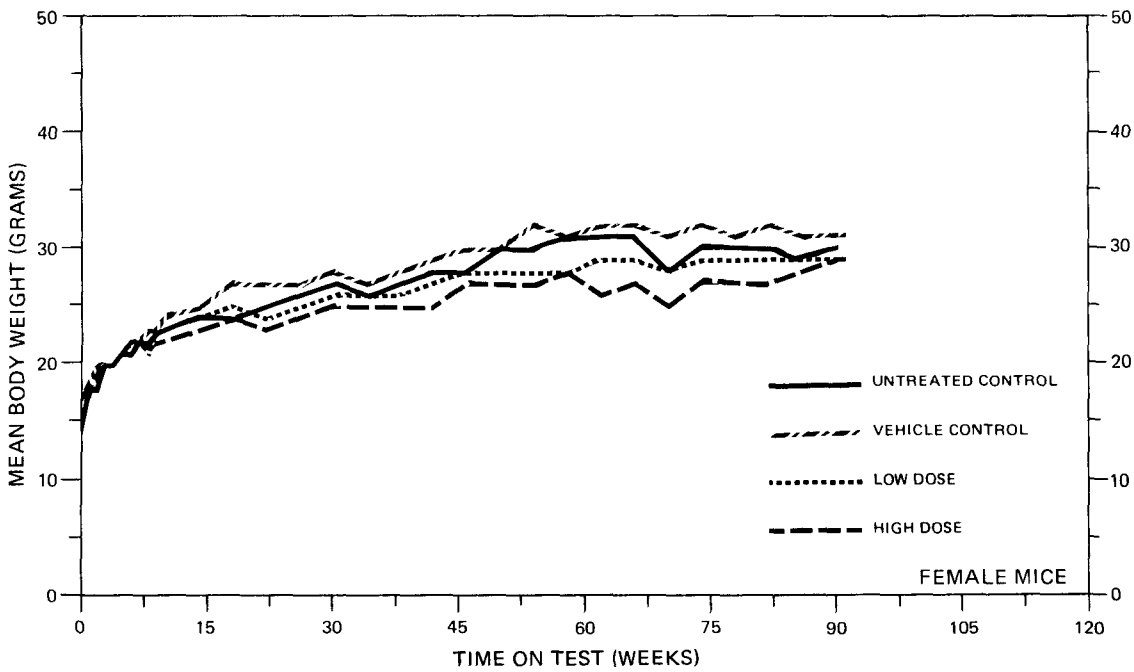


FIGURE 4
GROWTH CURVES FOR ALLYL CHLORIDE CHRONIC STUDY MICE

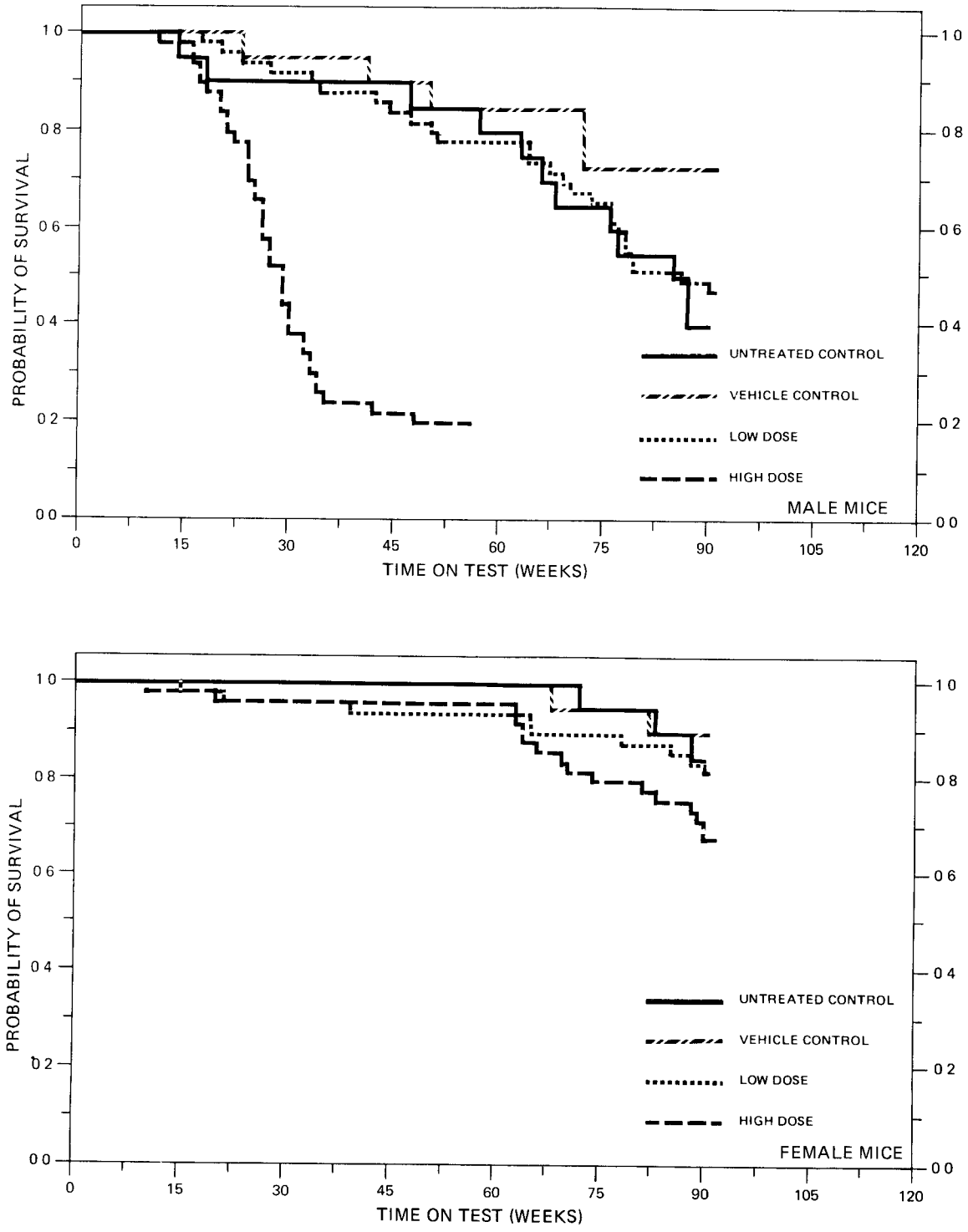


FIGURE 5
SURVIVAL COMPARISONS OF ALLYL CHLORIDE CHRONIC STUDY MICE

departure from linear trend ($P < 0.001$), primarily because of the extremely poor survival among the high dose group. Forty-eight percent (24/50) of the high dose group were dead by week 27; the 10 members of this group that survived past week 48 were sacrificed in week 56. At the same time, 10 of the 20 vehicle control mice were sacrificed. There was no indication of an association between the early deaths of high dose male mice and observed tumors. There were not adequate numbers of high dose male mice at risk from late-developing tumors. Survival of low dose male mice, however, was adequate for meaningful statistical analysis, with 50 percent (25/50) living at least 86 weeks.

In female mice the Tarone test also indicated a positive dose-related trend in mortality ($P = 0.022$). However, with 68 percent (34/50) of the high dose group and 80 percent (40/50) of the low dose group surviving to the end of the experiment, adequate numbers of female mice were at risk from late-developing tumors.

C. Pathology

Histopathologic findings on neoplasms in mice are tabulated in Appendix B (Tables B1 and B2); findings on nonneoplastic lesions are tabulated in Appendix D (Tables D1 and D2).

Increased incidences of stomach lesions, both neoplastic and nonneoplastic, were observed in treated male and female mice, as shown in the following table:

	Untreated Control	Vehicle Control	Low Dose	High Dose
Males				
Number of Animals Necropsied	(18)	(20)	(46)	(50)
Squamous-Cell Carcinoma	0	0	2	0
Squamous-Cell Papilloma	0	0	0	0
Leiomyosarcoma	0	0	1	0
Acanthosis	0	0	9	19
Hyperkeratosis	0	0	9	19
Females				
Number of Animals Necropsied	(20)	(19)	(48)	(45)
Squamous-Cell Carcinoma	0	0	2	0
Squamous-Cell Papilloma	0	0	1	3
Leiomyosarcoma	0	0	0	0
Acanthosis	0	0	17	25
Hyperkeratosis	0	0	17	25

Squamous-cell carcinomas of the forestomach were observed in four treated mice. Metastases of this lesion occurred in the two low dose males, but not in the two low dose females. These tumors were not observed in the control animals and are infrequently observed in B6C3F1 mice. Microscopically, early squamous-cell carcinoma of the stomach showed acanthosis of the squamous epithelium. The surface was covered with squames of irregular needle-like structures of keratin that projected into the lumen. At the base of the epithelial layer there were papillary cords and nests of anaplastic squamous epithelial cells, supported with dense bands of fibrous connective tissue invading and replacing the lamina propria and muscularis

mucosa. In well-differentiated lesions, nests of basophilic cells with intercellular spines surrounding central areas of keratin (epithelial pearls) were seen. The more undifferentiated squamous cells had large nuclei of varying shapes, contained coarse, irregular chromatin, and had one or more nucleoli. Mitotic figures were frequently seen. In advanced lesions the cords and nests of anaplastic squamous epithelial cells invaded the muscular layers and serosa, and extended to the glandular portion of the stomach and other organs. The tumor masses in the abdominal cavity consisted of squames of keratin enclosed in nests of anaplastic squamous epithelial cells, fibrinous mats, and necrotic tissues infiltrated with inflammatory cells. Squamous-cell papillomas of the stomach were present in one low dose female and three high dose females but not in any controls. Leiomyosarcoma of the stomach was present in a single treated male mouse. Acanthosis and hyperkeratosis of the forestomach occurred with increased incidence in the treated mice of both sexes.

