NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 253

CARCINOGENESIS STUDIES OF ALLYL ISOVALERATE (CAS NO. 2835-39-4) IN F344/N RATS AND B6C3F$_1$ MICE (GAVAGE STUDIES)

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

NATIONAL TOXICOLOGY PROGRAM

The National Toxicology Program (NTP), established in 1978, develops and evaluates scientific information about potentially toxic and hazardous chemicals. This knowledge can be used for protecting the health of the American people and for the primary prevention of chemically induced disease. By bringing together the relevant programs, staff, and resources from the U.S. Public Health Service, DHHS, the National Toxicology Program has centralized and strengthened activities relating to toxicology research, testing and test development, validation efforts, and the dissemination of toxicological information to the public and scientific communities and to the research and regulatory agencies.

The NTP is comprised of four charter DHHS agencies: the National Cancer Institute, National Institutes of Health; the National Institute of Environmental Health Sciences, National Institutes of Health; the National Center for Toxicological Research, Food and Drug Administration; and the National Institute for Occupational Safety and Health, Centers for Disease Control. In July 1981, the Carcinogenesis Bioassay Testing Program, NCI, was transferred to the NIEHS.

NTP TECHNICAL REPORT
ON THE

CARCINOGENESIS STUDIES OF ALLYL ISOVALERATE (CAS NO. 2835-39-4) IN F344/N RATS AND B6C3F1 MICE (GAVAGE STUDY)

NATIONAL TOXICOLOGY PROGRAM
P.O. Box 12233
Research Triangle Park
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May 1983

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

NOTE TO THE READER

This is one in a series of experiments designed to determine whether selected chemicals produce cancer in animals. Chemicals selected for testing in the NTP carcinogenesis bioassay program are chosen primarily on the bases of human exposure, level of production, and chemical structure. Selection per se is not an indicator of a chemical's carcinogenic potential. Negative results, in which the test animals do not have a greater incidence of cancer than control animals, do not necessarily mean that a test chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of conditions. Positive results demonstrate that a test chemical is carcinogenic for animals under the conditions of the test and indicate that exposure to the chemical has the potential for hazard to humans. The determination of the risk to humans from chemicals found to be carcinogenic in animals requires a wider analysis which extends beyond the purview of this study.

This study was initiated by the National Cancer Institute's Carcinogenesis Testing Program, now part of the National Institute of Environment Health Sciences, National Toxicology Program.

Comments and questions about the National Toxicology Program Technical Reports on Carcinogenesis Bioassays should be directed to the National Toxicology Program, located at Room 835B, Westwood Towers, 5401 Westbard Ave., Bethesda, MD 20205 (301-496-1152) or at Research Triangle Park, NC 27709 (919-541-3991).

Although every effort is made to prepare the Technical Reports as accurately as possible, mistakes may occur. Readers are requested to communicate any mistakes to the Deputy Director, NTP (P.O. Box 12233, Research Triangle Park, NC 27709), so that corrective action may be taken. Further, anyone who is aware of related ongoing or published studies not mentioned in this report is encouraged to make this information known to the NTP.

These NTP Technical Reports are available for sale from the National Technical Information Service, U.S. Department of Commerce, 5285 Port Royal Road, Springfield, VA 22161 (703-487-4650).

Single copies of this carcinogenesis bioassay technical report are available without charge (and while supplies last) from the NTP Public Information Office, National Toxicology Program, P.O. Box 12233, Research Triangle Park, NC 27709.

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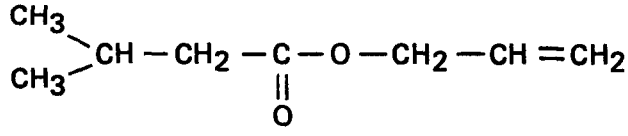

ALLYL ISOVALERATE

CAS NO. 2835-39-4

$C_8H_{14}O_2$ Mol. Wt. 142.22

ABSTRACT

Carcinogenesis studies of allyl isovalerate (96% pure) were conducted by administering the test chemical in corn oil by gavage to groups of 50 male and 50 female F344/N rats and to groups of 50 male and 50 female $B6C3F_1$ mice at doses of 31 or 62 mg/kg. The doses selected were based on the chemically-induced toxic effects and depressed weight gains obtained from the 13-week studies. Doses were administered five times per week for 103 weeks. Groups of 50 rats and 50 mice of each sex received corn oil by gavage on the same dosing schedule and served as vehicle controls.

Survival and mean body weight gain of rats of each sex and male mice were not adversely affected by the administration of allyl isovalerate. The significantly lower survival (P=0.001) and the lower mean body weight gain of low-dose female mice as compared with controls are likely consequences of the high incidence of a genital tract infection in the low-dose females. This infection was probably responsible for the deaths of 11/19 control, 22/33 low-dose, and 13/25 high-dose female mice that died before the end of the study.

Squamous cell papillomas and epithelial hyperplasia of the nonglandular stomach were observed in dosed male mice in the 2-year studies (squamous cell papillomas: 0/50, 1/50, 2%, 3/48, 6%; epithelial hyperplasia: 1/50, 2%; 1/50, 2%; 7/48, 15%). The papillomas occurred with a significant positive trend ($P<0.05$). The incidence of high-dose male mice with squamous cell papillomas of the nonglandular stomach was also higher ($P<0.01$) than the historical rate for vehicle control male $B6C3F_1$ mice in the Bioassay Program (5/881, 0.6%). Forestomach lesions were also observed in female mice: squamous cell papillomas (1/50, 0/50, 2/50) and epithelial hyperplasia of the nonglandular stomach (0/50, 2/50, 3/50). Pancreatic acinar-cell adenomas occurred at higher incidences in the dosed male rats than in the controls (control, 1/50, 2%; low-dose, 4/50, 8%; high-dose, 2/50, 4%). Pancreatic acinar-cell tumors were not observed in female rats. Preputial gland adenomas were observed in increased incidence in low-dose male rats (0/50, 4/50, 8%; $P<0.05$, 1/50, 2%).

Mononuclear-cell leukemias in rats and lymphomas in mice occurred with increased incidences. This consistent dose-response increase among both rats and mice indicates that allyl isovalerate adversely affects the hematopoietic system.

	Vehicle Control	31 mg/kg	62 mg/kg
Mononuclear-Cell Leukemia			
Male Rats *(a)*	1/50 (2%)	4/50 (8%)	7/50 (14%) *(b)*
Female Rats *(a)*	4/50 (8%)	6/50 (12%)	9/49 (18%) *(c)*
Lymphoma			
Male Mice	4/50 (8%)	6/50 (12%)	8/50 (16%)
Female Mice *(a)*	11/50 (22%)	11/50 (22%)	18/50 (36%) *(b)*

(a) Significant ($P<0.05$) dose response trend by life table analysis
(b) Significant ($P<0.05$) increase by life table analysis when compared with controls
(c) Includes one leukemia, NOS

Cholangiofibrosis, nodular regeneration, cirrhosis, focal necrosis, fatty metamorphosis, and cytoplasmic vacuolization were observed at increased incidences in the livers of high-dose male and female rats in the 2-year study. No compound-related nonneoplastic lesions were observed in the mice of either sex. Liver neoplasms were not increased in either dosed rats or mice of either sex. Significant ($P<0.05$) decreases in tumor incidences were observed in male mice for hepatocellular carcinomas (18/50, 6/50, 9/50), for alveolar/bronchiolar adenomas or carcinomas (13/50, 6/50, 5/49), and for follicular-cell adenomas of the thyroid gland (5/47, 0/46, 1/49).

Allyl isovalerate was not mutagenic for *Salmonella typhimurium* (tester strains TA 98, 100, 1535, and 1537) with or without metabolic activation.

Under the conditions of these studies, allyl isovalerate was carcinogenic for F344/N rats and $B6C3F_1$ mice, causing increased incidences of hematopoietic system neoplasms (mononuclear-cell leukemia in male rats and lymphoma in female mice).

CONTRIBUTORS

The carcinogenesis studies of allyl isovalerate were conducted at Southern Research Institute under a subcontract to Tracor Jitco, Inc., the prime contractor for the Carcinogenesis Testing Program. The 2-year studies (rats and mice) were begun in January 1979 and were completed in January 1981.

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The pathology report and selected slides were evaluated on 3 November 1981 by the NTP Pathology Working Group, which included Drs. G. Boorman (NTP), T. Brown (North Carolina State University), B. Bupta (NIEHS), P. Hildebrandt (Tracor Jitco), and R. Maronpot (NTP).

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SUMMARY OF PEER REVIEW COMMENTS ON THE CARCINOGENESIS STUDIES OF ALLYL ISOVALERATE

On 22 September 1982 this technical report on the carcinogenesis studies of allyl isovalerate underwent peer review by the National Toxicology Program Board of Scientific Counselors' Technical Reports Review Subcommittee and associated Panel of Experts. This public review meeting began at 9:00 a.m. in the Conference Center, Building 101, South Campus, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina. The following precis represents the critiques made by the principal reviewers, as well as comments from and discussion by the Peer Review Panel, NTP staff, and attendees.

Dr. Schwetz, a principal reviewer for the report on the carcinogenesis studies of allyl isovalerate, agreed with the conclusions that allyl isovalerate was carcinogenic for F344/N rats and $B6C3F_1$ mice, causing increased incidences of hematopoietic system lesions (mononuclear-cell leukemia in male rats and lymphoma in female mice). Allyl isovalerate was not mutagenic for *Salmonella typhimurium* tester strains TA98, 100, 1535, and 1537 (with or without metabolic activation using preincubation suspension). Dr. Schwetz said the abstract should mention the significant decreases observed in male mice of hepatocellular carcinomas, alveolar/bronchiolar adenomas or carcinomas, and follicular-cell adenomas of the thyroid. Dr. Schwetz observed that the historical control data from the testing laboratory supported the positive findings for lymphomas in female mice and for leukemia in male rats, but indicated an equivocal result for leukemias in male rats when the control range across laboratories was considered. He also stated that the genital tract infection which caused a significant number of deaths in female mice should be better defined and characterized in the results section, and the possible impact on the outcome of the study in females should be discussed.

As a second principal reviewer, Dr. Vore agreed with the conclusion which separated incidences of hematopoietic lesions in rats and mice. She mentioned the number of rats killed accidentally, the number of female mice likely to have died of infections, and the fact that the maximum tolerated dose appears not to have been attained.

As a third principal reviewer, Dr. Swenberg commented that for leukemias in male rats, the incidence in high-dose animals was within the historical control range for all laboratories and therefore probably not of biological significance. With regard to lymphomas in female mice, the findings were at best equivocal. He doubted the biological significance for squamous-cell papillomas of the mouse stomach, preputial gland tumors in rats, and pancreatic adenomas in male rats. In sum, he stated the opinion that there is little evidence of carcinogenicity with allyl isovalerate.

Dr. Huff, NTP, stated that the NTP policy was to compare dosed groups with (in order of preference) i) concurrent controls, ii) laboratory specific historical controls, and iii) historical controls across laboratories. Due to a considerable laboratory-to-laboratory variation, the NTP generally uses across laboratory historic rates only for rare tumors. The interlaboratory composite historic control tumor data were, in Dr. Huff's opinion, inappropriate for routine comparisons with individual carcinogenesis bioassays, and thus inappropriate for making interpretive evaluations. Comparing the incidences of hematopoietic lesions in dosed rats and mice with both the concurrent controls and the laboratory specific historic controls, Dr. Huff emphasized a clear dose response and a high-dose effect in two (male rats and female mice) of the four experiments and some evidence of a similar trend in the other two studies (female rats and male mice).

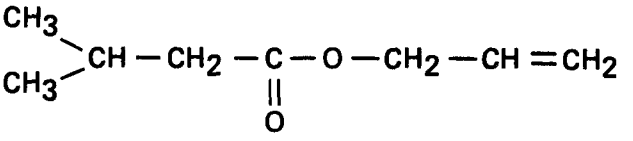
In further discussion, Dr. Elashoff said comparison of historical control data with concurrent controls was difficult because adjusted incidences i.e., correction for survivorship, were used for concurrent control comparisons but not for the historical controls. Dr. J. Haseman, NTP, said for the data on allyl isovalerate, there was little variability with regard to leukemias in rats in other

control groups from the same testing laboratory. [Statistical analyses utilizing historical control data that adjust for differences in survival were done subsequent to the Peer Review meeting and are shown in Appendix I, Table I3, Page 162.] Dr. Holland said the criteria for diagnosing leukemia may vary tremendously from laboratory to laboratory. Thus, he would ignore the historical control data in arriving at any decision about the merits, or lack thereof, of the findings on hematopoietic lesions. There was discussion by Dr. E. McConnell, NTP, about appropriateness of combining leukemias and lymphomas in rats for statistical purposes.

Dr. Schwetz moved that the report on the carcinogenesis studies of allyl isovalerate be accepted subject to the written and verbal revisions discussed. Dr. Vore seconded the motion. The technical report was approved by nine affirmative votes with one abstention (Dr. Holland).

I. INTRODUCTION

I. INTRODUCTION



ALLYL ISOVALERATE

CAS NO. 2835-39-4

$C_8H_{14}O_2$ Mol. Wt. 142.22

Allyl isovalerate, a synthetic fragrance and flavoring ingredient in use since the 1950s, may be found in various products at the following concentrations: soap, 30 ppm; detergent, 3 ppm; creams, 15 ppm; perfume, 50 ppm; nonalcoholic beverages, 9 ppm; ice cream, 18 ppm; candy, 22 ppm; baked goods, 15-48 ppm; and gelatins and puddings, 1 ppm (Opdyke, 1977; Fenaroli, 1971). A colorless liquid with an apple-like odor and taste, allyl isovalerate is approved by the U.S. Food and Drug Administration for use in foods (U.S. CFR, 1979). Specific production figures are not available, but U.S. production in 1980 exceeded 1,000 pounds (USITC, 1981).

An acute, oral LD_{50} value of 230 mg/kg has been reported for rats of unspecified sex and strain (Moreno, 1977).

Administered orally to rats for 10 days, allyl isovalerate caused necrosis and fibrosis of the liver at a dose of 60 mg/kg body weight/day and cell enlargement and bile duct proliferation at a dose of 150 mg/kg/day (Drake, 1975). Similar hepatic effects were observed in Osborne-Mendel rats administered the closely related chemicals allyl butyrate or allyl caproate at doses of 90 or 100 mg/kg (Hagan et al., 1967; Taylor et al., 1964).

Metabolism

Allyl isovalerate is hydrolyzed *in vivo* to allyl alcohol and isovaleric acid. Allyl alcohol is then oxidized to acrolein (Drake, 1975); isovaleric acid is converted in mice to isovaleryl-CoA (Holze and Panten, 1979). The proposed metabolic pattern of allyl isovalerate is illustrated in Figure 1. Isovaleryl-CoA is produced during the catabolism of leucine and thus is naturally present in humans, rats, and mice (Cohn et al., 1978; Holze and Panten, 1979; Goodman, 1977).

Allyl alcohol is a liver toxicant in rats (Butterworth et al., 1978). High levels of isovaleric acid in the blood (found in humans with metabolic defects) can produce vomiting and lethargy which progress to coma, pancytopenia, and ketoacidosis (Cohn et al., 1978).

Acrolein reacts with glutathione to produce 2-aldehydoethylglutathione, which is reduced to an alcohol and excreted as the N-acetylcysteine conjugate (mercapturic acid). Conjugation of acrolein with glutathione occurs in rat liver *in vivo* (Giles, 1979), but has not been demonstrated in other tissues.

Patel et al. (1980) demonstrated the ability of liver tissue from phenobarbital-pretreated rats to metabolize allyl alcohol to acrolein and allylic acid (2-propenoic acid). The characteristics of the oxidation of allyl alcohol to acrolein were consistent with catalysis by alcohol dehydrogenase, while those of oxidation of acrolein to allylic acid were consistent with catalysis by aldehyde dehydrogenase. Allyl alcohol and acrolein were also shown to undergo hepatic microsomal oxidation to the epoxides glycidol and glycidaldehyde (Patel et al., 1980). These epoxides were subsequently hydrolyzed to diols (glycerol, glyceraldehyde) or conjugated with glutathione. The products of the latter reaction were not isolated or identified.

The conjugation of the reactive aldehyde acrolein with glutathione occurs *in vitro* in the absence of enzyme mediation (Giles, 1979), but may be catalyzed by glutathione transferases *in vivo*. Conjugation of an allyl alcohol metabolite with glutathione would appear to be a detoxication reaction, as Hanson and Anders (1978) have reported that diethyl maleate-induced depletion of glutathione enhanced the lethal potency of allyl alcohol in rats.

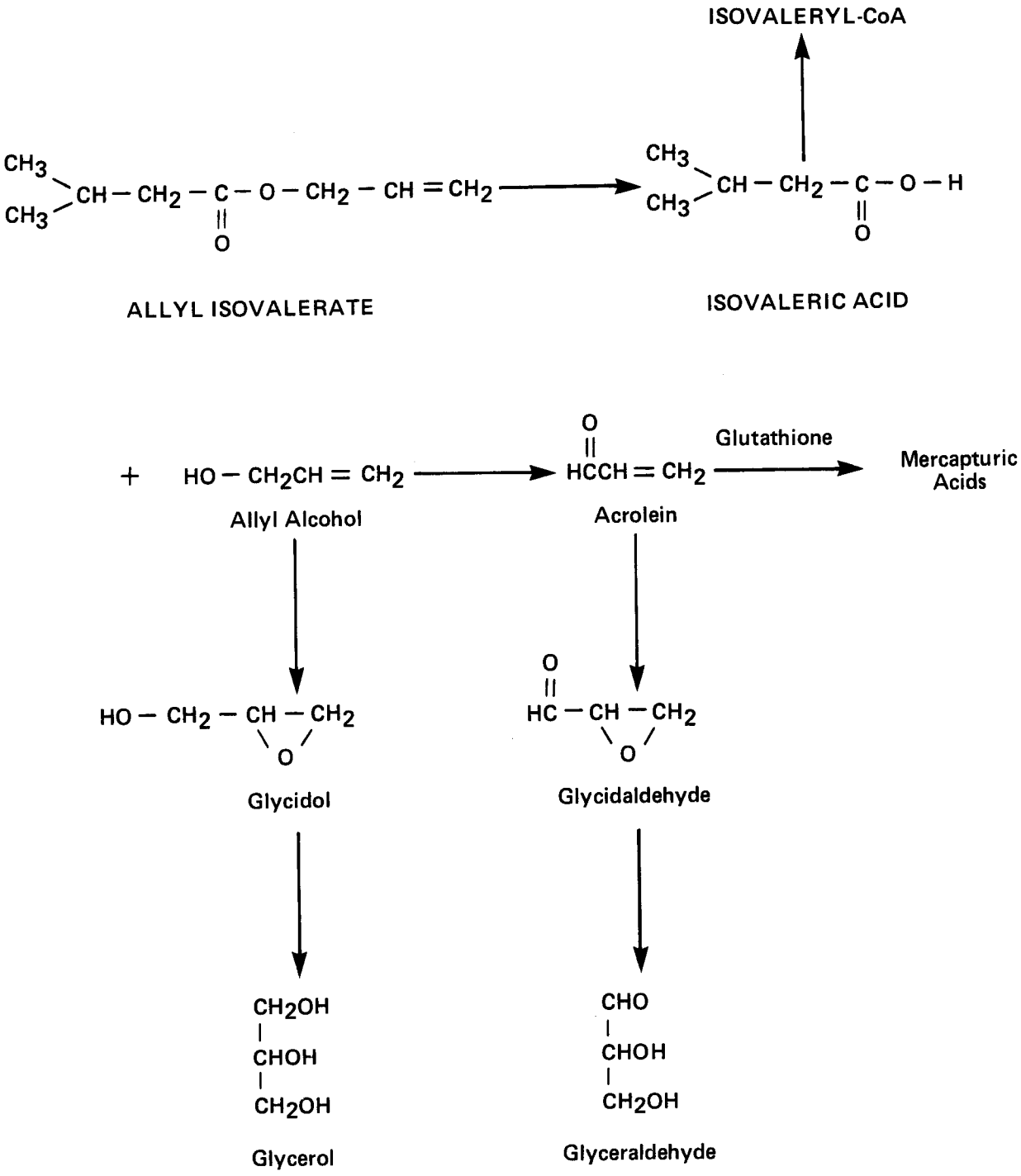


Figure 1. Metabolism of Allyl Isovalerate

The major toxic effect of the metabolite allyl alcohol in rats is periportal hepatocellular necrosis, a lesion believed to be caused by acrolein, the product of allyl alcohol oxidation (Rees and Tarlow, 1967; Reid, 1972). The hepatotoxic effects of allyl alcohol regress despite continued administration, suggesting adaptation of the liver to the presence of allyl alcohol or acrolein (Butterworth et al., 1978; Lake et al., 1978). The mechanism of the developed "resistence" to allyl alcohol is not known.

Mutagenicity

Allyl isovalerate did not induce any mutagenic response in *Salmonella typhimurium* tester strains TA 98, 100, 1535, and 1537 (with or without metabolic activation). Exogenous metabolic activation was provided by 9000 x g liver supernatant (S-9) fractions from Aroclor 1254-induced male Sprague-Dawley rats and male Syrian hamsters (see Appendix J) (NTP, 1982). This chemical is undergoing testing in *Drosophila melanogaster* to determine sex-linked recessive lethal mutations and reciprocal heritable translocations.

Although the allyl isovalerate metabolite allyl alcohol was mutagenic without activation in *Salmonella typhimurium* (strain unspecified) (Eder and Neudecker, 1978; Eder et al., 1980; Ortali, 1977), the structurally similar allyl caproate was not mutagenic in *S. typhimurium* TA 100 and TA 98, with or without microsomal activation (Oda et al., 1978). Allyl alcohol was shown to be weakly mutagenic to *S. typhimurium* (TA 1535) in the presence of the 9,000 x g supernatant fraction from Aroclor 1254-treated hamster liver, and acrolein was demonstrated to be a direct-acting mutagen in *S. typhimurium* TA 98 (Lijinsky and Andrews, 1980). The mutagenicity of acrolein to *S. typhimurium* has been confirmed by a second laboratory (NTP 1980), but acrolein failed to induce sex-linked recessive lethal mutations in *Drosophilia melanogaster* (NTP, 1982c). In cultured Chinese hamster ovary cells, acrolein induced both chromosome aberrations and sister chromatid exchanges (NTP unpublished results). The allyl alcohol metabolites glycidol and glycidaldehyde are direct-acting mutagens in *S. typhimurium* (McCann et al., 1979). There is considerable evidence, therefore, of genotoxic effects of purported allyl isovalerate metabolites, but not of the parent ester.

Carcinogenicity

A lifetime carcinogenicity study using male Fischer 344/N rats exposed to acrolein in drinking water is currently in progress (IARC, 1981). Inhalation of the respiratory tract irritant acrolein by hamsters at 4 ppm throughout their lifetimes (5 days per week) failed to cause an increase in tumors of the respiratory tract (Personal communication, Dr. P. Nettesheim, National Institute of Environmental Health Sciences; Feron and Kruysse, 1977). No information is currently available concerning the carcinogenic effects of oral administration. A literature survey on acrolein has been published (EPA, 1980).

Glycidaldehyde was reported to cause both benign and malignant local tumors when applied dermally to female Swiss mice throughout their lifetime (IARC, 1976; Van Duuren et al., 1965, 1966, 1967a, 1967b). There is limited evidence, therefore, for the carcinogenicity of one metabolite of allyl isovalerate (glycidaldehyde); the carcinogenic potential of other metabolites (allyl alcohol and acrolein) is currently under study (IARC, 1981; personal communication, Lijinsky).

Allyl isovalerate was tested by the Bioassay Program because of its use in food and cosmetics and because this chemical had not been previously tested for long-term effects or for potential carcinogenicity.

II. MATERIALS AND METHODS

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CHEMICAL ANALYSES

Food-grade allyl isovalerate was obtained from Research Organics Chemical Corporation (Belleview, NJ) in three lots. Each lot was initially analyzed for purity and identity at Midwest Research Institute (425 Volker Blvd., Kansas City, MO 64110); reanalysis of the bulk chemical and analysis of chemical/vehicle mixtures were performed at Southern Research Institute.

Lot No. 770217 was used for only the single-dose studies, being unsuitable for further testing because it contained 16.2% of the free acid and 79.7% of the ester. Lot No. A-634-F was used for only the 14-day studies; titration analysis indicated 94.7% of the ester and a small amount (2.1%) of the free acid. Vapor-phase chromatography showed the presence of two notable impurities that accounted for 3.9% and 2.3% of the area of the major peak. Use of this lot was discontinued when it was learned that the chemical had become contaminated with water and had apparently partially hydrolyzed.

Lot No. R011777, used for both the 13-week and 2-year studies, contained 95.6% of the ester (by titration) (Appendix E) and almost no free acid (0.37%). Vapor-phase chromatography indicated the presence of an impurity profile similar to that of Lot No. A-634-F, but with significantly fewer impurities (1.7% and 1.5% for the two major ones). No attempt was made to further characterize these impurities. Elemental analyses for carbon and hydrogen agreed with theoretical values. The infrared, ultraviolet, and nuclear magnetic resonance spectra were consistent with the structure and indicated that the levels of impurities were much lower than those found in the other two lots.

Each lot was stored at 5°C in the dark and was analyzed periodically at the bioassay laboratory during the course of the gavage experiments. Vapor-phase chromatography and infrared spectroscopy indicated that the purity of Lot No. R011777 did not change during the period of the studies.

DOSE PREPARATION

Allyl isovalerate was mixed with corn oil on a weight to volume basis to produce the desired concentration (Table 1). Rats received 5 ml/kg and mice received 10 ml/kg body weight. In the 13-week and 2-year studies, allyl isovalerate/corn oil mixtures were stored at 5°C at the bioassay laboratory for no longer than 7 days.

Allyl isovalerate in corn oil (2% w/v) was analyzed at Midwest Research Institute and was found to be stable at room temperature for 7 days (Appendix F). One set of samples from the 13-week studies and selected (blind) samples from the 2-year studies of allyl isovalerate in corn oil were analyzed periodically at Southern Research Institute (Appendix G). Results of these analyses and of referee analyses conducted at MRI and at Raltech indicated that the samples from the 13-week studies and all but three of the mixtures analyzed from the 2-year studies were within ±10% of the target concentration. One sample exceeded the optimum range (0.56-0.68 percent v/v) and two were below the acceptable range; both were from the same mixture, and this preparation was not used (Appendix G, Table G2).

SHORT-TERM STUDIES

Single-Dose Studies

Male and female F344/N rats and B6C3F$_1$ mice (C57BL/6N x C3H/HeN MTV$^-$) were obtained from Charles River Breeding Laboratories and held for approximately 2 weeks before the test began. Animals were approximately 6 weeks old when placed on study.

Groups of five rats and five mice of each sex were administered allyl isovalerate in corn oil by gavage at a dose of 31, 62, 125, 250, or 500 mg/kg body weight. No controls were used. All animals were observed twice daily for mortality for 14 days.

Animals were housed five per cage and received water and feed *ad libitum* during the observation period. Details of animal maintenance are presented in Table 1. Necropsies were not performed.

Fourteen-Day Studies

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories and held for approximately 2 weeks before the study began. The animals were approximately 6 weeks old when placed on study.

Groups of five males and five females of each species were administered allyl isovalerate in corn oil by gavage for 14 consecutive days at daily doses of 0, 31, 62, 125, 250, or 500 mg/kg body weight.

Animals were housed five per cage and received water and feed *ad libitum*. Details of animal maintenance are presented in Table 1. The rats and mice were observed twice daily for mortality and were weighed weekly. Necropsies were performed on all animals.

Thirteen-Week Studies

Thirteen-week studies were conducted to evaluate the cumulative toxicity of allyl isovalerate and to determine the doses to be used in the 2-year studies.

Four-week-old male and female F344/N rats and B6C3F$_1$ mice were obtained from Harlan Industries and observed for 16 days. Each species and sex was assigned to cages according to a table of random numbers. Cages were then assigned to control and dosed groups according to another table of random numbers.

Rats and mice were housed five per cage in polycarbonate cages (Table 1). Racks and filters were replaced once every 2 weeks. Cages and bedding were replaced twice per week. Water (via an automatic watering system) and feed were available *ad libitum*.

Groups of 10 rats and 10 mice of each sex were administered allyl isovalerate in corn oil by gavage at doses of 0, 15, 31, 62, 125, or 250 mg/kg body weight, five times per week for 13 weeks.

Animals were checked for mortality and signs of morbidity twice daily. Those judged moribund were killed and necropsied. Each animal was given a clinical examination weekly, including palpation for tissue masses or swelling. Body weight data were collected weekly.

At the end of the 91-day study, survivors were killed with carbon dioxide. Necropsies were performed on all animals, unless precluded by autolysis or cannibalization. The following tissues were examined microscopically in control and high-dose animals: grossly visible lesions, tissue masses, abnormal lymph nodes, skin, mandibular lymph nodes, mammary gland, salivary gland, thigh muscle, bone marrow, bone, thymus, trachea, lungs and bronchi, heart, thyroid, parathyroid, esophagus, stomach, duodenum, jejunum, ileum, colon, mesenteric lymph nodes, liver, gallbladder (mice), pancreas, spleen, kidneys, adrenals, urinary bladder, seminal vesicles/prostate/testes or ovaries/uterus, brain, and pituitary. Tissues were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin.

In addition, the liver was examined histopathologically in all groups except rats and mice of each sex administered 15 mg/kg allyl isovalerate and female rats and male and female mice administered 31 mg/kg; the stomachs from rats and mice administered 125 mg/kg were also examined histopathologically.

TWO-YEAR STUDIES

Study Design

Groups of 50 rats and 50 mice of each sex were administered allyl isovalerate in corn oil by gavage at doses of 31 or 62 mg/kg body weight, 5 days per week for 103 weeks. Groups of 50 rats and 50 mice of each sex received corn oil only and served as vehicle controls.

Source and Specifications of Test Animals

Four-week-old rats and 5-week-old mice were obtained from the Charles River Breeding Laboratories and observed for 2 weeks. Animals were produced under strict barrier conditions through a contract with the NTP Carcinogenesis Bioassay Program. Breeding starts for the foundation colony at the production facility originated at the National Institutes of Health Repository. Animals shipped for Bioassay testing were progeny of defined microbially associated parents that were transferred from isolators to barrier-maintained rooms. Animals were then assigned by species and sex to cages according to a table of random numbers. The cages were then assigned to dosed and control groups according to another table of random numbers.

A quality control skin grafting program has been in effect since early 1968 to monitor the genetic integrity of the inbred mice used to produce the hybrid $B6C3F_1$ test animal. In mid-1981, data were obtained that showed incompatibility between the NIH C3H reference colony and the C3H colony from Charles River Breeding Laboratories. In August 1981, inbred parental lines of mice were further tested for genetic homogeneity via isozyme and protein electrophoregrams which demonstrate phenotype expressions of known genetic loci. The C57BL/6 mice were homogeneous at all loci tested. Eighty-five percent of C3H mice monitored were variant at one to three loci, indicating some heterogeneity in the C3H line from this supplier. Nevertheless, the genome of this line is more homogeneous than that of random-bred stocks.

Male mice from the C3H colony and female mice from the C57BL/6 colony were used as parents for the hybrid $B6C3F_1$ mice used in this bioassay. The influence of the potential genetic non-uniformity in the hybrid mice on the bioassay results is not known. However, the bioassay is valid, since matched concurrent controls were included in the study.

Animal Maintenance

Rats and mice were housed five per cage in polycarbonate cages (Table 1). Cages and bedding were replaced twice per week. Dosed feed, control diets, and tap water were available *ad libitum*.

The temperature in the animal rooms was 20°-24°C and the humidity was 35%-70%. Fifteen changes of room air per hour were provided. Fluorescent lighting provided illumination 12 hours per day.

Clinical Examinations and Pathology

All animals were observed twice daily for signs of morbidity or mortality. Clinical signs were recorded when animals were weighed. Body weights by cage were recorded every week for the first 12 weeks and monthly thereafter. The mean body weight of each group was calculated by dividing the total weight of all animals in the group by the number of surviving animals in the group. Moribund animals and animals that survived to the end of the bioassay were killed using carbon dioxide and necropsied.

Examinations for grossly visible lesions were performed on major tissues or organs. Tissues were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. The following were examined microscopically: tissue masses, abnormal lymph nodes, skin, mandibular lymph nodes, mammary gland, salivary gland, thigh muscle, sciatic nerve, bone marrow, costochondral junction (rib), thymus, larynx, trachea, lungs and bronchi, heart, thyroid, parathyroid, esophagus, stomach, duodenum, jejunum, ileum, colon, mesenteric lymph nodes, liver, gallbladder (mice), pancreas, spleen, kidneys, adrenals, urinary bladder, seminal vesicles/prostate/testes or ovaries/uterus, nasal cavity, brain, pituitary, and spinal cord.

Necropsies were performed on all animals, unless precluded by autolysis or cannibalization. Thus, the number of animals from which particular organs or tissues were examined microscopically varies and is not necessarily equal to the number of animals that were placed on study in each group.

The classification of neoplastic nodules was done according to the recommendations of Squire

and Levitt (1975), and the National Academy of Sciences (1980). When the pathology examination was completed, the slides, individual animal data records, and summary tables were sent to an independent quality assurance laboratory. Individual animal records and tables were compared for accuracy, slides and tissue counts were verified, and histotechniques were evaluated. All tumor diagnoses, all target tissues, and all tissues from a randomly selected 10 percent of the animals were evaluated by an experienced pathologist. Slides of all target tissues and those about which the original and quality assurance pathologists disagreed were submitted to the Chairperson of the Pathology Working Group (PWG) for evaluation. Representative slides selected by the PWG Chairperson were reviewed blindly by the PWG's members, expert in rodent pathology, who reached a consensus and compared their findings with the original diagnoses. When conflicts were found, the PWG sent the appropriate slides and their comments to the original pathologist for review. (This procedure is described, in part, by Maronpot and Boorman, in press.) The final diagnosis represents a consensus of contractor pathologists and the NTP Pathology Working Group.

Data Recording and Statistical Methods

Data on this experiment were recorded in 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).

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) for testing two groups for equality and Tarone's (1975) extensions of Cox's methods for testing for a dose-related trend. All reported P values for the survival analyses were two-sided.

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 to the number of animals in which that site was examined. 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 (e.g., skin or mammary tumors) prior to histologic sampling, or when lesions could have appeared at multiple sites (e.g., lymphomas), the denominators consist of the number of animals on which necropsies were performed.

For the statistical analysis of tumor incidence data, two different methods of adjusting for intercurrent mortality were employed. Each used the classical method for combining contingency tables developed by Mantel and Haenszel (1959). Tests of significance included pairwise comparisons of high- and low-dose groups with controls and tests for overall dose-response trends.

The first method of analysis assumed that all tumors of a given type observed in animals dying before the end of the study were "fatal"; i.e., they either directly or indirectly caused the death of the animal. According to this approach, the proportions of tumor-bearing animals in the dosed and control groups were compared at each point in time at which an animal died with a tumor of interest. The denominators of these proportions were the total number of animals at risk in each group. These results, including the data from animals killed at the end of the study, were then combined by the Mantel-Haenszel method to obtain an overall P-value. This method of adjusting for intercurrent mortality is the life table method of Cox (1972) and of Tarone (1975).

The second method of analysis assumed that all tumors of a given type observed in animals dying before the end of the study were "incidental"; i.e., they were merely observed at autopsy in animals dying of an unrelated cause. According to this approach, the proportions of animals found to have tumors in dosed and control groups were compared in each of five time intervals: 0-52 weeks, 53-78 weeks, 79-92 weeks, week 93 to the week before the terminal kill, and the terminal kill period. The denominators of these proportions were the number of animals on which autopsies were performed during the time interval. The individual time interval comparisons were then combined by the previously described methods to obtain a single overall result. (See Peto et al., 1980, for the computational details of both methods.)

In addition to these tests, one other set of statistical analyses was carried out and reported in

the tables analyzing primary tumors: the Fisher's exact test for pairwise comparisons and Cochran-Armitage linear trend test for dose-response trends (Armitage, 1971; Gart et al., 1979). These tests were based on the overall proportion of tumor-bearing animals. Reported P values for tumor analyses are one-sided.

For studies in which there is little effect of compound administration on survival, the results of the three alternative analyses will generally be similar. When differing results are obtained by the three methods, the final interpretation of the data will depend on the extent to which the tumor under consideration is regarded as being the cause of death.

TABLE 1. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS OF SHORT-TERM AND TWO-YEAR STUDIES

	Single-Dose Studies	Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
Experimental Design				
Size of Test Groups	5 males and 5 females of each species	5 males and 5 females of each species	10 males and 10 females of each species	50 males and 50 females of each species
Doses	31, 62, 125, 250, or 500 mg/kg body weight in corn oil by gavage	0, 31, 62, 125, 250, or 500 mg/kg body weight in corn oil by gavage	0, 15, 31, 62, 125, or 250 mg/kg body weight in corn oil by gavage	0, 31, or 62 mg/kg body weight in corn oil by gavage
Duration of Dosing	Single dose	14 (consecutive) days	13 weeks (5 days/week)	103 weeks (5 days/week)
Type and Frequency of Observation	Observed twice daily for mortality and signs of morbidity	Same as single-dose study	Observed twice daily for mortality and signs of morbidity; weighed weekly	Observed twice daily for mortality and signs of morbidity; weighed weekly for first 12 weeks and monthly thereafter
Necropsy and Histologic Examination	None	Necropsies performed on all animals	Necrospies performed on all animals; following tissues examined histologically in control and high-dose groups: brain, pituitary, salivary glands, esophagus, mandibular lymph nodes, thymus, spleen, heart, thyroid, parathyroid, trachea, lungs, and bronchi, stomach, liver, large and small intestines, pancreas, mesenteric lymph nodes, seminal vesicles/prostate/testes or ovaries/uterus, mammary gland, skin, bone, bone marrow, thigh muscle, kidney, urinary bladder, adrenal glands, gallbladder (mice), gross	Necrospies performed on all animals; following tissues examined in all groups: tissue masses, abnormal lymph nodes, skin, mandibular lymph nodes, mammary gland, salivary gland, thigh muscle, sciatic nerve, bone marrow, costochondrial junction (rib), thymus, larynx, trachea, lungs and bronchi, heart, thyroid, parathyroid, esophagus, stomach, duodenum, jejunum, ileum, colon, mesenteric lymph nodes, liver, gall bladder (mice), pancreas, spleen, kidneys, adrenal glands, urinary bladder, seminal vesicles/prostate/testes

TABLE 1. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS OF SHORT-TERM AND TWO-YEAR STUDIES (Continued)

	Single-Dose Studies	Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
Necropsy and Histologic Examination (continued)			lesions, tissue masses, and abnormal lymph nodes; the liver of female rats and male and female mice administered 62 or 125 mg/kg and of male rats administered 31, 62, or 125 mg/kg was also examined histologically; stomach examined in rats and mice administered 125 mg/kg	or ovaries/uterus, nasal cavity, brain, pituitary, and spinal cord
Animals and Animal Maintenance				
Species	F344/N rats; B6C3F$_1$ mice	F344/N rats; B6C3F$_1$ mice	F344/N rats; B6C3F$_1$ mice	F344/N rats; B6C3F$_1$ mice
Animal Source	Charles River Breeding Laboratories (Portage, MI)	Charles River Breeding Laboratories	Harlan Industries (Indianapolis, IN)	Charles River Breeding Laboratories
Time Held Before Start of Test	2 weeks	2 weeks	16 days	2 weeks
Age When Placed on Study	6 weeks	6 weeks	6 weeks	Rats: 46 days Mice: 50 days
Age When Killed	8 weeks	8 weeks	20 weeks	Rats: 112-114 weeks Mice: 112-114 weeks
Method of Animal Distribution	Animals assigned by species and sex to cages according to a table of random numbers. Cages were then assigned to control and dosed groups according to another table of random numbers	Sames as single-dose study	Same as single-dose study	Same as single-dose study

TABLE 1. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS OF SHORT-TERM AND TWO-YEAR STUDIES (Continued)

	Single-Dose Studies	Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
Feed	Wayne Lab-Blox® pellets, Allied Mills, Inc. (Chicago, IL)	Same as single-dose study	Same as single-dose study	Same as single-dose study
Bedding	Beta-Chips® heat-treated hardwood chips, Northeastern Products Corp. (Warrensburg, NY)	Same as single-dose study or sawdust, PWI, Inc. (Louisville, KY)	Same as single-dose study	Same as single-dose study
Water	Edstrom automatic watering system, (Waterford, WI)	Same as single-dose study	Same as single-dose study	Same as single-dose study
Cages	Polycarbonate, Lab Products (Garfield, NJ)	Polycarbonate	Polycarbonate	Polycarbonate
Cage Filters	Reemay spun-bonded polyester filters, Snow Filtration (Cincinnatti, OH)	Same as single-dose study	Same as single-dose study	Same as single-dose study
Animals per Cage	Five	Five	Five	Five
Animal Room Environment	21°-23°C; 30%-60% relative humidity; room air changed 15 times per hour; 9 hours of fluorescent light per day	Same as single-dose study	Same as single-dose study	20°-24°C; 35%-70% relative humidity; room air changed 15 times per hour; 12 hours of fluorescent light per day
Other Chemical or Test in Same Room	None	None	None	None
Chemical/Vehicle				
Preparation	Allyl isovalerate was mixed with Mazola® corn oil	Same as single-dose study	Same as single-dose study	Same as single-dose study
Maximum Storage Time	—	3 days	1 week	1 week
Storage Conditions	—	21°-23°C	5°C	5°C in amber bottles

III. RESULTS

RATS

SHORT-TERM STUDIES

Single-Dose Studies

Fourteen-Day Studies

Thirteen-Week Studies

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

MICE

SHORT-TERM STUDIES

Single-Dose Studies

Fourteen-Day Studies

Thirteen-Week Studies

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

SHORT-TERM STUDIES

Single-Dose Studies

One male and two females receiving 500 mg/kg died. Deaths occurred on day 2 (one male and one female) and day 3 (one female). Decreased activity and ruffled fur were observed in all animals that received 500 mg/kg; these effects were considered to be compound related.

