NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 259

CARCINOGENESIS STUDIES

OF

ETHYL ACRYLATE

(CAS NO. 140-88-5)

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

Special Note: A draft of this Technical Report was peer reviewed in public session and approved by the NTP Board of Scientific Counselors' Technical Reports Review Subcommittee in February 1983, before the NTP adopted use of levels of evidence of carcinogenicity for its carcinogenesis studies. In October 1983, the NTP adopted the policy that the experimental data and laboratory records from all NTP Toxicology and Carcinogenesis Studies not yet printed and distributed would be audited. [A summary of the data audit is presented in Appendix N.] Consequently, printing and distribution of this Technical Report have been delayed and the format differs from that of Technical Reports peer reviewed more recently. This final Technical Report supercedes all previous versions of this report that have been distributed.

NTP TECHNICAL REPORT
ON THE

CARCINOGENESIS STUDIES

OF

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(CAS NO. 140-88-5)

IN F344/N RATS AND B6C3F$_1$ MICE

(GAVAGE STUDIES)

NATIONAL TOXICOLOGY PROGRAM
P.O. Box 12233
Research Triangle Park, NC 27709

December 1986

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
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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 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 Environmental Health Sciences, National Toxicology Program.

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

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 studies 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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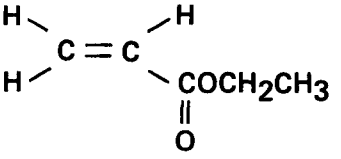

ETHYL ACRYLATE

CAS NO. 140-88-5

$C_5H_8O_2$ **Mol. Wt. 100.12**

ABSTRACT

Carcinogenesis studies of ethyl acrylate were conducted by administering this test chemical in corn oil by gavage to groups of 50 male and 50 female F344/N rats and B6C3F$_1$ mice at doses of 100 or 200 mg/kg. Ethyl acrylate was 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 schedule and served as vehicle controls.

Survival of dosed male and female rats and mice was comparable with that of the corresponding vehicle controls. There was no evidence of systemic toxicity in the prechronic or in the 2-year studies.

Compound-related increased incidences of hyperkeratosis, inflammation, and hyperplasia of the forestomach were observed in rats and mice in the prechronic as well as 2-year studies. In the 2-year studies, squamous cell papillomas and squamous cell carcinomas of the forestomach occurred at the site of chemical deposition with significant positive trends and increased incidences in dosed groups versus vehicle controls for both sexes of rats and mice. Nonneoplastic and neoplastic forestomach lesion frequencies were related to the concentration of ethyl acrylate in dosing solutions used. Significant negative trends for several common rodent tumors were found in treated animals in the 2-year studies.

Under the conditions of these studies, ethyl acrylate was carcinogenic for the forestomach of F344/N rats and B6C3F$_1$ mice, causing squamous cell carcinomas in male rats and male mice, squamous cell papillomas in male and female rats and male mice, and squamous cell papillomas or carcinomas (combined) in male and female rats and mice. Evidence for carcinogenicity was greater in males than in females. Ethyl acrylate also caused irritation of the forestomach mucosa in male and female rats and mice.

CONTRIBUTORS

The carcinogenesis studies of ethyl acrylate were conducted at Southern Research Institute under a subcontract to Tracor Jitco, Inc., the prime contractor for the Carcinogenesis Testing Program. The two-year studies were begun in February 1979 and completed in February 1981.

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SUMMARY OF PEER REVIEW COMMENTS ON THE CARCINOGENESIS STUDIES OF ETHYL ACRYLATE

On February 28, 1983, this report on ethyl acrylate received peer review by the National Toxicology Program Board of Scientific Counselors' Technical Reports Review Subcommittee and associated Panel of Experts. The 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.

Dr. Swenberg, a principal reviewer for the technical report on the carcinogenesis studies of ethyl acrylate, agreed with the stated conclusions. He indicated that the studies were interpreted objectively and the section on human toxicity and exposure put the findings in perspective for the reader. Dr. Swenberg said that while there was not a decrease in survival or body weight, he believed that because of inflammatory lesions observed in the forestomach, higher doses could not have been tolerated.

As a second principal reviewer, Dr. Davis agreed with the conclusions and said the study design was sound. She said the gavage route was appropriate, but bolus delivery may have provided a cofactor for carcinogenesis. She noted the increased incidence of retinopathy and cataracts in high dose male and low dose female rats. Dr. Davis commented that the discussion was comprehensive and explained the problems of conducting the study of lower molecular weight esters of acrylic acid.