Hepatocellular carcinomas occurred in increased numbers in the low dose male group (8/46 [17 percent] versus 2/20 [10 percent] in the vehicle controls; and 1/49 [2 percent] in the high dose males) but was not in excess of the incidence occasionally seen in control groups. Other proliferative, inflammatory, and degenerative lesions were seen in the control and treated animals without apparent relationship to the administration of the chemical.

Oral administration of allyl chloride was associated with squamous-cell carcinomas in the stomachs of two male and two female treated mice and papillomas in the stomachs of four females, and with proliferative lesions in the forestomach of male and female mice at both dose levels.

D. Statistical Analyses of Results

The results of the statistical analyses of tumor incidence in mice are summarized in Tables 5 and 6. Due to the high early mortality in high dose male mice, many may have died before they were at risk from late-developing tumors. To partially compensate for this, the analyses for males were performed based solely upon those male mice that survived at least 52 weeks or, in the event that the tumor of interest was observed earlier than 52 weeks, upon those males which survived at least until that tumor was detected. For both males and females the analysis for every type of tumor that was observed in more than 5 percent of any of the allyl chloride-dosed groups of either sex is included.

Neither the Cochran-Armitage tests nor the Fisher exact tests indicated any statistically significant increase in the proportion of tumors found in dosed mice over that found in control mice for any tumor type for either sex. For male mice the incidence of tumors at most sites was greater in the low dose than in the high dose group; probably due to the longer survival of the low dose mice.

TABLE 5

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT
SPECIFIC SITES IN MALE MICE TREATED WITH ALLYL CHLORIDE[a] AND SURVIVING AT LEAST 52 WEEKS

TOPOGRAPHY: MORPHOLOGY	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
Lung: Alveolar/Bronchiolar Adenoma[b]	0/12(0.00)	3/17(0.18)	6/35(0.17)	0/10(0.00)
P Values[c]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Untreated Control)[d]	---	---	Infinite	---
Lower Limit	---	---	0.600	---
Upper Limit	---	---	Infinite	---
Relative Risk (Vehicle Control)[d]	---	---	0.971	0.000
Lower Limit	---	---	0.245	0.000
Upper Limit	---	---	5.468	2.523
Weeks to First Observed Tumor	---	56	79	---
Liver: Hepatocellular Carcinoma[b]	1/12(0.08)	2/17(0.12)	8/36(0.22)	1/10(0.10)
P Values[c]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Untreated Control)[d]	---	---	2.667	1.200
Lower Limit	---	---	0.433	0.017
Upper Limit	---	---	114.336	84.143
Relative Risk (Vehicle Control)[d]	---	---	1.889	0.850
Lower Limit	---	---	0.442	0.015
Upper Limit	---	---	17.011	13.725
Weeks to First Observed Tumor	90	56	90	56

TABLE 5 (Concluded)

TOPOGRAPHY: MORPHOLOGY	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
Stomach: Squamous-Cell Carcinoma[b]	0/12(0.00)	0/17(0.00)	2/36(0.06)	0/10(0.00)
P Values[c]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Untreated Control)[d]	---	---	Infinite	---
Lower Limit	---	---	0.107	---
Upper Limit	---	---	Infinite	---
Relative Risk (Vehicle Control)[d]	---	---	Infinite	---
Lower Limit	---	---	0.146	---
Upper Limit	---	---	Infinite	---
Weeks to First Observed Tumor	---	---	76	---

[a]Treated groups received time-weighted average doses of 172 and 199 mg/kg by gavage.

[b]Number of tumor-bearing animals/number of animals examined at site (proportion).

[c]The probability level for the Cochran-Armitage test is given beneath the incidence of tumors in the corresponding control group when $P < 0.005$; otherwise, not significant (N.S.) is indicated. The probability level for the Fisher exact test for the comparison of a treated group with the untreated control group (*) or the vehicle control group (**) is given beneath the incidence of tumors in that treated group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. For both Cochran-Armitage and Fisher exact tests a negative designation (N) indicates a lower incidence in the treated group(s) than in the control group.

[d]The 95% confidence interval on the relative risk of the treated group to the control group.

TABLE 6

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT
SPECIFIC SITES IN FEMALE MICE TREATED WITH ALLYL CHLORIDE[a]

TOPOGRAPHY:MORPHOLOGY	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
Lung: Alveolar/Bronchiolar Adenoma[b]	1/20(0.05)	1/19(0.05)	5/48(0.10)	4/45(0.09)
P Values[c]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Untreated Control)[d]	---	---	2.083	1.778
Lower Limit	---	---	0.260	0.194
Upper Limit	---	---	96.358	85.520
Relative Risk (Vehicle Control)[d]	---	---	1.979	1.689
Lower Limit	---	---	0.247	0.187
Upper Limit	---	---	91.529	81.255
Weeks to First Observed Tumor	90	91	91	92
Hematopoietic System: Malignant Lymphoma[b]	3/20(0.15)	1/19(0.05)	6/48(0.13)	8/45(0.18)
P Values[c]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Untreated Control)[d]	---	---	0.833	1.185
Lower Limit	---	---	0.205	0.330
Upper Limit	---	---	4.799	6.425
Relative Risk (Vehicle Control)[d]	---	---	2.375	3.378
Lower Limit	---	---	0.325	0.511
Upper Limit	---	---	106.788	145.991
Weeks to First Observed Tumor	87	91	39	81

TABLE 6 (Concluded)

TOPOGRAPHY:MORPHOLOGY	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
Stomach: Squamous-Cell Papilloma or Squamous-Cell Carcinoma[b]	0/20(0.00)	0/19(0.00)	3/47(0.06)	3/45(0.07)
P Values[c]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Untreated Control)[d]	---	---	Infinite	Infinite
Lower Limit	---	---	0.266	0.279
Upper Limit	---	---	Infinite	Infinite
Relative Risk (Vehicle Control)[d]	---	---	Infinite	Infinite
Lower Limit	---	---	0.254	0.265
Upper Limit	---	---	Infinite	Infinite
Weeks to First Observed Tumor	---	---	91	92

[a]Treated groups received time-weighted average doses of 129 and 258 mg/kg by gavage.

[b]Number of tumor-bearing animals/number of animals examined at site (proportion).

[c]The probability level for the Cochran-Armitage test is given beneath the incidence of tumors in the corresponding control group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. The probability level for the Fisher exact test for the comparison of a treated group with the untreated control group (*) or the vehicle control group (**) is given beneath the incidence of tumors in that treated group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. For both Cochran-Armitage and Fisher exact tests a negative designation (N) indicates a lower incidence in the treated group(s) than in the control group.

[d]The 95% confidence interval on the relative risk of the treated group to the control group.

Rare stomach tumors--squamous-cell papillomas and squamous-cell carcinomas--were observed in 2/46 (4 percent) low dose males, 3/47 (6 percent) low dose females, and 3/45 (7 percent) high dose females. In historical vehicle control data tabulated by this laboratory for the NCI Carcinogenesis Testing Program, 1/180 male and 1/180 female B6C3F1 mice had either a squamous-cell papilloma or a squamous-cell carcinoma of the stomach. Assuming a binomial distribution with a probability of 1/180 of a spontaneous tumor, the probability of observing 2 or more tumors out of 46 males was $P < 0.029$. For a spontaneous tumor rate of 1/180, the probabilities of 3 such tumors occurring by chance in a sample of either 47 or 45 females is very small ($P < 0.003$).

To provide additional insight into the possible carcinogenicity of this compound, 95 percent confidence intervals on the relative risk have been estimated and entered in the tables based upon the observed tumor incidence rates. In all of the intervals shown in Tables 5 and 6, the value one is included; this indicates the absence of statistically significant results. It should also be noted that all of the confidence intervals have an upper limit greater than one, indicating the theoretical possibility of tumor induction in mice by allyl chloride that could not be established under the conditions of this test.

V. DISCUSSION

Because of excessive early mortality of high dose male rats, high dose female rats, and high dose male mice (50 percent of each group died by week 14, week 38, and week 27, respectively) the majority of animals in these groups did not survive long enough to be at risk from late-developing tumors. Any conclusions derived from this bioassay are, then, based on observations of the remaining groups.