Fourteen-Day Studies

All rats that received 500 mg/kg were dead by the afternoon of day 2 (Table 2). Two males and two females administered 250 mg/kg also died. Mean body weights relative to controls were depressed by 23% in male rats administered 250 mg/kg and by 13% in female rats that received 250 mg/kg. Other groups had comparable final body weights.

Inactivity, labored breathing, diarrhea, and ruffled fur were seen in male and female rats administered 250 or 500 mg/kg; these effects were considered to be compound related. At necropsy, grossly visible dark red areas were observed on the stomach wall of 3/5 males and 3/5 females that received 500 mg/kg.

TABLE 2. SURVIVAL AND MEAN BODY WEIGHTS OF RATS ADMINISTERED ALLYL ISOVALERATE BY GAVAGE FOR 14 DAYS

Dose (mg/kg)	Survival *(a)*	Mean Body Weight (grams)			Body Weight Relative to Controls *(c)* (percent)
		Initial	Final	Change *(b)*	
Males					
0	5/5	119.2 ± 6.6	170.6 ± 9.3	+ 51.4 ± 3.7	
31	5/5	113.6 ± 5.1	185.2 ± 11.3	+ 71.6 ± 6.8	+ 8.6
62	5/5	120.2 ± 7.6	171.0 ± 8.4	+ 50.8 ± 1.4	- 0.2
125	5/5	114.2 ± 3.5	161.6 ± 5.9	+ 47.4 ± 4.6	- 5.3
250	3/5	105.0 ± 3.6	131.3 ± 2.7	+ 26.3 ± 6.2	-23.0
500	0/5	*(d)*	*(d)*	*(d)*	
Females					
0	5/5	96.6 ± 4.1	129.4 ± 4.3	+ 32.8 ± 1.1	
31	5/5	102.2 ± 1.6	133.0 ± 2.5	+ 30.8 ± 1.9	+ 2.8
62	5/5	93.4 ± 4.0	119.2 ± 5.0	+ 25.8 ± 1.2	- 7.9
125	5/5	97.4 ± 2.9	125.2 ± 5.1	+ 27.8 ± 2.8	- 3.2
250	3/5	98.3 ± 1.7	112.0 ± 5.5	+ 13.7 ± 6.6	-13.4
500	0/5	*(d)*	*(d)*	*(d)*	

(a) Number surviving/number initially in the group. All calculations are based on those animals surviving to the end of the study.

(b) Mean weight change of the survivors of the group ± standard error of the mean

(c) Weight of the dosed group relative to that of the controls ◘

$$\frac{\text{Weight (Dosed Group)} - \text{Weight (Control Group)}}{\text{Weight (Control Group)}} \times 100$$

(d) No data are presented due to the 100% mortality.

III. RESULTS: RATS—SHORT-TERM STUDIES

Thirteen-Week Studies

All 10 males and 4/10 females that received 250 mg/kg died (Table 3). Mean body weight gains relative to controls were depressed 14% in male rats that received 125 mg/kg and 16% in female rats that received 250 mg/kg. Final body weights were comparable between other groups.

TABLE 3. SURVIVAL AND MEAN BODY WEIGHTS OF RATS ADMINISTERED ALLYL ISOVALERATE BY GAVAGE FOR 13 WEEKS

Dose (mg/kg)	Survival *(a)*	Mean Body Weight (grams)			Body Weight Relative to Controls *(c)* (percent)
		Initial	Final	Change *(b)*	
Males					
0	10/10	109.7 ± 3.0	304.1 ± 8.8	+194.4 ± 8.1	
15	10/10	107.8 ± 3.2	300.7 ± 7.3	+192.9 ± 6.2	- 1.1
31	10/10	106.0 ± 3.4	298.7 ± 7.5	+192.7 ± 6.5	- 1.8
62	10/10	106.7 ± 3.0	282.9 ± 3.5	+176.2 ± 3.4	- 7.0
125	10/10	109.3 ± 3.9	261.8 ± 6.9	+152.5 ± 5.0	-13.9
250	0/10 *(d)*	*(e)*	*(e)*	*(e)*	
Females					
0	10/10	91.4 ± 2.3	174.7 ± 3.9	+ 83.3 ± 3.5	
15	10/10	91.6 ± 3.1	178.4 ± 5.0	+ 86.8 ± 2.6	+ 2.1
31	10/10	90.7 ± 2.5	169.8 ± 3.9	+ 79.1 ± 2.6	- 2.8
62	10/10	93.5 ± 3.0	174.8 ± 3.4	+ 81.3 ± 3.1	0.0
125	10/10	89.3 ± 3.1	167.8 ± 7.3	+ 78.5 ± 4.4	- 3.9
250	6/10 *(f)*	87.8 ± 2.1	146.5 ± 7.5	+ 58.7 ± 6.6	-16.1

(a) Number surviving/number initially in the group. All calculations are based on those animals surviving to the end of the study.

(b) Mean weight change of the survivors of the group ± standard error of the mean

(c) Weight of the dosed group relative to that of the controls ◘

$$\frac{\text{Weight (Dosed Group)} - \text{Weight (Control Group)}}{\text{Weight (Control Group)}} \times 100$$

(d) Deaths occurred during weeks 6-13.

(e) No data are presented due to the 100% mortality.

(f) Deaths occurred during weeks 6, 9, 11, and 12.

Male and female rats administered 250 mg/kg were inactive after dosing and the fur in the pelvic area was yellow. These effects were related to administration of allyl isovalerate. The following dose-related effects were observed in male and female rats at necropsy: thickening of the intestinal wall, redness of the mucosal surfaces of the intestines and urinary bladder, and enlargement of the internal lymph nodes and adrenal glands; however, no lesions were identified histopathologically at these sites. Histopathologic examination revealed the following compound-related liver lesions in rats administered 250 mg/kg: multifocal coagulative necrosis (7/10 males and 5/9 females), cholangiofibrosis (6/10 males and 1/9 females), bile duct hyperplasia (7/10 males and 8/9 females), and nodular hyperplasia (2/10 males and 7/9 females). Liver lesions were observed in other dosed groups (particularly in males and females receiving 125 mg/kg) and are presented in Table 4.

Because of the depression in mean body weight gain and because of the liver lesions observed in the 13-week studies, doses of 31 and 62 mg/kg were set for rats on the 2-year study.

TABLE 4. NUMBERS OF F344/N RATS WITH LIVER LESIONS IN THE 13-WEEK STUDY

	Dose (mg/kg)								
	Males					Females			
	0	31	62	125	250	0	62	125	250
Number of animals examined	10	10	10	10	10	10	10	10	9
Diagnosis									
Coagulative necrosis (multi-focal)	0	0	0	0	7	0	0	0	5
Cholangiofibrosis	0	0	0	0	6	0	0	0	1
Bile duct hyperplasia	0	0	0	3	7	0	0	4	8
Nodular hyperplasia	0	0	0	0	2	0	0	0	7
Cytoplasmic vacuolation	6	9	7	9	0	0	0	1	1
Basophilic cytoplasmic change	0	0	1	8	0	0	0	7	0

TWO-YEAR STUDIES

Body Weights and Clinical Signs

There were no remarkable effects of allyl isovalerate on body weights. Throughout the second year of the study, mean body weights of low-dose male rats were higher than those for the controls (Figure 2 and Table 5). Mean body weight gains for high-dose males were lower than those for the controls until week 93. After week 70, mean body weights of low- and high-dose female rats were higher than those of the controls. No other compound-related clinical signs were observed.

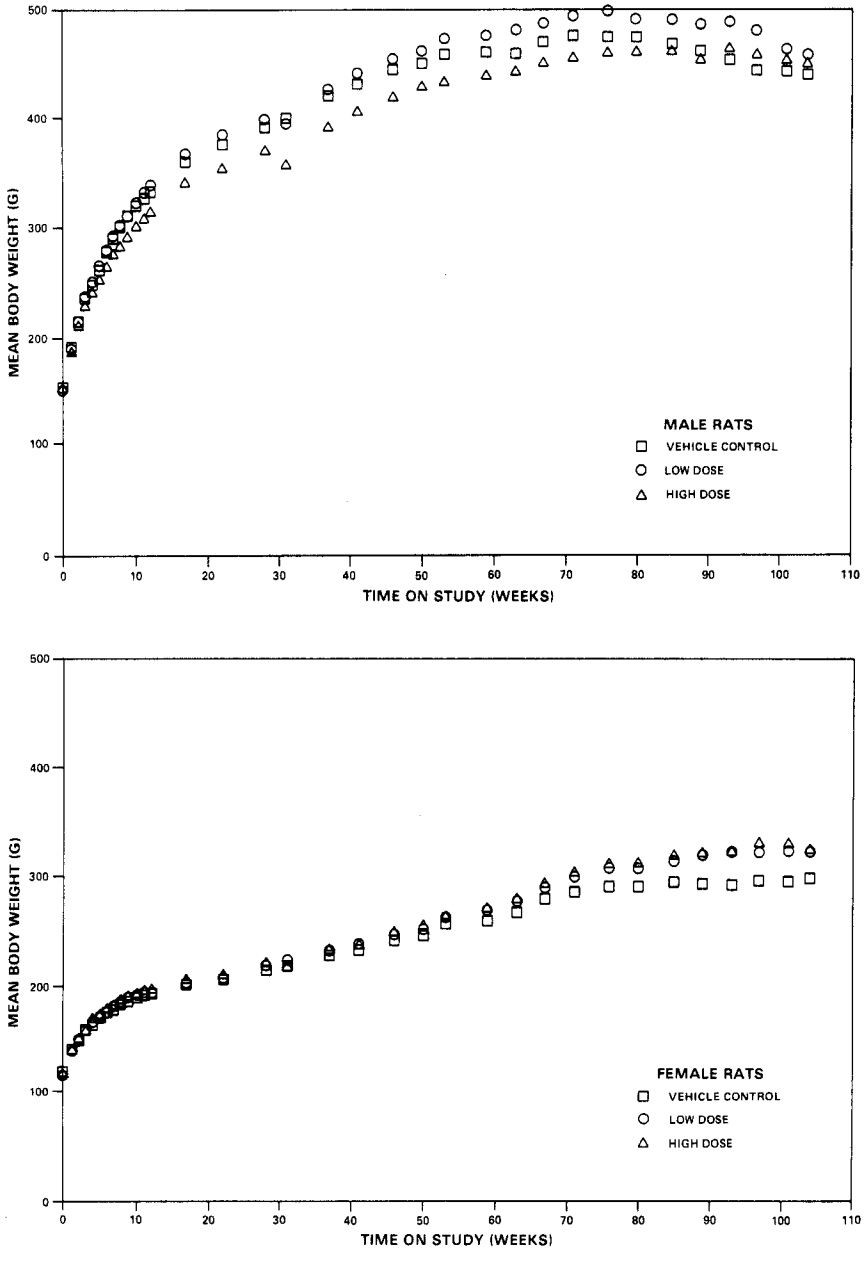


Figure 2. Growth Curves for Rats Administered Allyl Isovalerate in Corn Oil by Gavage

TABLE 5. CUMULATIVE MEAN BODY WEIGHT CHANGE (RELATIVE TO CONTROLS) OF RATS ADMINISTERED ALLYL ISOVALERATE BY GAVAGE FOR 2 YEARS

Week No.	Cumulative Mean Body Weight Change (grams)			Weight Change Relative to Controls (percent) *(a)*	
	Control	Low Dose	High Dose	Low Dose	High Dose
Males					
0	154 *(b)*	151 *(b)*	153 *(b)*		
1	37	38	33	+3	-11
22	221	233	203	+5	- 8
41	278	291	253	+5	- 9
59	307	326	286	+6	- 7
80	321	342	309	+7	- 4
101	289	313	302	+8	+ 4
Final Body Weights	443	464	455	+5 *(c)*	+ 3 *(c)*
Females					
0	119 *(b)*	115 *(b)*	117 *(b)*		
1	21	23	22	+10	+ 5
22	87	92	94	+ 6	+ 8
41	115	124	122	+ 8	+ 6
59	141	155	155	+10	+10
80	172	193	196	+12	+14
101	176	208	212	+18	+20
Final Body Weights	295	323	329	+ 9 *(c)*	+12 *(c)*

(a) Weight change of the dosed group relative to that of the controls $\blacksquare$

$$\frac{\text{Weight Change (Dosed Group)} - \text{Weight Change (Control Group)}}{\text{Weight Change (Control Group)}} \times 100$$

(b) Initial Weight

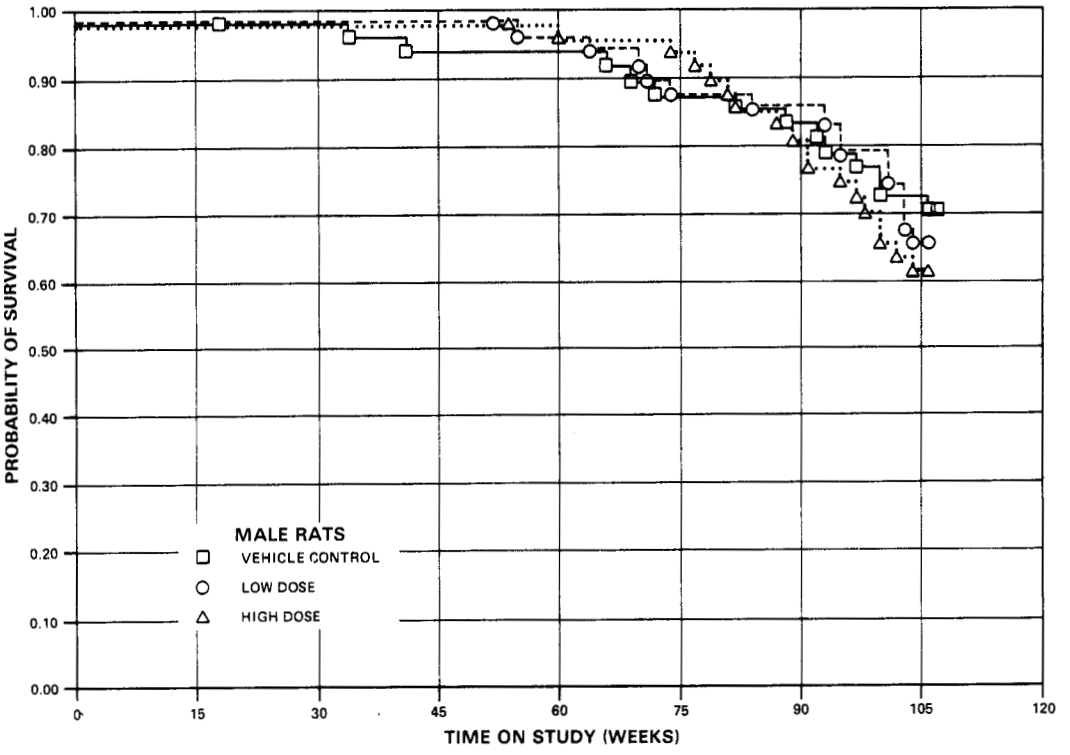
(c) Final body weight relative to controls (percent)

Survival

Estimates of the probabilities of survival of male and female rats administered allyl isovalerate by gavage at doses of 0, 31, or 62 mg/kg body weight are shown by the Kaplan and Meier curves in Figure 3. No significant differences in survival were observed between any groups of male rats or of female rats.

In male rats, 34/50 (68%) of the controls, 30/50 (60%) of the low-dose, and 28/50 (56%) of the high-dose group lived to the end of the study at 105-107 weeks. In female rats, 38/50 (76%) of the controls, 36/50 (72%) of the low-dose, and 29/50 (58%) of the high-dose group lived to the end of the study at 105-107 weeks. The survival data include one male and one female control animal that died during the termination period of the study. For the statistical evaluation of tumor incidence, these animals have been pooled with those killed at the end of the study.

Three control males, four low-dose males, four high-dose males, one low-dose female, and two high-dose females were accidentally killed. These 14 animals were censored from the statistical analysis of survival; they are included in the curve depicting the probability of survival (Figure 3) only until the time of death.



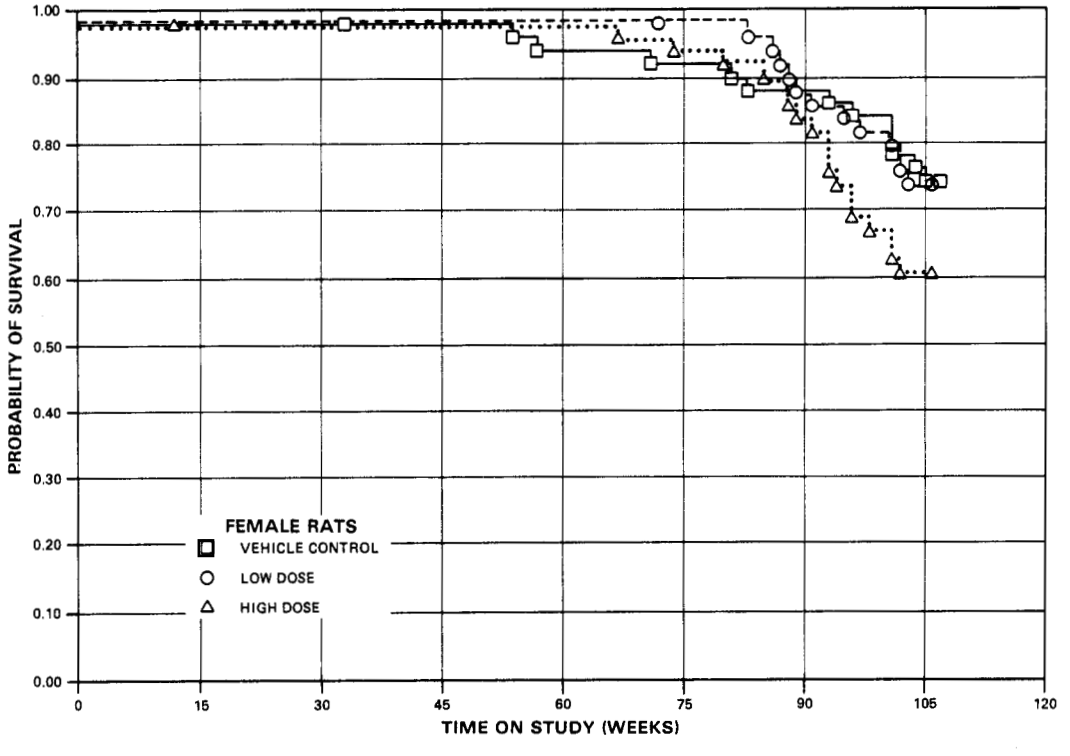


Figure 3. Survival Curves for Rats Administered Allyl Isovalerate in Corn Oil by Gavage

Pathology and Statistical Analyses of Results

Histopathologic findings on neoplasms in rats are summarized in Appendix A, Tables A1 and A2; Appendix Tables A3 and A4 give the survival and tumor status for individual male and female rats. Findings on nonneoplastic lesions are summarized in Appendix C, Tables C1 and C2. Historical incidences of tumors in control animals are listed in Appendix H. Appendix K, Tables K1 and K2, contain the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups. The statistical analyses used are discussed in Chapter II, (Data Recording and Statistical Methods) and Appendix K (footnotes).

Hematopoietic System: A significant positive trend was observed in the incidence of male rats with mononuclear-cell leukemia (referred to as monocytic leukemia in Appendix A), and the results of the pairwise comparison between the control and high-dose groups were statistically significant. A statistically significant trend was observed in the incidence of female rats with leukemia. Additionally, two other high-dose male rats and one control and one high-dose female rat had lymphomas.

TABLE 6. INCIDENCES OF HEMATOPOIETIC TUMORS IN F344/N RATS

	Vehicle Control	31 mg/kg	62 mg/kg
Males			
Leukemia			
Overall Incidence	1/50 (2%)	4/50 (8%)	7/50 (14%)
Adjusted Incidence	2.8%	10.9%	22.0%
Terminal Incidence	0/34 (0%)	0/30 (0%)	4/28 (14%)
Life Table Test	P=0.015	P=0.183	P=0.022
Incidental Tumor Test	P=0.023	P=0.482	P=0.044
Cochran-Armitage Trend, Fisher Exact Tests	P=0.021	P=0.181	P=0.030
Females			
Leukemia			
Overall Incidence	4/50 (8%)	6/50 (12%)	9/49 (18%)
Adjusted Incidence	9.9%	15.1%	22.8%
Terminal Incidence	3/38 (8%)	4/36 (11%)	2/29 (7%)
Life Table Test	P=0.050	P=0.354	P=0.075
Incidental Tumor Test	P=0.173	P=0.474	P=0.265
Cochran-Armitage Trend, Fisher Exact Tests	P=0.082	P=0.370	P=0.109

Preputial Gland: The incidences of low-dose male rats with adenomas alone or with adenomas or carcinomas combined were significantly higher than those in the controls. However, results of comparisons between the control and the high-dose groups were not statistically significant.

TABLE 7. INCIDENCES OF PREPUTIAL GLAND TUMORS IN MALE F344/N RATS

	Vehicle Control	31 mg/kg	62 mg/kg
Adenoma			
Overall Incidence	0/50 (0%)	4/50 (8%)	1/50 (2%)
Adjusted Incidence	0.0%	13.3%	3.6%
Terminal Incidence	0/34 (0%)	4/30 (13%)	1/28 (4%)
Life Table Test	P=0.322	P=0.048	P=0.461
Incidental Tumor Test	P=0.322	P=0.048	P=0.461
Cochran-Armitage Trend, Fisher Exact Tests	P=0.390	P=0.059	P=0.500
Adenoma or Carcinoma			
Overall Incidence	0/50 (0%)	5/50 (10%)	2/50 (4%)
Adjusted Incidence	0.0%	16.7%	7.1%
Terminal Incidence	0/34 (0%)	5/30 (17%)	2/28 (7%)
Life Table Test	P=0.175	P=0.023	P=0.196
Incidental Tumor Test	P=0.175	P=0.023	P=0.196
Cochran-Armitage Trend, Fisher Exact Tests	P=0.238	P=0.028	P=0.247

Pancreas: Acinar-cell adenomas were observed in 1/50(2%) control males, 4/50(8%) low-dose males, and 2/50(4%) high-dose males. These incidences were not statistically significant. Atrophy of the pancreas was increased slightly in the 62 mg/kg male rats (Appendix C, Table C1).

Liver: Several nonneoplastic lesions were observed in dosed male and female rats at incidences higher than those seen in the controls (Table 8). Enlarged hepatocytes around portal triads were observed in the low-dose animals. The cytomegalic changes in the affected hepatocytes included enlarged nuclei, increased cytoplasm, and slightly increased numbers of eosinophils in adjacent tissues. The composition of the lesion varied from only a few cells around portal triads to altered cells that extended midway to the central vein. Mild periportal fibrosis was observed in the livers of low-dose male and female rats. Yellow/green-staining granular pigment accumulated in the fibrous tissue in the periportal areas and was occasionally observed in cells lining the sinusoids. Extensive periportal fibrosis, with fibrous bands connecting portal areas, was observed in livers of some high-dose male and female rats. A few lymphocytes occasionally accumulated in this periportal area. Narrow rims of cytomegalic hepatocytes encircled the fibrous areas.

The occurrences of liver neoplasms were not different between groups.

TABLE 8. INCIDENCES OF F344/N RATS WITH NEOPLASTIC AND NONNEOPLASTIC LESIONS IN THE LIVER IN THE 2-YEAR STUDY

	Males			Females		
	Control	Low Dose	High Dose	Control	Low Dose	High Dose
No. of animals examined	50	50	50	50	50	49
Cholangiofibrosis	0	1	5	0	0	4
Cirrhosis	0	2	5	0	0	8
Focal Necrosis	1	2	7	0	2	4
Fatty Metamorphosis	3	2	8	0	3	5
Nodular Regeneration	0	5	8	1	3	8
Cytoplasmic Vacuolization	15	9	22	3	2	18
Pigmentation	0	0	1	0	1	2
Neoplastic Nodule	1	1	2	1	1	0
Hepatocellular Carcinoma	0	1	1	0	0	0

Eye: Retinopathy and cataracts were observed in increased incidences in high-dose males and low-dose females.

These findings were not considered to be related to the administration of allyl isovalerate because high incidences of retinopathy and cataracts in male and female rats at this laboratory have been previously correlated with the proximity of the animals to fluorescent light. In this study, the groups with high incidences of retinopathy and cataracts were housed in the uppermost racks—those closest to the fluorescent lights (Chignell et al., 1981; Greenman et al., 1982).

INCIDENCES OF RETINOPATHY AND CATARACTS IN F344/N RATS

	Males			Females		
	Control	Low Dose	High Dose	Control	Low Dose	High Dose
Retinopathy	1/50 (2%)	0/50 (0%)	21/50 (42%)	4/50 (8%)	21/50 (42%)	2/49 (4%)
Cataracts	1/50 (2%)	0/50 (0%)	21/50 (42%)	1/50 (2%)	19/50 (38%)	2/49 (4%)

Pituitary: The incidences of low-dose male rats with adenomas were significantly lower than the incidence in the controls, and a statistically significant negative trend was observed. The incidences of dosed female rats with this tumor were not statistically significant in comparison with controls (13/44; 17/49; 13/48).

TABLE 9. INCIDENCES OF PITUITARY ADENOMAS IN MALE F344/N RATS

	Vehicle Control	31 mg/kg	62 mg/kg
Overall Incidence	14/49 (29%)	5/46 (11%)	9/49 (18%)
Adjusted Incidence	37.5%	15.3%	24.8%
Terminal Incidence	11/34 (32%)	4/28 (14%)	3/27 (11%)
Life Table Test	P=0.231N	P=0.037N	P=0.315N
Incidental Tumor Test	P=0.041N	P=0.032N	P=0.048N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.125N	P=0.028N	P=0.170N

Thyroid: Low-dose male rats had a significantly ($P<0.05$) lower incidence of C-cell carcinomas than did the controls (control, 6/50; low-dose, 0/47; high-dose, 3/47). The results of the trend tests and the comparison of control versus high-dose incidences were not significant. The combined incidence of low-dose male rats with either C-cell adenomas or carcinomas was not significant (control, 10/50; low-dose, 7/47; high-dose, 5/47). These tumors were not seen in female rats in statistically significant proportions (control, 4/48; low-dose, 8/50; high-dose, 5/46).

SHORT-TERM STUDIES

Single-Dose Studies

Two males and one female administered 500 mg/kg died. Deaths occurred on day 2 (one male and one female) and day 3 (one male). Slight inactivity, ruffled fur, and yellowish feces were observed in mice that received 500 mg/kg; these effects were considered to be related to administration of allyl isovalerate.

Fourteen-Day Studies

All male and female mice that received 500 mg/kg were dead by the afternoon of day 2 (Table 10). Inactivity and ruffled fur were seen in mice administered 250 or 500 mg/kg, and these effects were considered to be compound related. Male mice that received 250 mg/kg gained no weight. Body weight differences at the end of the study were comparable among groups.

TABLE 10. SURVIVAL AND MEAN BODY WEIGHTS OF MICE ADMINISTERED ALLYL ISOVALERATE BY GAVAGE FOR 14 DAYS

Dose (mg/kg)	Survival *(a)*	Mean Body Weight (grams)			Body Weight Relative to Controls *(c)* (percent)
		Initial	Final	Change *(b)*	
Males					
0	5/5	23.4 ± 0.7	25.4 ± 1.0	+2.0 ± 0.4	
31	5/5	25.2 ± 0.6	26.8 ± 0.9	+1.6 ± 0.4	+5.5
62	5/5	25.8 ± 0.7	27.2 ± 0.6	+1.4 ± 0.4	+7.1
125	5/5	23.4 ± 1.3	24.8 ± 1.3	+1.4 ± 0.2	-2.4
250	5/5	25.2 ± 0.5	25.2 ± 0.5	0.0 ± 0.3	-0.8
500	0/5	*(d)*	*(d)*	*(d)*	
Females					
0	5/5	18.4 ± 0.2	20.8 ± 0.6	+2.4 ± 0.5	
31	5/5	18.2 ± 0.2	20.4 ± 0.2	+2.2 ± 0.2	-1.9
62	5/5	19.2 ± 0.2	19.6 ± 0.2	+0.4 ± 0.4	-5.8
125	5/5	19.0 ± 0.3	20.6 ± 0.5	+1.6 ± 0.2	-1.0
250	5/5	18.4 ± 0.4	20.2 ± 0.2	+1.8 ± 0.2	-2.9
500	0/5	*(d)*	*(d)*	*(d)*	

(a) Number surviving/number initially in the group.

(b) Mean weight change of the group ± standard error of the mean.

(c) Weight of the dosed group relative to that of the controls =

$$\frac{\text{Weight (Dosed Group)} - \text{Weight (Control Group)}}{\text{Weight (Control Group)}} \times 100$$

(d) No data are presented due to the 100% mortality.

Thirteen-Week Studies

Five of 10 males and 6/10 females that received 250 mg/kg died (Table 11). All but one of these deaths (a female) were considered to be compound related. The deaths occurring in other groups were caused by gavage error. Final body weights among control and dosed groups were comparable; for male rats, the 125 and 250 mg/kg groups weighed 10% less than controls.

Male and female mice administered 125 or 250 mg/kg were apparently less active after dosing. The following compound-related effects (Table 12) were observed at necropsy or during histopathologic examination in animals that received 250 mg/kg: "thickening" of the wall of the urinary bladder (2/10 males, 2/10 females), "thickening" of the mucosa of the stomach (6/10 males, 2/10 females), ulcerative inflammation of the stomach (2/10 males, 3/10 females), coagulative necrosis of the liver (3/10 males, 2/10 females), and cytoplasmic vacuolization of the liver (2/10 males). The following lesions were observed in mice that received 125 mg/kg: "thickening" of the stomach wall (3/10 males, 2/10 females), "thickening" of the urinary bladder wall (3/10 males, 1/10 females), and "thickening" of the wall of the small intestine (3/10 females).

No compound-related histopathologic effects on the liver, stomach, or bladder were seen in mice from other groups.

As a result of the weight gain depression and the gross or histologic toxic effects observed at necropsy in mice administered 125 mg/kg or higher, doses of 31 and 62 mg/kg were selected for mice on the 2-year study.

TABLE 11. SURVIVAL AND MEAN BODY WEIGHTS OF MICE ADMINISTERED ALLYL ISOVALERATE BY GAVAGE FOR 13 WEEKS

Dose (mg/kg)	Survival *(a)*	Mean Body Weight (grams)			Weight Relative to Controls *(c)* (percent)
		Initial	Final	Change *(b)*	
Males					
0	10/10	24.9 ± 0.8	37.3 ± 1.2	+12.4 ± 0.6	
15	10/10	24.6 ± 0.4	36.0 ± 1.0	+11.4 ± 1.0	- 3.5
31	10/10	24.3 ± 0.5	35.5 ± 0.7	+11.2 ± 0.7	- 4.8
62	9/10 *(d)*	24.4 ± 0.8	35.3 ± 1.2	+10.9 ± 0.5	- 5.4
125	10/10	22.7 ± 0.3	33.8 ± 0.8	+11.1 ± 0.7	- 9.4
250	5/10 *(e)*	24.2 ± 0.7	33.8 ± 1.4	+ 9.6 ± 0.9	- 9.4
Females					
0	10/10	18.1 ± 0.4	26.5 ± 0.6	8.4 ± 0.3	
15	8/10 *(d)*	18.3 ± 0.4	26.5 ± 0.5	8.2 ± 0.6	0.0
31	9/10 *(d)*	18.2 ± 0.5	26.6 ± 1.0	8.4 ± 0.7	+ 0.4
62	10/10	18.4 ± 0.4	25.0 ± 0.6	6.6 ± 0.3	- 5.7
125	7/10 *(d)*	18.9 ± 0.8	25.4 ± 0.9	6.5 ± 0.8	- 4.2
250	4/10 *(f)*	18.0 ± 0.7	27.8 ± 1.0	9.8 ± 0.5	+ 4.9

(a) Number surviving/number initially in the group. All calculations are based on those animals surviving to the end of the study.

(b) Mean weight change of the survivors of the group ± standard error of the mean.

(c) Weight of the dosed group relative to that of the controls ◘

$$\frac{\text{Weight (Dosed Group)} - \text{Weight (Control Group)}}{\text{Weight (Control Group)}} \times 100$$

(d) Deaths were the result of gavage error.

(e) Two deaths occurred during week 1 and three deaths occurred during week 11.

(f) Five deaths occurred during week 1; a death during week 13 was the result of gavage error.

TABLE 12. NUMBERS OF MICE WITH LESIONS IN THE 13-WEEK STUDY

	Dose (mg/kg)							
	Males				Females			
Lesion	**0**	**62**	**125**	**250**	**0**	**62**	**125**	**250**
Numbers of animals examined	10	10	10	10	10	10	10	10
Diagnosis								
Coagulative necrosis in the liver	0	0	0	3	0	0	0	2
Cytoplasmic vacuolization in the liver	0	0	0	2	0	0	0	0
Thickened urinary bladder wall	0	0	3	2	0	0	1	2
Thickened stomach mucosa	0	0	3	6	0	0	2	2
Ulcerative inflammation of stomach	0	0	0	2	0	0	0	3

TWO-YEAR STUDIES

Body Weights and Clinical Signs

After week 20, mean body weights of dosed male mice were higher than those of the controls (Figure 4 and Table 13). After week 30, mean body weights of low-dose female mice were lower than those of controls; and after week 70, mean body weights of high-dose females were slightly lower than the control values. No other compound-related clinical signs were observed. Except for the low-dose females, with final body weights 16% lower than those of controls, the dosed and control groups had comparable body weights.

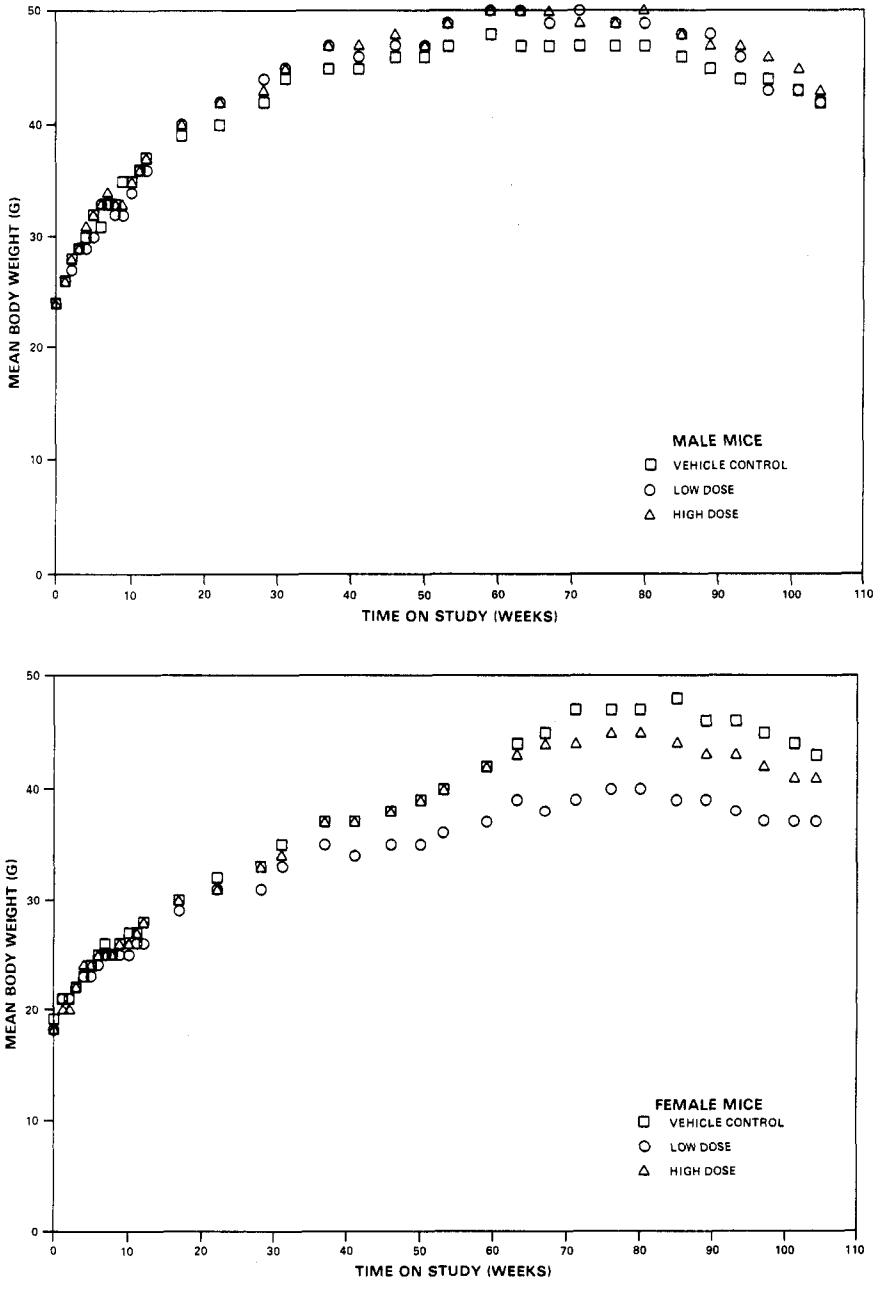


Figure 4. Growth Curves for Mice Administered Allyl Isovalerate in Corn Oil by Gavage

TABLE 13. CUMULATIVE MEAN BODY WEIGHT CHANGE (RELATIVE TO CONTROLS) OF MICE ADMINISTERED ALLYL ISOVALERATE BY GAVAGE FOR 2 YEARS

Week No.	Cumulative Mean Body Weight Change (grams)			Weight Change Relative to Controls *(b)* (Percent)	
	Control	Low Dose	High Dose	Low Dose	High Dose
Males					
0	24 *(b)*	24 *(b)*	24 *(b)*		
1	2	2	2	0	0
22	16	18	18	+13	+13
41	21	22	23	+ 5	+10
59	24	26	26	+ 8	+ 8
80	23	25	26	+ 9	+13
101	19	19	21	0	+11
Final Body Weights	43	43	45	0 *(c)*	+ 5 *(c)*
Females					
0	19 *(b)*	18 *(b)*	18 *(b)*		
1	2	3	2	+50	0
22	13	13	13	0	0
41	18	16	19	-11	+ 6
59	23	19	24	-17	+ 4
80	28	22	27	-21	- 4
101	25	19	23	-24	- 8
Final Body Weights	44	37	41	-16 *(c)*	- 7 *(c)*

(a) Weight change of the dosed group relative to that of the controls = $\frac{\text{Weight Change (Dosed Group)} - \text{Weight Change (Control Group)}}{\text{Weight Change (Control Group)}} \times 100$

(b) Initial weight

(c) Final body weight relative to controls (percent)

Survival

Estimates of the probabilities of survival of male and female mice administered allyl isovalerate at doses of 0, 31, and 62 mg/kg body weight are shown by the Kaplan and Meier curves in Figure 5. Overall survival of low-dose female mice was significantly lower (P=0.001) than that of the controls; this difference became apparent after about week 90. No other significant differences in survival were observed between any groups of either sex. Two control males, two low-dose males, six high-dose males, one low-dose female, and one high-dose female were accidentally killed. These 12 animals were censored from the statistical analysis of survival; they are included in the curve depicting probability of survival (Figure 5) only until the time of death.

In male mice, 29/50 (58%) of the controls, 31/50 (62%) of the low-dose, and 31/50 (62%) of the high-dose group lived to the termination period of the study at 105-107 weeks. In female mice, 32/50 (64%) of the controls, 17/50 (34%) of the low-dose, and 24/50 (48%) of the high-dose group lived to the termination period of the study at 105-107 weeks. The survival data include one control and one low-dose female that died during the termination period of the study. For statistical evaluation of tumor incidences, these animals have been pooled with those killed at the end of the study. The probable cause of death of many female mice was a suppurative lesion of the ovaries/uterus which often spread to other areas in the abdominal cavity.

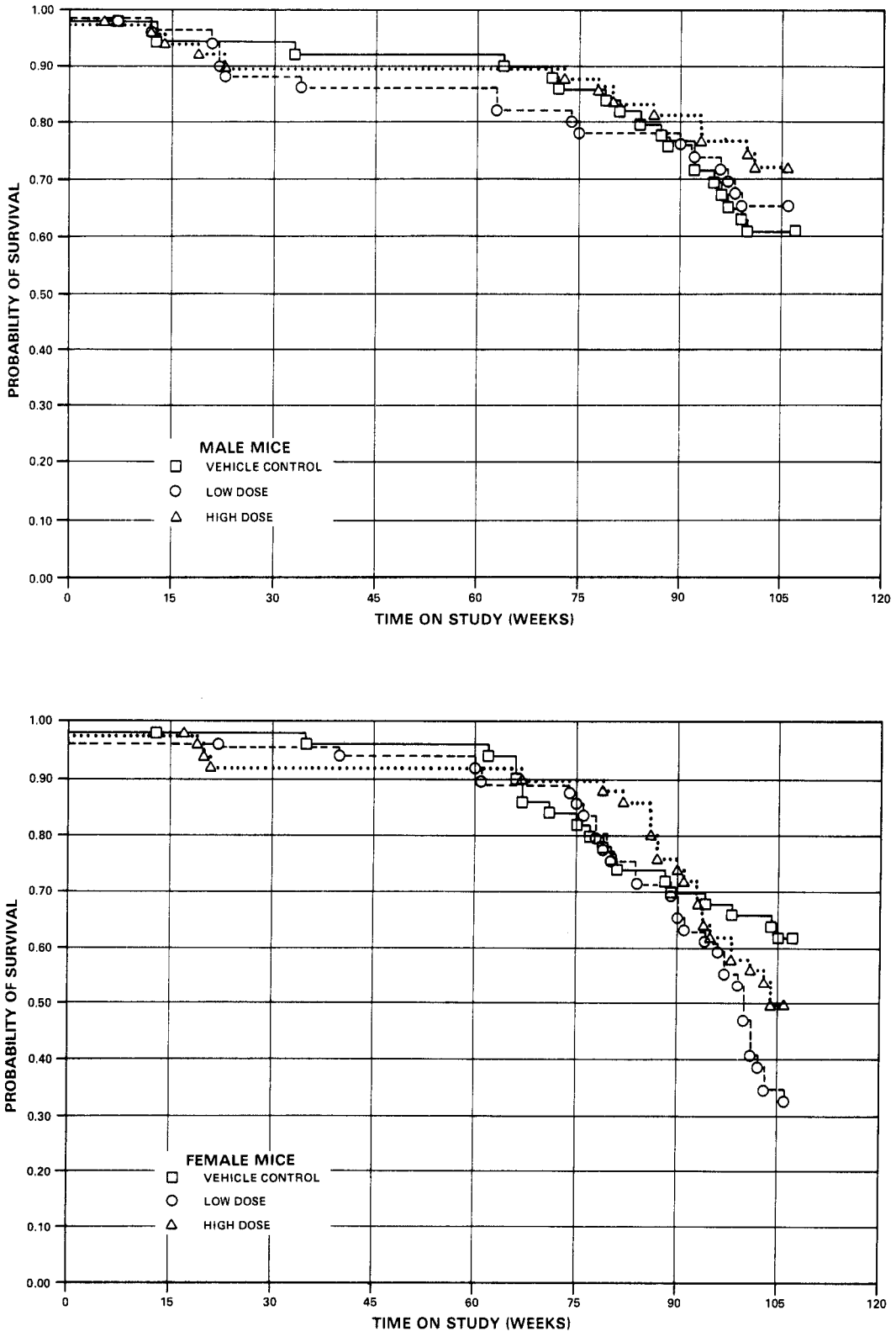


Figure 5. Survival Curves for Mice Administered Allyl Isovalerate in Corn Oil by Gavage

Pathology and Statistical Analyses of Results

Histopathologic findings on neoplasms in mice are summarized in Appendix B, Tables B1 and B2; Appendix Tables B3 and B4 give the survival and tumor status for individual male and female mice. Findings on nonneoplastic lesions are summarized in Appendix D, Tables D1 and D2. Historical incidences of tumors in control animals are listed in Appendix H. Appendix K, Tables K3 and K4, contain the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups. The statistical analyses used are discussed in Chapter II (Data Recording and Statistical Methods) and Appendix K (footnotes).

Hematopoietic System: A statistically significant positive trend was seen in the incidences of female mice with malignant lymphomas (all types), and the incidence in the high-dose group was significantly greater than that in the controls. A significant positive trend was also observed in the incidence of females with malignant histiocytic lymphomas (Table 14). Though not statistically significant, these malignant lymphomas were observed in increasing proportions of male mice (control, 4/50; low-dose, 6/50; high-dose, 8/50).

TABLE 14. INCIDENCES OF HEMATOPOIETIC TUMORS IN B6C3F$_1$ MICE

	Vehicle Control	31 mg/kg	62 mg/kg
Males			
Malignant Lymphoma, Lymphocytic Type			
Overall Incidence	1/50 (2%)	2/50 (4%)	1/50 (2%)
Adjusted Incidence	2.7%	5.7%	2.6%
Terminal Incidence	0/29 (0%)	1/31 (3%)	0/31 (0%)
Life Table Test	P=0.617	P=0.499	P=0.751
Incidental Tumor Test	P=0.518	P=0.444	P=0.692
Cochran-Armitage Trend, Fisher Exact Tests	P=0.622	P=0.500	P=0.753N
Malignant Lymphoma, Histiocytic Type			
Overall Incidence	0/50 (0%)	2/50 (4%)	1/50 (2%)
Adjusted Incidence	0.0%	6.3%	2.7%
Terminal Incidence	0/29 (0%)	1/31 (3%)	0/31 (0%)
Life Table Test	P=0.373	P=0.251	P=0.500
Incidental Tumor Test	P=0.303	P=0.202	P=0.433
Cochran-Armitage Trend, Fisher Exact Tests	P=0.361	P=0.247	P=0.500
Malignant Lymphoma, Mixed Type			
Overall Incidence	3/50 (6%)	2/50 (4%)	6/50 (12%)
Adjusted Incidence	10.0%	6.2%	17.2%
Terminal Incidence	2/29 (7%)	1/31 (3%)	4/31 (13%)
Life Table Test	P=0.192	P=0.473N	P=0.272
Incidental Tumor Test	P=0.130	P=0.556N	P=0.193
Cochran-Armitage Trend, Fisher Exact Tests	P=0.169	P=0.500N	P=0.243
Lymphoma, All Malignant			
Overall Incidence	4/50 (8%)	6/50 (12%)	8/50 (16%)
Adjusted Incidence	12.4%	17.3%	21.5%
Terminal Incidence	2/29 (7%)	3/31 (10%)	4/31 (13%)
Life Table Test	P=0.167	P=0.397	P=0.204
Incidental Tumor Test	P=0.077	P=0.283	P=0.105
Cochran-Armitage Trend, Fisher Exact Tests	P=0.141	P=0.370	P=0.178

TABLE 14. INCIDENCES OF HEMATOPOIETIC TUMORS IN B6C3F$_1$ MICE (Continued)

	Vehicle Control	31 mg/kg	62 mg/kg
Females			
Malignant Lymphoma, Lymphocytic Type			
Overall Incidence	5/50 (10%)	5/50 (10%)	4/50 (8%)
Adjusted Incidence	12.3%	21.9%	12.6%
Terminal Incidence	2/32 (6%)	3/17 (18%)	2/24 (8%)
Life Table Test	P=0.515N	P=0.422	P=0.557N
Incidental Tumor Test	P=0.432	P=0.422	P=0.447
Cochran-Armitage Trend, Fisher Exact Tests	P=0.432N	P=0.630N	P=0.500N
Malignant Lymphoma, Histiocytic Type			
Overall Incidence	0/50 (0%)	1/50 (2%)	4/50 (8%)
Adjusted Incidence	0.0%	5.9%	12.8%
Terminal Incidence	0/32 (0%)	1/17 (6%)	0/24 (0%)
Life Table Test	P=0.024	P=0.374	P=0.052
Incidental Tumor Test	P=0.058	P=0.374	P=0.336
Cochran-Armitage Trend, Fisher Exact Tests	P=0.026	P=0.500	P=0.059
Malignant Lymphoma, Mixed Type			
Overall Incidence	6/50 (12%)	5/50 (10%)	10/50 (20%)
Adjusted Incidence	18.8%	23.1%	37.8%
Terminal Incidence	6/32 (19%)	2/17 (12%)	8/24 (33%)
Life Table Test	P=0.064	P=0.368	P=0.073
Incidental Tumor Test	P=0.136	P=0.573N	P=0.133
Cochran-Armitage Trend, Fisher Exact Tests	P=0.157	P=0.500N	P=0.207
Lymphoma, All Malignant			
Overall Incidence	11/50 (22%)	11/50 (22%)	18/50 (36%)
Adjusted Incidence	29.8%	46.5%	54.7%
Terminal Incidence	8/32 (25%)	6/17 (35%)	10/24 (42%)
Life Table Test	P=0.026	P=0.172	P=0.034
Incidental Tumor Test	P=0.037	P=0.360	P=0.052
Cochran-Armitage Trend, Fisher Exact Tests	P=0.071	P=0.595	P=0.093

Stomach: A positive trend (incidental tumor test) was observed in the incidences of male mice with squamous cell papillomas of the (nonglandular) gastric mucosa (Table 15); the incidences for female mice were: control, 1/50; low-dose, 0/50; high-dose, 2/50. Pairwise comparisons between the control and dosed groups were not significant. Grossly, the papillomas were cauliflower-like masses 2-3 mm in diameter or thin stalks attached to the mucosa of the nonglandular portion of the stomach. Histopathologic examinations of the papillomas showed the lesions as papillary growths composed of thin, fibrous cones covered by hyperplastic squamous epithelium.

TABLE 15. INCIDENCES OF MALE B6C3F$_1$ MICE WITH SQUAMOUS CELL PAPILLOMAS OF THE GASTRIC MUCOSA

	Vehicle Control	31 mg/kg	62 mg/kg
Overall Incidence	0/50 (0%)	1/50 (2%)	3/48 (6%)
Adjusted Incidence	0.0%	3.2%	9.4%
Terminal Incidence	0/29 (0%)	1/31 (3%)	2/31 (6%)
Life Table Test	P=0.068	P=0.513	P=0.137
Incidental Tumor Test	P=0.048	P=0.513	P=0.090
Cochran-Armitage Trend, Fisher Exact Tests	P=0.056	P=0.500	P=0.114

The incidence of high-dose mice with epithelial hyperplasia of the stomach or forestomach was higher than that of the controls (Table 16). These lesions were not visible on gross examination; histopathologically, they were characterized by focal acanthosis and hyperkeratosis of the nonglandular epithelium. These did not appear to be papillary lesions. Adenomatous hyperplasia was found in the gastric mucosa of a single low-dose mouse. Three of the four dosed male mice with squamous cell papillomas also had epithelial hyperplasia; one of the two high-dose females with papillomas also had hyperplasia.

TABLE 16. INCIDENCES OF HYPERPLASTIC AND NEOPLASTIC LESIONS IN THE STOMACH OR GASTRIC MUCOSA OF MICE ADMINISTERED ALLYL ISOVALERATE IN CORN OIL BY GAVAGE

	Males			Females		
	Vehicle Control	31 mg/kg	62 mg/kg	Vehicle Control	31 mg/kg	62 mg/kg
Number of stomachs evaluated	50	50	48	50	50	50
Diagnosis						
Epithelial hyperplasia	1	1	7	0	2	3
Squamous cell papilloma	0	1	3	1	0	2
Squamous cell carcinoma	0	0	0	0	0	0

Liver: A negative trend was observed in the incidences of male mice with hepatocellular carcinomas (Table 17). Pairwise comparisions of dosed males with controls indicated significantly decreased incidences in both the low- and high-dose groups. The combined incidence of low-dose males with adenomas or carcinomas was decreased when compared with the control value. The incidences of dosed female mice with adenomas or carcinomas (combined) were: control, 3/50; low-dose, 0/50; high-dose, 1/50.

TABLE 17. INCIDENCES OF LIVER TUMORS IN MALE B6C3F$_1$ MICE

	Vehicle Control	31 mg/kg	62 mg/kg
Adenoma			
Overall Incidence	7/50 (14%)	8/50 (16%)	8/50 (16%)
Adjusted Incidence	23.1%	23.2%	24.4%
Terminal Incidence	6/29 (21%)	6/31 (19%)	7/31 (23%)
Life Table Test	P=0.487	P=0.543	P=0.549
Incidental Tumor Test	P=0.406	P=0.523	P=0.489
Cochran-Armitage Trend, Fisher Exact Tests	P=0.445	P=0.500	P=0.500
Carcinoma			
Overall Incidence	18/50 (36%)	6/50 (12%)	9/50 (18%)
Adjusted Incidence	47.6%	16.7%	25.4%
Terminal Incidence	10/29 (34%)	3/31 (10%)	6/31 (19%)
Life Table Test	P=0.021N	P=0.006N	P=0.038N
Incidental Tumor Test	P=0.044N	P=0.013N	P=0.069N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.020N	P=0.005N	P=0.035N
Adenoma or Carcinoma			
Overall Incidence	23/50 (46%)	14/50 (28%)	15/50 (30%)
Adjusted Incidence	59.9%	37.6%	43.3%
Terminal Incidence	14/29 (48%)	9/31 (29%)	12/31 (39%)
Life Table Test	P=0.052N	P=0.049N	P=0.066N
Incidental Tumor Test	P=0.108N	P=0.092N	P=0.117N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.058N	P=0.048N	P=0.074N

Lung: A negative trend was seen in the incidences of male mice with alveolar/bronchiolar adenomas, and the incidence in the high-dose group was significantly lower than that in the controls (Table 18).

The combined incidences of male mice with alveolar/bronchiolar adenomas or carcinomas occurred with a negative trend, and the incidence in the high-dose group was significantly lower than that in the controls. These tumors were not observed in different proportions of female mice (control, 4/50; low-dose, 4/49; high-dose, 3/50).

TABLE 18. INCIDENCES OF LUNG TUMORS IN MALE B6C3F$_1$ MICE

	Vehicle Control	31 mg/kg	62 mg/kg
Alveolar/Bronchiolar Adenoma			
Overall Incidence	10/50 (20%)	5/50 (10%)	3/49 (6%)
Adjusted Incidence	31.6%	15.1%	9.0%
Terminal Incidence	8/29 (28%)	4/31 (13%)	2/31 (6%)
Life Table Test	P=0.018N	P=0.108N	P=0.031N
Incidental Tumor Test	P=0.030N	P=0.149N	P=0.047N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.025N	P=0.131N	P=0.039N
Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Incidence	13/50 (26%)	6/50 (12%)	5/49 (10%)
Adjusted Incidence	38.1%	18.3%	14.6%
Terminal Incidence	9/29 (31%)	5/31 (16%)	3/31 (10%)
Life Table Test	P=0.017N	P=0.053N	P=0.031N
Incidental Tumor Test	P=0.034N	P=0.087N	P=0.057N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.022N	P=0.062N	P=0.037N

Thyroid: A negative trend was observed in the incidences of male mice with follicular-cell adenomas (Table 19). The incidence for low-dose males was significantly lower than that for the controls. In female mice, this tumor did not occur in significant proportions (control, 3/49; low-dose, 2/48; high-dose, 2/48).

TABLE 19. INCIDENCES OF FOLLICULAR-CELL ADENOMAS OF THE THYROID GLAND IN MALE B6C3F$_1$ MICE

	Vehicle Control	31 mg/kg	62 mg/kg
Overall Incidence	5/47 (11%)	0/46 (0%)	1/49 (2%)
Adjusted Incidence	16.5%	0.0%	3.2%
Terminal Incidence	4/29 (14%)	0/30 (0%)	1/31 (3%)
Life Table Test	P=0.032N	P=0.031N	P=0.090N
Incidental Tumor Test	P=0.039N	P=0.038N	P=0.105N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.034N	P=0.030N	P=0.093N

Pituitary: The incidence of low-dose female mice with adenomas was significantly lower than that of the controls; however, this decrease was not statistically different when survival differences were taken into account (Table 20). Tests for trend and comparisons of high-dose versus control females were not significant. This lesion was not observed in male mice.

TABLE 20. INCIDENCES OF ADENOMAS OF THE PITUITARY GLAND IN FEMALE B6C3F$_1$ MICE

	Vehicle Control	31 mg/kg	62 mg/kg
Overall Incidence	11/43 (26%)	2/43 (5%)	7/44 (16%)
Adjusted Incidence	36.7%	8.5%	30.4%
Terminal Incidence	11/30 (37%)	1/16 (6%)	7/23 (30%)
Life Table Test	P=0.316N	P=0.076N	P=0.428N
Incidental Tumor Test	P=0.362N	P=0.081N	P=0.428N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.139N	P=0.007N	P=0.198N

Ovaries/Uterus: Suppurative inflammation of the ovaries, uterus, or multiple organs was found in 11/19 control, 22/33 low-dose, and 13/25 high-dose females that died before the end of the study (Appendix D, Table D2). At necropsy, an enlarged uterus was observed in 23 vehicle control, 31 low-dose, and 28 high-dose females; ovarian masses with suppurative exudate were seen in 15 control, 18 low-dose, and 17 high-dose females. The etiology is not known. Although microbiologic examinations were not performed on mice in this study, *Klebsiella oxytoca* has been isolated from mice that have had similar lesions in other studies.

IV. DISCUSSION AND CONCLUSIONS

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The doses of allyl isovalerate administered to rats and mice in the 2-year study were 31 and 62 mg/kg body weight. The survival and mean body weight gains of animals in this study (except for low-dose female mice) were not adversely affected by administration of allyl isovalerate. The lower survival and decrease in mean body weight gain of low-dose female mice as compared with controls were not considered to be compound related, but rather were due to a genital tract infection that may have been responsible for the deaths of 11/19 control, 22/33 low-dose, and 13/25 high-dose female mice that died after week 90 but before the end of the study. These survival and weight gain data suggest that higher doses might have been tolerated in the two-year study.

The effects observed in the short-term and the two-year studies indicate that the pancreas in rats and the liver, stomach, and hematopoietic system in rats and mice were the sites primarily affected by administration of allyl isovalerate. The current studies confirm that allyl isovalerate is hepatotoxic in F344/N rats and B6C3F$_1$ mice, as reported by Drake (1975), who observed necrosis and fibrosis of the liver and bile duct hyperplasia in male rats (strain unspecified) administered allyl isovalerate by gavage at doses of 60 or 150 mg/kg body weight for 10 days. In the current 13-week studies, chemical-related nonneoplastic lesions were observed in livers of rats administered 125 mg/kg and of rats and mice that received 250 mg/kg. Bile duct hyperplasia and basophilic cytoplasmic changes were seen in livers of male and female rats administered 125 mg/kg; rats and mice that received 250 mg/kg doses for 13 weeks had multifocal coagulative necrosis, cholangiofibrosis, bile duct hyperplasia, nodular hyperplasia, and cytoplasmic vacuolization (Tables 4 and 12). The findings from the 13-week exposure study forecast correctly that the liver would be a target organ for allyl isovalerate in the two-year study.

Rats administered 31 or 62 mg/kg doses of allyl isovalerate for two years had cholangiofibrosis, nodular regeneration, cirrhosis, fatty metamorphosis, and cytoplasmic vacuolization (Table 8). No compound-related nonneoplastic effects were seen in mice administered 31 or 62 mg/kg for two years.

In contrast to this high frequency of nonneoplastic hepatic lesions, incidences of dosed rats and mice with neoplastic lesions of the liver in the two-year study were not significantly increased. Hepatocellular carcinomas in male and female mice, hepatocellular adenomas in female mice, and neoplastic nodules in female rats occurred at lower incidences in the high-dose groups than in the respective controls.

Reports of hepatotoxic effects in rats administered allyl alcohol—an hydrolysis product of allyl isovalerate—suggest that a similar mechanism of toxic effects may exist for allyl isovalerate. Lake et al. (1978) observed periportal necrosis and reductions in alcohol dehydrogenase and succinic dehydrogenase activities in the portal areas of the liver lobules of male Wistar rats given a single dose of allyl alcohol (30 mg/kg body weight) in corn oil by gavage. Livers of those rats that had received 10 or 28 daily consecutive doses of 30 mg/kg appeared normal, indicating that the effects on the liver may have been reversible and that the metabolism of allyl alcohol changes with time. Similarly, Carpanini et al. (1978) found no histological evidence of liver damage in male and female Wistar rats given up to 800 ppm allyl alcohol in drinking water for 15 weeks. These authors considered this lack of response "exceptional," particularly since Reid (1972) and others reported extensive periportal necrosis within 24 hours following a single intraperitoneal injection of 50 mg allyl alcohol/kg body weight to male Sprague-Dawley rats. In the present studies, nodular regeneration was not apparent in animals administered allyl isovalerate at doses of 125 or 250 mg/kg for 13 weeks; however, these effects were observed in 5/50 and 8/50 male rats that received 31 or 62 mg/kg for two years.

Cyclophosphamide—a "prodrug" used therapeutically as an antitumor and immunosuppressive agent—apparently undergoes metabolism to acrolein, especially in patients who excrete alkaline urine (Low et al., 1982). Others (Brock et al., 1979; Cox, 1979) have proposed that the clinically-observed urotoxic effects of cyclophosphamide are largely due to the acrolein generated in the urine from 4-hydroxycyclophosphamide. Allyl isovalerate is also converted via allyl alcohol to acrolein in rodent liver (Patel et al., 1980; Serafini-Cessi, 1972), the acrolein probably being responsible for the observed hepatotoxicity (Table 8). This mechanism of local toxicity mimics that of the urotoxic responses diagnosed in humans taking cyclophosphamide. Acrolein is highly reactive and unstable, and thus the location of toxicity probably depends on the site of the parent compound's metabolism to acrolein.

Another hydrolysis product of allyl isovalerate—isovaleric acid—produced lethargy, coma, pancytopenia, and ketoacidosis in humans with

isovaleric acidemia (Cohn et al., 1978), yet these clinical effects have not been observed in rats and mice.

Neoplastic and nonneoplastic lesions were observed in acinar cells of the pancreas in male rats administered allyl isovalerate for two years (current study) at doses of 31 or 62 mg/kg body weight; similar findings were seen in another study in which male and female CFY rats received a single oral dose (50 mg/kg) of allyl alcohol (Nizze et al., 1979). In the present study, the incidences of dosed male rats with acinar-cell adenomas were higher than those found in the concurrent control group or in any other control group of the same sex and strain (Appendix H, Table H1) in the Bioassay Program (concurrent control, 1/50; laboratory control, 2/248, 0.8% historical control, 6/976, 0.6%; low-dose, 4/50; high-dose, 2/50). In the study reported by Nizze and coworkers (1979), administration of allyl alcohol was associated with acidophila, necrosis, and vacuolization of the pancreatic acinar cells.

The irritant effects of allyl isovalerate on the mucosal surfaces of the stomach or forestomach were observed in both rats and mice. Rats administered 500 mg/kg for 2 days had dark red areas on the "stomach wall" (3/5 males and 3/5 females); males and females administered 250 mg/kg for 13 weeks developed thickening of the intestinal wall and reddening of the mucosal surfaces in the intestines and urinary bladder. Histopathologic examination of tissues taken from these grossly visible lesions in rats that received 250 mg/kg for 13 weeks or 31 or 62 mg/kg for 2 years did not reveal any compound-related microscopic lesions. Similar effects were observed in mice administered 250 mg/kg for 13 weeks: thickening and ulcerative inflammation of the mucosa of the stomach and thickening of the urinary bladder wall, but no lesions were detected histopathologically. In the two-year study, however, a significant ($P<0.05$) positive trend was observed in the incidences of male mice with squamous cell papillomas of the gastric mucosa (control, 0/50; low-dose, 1/50; high-dose, 3/48); the incidence of high-dose male mice with squamous cell hyperplasia was higher than that in the controls (control, 1/50; low-dose, 1/50; high-dose, 7/48). Since the incidence of high-dose males with squamous cell papillomas is significantly ($P<0.01$) higher than the historical rate seen in vehicle controls in the Bioassay Program (5/881, 0.57%; Appendix H, Table H7), this lesion may have been related to administration of allyl isovalerate.

Regarding other allyl compounds tested in the Program, allyl isothiocyanate (NTP, 1982a) caused transitional-cell tumors of the urinary bladder in male rats, while allyl chloride (NCI, 1978) produced squamous cell carcinomas and papillomas of the forestomach in male and female mice. Diallyl phthalate caused chronic forestomach inflammation and forestomach hyperplasia, as well as squamous cell papillomas of the forestomach in mice (NTP, 1983). Thus at least two other allyl compounds have been shown to produce proliferative lesions of the forestomach similar to those caused by allyl isovalerate. Each utilizes similar metabolic pathways: allyl alcohol to acrolein (Figure 1).

Mononuclear-cell leukemia in male rats and malignant lymphoma in female mice occurred with statistically significant positive trends, and the incidences in the high-dose groups were significantly higher than those in the controls. Further, although not statistically significant, the increased incidences of hematopoietic lesions in female rats (trend, P=0.050) and in male mice were dose-related (Table 21). Taken together,

TABLE 21. INCIDENCES OF LEUKEMIA IN F344/N RATS AND LYMPHOMA IN B6C3F$_1$ MICE

				Life Table P Values		
	Control	31 mg/kg	62 mg/kg	Trend	Low Dose	High Dose
Rats: Male	1/50	4/50	7/50	0.015	0.183	0.022
Female	4/50	6/50	9/49	0.050	0.354	0.075
Mice: Male	4/50	6/50	8/50	0.167	0.397	0.204
Female	11/50	11/50	18/50	0.026	0.172	0.034

these toxic effects were considered to have been induced by allyl isovalerate (Historical incidences are shown in Appendix H, Tables H2, H3, H5, and H6). Appendix I (Tables I1-I4) compares concurrent and historical data on hematopoietic tumors from the five gavage studies completed to date at Southern Research Institute. These additional analyses further support the conclusion that allyl isovalerate increased the incidences of hematopoietic system lesions in male rats and female mice.

Preputial gland adenomas were observed in low-dose male rats at increased incidences. This increase was significantly ($P<0.005$) greater than the historical vehicle control rate in the Bioassay Program (16/999, 1.6%; see Appendix H, Table H4). However, because there was no observable dose response trend and no high-dose effect, this increase was not regarded as clearly being related to allyl isovalerate administration.

Allyl compounds can be alkylating agents and direct-acting mutagens, depending on the degree of polarity (electron deficiency, electrophilicity) introduced into the molecule by substituents on the saturated (terminal) carbon atom (Eder et al., 1980). Allyl methanesulfonate, for example, is a strong alkylating agent because of the electronegativity of the methane sulfonate group, whereas allyl isothiocyanate is a very weak alkylating agent. By this criterion (electrophilicity), allyl alcohol would be expected to be a very weak direct-acting alkylating agent. The available data suggest that allyl isovalerate, although not mutagenic, may be metabolized to the electrophile acrolein and to the epoxides glycidol and glycidaldehyde.

Studies on the carcinogenic potential of acrolein and allyl alcohol are currently in progress (IARC, 1981), and Van Duuren et al. (1965, 1966, 1967a, 1967b) have reported that glycidaldehyde is carcinogenic in mice by skin application and subcutaneous injection and in rats by subcutaneous injection (IARC, 1976). Experimentation to determine the extent, dose-dependency, and species-dependency of the metabolism of allyl isovalerate to allyl alcohol, acrolein, and epoxides may therefore provide additional insight into the carcinogenic potential of this compound. Metabolism studies have been initiated in F344/N rats and in $B6C3F_1$ mice with diallyl phthalate labelled with carbon-14 in the allyl portion to follow specifically the allyl alcohol pathway (NTP, 1982b). These results should be equally applicable to allyl isovalerate. Emphasis should also be placed on hematologic indices, since pancytopenia has been observed in infant humans with isovaleric acidemia (Cohn et al., 1978) and since chemically-induced hematopoietic lesions were diagnosed in this study. To better characterize the effects of allyl isovalerate (and *in situ* metabolites) on the hematologic and immunologic systems in F344/N rats and $B6C3F_1$ mice, the NTP has initiated 14-day repeated-dose studies using gavage doses of 0, 31, 62, 125, and 250 mg/kg.

In an NTP-sponsored subchronic inhalation study of acrolein, F344/N rats were exposed to 0, 0.4, 1.4, or 4.0 ppm acrolein for 62 days (Kutzman, 1981). The only effects observed histologically were in the 4.0-ppm dose group: bronchiolar epithelial necrosis and sloughing, bronchiolar edema with macrophages, and focal pulmonary edema. Acrolein had no detectable effects on sister chromatid exchanges and cell proliferation kinetics in bone marrow cells and in peripheral blood lymphocytes. Sperm morphology and reproductive potential were also unaffected.

Conclusions: Under the conditions of these studies, allyl isovalerate was carcinogenic for F344/N rats and $B6C3F_1$ mice, causing increased incidences of hematopoietic system neoplasms (mononuclear-cell leukemia in male rats and lymphoma in female mice).

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APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS ADMINISTERED ALLYL ISOVALERATE IN CORN OIL BY GAVAGE

TABLE A1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS ADMINISTERED ALLYL ISOVALERATE IN CORN OIL BY GAVAGE

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
SQUAMOUS CELL PAPILLOMA	1 (2%)		2 (4%)
SQUAMOUS CELL CARCINOMA	1 (2%)		
BASAL-CELL TUMOR	1 (2%)		1 (2%)
SEBACEOUS ADENOMA	1 (2%)		
KERATOACANTHOMA	1 (2%)	1 (2%)	1 (2%)
*SUBCUT TISSUE	(50)	(50)	(50)
SARCOMA, NOS	2 (4%)		1 (2%)
FIBROMA	5 (10%)	4 (8%)	3 (6%)
FIBROADENOMA			1 (2%)
RESPIRATORY SYSTEM			
#LUNG	(50)	(50)	(49)
ALVEOLAR/BRONCHIOLAR ADENOMA	2 (4%)		
ALVEOLAR/BRONCHIOLAR CARCINOMA	1 (2%)	2 (4%)	
ADENOCA/SQUAMOUS METAPLASIA			1 (2%)
SYNOVIAL SARCOMA, METASTATIC			1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			2 (4%)
MONOCYTIC LEUKEMIA	1 (2%)	4 (8%)	7 (14%)
CIRCULATORY SYSTEM			
#SPLEEN	(50)	(49)	(50)
HEMANGIOSARCOMA	2 (4%)		

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#HEART	(50)	(49)	(50)
MESOTHELIOMA, MALIGNANT	1 (2%)		
DIGESTIVE SYSTEM			
*TONGUE	(50)	(50)	(50)
SQUAMOUS CELL PAPILLOMA			1 (2%)
#LIVER	(50)	(50)	(50)
BILE DUCT ADENOMA	1 (2%)		
NEOPLASTIC NODULE	1 (2%)	1 (2%)	2 (4%)
HEPATOCELLULAR CARCINOMA		1 (2%)	1 (2%)
PHEOCHROMOCYTOMA, INVASIVE	1 (2%)		
#PANCREAS	(50)	(50)	(50)
ACINAR-CELL ADENOMA	1 (2%)	4 (8%)	2 (4%)
#STOMACH	(50)	(50)	(50)
LEIOMYOSARCOMA			1 (2%)
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#PITUITARY	(49)	(46)	(49)
ADENOMA, NOS	14 (29%)	4 (9%)	9 (18%)
ACIDOPHIL ADENOMA		1 (2%)	
#ADRENAL	(50)	(50)	(50)
CORTICAL ADENOMA	1 (2%)		
PHEOCHROMOCYTOMA	15 (30%)	15 (30%)	15 (30%)
PHEOCHROMOCYTOMA, MALIGNANT	1 (2%)		
#THYROID	(50)	(47)	(47)
FOLLICULAR-CELL ADENOMA		1 (2%)	
FOLLICULAR-CELL CARCINOMA	1 (2%)	1 (2%)	1 (2%)
C-CELL ADENOMA	5 (10%)	7 (15%)	3 (6%)
C-CELL CARCINOMA	6 (12%)		3 (6%)
#PANCREATIC ISLETS	(50)	(50)	(50)
ISLET-CELL ADENOMA	2 (4%)		2 (4%)

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ISLET-CELL CARCINOMA	1 (2%)		
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
FIBROADENOMA	2 (4%)	1 (2%)	2 (4%)
*PREPUTIAL GLAND	(50)	(50)	(50)
CARCINOMA,NOS		1 (2%)	
SQUAMOUS CELL CARCINOMA			1 (2%)
ADENOMA, NOS		4 (8%)	1 (2%)
#TESTIS	(50)	(50)	(50)
INTERSTITIAL-CELL TUMOR	40 (80%)	44 (88%)	40 (80%)
NERVOUS SYSTEM			
#BRAIN	(50)	(50)	(50)
GLIOMA, NOS			1 (2%)
#CEREBRAL HEMISPHERE	(50)	(50)	(50)
ASTROCYTOMA			1 (2%)
SPECIAL SENSE ORGANS			
*EXTERNAL EAR	(50)	(50)	(50)
NEURILEMOMA		1 (2%)	
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*MEDIASTINUM	(50)	(50)	(50)
LIPOMA			1 (2%)
*ABDOMINAL WALL	(50)	(50)	(50)
FIBROSARCOMA		1 (2%)	
*MESENTERY	(50)	(50)	(50)
FIBROSARCOMA, INVASIVE		1 (2%)	

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
LIPOSARCOMA		1 (2%)	
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
SARCOMA, NOS		1 (2%)	
LEIOMYOSARCOMA, INVASIVE			1 (2%)
MESOTHELIOMA, MALIGNANT	1 (2%)		
HEAD			
SQUAMOUS CELL CARCINOMA		1	
LEG			
FIBROSARCOMA		1	1
SYNOVIAL SARCOMA			1
SOLE OF FOOT			
SQUAMOUS CELL PAPILLOMA			1
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	6	10	10
MORIBUND SACRIFICE	8	6	8
SCHEDULED SACRIFICE	3		
TERMINAL SACRIFICE	30	30	28
ACCIDENTALLY KILLED, NOS	3	4	4
ANIMAL MISSING			
ANIMAL MISSEXED			
OTHER CASES			

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	45	45	47
TOTAL PRIMARY TUMORS	111	102	109
TOTAL ANIMALS WITH BENIGN TUMORS	45	45	47
TOTAL BENIGN TUMORS	92	87	85
TOTAL ANIMALS WITH MALIGNANT TUMORS	17	13	21
TOTAL MALIGNANT TUMORS	18	14	22
TOTAL ANIMALS WITH SECONDARY TUMORS#	1	1	2
TOTAL SECONDARY TUMORS	1	1	2
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	1	1	2
TOTAL UNCERTAIN TUMORS	1	1	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

TABLE A2.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS ADMINISTERED ALLYL ISOVALERATE IN CORN OIL BY GAVAGE

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	49
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(49)
BASAL-CELL TUMOR			1 (2%)
KERATOACANTHOMA			1 (2%)
*SUBCUT TISSUE	(50)	(50)	(49)
BASAL-CELL TUMOR	1 (2%)		
FIBROMA		3 (6%)	
FIBROSARCOMA	1 (2%)		
LIPOMA		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(50)	(50)	(49)
ALVEOLAR/BRONCHIOLAR CARCINOMA		1 (2%)	
CHONDROSARCOMA, METASTATIC	1 (2%)		
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(49)
LEUKEMIA,NOS			1 (2%)
MONOCYTIC LEUKEMIA	4 (8%)	6 (12%)	8 (16%)
#MESENTERIC L. NODE	(50)	(50)	(49)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (2%)		
*MESENTERY	(50)	(50)	(49)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)
#THYMUS	(41)	(43)	(39)
THYMOMA			1 (3%)
CIRCULATORY SYSTEM			
NONE			

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
*TONGUE	(50)	(50)	(49)
SQUAMOUS CELL PAPILLOMA			1 (2%)
#LIVER	(50)	(50)	(49)
BILE DUCT ADENOMA		1 (2%)	
NEOPLASTIC NODULE	1 (2%)	1 (2%)	
#STOMACH	(50)	(50)	(49)
SQUAMOUS CELL PAPILLOMA	1 (2%)		
#FORESTOMACH	(50)	(50)	(49)
SQUAMOUS CELL PAPILLOMA			1 (2%)
#JEJUNUM	(49)	(50)	(46)
MUCINOUS ADENOCARCINOMA			1 (2%)
*RECTUM	(50)	(50)	(49)
FIBROSARCOMA		1 (2%)	
URINARY SYSTEM			
#URINARY BLADDER	(49)	(50)	(48)
TRANSITIONAL-CELL PAPILLOMA	1 (2%)		
ENDOCRINE SYSTEM			
#PITUITARY	(48)	(49)	(48)
ADENOMA, NOS	13 (27%)	16 (33%)	13 (27%)
ACIDOPHIL ADENOMA		1 (2%)	
#ADRENAL	(50)	(50)	(49)
CORTICAL ADENOMA	1 (2%)	1 (2%)	
PHEOCHROMOCYTOMA	5 (10%)	8 (16%)	6 (12%)
#THYROID	(48)	(50)	(46)
FOLLICULAR-CELL ADENOMA		1 (2%)	
C-CELL ADENOMA	2 (4%)	7 (14%)	4 (9%)
C-CELL CARCINOMA	2 (4%)	1 (2%)	1 (2%)
#PARATHYROID	(48)	(44)	(37)
ADENOMA, NOS		1 (2%)	

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#PANCREATIC ISLETS	(49)	(50)	(46)
ISLET-CELL ADENOMA		1 (2%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(49)
ADENOCARCINOMA, NOS	2 (4%)	1 (2%)	
SARCOMA, NOS		1 (2%)	
FIBROADENOMA	17 (34%)	23 (46%)	11 (22%)
*PREPUTIAL GLAND	(50)	(50)	(49)
CARCINOMA,NOS		1 (2%)	1 (2%)
ADENOMA, NOS		1 (2%)	1 (2%)
ADENOSQUAMOUS CARCINOMA		1 (2%)	
*VAGINA	(50)	(50)	(49)
ENDOMETRIAL STROMAL SARCOMA, INV			1 (2%)
#UTERUS	(50)	(50)	(48)
LEIOMYOMA	1 (2%)		
LEIOMYOSARCOMA	1 (2%)		
ENDOMETRIAL STROMAL POLYP	11 (22%)	8 (16%)	13 (27%)
ENDOMETRIAL STROMAL SARCOMA	2 (4%)		1 (2%)
NERVOUS SYSTEM			
#BRAIN	(50)	(50)	(49)
ASTROCYTOMA			1 (2%)
#CEREBELLUM	(50)	(50)	(49)
MEDULLOBLASTOMA			1 (2%)
SPECIAL SENSE ORGANS			
*ZYMBAL'S GLAND	(50)	(50)	(49)
ADENOSQUAMOUS CARCINOMA			1 (2%)
MUSCULOSKELETAL SYSTEM			
NONE			

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
BODY CAVITIES			
*PELVIS	(50)	(50)	(49)
CHONDROSARCOMA	1 (2%)		
*MESENTERY	(50)	(50)	(49)
FIBROSARCOMA			1 (2%)
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(49)
SARCOMA, NOS		1 (2%)	
SARCOMA, NOS, METASTATIC		1 (2%)	
ENDOMETRIAL STROMAL SARCOMA, MET			1 (2%)
OSTEOSARCOMA		1 (2%)	
LEG			
OSTEOSARCOMA			1
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	4	8	13
MORIBUND SACRIFICE	9	5	6
SCHEDULED SACRIFICE	1		
TERMINAL SACRIFICE	36	36	29
ACCIDENTALLY KILLED, NOS		1	2
ANIMAL MISSING			
ANIMAL MISSEXED			
OTHER CASES			