Although a compound-related reduction in mortality was also observed among low dose rats, 50 percent of the low dose males survived until week 77 and 50 percent of the low dose females survived until week 99. This survival was considered adequate for meaningful statistical analysis of tumor incidence. Survival of low dose male mice (50 percent living at least 86 weeks) was also considered adequate for statistical analysis. Female mice, with 68 percent of the high dose group and 80 percent of the low dose group surviving until the end of the experiment, were the only species and sex for which animals in all groups could be considered to have lived long enough to be at risk from late-developing tumors.

Among the groups in which an adequate number of mice had survived long enough to be at risk from late-appearing tumors, proliferative nonneoplastic stomach lesions (i.e., acanthosis and hyperkeratosis) were observed in 20 percent of the low dose males, 39 percent of the high dose males, 36 percent of the low dose females, and 56 percent

of the high dose females, but in none of the control mice. In addition, squamous-cell carcinomas of the forestomach were detected in 2/46 low dose males and 2/47 low dose females. Metastases of this lesion occurred in the two low dose males. Squamous-cell papillomas of the forestomach were observed in 1/47 low dose females and 3/45 high dose females. These neoplasms were not observed in any other treated or control mice. The historical data for vehicle control B6C3F1 mice at this laboratory for the NCI Carcinogenesis Testing Program indicate that 1/180 males and 1/180 females had either a squamous-cell papilloma or a squamous-cell carcinoma of the forestomach. The occurrence of these neoplasms at the incidences observed in this bioassay was statistically and significantly higher than in the historical incidences. The proliferative nonneoplastic stomach lesions, squamous-cell papillomas and squamous-cell carcinomas, may all represent progressive stages in a neoplastic process. When the probable pathogenesis of this tumor is coupled with the known chemical reactivity of the compound and the statistical evidence for the rare occurrence of this tumor, the results are strongly suggestive of the carcinogenic action of allyl chloride in mice.

There were no other neoplasms in rats or mice for which statistical significance could be attributed to differences in incidence between control and treated groups.

Under the conditions of this bioassay no convincing evidence was presented for the carcinogenicity of allyl chloride in Osborne-Mendel

rats of either sex. The results are strongly suggestive that allyl chloride is carcinogenic in male and female B6C3F1 mice since the compound, when administered by gavage, is associated with neoplastic and nonneoplastic lesions of the forestomach.

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Review of the Bioassay of Allyl Chloride* for Carcinogenicity
by the Data Evaluation/Risk Assessment Subgroup
of the Clearinghouse on Environmental Carcinogens

June 29, 1978

The Clearinghouse on Environmental Carcinogens was established in May, 1976, in compliance with DHEW Committee Regulations and the Provisions of the Federal Advisory Committee Act. The purpose of the Clearinghouse is to advise the Director of the National Cancer Institute (NCI) on its bioassay program to identify and to evaluate chemical carcinogens in the environment to which humans may be exposed. The members of the Clearinghouse have been drawn from academia, industry, organized labor, public interest groups, State health officials, and quasi-public health and research organizations. Members have been selected on the basis of their experience in carcinogenesis or related fields and, collectively, provide expertise in chemistry, biochemistry, biostatistics, toxicology, pathology, and epidemiology. Representatives of various Governmental agencies participate as ad hoc members. The Data Evaluation/Risk Assessment Subgroup of the Clearinghouse is charged with the responsibility of providing a peer review of reports prepared on NCI-sponsored bioassays of chemicals studied for carcinogenicity. It is in this context that the below critique is given on the bioassay of Allyl Chloride for carcinogenicity.

The reviewer said that the study should be considered inadequate for drawing any conclusion about the compound's carcinogenicity. After a brief description of the experimental design, the reviewer said that the poor survival in the high dose treatment groups precluded an evaluation of the carcinogenicity of Allyl Chloride. A Program staff member said that the compound would be considered by the Chemical Selection Working Group to determine if it should be retested. The reviewer moved that the bioassay of Allyl Chloride was inadequate for drawing any conclusion on its carcinogenicity. The motion was approved without objection.

Clearinghouse Members present:
Arnold L. Brown (Chairman), Mayo Clinic
Paul Nettesheim, National Institute of Environmental Health Sciences
Verne Ray, Pfizer Medical Research Laboratory
Verald K. Rowe, Dow Chemical U.S.A.
Michael B. Shimkin, University of California at San Diego
Louise Strong, University of Texas Health Sciences Center

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* Subsequent to this review, changes may have been made in the bioassay report either as a result of the review or other reasons. Thus, certain comments and criticisms reflected in the review may no longer be appropriate.

APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS TREATED WITH ALLYL CHLORIDE

TABLE A1
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS TREATED WITH ALLYL CHLORIDE

	CONTROL (UNTR) 01-031M	CONTROL (VEH) 01-021M	LOW DOSE 01-032M	HIGH DOSE 01-033M
ANIMALS INITIALLY IN STUDY	20	20	50	50
ANIMALS MISSING		1		
ANIMALS NECROPSIED	20	19	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	19	50	50
INTEGUMENTARY SYSTEM				
*SUBCUT TISSUE	(20)	(19)	(50)	(50)
FIBROMA			3 (6%)	
FIBROSARCOMA	1 (5%)		1 (2%)	
FIBROUS HISTIOCYTOMA		1 (5%)		
FIBROUS HISTIOCYTOMA, MALIGNANT		1 (5%)		
LIPOMA			1 (2%)	
HEMANGIOSARCOMA			1 (2%)	1 (2%)
RESPIRATORY SYSTEM				
NONE				
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(20)	(19)	(50)	(50)
LYMPHOCYTIC LEUKEMIA	1 (5%)			
*SPLEEN	(20)	(17)	(50)	(50)
HEMANGIOSARCOMA		1 (6%)	1 (2%)	1 (2%)
#MESENTERIC L. NODE	(19)	(17)	(50)	(49)
HEMANGIOMA				1 (2%)
CIRCULATORY SYSTEM				
NONE				
DIGESTIVE SYSTEM				
#SALIVARY GLAND	(14)	(17)	(41)	(18)
CARCINOMA,NOS	1 (7%)			

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
**EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE A1 (CONTINUED)

	CONTROL (UNTR) 01-031M	CONTROL (VEH) 01-021M	LOW DOSE 01-032M	HIGH DOSE 01-033M
*PANCREAS	(20)	(16)	(50)	(50)
OSTEOSARCOMA, METASTATIC			1 (2%)	
*STOMACH	(20)	(19)	(50)	(50)
OSTEOSARCOMA, METASTATIC			1 (2%)	
*SMALL INTESTINE	(20)	(19)	(49)	(50)
FIBROSARCOMA	1 (5%)			
URINARY SYSTEM				
*KIDNEY	(20)	(19)	(50)	(50)
HAMARTOMA +			1 (2%)	
ENDOCRINE SYSTEM				
*PITUITARY	(20)	(16)	(50)	(50)
CHROMOPHOBE ADENOMA	2 (10%)		1 (2%)	
*ADRENAL	(20)	(19)	(49)	(50)
CORTICAL CARCINOMA	2 (10%)		1 (2%)	
PHEOCHROMOCYTOMA		1 (5%)		
HEMANGIOSARCOMA		1 (5%)		
*THYROID	(19)	(19)	(49)	(49)
FOLLICULAR-CELL ADENOMA		1 (5%)	1 (2%)	
FOLLICULAR-CELL CARCINOMA	1 (5%)	2 (11%)	5 (10%)	1 (2%)
C-CELL ADENOMA		1 (5%)		
*PANCREATIC ISLETS	(20)	(16)	(50)	(50)
ISLET-CELL ADENOMA		1 (6%)	1 (2%)	
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(20)	(19)	(50)	(50)
ADENOCARCINOMA, NOS	1 (5%)	1 (5%)		
FIBROADENOMA	1 (5%)			
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
NONE				

* NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
+ THIS IS CONSIDERED TO BE A BENIGN FORM OF THE MALIGNANT MIXED TUMOR OF THE KIDNEY AND CONSISTS OF PROLIFERATIVE LIPOCYTES, TUBULAR STRUCTURES, FIBROBLASTS, AND VASCULAR SPACES IN VARYING PROPORTIONS.