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	38	43	43
TOTAL PRIMARY TUMORS	68	89	72
TOTAL ANIMALS WITH BENIGN TUMORS	35	41	33
TOTAL BENIGN TUMORS	53	73	53
TOTAL ANIMALS WITH MALIGNANT TUMORS	13	14	18
TOTAL MALIGNANT TUMORS	14	15	19
TOTAL ANIMALS WITH SECONDARY TUMORS#	1	1	1
TOTAL SECONDARY TUMORS	1	1	2
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	1	1	
TOTAL UNCERTAIN TUMORS	1	1	
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 A3.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE 2-YEAR STUDY OF ALLYL ISOVALERATE

VEHICLE CONTROL

ANIMAL NUMBER	0011	0012	0013	0014	0015	0016	0017	0018	0019	0110	0111	0112	0113	0114	0115	0116	0117	0118	0119	0120	0121	0122	0123	0124	0125
WEEKS ON STUDY	050	105	051	105	106	106	106	106	106	106	106	106	106	105	106	106	106	106	106	106	101	107	055	107	107
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL PAPILLOMA															X										
SQUAMOUS CELL CARCINOMA																								X	
BASAL-CELL TUMOR																									
SEBACEOUS ADENOMA																									
KERATOACANTHOMA																									
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SARCOMA, NOS																									
FIBROMA					X																				
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALVEOLAR/BRONCHIOLAR ADENOMA																								X	
ALVEOLAR/BRONCHIOLAR CARCINOMA																	X								
TRACHEA	+	+	+	+	+	+	-	-	+	+	+	+	+	-	-	+	+	+	+	+	-	+	-	-	
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMANGIOSARCOMA							X			X															
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MESOTHELIOMA, MALIGNANT																									X
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
BILE DUCT ADENOMA																									
NEOPLASTIC NODULE							X																		
PHEOCHROMOCYTOMA, INVASIVE																									
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ACINAR-CELL ADENOMA													X												
ESOPHAGUS	+	+	+	+	+	+	+	+	+	•	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOMA, NOS		X												X					X			X		X	
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CORTICAL ADENOMA																									
PHEOCHROMOCYTOMA		X	X			X			X			X	X		X			X	X				X	
PHEOCHROMOCYTOMA, MALIGNANT																									
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FOLLICULAR-CELL CARCINOMA									X																
C-CELL ADENOMA																					X	X			
C-CELL CARCINOMA		X						X			X										X				
PARATHYROID	+	+	+	-	+	-	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ISLET-CELL ADENOMA																		X							
ISLET-CELL CARCINOMA																			X						
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+
FIBROADENOMA					X																				
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
INTERSTITIAL-CELL TUMOR		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
MESOTHELIOMA, MALIGNANT																					X				
MONOCYTIC LEUKEMIA																									

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A3. MALE RATS: TUMOR PATHOLOGY (CONTINUED) VEHICLE CONTROL

ANIMAL NUMBER	0 2 6 7	0 2 7 8	0 2 8 9	0 3 0 1	0 3 1 1	0 3 1 2	0 3 1 3	0 3 1 4	0 3 1 5	0 3 1 6	0 3 1 7	0 3 1 8	0 3 1 9	0 4 0 1	0 4 1 1	0 4 1 2	0 4 1 3	0 4 1 4	0 4 1 5	0 4 1 6	0 4 1 7	0 4 1 8	0 4 1 9	0 5 0 0	TOTAL
WEEKS ON STUDY	0 5 5	0 1 8	0 9 2	0 6 6	0 8 8	0 4 1	1 0 1 7	0 8 2	0 6 9	0 7 2	1 0 2 7	0 3 4	1 0 0	1 0 0 7	1 0 9 7	0 9 3	1 1 0 7	1 0 0 7	1 1 0 7	1 1 0 7	1 1 0 6	1 1 0 7	1 1 0 7	1 1 0 7	1 1 0 7	TISSUES TUMORS
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
SQUAMOUS CELL PAPILLOMA																									1
SQUAMOUS CELL CARCINOMA																									1
BASAL-CELL TUMOR																	X								1
SEBACEOUS ADENOMA						X																			1
KERATOACANTHOMA																X									1
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
SARCOMA, NOS			X						X																2
FIBROMA			X	X													X				X				5
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALVEOLAR/BRONCHIOLAR ADENOMA																					X				2
ALVEOLAR/BRONCHIOLAR CARCINOMA																									1
TRACHEA	+	+	+	+	+	+	-	-	+	-	+	+	+	+	-	+	+	-	-	+	+	+	-	+	35
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMANGIOSARCOMA																									2
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
THYMUS	-	+	+	-	+	+	+	+	-	+	+	+	+	+	+	+	+	+	-	-	+	+	+	+	44
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
MESOTHELIOMA, MALIGNANT	5	8	2	6	8	1	7	2	9	2	7	4	0	7	7	3	7	7	7	6	7	7	7	7	1
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
BILE DUCT ADENOMA																					X				1
NEOPLASTIC NODULE																									1
PHEOCHROMOCYTOMA, INVASIVE														X											1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ACINAR-CELL ADENOMA																									1
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ADENOMA, NOS								X					X	X		X	X	X	X		X			X		14
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CORTICAL ADENOMA																		X							1
PHEOCHROMOCYTOMA							X							X	X					X				X	15
PHEOCHROMOCYTOMA, MALIGNANT														X											1
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
FOLLICULAR-CELL CARCINOMA																									1
C-CELL ADENOMA													X	X										X	5
C-CELL CARCINOMA																		X		X					6
PARATHYROID	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	45
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ISLET-CELL ADENOMA															X										2
ISLET-CELL CARCINOMA																									1
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
FIBROADENOMA																		X							2
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
INTERSTITIAL-CELL TUMOR			X		X		X		X	X	X		X	X		X	X	X	X	X	X	X	X	X	40
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
MESOTHELIOMA, MALIGNANT																							X		1
MONOCYTIC LEUKEMIA																									1

* ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
.: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A3.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE 2-YEAR STUDY OF ALLYL ISOVALERATE

LOW DOSE

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	106	106	105	106	074	103	106	070	055	106	106	106	106	106	055	052	071	106	061	106	103	106	103	106	059
INTEGUMENTARY SYSTEM																									
SKIN	+	+	N	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
KERATOACANTHOMA																						X			
SUBCUTANEOUS TISSUE	+	+	N	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FIBROMA													X									X			
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALVEOLAR/BRONCHIOLAR CARCINOMA																									
TRACHEA	+	+	+	-	-	+	+	-	+	-	-	+	+	-	+	+	-	+	+	-	-	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	●	+	●	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	-	+	+	-	-	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	-
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NEOPLASTIC NODULE			X																						
HEPATOCELLULAR CARCINOMA							X																		
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ACINAR-CELL ADENOMA		X	X		X																				
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	-	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	-	+	+	+	+	+	-	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	-	-	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+
ADENOMA, NOS											X														
ACIDOPHIL ADENOMA													X												
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PHEOCHROMOCYTOMA			X	X		X		X						X						X	X	X		X	
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FOLLICULAR-CELL ADENOMA			X																						
FOLLICULAR-CELL CARCINOMA																									
C-CELL ADENOMA	X				X									X						X					
PARATHYROID	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FIBROADENOMA																			X						
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
INTERSTITIAL-CELL TUMOR	X	X	X	X	X	X	X	X		X	X	X	X	X			X	X	X	X	X	X	X	X	
PROSTATE	-	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
CARCINOMA,NOS													X						X					X	
ADENOMA, NOS																									
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
EAR	N	N	N	N	N	N	+	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N
NEURILEMOMA							X																		
BODY CAVITIES																									
PERITONEUM	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
FIBROSARCOMA																									
MESENTERY	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
FIBROSARCOMA, INVASIVE												X													
LIPOSARCOMA																									
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
SARCOMA, NOS					X																				
MONOCYTIC LEUKEMIA																				X					
HEAD NOS																									
SQUAMOUS CELL CARCINOMA								X																	
LEG NOS																									
FIBROSARCOMA																									

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A3. MALE RATS: TUMOR PATHOLOGY (CONTINUED) LOW DOSE

ANIMAL NUMBER	026	027	028	029	031	032	033	034	035	036	037	038	039	041	041	042	043	044	045	046	047	048	049	050	TOTAL
WEEKS ON STUDY	106	106	106	106	064	106	091	104	106	085	094	095	105	106	106	101	106	055	056	106	101	055	093	106	TISSUES TUMORS
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
KERATOACANTHOMA																									1
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
FIBROMA								X																X	4
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALVEOLAR/BRONCHIOLAR CARCINOMA										X												X			2
TRACHEA	+	+	−	+	−	+	+	−	+	+	−	+	+	+	+	+	−	+	+	+	+	+	−	+	35
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	•	+	+	+	+	+	+	+	+	+	+	50
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	•	+	50
THYMUS	+	+	+	+	−	−	−	−	+	−	+	+	+	+	+	+	−	−	+	+	+	−	−	+	36
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	49
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	+	48
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NEOPLASTIC NODULE																									1
HEPATOCELLULAR CARCINOMA																									1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ACINAR-CELL ADENOMA																	X								4
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	+	46
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	46
ADENOMA, NOS						X					X			X											4
ACIDOPHIL ADENOMA																									1
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
PHEOCHROMOCYTOMA	X			X	X														X	X				X	15
THYROID	+	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	47
FOLLICULAR-CELL ADENOMA																									1
FOLLICULAR-CELL CARCINOMA																				X					1
C-CELL ADENOMA		X					X							X											7
PARATHYROID	+	+	+	+	+	−	+	−	−	−	+	+	+	+	+	+	+	−	+	+	+	+	−	+	42
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	N	+	+	50*
FIBROADENOMA																									1
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
INTERSTITIAL-CELL TUMOR	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	44
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
CARCINOMA, NOS																									1
ADENOMA, NOS				X					X																1
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																									
EAR	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
NEURILEMOMA																									1
BODY CAVITIES																									
PERITONEUM	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
FIBROSARCOMA																	X								1
MESENTERY	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
FIBROSARCOMA, INVASIVE																	X								1
LIPOSARCOMA																									1
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
SARCOMA, NOS																									1
MONOCYTIC LEUKEMIA									X				X										X		4
HEAD NOS																									
SQUAMOUS CELL CARCINOMA																									1
LEG NOS																									
FIBROSARCOMA																				X					1

* ANIMALS *NECROPSIED*

+: TISSUE EXAMINED MICROSCOPICALLY
−: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
•: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A3.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE 2-YEAR STUDY OF ALLYL ISOVALERATE

HIGH DOSE

ANIMAL NUMBER	0011	0012	0013	0014	0015	0016	0017	0018	0019	0110	0111	0112	0113	0114	0115	0116	0117	0118	0119	0120	0121	0122	0123	0124	0125
WEEKS ON STUDY	105	095	065	074	105	105	105	105	065	105	051	089	105	100	105	096	096	061	105	079	096	061	061	060	054
INTEGUMENTARY SYSTEM																									
SKIN	+	+	N	+	+	N	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL PAPILLOMA								X																	
BASAL-CELL TUMOR					X																				
KERATOACANTHOMA																									
SUBCUTANEOUS TISSUE	+	+	N	+	+	N	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+
SARCOMA, NOS																									
FIBROMA																		X							
FIBROADENOMA																									
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOCA/SQUAMOUS METAPLASIA																									
SYNOVIAL SARCOMA, METASTATIC																									
TRACHEA	+	-	+	+	+	+	+	-	+	-	-	+	+	-	+	+	-	-	+	+	+	+	+	-	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	-	+	
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
ORAL CAVITY	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
SQUAMOUS CELL PAPILLOMA													X												
SALIVARY GLAND	+	+	+	+	+	+	+	+	-	+	+	•	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	•	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NEOPLASTIC NODULE																		X							
HEPATOCELLULAR CARCINOMA								X																	
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ACINAR-CELL ADENOMA								X								X								
ESOPHAGUS	+	+	+	-	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LEIOMYOSARCOMA																									
SMALL INTESTINE	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	•	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-
ENDOCRINE SYSTEM																									
PITUITARY	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOMA, NOS							X					X			X			X							
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PHEOCHROMOCYTOMA					X		X			X					X				X					
THYROID	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+
FOLLICULAR-CELL CARCINOMA																							X		
C-CELL ADENOMA											X														
C-CELL CARCINOMA					X																				
PARATHYROID	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	-
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ISLET-CELL ADENOMA																									
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FIBROADENOMA					X																		X		
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
INTERSTITIAL-CELL TUMOR	X	X	X		X	X	X	X	X	X	X	X		X		X	X	X	X	X	X	X	X		
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
SQUAMOUS CELL CARCINOMA															X	X									
ADENOMA, NOS																									
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GLIOMA, NOS																									
ASTROCYTOMA	X																								
BODY CAVITIES																									
MEDIASTINUM	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
LIPOMA				X																					
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
LEIOMYOSARCOMA, INVASIVE																									
MALIG.LYMPHOMA, HISTIOCYTIC TYPE														X											
MONOCYTIC LEUKEMIA		X				X												X							
LEG NOS																									
FIBROSARCOMA																									
SYNOVIAL SARCOMA																									
SOLE OF FOOT																									
SQUAMOUS CELL PAPILLOMA																		X							

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
5: ANIMAL MIS-SEXED
.: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A3. MALE RATS: TUMOR PATHOLOGY (CONTINUED) HIGH DOSE

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL
WEEKS ON STUDY	110	104	106	056	082	102	097	106	081	106	061	077	106	087	083	106	051	100	106	091	098	106	091	105		TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
SKIN	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	50*	
SQUAMOUS CELL PAPILLOMA											X														2	
BASAL-CELL TUMOR																									1	
KERATOACANTHOMA																	X								1	
SUBCUTANEOUS TISSUE	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	50*	
SARCOMA, NOS			X																						1	
FIBROMA																		X						X	3	
FIBROADENOMA			X																						1	
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	49	
ADENOCA/SQUAMOUS METAPLASIA		X																							1	
SYNOVIAL SARCOMA, METASTATIC																X									1	
TRACHEA	+	-	+	+	+	-	-	-	+	-	+	+	-	+	+	+	+	+	+	+	-	-	+	-	+	33
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
THYMUS	-	+	+	+	+	+	-	-	+	-	+	+	+	+	-	+	+	-	-	+	+	-	+	+	39	
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
DIGESTIVE SYSTEM																										
ORAL CAVITY	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*	
SQUAMOUS CELL PAPILLOMA																									1	
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	48	
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
NEOPLASTIC NODULE										X															2	
HEPATOCELLULAR CARCINOMA																									1	
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*	
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
ACINAR-CELL ADENOMA																									2	
ESOPHAGUS	+	+	+	-	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	46	
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
LEIOMYOSARCOMA							X																		1	
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
ADENOMA, NOS		X			X		X		X															X	9	
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
PHEOCHROMOCYTOMA	X	X	X								X				X		X	X				X	X	X	15	
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	47	
FOLLICULAR-CELL CARCINOMA																									1	
C-CELL ADENOMA	X											X													3	
C-CELL CARCINOMA										X		X													3	
PARATHYROID	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	+	+	+	-	+	43
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
ISLET-CELL ADENOMA										X	X														2	
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*	
FIBROADENOMA																									2	
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
INTERSTITIAL-CELL TUMOR	X	X	X			X	X	X		X	X	X	X	X	X	X	X		X	X	X	X		X	40	
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*	
SQUAMOUS CELL CARCINOMA																									1	
ADENOMA, NOS																									1	
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
GLIOMA, NOS																					X				1	
ASTROCYTOMA																									1	
BODY CAVITIES																										
MEDIASTINUM	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*	
LIPOMA																									1	
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*	
LEIOMYOSARCOMA, INVASIVE							X																		1	
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																								X	2	
MONOCYTIC LEUKEMIA						X						X						X	X						7	
LEG NOS																						X			1	
FIBROSARCOMA																X									1	
SYNOVIAL SARCOMA																										
SOLE OF FOOT																										
SQUAMOUS CELL PAPILLOMA																									1	

* ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION

: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A4.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE 2-YEAR STUDY OF ALLYL ISOVALERATE

VEHICLE CONTROL

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	051	061	061	051	096	081	061	061	061	061	061	061	061	011	061	061	061	061	061	097	054	071	093	071	071
INTEGUMENTARY SYSTEM																									
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	N	+	+	+	
BASAL-CELL TUMOR			X																						
FIBROSARCOMA																									
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
CHONDROSARCOMA, METASTATIC																						X			
TRACHEA	+	+	+	-	-	+	+	+	+	-	-	-	-	-	+	-	+	+	-	+	+	+	-	+	
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																									
THYMUS	+	+	+	-	+	+	-	+	-	+	+	+	+	+	+	-	+	-	-	+	+	+	+	+	
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
NEOPLASTIC NODULE																									
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
SQUAMOUS CELL PAPILLOMA																									
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
TRANSITIONAL-CELL PAPILLOMA														X											
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	
ADENOMA, NOS	X	X			X		X																		
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
CORTICAL ADENOMA		X								X															
PHEOCHROMOCYTOMA																									
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	
C-CELL ADENOMA													X					X							
C-CELL CARCINOMA																									
PARATHYROID	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	
ADENOCARCINOMA, NOS									X																
FIBROADENOMA				X			X			X				X		X							X		
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
LEIOMYOMA																									
LEIOMYOSARCOMA							X																		
ENDOMETRIAL STROMAL POLYP														X		X		X		X					
ENDOMETRIAL STROMAL SARCOMA														X							X				
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
BODY CAVITIES																									
PERITONEUM	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
CHONDROSARCOMA																							X		
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
MONOCYTIC LEUKEMIA		X				X																			

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A4. FEMALE RATS: TUMOR PATHOLOGY (CONTINUED) VEHICLE CONTROL

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL
WEEKS ON STUDY	107	107	107	107	107	107	107	107	107	070	104	107	107	107	107	107	107	107	107	107	107	107	107	083	107	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
BASAL-CELL TUMOR																										1
FIBROSARCOMA												X														1
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CHONDROSARCOMA, METASTATIC																										1
TRACHEA	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	-	-	+	+	-	-	-	+	+	34
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		X																								1
THYMUS	+	+	+	+	-	+	+	+	+	+	+	+	-	+	-	+	+	+	+	+	+	+	+	+	+	41
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NEOPLASTIC NODULE																									X	1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	49
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SQUAMOUS CELL PAPILLOMA												X														1
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	49
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	49
TRANSITIONAL-CELL PAPILLOMA																										1
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	48
ADENOMA, NOS	X		X	X		X	X			X	X	X			X											13
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CORTICAL ADENOMA									X																	1
PHEOCHROMOCYTOMA							X											X			X					5
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	48
C-CELL ADENOMA																										2
C-CELL CARCINOMA						X															X					2
PARATHYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	48
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
ADENOCARCINOMA, NOS											X															2
FIBROADENOMA			X		X		X	X		X				X	X	X		X					X		X	17
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LEIOMYOMA								X																		1
LEIOMYOSARCOMA																										1
ENDOMETRIAL STROMAL POLYP		X				X		X							X			X			X	X				11
ENDOMETRIAL STROMAL SARCOMA																										2
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
BODY CAVITIES																										
PERITONEUM	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
CHONDROSARCOMA																										1
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
MONOCYTIC LEUKEMIA			X			X																				4

* ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL *MISSING*
B: NO NECROPSY PERFORMED

TABLE A4.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE 2-YEAR STUDY OF ALLYL ISOVALERATE

LOW DOSE

ANIMAL NUMBER	00112	00203	00304	00405	00506	00607	00708	00809	00910	01101	01202	01303	01404	01505	01606	01707	01808	01909	02010	02111	02212	02313	02414	02515
WEEKS ON STUDY	11061	10961	11061	07202	10216	10961	10161	10961	10867	09011	10161	10161	10961	10161	10197	10161	10961	10161	10961	10183	10161	09195	10961	10961
INTEGUMENTARY SYSTEM																								
SUBCUTANEOUS TISSUE	+	N	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	N	N	+
FIBROMA																						X		
LIPOMA																								
RESPIRATORY SYSTEM																								
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALVEOLAR/BRONCHIOLAR CARCINOMA																								
TRACHEA	+	+	+	+	+	+	-	+	+	+	-	+	+	+	+	-	+	+	+	-	+	+	+	-
HEMATOPOIETIC SYSTEM																								
BONE MARROW	+	+	+	+	+	+	+	+	+	+	•	+	+	+	+	+	+	+	+	+	+	-	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	+	+	+	+	..	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	+	+	+	+	-	+	+	+	+	+	-	-	+	+	+	+	+	+	+	+	+	-	+	+
CIRCULATORY SYSTEM																								
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																								
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
BILE DUCT ADENOMA																								
NEOPLASTIC NODULE			X																					
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+
RECTUM	+	+	+	N	+	+	+	+	+	N	N	+	N	+	+	+	+	+	+	N	+	+	+	+
FIBROSARCOMA																	X							
URINARY SYSTEM																								
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																								
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOMA, NOS				X		X		X						X		X			X			X	X	X
ACIDOPHIL ADENOMA																								
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CORTICAL ADENOMA																								
PHEOCHROMOCYTOMA		X	X																X		X			
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FOLLICULAR-CELL ADENOMA																	X							
C-CELL ADENOMA					X			X				X												
C-CELL CARCINOMA																							X	
PARATHYROID	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	-	+	+	+	+
ADENOMA, NOS																								X
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	•	+	+	+	+	+
ISLET-CELL ADENOMA																								
REPRODUCTIVE SYSTEM																								
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOCARCINOMA, NOS																								
SARCOMA, NOS																								
FIBROADENOMA		X	X			X	X	X	X					X	X	X		X	X			X		X
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
CARCINOMA,NOS																								
ADENOMA, NOS																								
ADENOSQUAMOUS CARCINOMA																								X
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	•	+	+	+
ENDOMETRIAL STROMAL POLYP										X				X						X			X	
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	•	+	+	+	+	+	+
NERVOUS SYSTEM																								
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALL OTHER SYSTEMS																								
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
SARCOMA, NOS										X														
SARCOMA, NOS, METASTATIC											X													
OSTEOSARCOMA																								
MONOCYTIC LEUKEMIA					X								X		X		X							

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A4. FEMALE RATS: TUMOR PATHOLOGY (CONTINUED) LOW DOSE

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL
WEEKS ON STUDY	106	102	106	106	106	106	106	106	106	106	071	106	086	086	106	089	103	106	111	106	106	088	106	106	106	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
FIBROMA									X			X							X							3
LIPOMA																										1
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALVEOLAR/BRONCHIOLAR CARCINOMA																							X			1
TRACHEA	+	-	-	-	+	+	+	+	+	+	+	+	+	-	-	+	+	+	-	+	-	-	+	+	+	37
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
THYMUS	+	+	+	-	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	43
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
BILE DUCT ADENOMA																								X		1
NEOPLASTIC NODULE																										1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
RECTUM	+	N	+	N	+	N	+	+	+	+	N	+	+	N	+	N	+	+	+	+	+	N	+	N	+	50*
FIBROSARCOMA																										1
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	49
ADENOMA, NOS	X	X	X										X			X	X	X								16
ACIDOPHIL ADENOMA					X																					1
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CORTICAL ADENOMA																								X		1
PHEOCHROMOCYTOMA	X				X		X											X								8
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
FOLLICULAR-CELL ADENOMA																										1
C-CELL ADENOMA			X		X													X						X		7
C-CELL CARCINOMA																										1
PARATHYROID	+	-	-	+	+	+	+	+	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
ADENOMA, NOS																										1
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ISLET-CELL ADENOMA																			X							1
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
ADENOCARCINOMA, NOS	X																									1
SARCOMA, NOS																										1
FIBROADENOMA					X				X			X	X		X					X	X		X		X	23
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
CARCINOMA,NOS												X														1
ADENOMA, NOS																										1
ADENOSQUAMOUS CARCINOMA																										1
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOMETRIAL STROMAL POLYP			X											X						X		X				8
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
SARCOMA, NOS																										1
SARCOMA, NOS, METASTATIC																							X			1
OSTEOSARCOMA																										1
MONOCYTIC LEUKEMIA														X											X	6

* ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A4.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE 2-YEAR STUDY OF ALLYL ISOVALERATE

HIGH DOSE

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	105	105	105	106	106	102	101	106	094	106	089	074	106	106	106	106	105	106	101	106	106	088	084	106	072
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
BASAL-CELL TUMOR													X												
KERATOACANTHOMA																									
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
TRACHEA	+	+	+	+	-	+	+	-	+	+	-	-	-	+	+	+	-	-	-	+	+	-	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	+	+	+	+	+	-	+	+	+	+	-	-	+	+	+	+	+	+	-	+	+	+	+	+	+
THYMOMA		X																							
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
ORAL CAVITY	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
SQUAMOUS CELL PAPILLOMA										X															
SALIVARY GLAND	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
PANCREAS	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	-	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL PAPILLOMA					X																				
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MUCINOUS ADENOCARCINOMA																									
LARGE INTESTINE	+	+	+	+	+	+	+	+	-	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+
ADENOMA, NOS		X				X							X		X			X					X		X
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PHEOCHROMOCYTOMA			X							X															X
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-CELL ADENOMA								X																	
C-CELL CARCINOMA																									
PARATHYROID	+	+	+	-	+	+	+	+	+	+	-	+	-	-	+	+	+	-	+	+	+	+	+	+	+
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FIBROADENOMA						X	X			X					X			X						X	
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
CARCINOMA,NOS				X																					
ADENOMA, NOS																									
VAGINA	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ENDOMETRIAL STROMAL SARCOMA, INVA									X																
UTERUS	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOMETRIAL STROMAL POLYP		X		X					X							X			X		X				
ENDOMETRIAL STROMAL SARCOMA										X															
OVARY	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ASTROCYTOMA																									
MEDULLOBLASTOMA					X																				
SPECIAL SENSE ORGANS																									
ZYMBAL'S GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N
ADENOSQUAMOUS CARCINOMA																						X			
BODY CAVITIES																									
MESENTERY	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
FIBROSARCOMA																									
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																									
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ENDOMETRIAL STROMAL SARCOMA, META									X																
LEUKEMIA,NOS																									
MONOCYTIC LEUKEMIA						X					X	X		X									X		
LEG NOS																									
OSTEOSARCOMA																									

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A4. FEMALE RATS: TUMOR PATHOLOGY (CONTINUED) HIGH DOSE

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL
WEEKS ON STUDY	105	106	106	106	085	096	106	106	096	080	106	067	093	088	012	106	061	093	106	091	106	098	106	096	093	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
SKIN	+	+	+	+	+	N	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	X	+	49*
BASAL-CELL TUMOR																										1
KERATOACANTHOMA																										1
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	49
TRACHEA	+	+	+	+	-	+	+	+	+	-	-	+	+	-	A	+	-	+	+	+	-	-	+	-	+	32
HEMATOPOIETIC SYSTEM																										
BONE MARROW	-	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	47
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	49
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	49
THYMUS	+	+	+	+	+	-	+	+	+	+	+	+	-	+	A	+	+	-	+	+	-	+	-	+	-	39
THYMOMA																										1
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
ORAL CAVITY	N	N	N	N	N	N	N	N	N	N	N	N	N	N	A	N	N	N	N	N	N	N	N	N	N	49*
SQUAMOUS CELL PAPILLOMA																										1
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	-	+	+	A	+	+	+	+	+	+	+	+	+	+	46
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	49
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	49
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	A	N	N	N	N	N	N	N	N	N	N	49*
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	-	+	+	A	+	+	+	+	+	+	+	+	+	+	46
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	-	+	+	A	+	+	+	+	+	+	+	+	+	+	47
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	49
SQUAMOUS CELL PAPILLOMA																										1
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	-	+	+	A	+	+	-	+	+	+	+	+	+	+	46
MUCINOUS ADENOCARCINOMA																					X					1
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	-	+	+	A	+	+	-	+	+	+	+	+	+	+	45
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	49
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	48
ADENOMA, NOS					X	X							X									X	X	X		13
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	49
PHEOCHROMOCYTOMA		X					X															X				6
THYROID	+	+	+	+	+	+	+	+	+	+	-	-	+	-	A	+	+	+	+	+	+	+	+	+	+	46
C-CELL ADENOMA				X			X									X										4
C-CELL CARCINOMA																				X						1
PARATHYROID	+	+	+	+	+	+	+	+	+	-	-	-	-	-	A	+	+	-	-	+	+	+	+	+	+	37
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	49*
FIBROADENOMA	X		X													X	X							X		11
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	A	N	N	N	N	N	N	N	N	N	N	49*
CARCINOMA,NOS																										1
ADENOMA, NOS						X																				1
VAGINA	N	N	N	N	N	N	N	N	N	N	N	N	N	N	A	N	N	N	N	N	N	N	N	N	N	49*
ENDOMETRIAL STROMAL SARCOMA, INVA																										1
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	48
ENDOMETRIAL STROMAL POLYP				X				X	X		X					X	X			X						13
ENDOMETRIAL STROMAL SARCOMA																										1
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	-	+	+	+	+	+	+	+	47
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	49
ASTROCYTOMA										X																1
MEDULLOBLASTOMA																										1
SPECIAL SENSE ORGANS																										
ZYMBAL'S GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	A	N	N	N	N	N	N	N	N	N	N	49*
ADENOSQUAMOUS CARCINOMA																										1
BODY CAVITIES																										
MESENTERY	N	N	N	N	N	N	N	N	N	N	N	N	N	N	A	N	N	N	N	N	N	N	N	N	N	49*
FIBROSARCOMA														X												1
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																									X	1
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	A	N	N	N	N	N	N	N	N	N	N	49*
ENDOMETRIAL STROMAL SARCOMA, META																		X								1
LEUKEMIA,NOS																										1
MONOCYTIC LEUKEMIA	X					X			X																	8
LEG NOS															A											
OSTEOSARCOMA	X																									1

* ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

APPENDIX B

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE ADMINISTERED ALLYL ISOVALERATE IN CORN OIL BY GAVAGE

TABLE B1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE ADMINISTERED ALLYL ISOVALERATE IN CORN OIL BY GAVAGE

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
BASAL-CELL TUMOR	2 (4%)	1 (2%)	
FIBROMA	3 (6%)	1 (2%)	
*SUBCUT TISSUE	(50)	(50)	(50)
SARCOMA, NOS	1 (2%)	2 (4%)	1 (2%)
FIBROSARCOMA	2 (4%)		1 (2%)
RESPIRATORY SYSTEM			
#LUNG	(50)	(50)	(49)
HEPATOCELLULAR CARCINOMA, METAST	3 (6%)	2 (4%)	3 (6%)
ALVEOLAR/BRONCHIOLAR ADENOMA	10 (20%)	5 (10%)	3 (6%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	3 (6%)	1 (2%)	2 (4%)
MESOTHELIOMA, METASTATIC		1 (2%)	
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	1 (2%)	2 (4%)	1 (2%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		2 (4%)	
MALIGNANT LYMPHOMA, MIXED TYPE	3 (6%)	2 (4%)	6 (12%)
#MESENTERIC L. NODE	(50)	(50)	(49)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)
CIRCULATORY SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
HEMANGIOSARCOMA		1 (2%)	

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#SPLEEN	(50)	(50)	(50)
HEMANGIOMA			1 (2%)
HEMANGIOSARCOMA	1 (2%)		
DIGESTIVE SYSTEM			
#LIVER	(50)	(50)	(50)
HEPATOCELLULAR ADENOMA	7 (14%)	8 (16%)	8 (16%)
HEPATOCELLULAR CARCINOMA	18 (36%)	6 (12%)	9 (18%)
#GASTRIC MUCOSA	(50)	(50)	(48)
SQUAMOUS CELL PAPILLOMA		1 (2%)	3 (6%)
#JEJUNUM	(50)	(49)	(48)
ADENOCARCINOMA, NOS		1 (2%)	2 (4%)
#COLON	(50)	(50)	(49)
ADENOCARCINOMA, NOS		1 (2%)	
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#ADRENAL	(49)	(46)	(48)
CORTICAL ADENOMA	1 (2%)		1 (2%)
PHEOCHROMOCYTOMA	4 (8%)	2 (4%)	2 (4%)
PHEOCHROMOCYTOMA, MALIGNANT	1 (2%)	1 (2%)	
#THYROID	(47)	(46)	(49)
FOLLICULAR-CELL ADENOMA	5 (11%)		1 (2%)
REPRODUCTIVE SYSTEM			
#TESTIS	(49)	(50)	(50)
INTERSTITIAL-CELL TUMOR		1 (2%)	
NERVOUS SYSTEM			
NONE			

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
SPECIAL SENSE ORGANS			
*HARDERIAN GLAND	(50)	(50)	(50)
ADENOMA, NOS	4 (8%)	4 (8%)	2 (4%)
*EAR	(50)	(50)	(50)
SARCOMA, NOS			1 (2%)
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*MEDIASTINUM	(50)	(50)	(50)
ALVEOLAR/BRONCHIOLAR CA, INVASIV	1 (2%)		
*MESENTERY	(50)	(50)	(50)
MESOTHELIOMA, MALIGNANT		1 (2%)	
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
PHEOCHROMOCYTOMA, METASTATIC	1 (2%)		
SARCOMA, NOS	1 (2%)		1 (2%)
NEURILEMOMA	1 (2%)	1 (2%)	
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	11	10	11
MORIBUND SACRIFICE	8	7	2
SCHEDULED SACRIFICE	3		
TERMINAL SACRIFICE	26	31	31
ACCIDENTALLY KILLED, NOS	2	2	6
ANIMAL MISSING			
ANIMAL MISSEXED			
OTHER CASES			

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	36	33	34
TOTAL PRIMARY TUMORS	68	44	46
TOTAL ANIMALS WITH BENIGN TUMORS	25	17	19
TOTAL BENIGN TUMORS	37	24	21
TOTAL ANIMALS WITH MALIGNANT TUMORS	24	20	23
TOTAL MALIGNANT TUMORS	31	20	25
TOTAL ANIMALS WITH SECONDARY TUMORS#	4	3	3
TOTAL SECONDARY TUMORS	5	3	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 B2.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE ADMINISTERED ALLYL ISOVALERATE IN CORN OIL BY GAVAGE

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE	(50)	(50)	(50)
SARCOMA, NOS	1 (2%)		1 (2%)
FIBROSARCOMA	1 (2%)		
RESPIRATORY SYSTEM			
#LUNG	(50)	(49)	(50)
ALVEOLAR/BRONCHIOLAR ADENOMA	2 (4%)	4 (8%)	2 (4%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	2 (4%)		1 (2%)
OSTEOSARCOMA, METASTATIC	1 (2%)		
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	4 (8%)	5 (10%)	4 (8%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)	4 (8%)
MALIGNANT LYMPHOMA, MIXED TYPE	6 (12%)	5 (10%)	8 (16%)
#SPLEEN	(50)	(50)	(50)
MALIGNANT LYMPHOMA, MIXED TYPE			2 (4%)
#LUNG	(50)	(49)	(50)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	1 (2%)		
CIRCULATORY SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
HEMANGIOSARCOMA			1 (2%)
#SPLEEN	(50)	(50)	(50)
HEMANGIOSARCOMA		1 (2%)	1 (2%)

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
#LIVER	(50)	(50)	(50)
HEPATOCELLULAR ADENOMA	2 (4%)		1 (2%)
HEPATOCELLULAR CARCINOMA	1 (2%)		
#GASTRIC MUCOSA	(50)	(50)	(50)
SQUAMOUS CELL PAPILLOMA	1 (2%)		2 (4%)
ADENOMA, NOS	1 (2%)		
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#PITUITARY	(43)	(43)	(44)
ADENOMA, NOS	11 (26%)	2 (5%)	7 (16%)
#ADRENAL	(50)	(46	(47)
CORTICAL ADENOMA	1 (2%)		2 (4%)
PHEOCHROMOCYTOMA			1 (2%)
#THYROID	(49)	(48	(48)
FOLLICULAR-CELL ADENOMA	3 (6%)	2 (4%)	2 (4%)
FOLLICULAR-CELL CARCINOMA	1 (2%)		
#PANCREATIC ISLETS	(47)	(47)	(48)
ISLET-CELL ADENOMA		1 (2%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
ADENOMA, NOS	1 (2%)		
ADENOCARCINOMA, NOS	2 (4%)	3 (6%)	2 (4%)
#UTERUS	(50)	(50)	(50)
ENDOMETRIAL STROMAL POLYP	1 (2%)	1 (2%)	1 (2%)
ENDOMETRIAL STROMAL SARCOMA	1 (2%)		
NERVOUS SYSTEM			
NONE			

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
SPECIAL SENSE ORGANS			
*HARDERIAN GLAND	(50)	(50)	(50)
ADENOMA, NOS	1 (2%)	1 (2%)	
MUSCULOSKELETAL SYSTEM			
*BONE	(50)	(50)	(50)
OSTEOSARCOMA	1 (2%)		
*FEMUR	(50)	(50)	(50)
OSTEOSARCOMA		1 (2%)	
BODY CAVITIES			
*MESENTERY	(50)	(50)	(50)
NEURILEMOMA	1 (2%)		
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
SARCOMA, NOS		1 (2%)	
ENDOMETRIAL STROMAL SARCOMA, MET	1 (2%)		
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	15	27	20
MORIBUND SACRIFICE	4	6	5
SCHEDULED SACRIFICE			
TERMINAL SACRIFICE	31	16	24
ACCIDENTALLY KILLED, NOS		1	1
ANIMAL MISSING			
ANIMAL MISSEXED			
OTHER CASES			

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	31	20	30
TOTAL PRIMARY TUMORS	46	28	42
TOTAL ANIMALS WITH BENIGN TUMORS	18	9	15
TOTAL BENIGN TUMORS	25	11	18
TOTAL ANIMALS WITH MALIGNANT TUMORS	20	16	24
TOTAL MALIGNANT TUMORS	21	17	24
TOTAL ANIMALS WITH SECONDARY TUMORS#	2		
TOTAL SECONDARY TUMORS	2		
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 B3.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE 2-YEAR STUDY OF ALLYL ISOVALERATE

VEHICLE CONTROL

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	105	105	105	071	106	103	103	106	087	106	079	064	106	103	106	106	106	081	106	106	099	105	106	106	106
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
BASAL-CELL TUMOR																									
FIBROMA					X																			X	
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SARCOMA, NOS								X																	
FIBROSARCOMA												X													
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR CARCINOMA, METASTA											X									X					
ALVEOLAR/BRONCHIOLAR ADENOMA		X								X						X		X	X			X		X	X
ALVEOLAR/BRONCHIOLAR CARCINOMA											X														
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMANGIOSARCOMA																									
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	+	+	-	+	+	+	+	+	+	-	+	-	+	+	-	+	+	+	+	+	+	+	+	-	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR ADENOMA	X							X															X	X	
HEPATOCELLULAR CARCINOMA	X									X	X		X							X		X	X		X
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	+	+	+	N	+	N	+	N	+	+	N	+	+	+	+	+	+	N	N	+	+
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	-	-	+	+	+	-	+	+	+	+	+	-	+	+
ADRENAL	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CORTICAL ADENOMA																									
PHEOCHROMOCYTOMA	X																							X	
PHEOCHROMOCYTOMA, MALIGNANT																									
THYROID	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FOLLICULAR-CELL ADENOMA	X		X																						
PARATHYROID	+	+	+	+	+	+	-	+	-	-	+	+	+	-	+	-	+	+	+	+	+	-	+	+	+
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
HARDERIAN GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ADENOMA, NOS		X						X																	X
BODY CAVITIES																									
MEDIASTINUM	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ALVEOLAR/BRONCHIOLAR CA, INVASIVE											X														
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
PHEOCHROMOCYTOMA, METASTATIC																									
SARCOMA, NOS																									
NEURILEMOMA									X																
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE																									
MALIGNANT LYMPHOMA, MIXED TYPE																									