TABLE A1 (CONTINUED)

	CONTROL (UNTR) 01-031M	CONTROL (VEH) 01-021M	LOW DOSE 01-032M	HIGH DOSE 01-033M
MUSCULOSKELETAL SYSTEM				
*SKELETAL MUSCLE	(20)	(19)	(50)	(50)
FIBROUS HISTIOCYTOMA, MALIGNANT		1 (5%)		
BODY CAVITIES				
*MESENTERY	(20)	(19)	(50)	(50)
OSTEOSARCOMA, METASTATIC			1 (2%)	
ALL OTHER SYSTEMS				
NONE				
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	20	20	50	50
NATURAL DEATH@	11	12	42	50
MORIBUND SACRIFICE			1	
SCHEDULED SACRIFICE	5			
ACCIDENTALLY KILLED				
TERMINAL SACRIFICE	4	7	7	
ANIMAL MISSING		1		

@ INCLUDES AUTOLYZED ANIMALS

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A1 (CONCLUDED)

	CONTROL (UNTR) 01-031M	CONTROL (VEH) 01-021M	LOW DOSE 01-032M	HIGH DOSE 01-033M
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	6	9	14	4
TOTAL PRIMARY TUMORS	11	12	17	4
TOTAL ANIMALS WITH BENIGN TUMORS	2	5	8	1
TOTAL BENIGN TUMORS	3	5	8	1
TOTAL ANIMALS WITH MALIGNANT TUMORS	6	4	9	3
TOTAL MALIGNANT TUMORS	8	7	9	3
TOTAL ANIMALS WITH SECONDARY TUMORS#			1	
TOTAL SECONDARY TUMORS			3	
TOTAL ANIMALS WITH TUMORS UNCERTAIN- BENIGN OR MALIGNANT				
TOTAL UNCERTAIN TUMORS				
TOTAL ANIMALS WITH TUMORS UNCERTAIN- PRIMARY OR METASTATIC				
TOTAL UNCERTAIN TUMORS				

* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

TABLE A2
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS TREATED WITH ALLYL CHLORIDE

	CONTROL (UNTR) 01-031F	CONTROL (VEH) 01-021F	LOW DOSE 01-034F	HIGH DOSE 01-035F
ANIMALS INITIALLY IN STUDY	20	20	50	50
ANIMALS NECROPSIED	20	20	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	20	50	50
INTEGUMENTARY SYSTEM				
*SKIN	(20)	(20)	(50)	(50)
SEBACEOUS ADENOMA				1 (2%)
*SUBCUT TISSUE	(20)	(20)	(50)	(50)
SQUAMOUS CELL CARCINOMA, METASTA			1 (2%)	
FIBROMA			1 (2%)	2 (4%)
FIBROSARCOMA			2 (4%)	1 (2%)
HEMANGIOSARCOMA			2 (4%)	
RESPIRATORY SYSTEM				
#LUNG	(20)	(20)	(50)	(50)
SQUAMOUS CELL CARCINOMA, METASTA			1 (2%)	
ADENOCARCINOMA, NOS, METASTATIC				1 (2%)
FIBROSARCOMA			1 (2%)	
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(20)	(20)	(50)	(50)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)	
#SPLEEN	(20)	(20)	(50)	(49)
HEMANGIOSARCOMA			1 (2%)	1 (2%)
#LYMPH NODE	(20)	(20)	(50)	(49)
ADENOCARCINOMA, NOS, METASTATIC				1 (2%)
#THYMUS	(15)	(19)	(39)	(37)
SQUAMOUS CELL CARCINOMA			1 (3%)	
ADENOCARCINOMA, NOS, METASTATIC				1 (3%)
CIRCULATORY SYSTEM				
#HEART	(20)	(20)	(50)	(50)
MIXED TUMOR, METASTATIC	1 (5%)			

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
**EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE A2 (CONTINUED)

	CONTROL (UNTR) 01-031F	CONTROL (VEH) 01-021F	LOW DOSE 01-034F	HIGH DOSE 01-035F
DIGESTIVE SYSTEM				
#LIVER	(20)	(20)	(50)	(50)
NEOPLASTIC NODULE		2 (10%)		
HEPATOCELLULAR CARCINOMA	1 (5%)			
#PANCREAS	(20)	(20)	(50)	(50)
LIPOMA				1 (2%)
#ESOPHAGUS	(15)	(14)	(50)	(50)
SQUAMOUS CELL CARCINOMA, METASTA			1 (2%)	
URINARY SYSTEM				
#KIDNEY	(20)	(20)	(50)	(50)
TUBULAR-CELL ADENOMA			1 (2%)	1 (2%)
MIXED TUMOR, MALIGNANT	1 (5%)		1 (2%)	1 (2%)
HAMARTOMA +	2 (10%)			
ENDOCRINE SYSTEM				
#PITUITARY	(19)	(20)	(50)	(50)
CHROMOPHOBE ADENOMA	6 (32%)	6 (30%)	6 (12%)	1 (2%)
#ADRENAL	(20)	(20)	(50)	(50)
CORTICAL ADENOMA		1 (5%)		
PHEOCHROMOCYTOMA		1 (5%)		
#THYROID	(20)	(19)	(50)	(48)
FOLLICULAR-CELL ADENOMA		1 (5%)		
FOLLICULAR-CELL CARCINOMA			1 (2%)	1 (2%)
C-CELL ADENOMA	2 (10%)			
C-CELL CARCINOMA	2 (10%)		1 (2%)	
#PANCREATIC ISLETS	(20)	(20)	(50)	(50)
ISLET-CELL ADENOMA	1 (5%)	1 (5%)		
ISLET-CELL CARCINOMA		1 (5%)		
REPRODUCTIVE SYSTEM				
#MAMMARY GLAND	(20)	(20)	(50)	(50)
ADENOCARCINOMA, NOS	2 (10%)			1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
+ THIS IS CONSIDERED TO BE A BENIGN FORM OF THE MALIGNANT MIXED TUMOR OF THE KIDNEY AND CONSISTS OF PROLIFERATIVE LIPOCYTES, TUBULAR STRUCTURES, FIBROBLASTS, AND VASCULAR SPACES IN VARYING PROPORTIONS.

TABLE A2 (CONTINUED)

	CONTROL (UNTR) 01-031F	CONTROL (VEH) 01-021F	LOW DOSE 01-034F	HIGH DOSE 01-035F
FIBROSARCOMA		1 (5%)		
FIBROADENOMA	2 (10%)	7 (35%)	13 (26%)	4 (8%)
#UTERUS	(20)	(20)	(50)	(49)
SQUAMOUS CELL CARCINOMA		1 (5%)		
ENDOMETRIAL STROMAL POLYP			3 (6%)	
HEMANGIOMA	1 (5%)			
#OVARY	(20)	(20)	(50)	(49)
CYSTADENOCARCINOMA, NOS	1 (5%)			1 (2%)
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
NONE				
ALL OTHER SYSTEMS				
DIAPHRAGM				
SQUAMOUS CELL CARCINOMA, METASTA			1	
ADENOCARCINOMA, NOS, METASTATIC				1
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	20	20	50	50
NATURAL DEATH@	2	5	31	42
MORIBUND SACRIFICE				2
SCHEDULED SACRIFICE	5			
ACCIDENTALLY KILLED				
TERMINAL SACRIFICE	13	15	19	6
ANIMAL MISSING				

@ INCLUDES AUTOLYZED ANIMALS

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A2 (CONCLUDED)

	CONTROL (UNTR) 01-031F	CONTROL (VEH) 01-021F	LOW DOSE 01-034F	HIGH DOSE 01-035F
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	14	12	26	11
TOTAL PRIMARY TUMORS	21	22	35	18
TOTAL ANIMALS WITH BENIGN TUMORS	12	12	21	8
TOTAL BENIGN TUMORS	14	17	24	12
TOTAL ANIMALS WITH MALIGNANT TUMORS	6	2	9	4
TOTAL MALIGNANT TUMORS	7	3	11	6
TOTAL ANIMALS WITH SECONDARY TUMORS#	1		1	1
TOTAL SECONDARY TUMORS	1		4	4
TOTAL ANIMALS WITH TUMORS UNCERTAIN- BENIGN OR MALIGNANT		2		
TOTAL UNCERTAIN TUMORS		2		
TOTAL ANIMALS WITH TUMORS UNCERTAIN- PRIMARY OR METASTATIC				
TOTAL UNCERTAIN TUMORS				

* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
\# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

APPENDIX B

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE TREATED WITH ALLYL CHLORIDE

TABLE B1
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE TREATED WITH ALLYL CHLORIDE

	CONTROL (UNTR) 02-M041	CONTROL (VEH) 02-M031	LOW DOSE 02-M032	HIGH DOSE 02-M033
ANIMALS INITIALLY IN STUDY	20	20	50	50
ANIMALS NECROPSIED	18	20	46	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	15	20	45	49
INTEGUMENTARY SYSTEM				
*SUBCUT TISSUE	(18)	(20)	(46)	(50)
FIBROMA			1 (2%)	
RESPIRATORY SYSTEM				
*LUNG	(15)	(20)	(45)	(49)
SQUAMOUS CELL CARCINOMA, METASTA			1 (2%)	
ALVEOLAR/BRONCHIOLAR ADENOMA		3 (15%)	6 (13%)	
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(18)	(20)	(46)	(50)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		1 (5%)	1 (2%)	2 (4%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)	
LYMPHOCYTIC LEUKEMIA			2 (4%)	
*MESENTERIC L. NODE	(15)	(19)	(39)	(28)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE			1 (3%)	
CIRCULATORY SYSTEM				
NONE				
DIGESTIVE SYSTEM				
*LIVER	(15)	(20)	(46)	(49)
SQUAMOUS CELL CARCINOMA, METASTA			1 (2%)	
HEPATOCELLULAR CARCINOMA	1 (7%)	2 (10%)	8 (17%)	1 (2%)
LYIOMYOSARCOMA, METASTATIC			1 (2%)	
HEMANGIOMA			1 (2%)	

* NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
**EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE B1 (CONTINUED)

	CONTROL (UNTR) 02-M041	CONTROL (VEH) 02-M031	LOW DOSE 02-M032	HIGH DOSE 02-M033
#PANCREAS	(14)	(20)	(45)	(43)
SQUAMOUS CELL CARCINOMA, METASTA			1 (2%)	
#STOMACH	(15)	(20)	(46)	(49)
SQUAMOUS CELL CARCINOMA			2 (4%)	
LEIOMYOSARCOMA			1 (2%)	
URINARY SYSTEM				
NONE				
ENDOCRINE SYSTEM				
NONE				
REPRODUCTIVE SYSTEM				
*EPIDIDYMIS	(18)	(20)	(46)	(50)
SQUAMOUS CELL CARCINOMA, METASTA			1 (2%)	
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
NONE				
ALL OTHER SYSTEMS				
NONE				

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B1 (CONCLUDED)

	CONTROL (UNTR) 02-M041	CONTROL (VEH) 02-M031	LOW DOSE 02-M032	HIGH DOSE 02-M033
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	20	20	50	50
NATURAL DEATH@	12	4	27	40
MORIBUND SACRIFICE			1	
SCHEDULED SACRIFICE		10		
ACCIDENTALLY KILLED			1	
TERMINAL SACRIFICE	8	6	21	10
ANIMAL MISSING				
@ INCLUDES AUTOLYZED ANIMALS				
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	1	5	19	3
TOTAL PRIMARY TUMORS	1	6	24	3
TOTAL ANIMALS WITH BENIGN TUMORS		3	8	
TOTAL BENIGN TUMORS		3	8	
TOTAL ANIMALS WITH MALIGNANT TUMORS	1	3	12	3
TOTAL MALIGNANT TUMORS	1	3	16	3
TOTAL ANIMALS WITH SECONDARY TUMORS#			2	
TOTAL SECONDARY TUMORS			5	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT				
TOTAL UNCERTAIN TUMORS				
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC				
TOTAL UNCERTAIN TUMORS				

* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

TABLE B2
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE TREATED WITH ALLYL CHLORIDE

	CONTROL (UNTR) 02-F041	CONTROL (VEH) 02-F031	LOW DOSE 02-F034	HIGH DOSE 02-F035
ANIMALS INITIALLY IN STUDY	20	20	50	50
ANIMALS NECROPSIED	20	19	48	45
ANIMALS EXAMINED HISTOPATHOLOGICALLY **	20	19	48	44
INTEGUMENTARY SYSTEM				
*SUBCUT TISSUE	(20)	(19)	(48)	(45)
FIBROSARCOMA			1 (2%)	
LEIOMYOSARCOMA	1 (5%)			
RESPIRATORY SYSTEM				
#LUNG	(20)	(19)	(48)	(45)
ADENOCARCINOMA, NOS, METASTATIC			1 (2%)	
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (5%)	1 (5%)	5 (10%)	4 (9%)
OSTEOSARCOMA, METASTATIC			1 (2%)	
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(20)	(19)	(48)	(45)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	1 (5%)		1 (2%)	
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	2 (10%)	1 (5%)	4 (8%)	6 (13%)
MALIGNANT LYMPHOMA, MIXED TYPE				1 (2%)
#SPLEEN	(20)	(19)	(48)	(45)
LEIOMYOSARCOMA, METASTATIC	1 (5%)			
#MESENTERIC L. NODE	(20)	(19)	(45)	(42)
LEIOMYOSARCOMA, METASTATIC	1 (5%)			
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)	
#SMALL INTESTINE	(20)	(19)	(47)	(44)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE				1 (2%)
CIRCULATORY SYSTEM				
NONE				

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
**EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE B2 (CONTINUED)

	CONTROL (UNTR) 02-F041	CONTROL (VEH) 02-F031	LOW DOSE 02-F034	HIGH DOSE 02-F035
DIGESTIVE SYSTEM				
#LIVER	(20)	(19)	(48)	(45)
HEPATOCELLULAR CARCINOMA	1 (5%)		1 (2%)	1 (2%)
FIBROSARCOMA, METASTATIC			1 (2%)	
#STOMACH	(20)	(19)	(47)	(45)
SQUAMOUS CELL PAPILLOMA			1 (2%)	3 (7%)
SQUAMOUS CELL CARCINOMA			2 (4%)	
URINARY SYSTEM				
NONE				
ENDOCRINE SYSTEM				
#PITUITARY	(17)	(18)	(43)	(41)
CHROMOPHOBE ADENOMA	1 (6%)			
#ADRENAL	(20)	(19)	(47)	(45)
CORTICAL CARCINOMA				1 (2%)
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(20)	(19)	(48)	(45)
ADENOCARCINOMA, NOS			1 (2%)	
#OVARY	(20)	(19)	(48)	(43)
CYSTADENOMA, NOS		1 (5%)		
HEMANGIOSARCOMA			1 (2%)	
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
*HARDERIAN GLAND	(20)	(19)	(48)	(45)
ADENOMA, NOS		1 (5%)	1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B2 (CONTINUED)

	CONTROL (UNTR) 02-F041	CONTROL (VEH) 02-F031	LOW DOSE 02-F034	HIGH DOSE 02-F035
MUSCULOSKELETAL SYSTEM				
*FEMUR	(20)	(19)	(48)	(45)
OSTEOSARCOMA			1 (2%)	
BODY CAVITIES				
NONE				
ALL OTHER SYSTEMS				
NONE				
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	20	20	50	50
NATURAL DEATH@	3	2	9	15
MORIBUND SACRIFICE				1
SCHEDULED SACRIFICE				
ACCIDENTALLY KILLED	1		1	
TERMINAL SACRIFICE	16	18	40	34
ANIMAL MISSING				

@ INCLUDES AUTOLYZED ANIMALS

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B2 (CONCLUDED)

	CONTROL (UNTR) 02-F041	CONTROL (VEH) 02-F031	LOW DOSE 02-F034	HIGH DOSE 02-F035
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	7	4	18	15
TOTAL PRIMARY TUMORS	7	4	20	17
TOTAL ANIMALS WITH BENIGN TUMORS	2	3	7	7
TOTAL BENIGN TUMORS	2	3	7	7
TOTAL ANIMALS WITH MALIGNANT TUMORS	5	1	11	9
TOTAL MALIGNANT TUMORS	5	1	13	10
TOTAL ANIMALS WITH SECONDARY TUMORS#	1		2	
TOTAL SECONDARY TUMORS	2		3	
TOTAL ANIMALS WITH TUMORS UNCERTAIN- BENIGN OR MALIGNANT				
TOTAL UNCERTAIN TUMORS				
TOTAL ANIMALS WITH TUMORS UNCERTAIN- PRIMARY OR METASTATIC				
TOTAL UNCERTAIN TUMORS				

* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

APPENDIX C

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS TREATED WITH ALLYL CHLORIDE

TABLE C1
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS TREATED WITH ALLYL CHLORDE

	CONTROL (UNTR) 01-031M	CONTROL (VEH) 01-021M	LOW DOSE 01-032M	HIGH DOSE 01-033M
ANIMALS INITIALLY IN STUDY	20	20	50	50
ANIMALS MISSING		1		
ANIMALS NECROPSIED	20	19	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY **	20	19	50	50
INTEGUMENTARY SYSTEM				
*SKIN	(20)	(19)	(50)	(50)
EPIDERMAL INCLUSION CYST				1 (2%)
INFLAMMATION, NOS	1 (5%)			1 (2%)
INFLAMMATION, SUPPURATIVE		1 (5%)		
RESPIRATORY SYSTEM				
*NASAL CAVITY	(20)	(19)	(50)	(50)
INFLAMMATION, NOS				1 (2%)
*TRACHEA	(15)	(19)	(50)	(50)
INFLAMMATION, NOS		3 (16%)		
INFLAMMATION, SUPPURATIVE		3 (16%)		
*LUNG/BRONCHIOLE	(20)	(19)	(50)	(50)
INFLAMMATION, SUPPURATIVE		2 (11%)		
*LUNG	(20)	(19)	(50)	(50)
PNEUMONIA, CHRONIC MURINE	16 (80%)	13 (68%)	43 (86%)	45 (90%)
CALCIUM DEPOSIT	1 (5%)			2 (4%)
ALVEOLAR MACROPHAGES		1 (5%)		
HEMATOPOIETIC SYSTEM				
*BONE MARROW	(3)	(19)	(50)	(50)
METAMORPHOSIS FATTY				1 (2%)
*SPLEEN	(20)	(17)	(50)	(50)
HEMATOPOIESIS	1 (5%)	1 (6%)	1 (2%)	
*CERVICAL LYMPH NODE	(19)	(17)	(50)	(49)
INFLAMMATION, NOS	1 (5%)		1 (2%)	

* NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
**EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE C1 (CONTINUED)