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED

: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B3. MALE MICE: TUMOR PATHOLOGY (CONTINUED) VEHICLE CONTROL

ANIMAL NUMBER	026	027	028	029	031	033	033	033	033	035	035	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL
WEEKS ON STUDY	088	100	106	092	106	107	107	097	107	107	007	007	007	007	094	084	054	054	107	072	092	106	071	096	107	107	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
BASAL-CELL TUMOR							X																		X	2
FIBROMA									X																	3
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
SARCOMA, NOS																										1
FIBROSARCOMA	X																									2
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEPATOCELLULAR CARCINOMA, METASTA																										3
ALVEOLAR/BRONCHIOLAR ADENOMA																	X								X	10
ALVEOLAR/BRONCHIOLAR CARCINOMA	X						X																			3
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	•	+	+	+	+	48
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMANGIOSARCOMA								X																		1
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
THYMUS	+	+	+	−	−	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	−	+	+	+	−	39
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEPATOCELLULAR ADENOMA									X								X							X		7
HEPATOCELLULAR CARCINOMA	X					X	X	X					X	X	X							X			X	18
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	N	+	+	+	N	+	N	+	N	+	+	+	+	+	+	N	N	+	+	+	N	N	+	+	+	50*
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	49
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	−	+	+	−	−	+	−	+	+	+	41
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
CORTICAL ADENOMA																							X			1
PHEOCHROMOCYTOMA																						X				4
PHEOCHROMOCYTOMA, MALIGNANT									X																X	1
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	−	+	+	+	+	+	+	47
FOLLICULAR-CELL ADENOMA						X		X																	X	5
PARATHYROID	+	+	+	+	−	+	+	−	−	+	−	+	+	+	−	−	+	+	−	+	+	+	+	+	+	37
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	49
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	49
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
HARDERIAN GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
ADENOMA, NOS			X																							4
BODY CAVITIES																										
MEDIASTINUM	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
ALVEOLAR/BRONCHIOLAR CA, INVASIVE																										1
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
PHEOCHROMOCYTOMA, METASTATIC									X																	1
SARCOMA, NOS																					X					1
NEURILEMOMA																										1
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE			X																							1
MALIGNANT LYMPHOMA, MIXED TYPE		X					X																		X	3

* ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
−: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION

: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B3.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE 2-YEAR STUDY OF ALLYL ISOVALERATE

LOW DOSE

ANIMAL NUMBER	0011	0012	0013	0014	0015	0016	0017	0018	0019	0110	0111	0112	0113	0114	0115	0116	0117	0118	0119	0120	0121	0122	0123	0124	0125
WEEKS ON STUDY	106	096	022	061	061	021	061	061	061	061	061	061	092	090	012	061	061	061	061	063	034	061	056	061	098
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
BASAL-CELL TUMOR					X																				
FIBROMA																									
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SARCOMA, NOS		X																							
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR CARCINOMA, METASTA																									
ALVEOLAR/BRONCHIOLAR ADENOMA				X					X					X											
ALVEOLAR/BRONCHIOLAR CARCINOMA																							X		
MESOTHELIOMA, METASTATIC																									
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	+	+	+	+	+	+	-	+	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR ADENOMA	X							Y	X							X		X		X				X	
HEPATOCELLULAR CARCINOMA												X													
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	N	+	+	+	N	+	+	+	+	+
PANCREAS	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL PAPILLOMA																									
SMALL INTESTINE	•	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+
ADENOCARCINOMA, NOS																									
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOCARCINOMA, NOS													X												
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	-	+	+	+	+
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	-	+	+	+	+	+	+	+	+	+
PHEOCHROMOCYTOMA	X				X																				
PHEOCHROMOCYTOMA, MALIGNANT							X																		
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+
PARATHYROID	+	+	+	+	+	+	-	-	-	-	+	-	-	-	-	-	-	-	-	+	+	-	-	-	-
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
INTERSTITIAL-CELL TUMOR																									
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
HARDERIAN GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ADENOMA, NOS													X	X											
BODY CAVITIES																									
MESENTERY	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
MESOTHELIOMA, MALIGNANT																									
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
HEMANGIOSARCOMA																									
NEURILEMOMA																									
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE																									
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																									
MALIGNANT LYMPHOMA, MIXED TYPE										X															X

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED

: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B3. MALE MICE: TUMOR PATHOLOGY (CONTINUED) LOW DOSE

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL
WEEKS ON STUDY	106	106	105	022	090	105	106	097	023	099	106	106	106	106	091	106	106	106	074	106	106	106	063	106	075	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
SKIN	+	+	+	N	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
BASAL-CELL TUMOR																										1
FIBROMA																								X		1
SUBCUTANEOUS TISSUE	+	+	+	N	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
SARCOMA, NOS											X															2
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEPATOCELLULAR CARCINOMA, METASTA					X														X							2
ALVEOLAR/BRONCHIOLAR ADENOMA						X															X					5
ALVEOLAR/BRONCHIOLAR CARCINOMA																										1
MESOTHELIOMA, METASTATIC																							X			1
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	-	48
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	49
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	50
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
THYMUS	+	+	-	+	-	+	+	-	+	+	+	+	-	+	+	+	+	+	+	-	+	+	+	+	-	41
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEPATOCELLULAR ADENOMA																				X					X	8
HEPATOCELLULAR CARCINOMA					X			X									X		X							6
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	50*
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	48
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	-	48
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SQUAMOUS CELL PAPILLOMA		X																								1
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ADENOCARCINOMA, NOS																				X						1
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ADENOCARCINOMA, NOS																										1
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	-	+	+	-	+	-	+	-	+	+	+	-	+	+	-	+	+	-	+	+	-	40
ADRENAL	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	-	+	+	+	+	+	46
PHEOCHROMOCYTOMA																										2
PHEOCHROMOCYTOMA, MALIGNANT																										1
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	-	+	+	-	46
PARATHYROID	-	-	-	+	+	+	+	+	+	-	+	+	-	+	-	-	+	+	-	-	-	-	-	-	-	20
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	50*
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
INTERSTITIAL-CELL TUMOR						X																				1
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
HARDERIAN GLAND	N	N	N	N	N	N	N	N	N	N	N	N	X	N	N	N	N	N	N	N	X	N	N	N	N	50*
ADENOMA, NOS																										4
BODY CAVITIES																										
MESENTERY	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	X	N	50*
MESOTHELIOMA, MALIGNANT																										1
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
HEMANGIOSARCOMA		X																								1
NEURILEMOMA						X																				1
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE																		X							X	2
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			X							X																2
MALIGNANT LYMPHOMA, MIXED TYPE																										2

* ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B3.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE 2-YEAR STUDY OF ALLYL ISOVALERATE

HIGH DOSE

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	105	105	118	105	105	105	105	073	105	091	105	105	121	121	090	105	105	105	096	091	106	101	106	106	106
INTEGUMENTARY SYSTEM																									
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SARCOMA, NOS																									
FIBROSARCOMA																									
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR CARCINOMA, METASTA					X					X					X										
ALVEOLAR/BRONCHIOLAR ADENOMA																				X	X				
ALVEOLAR/BRONCHIOLAR CARCINOMA																									
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMANGIOMA						X																			
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																				X					
THYMUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	-	+	-	+	+	+	-	+	-
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR ADENOMA					X			X			X														X
HEPATOCELLULAR CARCINOMA					X			X	X	X		X			X										
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	+	+	N	+	+	N	+	+	+	N	+	+	+	N	+	+	N	N	+	+	+	+	+	+	+
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL PAPILLOMA																	X			X	X				
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOCARCINOMA, NOS											X														X
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	-	-	+	-	+	+	+	+	-	+	+	+	+	-	+	+	+	+	-
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CORTICAL ADENOMA																									
PHEOCHROMOCYTOMA																									
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FOLLICULAR-CELL ADENOMA																							X		
PARATHYROID	-	-	-	-	+	+	+	+	+	+	-	+	-	+	+	-	-	+	+	+	+	-	+	+	-
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
HARDERIAN GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ADENOMA, NOS																				X					
EAR	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
SARCOMA, NOS																									
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
SARCOMA, NOS																						X			
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE																									
MALIGNANT LYMPHOMA, MIXED TYPE																	X								

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B3. MALE MICE: TUMOR PATHOLOGY (CONTINUED) HIGH DOSE

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL
WEEKS ON STUDY	106	106	106	023	231	106	105	141	100	109	106	106	106	106	106	078	106	106	086	106	106	106	080	093	093	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+ X	+	+	+	+	+	+	+	+	+	+	50*
SARCOMA, NOS																										1
FIBROSARCOMA																								X		1
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	49
HEPATOCELLULAR CARCINOMA, METASTA																										3
ALVEOLAR/BRONCHIOLAR ADENOMA													X													3
ALVEOLAR/BRONCHIOLAR CARCINOMA																				X				X		2
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMANGIOMA																										1
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																										1
THYMUS	+	-	+	+	+	+	+	-	+	+	+	-	+	+	+	-	+	+	-	+	+	+	-	-	+	37
CIRCULATORY SYSTEM																										
HEART	+	•	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEPATOCELLULAR ADENOMA		X				X					X											X				8
HEPATOCELLULAR CARCINOMA												X		X					X							9
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	+	+	+	N	+	+	+	+	N	N	+	N	+	+	+	+	N	N	+	N	+	+	+	+	N	50*
PANCREAS	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	48
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	49
STOMACH	+	+	+	+	+	+	+	+	+	+	+	•	+	+	+	+	+	+	+	+	+	+	-	+	-	48
SQUAMOUS CELL PAPILLOMA																										3
SMALL INTESTINE	+	+	+	+	+	+	•	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	-	48
ADENOCARCINOMA, NOS																										2
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	•	•	+	+	-	+	+	49
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	•	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
PITUITARY	+	-	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	41
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	-	+	+	48
CORTICAL ADENOMA							X																			1
PHEOCHROMOCYTOMA									X									X								2
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	49
FOLLICULAR-CELL ADENOMA																										1
PARATHYROID	+	-	-	-	+	-	+	+	+	+	+	+	+	+	+	+	+	-	-	+	+	+	+	+	+	34
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
HARDERIAN GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
ADENOMA, NOS							X																			2
EAR	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	50*
SARCOMA, NOS														X												1
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
SARCOMA, NOS																										1
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE																								X		1
MALIGNANT LYMPHOMA, MIXED TYPE			X													X	X		X		X					6

* ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION

: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B4.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE 2-YEAR STUDY OF ALLYL ISOVALERATE

VEHICLE CONTROL

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	066	106	075	106	061	062	035	061	086	086	086	088	080	077	077	077	077	077	077	071	013	077	077	081	104
INTEGUMENTARY SYSTEM																									
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SARCOMA, NOS																									
FIBROSARCOMA																								X	
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALVEOLAR/BRONCHIOLAR ADENOMA																									
ALVEOLAR/BRONCHIOLAR CARCINOMA																									
OSTEOSARCOMA, METASTATIC												X													
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE			X																						
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	-	+	+	+	+	-
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR ADENOMA													X												
HEPATOCELLULAR CARCINOMA																									
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	+	N	N	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-
ESOPHAGUS	+	+	+	+	+	-	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL PAPILLOMA																									
ADENOMA, NOS																									
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-
ADENOMA, NOS		X			X						X				X		X	X		X					
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CORTICAL ADENOMA																									
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+
FOLLICULAR-CELL ADENOMA				X							X									X					
FOLLICULAR-CELL CARCINOMA																									
PARATHYROID	-	+	+	+	+	+	+	+	+	+	-	+	+	-	+	+	+	+	+	-	-	+	+	-	+
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	+	+	N	+	N	N	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOMA, NOS																									
ADENOCARCINOMA, NOS																									X
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOMETRIAL STROMAL POLYP																				X					
ENDOMETRIAL STROMAL SARCOMA																									
OVARY	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
HARDERIAN GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ADENOMA, NOS				X																					
MUSCULOSKELETAL SYSTEM																									
BONE	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
OSTEOSARCOMA												X													
BODY CAVITIES																									
MESENTERY	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
NEURILEMOMA								X																	
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ENDOMETRIAL STROMAL SARCOMA, META																				X					
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	X				X	X									X			X							
MALIGNANT LYMPHOMA, MIXED TYPE								X		X															

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B4. FEMALE MICE: TUMOR PATHOLOGY (CONTINUED) VEHICLE CONTROL

ANIMAL NUMBER	02 16	02 17	02 28	02 29	03 30	03 31	03 32	03 33	03 34	03 35	03 36	03 37	03 38	03 39	04 01	04 11	04 23	04 43	04 44	04 45	04 46	04 47	04 48	04 49	05 00	TOTAL
WEEKS ON STUDY	10 7	10 7	10 7	10 7	08 9	09 7	07 9	11 7	08 0	10 7	06 7	10 7	10 7	06 7	07 1	07 1	09 8	10 7	10 7	10 7	06 6	09 9	09 4	10 5	11 7	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	50*
SARCOMA, NOS																		X								1
FIBROSARCOMA																										1
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALVEOLAR/BRONCHIOLAR ADENOMA					X			X																		2
ALVEOLAR/BRONCHIOLAR CARCINOMA	X															X										2
OSTEOSARCOMA, METASTATIC																										1
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE																										1
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
THYMUS	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEPATOCELLULAR ADENOMA								X																		2
HEPATOCELLULAR CARCINOMA						X																				1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	+	+	+	+	N	+	+	+	+	N	N	+	+	+	+	+	+	+	+	+	+	50*
PANCREAS	+	+	+	+	-	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SQUAMOUS CELL PAPILLOMA				X																						1
ADENOMA, NOS	X																									1
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	-	+	+	+	-	+	+	+	+	+	+	+	+	+	+	47
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
PITUITARY	+	-	+	+	+	+	+	+	+	-	+	+	+	-	+	+	-	+	+	+	-	+	+	+	+	43
ADENOMA, NOS	X			X				X					X													11
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CORTICAL ADENOMA												X														1
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
FOLLICULAR-CELL ADENOMA								X																		3
FOLLICULAR-CELL CARCINOMA																										1
PARATHYROID	+	+	+	+	+	+	+	+	+	-	+	+	+	-	-	+	+	+	+	+	+	+	+	+	+	41
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	50*
ADENOMA, NOS																								X		1
ADENOCARCINOMA, NOS								X																		2
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOMETRIAL STROMAL POLYP																X										1
ENDOMETRIAL STROMAL SARCOMA																										1
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
HARDERIAN GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
ADENOMA, NOS																										1
MUSCULOSKELETAL SYSTEM																										
BONE	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
OSTEOSARCOMA																										1
BODY CAVITIES																										
MESENTERY	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
NEURILEMOMA																										1
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
ENDOMETRIAL STROMAL SARCOMA, META																										1
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE																			X				X		X	4
MALIGNANT LYMPHOMA, MIXED TYPE																										6

* ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B4.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE 2-YEAR STUDY OF ALLYL ISOVALERATE

LOW DOSE

ANIMAL NUMBER	0011	0012	0013	0014	0015	0016	0017	0018	0019	0020	0021	0022	0023	0024	0025	0026	0027	0028	0029	0030	0031	0032	0033	0034	0035
WEEKS ON STUDY	089	080	106	106	101	084	106	103	106	076	022	011	106	105	060	106	075	040	106	106	097	106	101	106	102
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+
ALVEOLAR/BRONCHIOLAR ADENOMA			X													X									X
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMANGIOSARCOMA													X												
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	+	-	+	+	+	-	+	-	+	+	+	+	-	-	-	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+
PANCREAS	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	-	+	+	+	+	+	+	+	+	-	+	-	+	+	+	+	+	+	+	+
ADENOMA, NOS																									
ADRENAL	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+
FOLLICULAR-CELL ADENOMA																X									
PARATHYROID	+	+	+	+	-	+	-	-	+	+	+	-	+	-	+	-	+	-	+	-	-	+	+	+	+
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ISLET-CELL ADENOMA																									
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	N	+	+	+	+	+	+	+	+	+	N	+	+	+	N	+	+	+	+	+	+	+	N	+
ADENOCARCINOMA, NOS													X										X		
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOMETRIAL STROMAL POLYP																									
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
HARDERIAN GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ADENOMA, NOS													X												
MUSCULOSKELETAL SYSTEM																									
BONE	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
OSTEOSARCOMA																									X
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
SARCOMA, NOS																									
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	X		X				X		X								X								
MALIG.LYMPHOMA, HISTIOCYTIC TYPE														X											
MALIGNANT LYMPHOMA, MIXED TYPE												X												X	

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B4. FEMALE MICE: TUMOR PATHOLOGY (CONTINUED) LOW DOSE

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL
WEEKS ON STUDY	097	096	016	022	011	079	106	106	066	078	090	090	033	084	106	094	061	033	010	106	099	078	091	010	074	TISSUES TUMORS
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ALVEOLAR/BRONCHIOLAR ADENOMA												X														4
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMANGIOSARCOMA																										1
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
THYMUS	+	+	+	+	+	–	+	–	–	+	+	+	+	+	–	+	–	+	+	+	+	+	+	+	+	39
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	–	+	+	+	+	46
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	+	N	+	N	+	+	+	+	+	N	+	N	+	+	N	+	+	+	+	+	+	N	+	+	+	50*
PANCREAS	+	–	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	47
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	–	+	+	+	+	+	+	–	+	+	46
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	48
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
PITUITARY	+	+	–	+	–	+	+	+	+	+	+	+	+	–	+	+	–	+	+	+	+	+	+	+	+	43
ADENOMA, NOS									X													X				2
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+	46
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	48
FOLLICULAR-CELL ADENOMA																								X		2
PARATHYROID	+	+	+	+	+	+	–	–	–	+	+	+	–	+	+	–	+	–	+	+	–	+	–	–	–	31
PANCREATIC ISLETS	+	–	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	47
ISLET-CELL ADENOMA									X																	1
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	50*
ADENOCARCINOMA, NOS																								X		3
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOMETRIAL STROMAL POLYP	X																									1
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
HARDERIAN GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
ADENOMA, NOS																										1
MUSCULOSKELETAL SYSTEM																										
BONE	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
OSTEOSARCOMA																										1
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
SARCOMA, NOS																						X				1
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE																										5
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																										1
MALIGNANT LYMPHOMA, MIXED TYPE			X				X											X								5

* ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
–: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B4.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE 2-YEAR STUDY OF ALLYL ISOVALERATE

HIGH DOSE

ANIMAL NUMBER	0001	0002	0003	0004	0005	0006	0007	0008	0009	0010	0011	0012	0013	0014	0015	0016	0017	0018	0019	0020	0021	0022	0023	0024	0025
WEEKS ON STUDY	104	105	120	105	094	105	105	106	106	106	098	106	091	090	106	086	119	104	093	101	082	086	101	079	091
INTEGUMENTARY SYSTEM																									
SUBCUTANEOUS TISSUE	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SARCOMA, NOS													X												
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALVEOLAR/BRONCHIOLAR ADENOMA																X		X							
ALVEOLAR/BRONCHIOLAR CARCINOMA				X																					
TRACHEA	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMANGIOSARCOMA											X														
MALIGNANT LYMPHOMA, MIXED TYPE																									
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	-	+	-	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR ADENOMA																								X	
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	N	+	N	N	N	+	+	+
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL PAPILLOMA							X																		
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	-	-	+	-
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	-	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	-	-	+	-	-
ADENOMA, NOS		X					X																X		
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	-	+	+	+	+
CORTICAL ADENOMA																									
PHEOCHROMOCYTOMA							X																		
THYROID	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FOLLICULAR-CELL ADENOMA									X																
PARATHYROID	-	+	+	+	-	+	+	+	+	+	+	+	-	-	+	+	-	-	+	+	+	+	+	+	-
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	+	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOCARCINOMA, NOS									X																
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOMETRIAL STROMAL POLYP									X																
OVARY	+	+	+	+	+	+	-	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
HEMANGIOSARCOMA													X												
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE										X						X							X		
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																		X	X						
MALIGNANT LYMPHOMA, MIXED TYPE		X																		X					

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION

: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: *NO NECROPSY PERFORMED*

TABLE B4. FEMALE MICE: TUMOR PATHOLOGY (CONTINUED) HIGH DOSE

ANIMAL NUMBER	026	027	028	029	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL
WEEKS ON STUDY	067	021	016	098	016	012	016	016	093	011	015	086	087	087	103	016	017	106	106	106	105	106	106	095	106	TISSUES TUMORS
INTEGUMENTARY SYSTEM																									
SUBCUTANEOUS TISSUE SARCOMA, NOS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50* 1
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI ALVEOLAR/BRONCHIOLAR ADENOMA ALVEOLAR/BRONCHIOLAR CARCINOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50 2 1
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	•	+	+	•	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPLEEN HEMANGIOSARCOMA MALIGNANT LYMPHOMA, MIXED TYPE	+	+	+	+	+ X	+	+	+	+	+	+	+	+	+	+	+	+	+	+ X	+	+	+	+	+	50 1 2
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
THYMUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	47
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	•	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	47
LIVER HEPATOCELLULAR ADENOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50 1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	+	N	+	+	+	+	+	N	N	+	+	+	+	+	+	+	+	+	+	+	50*
PANCREAS	-	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
STOMACH SQUAMOUS CELL PAPILLOMA	+	+	+ X	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50 2
SMALL INTESTINE	+	+	+	•	+	+	+	+	+	+	+	+	+	•	+	+	+	+	+	+	+	+	-	+	45
LARGE INTESTINE	+	+	•	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	47
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																									
PITUITARY ADENOMA, NOS	+	+	+ X	+	+ X	-	+	+	+	+	+	+	+	+	+	+	+	+ X	+	+	+	+ X	+	+	44 7
ADRENAL CORTICAL ADENOMA PHEOCHROMOCYTOMA	+	+	+	+	+	+	+	+ X	+	+	+	-	+	+	+	+	+	+	+ X	+	+	+	+	+	47 2 1
THYROID FOLLICULAR-CELL ADENOMA	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+ X	48 2
PARATHYROID	+	-	+	-	+	+	+	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+	-	+	38
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND ADENOCARCINOMA, NOS	+	+	+ X	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50* 2
UTERUS ENDOMETRIAL STROMAL POLYP	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50 1
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS HEMANGIOSARCOMA MALIG.LYMPHOMA, LYMPHOCYTIC TYPE MALIG.LYMPHOMA, HISTIOCYTIC TYPE MALIGNANT LYMPHOMA, MIXED TYPE	N	N	N	N X	N	N X	N	N	N	N X	N	N X	N	N	N X	N	N	N X	N	N	N	N X	N X	N	50* 1 4 4 8

* ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: *NO NECROPSY PERFORMED*

Allyl Isovalerate

APPENDIX C

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS ADMINISTERED ALLYL ISOVALERATE IN CORN OIL BY GAVAGE

TABLE C1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS ADMINISTERED ALLYL ISOVALERATE IN CORN OIL BY GAVAGE

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
EPIDERMAL INCLUSION CYST			1 (2%)
ULCER, NOS		1 (2%)	
INFLAMMATION, CHRONIC FOCAL			1 (2%)
*SUBCUT TISSUE	(50)	(50)	(50)
CYST, NOS		1 (2%)	
EDEMA, NOS		1 (2%)	
ULCER, NOS	1 (2%)		
INFLAMMATION, FOCAL			1 (2%)
GRANULATION, TISSUE			1 (2%)
RESPIRATORY SYSTEM			
*NOSE	(50)	(50)	(50)
INFLAMMATION, SUPPURATIVE	1 (2%)		
HYPERKERATOSIS		1 (2%)	
ACANTHOSIS		1 (2%)	
#LUNG	(50)	(50)	(49)
ASPIRATION, FOREIGN BODY	3 (6%)	6 (12%)	3 (6%)
CONGESTION, NOS	2 (4%)	5 (10%)	3 (6%)
EDEMA, NOS		1 (2%)	
EDEMA, INTERSTITIAL			2 (4%)
HEMORRHAGE			1 (2%)
PNEUMONIA, ASPIRATION		1 (2%)	
INFLAMMATION, SUPPURATIVE	1 (2%)		
PNEUMONIA, CHRONIC MURINE	1 (2%)		
INFLAMMATION, CHRONIC SUPPURATIV			1 (2%)
ABSCESS, CHRONIC			1 (2%)
INFLAMMATION, FOCAL GRANULOMATOU			1 (2%)
HYPERPLASIA, ALVEOLAR EPITHELIUM	2 (4%)	2 (4%)	1 (2%)

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
HISTIOCYTOSIS			2 (4%)
#LUNG/ALVEOLI	(50)	(50)	(49)
HYPERPLASIA, ADENOMATOUS	1 (2%)	1 (2%)	
HISTIOCYTOSIS	3 (6%)	5 (10%)	3 (6%)
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(50)	(50)	(50)
ATROPHY, EXHAUSTION		1 (2%)	
MYELOFIBROSIS		1 (2%)	
HYPERPLASIA, HEMATOPOIETIC			1 (2%)
HYPOPLASIA, HEMATOPOIETIC			1 (2%)
#SPLEEN	(50)	(49)	(50)
HEMATOMA, NOS		1 (2%)	
FIBROSIS			1 (2%)
FIBROSIS, FOCAL			1 (2%)
DEGENERATION, CYSTIC	1 (2%)		
INFARCT, NOS		1 (2%)	1 (2%)
METAMORPHOSIS FATTY			1 (2%)
ATROPHY, NOS			1 (2%)
HEMATOPOIESIS	3 (6%)	1 (2%)	3 (6%)
#MANDIBULAR L. NODE	(50)	(50)	(50)
HYPERPLASIA, NOS	1 (2%)		
#MESENTERIC L. NODE	(50)	(50)	(50)
HYPERPLASIA, NOS			1 (2%)
ANGIECTASIS			1 (2%)
#LUNG	(50)	(50)	(49)
LEUKOCYTOSIS, NOS	1 (2%)		4 (8%)
#LIVER	(50)	(50)	(50)
LEUKOCYTOSIS, NOS			5 (10%)
*MESENTERY	(50)	(50)	(50)
MASTOCYTOSIS	1 (2%)		
#THYMUS	(44)	(36)	(39)
HYPERPLASIA, LYMPHOID		1 (3%)	
CIRCULATORY SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
EMBOLUS, FOREIGN BODY	1 (2%)		1 (2%)

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
PERIARTERITIS			1 (2%)
#LUNG	(50)	(50)	(49)
THROMBOSIS, NOS		1 (2%)	
#MYOCARDIUM	(50)	(49)	(50)
INFLAMMATION, FOCAL	1 (2%)		
INFLAMMATION, CHRONIC FOCAL		1 (2%)	1 (2%)
FIBROSIS, FOCAL	6 (12%)	8 (16%)	2 (4%)
*CORONARY ARTERY	(50)	(50)	(50)
PERIARTERITIS	1 (2%)		
*MESENTERIC ARTERY	(50)	(50)	(50)
HYPERTROPHY, NOS		1 (2%)	
#LIVER	(50)	(50)	(50)
EMBOLUS, FOREIGN BODY	1 (2%)	2 (4%)	
#ADRENAL	(50)	(50)	(50)
THROMBOSIS, NOS	1 (2%)		1 (2%)
DIGESTIVE SYSTEM			
#PAROTID GLAND	(49)	(48)	(48)
INFLAMMATION, NOS			1 (2%)
#LIVER	(50)	(50)	(50)
DEFORMITY, NOS	2 (4%)		2 (4%)
CONGESTION, NOS	1 (2%)	2 (4%)	2 (4%)
PETECHIA			1 (2%)
INFLAMMATION, NECROTIZING	1 (2%)		
INFLAMMATION, FOCAL GRANULOMATOU		1 (2%)	
CHOLANGIOFIBROSIS		1 (2%)	5 (10%)
CIRRHOSIS, NOS		2 (4%)	5 (10%)
DEGENERATION, CYSTIC		2 (4%)	
NECROSIS, FOCAL		2 (4%)	7 (14%)
METAMORPHOSIS FATTY	1 (2%)	2 (4%)	8 (16%)
PIGMENTATION, NOS			1 (2%)
CYTOPLASMIC VACUOLIZATION	15 (30%)	9 (18%)	22 (44%)
BASOPHILIC CYTO CHANGE	17 (34%)	1 (2%)	9 (18%)
FOCAL CELLULAR CHANGE			2 (4%)
REGENERATION, NOS		1 (2%)	2 (4%)
NODULAR REGENERATION		5 (10%)	8 (16%)

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#PORTAL TRACT	(50)	(50)	(50)
FIBROSIS		1 (2%)	
#LIVER/CENTRILOBULAR	(50)	(50)	(50)
CONGESTION, NOS	1 (2%)	1 (2%)	
NECROSIS, NOS	1 (2%)	4 (8%)	2 (4%)
NECROSIS, FOCAL	1 (2%)		
METAMORPHOSIS FATTY	2 (4%)		
ATROPHY, NOS	1 (2%)	1 (2%)	1 (2%)
#BILE DUCT	(50)	(50)	(50)
HYPERPLASIA, NOS	46 (92%)	32 (64%)	45 (90%)
HYPERPLASIA, FOCAL		1 (2%)	
#PANCREAS	(50)	(50)	(50)
CYSTIC DUCTS	1 (2%)		
FIBROSIS, FOCAL		1 (2%)	
DEGENERATION, CYSTIC			2 (4%)
ATROPHY, NOS			2 (4%)
ATROPHY, FOCAL	6 (12%)	5 (10%)	9 (18%)
#PANCREATIC ACINUS	(50)	(50)	(50)
ATROPHY, FOCAL			2 (4%)
HYPERPLASIA, FOCAL	1 (2%)	2 (4%)	1 (2%)
#ESOPHAGUS	(50)	(46)	(46)
INFLAMMATION, CHRONIC	1 (2%)		
#STOMACH	(50)	(50)	(50)
HYPERPLASIA, EPITHELIAL		2 (4%)	2 (4%)
#GASTRIC MUCOSA	(50)	(50)	(50)
INFLAMMATION, NOS			2 (4%)
ULCER, NOS	1 (2%)		4 (8%)
ULCER, PERFORATED		1 (2%)	
#GASTRIC SUBMUCOSA	(50)	(50)	(50)
EDEMA, NOS			1 (2%)
#SMALL INTESTINE	(50)	(50)	(49)
DIVERTICULUM			1 (2%)
#COLON	(50)	(50)	(50)
DIVERTICULUM	1 (2%)		

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
INFLAMMATION, HEMORRHAGIC			1 (2%)
PARASITISM		1 (2%)	
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
HYDRONEPHROSIS			1 (2%)
CYST, NOS		1 (2%)	
INFLAMMATION, SUPPURATIVE		2 (4%)	1 (2%)
NEPHROPATHY			1 (2%)
NEPHROSIS, NOS	35 (70%)	42 (84%)	40 (80%)
METAMORPHOSIS FATTY			1 (2%)
#KIDNEY/PELVIS	(50)	(50)	(50)
HYPERPLASIA, EPITHELIAL			1 (2%)
#URINARY BLADDER	(50)	(47)	(49)
HEMORRHAGE		1 (2%)	
INFLAMMATION, HEMORRHAGIC			1 (2%)
HYPERPLASIA, EPITHELIAL	1 (2%)		1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(49)	(46)	(49)
EMBRYONAL DUCT CYST		1 (2%)	
MULTILOCULAR CYST		1 (2%)	
DEGENERATION, CYSTIC	1 (2%)		
CYTOPLASMIC VACUOLIZATION		1 (2%)	1 (2%)
HYPERPLASIA, NOS	2 (4%)		
HYPERPLASIA, FOCAL	4 (8%)	3 (7%)	8 (16%)
ANGIECTASIS	1 (2%)	1 (2%)	2 (4%)
#ADRENAL	(50)	(50)	(50)
METAMORPHOSIS FATTY		1 (2%)	
ANGIECTASIS			1 (2%)
#ADRENAL CORTEX	(50)	(50)	(50)
CONGESTION, NOS			1 (2%)
CYTOPLASMIC VACUOLIZATION		4 (8%)	5 (10%)
FOCAL CELLULAR CHANGE			1 (2%)
#ADRENAL MEDULLA	(50)	(50)	(50)
FIBROSIS, FOCAL	1 (2%)		

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
FOCAL CELLULAR CHANGE		1 (2%)	1 (2%)
HYPERPLASIA, NOS			1 (2%)
HYPERPLASIA, FOCAL	2 (4%)	3 (6%)	1 (2%)
#THYROID	(50)	(47)	(47)
CYSTIC FOLLICLES	2 (4%)	2 (4%)	1 (2%)
DEGENERATION, CYSTIC	1 (2%)		1 (2%)
HYPERPLASIA, CYSTIC			1 (2%)
HYPERPLASIA, C-CELL	6 (12%)	1 (2%)	2 (4%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
CYSTIC DUCTS		1 (2%)	
CYSTIC DISEASE	36 (72%)	25 (50%)	30 (60%)
*PREPUTIAL GLAND	(50)	(50)	(50)
CYSTIC DUCTS	1 (2%)		1 (2%)
INFLAMMATION, SUPPURATIVE		2 (4%)	1 (2%)
INFLAMMATION, CHRONIC			1 (2%)
HYPERPLASIA, EPITHELIAL		1 (2%)	
#PROSTATE	(50)	(48)	(50)
INFLAMMATION, FOCAL			1 (2%)
INFLAMMATION, SUPPURATIVE	25 (50%)	12 (25%)	18 (36%)
FIBROSIS, FOCAL			1 (2%)
HYPERPLASIA, EPITHELIAL	1 (2%)		
*SEMINAL VESICLE	(50)	(50)	(50)
INFLAMMATION, SUPPURATIVE		2 (4%)	
HYPERPLASIA, EPITHELIAL		1 (2%)	
#TESTIS	(50)	(50)	(50)
ATROPHY, NOS	1 (2%)	3 (6%)	7 (14%)
HYPERPLASIA, INTERSTITIAL CELL	2 (4%)	1 (2%)	3 (6%)
*EPIDIDYMIS	(50)	(50)	(50)
INFLAMMATION, CHRONIC SUPPURATIV			1 (2%)
NERVOUS SYSTEM			
#BRAIN	(50)	(50)	(50)
HEMORRHAGE			1 (2%)

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
GLIOSIS			1 (2%)
#PONS	(50)	(50)	(50)
NECROSIS, NOS	1 (2%)		
ATROPHY, PRESSURE	1 (2%)		
SPECIAL SENSE ORGANS			
*EYE	(50)	(50)	(50)
RETINOPATHY	1 (2%)		21 (42%)
CATARACT	1 (2%)		21 (42%)
*EXTERNAL EAR	(50)	(50)	(50)
ULCER, PERFORATED		1 (2%)	
MUSCULOSKELETAL SYSTEM			
*MUSCLE OF LEG	(50)	(50)	(50)
HEMORRHAGE			1 (2%)
BODY CAVITIES			
*THORACIC CAVITY	(50)	(50)	(50)
FOREIGN BODY, NOS			1 (2%)
*MEDIASTINUM	(50)	(50)	(50)
INFLAMMATION, SUPPURATIVE	1 (2%)		
*PERITONEUM	(50)	(50)	(50)
INFLAMMATION, FOCAL	1 (2%)		
*PLEURA	(50)	(50)	(50)
LIPOGRANULOMA	1 (2%)		
*EPICARDIUM	(50)	(50)	(50)
EDEMA, NOS	1 (2%)		
*MESENTERY	(50)	(50)	(50)
FOREIGN BODY, NOS			1 (2%)
HEMORRHAGE			1 (2%)
STEATITIS			1 (2%)
GRANULATION, TISSUE			2 (4%)

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
NECROSIS, FAT	5 (10%)	12 (24%)	4 (8%)
HYPERPLASIA, MESOTHELIAL			1 (2%)
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
HEMORRHAGE	1 (2%)		
LEG			
HEMORRHAGE			1
INFLAMMATION, SUPPURATIVE			1
SOLE OF FOOT			
ULCER, CHRONIC			1
CALLUS			3
OMENTUM			
NECROSIS, FAT	2		
SPECIAL MORPHOLOGY SUMMARY			
NONE			

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

TABLE C2.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS ADMINISTERED ALLYL ISOVALERATE IN CORN OIL BY GAVAGE

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	49
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(49)
ULCER, CHRONIC		1 (2%)	
POLYPOID HYPERPLASIA			1 (2%)
*SUBCUT TISSUE	(50)	(50)	(49)
ABSCESS, NOS		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(50)	(50)	(49)
CONGESTION, NOS	2 (4%)	1 (2%)	7 (14%)
EDEMA, NOS	1 (2%)	2 (4%)	4 (8%)
PNEUMONIA, ASPIRATION		1 (2%)	1 (2%)
HYPERPLASIA, ALVEOLAR EPITHELIUM			2 (4%)
#LUNG/ALVEOLI	(50)	(50)	(49)
HYPERPLASIA, ADENOMATOUS	1 (2%)		
HISTIOCYTOSIS	2 (4%)		3 (6%)
#ALVEOLAR EPITHELIUM	(50)	(50)	(49)
HYPERPLASIA, ADENOMATOUS		1 (2%)	
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(50)	(49)	(47)
MYELOFIBROSIS			2 (4%)
#SPLEEN	(50)	(50)	(49)
FIBROSIS, FOCAL			1 (2%)
HEMATOPOIESIS	2 (4%)	5 (10%)	5 (10%)
#MANDIBULAR L. NODE	(50)	(50)	(49)
INFLAMMATION, NOS			1 (2%)

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
HYPERPLASIA, NOS	2 (4%)		
#MEDIASTINAL L.NODE	(50)	(50)	(49)
HEMOSIDEROSIS		1 (2%)	
ANGIECTASIS		1 (2%)	
#MESENTERIC L. NODE	(50)	(50)	(49)
HYPERPLASIA, NOS			1 (2%)
#LUNG	(50)	(50)	(49)
LEUKOCYTOSIS, NOS	2 (4%)	1 (2%)	1 (2%)
HYPERPLASIA, LYMPHOID			1 (2%)
#LIVER	(50)	(50)	(49)
LEUKOCYTOSIS, NOS	1 (2%)	3 (6%)	1 (2%)
HEMATOPOIESIS	1 (2%)		
#ADRENAL	(50)	(50)	(49)
HEMATOPOIESIS		1 (2%)	
CIRCULATORY SYSTEM			
#MYOCARDIUM	(50)	(50)	(49)
INFLAMMATION, FOCAL	2 (4%)	1 (2%)	
INFLAMMATION, CHRONIC FOCAL	1 (2%)		
FIBROSIS, FOCAL		4 (8%)	2 (4%)
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(50)	(50)	(46)
FIBROSIS		1 (2%)	
#LIVER	(50)	(50)	(49)
DEFORMITY, NOS	7 (14%)		1 (2%)
CONGESTION, NOS	1 (2%)	1 (2%)	1 (2%)
CHOLANGIOFIBROSIS			4 (8%)
CIRRHOSIS, NOS			8 (16%)
NECROSIS, FOCAL		2 (4%)	4 (8%)
METAMORPHOSIS FATTY		2 (4%)	3 (6%)
PIGMENTATION, NOS		1 (2%)	2 (4%)
CYTOPLASMIC VACUOLIZATION	3 (6%)	2 (4%)	18 (37%)
BASOPHILIC CYTO CHANGE	32 (64%)	24 (48%)	18 (37%)
FOCAL CELLULAR CHANGE		1 (2%)	

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
NODULAR REGENERATION	1 (2%)	3 (6%)	8 (16%)
#LIVER/CENTRILOBULAR	(50)	(50)	(49)
CONGESTION, NOS			2 (4%)
NECROSIS, NOS			1 (2%)
METAMORPHOSIS FATTY		1 (2%)	2 (4%)
ATROPHY, NOS			3 (6%)
#BILE DUCT	(50)	(50)	(49)
DILATATION, NOS			1 (2%)
HYPERPLASIA, NOS	39 (78%)	36 (72%)	44 (90%)
HYPERPLASIA, FOCAL	3 (6%)		
#PANCREAS	(49)	(50)	(46)
CYSTIC DUCTS			1 (2%)
ATROPHY, NOS		1 (2%)	
ATROPHY, FOCAL	8 (16%)	11 (22%)	3 (7%)
#PANCREATIC ACINUS	(49)	(50)	(46)
ATROPHY, FOCAL			1 (2%)
#STOMACH	(50)	(50)	(49)
HYPERPLASIA, EPITHELIAL	1 (2%)	1 (2%)	
#GASTRIC FUNDAL GLAND	(50)	(50)	(49)
DILATATION, NOS		1 (2%)	
#FORESTOMACH	(50)	(50)	(49)
INFLAMMATION, CHRONIC FOCAL	1 (2%)		
HYPERPLASIA, EPITHELIAL	1 (2%)		
#SMALL INTESTINE	(49)	(50)	(46)
INFLAMMATION, NOS			1 (2%)
#COLONIC SUBMUCOSA	(50)	(49)	(45)
INFLAMMATION, NOS	1 (2%)		
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(49)
NEPHROSIS, NOS	6 (12%)	13 (26%)	7 (14%)
#KIDNEY/TUBULE	(50)	(50)	(49)
PIGMENTATION, NOS	3 (6%)	1 (2%)	