	CONTROL (UNTR) 01-031M	CONTROL (VEH) 01-021M	LOW DOSE 01-032M	HIGH DOSE 01-033M
#THYMUS	(13)	(2)	(40)	(26)
ANGIECTASIS			1 (3%)	
CIRCULATORY SYSTEM				
#HEART	(20)	(19)	(50)	(50)
FIBROSIS			1 (2%)	
CALCIUM DEPOSIT	1 (5%)		7 (14%)	2 (4%)
#MYOCARDIUM	(20)	(19)	(50)	(50)
INFLAMMATION, NOS	2 (10%)	3 (16%)		1 (2%)
INFLAMMATION, INTERSTITIAL		2 (11%)		
FIBROSIS		13 (68%)	5 (10%)	1 (2%)
DEGENERATION, NOS	1 (5%)		4 (8%)	
CALCIUM DEPOSIT				1 (2%)
CALCIFICATION, NOS			1 (2%)	
#ENDOCARDIUM	(20)	(19)	(50)	(50)
HYPERPLASIA, NOS	1 (5%)		1 (2%)	
*AORTA	(20)	(19)	(50)	(50)
MEDIAL CALCIFICATION	2 (10%)		8 (16%)	4 (8%)
CALCIFICATION, NOS		3 (16%)		
*CORONARY ARTERY	(20)	(19)	(50)	(50)
MEDIAL CALCIFICATION			1 (2%)	1 (2%)
CALCIFICATION, NOS		1 (5%)		
*PULMONARY ARTERY	(20)	(19)	(50)	(50)
CALCIFICATION, FOCAL		1 (5%)		
*MESENTERIC ARTERY	(20)	(19)	(50)	(50)
PERIARTERITIS		2 (11%)		
MEDIAL CALCIFICATION	1 (5%)		5 (10%)	4 (8%)
*PROSTATIC ARTERY	(20)	(19)	(50)	(50)
MEDIAL CALCIFICATION				1 (2%)
DIGESTIVE SYSTEM				
#LIVER	(20)	(19)	(50)	(49)
THROMBUS, ORGANIZED			1 (2%)	
INFLAMMATION, NOS	1 (5%)		1 (2%)	1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C1 (CONTINUED)

	CONTROL (UNTR) 01-031M	CONTROL (VEH) 01-021M	LOW DOSE 01-032M	HIGH DOSE 01-033M
FIBROSIS			1 (2%)	8 (16%)
CIRRHOSIS, NOS			4 (8%)	
PELIOSIS HEPATIS			2 (4%)	
NECROSIS, NOS			1 (2%)	
METAMORPHOSIS FATTY	2 (10%)	3 (16%)	12 (24%)	4 (8%)
CYTOPLASMIC VACUOLIZATION		7 (37%)		
HEPATOCYTOMEGALY		7 (37%)		
ANGIECTASIS	3 (15%)		8 (16%)	4 (8%)
#LIVER/CENTRILOBULAR	(20)	(19)	(50)	(49)
NECROSIS, NOS				1 (2%)
*BILE DUCT	(20)	(19)	(50)	(50)
INFLAMMATION, NOS		8 (42%)		
FIBROSIS		5 (26%)		
HYPERPLASIA, NOS	4 (20%)	11 (58%)		
#PANCREAS	(20)	(16)	(50)	(50)
FIBROSIS, FOCAL		3 (19%)		
PERIARTERITIS	4 (20%)		8 (16%)	2 (4%)
#STOMACH	(20)	(19)	(50)	(50)
ULCER, FOCAL			1 (2%)	2 (4%)
CALCIUM DEPOSIT	2 (10%)		6 (12%)	4 (8%)
HYPERKERATOSIS			1 (2%)	
ACANTHOSIS			1 (2%)	
#GASTRIC MUCOSA	(20)	(19)	(50)	(50)
CALCIFICATION, NOS		2 (11%)		
#COLON	(19)	(19)	(49)	(50)
NEMATODIASIS	1 (5%)			
URINARY SYSTEM				
#KIDNEY	(20)	(19)	(50)	(50)
HYDRONEPHROSIS			2 (4%)	
CYST, NOS			1 (2%)	1 (2%)
PYELONEPHRITIS, NOS	1 (5%)		3 (6%)	4 (8%)
ABSCESS, NOS		1 (5%)		
INFLAMMATION, CHRONIC	15 (75%)	19 (100%)	42 (84%)	14 (28%)
CALCIUM DEPOSIT	1 (5%)		7 (14%)	5 (10%)
#KIDNEY/MEDULLA	(20)	(19)	(50)	(50)
CALCIFICATION, NOS		2 (11%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C1 (CONTINUED)

	CONTROL (UNTR) 01-031M	CONTROL (VEH) 01-021M	LOW DOSE 01-032M	HIGH DOSE 01-033M
#KIDNEY/PELVIS	(20)	(19)	(50)	(50)
HYPERPLASIA, EPITHELIAL		2 (11%)		
#URINARY BLADDER	(19)	(18)	(49)	(49)
INFLAMMATION, NOS	1 (5%)		3 (6%)	4 (8%)
INFLAMMATION, SUPPURATIVE		1 (6%)		
HYPERPLASIA, EPITHELIAL		1 (6%)		
ENDOCRINE SYSTEM				
#PITUITARY	(20)	(16)	(50)	(50)
ANGIECTASIS	1 (5%)			
#ADRENAL CORTEX	(20)	(19)	(49)	(50)
DEGENERATION, NOS			1 (2%)	
CYTOMEGALY		1 (5%)		
ANGIECTASIS	1 (5%)		3 (6%)	
#THYROID	(19)	(19)	(49)	(49)
ULTIMOBRANCHIAL CYST	2 (11%)	1 (5%)		
FOLLICULAR CYST, NOS			4 (8%)	1 (2%)
HYPERPLASIA, C-CELL	1 (5%)	4 (21%)		
HYPERPLASIA, FOLLICULAR-CELL	1 (5%)	1 (5%)		
#PARATHYROID	(3)	(18)	(23)	(26)
HYPERPLASIA, NOS	2 (67%)	4 (22%)	5 (22%)	3 (12%)
REPRODUCTIVE SYSTEM				
#PROSTATE	(20)	(18)	(43)	(33)
INFLAMMATION, NOS	5 (25%)		4 (9%)	5 (15%)
INFLAMMATION, SUPPURATIVE		8 (44%)		
HYPERPLASIA, EPITHELIAL		1 (6%)		
METAPLASIA, SQUAMOUS		4 (22%)		
#SEMINAL VESICLE	(20)	(19)	(50)	(50)
INFLAMMATION, NOS	1 (5%)		2 (4%)	3 (6%)
#TESTIS	(20)	(18)	(49)	(49)
GRANULOMA, SPERMATIC	1 (5%)			
PERIARTERITIS		2 (11%)		
CALCIUM DEPOSIT				1 (2%)
ATROPHY, NOS	11 (55%)	8 (44%)	20 (41%)	9 (18%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C1 (CONCLUDED)

	CONTROL (UNTR) 01-031M	CONTROL (VEH) 01-021M	LOW DOSE 01-032M	HIGH DOSE 01-033M
*EPIDIDYMIS	(20)	(19)	(50)	(50)
NECROSIS, FAT	1 (5%)			
ATROPHY, NOS	3 (15%)			
HYPERPLASIA, EPITHELIAL		1 (5%)		
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
*EYE/LACRIMAL GLAND	(20)	(19)	(50)	(50)
INFLAMMATION, NOS	1 (5%)			
MUSCULOSKELETAL SYSTEM				
*BONE	(20)	(19)	(50)	(50)
OSTEOPOROSIS		1 (5%)		
BODY CAVITIES				
*PERITONEUM	(20)	(19)	(50)	(50)
INFLAMMATION, NOS	1 (5%)			
*PERICARDIUM	(20)	(19)	(50)	(50)
INFLAMMATION, NOS	2 (10%)		1 (2%)	2 (4%)
*MESENTERY	(20)	(19)	(50)	(50)
PERIARTERITIS	4 (20%)		5 (10%)	1 (2%)
NECROSIS, FAT			1 (2%)	
ALL OTHER SYSTEMS				
NONE				
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED			1	
ANIMAL MISSING/NO NECROPSY		1		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C2
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS TREATED WITH ALLYL CHLORIDE

	CONTROL (UNTR) 01-031F	CONTROL (VEH) 01-021F	LOW DOSE 01-034F	HIGH DOSE 01-035F
ANIMALS INITIALLY IN STUDY	20	20	50	50
ANIMALS NECROPSIED	20	20	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	20	50	50
INTEGUMENTARY SYSTEM				
*SUBCUT TISSUE	(20)	(20)	(50)	(50)
ABSCESS, NOS				1 (2%)
RESPIRATORY SYSTEM				
#TRACHEA	(15)	(20)	(50)	(50)
INFLAMMATION, NOS		5 (25%)	1 (2%)	
INFLAMMATION, SUPPURATIVE		1 (5%)		
METAPLASIA, SQUAMOUS		1 (5%)		
#LUNG/BRONCHIOLE	(20)	(20)	(50)	(50)
INFLAMMATION, SUPPURATIVE		4 (20%)		
#LUNG	(20)	(20)	(50)	(50)
FOREIGN BODY, NOS		1 (5%)		
CONGESTION, NOS		1 (5%)		
HEMORRHAGE		2 (10%)		
PNEUMONIA, CHRONIC MURINE	18 (90%)	13 (65%)	44 (88%)	43 (86%)
ALVEOLAR MACROPHAGES		6 (30%)		
HYPERPLASIA, ALVEOLAR EPITHELIUM		1 (5%)		
HEMATOPOIETIC SYSTEM				
#SPLEEN	(20)	(20)	(50)	(49)
HEMORRHAGE		1 (5%)		
FIBROSIS, FOCAL		1 (5%)		
HEMATOPOIESIS		4 (20%)	6 (12%)	1 (2%)
#CERVICAL LYMPH NODE	(20)	(20)	(50)	(49)
INFLAMMATION, NOS				1 (2%)
ANGIECTASIS			3 (6%)	1 (2%)
HYPERPLASIA, LYMPHOID		2 (10%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
**EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE C2 (CONTINUED)

	CONTROL (UNTR) 01-031F	CONTROL (VEH) 01-021F	LOW DOSE 01-034F	HIGH DOSE 01-035F
#THYMUS	(15)	(19)	(39)	(37)
ANGIECTASIS				1 (3%)
CIRCULATORY SYSTEM				
#MYOCARDIUM	(20)	(20)	(50)	(50)
INFLAMMATION, SUPPURATIVE		1 (5%)		
FIBROSIS	1 (5%)	1 (5%)		1 (2%)
#ENDOCARDIUM	(20)	(20)	(50)	(50)
INFLAMMATION, NOS			1 (2%)	
*AORTA	(20)	(20)	(50)	(50)
MEDIAL CALCIFICATION	1 (5%)			
*MESENTERIC ARTERY	(20)	(20)	(50)	(50)
PERIARTERITIS		3 (15%)		
DIGESTIVE SYSTEM				
#LIVER	(20)	(20)	(50)	(50)
INFLAMMATION, NOS			3 (6%)	1 (2%)
FIBROSIS				1 (2%)
PELIOSIS HEPATIS			2 (4%)	
NECROSIS, NOS				1 (2%)
METAMORPHOSIS FATTY	1 (5%)		4 (8%)	1 (2%)
CYTOPLASMIC VACUOLIZATION		6 (30%)		
FOCAL CELLULAR CHANGE				1 (2%)
HEPATOCYTOMEGALY		6 (30%)		
ANGIECTASIS		2 (10%)	2 (4%)	2 (4%)
#LIVER/CENTRILOBULAR	(20)	(20)	(50)	(50)
DEGENERATION, NOS				1 (2%)
NECROSIS, NOS	1 (5%)		1 (2%)	
*BILE DUCT	(20)	(20)	(50)	(50)
INFLAMMATION, NOS		8 (40%)		
FIBROSIS		3 (15%)		
HYPERPLASIA, NOS		14 (70%)		
#PANCREAS	(20)	(20)	(50)	(50)
FIBROSIS		1 (5%)		
PERIARTERITIS		1 (5%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C2 (CONTINUED)

	CONTROL (UNTR) 01-031F	CONTROL (VEH) 01-021F	LOW DOSE 01-034F	HIGH DOSE 01-035F
#PANCREATIC ACINUS	(20)	(20)	(50)	(50)
HYPERPLASIA, FOCAL		1 (5%)		
#ESOPHAGUS	(15)	(14)	(50)	(50)
GRANULOMA, FOREIGN BODY		1 (7%)		
#STOMACH	(20)	(20)	(50)	(50)
INFLAMMATION, NOS	1 (5%)			
ULCER, FOCAL			1 (2%)	
HYPERKERATOSIS	1 (5%)			
ACANTHOSIS	1 (5%)			
URINARY SYSTEM				
#KIDNEY	(20)	(20)	(50)	(50)
HYDRONEPHROSIS				1 (2%)
PYELONEPHRITIS, NOS			2 (4%)	2 (4%)
INFLAMMATION, CHRONIC	9 (45%)	14 (70%)	16 (32%)	1 (2%)
CALCIUM DEPOSIT	1 (5%)		1 (2%)	1 (2%)
#KIDNEY/PELVIS	(20)	(20)	(50)	(50)
HYPERPLASIA, EPITHELIAL		4 (20%)		
#URINARY BLADDER	(19)	(20)	(50)	(48)
INFLAMMATION, NOS				2 (4%)
ENDOCRINE SYSTEM				
#PITUITARY	(19)	(20)	(50)	(50)
ANGIECTASIS			1 (2%)	1 (2%)
#ADRENAL CORTEX	(20)	(20)	(50)	(50)
DEGENERATION, NOS			1 (2%)	1 (2%)
CYTOMEGALY		4 (20%)		
ANGIECTASIS	3 (15%)		10 (20%)	2 (4%)
#ADRENAL MEDULLA	(20)	(20)	(50)	(50)
HYPERPLASIA, FOCAL		1 (5%)		
#THYROID	(20)	(19)	(50)	(48)
ULTIMOBRANCHIAL CYST		2 (11%)		
HYPERPLASIA, C-CELL	4 (20%)	7 (37%)		
#PARATHYROID	(1)	(16)	(8)	(6)
HYPERPLASIA, NOS	1 (100%)	3 (19%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C7 (CONTINUED)

	CONTROL (UNTR) 01-031F	CONTROL (VEH) 01-021F	LOW DOSE 01-034F	HIGH DOSE 01-035F
REPRODUCTIVE SYSTEM				
*VAGINA	(20)	(20)	(50)	(50)
INFLAMMATION, NOS			4 (8%)	3 (6%)
#UTERUS	(20)	(20)	(50)	(49)
HYDROMETRA	4 (20%)		4 (8%)	4 (8%)
#UTERUS/ENDOMETRIUM	(20)	(20)	(50)	(49)
CYST, NOS		1 (5%)		
INFLAMMATION, NOS	1 (5%)		3 (6%)	1 (2%)
INFLAMMATION, SUPPURATIVE		2 (10%)		
HYPERPLASIA, CYSTIC	1 (5%)	1 (5%)	1 (2%)	1 (2%)
#OVARY	(20)	(20)	(50)	(49)
CYST, NOS		1 (5%)		
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
*EYE/CORNEA	(20)	(20)	(50)	(50)
INFLAMMATION, NOS			1 (2%)	
MUSCULOSKELETAL SYSTEM				
*SKELETAL MUSCLE	(20)	(20)	(50)	(50)
GRANULOMA, NOS		2 (10%)		
BODY CAVITIES				
*MEDIASTINUM	(20)	(20)	(50)	(50)
GRANULOMA, FOREIGN BODY		1 (5%)		
*PLEURA	(20)	(20)	(50)	(50)
FIBROSIS, FOCAL		1 (5%)		
*PERICARDIUM	(20)	(20)	(50)	(50)
INFLAMMATION, NOS			3 (6%)	2 (4%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C2 (CONCLUDED)

	CONTROL (UNTR) 01-031F	CONTROL (VEH) 01-021F	LOW DOSE 01-034F	HIGH DOSE 01-035F
METAPLASIA, OSSEOUS			1 (2%)	
*EPICARDIUM	(20)	(20)	(50)	(50)
INFLAMMATION, SUPPURATIVE		2 (10%)		
*MESENTERY	(20)	(20)	(50)	(50)
PERIARTERITIS			1 (2%)	
NECROSIS, FAT			1 (2%)	
ALL OTHER SYSTEMS				
NONE				
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED				3

& NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

APPENDIX D

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE TREATED WITH ALLYL CHLORIDE

TABLE D1
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE TREATED WITH ALLYL CHLORIDE

	CONTROL (UNTR) 02-M041	CONTROL (VEH) 02-M031	LOW DOSE 02-M032	HIGH DOSE 02-M033
ANIMALS INITIALLY IN STUDY	20	20	50	50
ANIMALS NECROPSIED	18	20	46	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	15	20	45	49
INTEGUMENTARY SYSTEM				
#SKIN	(18)	(20)	(46)	(50)
INFLAMMATION, NOS		2 (10%)	2 (4%)	1 (2%)
#SUBCUTIS TISSUE	(18)	(20)	(46)	(50)
ABSCESS, NOS	1 (6%)	1 (5%)	3 (7%)	1 (2%)
RESPIRATORY SYSTEM				
#LUNG	(15)	(20)	(45)	(49)
PNEUMONIA, CHRONIC MURINE			4 (9%)	3 (6%)
HYPERPLASIA, ALVEOLAR EPITHELIUM			1 (2%)	
HEMATOPOIETIC SYSTEM				
#SPLEEN	(15)	(20)	(46)	(48)
AMYLOIDOSIS	7 (47%)	2 (10%)	6 (13%)	3 (6%)
HEMATOPOIESIS		3 (15%)	1 (2%)	4 (8%)
#LYMPH NODE	(15)	(19)	(39)	(28)
INFLAMMATION, NOS			1 (3%)	
#CERVICAL LYMPH NODE	(15)	(19)	(39)	(28)
INFLAMMATION, NOS		1 (5%)		
#MESENTERIC L. NODE	(15)	(19)	(39)	(28)
INFLAMMATION, NOS	1 (7%)	7 (37%)	10 (26%)	
ANGIECTASIS			1 (3%)	
CIRCULATORY SYSTEM				
#HEART	(15)	(20)	(46)	(49)
FIBROSIS			1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
**EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE D1 (CONTINUED)