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
CYTOPLASMIC VACUOLIZATION	1 (2%)		
ENDOCRINE SYSTEM			
#PITUITARY	(48)	(49)	(48)
FOCAL CELLULAR CHANGE			1 (2%)
HYPERPLASIA, NOS		1 (2%)	
HYPERPLASIA, FOCAL	8 (17%)	5 (10%)	2 (4%)
ANGIECTASIS	4 (8%)	5 (10%)	6 (13%)
#ADRENAL	(50)	(50)	(49)
CYTOPLASMIC VACUOLIZATION			1 (2%)
#ADRENAL CORTEX	(50)	(50)	(49)
ACCESSORY STRUCTURE	1 (2%)	1 (2%)	
DEGENERATION, CYSTIC	1 (2%)		
CYTOPLASMIC VACUOLIZATION	3 (6%)	5 (10%)	8 (16%)
ANGIECTASIS			1 (2%)
#ADRENAL MEDULLA	(50)	(50)	(49)
CYTOLOGIC ALTERATION, NOS		1 (2%)	
HYPERPLASIA, FOCAL	3 (6%)		2 (4%)
#THYROID	(48)	(50)	(46)
ULTIMOBRANCHIAL CYST	1 (2%)	1 (2%)	
CYSTIC FOLLICLES	1 (2%)		1 (2%)
DEGENERATION, CYSTIC			1 (2%)
HYPERPLASIA, C-CELL	5 (10%)	5 (10%)	4 (9%)
#PARATHYROID	(48)	(44)	(37)
HYPERPLASIA, FOCAL			1 (3%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(49)
GALACTOCELE	1 (2%)		
HYPERPLASIA, CYSTIC	1 (2%)	1 (2%)	1 (2%)
CYSTIC DISEASE	41 (82%)	44 (88%)	35 (71%)
*PREPUTIAL GLAND	(50)	(50)	(49)
INFLAMMATION, SUPPURATIVE	1 (2%)	2 (4%)	2 (4%)
HYPERPLASIA, CYSTIC		2 (4%)	
*CLITORAL GLAND	(50)	(50)	(49)
CYSTIC DUCTS	1 (2%)		

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
*VAGINA	(50)	(50)	(49)
INFLAMMATION, SUPPURATIVE		2 (4%)	
#UTERUS	(50)	(50)	(48)
HEMATOMETRA		1 (2%)	
INFLAMMATION, SUPPURATIVE	3 (6%)	3 (6%)	1 (2%)
ADENOMYOSIS		1 (2%)	
#UTERUS/ENDOMETRIUM	(50)	(50)	(48)
CYST, NOS	2 (4%)	5 (10%)	4 (8%)
HYPERPLASIA, CYSTIC	2 (4%)		
#ENDOMETRIAL GLAND	(50)	(50)	(48)
CYST, NOS		1 (2%)	
#FALLOPIAN TUBE	(50)	(50)	(48)
DILATATION, NOS		1 (2%)	
HYPERPLASIA, EPITHELIAL		1 (2%)	
#OVARY	(50)	(50)	(47)
CYST, NOS	3 (6%)	4 (8%)	1 (2%)
FOLLICULAR CYST, NOS	6 (12%)	1 (2%)	7 (15%)
METAMORPHOSIS FATTY			1 (2%)
NERVOUS SYSTEM			
#BRAIN	(50)	(50)	(49)
HYDROCEPHALUS, NOS			1 (2%)
HEMORRHAGE			1 (2%)
#BRAIN/THALAMUS	(50)	(50)	(49)
ATROPHY, PRESSURE		3 (6%)	
#HYPOTHALAMUS	(50)	(50)	(49)
ATROPHY, PRESSURE	1 (2%)	1 (2%)	1 (2%)
#MIDBRAIN	(50)	(50)	(49)
ATROPHY, PRESSURE	2 (4%)		
SPECIAL SENSE ORGANS			
*EYE	(50)	(50)	(49)
HEMORRHAGE	1 (2%)		

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
RETINOPATHY	4 (8%)	21 (42%)	2 (4%)
CATARACT	1 (2%)	19 (38%)	2 (4%)
*HARDERIAN GLAND	(50)	(50)	(49)
ECTOPIA			2 (4%)
*EAR	(50)	(50)	(49)
INFLAMMATION, ACUTE		1 (2%)	
*ZYMBAL'S GLAND	(50)	(50)	(49)
INFLAMMATION, SUPPURATIVE		1 (2%)	
HYPERPLASIA, NOS		1 (2%)	
MUSCULOSKELETAL SYSTEM			
*FEMUR	(50)	(50)	(49)
ENOSTOSIS	1 (2%)		
BODY CAVITIES			
*MEDIASTINUM	(50)	(50)	(49)
LIPOGRANULOMA	1 (2%)		
*PERITONEUM	(50)	(50)	(49)
INFLAMMATION, SUPPURATIVE			1 (2%)
*PLEURA	(50)	(50)	(49)
ABSCESS, NOS	1 (2%)		
LIPOGRANULOMA	1 (2%)		
*MESENTERY	(50)	(50)	(49)
STEATITIS			1 (2%)
INFLAMMATION, CHRONIC	1 (2%)		
GRANULATION, TISSUE			1 (2%)
NECROSIS, FAT	5 (10%)	4 (8%)	3 (6%)
ALL OTHER SYSTEMS			
SOLE OF FOOT			
ULCER, CHRONIC		1	
EROSION		1	
CALLUS	6	4	3

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
OMENTUM			
NECROSIS, FAT	2	2	2
SPECIAL MORPHOLOGY SUMMARY			
AUTOLYSIS/NO NECROPSY			1

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

APPENDIX D

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE ADMINISTERED ALLYL ISOVALERATE IN CORN OIL BY GAVAGE

TABLE D1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE ADMINISTERED ALLYL ISOVALERATE IN CORN OIL BY GAVAGE

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
ULCER, NOS	1 (2%)	1 (2%)	
INFLAMMATION, ACUTE FOCAL	1 (2%)		
INFLAMMATION, ACUTE/CHRONIC	2 (4%)	3 (6%)	1 (2%)
INFLAMMATION, CHRONIC		3 (6%)	
INFLAMMATION, CHRONIC FOCAL	5 (10%)		1 (2%)
FIBROSIS	1 (2%)		
FIBROSIS, FOCAL		2 (4%)	1 (2%)
HYPERPLASIA, NOS			1 (2%)
METAPLASIA, OSSEOUS	1 (2%)		
*SUBCUT TISSUE	(50)	(50)	(50)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)		
INFLAMMATION, CHRONIC			1 (2%)
RESPIRATORY SYSTEM			
#LUNG	(50)	(50)	(49)
FOREIGN BODY, NOS	2 (4%)	1 (2%)	
CONGESTION, NOS	1 (2%)		2 (4%)
BRONCHOPNEUMONIA, FOCAL	4 (8%)	1 (2%)	
PNEUMONIA, LIPID	3 (6%)	1 (2%)	1 (2%)
PNEUMONIA, ASPIRATION	1 (2%)	2 (4%)	
INFLAMMATION, SUPPURATIVE	1 (2%)		
BRONCHOPNEUMONIA, ACUTE	1 (2%)	8 (16%)	7 (14%)
INFLAMMATION, CHRONIC FOCAL	1 (2%)		
GRANULOMA, FOREIGN BODY	1 (2%)		
CHOLESTEROL DEPOSIT		1 (2%)	
HYPERPLASIA, ADENOMATOUS		1 (2%)	1 (2%)
HYPERPLASIA, ALVEOLAR EPITHELIUM		1 (2%)	3 (6%)
HISTIOCYTOSIS	1 (2%)		

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
HEMATOPOIETIC SYSTEM			
#SPLEEN	(50)	(50)	(50)
NECROSIS, NOS		1 (2%)	1 (2%)
HEMATOPOIESIS	3 (6%)	2 (4%)	2 (4%)
#MESENTERIC L. NODE	(50)	(50)	(49)
NECROSIS, NOS		1 (2%)	
ANGIECTASIS	1 (2%)		2 (4%)
HYPERPLASIA, LYMPHOID	1 (2%)		
#RENAL LYMPH NODE	(50)	(50)	(49)
HYPERPLASIA, LYMPHOID		1 (2%)	
#LIVER	(50)	(50)	(50)
LEUKOCYTOSIS, NOS	1 (2%)		
#THYMUS	(39)	(41)	(37)
CYST, NOS		3 (7%)	
INFLAMMATION, ACUTE SUPPURATIVE	1 (3%)		
CIRCULATORY SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
PERIVASCULITIS	1 (2%)		
#HEART	(50)	(50)	(49)
LYMPHOCYTIC INFLAMMATORY INFILTR			1 (2%)
INFLAMMATION, CHRONIC FOCAL	1 (2%)		
DEGENERATION, NOS	1 (2%)		
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(50)	(50)	(49)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)		
FIBROSIS	1 (2%)		
#LIVER	(50)	(50)	(50)
CYST, NOS	1 (2%)		
FIBROSIS, FOCAL			1 (2%)
NECROSIS, NOS	4 (8%)		3 (6%)
NECROSIS, FOCAL		1 (2%)	1 (2%)

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
NECROSIS, ZONAL			1 (2%)
FOCAL CELLULAR CHANGE	1 (2%)		1 (2%)
CYTOLOGIC ALTERATION, NOS	1 (2%)	2 (4%)	
ANGIECTASIS			2 (4%)
#PANCREAS	(49)	(48)	(48)
NECROSIS, FOCAL	1 (2%)		
ATROPHY, NOS			1 (2%)
#ESOPHAGUS	(50)	(48)	(49)
FOREIGN BODY, NOS			1 (2%)
GRANULOMA, FOREIGN BODY			1 (2%)
#ESOPHAGEAL MUSCULARI	(50)	(48)	(49)
INFLAMMATION, SUPPURATIVE		1 (2%)	
#STOMACH	(50)	(50)	(48)
CYST, NOS	2 (4%)	2 (4%)	1 (2%)
INFLAMMATION, ACUTE SUPPURATIVE			1 (2%)
HYPERPLASIA, EPITHELIAL	1 (2%)	1 (2%)	7 (15%)
#GASTRIC MUCOSA	(50)	(50)	(48)
INFLAMMATION, ACUTE SUPPURATIVE			2 (4%)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)		
INFLAMMATION, CHRONIC FOCAL			2 (4%)
HYPERPLASIA, ADENOMATOUS		1 (2%)	
#JEJUNUM	(50)	(49)	(48)
ULCER, NOS		1 (2%)	
INFLAMMATION, ACUTE SUPPURATIVE			1 (2%)
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
LYMPHOCYTIC INFLAMMATORY INFILTR	7 (14%)	2 (4%)	5 (10%)
SCAR	1 (2%)		
NEPHROPATHY	1 (2%)	3 (6%)	
INFARCT, NOS			1 (2%)
#KIDNEY/PELVIS	(50)	(50)	(50)
LYMPHOCYTIC INFLAMMATORY INFILTR	2 (4%)	1 (2%)	
ENDOCRINE SYSTEM			
#ADRENAL CORTEX	(49)	(46)	(48)
CYST, NOS	1 (2%)		

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#ADRENAL MEDULLA	(49)	(46)	(48)
HYPERPLASIA, FOCAL	1 (2%)		1 (2%)
#THYROID	(47)	(46)	(49)
CYSTIC FOLLICLES	5 (11%)		3 (6%)
DEGENERATION, CYSTIC	3 (6%)	1 (2%)	2 (4%)
HYPERPLASIA, FOLLICULAR-CELL	5 (11%)	7 (15%)	3 (6%)
#PANCREATIC ISLETS	(49)	(48)	(48)
HYPERPLASIA, NOS			2 (4%)
REPRODUCTIVE SYSTEM			
*PREPUTIAL GLAND	(50)	(50)	(50)
CYST, NOS		1 (2%)	
CYSTIC DUCTS	4 (8%)	5 (10%)	5 (10%)
INFLAMMATION, ACUTE SUPPURATIVE		2 (4%)	
INFLAMMATION, ACUTE/CHRONIC	1 (2%)		1 (2%)
INFLAMMATION, CHRONIC	1 (2%)	2 (4%)	
HYPERPLASIA, NOS			1 (2%)
#TESTIS	(49)	(50)	(50)
NECROSIS, NOS			1 (2%)
*EPIDIDYMIS	(50)	(50)	(50)
CYST, NOS		1 (2%)	
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*EYE	(50)	(50)	(50)
CATARACT		1 (2%)	
PHTHISIS BULBI		1 (2%)	
MUSCULOSKELETAL SYSTEM			
NONE			

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
BODY CAVITIES			
*MEDIASTINUM	(50)	(50)	(50)
FOREIGN BODY, NOS		3 (6%)	2 (4%)
INFLAMMATION, ACUTE			2 (4%)
INFLAMMATION, ACUTE SUPPURATIVE	2 (4%)	3 (6%)	
INFLAMMATION, ACUTE/CHRONIC			1 (2%)
GRANULOMA, FOREIGN BODY	1 (2%)	1 (2%)	
*ABDOMINAL CAVITY	(50)	(50)	(50)
INFLAMMATION, SUPPURATIVE			1 (2%)
*PLEURA	(50)	(50)	(50)
INFLAMMATION, ACUTE SUPPURATIVE	1 (2%)		
*MESENTERY	(50)	(50)	(50)
INFLAMMATION, ACUTE SUPPURATIVE	1 (2%)		
NECROSIS, FAT	1 (2%)	4 (8%)	4 (8%)
CALCIFICATION, FOCAL			1 (2%)
ANGIECTASIS	1 (2%)		
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
INFLAMMATION, SUPPURATIVE		1 (2%)	
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	4	7	6

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

TABLE D2.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE ADMINISTERED ALLYL ISOVALERATE IN CORN OIL BY GAVAGE

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
INFLAMMATION, SUPPURATIVE		1 (2%)	
*SUBCUT TISSUE	(50)	(50)	(50)
ABSCESS, NOS			1 (2%)
INFLAMMATION, CHRONIC FOCAL			1 (2%)
RESPIRATORY SYSTEM			
#TRACHEA	(49)	(48)	(49)
INFLAMMATION, ACUTE SUPPURATIVE	1 (2%)		
#LUNG	(50)	(49)	(50)
BRONCHOPNEUMONIA, FOCAL		2 (4%)	
LYMPHOCYTIC INFLAMMATORY INFILTR			1 (2%)
PNEUMONIA, LIPID	1 (2%)	1 (2%)	
BRONCHOPNEUMONIA, ACUTE	3 (6%)	1 (2%)	3 (6%)
INFLAMMATION, ACUTE SUPPURATIVE		1 (2%)	1 (2%)
BRONCHOPNEUMONIA, CHRONIC	1 (2%)		
CHOLESTEROL DEPOSIT			1 (2%)
HYPERPLASIA, ADENOMATOUS		1 (2%)	2 (4%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
HEMATOPOIESIS			1 (2%)
#SPLEEN	(50)	(50)	(50)
NECROSIS, NOS	1 (2%)		
HEMATOPOIESIS	12 (24%)	19 (38%)	12 (24%)
#MEDIASTINAL L.NODE	(49)	(50)	(50)
ABSCESS, NOS	1 (2%)		

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
HYPERPLASIA, NOS			1 (2%)
#LUMBAR LYMPH NODE	(49)	(50)	(50)
HYPERPLASIA, NOS		1 (2%)	1 (2%)
#MESENTERIC L. NODE	(49)	(50)	(50)
HYPERPLASIA, NOS			2 (4%)
ANGIECTASIS	2 (4%)	1 (2%)	
HYPERPLASIA, LYMPHOID	1 (2%)		
#RENAL LYMPH NODE	(49)	(50)	(50)
HYPERPLASIA, NOS	1 (2%)	1 (2%)	2 (4%)
#ILIAC LYMPH NODE	(49)	(50)	(50)
HYPERPLASIA, NOS	1 (2%)		1 (2%)
#LUNG	(50)	(49)	(50)
HYPERPLASIA, LYMPHOID	1 (2%)		
#LIVER	(50)	(50)	(50)
LEUKOCYTOSIS, NOS	8 (16%)	17 (34%)	10 (20%)
HEMATOPOIESIS		1 (2%)	
#THYMUS	(46)	(39)	(47)
INFLAMMATION, SUPPURATIVE		1 (3%)	
NECROSIS, NOS		1 (3%)	
CIRCULATORY SYSTEM			
#MESENTERIC L. NODE	(49)	(50)	(50)
PERIVASCULITIS		1 (2%)	
#HEART	(50)	(49)	(50)
LYMPHOCYTIC INFLAMMATORY INFILTR		1 (2%)	
#SALIVARY GLAND	(48)	(46)	(47)
PERIARTERITIS			1 (2%)
#LIVER	(50)	(50)	(50)
THROMBOSIS, NOS			1 (2%)
#PITUITARY	(43)	(43)	(44)
THROMBOSIS, NOS			1 (2%)
#THYROID	(49)	(48)	(48)
PERIVASCULITIS		1 (2%)	

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
#LIVER	(50)	(50)	(50)
DEGENERATION, NOS	1 (2%)		
NECROSIS, NOS	2 (4%)	2 (4%)	
NECROSIS, FOCAL	1 (2%)	1 (2%)	4 (8%)
FOCAL CELLULAR CHANGE		1 (2%)	1 (2%)
CYTOLOGIC ALTERATION, NOS		1 (2%)	2 (4%)
ANGIECTASIS			2 (4%)
#PANCREAS	(47)	(47)	(48)
CYSTIC DUCTS	1 (2%)		1 (2%)
ATROPHY, NOS	1 (2%)		
ATROPHY, FOCAL	1 (2%)		
#ESOPHAGUS	(48)	(49)	(49)
INFLAMMATION, FOCAL		1 (2%)	
#STOMACH	(50)	(50)	(50)
CYST, NOS	1 (2%)		1 (2%)
INFLAMMATION, ACUTE SUPPURATIVE	1 (2%)		
INFLAMMATION, CHRONIC FOCAL			1 (2%)
HYPERPLASIA, EPITHELIAL		2 (4%)	3 (6%)
#GASTRIC MUCOSA	(50)	(50)	(50)
INFLAMMATION, ACUTE FOCAL	1 (2%)		
INFLAMMATION, ACUTE SUPPURATIVE	1 (2%)	2 (4%)	
#GASTRIC FUNDAL GLAND	(50)	(50)	(50)
DILATATION, NOS			1 (2%)
#FORESTOMACH	(50)	(50)	(50)
HYPERPLASIA, EPITHELIAL	1 (2%)	1 (2%)	
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
LYMPHOCYTIC INFLAMMATORY INFILTR	11 (22%)	1 (2%)	
INFLAMMATION, ACUTE SUPPURATIVE	1 (2%)		
INFLAMMATION, CHRONIC FOCAL	1 (2%)		
NEPHROPATHY	2 (4%)		
GLOMERULOSCLEROSIS, NOS	1 (2%)		
NECROSIS, MEDULLARY		1 (2%)	

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#KIDNEY/GLOMERULUS	(50)	(50)	(50)
AMYLOIDOSIS	1 (2%)		
#KIDNEY/PELVIS	(50)	(50)	(50)
LYMPHOCYTIC INFLAMMATORY INFILTR		3 (6%)	1 (2%)
#URINARY BLADDER	(49)	(50)	(48)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)	1 (2%)	
ENDOCRINE SYSTEM			
#PITUITARY	(43)	(43)	(44)
CYST, NOS	2 (5%)		1 (2%)
HYPERPLASIA, NOS			2 (5%)
HYPERPLASIA, FOCAL	2 (5%)	1 (2%)	
ANGIECTASIS	8 (19%)	1 (2%)	6 (14%)
#ADRENAL CORTEX	(50)	(46)	(47)
CYST, NOS	2 (4%)		
#ADRENAL MEDULLA	(50)	(46)	(47)
CYST, NOS	1 (2%)		
HYPERPLASIA, NOS	1 (2%)		
HYPERPLASIA, FOCAL	2 (4%)		
#THYROID	(49)	(48)	(48)
CYSTIC FOLLICLES	3 (6%)	1 (2%)	3 (6%)
DEGENERATION, CYSTIC	6 (12%)	1 (2%)	
HYPERPLASIA, FOLLICULAR-CELL	5 (10%)	1 (2%)	6 (13%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
CYSTIC DUCTS	13 (26%)	2 (4%)	9 (18%)
*PREPUTIAL GLAND	(50)	(50)	(50)
CYSTIC DUCTS			1 (2%)
*CLITORAL GLAND	(50)	(50)	(50)
CYSTIC DUCTS		1 (2%)	
*VAGINA	(50)	(50)	(50)
POLYPOID HYPERPLASIA		1 (2%)	

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#UTERUS	(50)	(50)	(50)
HEMORRHAGE		1 (2%)	
HEMATOMA, NOS			1 (2%)
INFLAMMATION, ACUTE SUPPURATIVE	4 (8%)	7 (14%)	9 (18%)
AMYLOIDOSIS	1 (2%)		
#UTERUS/ENDOMETRIUM	(50)	(50)	(50)
HYDROMETRA			1 (2%)
HYPERPLASIA, CYSTIC	42 (84%)	38 (76%)	38 (76%)
#UTERUS/MYOMETRIUM	(50)	(50)	(50)
FIBROSIS	1 (2%)		
#OVARY	(49)	(50)	(48)
CYST, NOS	5 (10%)	6 (12%)	4 (8%)
HEMATOMA, NOS		1 (2%)	
INFLAMMATION, ACUTE SUPPURATIVE	5 (10%)	5 (10%)	5 (10%)
NERVOUS SYSTEM			
#BRAIN/MENINGES	(50)	(50)	(50)
INFLAMMATION, CHRONIC	1 (2%)		
#BRAIN	(50)	(50)	(50)
HEMORRHAGE	1 (2%)		
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
*SKELETAL MUSCLE	(50)	(50)	(50)
INFLAMMATION, ACUTE SUPPURATIVE			1 (2%)
INFLAMMATION, CHRONIC SUPPURATIV			1 (2%)
*MUSCLE HIP/THIGH	(50)	(50)	(50)
INFLAMMATION, ACUTE SUPPURATIVE			1 (2%)
BODY CAVITIES			
*MEDIASTINUM	(50)	(50)	(50)
INFLAMMATION, ACUTE			1 (2%)

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
INFLAMMATION, ACUTE SUPPURATIVE	1 (2%)	1 (2%)	1 (2%)
*PERITONEUM	(50)	(50)	(50)
INFLAMMATION, ACUTE SUPPURATIVE	1 (2%)	2 (4%)	1 (2%)
INFLAMMATION, CHRONIC		1 (2%)	
*PLEURA	(50)	(50)	(50)
INFLAMMATION, ACUTE SUPPURATIVE			1 (2%)
*EPICARDIUM	(50)	(50)	(50)
INFLAMMATION, ACUTE SUPPURATIVE	1 (2%)		
INFLAMMATION, PYOGRANULOMATOUS	1 (2%)		
*MESENTERY	(50)	(50)	(50)
NECROSIS, FAT	3 (6%)	1 (2%)	2 (4%)
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
LYMPHOCYTIC INFLAMMATORY INFILTR		1 (2%)	
INFLAMMATION, ACUTE	1 (2%)		
INFLAMMATION, ACUTE SUPPURATIVE	7 (14%)	14 (28%)	10 (20%)
NECROSIS, FAT	1 (2%)		
TAIL			
INFLAMMATION, ACUTE SUPPURATIVE			1
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	1	2	2

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

APPENDIX E

ANALYSIS OF ALLYL ISOVALERATE
MIDWEST RESEARCH INSTITUTE

APPENDIX E

A. ELEMENTAL ANALYSIS

Element	C	H
Theory	67.57	9.92
1. Lot 770217: Determined	65.78	9.89
	65.92	10.00
2. Lot A-634-F: Determined	67.52	9.86
	67.75	9.80
3. Lot RO11777: Determined	67.61	9.94
	67.74	9.87

B. WATER ANALYSIS

(Karl Fisher)

1. Lot 770217: 0.10 ± 0.03 (δ)%
2. Lot A-634-F: 0.118 ± 0.003 (δ)%
3. Lot RO11777: 0.044 ± 0.001 (δ)%

C. ESTER VALUE (ASTM, 1974)

Potassium hydroxide hydrolysis and sulfuric acid back-titration

1. Lot 770217: 79.7 ± 0.2 (δ)%
2. Lot A-634-F: 94.7 ± 0.7 (δ)%
3. Lot RO11777: 95.6 ± 0.3 (δ)%

D. TITRATION FOR FREE ACIDITY

(with 0.1 N sodium hydroxide)

1. Lot 770217: 16.2 ± 0.1 (δ)% acidity (assumed to be *iso*-valeric acid)
2. Lot A-634-F: 2.14 ± 0.1 (δ)%
3. Lot RO11777: 0.37 ± 0.01 (δ)%

E. BOILING POINT (Lot A-634-F)

Determined	Literature Values
b.p.: 152.3 ± 1.1 (δ)°C at 729 torr (visual, micro boiling point). 153.6° to 157.2°C (DuPont 900 DTA)	162.5°C (Harris, 1965) 155°C (Hodgeman et al., 1963)

F. INDEX OF REFRACTION (Lot A-634-F)

Determined	Literature Values
n_D^{20}: 1.4134 ± 0.0001 (δ)	n_D^{21}: 1.4162 (Fenaroli, 1971) This literature value is suspect because the boiling point reported in the same reference is 89° to 90°C, which is greatly different from other literature or measured values.

APPENDIX E

G. DENSITY (Lot A-634-F)

Determined	Literature Value
d_{22}^{24} : 0.8820 ± 0.0003 (δ) g/ml	No literature value found

H. VAPOR-PHASE CHROMATOGRAPHY

1. Lot 770217

Instrument: Tracor MT-220
Detector: Flame ionization
Inlet temperature: 150°C
Detector temperature: 200°C
Carrier gas: Nitrogen
Carrier flow rate: 70 cc/min

a. System 1

Column: GP20% SP2100/0.1% Carbowax 1500 on 100/120 Supelcoport, 1.7 M x 4 mm I.D., glass

Oven temperature program: 50°C, 5 min; 50° to 170°C at 10°/min.

Sample Injected: 6.5 μl 50% in diethyl ether, and 1% and 0.5% in diethyl ether to check for over-loading and quantitate major peak.

Results: major peak and 21 impurities. Five impurities had peaks which were 0.68%, 1.2%, 0.37%, 0.73%, and 0.58% of the area of the major peak. The area of the remaining 16 impurities totals <1.0% of the major peak.

Peak	Retention Time (min)	Relative to Allyl Isovalerate	Area (Percent of Allyl Isovalerate)
1	0.2	0.02	0.001
2	0.3	0.03	0.0002
3	0.4	0.04	0.0002
4	2.5	0.24	0.68
5	3.0	0.30	1.2
6	3.5	0.34	0.37
7	4.3	0.42	0.003
8	5.3	0.51	0.03
9	6.3	0.61	0.01
10	8.4	0.82	0.08
11	9.0	0.87	0.73
12	10.3	1.00	100
13	10.9	1.06	0.58
14	11.3	1.10	0.03
15	11.5	1.12	0.04
16	11.9	1.16	0.09
17	12.4	1.20	0.01
18	12.6	1.22	0.22
19	13.5	1.31	0.0001
20	13.8	1.34	0.001
21	14.4	1.40	0.009
22	14.9	1.45	0.004

b. System 2

Column: 3% SP2250 on 80/100 Supelcoport, 1.8 m x 4 mm I.D. glass

Oven Temperature Program: 50°C, 5 min; 50° to 250°C at 10°/min.

Sample injected: 7.9 μl of 1.0% allyl isovalerate in diethyl ether, 0.5% in diethyl ether to check for overloading.

Results: Major peak and 4 impurities. The impurities had areas of 0.70%, 0.12%, 0.30%, and 0.17% of the major peak.

Peak	Retention Time (min)	Relative to Allyl Isovalerate	Area (Percent of Allyl Isovalerate)
1	9.0	0.89	0.70
2	9.6	0.95	0.12
3	10.1	1.00	100
4	11.3	1.12	0.30
5	12.5	1.24	0.17

2. Lot A-634-F

Instrument: Varian 2400

Detector: Flame ionization

Inlet temperature: 150°C

Detector temperature: 200°C

Carrier gas: Nitrogen

Carrier flow rate: 40 cc/min

a. System 1

Column: GP 20% SP2100/0.1% Carbowax 1500 on 100/120 Supelcoport, 1.7 m x 4 mm I.D., glass

Oven temperature program: 50°C, 5 min; 50° to 170°C at 10°/min.

Sample Injected: 4.0 μl in diethyl ether 50% (v/v), and 1% and 0.5% in diethyl ether to check for over-loading and quantitate major peak.

Results: Major peak and nine impurities. Three impurities had areas which were 0.9%, 3.9%, and 2.3% of the major peak. The remaining six impurities totaled less than 0.8% of the major peak area. Peak No. 1 (see listings below) was enhanced by addition of allyl alcohol and determined to be present at a level of 0.6 ± 0.1% v/v by standard addition.

APPENDIX E

Peak	Retention Time (min)	Relative to Allyl Isovalerate	Area (Percent of Allyl Isovalerate)
1	3.2	0.21	0.9
2	8.0	0.54	3.9
3	11.6	0.77	0.03
4	12.8	0.86	0.1
5	13.4	0.89	0.3
6	13.6	0.91	2.3
7	15.0	1.00	100.0
8	16.2	1.08	0.1
9	17.6	1.17	0.002
10	18.8	1.25	0.009

b. System 2

Column: 3% SP2250 on 80/100 Supelcoport, 1.8 m x 4 mm I.D., glass

Oven Temperature Program: 50°C, 5 min; 50° to 170°C at 10°/min.

Sample Injected: 4.0 μl in diethyl ether 50% (v/v), and 1% and 0.5% in diethyl ether to check for over-loading and quantitate major peak.

Results: Major peak and eight impurities. Three impurities had peak areas which were 0.9%, 3.0%, and 1.1% of the area of the major peak. The remaining five impurities totaled less than 0.5% of the major peak area.

Peak	Retention Time (min)	Relative to Allyl Isovalerate	Area (Percent of Allyl Isovalerate)
1	1.4	0.16	0.9
2	2.1	0.24	0.02
3	2.5	0.28	3.0
4	6.4	0.72	0.09
5	6.6	0.74	1.1
6	8.1	0.91	0.1
7	8.3	0.93	0.07
8	8.9	1.00	100.0
9	10.6	1.19	0.2

3. Lot RO11777

Instrument: Varian 3700

Detector: Flame ionization

Carrier gas: Nitrogen

Carrier flow rate: 70 ml/min

a. System 1

Column: 20% SP 2100/0.1% Carbowax 1500 on 100/120 Supelcoport, 1.8 m x 4 mm I.D., glass

Oven Temperature Program: 50° to 170°C at 10°/min; 5 min initial hold

Inlet Temperature: 200°C

Detector Temperature: 250°C

Sample Injected: 3.5 μl neat liquid to detect impurities, and a 1% and 0.5% solution in diethyl ether to quantitate major peak and to check for overloading.

Results: Major peak preceded by eight impurity peaks and followed by three impurity peaks. Four overlapping peaks of 1.5% and one peak of 1.7% of the major peak area. The other six impurities had areas totaling 0.32% of the major peak area.

Peak	Retention Time (min)	Relative to Allyl Isovalerate	Area (Percent of Allyl Isovalerate)
1	5.8	0.47	1.7
2	8.4	0.68	0.03
3	10.3	0.84	0.10
4	10.6	0.86	0.01
5	11.1	0.90	
6 (shoulder)	11.3	0.92	1.5
7 (shoulder)	11.5	0.94	
8 (shoulder)	11.8	0.96	
9	12.3	1.00	100.00
10	13.3	1.08	0.16
11	13.8	1.12	0.01
12	16.2	1.32	0.01

b. System 2

Column: 3% OV-17 on 80/100 Supelcoport, 1.8 m x 4 mm I.D., glass*

Oven Temperature Program: 50° to 250°C at 10°/min; 5 min initial hold

Inlet Temperature: 200°C

Detector Temperature: 250°C

Sample Injected: Neat liquid (3.5 μl) to detect impurities, diluted to 1% and 0.5% in diethyl ether to check for overloading and to quantitate the major peak.

*Comparable to SP 2250 column used in System 2 for the other two lots.

Results: Major peak preceded by four impurity peaks and followed by four impurity peaks. Two impurities had areas of 1.5% and 0.83% of the major peak area. The other six impurities totaled 0.22% of the major peak.

Peak	Retention Time (min)	Relative to Allyl Isovalerate	Area (Percent of Allyl Isovalerate)
1	1.5	0.22	1.5
2	2.0	0.30	0.01
3	4.2	0.63	0.83
4	6.0	0.90	0.05
5	6.7	1.00	100.00
6	8.6	1.28	0.12
7	9.8	1.46	0.01
8	11.2	1.67	0.02
9	16.3	2.43	0.01

J. SPECTRAL DATA

1. Infrared

a. Lot 770217

Instrument: Perkin-Elmer Model 137 Infracord
Cell: Liquid between silver chloride plates
Results: See Figure 6.

Peaks at 2370, 1620, 1590, 1540, and 1520 cm^{-1} in sample spectrum and not in literature spectrum (Sadtler Standard Spectra). In other respects the sample spectrum is consistent with the literature spectrum.

b. Lots A-634-F and RO11777

Instrument: Beckman IR 12
Cell: Thin film between silver chloride plates
Results: See Figures 7 and 8.

The sample spectra are consistent with the literature spectrum (Sadtler Standard Spectra).

2. Ultraviolet/Visible

a. Lot 770217

Instrument: Cary 118

λ max (nm)	ε
273	7.23 ± 0.02 (δ)
269	7.09 ± 0.03 (δ)
261	6.92 ± 0.03 (δ)
255	6.91 ± 0.04 (δ)
248.5	7.24 ± 0.04 (δ)

No absorbance between 350 and 800 nm (visible range) at a concentration of 1% v/v.

Solvent: Methanol

No literature values found

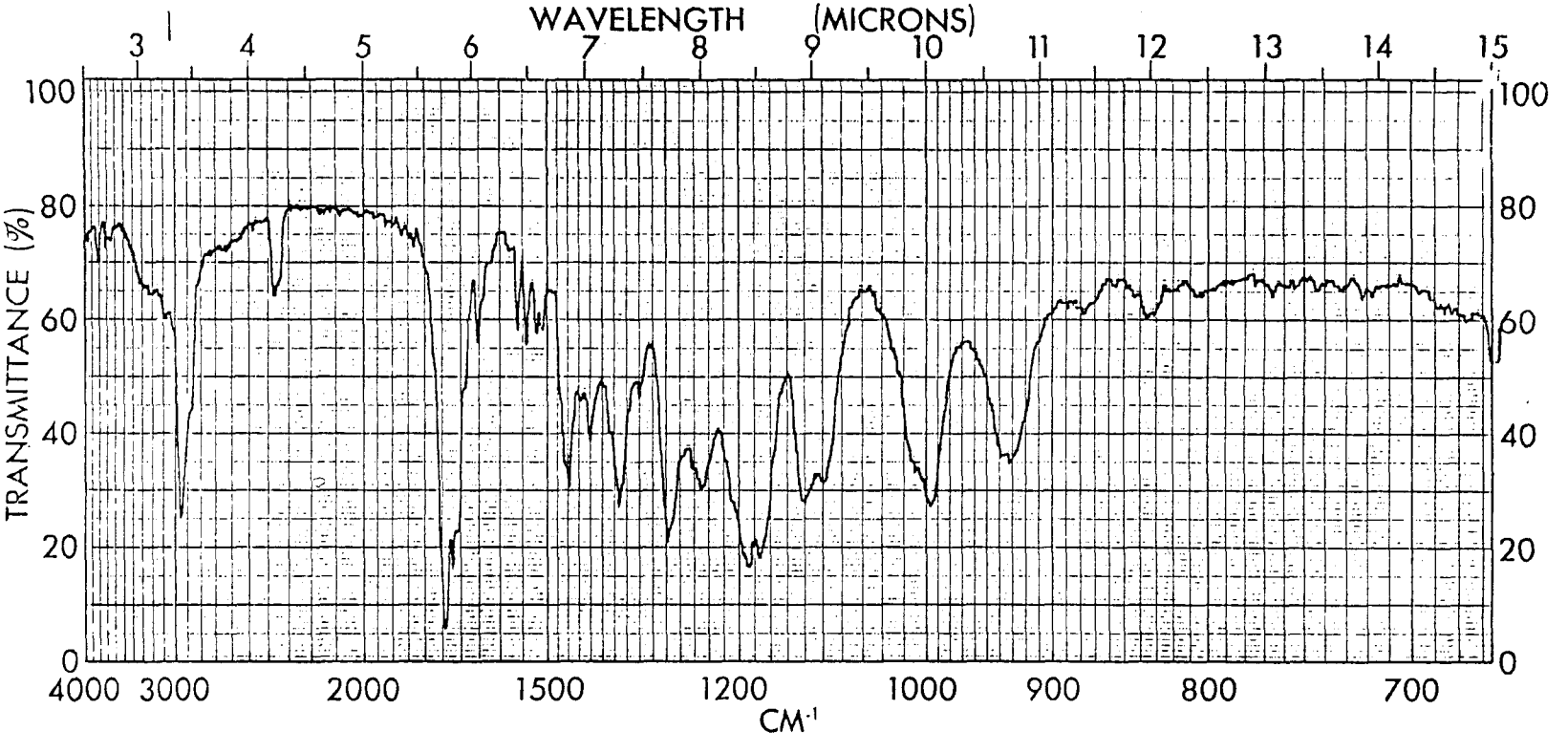

Figure 6. Infrared Absorption Spectrum of Allyl Isovalerate (Lot No. 770217)

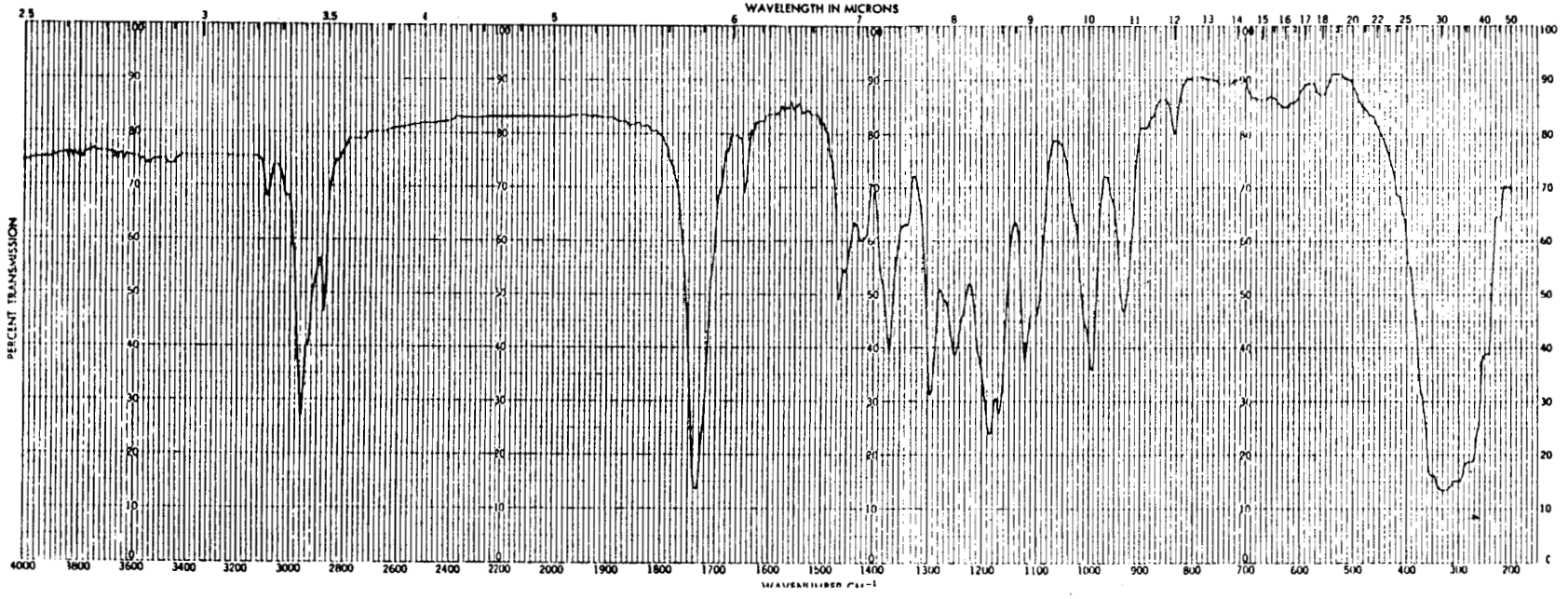

Figure 7. Infrared Absorption Spectrum of Allyl Isovalerate (Lot No. A-634-F)

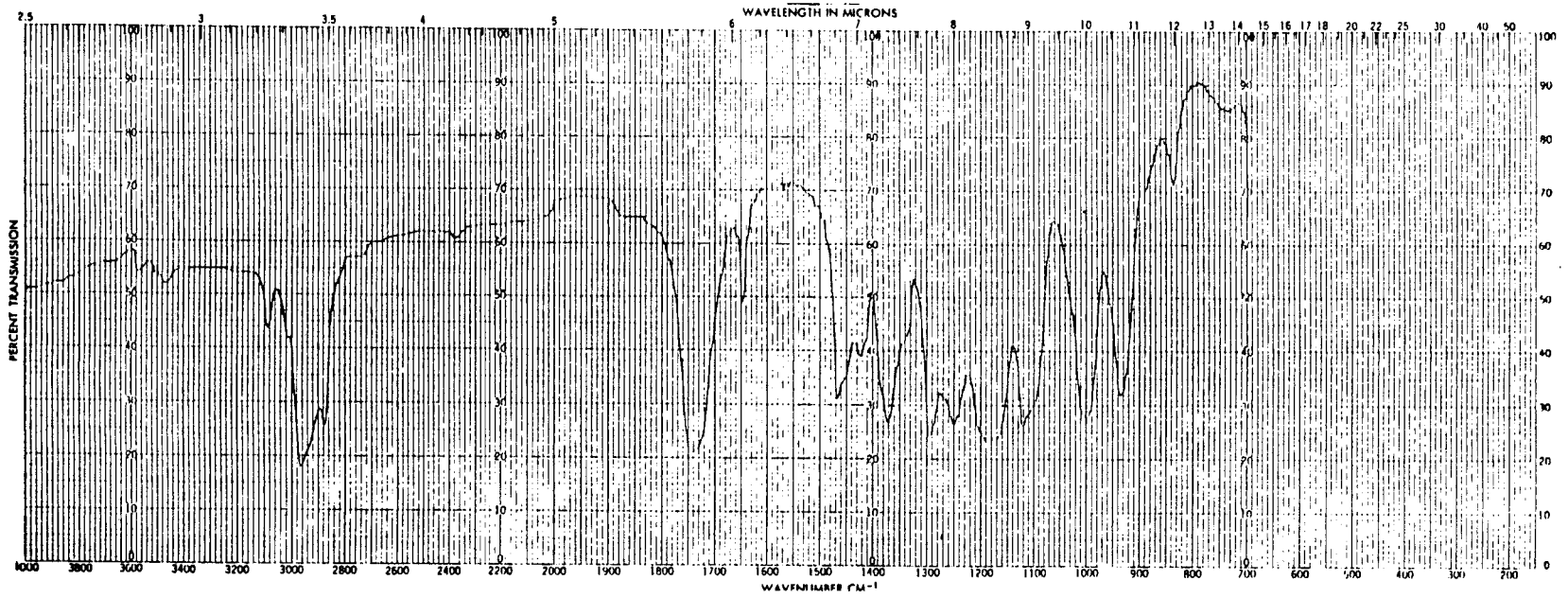

Figure 8. Infrared Absorption Spectrum of Allyl Isovalerate (Lot No. RO 11777)

b. Lot A-634-F
Instrument: Cary 118

λ max (nm)	ε
280	1.90 ± 0.02 (δ)

No absorbance between 350 and 800 nm (visible range) at a concentration of 1% v/v.
Solvent: Methanol

c. Lot RO11777
Instrument: Cary 118
Solvent: 95% ethanol
A 1% (vol/vol) solution exhibited a steady increase in absorbance from 249 nm to 215 nm with no λmax.
A 1% (vol/vol) solution had no absorbance between 350 and 800 nm (visible region).

3. Nuclear Magnetic Resonance

a. Lot 770217
Instrument: Varian HA-100
Solvent: Neat, tetramethylsilane added
Assignments: (see Figure 9).

No literature spectrum found. Spectrum consistent with structure but indicates two impurity peaks.

	Chemical Shift (δ)	Coupling Constant	Integration Ratio
(a) m,	0.93 ppm	J_{ab} = 6.75 Hz	5.99
(b) m,	2.10 ppm		3.40
(c) dt,	4.45 ppm	J_{cd} = 1.5 Hz	1.66
	J_{cf} = 5.5 Hz		
(d) m,	5.05 ppm	J_{de} = 1.5 Hz	
	J_{df} = 9.0 Hz	1.80	1.80
(e) m,	5.18 ppm	J_{ef} ◻ 16.5 Hz	
(f) m,	5.60 -		
	6.05 ppm		1.08
(g) m,	7.20 ppm*		0.07
(h) m,	10.97 ppm*		0.22

*Peaks g and h are impurities

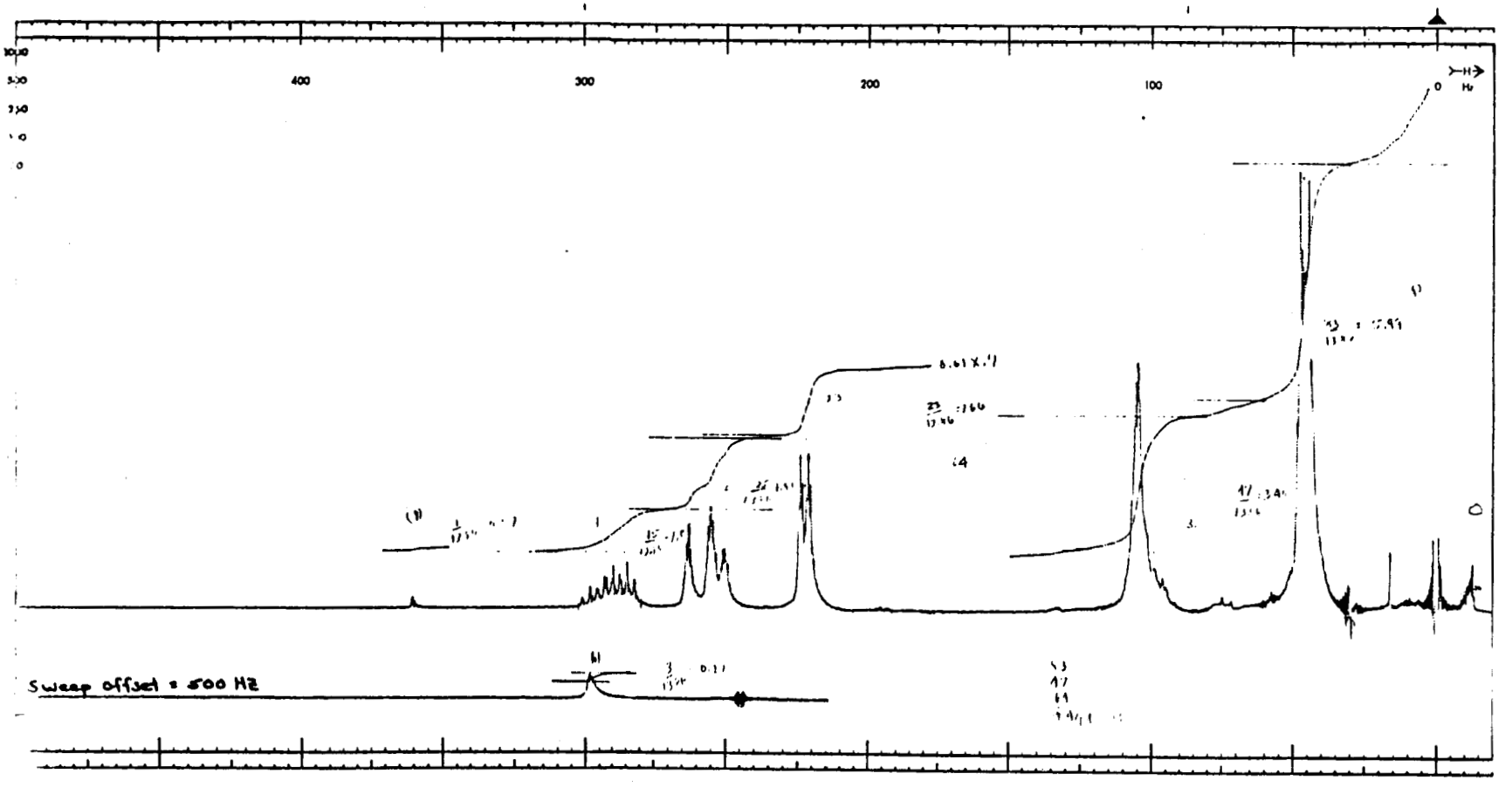

Figure 9. Nuclear Magnetic Resonance Spectrum of Allyl Isovalerate (Lot No. 770217)

b. Lot A-634-F

Instrument: Varian HA-100
Solvent: Neat with internal tetramethylsilane added
Assignments: (see Figure 10).

Spectrum consistent with structure, with some impurity peaks present

	Chemical Shift (δ)	Coupling Constant	Integration Ratio
(a) d,	0.92 ppm	J_{ab} = 6 Hz	5.85 (a+g)
(b) m,	2.10 ppm		3.02 (b+h)
(c) d,	4.46 ppm	J_{cf} = 3 Hz	2.10
(d) d,	5.06 ppm	J_{df} = 10 Hz	2.10
(e) d,	5.18 ppm	J_{ef} = 16 Hz	
(f) m,	5.82 ppm		0.92
(g) m,	1.15 - 1.29 ppm*		
(h) m,	1.88 - 2.06 ppm*		

*Peaks g and h are impurities

c. Lot RO11777

Instrument: Varian EM-360A
Solvent: $CDCl_3$ with internal tetramethylsilane
Assignments: (see Figure 11).

	Chemical Shift (δ)	Coupling Constant	Integration Ratio
(a) d,	0.95 ppm	J_{ab} = 6 Hz	5.90
(b) m,	1.95-2.35 ppm	J_{bc} = 2 Hz	2.98
(c) d,	2.20 ppm		
(d) m,	4.54 ppm	J_{dg} = 5 Hz	2.07
(e) d,	5.17 ppm	J_{eg} = 10 Hz	2.01
(f) m,	5.22 ppm	J_{fg} = 18 Hz	
(g) m,	5.60-6.28 ppm		1.04
(h) m,	1.18*		0.19

*Peak h is an impurity. The proton designations for Lot R011777 are not the same as those for the other two lots.

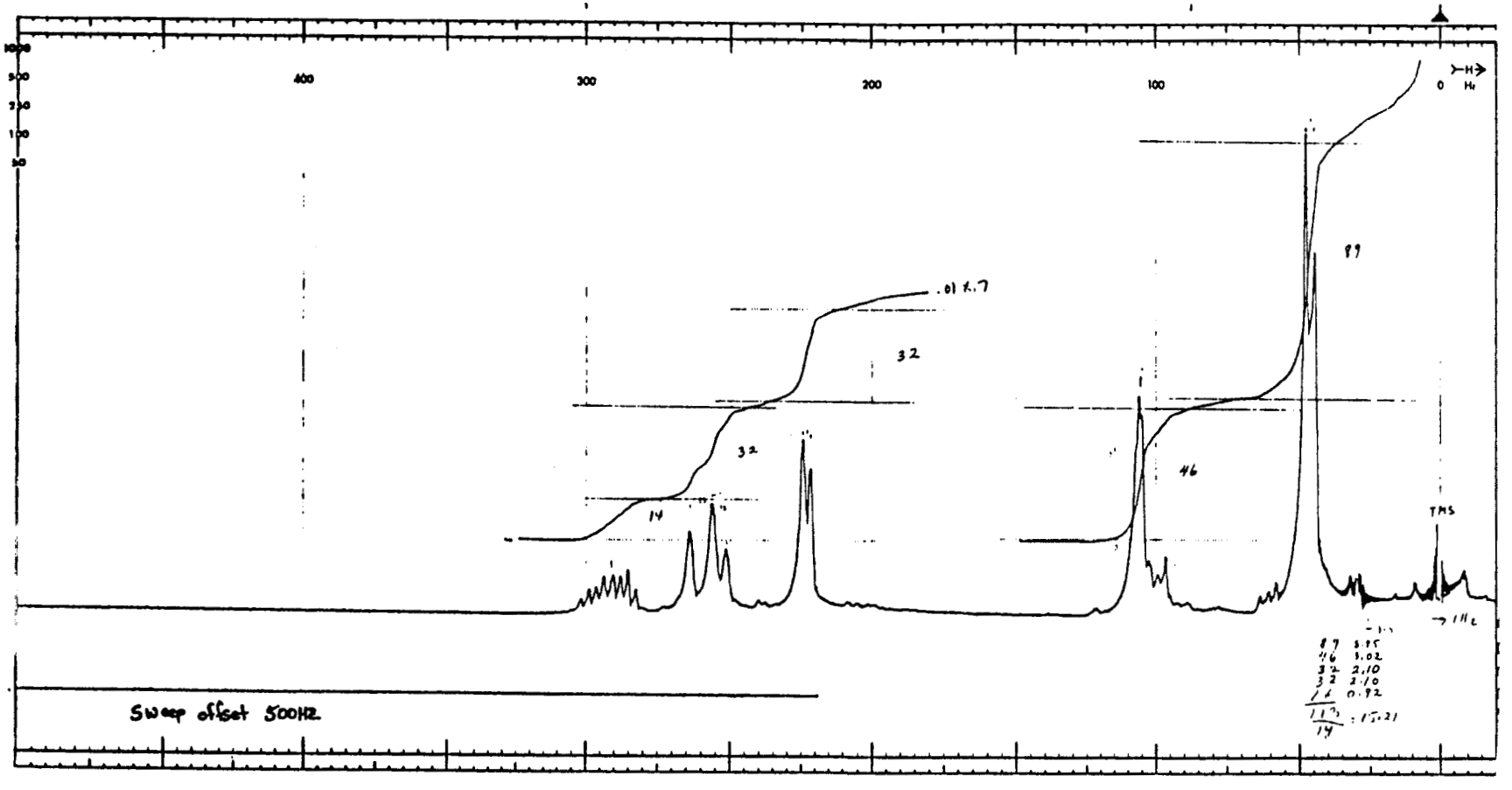

Figure 10. Nuclear Magnetic Resonance Spectrum of Allyl Isovalerate (Lot No. A-634-F)

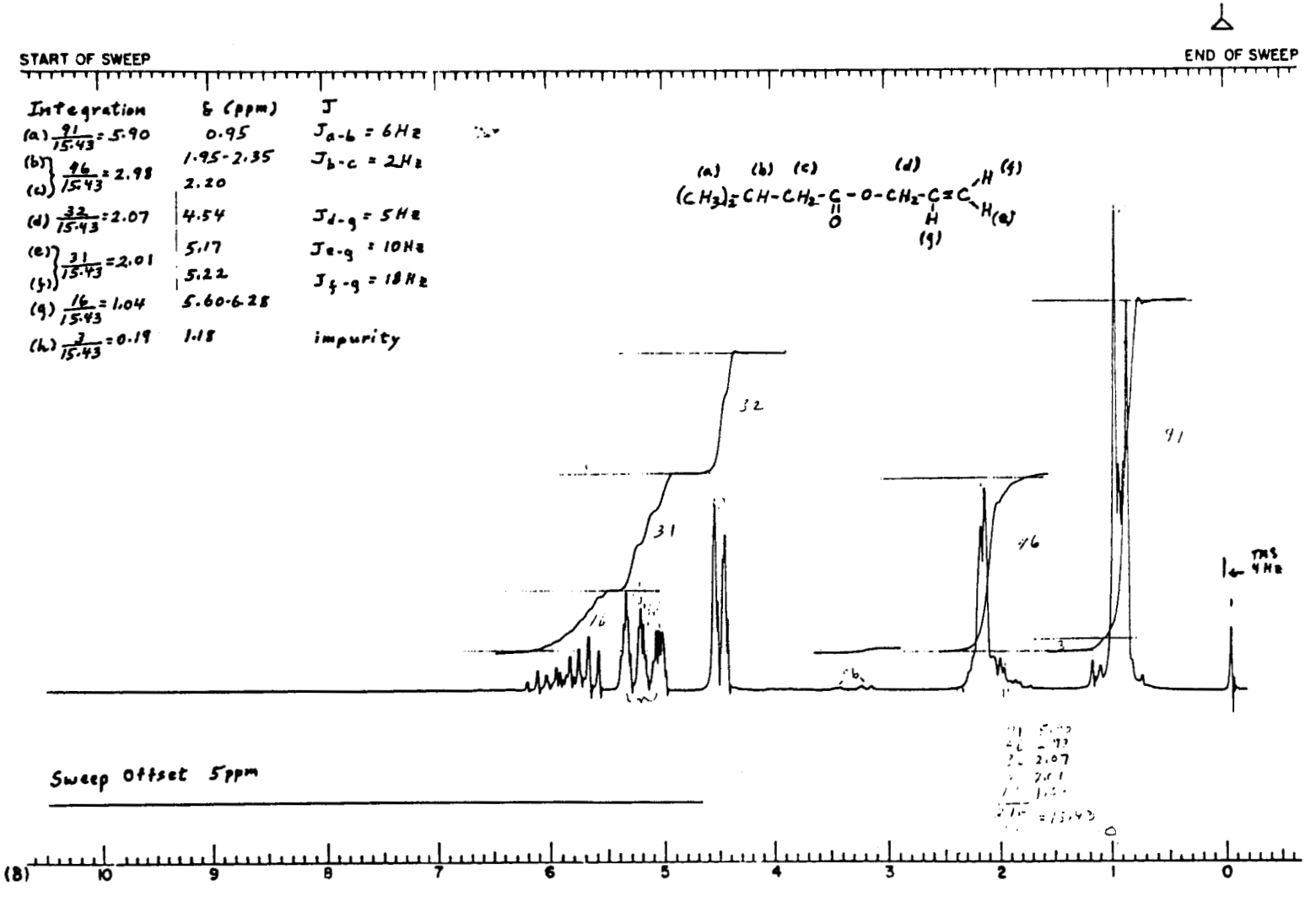

Figure 11. Nuclear Magnetic Resonance Spectrum of Allyl Isovalerate (Lot No. RO 11777)

APPENDIX F

ANALYSIS OF ALLYL ISOVALERATE/CORN OIL MIXTURES FOR STABILITY OF ALLYL ISOVALERATE

APPENDIX F

A. SAMPLE PREPARATION AND STORAGE

Solutions of allyl isovalerate in corn oil (2% weight/volume) were prepared in duplicate and stored for 0, 2, 3, and 7 days, respectively. A typical sample was prepared as follows: 2 ml of corn oil was transferred into an 8.5-ml septum vial and the vial was sealed (Microsep F-138 gas chromatography septa with Teflon® film facing, from Canton Bio-Medical Products, Inc.; aluminum crimp seals from Wheaton Scientific Company, Inc.) and weighed. Approximately 40 mg of allyl isovalerate was then injected, and the vial was reweighed to determine the exact amount of allyl isovalerate added. The sample was agitated on a vortex mixer for 30 seconds and then stored at room temperature (25°C) for the appropriate time period. No attempt was made to protect these samples from light.

B. EXTRACTION AND ANALYSIS

At the end of each storage time segment, the appropriate samples were extracted with 2 ml of methanol, which was injected into the vials with a 2-ml syringe. The two-phase mixtures were agitated on the vortex mixer (1 minute) and placed in an ultrasonic vibratory bath for 2 minutes. Aliquots for analysis were removed directly from the top (methanol) layer of each sample by microliter syringe and analyzed by the vapor-phase chromatographic system described below.

Instrument: Bendix 2500 with a Hewlett-Packard model 3380A automatic integrator

Column: 3% OV-17 on 80/100 Supelcoport, 1.8 m x 4 mm ID, glass

Detection: Flame ionization

Temperatures: Inlet, 195°C
Oven, 75°C, isothermal
Detector, 285°C

Carrier gas: Nitrogen, flow rate, 30 cc/min

Retention time of nominal component: 2.3 min

C. RESULTS

Storage Time (Days)	Average Percent Chemical Found in Chemical/Vehicle Mixtures *(a, b)*
0	2.00 ± 0.03 *(c)*
2	1.96 ± 0.03
3	1.97 ± 0.03
7	1.93 ± 0.03

(a) Corrected for a spike recovery of 65.5 ± 0.6%.

(b) Original concentration of allyl isovalerate in corn oil at time of sample preparation, 2.00%, with a variation among samples of 0.03%.

(c) The error figures in the table were calculated from individual experimental error values by standard error propagation methods.

APPENDIX G

ANALYSIS OF ALLYL ISOVALERATE/CORN OIL MIXTURES FOR CONCENTRATIONS OF ALLYL ISOVALERATE

APPENDIX G

A. METHOD USED DURING THE 13-WEEK STUDY AND DURING THE FIRST MONTH OF THE 2-YEAR STUDY

Samples were received as corn oil gavages mixtures. Aliquots of these mixtures (0.5ml) were dissolved in 10.0 ml of chloroform and analyzed directly vapor-phase chromatography. GC conditions were as follows:

Column: 3% OV-1 on 80/100 Supelcoport, 1.8 m x 4 mm, glass

Detection: Flame ionization

Temperatures: Inlet, 130°C

Oven, 50°C

Detector, 220°C

Retention Time: 4.2 min

Injection Size: 2 μl

There was no correction for work-up loss, since samples were injected with no extraction or work-up procedure. The gavage samples were compared with reference standards of allyl isovalerate prepared volume/volume in corn oil, dissolved in chloroform in the same manner as the gavage samples, and analyzed under the same conditions.

B. METHOD USED DURING MOST OF THE 2-YEAR STUDY

Samples were received as corn oil gavage mixtures. The samples were extracted 1:1 with methanol (5 ml of methanol with 5 ml of sample made up in corn oil). Analysis of the extracts was by vapor-phase chromatography under the following conditions:

Column: 3% OV-1 on 80/100 Supelcoport, 1.8 m x 4 mm, glass

Detection: Flame ionization

Temperatures: Inlet, 130°C

Oven, 50°C

Detector, 220°C

Retention Time: 4.08 min

Injection Size: 2 μl

The gavage samples were compared with reference standards of allyl isovalerate prepared volume/volume in corn oil, then extracted with methanol in the same manner as sample. There was no correction applied to the samples, since samples and reference standards were treated in the same manner.

To improve the extraction efficiency, the extraction procedure was changed on April 16, 1979 such that 2.0 ml of the mix was extracted with 8.0 ml of methanol.

C. RESULTS

See Tables G1 and G2.

TABLE G1. ANALYSIS OF ALLYL ISOVALERATE/CORN OIL MIXTURES IN THE 13-WEEK STUDY

Date Mixed	Target Concentration (Percent, v/v)	Measured Concentration (Percent, v/v)
4/21/78	5.00	5.23
	2.50	2.58
	1.24	1.25
	0.62	0.63
	0.30	0.30
	2.50	2.57
	1.25	1.32
	0.62	0.64
	0.31	0.32
	0.15	0.16

TABLE G2. ANALYSIS OF ALLYL ISOVALERATE/CORN OIL MIXTURES IN THE 2-YEAR STUDY

Date Mixed	Used During Week of:	Concentration *(a)* of Allyl Isovalerate or Target Concentration of (Percent v/v)		
		0.3 (0.27-0.33)	0.62 (0.56-0.68)	1.24 (1.11-1.47)
1/10/79	1/10/79			1.27
1/23/79	1/28/79		0.75	
2/19/79	2/20/79			1.20
				1.35 *(b)*
3/20/79	3/20/79		0.58	
4/16/79	4/16/79			1.34
5/14/79	5/14/79		0.59	
6/11/79	6/11/79			1.31
7/9/79	7/10/79		0.68	
8/06/79	8/06/79			1.28
				1.38 *(c)*
9/03/79	9/03/79		0.68	
10/02/79	10/03/79			1.24
10/29/79	10/29/79		0.68	
11/26/79	11/26/79			1.30
12/17/79	12/18/79		0.64	
1/21/80	1/22/80		0.46 *(d)*	1.26
			0.49 *(b)*	
1/22/80	1/23/80		0.66	
2/18/80	2/18/80	0.30	0.66	
3/10/80	3/10/80		0.68	1.35
4/14/80	4/14/80	0.33	0.63	
5/12/80	5/13/80		0.67	1.32
6/09/80	6/09/80	0.34	0.65	
7/07/80	7/07/80		0.68	1.36
			0.63 *(b)*	
8/04/80	8/04/80	0.31	0.61	
9/01/80	9/01/80		0.65	1.30
9/29/80	9/30/80	0.32	0.66	
10/27/80	10/28/80		0.65	1.30
11/24/80	11/24/80	0.31	0.68	
12/08/80	12/08/80		0.67	1.29
Mean (%.v/v) *(e)*		0.32	0.66	1.29
Standard deviation		0.015	0.037	0.043
Coefficient of variation (%)		4.6	5.6	3.3
Range (%, v/v)		0.30-0.34	0.58-0.75	1.20-1.36
Number of samples		6	20	14

(a) The data presented are the average of the results of duplicate analyses.
(b) Referee analysis by Midwest Research Institute
(c) Referee analysis by Raltech
(d) Mixture was not used.
(e) The results designated *(b)*, *(c)*, and *(d)* are not included in the calculations.

APPENDIX H

HISTORICAL INCIDENCES OF TUMORS IN F344/N RATS AND B6C3F$_1$ MICE

TABLE H1. HISTORICAL INCIDENCE OF PANCREATIC ACINAR-CELL ADENOMAS IN MALE F344/N RATS RECEIVING CORN OIL BY GAVAGE *(a)*

Laboratory	Incidence (Percent)
Battelle	0/100 (0.0%)
Gulf South	2/286 (0.7%)
Hazleton	0/49 (0.0%)
Litton	1/125 (0.8%)
Mason	1/121 (0.8%)
Papanicolaou	0/47 (0.0%)
Southern	2/248 (0.8%)
Total	6/976 (0.6%)
Overall Historical Range	
High	1/47 (2.1%)
Low	0/50 (0.0%)

(a) Data as of November 30, 1981 for studies of at least 104 weeks. The range is presented for groups of 35 or more animals. No acinar-cell carcinomas have been observed in male rats receiving corn oil by gavage.

TABLE H2. HISTORICAL INCIDENCE OF HEMATOPOIETIC TUMORS IN MALE F344/N RATS RECEIVING CORN OIL BY GAVAGE *(a)*

Laboratory	Leukemia	Lymphoma	Lymphoma or Leukemia
Battelle	14/100 (14.0%)	4/100 (4.0%)	18/100 (18.0%)
Gulf South	29/294 (9.9%)	4/294 (1.4%)	31/294 (10.5%)
Hazleton	12/50 (24.0%)	2/50 (4.0%)	14/50 (28.0%)
Litton	13/130 (10.0%)	0/130 (0.0%)	13/130 (10.0%)
Mason	13/125 (10.4%)	2/125 (1.6%)	15/125 (12.0%)
Papanicolaou	5/50 (10.0%)	1/50 (2.0%)	6/50 (12.0%)
Southern	10/250 (4.0%)	1/250 (0.4%)	11/250 (4.4%)
Total	96/999 (9.6%)	14/999 (1.4%)	108/999 (10.8%)
Overall Historical Range			
High	12/50 (24.0%)	4/50 (8.0%)	14/50 (28.0%)
Low	1/50 (2.0%)	0/50 (0.0%)	1/50 (2.0%)

(a) Data as of November 30, 1981, for studies of at least 104 weeks. The range is presented for groups of 35 or more animals.

TABLE H3. HISTORICAL INCIDENCE OF HEMATOPOIETIC TUMORS IN FEMALE F344/N RATS RECEIVING CORN OIL BY GAVAGE *(a)*

Laboratory	Leukemia	Lymphoma	Lymphoma or Leukemia
Battelle	18/100 (18.0%)	3/100 (3.0%)	21/100 (21%)
Gulf South	30/295 (10.2%)	6/295 (2.0%)	36/295 (12.2%)
Hazleton	2/50 (4.0%)	1/50 (2.0%)	3/50 (6.0%)
Litton	28/130 (21.5%)	2/130 (1.5%)	30/130 (23.1%)
Mason	14/124 (11.3%)	1/124 (0.8%)	15/124 (12.1%)
Papanicolaou	14/50 (28.0%)	0/50 (0.0%)	14/50 (28.0%)
Southern	26/250 (10.4%)	2/250 (0.8%)	28/250 (11.2%)
Total	132/999 (13.2%)	15/999 (1.5%)	147/999 (14.7%)
Overall Historical Range			
High	21/50	3/49	22/50
Low	1/49	0/50	2/50

(a) Data as of November 30, 1981 for studies of at least 104 weeks. The ange is presented for groups of 35 or more animals.

TABLE H4. HISTORICAL INCIDENCE OF PREPUTIAL GLAND TUMORS IN MALE F344/N RATS RECEIVING CORN OIL BY GAVAGE *(a, b)*

Laboratory	Adenoma	Carcinoma	Adenocarcinoma
Battelle	0/100 (0.0%)	0/100 (0.0%)	0/100 (0.0%)
Gulf South	0/294 (0.0%)	6/294 (2.0%)	0/294 (0.0%)
Hazleton	0/50 (0.0%)	7/50 (14.0%)	0/50 (0.0%)
Litton	8/130 (6.2%)	0/130 (0.0%)	0/130 (0.0%)
Mason	0/125 (0.0%)	3/125 (2.4%)	0/125 (0.0%)
Papanicolaou	4/50 (8.0%)	0/50 (0.0%)	1/50 (2.0%)
Southern	4/250 (1.6%)	1/250 (0.4%)	4/250 (1.6%)
Total	16/999 (1.6%)	17/999 (1.7%)	5/999 (0.5%)
Overall Historical Range			
High	7/50 (14.0%)	7/50 (14.0%)	4/50 (8.0%)
Low	0/50 (0.0%)	0/50 (0.0%)	0/50 (0.0%)

(a) Data as of November 30, 1981 for studies of at least 104 weeks. The range is presented for groups of 35 or more animals.

(b) The only tissues observed microscopically were those in which a tumor was observed grossly.

TABLE H5. HISTORICAL INCIDENCE OF HEMATOPOIETIC TUMORS IN FEMALE B6C3F$_1$ MICE RECEIVING CORN OIL BY GAVAGE *(a)*

Laboratory	Leukemia	Lymphoma	Lymphoma or Leukemia
Battelle	3/99 (3.0%)	20/99 (20.2%)	23/99 (23.2%)
Gulf South	19/341 (5.6%)	61/341 (17.9%)	80/341 (23.5%)
Litton	5/119 (4.2%)	30/119 (25.2%)	34/119 (28.6%)
Mason	0/150 (0.0%)	46/150 (30.7%)	46/150 (30.7%)
Papanicolaou	0/48 (0.0%)	7/48 (14.6%)	7/48 (14.6%)
Southern	1/250 (0.4%)	38/250 (15.2%)	39/250 (15.6%)
Total	28/1007 (2.8%)	202/1007 (20.1%)	229/1007 (22.7%)
Overall Historical Range			
High	9/49 (18.2%)	17/49 (34.7%)	20/49 (40.8%)
Low	0/50 (0.0%)	2/48 (4.2%)	5/50 (10.0%)

(a) Data as of November 30, 1981, for studies of at least 104 weeks. The range is presented for groups of 35 or more animals.

TABLE H6. HISTORICAL INCIDENCE OF HEMATOPOIETIC TUMORS IN MALE B6C3F$_1$ MICE RECEIVING CORN OIL BY GAVAGE *(a)*

Laboratory	Lymphoma	Lymphoma or Leukemia
Battelle	13/100 (13.0%)	13/100 (13.0%)
Gulf South	20/241 (8.3%)	28/241 (11.6%)
Litton	18/120 (15.0%)	19/120 (15.8%)
Mason	21/150 (14.0%)	21/150 (14.0%)
Papanicolaou	11/50 (22.0%)	11/50 (22.0%)
Southern	28/249 (11.2%)	28/249 (11.2%)
Total	111/910 (12.2%)	120/910 (13.2%)
Overall Historical Range		
High	9/49 (18.2%)	15/48 (31.3%)
Low	0/50 (0.0%)	2/48 (4.2%)

(a) Data as of November 30, 1981, for studies of at least 104 weeks. The range is presented for groups of 35 or more animals.

TABLE H7. HISTORICAL INCIDENCE OF STOMACH TUMORS IN MALE B6C3F$_1$ MICE RECEIVING CORN OIL BY GAVAGE *(a)*

Laboratory	Incidence (Percent)	Lesion
Battelle	0/100 (0.0%)	
Gulf South	1/224 (0.5%)	Stomach, NOS; Papilloma, NOS
Litton	1/117 (0.9%)	Forestomach Papilloma, NOS
Mason	0/146 (0.0%)	
Papanicolaou	1/48 (2.0%)	Stomach, NOS; Squamous cell Carcinoma
Southern	1/246 (0.4%)	Stomach, NOS; Squamous cell Papilloma
Total	5/881 (0.6%)	

(a) Data as of November 30, 1981, for studies of at least 104 weeks.

APPENDIX I

HISTORICAL CONTROL DATA ON HEMATOPOIETIC TUMORS FROM SOUTHERN RESEARCH INSTITUTE (SoRI)

TABLE I1. INCIDENCES OF HEMATOPOIETIC TUMORS IN CORN OIL VEHICLE CONTROL RATS AND MICE IN TWO-YEAR GAVAGE STUDIES AT SOUTHERN RESEARCH INSTITUTE (SoRI)

Chemical	All Leukemia		All Lymphoma	
	Male Rats	Female Rats	Male Mice	Female Mice
Allyl Isovalerate	1/50 (2%)	4/50 (8%)	4/50 (8%)	11/50 (22%)
Allyl Isothiocyanate	2/50 (4%)	7/50 (14%)	3/50 (6%)	5/50 (10%)
Benzyl Acetate	5/50 (10%)	2/50 (4%)	5/50 (10%)	5/50 (10%)
Geranyl Acetate	1/50 (2%)	8/50 (16%)	7/50 (14%)	6/50 (12%)
Ethyl Acrylate	1/50 (2%)	5/50 (10%)	9/49 (18%)	11/50 (22%)
Total	10/250 (4%)	26/250 (10%)	28/249 (11%)	38/250 (15%)
SD	3.5%	4.8%	5.0%	6.3%

TABLE I2. COMPARISON OF THE HIGH-DOSE INCIDENCE RATE OF HEMATOPOIETIC TUMORS IN THE ALLYL ISOVALERATE STUDY WITH THE SoRI HISTORICAL CONTROL RANGE

Lesion/ Species	SoRI Historical Control Range	Allyl Isovalerate High-Dose Rate	Comment
All Leukemia			
Male Rats	2%-10%	14%	Outside Range
Female Rats	4%-16%	18%	Outside Range
All Lymphoma			
Male Mice	6%-18%	16%	Within Range
Female Mice	10%-22%	36%	Outside Range

TABLE I3. STATISTICAL COMPARISON OF HEMATOPOIETIC TUMORS IN THE ALLYL ISOVALERATE STUDY WITH CONCURRENT AND HISTORICAL CONTROLS AT SoRI

Lesion/Species	Control		Allyl Isovalerate		Life Table P Values					
					vs Historical Controls			vs Concurrent Controls		
	Historical *(a)*	Concurrent	Low-Dose	High-Dose	Trend	Low-Dose	High-Dose	Trend	Low-Dose	High-Dose
All Leukemia										
Male Rats	9/200	1/50	4/50	7/50	.002	.188	.004	.015	.183	.022
Female Rats	22/200	4/50	6/50	9/49	.067	.517	.067	.050	.354	.075
All Lymphoma										
Male Mice	24/199	4/50	6/50	8/50	.295	.590N	.310	.167	.397	.204
Female Mice	27/210	11/50	11/50	18/50	.002	.060	.004	.026	.172	.034

(a) Excluding allyl isovalerate

TABLE I4. INCIDENCES OF HEMATOPOIETIC TUMORS FOR VEHICLE CONTROL AND DOSED GROUPS IN FIVE GAVAGE STUDIES AT SoRI

Lesion/ Species	Chemical	Male			Female		
		Vehicle Control	Low-Dose	High-Dose	Vehicle Control	Low-Dose	High-Dose
All Leukemia/Rat							
	Allyl Isovalerate	1/50	4/50	7/50	4/50	6/50	9/49
	Allyl Isothiocyanate	2/50	6/50	8/50	7/50	9/50	12/50
	Benzyl Acetate	5/50	5/50	6/50	2/50	3/50	1/50
	Geranyl Acetate	1/50	1/50	2/50	8/50	7/50	7/50
	Ethyl Acrylate	1/50	6/50	1/50	5/50	8/50	7/50
All Lymphoma/Mice							
	Allyl Isovalerate	4/50	6/50	8/50	11/50	11/50	18/50
	Allyl Isothiocyanate	3/50	2/50	0/50	5/50	4/50	4/49
	Benzyl Acetate	5/50	7/49	3/50	5/50	6/50	7/50
	Geranyl Acetate	7/50	2/50	1/50	6/50	6/50	3/50
	Ethyl Acrylate	9/49	4/49	5/50	11/50	13/50	13/50

APPENDIX J

MUTAGENESIS RESULTS FOR ALLYL ISOVALERATE IN *SALMONELLA TYPHIMURIUM*

APPENDIX J

A. METHODS FOR *SALMONELLA*/MICROSOME MUTAGENICITY TEST SYSTEM

Allyl isovalerate was tested and evaluated blindly in each of 4 tester strains of *Salmonella typhimurium,* using a preincubation modification (Yahagi et al., 1975) of the *Salmonella* assay (Ames et al., 1975). Strains of TA 98 and TA 1537 are more sensitive to chemicals that express frameshift mutagenic activity; strains TA 100 and TA 1535 are more sensitive to chemicals that cause base-pair substitutions. Allyl isovalerate was dissolved in dimethyl sulfoxide and then added to the suspension culture. The mixture was then incubated with the tester strains in suspension culture (20 min. at 37° C) prior to the addition of soft agar and plating for detection of induced mutants. Exogenous metabolic activation was provided by liver S-9 preparations from Arochlor-1254 induced rats and hamsters. Coded chemicals were tested at 5 doses (μg/plate), in triplicate (A,B, and C), in each strain and were retested at least two weeks later.

B. RESULTS

See Tables J1-J4.