	CONTROL (UNTR) 02-M041	CONTROL (VEH) 02-M031	LOW DOSE 02-M032	HIGH DOSE 02-M033
#MYOCARDIUM	(15)	(20)	(46)	(49)
DEGENERATION, NOS			1 (2%)	
DIGESTIVE SYSTEM				
#LIVER	(15)	(20)	(46)	(49)
THROMBUS, ORGANIZED			1 (2%)	
AMYLOIDOSIS			1 (2%)	2 (4%)
METAMORPHOSIS FATTY			1 (2%)	
#PANCREAS	(14)	(20)	(45)	(43)
CYST, NOS			1 (2%)	
INFLAMMATION, NOS	1 (7%)			
#STOMACH	(15)	(20)	(46)	(49)
ULCER, NOS				1 (2%)
CALCIUM DEPOSIT			1 (2%)	
HYPERKERATOSIS			9 (20%)	19 (39%)
ACANTHOSIS			9 (20%)	19 (39%)
#COLON	(13)	(20)	(44)	(46)
NEMATODIASIS			1 (2%)	
URINARY SYSTEM				
#KIDNEY	(15)	(20)	(46)	(49)
HYDRONEPHROSIS			1 (2%)	
CYST, NOS		1 (5%)		
PYELONEPHRITIS, NOS		2 (10%)	5 (11%)	5 (10%)
INFLAMMATION, CHRONIC	12 (80%)	2 (10%)	10 (22%)	3 (6%)
AMYLOIDOSIS	7 (47%)	2 (10%)	5 (11%)	2 (4%)
#URINARY BLADDER	(15)	(19)	(44)	(47)
CALCULUS, NOS				1 (2%)
INFLAMMATION, NOS		2 (11%)	1 (2%)	1 (2%)
HYPERPLASIA, EPITHELIAL				1 (2%)
ENDOCRINE SYSTEM				
#THYROID	(10)	(20)	(38)	(37)
FOLLICULAR CYST, NOS	1 (10%)	1 (5%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D1 (CONTINUED)

	CONTROL (UNTR) 02-M041	CONTROL (VEH) 02-M031	LOW DOSE 02-M032	HIGH DOSE 02-M033
REPRODUCTIVE SYSTEM				
#PROSTATE	(15)	(12)	(40)	(43)
INFLAMMATION, NOS			1 (3%)	4 (9%)
#SEMINAL VESICLE	(18)	(20)	(46)	(50)
INFLAMMATION, NOS			1 (2%)	1 (2%)
#TESTIS	(15)	(20)	(46)	(49)
ATROPHY, NOS	1 (7%)			
#EPIDIDYMIS	(18)	(20)	(46)	(50)
INFLAMMATION, NOS				1 (2%)
GRANULOMA, SPERMATIC			1 (2%)	1 (2%)
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
#HARDERIAN GLAND	(18)	(20)	(46)	(50)
INFLAMMATION, NOS			1 (2%)	
HYPERPLASIA, NOS			1 (2%)	
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
NONE				
ALL OTHER SYSTEMS				
NONE				
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED	3	7	5	18

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D1 (CONCLUDED)

	CONTROL (UNTR) 02-M041	CONTROL (VEH) 02-M031	LOW DOSE 02-M032	HIGH DOSE 02-M033
AUTO/NECROPSY/HISTO PERF				1
AUTO/NECROPSY/NO HISTO	3		1	1
AUTOLYSIS/NO NECROPSY	2		4	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D2
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE TREATED WITH ALLYL CHLORIDE

	CONTROL (UNTR) 02-F041	CONTROL (VEH) 02-F031	LOW DOSE 02-F034	HIGH DOSE 02-F035
ANIMALS INITIALLY IN STUDY	20	20	50	50
ANIMALS NECROPSIED	20	19	48	45
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	19	48	44
INTEGUMENTARY SYSTEM				
*SKIN	(20)	(19)	(48)	(45)
INFLAMMATION, GRANULOMATOUS			1 (2%)	
*SUBCUT TISSUE	(20)	(19)	(48)	(45)
ABSCESS, NOS				1 (2%)
RESPIRATORY SYSTEM				
#LUNG	(20)	(19)	(48)	(45)
PNEUMONIA, CHRONIC MURINE	1 (5%)	1 (5%)	3 (6%)	5 (11%)
HEMATOPOIETIC SYSTEM				
#SPLEEN	(20)	(19)	(48)	(45)
HEMATOPOIESIS			1 (2%)	3 (7%
#LYMPH NODE	(20)	(19)	(45)	(42)
INFLAMMATION, NOS	1 (5%)		1 (2%)	
#BRONCHIAL LYMPH NODE	(20)	(19)	(45)	(42)
INFLAMMATION, NOS				1 (2%)
#MESENTERIC L. NODE	(20)	(19)	(45)	(42)
INFLAMMATION, NOS		1 (5%)	1 (2%)	1 (2%)
ANGIECTASIS		1 (5%)		
CIRCULATORY SYSTEM				
#ENDOCARDIUM	(20)	(19)	(48)	(45)
HYPERPLASIA, NOS				1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
**EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE D2 (CONTINUED)

	CONTROL (UNTR) 02-F041	CONTROL (VEH) 02-F031	LOW DOSE 02-F034	HIGH DOSE 02-F035
DIGESTIVE SYSTEM				
#LIVER	(20)	(19)	(48)	(45)
LEUKEMOID REACTION	1 (5%)			
#BILE DUCT	(20)	(19)	(48)	(45)
DILATATION, NOS	1 (5%)			
HYPERPLASIA, NOS		1 (5%)		
#PANCREAS	(20)	(19)	(46)	(45)
CYST, NOS		1 (5%)		
CYSTIC DUCTS			2 (4%)	1 (2%)
INFLAMMATION, NOS		1 (5%)		2 (4%)
ATROPHY, NOS			2 (4%)	1 (2%)
#STOMACH	(20)	(19)	(47)	(45)
ULCER, NOS			1 (2%)	1 (2%)
HYPERKERATOSIS			17 (36%)	25 (56%)
ACANTHOSIS			17 (36%)	25 (56%)
#SMALL INTESTINE	(20)	(19)	(47)	(44)
HYPERPLASIA, LYMPHOID			2 (4%)	2 (5%)
#PEYERS PATCH	(20)	(19)	(47)	(44)
HYPERPLASIA, LYMPHOID			1 (2%)	
URINARY SYSTEM				
NONE				
ENDOCRINE SYSTEM				
#THYROID	(16)	(16)	(43)	(41)
FOLLICULAR CYST, NOS	1 (6%)			
HYPERPLASIA, FOLLICULAR-CELL	1 (6%)			
REPRODUCTIVE SYSTEM				
*VAGINA	(20)	(19)	(48)	(45)
INFLAMMATION, NOS		1 (5%)		
#UTERUS	(20)	(19)	(48)	(43)
HYDROMETRA	5 (25%)	2 (11%)	15 (31%)	12 (28%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D2 (CONCLUDED)

	CONTROL (UNTR) 02-F041	CONTROL (VEH) 02-F031	LOW DOSE 02-F034	HIGH DOSE 02-F035
INFLAMMATION, NOS			1 (2%)	
*UTERUS/ENDOMETRIUM	(20)	(19)	(48)	(43)
INFLAMMATION, NOS	3 (15%)	2 (11%)		5 (12%)
HYPERPLASIA, CYSTIC	6 (30%)	9 (47%)	19 (40%)	13 (30%)
*OVARY/OVIDUCT	(20)	(19)	(48)	(43)
INFLAMMATION, NOS		1 (5%)	1 (2%)	2 (5%)
*OVARY	(20)	(19)	(48)	(43)
CYST, NOS	12 (60%)	4 (21%)	11 (23%)	11 (26%)
INFLAMMATION, NOS	5 (25%)	4 (21%)		3 (7%)
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
*HARDERIAN GLAND	(20)	(19)	(48)	(45)
INFLAMMATION, NOS			1 (2%)	
HYPERPLASIA, NOS			2 (4%)	4 (9%)
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
*PERITONEUM	(20)	(19)	(48)	(45)
INFLAMMATION, NOS		1 (5%)		1 (2%)
ALL OTHER SYSTEMS				
*MULTIPLE ORGANS	(20)	(19)	(48)	(45)
LEUKEMOID REACTION			1 (2%)	
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED	1	3	2	2
AUTO/NECROPSY/NO HISTO				1
AUTOLYSIS/NO NECROPSY		1	2	5

* NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

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