TABLE J1. RESULTS OF MUTAGENICITY TESTS OF ALLYL ISOVALETATE IN *SALMONELLA TYPHIMURIUM* TA 98

Dose (μg/plate)	Number of Revertants per Plate *(a)* Initial Test A	B	C	Mean ± SE	Dose (μg/plate)	Retest *(b)* A	B	C	Mean ± SE
0.0 *(c)*	13	18	10	14 ± 2.3	0.0	11	10	9	10 ± 0.6
100.0	16	11	12	13 ± 1.5	10.0	17	16	17	17 ± 0.3
333.0	5	2	1	3 ± 1.2	33.0	14	12	17	14 ± 1.5
1,000.0	2	1	0 *(d)*	1 ± 0.5	100.0	19	12	17	16 ± 2.1
3,333.0	0	0	0	0 ± 0.0	333.0	9	15	19	14 ± 2.9
10,000.0	0	0	0	0 ± 0.0	1,000.0	11	10	10	10 ± 0.3
B. Preincubation with Arochlor-1254 Induced Sprague-Dawley Rat Liver S-9 Preparation									
0.0 *(c)*	20	20	16	19 ± 0.9	0.0 *(c)*	19	12	19	17 ± 2.3
100.0	10	14	12	12 ± 2.1	3.3	15	21	28	21 ± 3.8
333.0	7	10	8	8 ± 0.9	10.0	23	18	12	18 ± 3.2
1,000.0	0	0	0	0 ± 0.0	33.0	13	12	14	13 ± 0.6
3,333.0	0	0	0	0 ± 0.0	100.0	16	18	17	17 ± 0.6
10,000.0	0	1	0	0 ± 0.0	333.0	10	14	12	12 ± 1.2
C. Preincubation with Arochlor-1254 Induced Syrian Hamster Liver S-9 Preparation									
0.0 *(c)*	9	21	20	17 ± 3.8	0.0 *(c)*	21	26	12	20 ± 4.1
100.0	9	7	5	7 ± 1.2	3.3	16	12	11	13 ± 1.5
333.0	7	5	11	8 ± 1.8	10.0	16	8	12	12 ± 2.3
1,000.0	0	0	0	0 ± 0.0	33.0	9	12	10	10 ± 0.9
3,333.0	1	0	0	0 ± 0.3	100.0	3	8	0	4 ± 2.3
10,000.0	0	0	0	0 ± 0.0	333.0	5	8	4	6 ± 1.2

(a) Measured in triplicate
(b) Retest was 2 weeks after initial test
(c) DMSO solvent control

TABLE J2. RESULTS OF MUTAGENICITY TESTS OF ALLYL ISOVALERATE IN *SALMONELLA TYPHIMURIUM* TA 100

Dose (μg/plate)	Number of Revertants per Plate *(a)* Initial Test A	B	C	Mean ± SE	Dose (μg/plate)	Retest *(b)* A	B	C	Mean ± SE
A. No Activation									
0.0 *(c)*	42	92	90	75 ± 16.3	0.0 *(c)*	59	67	83	70 ± 7.1
100.0	68	80	46	65 ± 10.0	10.0	68	73	79	73 ± 3.2
333.0	0 *(d)*	10	0 *(d)*	10	33.0	65	91	65	74 ± 8.7
1,000.0	8	1	3	6 ± 2.5	100.0	79	65	70	71 ± 4.1
3,333.0	7 *(d)*	10	3 *(d)*		333.0	80	89	77	82 ± 3.6
10,000.0	0	0	0	0 ± 0.0	1,000.0	70	87	60	72 ± 7.9
B. Preincubation with Arochlor-1254 Induced Sprague-Dawley Rat Liver S-9 Preparation									
0.0 *(c)*	121	72	97	97 ± 14.1	0.0	61	82	88	77 ± 8.2
100.0	44	58	45	49 ± 4.5	3.3	87	61	78	75 ± 7.6
333.0	27	22	27	25 ± 1.7	10.0	64	64	62	63 ± 0.7
1,000.0	5	3	0	3 ± 1.5	33.0	64	70	77	70 ± 3.8
3,333.0	0	0	0	0 ± 0.0	100.0	47	47	39	44 ± 2.7
10,000.0	0	0	0	0 ± 0.0	333.0	17	34	36	29 ± 6.0
C. Preincubation with Arochlor-1254 Induced Syrian Hamster Liver S-9 Preparation									
0.0 *(c)*	87	79	86	84 ± 2.4	0.0 *(c)*	69	78	72	73 ± 2.6
100.0	73	49	58	60 ± 7.0	3.3	56	61	77	65 ± 6.3
333.0	49	25	27	34 ± 7.7	10.0	50	56	42	49 ± 4.1
1,000.0	2	0	3	2 ± 0.9	33.0	39	41	62	47 ± 7.4
3,333.0	0	0	0	0 ± 0.0	100.0	26	42	40	36 ± 5.0
10,000.0	0	0	0	0 ± 0.0	333.0	17	29	19	22 ± 3.7

(a) Measured in triplicate
(b) Retest was 2 weeks after initial test
(c) DMSO solvent control
(d) Chemical was toxic

TABLE J3. RESULTS OF MUTAGENICITY TESTS OF ALLYL ISOVALERATE IN *SALMONELLA TYPHIMURIUM* TA 1535

Dose (μg/plate)	Number of Revertants per Plate *(a)* Initial Test A	B	C	Mean ± SE	Dose (μg/plate)	Retest *(b)* A	B	C	Mean ± SE
A. No Activation									
0.0	3	2	4	3 ± 0.6	0.0	5	4	2	4 ± 0.9
100.0	5	2	3	3 ± 0.9	3.3	1	2	2	2 ± 0.3
333.0	1	2	1	1 ± 0.3	10.0	1	1	3	2 ± 0.7
1,000.0	0	0	0	0 ± 0.0	33.0	0	3	3	2 ± 1.0
3,333.0	0	0	0	0 ± 0.0	100.0	5	4	6	5 ± 0.6
10,000.0	0	0	0	0 ± 0.0	333.0	1	3	1	2 ± 0.7
B. Preincubation with Arochlor-1254 Induced Sprague-Dawley Rat Liver S-9 Preparation									
0.0 *(c)*	5	6	6	5 ± 0.3	0.0 *(c)*	4	8	3	5 ± 1.5
100.0	2	1	2	2 ± 0.6	3.3	3	6	3	4 ± 1.0
333.0	0	1	2	1 ± 0.6	10.0	3	4	7	5 ± 1.2
1,000.0	0	0	0	0 ± 0.0	33.0	7	6	3	5 ± 1.2
3,333.0	0	0	0	0 ± 0.0	100.0	6	2	4	4 ± 1.2
10,000.0	0	0	0	0 ± 0.0	333.0	2	8	5	5 ± 1.7
C. Preincubation with Arochlor-1254 Induced Syrian Hamster Liver S-9 Preparation									
0.0 *(c)*	3	3	10	5 ± 2.3	0.0 *(c)*	3	3	2	3 ± 0.3
100.0	2	4	2	3 ± 0.7	10.0	4	5	5	5 ± 0.3
333.0	2	2	1	2 ± 0.3	33.0	7	4	6	6 ± 0.9
1,000.0	3	0	0	1 ± 1.0	100.0	1	3	4	3 ± 0.9
3,333.0	1	0	0	0 ± 0.0	333.0	2	3	3	3 ± 0.3
10,000.0	0	0	0	0 ± 0.0	1,000.0	1	0	1	1 ± 0.3

(a) Measured in triplicate
(b) Retest was 2 weeks after initial test
(c) DMSO solvent control

TABLE J4. RESULTS OF MUTAGENICITY TESTS OF ALLYL ISOVALERATE IN *SALMONELLA TYPHIMURIUM* TA 1537

Dose (μg/plate)	Number of Revertants per Plate *(a)* Initial Test A	B	C	Mean ± SE	Dose (μg/plate)	Retest *(b)* A	B	C	Mean ± SE
A. No Activation									
0.0 *(c)*	1	0	2	1 ± 0.6	0.0 *(c)*	2	5	3	3 ± 0.9
100.0	2	2	4	3 ± 0.7	10.0	1	2	4	2 ± 0.9
333.0	1	*(d)*	1	1 ± 0.0	33.0	5	7	2	5 ± 1.5
1,000.0	5	0 *(e)*	1	3 ± 0.0	100.0	9	7	2	6 ± 2.1
3,333.0	1	0	5	2 ± 1.5	333.0	8	9	5	7 ± 1.2
10,000.0	0 *(e)*	0 *(e)*	0 *(e)*	0 ± 0.0	1,000.0	7	5	8	7 ± 0.9
B. Preincubation with Arochlor-1254 Induced Sprague-Dawley Rat Liver S-9 Preparation									
0.0 *(c)*	4	1	3	3 ± 0.9	0.0 *(c)*	5	4	3	4 ± 0.6
100.0	5	10	3	6 ± 2.1	10.0	4	3	5	4 ± 0.6
333.0	0	2	3	2 ± 0.9	33.0	4	4	3	4 ± 0.3
1,000.0	1	0	0	0 ± 0.3	100.0	4	4	5	4 ± 0.3
3,333.0	0	0	0	0 ± 0.0	333.0	6	2	4	4 ± 1.2
10,000.0	0	1	0	0 ± 0.3	1,000.0	1	2	3	2 ± 0.6
C. Preincubation with Arochlor-1254 Induced Syrian Hamster Liver S-9 Preparation									
0.0 *(c)*	4	3	2	3 ± 0.6	0.0 *(c)*	5	7	5	6 ± 0.7
100.0	1	1	2	1 ± 0.3	10.0	3	6	4	4 ± 0.9
333.0	0	3	1	1 ± 0.9	33.0	4	0	2	2 ± 1.2
1,000.0	1	1	0	1 ± 0.3	100.0	1	3	2	2 ± 0.6
3,333.0	1	2	1	1 ± 0.3	333.0	8	4	4	5 ± 1.3
10,000.0	0	0	0	0 ± 0.0	1,000.0	1	1	1	1 ± 0.0

(a) Measured in triplicate
(b) Retest was 2 weeks after initial test
(c) DMSO solvent control
(d) Plate was contaminated
(e) Chemical was toxic

APPENDIX K

ANALYSES OF PRIMARY TUMORS IN RATS AND MICE

TABLE K1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS

	Vehicle Control	31 mg/kg	62 mg/kg
Subcutaneous Tissue: Fibroma			
Tumor Rates			
Overall *(a)*	5/50 (10%)	4/50 (8%)	3/50 (6%)
Adjusted *(b)*	13.2%	12.4%	10.7%
Terminal *(c)*	3/34 (9%)	3/30 (10%)	3/28 (11%)
Statistical Tests *(d)*			
Life Table	P=0.376N	P=0.551N	P=0.445N
Incidental Tumor Test	P=0.280N	P=0.529N	P=0.349N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.290N	P=0.500N	P=0.357N
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Tumor Rates			
Overall *(a)*	3/50 (6%)	2/50 (4%)	0/49 (0%)
Adjusted *(b)*	8.8%	6.0%	0.0%
Terminal *(c)*	3/34 (9%)	1/30 (3%)	0/27 (0%)
Statistical Tests *(d)*			
Life Table	P=0.115N	P=0.540N	P=0.164N
Incidental Tumor Test	P=0.092N	P=0.475N	P=0.164N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.084N	P=0.500N	P=0.125N
Hematopoietic System: Mononuclear Cell Leukemia			
Tumor Rates			
Overall *(a)*	1/50 (2%)	4/50 (8%)	7/50 (14%)
Adjusted *(b)*	2.8%	10.9%	22.0%
Terminal *(c)*	0/34 (0%)	0/30 (0%)	4/28 (14%)
Statistical Tests *(d)*			
Life Table	P=0.015	P=0.183	P=0.022
Incidental Tumor Test	P=0.023	P=0.482	P=0.044
Cochran-Armitage Trend, Fisher Exact Tests	P=0.021	P=0.181	P=0.030
Hematopoietic System: Lymphoma or Leukemia *(e)*			
Tumor Rates			
Overall *(a)*	1/50 (2%)	4/50 (8%)	9/50 (18%)
Adjusted *(b)*	2.8%	10.9%	26.6%
Terminal *(c)*	0/34 (0%)	0/30 (0%)	4/28 (14%)
Statistical Tests *(d)*			
Life Table	P=0.004	P=0.183	P=0.007
Incidental Tumor Test	P=0.008	P=0.482	P=0.020
Cochran-Armitage Trend, Fisher Exact Tests	P=0.005	P=0.181	P=0.008
Liver: Neoplastic Nodule or Hepatocellular Carcinoma			
Tumor Rates			
Overall *(a)*	1/50 (2%)	2/50 (4%)	3/50 (6%)
Adjusted *(b)*	2.9%	6.7%	10.7%
Terminal *(c)*	1/34 (3%)	2/30 (7%)	3/28 (11%)
Statistical Tests *(d)*			
Life Table	P=0.166	P=0.456	P=0.237
Incidental Tumor Test	P=0.166	P=0.456	P=0.237
Cochran-Armitage Trend, Fisher Exact Tests	P=0.222	P=0.500	P=0.309

TABLE K1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS (Continued)

	Vehicle Control	31 mg/kg	62 mg/kg
Pancreas: Acinar-Cell Adenoma			
Tumor Rates			
Overall *(a)*	1/50 (2%)	4/50 (8%)	2/50 (4%)
Adjusted *(b)*	2.9%	12.2%	7.1%
Terminal *(c)*	1/34 (3%)	3/30 (10%)	2/28 (7%)
Statistical Tests *(d)*			
Life Table	P=0.342	P=0.152	P=0.432
Incidental Tumor Test	P=0.352	P=0.183	P=0.432
Cochran-Armitage Trend, Fisher Exact Tests	P=0.406	P=0.181	P=0.500
Pituitary: All Adenomas			
Tumor Rates			
Overall *(a)*	14/49 (29%)	5/46 (11%)	9/49 (18%)
Adjusted *(b)*	37.5%	15.3%	24.8%
Terminal *(c)*	11/34 (32%)	4/28 (14%)	3/27 (11%)
Statistical Tests *(d)*			
Life Table	P=0.231N	P=0.037N	P=0.315N
Incidental Tumor Test	P=0.041N	P=0.032N	P=0.048N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.125N	P=0.028N	P=0.170N
Adrenal: Pheochromocytoma			
Tumor Rates			
Overall *(a)*	15/50 (30%)	15/50 (30%)	15/50 (30%)
Adjusted *(b)*	41.5%	44.8%	47.9%
Terminal *(c)*	13/34 (38%)	12/30 (40%)	12/28 (43%)
Statistical Tests *(d)*			
Life Table	P=0.317	P=0.451	P=0.357
Incidental Tumor Test	P=0.454	P=0.567N	P=0.512
Cochran-Armitage Trend, Fisher Exact Tests	P=0.543	P=0.586N	P=0.586N
Thyroid: C-Cell Adenoma			
Tumor Rates			
Overall *(a)*	5/50 (10%)	7/47 (15%)	3/47 (6%)
Adjusted *(b)*	13.8%	22.0%	10.7%
Terminal *(c)*	3/34 (9%)	6/30 (20%)	3/27 (11%)
Statistical Tests *(d)*			
Life Table	P=0.429N	P=0.316	P=0.472N
Incidental Tumor Test	P=0.383N	P=0.393	P=0.395N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.346N	P=0.336	P=0.393N
Thyroid: C-Cell Carcinoma			
Tumor Rates			
Overall *(a)*	6/50 (12%)	0/47 (0%)	3/47 (6%)
Adjusted *(b)*	17.1%	0.0%	10.7%
Terminal *(c)*	5/34 (15%)	0/30 (0%)	3/27 (11%)
Statistical Tests *(d)*			
Life Table	P=0.207N	P=0.024N	P=0.342N
Incidental Tumor Test	P=0.218N	P=0.020N	P=0.316N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.166N	P=0.016N	P=0.275N

TABLE K1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS (Continued)

	Vehicle Control	31 mg/kg	62 mg/kg
Thyroid: C-Cell Adenoma or Carcinoma			
Tumor Rates			
Overall *(a)*	10/50 (20%)	7/47 (15%)	5/47 (11%)
Adjusted *(b)*	27.7%	22.0%	17.9%
Terminal *(c)*	8/34 (24%)	6/30 (20%)	5/27 (19%)
Statistical Tests *(d)*			
Life Table	P=0.195N	P=0.384N	P=0.247N
Incidental Tumor Test	P=0.165N	P=0.312N	P=0.200N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.127N	P=0.348N	P=0.160N
Pancreatic Islets: Islet-Cell Adenoma or Carcinoma			
Tumor Rates			
Overall *(a)*	3/50 (6%)	0/50 (0%)	2/50 (4%)
Adjusted *(b)*	8.4%	0.0%	7.1%
Terminal *(c)*	2/34 (6%)	0/30 (0%)	2/28 (7%)
Statistical Tests *(d)*			
Life Table	P=0.453N	P=0.136N	P=0.578N
Incidental Tumor Test	P=0.413N	P=0.089N	P=0.521N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.390N	P=0.121N	P=0.500N
Preputial Gland: Adenoma			
Tumor Rates			
Overall *(a)*	0/50 (0%)	4/50 (8%)	1/50 (2%)
Adjusted *(b)*	0.0%	13.3%	3.6%
Terminal *(c)*	0/34 (0%)	4/30 (13%)	1/28 (4%)
Statistical Tests *(d)*			
Life Table	P=0.322	P=0.048	P=0.461
Incidental Tumor Test	P=0.322	P=0.048	P=0.461
Cochran-Armitage Trend, Fisher Exact Tests	P=0.390	P=0.059	P=0.500
Preputial Gland: Adenoma or Carcinoma			
Tumor Rates			
Overall *(a)*	0/50 (0%)	5/50 (10%)	2/50 (4%)
Adjusted *(b)*	0.0%	16.7%	7.1%
Terminal *(c)*	0/34 (0%)	5/30 (17%)	2/28 (7%)
Statistical Tests *(d)*			
Life Table	P=0.175	P=0.023	P=0.196
Incidental Tumor Test	P=0.175	P=0.023	P=0.196
Cochran-Armitage Trend, Fisher Exact Tests	P=0.238	P=0.028	P=0.247
Testis: Interstitial-Cell Tumor			
Tumor Rates			
Overall *(a)*	40/50 (80%)	44/50 (88%)	40/50 (80%)
Adjusted *(b)*	100.0%	100.0%	92.9%
Terminal *(c)*	34/34 (100%)	30/30 (100%)	25/28 (89%)
Statistical Tests *(d)*			
Life Table	P=0.121	P=0.060	P=0.146
Incidental Tumor Test	P=0.419N	P=0.142	P=0.530N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.553	P=0.207	P=0.598

TABLE K1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS (Continued)

(a) Number of tumor bearing animals/number of animals examined at the site.
(b) Kaplan-Meier estimated lifetime tumor incidence after adjusting for intercurrent mortality.
(c) Observed tumor incidence at terminal kill.
(d) Beneath the control incidence are the P-values associated with the trend test. Beneath the dosed group incidence are the P-values corresponding to pairwise comparisons between that dosed group and the controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as non-fatal. The Cochran-Armitage and Fisher's exact tests compare directly the overall incidence rates. A negative trend or significantly lower incidence is indicated by (N).
(e) Two additional male rats had lymphomas.

TABLE K2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS

	Vehicle Control	31 mg/kg	62 mg/kg
Subcutaneous Tissue: Fibroma			
Tumor Rates			
Overall *(a)*	0/50 (0%)	3/50 (6%)	0/49 (0%)
Adjusted *(b)*	0.0%	7.9%	0.0%
Terminal *(c)*	0/38 (0%)	2/36 (6%)	0/29 (0%)
Statistical Tests *(d)*			
Life Table	P=0.568	P=0.114	(e)
Incidental Tumor Test	P=0.637N	P=0.117	(e)
Cochran-Armitage Trend, Fisher Exact Tests	P=0.634	P=0.121	(e)
Hematopoietic System: Mononuclear Cell Leukemia			
Tumor Rates			
Overall *(a)*	4/50 (8%)	6/50 (12%)	8/49 (16%)
Adjusted *(b)*	9.9%	15.1%	20.8%
Terminal *(c)*	3/38 (8%)	4/36 (11%)	2/29 (7%)
Statistical Tests *(d)*			
Life Table	P=0.081	P=0.354	P=0.118
Incidental Tumor Test	P=0.241	P=0.474	P=0.343
Cochran-Armitage Trend, Fisher Exact Tests	P=0.132	P=0.370	P=0.168
Hematopoietic System: Leukemia			
Tumor Rates			
Overall *(a)*	4/50 (8%)	6/50 (12%)	9/49 (18%)
Adjusted *(b)*	9.9%	15.1%	22.8%
Terminal *(c)*	3/38 (8%)	4/36 (11%)	2/29 (7%)
Statistical Tests *(d)*			
Life Table	P=0.050	P=0.354	P=0.075
Incidental Tumor Test	P=0.173	P=0.474	P=0.265
Cochran-Armitage Trend, Fisher Exact Tests	P=0.082	P=0.370	P=0.109
Hematopoietic System: Lymphoma or Leukemia			
Tumor Rates			
Overall *(a)*	5/50 (10%)	6/50 (12%)	10/49 (20%)
Adjusted *(b)*	12.5%	15.1%	24.8%
Terminal *(c)*	4/38 (11%)	4/36 (11%)	2/29 (7%)
Statistical Tests *(d)*			
Life Table	P=0.055	P=0.478	P=0.081
Incidental Tumor Test	P=0.190	P=0.600	P=0.288
Cochran-Armitage Trend, Fisher Exact Tests	P=0.090	P=0.500	P=0.122
Pituitary: All Adenomas			
Tumor Rates			
Overall *(a)*	13/48 (27%)	17/49 (35%)	13/48 (27%)
Adjusted *(b)*	32.7%	41.8%	35.5%
Terminal *(c)*	10/36 (28%)	12/35 (34%)	6/28 (21%)
Statistical Tests *(d)*			
Life Table	P=0.297	P=0.244	P=0.350
Incidental Tumor Test	P=0.495N	P=0.241	P=0.513N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.544	P=0.277	P=0.591

TABLE K2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS (Continued)

	Vehicle Control	31 mg/kg	62 mg/kg
Adrenal: Pheochromocytoma			
Tumor Rates			
Overall *(a)*	5/50 (10%)	8/50 (16%)	6/49 (12%)
Adjusted *(b)*	13.2%	22.2%	20.7%
Terminal *(c)*	5/38 (13%)	8/36 (22%)	6/29 (21%)
Statistical Tests *(d)*			
Life Table	P=0.248	P=0.238	P=0.313
Incidental Tumor Test	P=0.248	P=0.238	P=0.313
Cochran-Armitage Trend, Fisher Exact Tests	P=0.425	P=0.277	P=0.486
Thyroid: C-Cell Adenoma			
Tumor Rates			
Overall *(a)*	2/48 (4%)	7/50 (14%)	4/46 (9%)
Adjusted *(b)*	5.4%	18.8%	14.3%
Terminal *(c)*	2/37 (5%)	6/36 (17%)	4/28 (14%)
Statistical Tests *(d)*			
Life Table	P=0.165	P=0.076	P=0.216
Incidental Tumor Test	P=0.196	P=0.080	P=0.216
Cochran-Armitage Trend, Fisher Exact Tests	P=0.273	P=0.090	P=0.318
Thyroid: C-Cell Adenoma or Carcinoma			
Tumor Rates			
Overall *(a)*	4/48 (8%)	8/50 (16%)	5/46 (11%)
Adjusted *(b)*	10.8%	21.5%	17.9%
Terminal *(c)*	4/37 (11%)	7/36 (19%)	5/28 (18%)
Statistical Tests *(d)*			
Life Table	P=0.255	P=0.165	P=0.327
Incidental Tumor Test	P=0.290	P=0.172	P=0.327
Cochran-Armitage Trend, Fisher Exact Tests	P=0.407	P=0.199	P=0.473
Mammary Gland: Fibroadenoma			
Tumor Rates			
Overall *(b)*	17/50 (34%)	23/50 (46%)	11/49 (22%)
Adjusted *(b)*	40.1%	57.1%	33.3%
Terminal *(d)*	13/38 (34%)	19/36 (53%)	7/29 (24%)
Statistical Tests *(e)*			
Life Table	P=0.393N	P=0.123	P=0.376N
Incidental Tumor Test	P=0.177N	P=0.125	P=0.175N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.137N	P=0.154	P=0.146N
Preputial Gland: Adenoma, Adenosquamous Carcinoma, or Carcinoma			
Tumor Rates			
Overall *(a)*	0/50 (0%)	3/50 (6%)	2/49 (4%)
Adjusted *(b)*	0.0%	8.3%	6.2%
Terminal *(c)*	0/38 (0%)	3/36 (8%)	1/29 (3%)
Statistical Tests *(d)*			
Life Table	P=0.140	P=0.111	P=0.189
Incidental Tumor Test	P=0.175	P=0.111	P=0.262
Cochran-Armitage Trend, Fisher Exact Tests	P=0.196	P=0.121	P=0.242

TABLE K2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS (Continued)

	Vehicle Control	31 mg/kg	62 mg/kg
Uterus: Endometrial Stromal Polyp			
Tumor Rates			
Overall *(a)*	11/50 (22%)	8/50 (16%)	13/48 (27%)
Adjusted *(b)*	27.3%	18.5%	43.1%
Terminal *(c)*	9/38 (24%)	4/36 (11%)	12/29 (41%)
Statistical Tests *(d)*			
Life Table	P=0.168	P=0.339N	P=0.157
Incidental Tumor Test	P=0.307	P=0.168N	P=0.227
Cochran-Armitage Trend, Fisher Exact Tests	P=0.318	P=0.306N	P=0.363
Uterus: Endometrial Stromal Polyp or Sarcoma			
Tumor Rates			
Overall *(a)*	12/50 (24%)	8/50 (16%)	14/48 (29%)
Adjusted *(b)*	28.8%	18.5%	44.6%
Terminal *(c)*	9/38 (24%)	4/36 (11%)	12/29 (41%)
Statistical Tests *(d)*			
Life Table	P=0.173	P=0.261N	P=0.165
Incidental Tumor Test	P=0.330	P=0.128N	P=0.255
Cochran-Armitage Trend, Fisher Exact Tests	P=0.319	P=0.227N	P=0.363

(a) Number of tumor bearing animals/number of animals examined at the site.
(b) Kaplan-Meier estimated lifetime tumor incidence after adjusting for intercurrent mortality.
(c) Observed tumor incidence at terminal kill.
(d) Beneath the control incidence are the P-values associated with the trend test. Beneath the dosed group incidence are the P-values corresponding to pairwise comparisons between that dosed group and the controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as non-fatal. The Cochran-Armitage and Fisher's exact tests compare directly the overall incidence rates. A negative trend or significantly lower incidence is indicated by (N).
(e) The configuration of tumor incidence precludes use of this statistic.

TABLE K3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE

	Vehicle Control	31 mg/kg	62 mg/kg
Skin: Fibroma			
Tumor Rates			
Overall *(a)*	3/50 (6%)	1/50 (2%)	0/50 (0%)
Adjusted *(b)*	10.3%	3.2%	0.0%
Terminal *(c)*	3/29 (10%)	1/31 (3%)	0/31 (0%)
Statistical Tests *(d)*			
Life Table	P=0.052N	P=0.280N	P=0.109N
Incidental Tumor Test	P=0.052N	P=0.280N	P=0.109N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.060N	P=0.309N	P=0.121N
Subcutaneous Tissue: All Sarcomas			
Tumor Rates			
Overall *(a)*	3/50 (6%)	2/50 (4%)	2/50 (4%)
Adjusted *(b)*	8.1%	6.0%	6.0%
Terminal *(c)*	1/29 (3%)	1/31 (3%)	1/31 (3%)
Statistical Tests *(d)*			
Life Table	P=0.400N	P=0.489N	P=0.494N
Incidental Tumor Test	P=0.508N	P=0.573N	P=0.614N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.406N	P=0.500N	P=0.500N
Lung: Alveolar/Bronchiolar Adenoma			
Tumor Rates			
Overall *(a)*	10/50 (20%)	5/50 (10%)	3/49 (6%)
Adjusted *(b)*	31.6%	15.1%	9.0%
Terminal *(c)*	8/29 (28%)	4/31 (13%)	2/31 (6%)
Statistical Tests *(d)*			
Life Table	P=0.018N	P=0.108N	P=0.031N
Incidental Tumor Test	P=0.030N	P=0.149N	P=0.047N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.025N	P=0.131N	P=0.039N
Lung: Alveolar/Bronchiolar Carcinoma			
Tumor Rates			
Overall *(a)*	3/50 (6%)	1/50 (2%)	2/49 (4%)
Adjusted *(b)*	8.2%	3.2%	6.0%
Terminal *(c)*	1/29 (3%)	1/31 (3%)	1/31 (3%)
Statistical Tests *(d)*			
Life Table	P=0.391N	P=0.300N	P=0.492N
Incidental Tumor Test	P=0.495N	P=0.392N	P=0.624N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.407N	P=0.309N	P=0.510N
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Tumor Rates			
Overall *(a)*	13/50 (26%)	6/50 (12%)	5/49 (10%)
Adjusted *(b)*	38.1%	18.3%	14.6%
Terminal *(c)*	9/29 (31%)	5/31 (16%)	3/31 (10%)
Statistical Tests *(d)*			
Life Table	P=0.017N	P=0.053N	P=0.031N
Incidental Tumor Test	P=0.034N	P=0.087N	P=0.057N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.022N	P=0.062N	P=0.037N

TABLE K3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE (Continued)

	Vehicle Control	31 mg/kg	62 mg/kg
Hematopoietic System: Malignant Lymphoma, Lymphocytic Type			
Tumor Rates			
Overall *(a)*	1/50 (4%)	2/50 (4%)	1/50 (2%)
Adjusted *(b)*	2.7%	5.7%	2.6%
Terminal *(c)*	0/29 (0%)	1/31 (3%)	0/31 (0%)
Statistical Tests *(d)*			
Life Table	P=0.617	P=0.499	P=0.751
Incidental Tumor Test	P=0.518	P=0.444	P=0.692
Cochran-Armitage Trend, Fisher Exact Tests	P=0.622	P=0.500	P=0.753N
Hematopoietic System: Malignant Lymphoma, Histiocytic Type			
Tumor Rates			
Overall *(a)*	0/50 (0%)	2/50 (4%)	1/50 (2%)
Adjusted *(b)*	0.0%	6.3%	2.7%
Terminal *(c)*	0/29 (0%)	1/31 (3%)	0/31 (0%)
Statistical Tests *(d)*			
Life Table	P=0.373	P=0.251	P=0.500
Incidental Tumor Test	P=0.303	P=0.202	P=0.433
Cochran-Armitage Trend, Fisher Exact Tests	P=0.361	P=0.247	P=0.500
Hematopoietic System: Malignant Lymphoma, Mixed Type			
Tumor Rates			
Overall *(a)*	3/50 (6%)	2/50 (4%)	6/50 (12%)
Adjusted *(b)*	10.0%	6.2%	17.2%
Terminal *(c)*	2/29 (7%)	1/31 (3%)	4/31 (13%)
Statistical Tests *(d)*			
Life Table	P=0.192	P=0.473N	P=0.272
Incidental Tumor Test	P=0.130	P=0.556N	P=0.193
Cochran-Armitage Trend, Fisher Exact Tests	P=0.169	P=0.500N	P=0.243
Hematopoietic System: Lymphoma, All Malignant			
Tumor Rates			
Overall *(a)*	4/50 (8%)	6/50 (12%)	8/50 (16%)
Adjusted *(b)*	12.4%	17.3%	21.5%
Terminal *(c)*	2/29 (7%)	3/31 (10%)	4/31 (13%)
Statistical Tests *(d)*			
Life Table	P=0.167	P=0.397	P=0.204
Incidental Tumor Test	P=0.077	P=0.283	P=0.105
Cochran-Armitage Trend, Fisher Exact Tests	P=0.141	P=0.370	P=0.178
Liver: Hepatocellular Adenoma			
Tumor Rates			
Overall *(a)*	7/50 (14%)	8/50 (16%)	8/50 (16%)
Adjusted *(b)*	23.1%	23.2%	24.4%
Terminal *(c)*	6/29 (21%)	6/31 (19%)	7/31 (23%)
Statistical Tests *(d)*			
Life Table	P=0.487	P=0.543	P=0.549
Incidental Tumor Test	P=0.406	P=0.523	P=0.489
Cochran-Armitage Trend, Fisher Exact Tests	P=0.445	P=0.500	P=0.500

TABLE K3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE (Continued)

	Vehicle Control	31 mg/kg	62 mg/kg
Liver: Hepatocellular Carcinoma			
Tumor Rates			
Overall *(a)*	18/50 (36%)	6/50 (12%)	9/50 (18%)
Adjusted *(b)*	47.6%	16.7%	25.4%
Terminal *(c)*	10/29 (34%)	3/31 (10%)	6/31 (19%)
Statistical Tests *(d)*			
Life Table	P=0.021N	P=0.006N	P=0.038N
Incidental Tumor Test	P=0.044N	P=0.013N	P=0.069N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.020N	P=0.005N	P=0.035N
Liver: Hepatocellular Adenoma or Carcinoma			
Tumor Rates			
Overall *(a)*	23/50 (46%)	14/50 (28%)	15/50 (30%)
Adjusted *(b)*	59.9%	37.6%	43.3%
Terminal *(c)*	14/29 (48%)	9/31 (29%)	12/31 (39%)
Statistical Tests *(d)*			
Life Table	P=0.052N	P=0.049N	P=0.066N
Incidental Tumor Test	P=0.108N	P=0.092N	P=0.117N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.058N	P=0.048N	P=0.074N
Gastric Mucosa: Squamous Cell Papilloma			
Tumor Rates			
Overall *(a)*	0/50 (0%)	1/50 (2%)	3/48 (6%)
Adjusted *(b)*	0.0%	3.2%	9.4%
Terminal *(c)*	0/29 (0%)	1/31 (3%)	2/31 (6%)
Statistical Tests *(d)*			
Life Table	P=0.068	P=0.513	P=0.137
Incidental Tumor Test	P=0.048	P=0.513	P=0.090
Cochran-Armitage Trend, Fisher Exact Tests	P=0.056	P=0.500	P=0.114
Adrenal: Pheochromocytoma			
Tumor Rates			
Overall *(a)*	4/49 (8%)	2/46 (4%)	2/48 (4%)
Adjusted *(b)*	13.8%	7.4%	6.3%
Terminal *(c)*	4/29 (14%)	2/27 (7%)	1/30 (3%)
Statistical Tests *(d)*			
Life Table	P=0.238N	P=0.368N	P=0.317N
Incidental Tumor Test	P=0.263N	P=0.368N	P=0.354N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.262N	P=0.369N	P=0.349N
Adrenal: Pheochromocytoma or Pheochromocytoma, Malignant			
Tumor Rates			
Overall *(a)*	5/49 (10%)	3/46 (7%)	2/48 (4%)
Adjusted *(b)*	17.2%	11.1%	6.3%
Terminal *(c)*	5/29 (17%)	3/27 (11%)	1/30 (3%)
Statistical Tests *(d)*			
Life Table	P=0.146N	P=0.393N	P=0.199N
Incidental Tumor Test	P=0.163N	P=0.393N	P=0.227N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.167N	P=0.393N	P=0.226N

TABLE K3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE (Continued)

	Vehicle Control	31 mg/kg	62 mg/kg
Thyroid: Follicular-Cell Adenoma			
Tumor Rates			
Overall *(a)*	5/47 (11%)	0/46 (0%)	1/49 (2%)
Adjusted *(b)*	16.5%	0.0%	3.2%
Terminal *(c)*	4/29 (14%)	0/30 (0%)	1/31 (3%)
Statistical Tests *(d)*			
Life Table	P=0.032N	P=0.031N	P=0.090N
Incidental Tumor Test	P=0.039N	P=0.038N	P=0.105N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.034N	P=0.030N	P=0.093N
Harderian Gland: Adenoma			
Tumor Rates			
Overall *(a)*	4/50 (8%)	4/50 (8%)	2/50 (4%)
Adjusted *(b)*	13.8%	11.4%	6.5%
Terminal *(c)*	4/29 (14%)	2/31 (6%)	2/31 (6%)
Statistical Tests *(d)*			
Life Table	P=0.251N	P=0.613N	P=0.304N
Incidental Tumor Test	P=0.284N	P=0.597	P=0.304N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.274N	P=0.643	P=0.339N

(a) Number of tumor bearing animals/number of animals examined at the site.
(b) Kaplan-Meier estimated lifetime tumor incidence after adjusting for intercurrent mortality.
(c) Observed tumor incidence at terminal kill.
(d) Beneath the control incidence are the P-values associated with the trend test. Beneath the dosed group incidence are the P-values corresponding to pairwise comparisons between that dosed group and the controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as non-fatal. The Cochran-Armitage and Fisher's exact tests compare directly the overall incidence rates. A negative trend or a significantly lower incidence is indicated by (N).

TABLE K4. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE

	Vehicle Control	31 mg/kg	62 mg/kg
Lung: Alveolar/Bronchiolar Adenoma			
Tumor Rates			
Overall *(a)*	2/50 (4%)	4/49 (8%)	2/50 (4%)
Adjusted *(b)*	5.8%	18.6%	6.1%
Terminal *(c)*	1/32 (3%)	2/17 (12%)	0/24 (0%)
Statistical Tests *(d)*			
Life Table	P=0.519	P=0.176	P=0.664
Incidental Tumor Test	P=0.438N	P=0.358	P=0.494N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.588	P=0.329	P=0.691
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Tumor Rates			
Overall *(a)*	4/50 (8%)	4/49 (8%)	3/50 (6%)
Adjusted *(b)*	11.9%	18.6%	10.0%
Terminal *(c)*	3/32 (9%)	2/17 (12%)	1/24 (4%)
Statistical Tests *(d)*			
Life Table	P=0.530N	P=0.381	P=0.590N
Incidental Tumor Test	P=0.348N	P=0.590	P=0.404N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.424N	P=0.631	P=0.500N
Hematopoietic System: Malignant Lymphoma, Lymphocytic Type			
Tumor Rates			
Overall *(a)*	5/50 (10%)	5/50 (10%)	4/50 (8%)
Adjusted *(b)*	12.3%	21.9%	12.6%
Terminal *(c)*	2/32 (6%)	3/17 (18%)	2/24 (8%)
Statistical Tests *(d)*			
Life Table	P=0.515N	P=0.422	P=0.557N
Incidental Tumor Test	P=0.432	P=0.422	P=0.447
Cochran-Armitage Trend, Fisher Exact Tests	P=0.432N	P=0.630N	P=0.500N
Hematopoietic System: Malignant Lymphoma, Histiocytic Type			
Tumor Rates			
Overall *(a)*	0/50 (0%)	1/50 (2%)	4/50 (8%)
Adjusted *(b)*	0.0%	5.9%	12.8%
Terminal *(c)*	0/32 (0%)	1/17 (6%)	0/24 (0%)
Statistical Tests *(d)*			
Life Table	P=0.024	P=0.374	P=0.052
Incidental Tumor Test	P=0.058	P=0.374	P=0.336
Cochran-Armitage Trend, Fisher Exact Tests	P=0.026	P=0.500	P=0.059
Hematopoietic System: Malignant Lymphoma, Mixed Type			
Tumor Rates			
Overall *(a)*	6/50 (12%)	5/50 (10%)	10/50 (20%)
Adjusted *(b)*	18.8%	23.1%	37.8%
Terminal *(c)*	6/32 (19%)	2/17 (12%)	8/24 (33%)
Statistical Tests *(d)*			
Life Table	P=0.064	P=0.368	P=0.073
Incidental Tumor Test	P=0.136	P=0.573N	P=0.133
Cochran-Armitage Trend, Fisher Exact Tests	P=0.157	P=0.500N	P=0.207

TABLE K4. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE (Continued)

	Vehicle Control	31 mg/kg	62 mg/kg
Hematopoietic System: Lymphoma, All Malignant			
Tumor Rates			
Overall *(a)*	11/50 (22%)	11/50 (22%)	18/50 (36%)
Adjusted *(b)*	29.8%	46.5%	54.7%
Terminal *(c)*	8/32 (25%)	6/17 (35%)	10/24 (42%)
Statistical Tests *(d)*			
Life Table	P=0.026	P=0.172	P=0.034
Incidental Tumor Test	P=0.037	P=0.360	P=0.052
Cochran-Armitage Trend, Fisher Exact Tests	P=0.071	P=0.595	P=0.093
Liver: Hepatocellular Adenoma or Carcinoma			
Tumor Rates			
Overall *(a)*	3/50 (6%)	0/50 (0%)	1/50 (2%)
Adjusted *(b)*	9.4%	0.0%	2.2%
Terminal *(c)*	3/32 (9%)	0/17 (0%)	0/24 (0%)
Statistical Tests *(d)*			
Life Table	P=0.238N	P=0.251N	P=0.374N
Incidental Tumor Test	P=0.210N	P=0.251N	P=0.329N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.176N	P=0.121N	P=0.309N
Pituitary: Adenoma			
Tumor Rates			
Overall *(a)*	11/43 (26%)	2/43 (5%)	7/44 (16%)
Adjusted *(b)*	36.7%	8.5%	30.4%
Terminal *(c)*	11/30 (37%)	1/16 (6%)	7/23 (30%)
Statistical Tests *(d)*			
Life Table	P=0.316N	P=0.076N	P=0.428N
Incidental Tumor Test	P=0.362N	P=0.081N	P=0.428N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.139N	P=0.007N	P=0.198N
Thyroid: Follicular-Cell Adenoma			
Tumor Rates			
Overall *(a)*	3/49 (6%)	2/48 (4%)	2/48 (4%)
Adjusted *(b)*	9.7%	9.5%	8.3%
Terminal *(c)*	3/31 (10%)	1/17 (6%)	2/24 (8%)
Statistical Tests *(d)*			
Life Table	P=0.523N	P=0.633	P=0.617N
Incidental Tumor Test	P=0.461N	P=0.606N	P=0.617N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.415N	P=0.510N	P=0.510N
Thyroid: Follicular-Cell Adenoma or Carcinoma			
Tumor Rates			
Overall *(a)*	4/49 (8%)	2/48 (4%)	2/48 (4%)
Adjusted *(b)*	12.9%	9.5%	8.3%
Terminal *(c)*	4/31 (13%)	1/17 (6%)	2/24 (8%)
Statistical Tests *(d)*			
Life Table	P=0.371N	P=0.600N	P=0.459N
Incidental Tumor Test	P=0.313N	P=0.470N	P=0.459N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.260N	P=0.349N	P=0.349N

TABLE K4. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE (Continued)

	Vehicle Control	31 mg/kg	62 mg/kg
Mammary Gland: Adenocarcinoma			
Tumor Rates			
Overall *(a)*	2/50 (4%)	3/50 (6%)	2/50 (4%)
Adjusted *(b)*	6.1%	15.2%	8.3%
Terminal *(c)*	1/32 (3%)	2/17 (12%)	2/24 (8%)
Statistical Tests *(d)*			
Life Table	P=0.467	P=0.261	P=0.592
Incidental Tumor Test	P=0.581N	P=0.577	P=0.672N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.594	P=0.500	P=0.691

(a) Number of tumor bearing animals/number of animals examined at the site.
(b) Kaplan-Meier estimated lifetime tumor incidence after adjusting for intercurrent mortality.
(c) Observed tumor incidence at terminal kill.
(d) Beneath the control incidence are the P-values associated with the trend test. Beneath the dosed group incidence are the P-values corresponding to pairwise comparisons between that dosed group and the controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as non-fatal. The Cochran-Armitage and Fisher's exact tests compare directly the overall incidence rates. A negative trend or a significantly lower incidence is indicated by (N).

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