As a third principal reviewer, Dr. Friess stated that the finding of increased incidence of squamous cell carcinomas with increased concentration of chemical in the bolus suggests a direct linkage of the effect with irritant/necrotic stresses rather than direct chemical initiation of carcinogenesis, and he said this view is further supported by lack of carcinogenic effect reported in a recently completed inhalation study. Dr. Friess commented on the dose-dependent negative trends in tumor incidence in both rats and mice and wondered whether there were any dietary, stress, or metabolic factors different in dosed than in control animals. He observed that the genetic variance or lack of genetic homogeneity of the $B6C3F_1$ stock in this study as well as in other studies did nothing to invalidate these experimental findings.

Dr. Beliczky questioned whether too much emphasis was given to the negative trends for tumor incidence, while Dr. Davis noted the analogy with the divergent antitumor and carcinogenic effects of many cancer chemotherapeutic agents. Dr. Scala thought the inclusion of sentinel animal data in recent reports was good, and requested that further effort be devoted to the meaning or significance of these data.

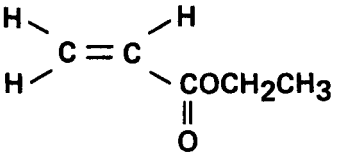
Panel members and NTP staff discussed the differential degree of carcinogenic response between male and female animal groups and the statistically non-significant increases for squamous cell papillomas only in female mice. Dr. Swenberg stated that for forestomach tumors, progression was likely, and thus the papillomas observed in female mice should not be ignored.

Dr. Swenberg moved that the technical report on the carcinogenesis studies of ethyl acrylate be accepted with the revisions discussed. Dr. Davis seconded the motion and the report was approved unanimously by the Peer Review Panel.

I. INTRODUCTION

Chemical Identification
Production and Use
Metabolism
Animal Toxicity and Teratogenicity
Human Toxicity and Exposure
Mutagenicity and Carcinogenicity
Rationale for Testing

I. INTRODUCTION



ETHYL ACRYLATE

CAS NO. 140-88-5

$C_5H_8O_2$ **Mol. Wt. 100.12**

Chemical Identification

Ethyl acrylate (2-propenoic acid, ethyl ester) is a colorless liquid with a penetrating acrid odor. This ester is soluble in ethanol, ether, and chloroform and is slightly soluble in water. Typical U.S. commercial grade ethyl acrylate is 99% pure (IARC, 1979).

Production and Use

Ethyl acrylate is a monomer used to produce polymers and copolymers for use in latex paints, textiles, paper coatings, fabric finishes, dirt release agents, and specialty plastics (IARC, 1979). In 1980, 268 million pounds of ethyl acrylate were produced in the United States, of which 209 million pounds were used by the producers and 59 million pounds sold (USITC, 1981).

Polymers and copolymers containing ethyl acrylate are approved as components of various products intended for use in contact with food (U.S. CFR, 1978a, 1978b, 1978c). In the past, minor uses of copolymers have included components of fingernail elongators (Balsam and Sagrin, 1982) and denture bases (Kirk-Othmer, 1965).

Ethyl acrylate occurs naturally in pineapples and raspberries (NTIS, 1974), has been used since the 1950's as a fragrance (Opdyke, 1975), and has been approved by the U.S. Food and Drug Administration as a flavoring agent (U.S. CFR, 1979). Its use as a flavoring agent has been decreasing (1970 153 lbs.; 1975 80 lbs; 1976 0.2 lbs.) (NAS/NRC 1970, 1975, 1976). As a fragrance less than 1,000 lbs. have been used per year in the U.S. (Opdyke, 1975).

Metabolism

Ethyl acrylate is enzymatically hydrolyzed to acrylic acid by plasma and homogenates of rat liver, kidneys, and lungs with greatest esterase activity toward ethyl acrylate in the liver (Silver and Murphy, 1981; Miller et al., 1981). Ethyl acrylate binds with glutathione *in vitro* and decreases tissue nonprotein sulfhydryl *in vivo* (Silver and Murphy, 1981).

The metabolism of ethyl acrylate *in vivo* and in selected tissues *in vitro* has also been studied by the NTP (unpublished NTP data reported in Appendix M). Ethyl acrylate was metabolized *in vitro* by forestomach, glandular stomach, stomach contents, and blood of male and female F344 rats. Metabolism was first order and most rapid in blood. Half-life estimates were 14 and 11 minutes (males and females) in blood, 74 and 94 minutes in forestomach tissue, 64 and 62 minutes in glandular stomach tissue, and 49 and 68 minutes in stomach contents. The sex-differences were not significant.

Concentrations of non-protein thiols in the forestomach and in the glandular stomach were substantially reduced 30 and 120 minutes after F344 rats were given 100 mg/kg (2% solution) or 200 mg/kg (4% solution) of ethyl acrylate by gavage in corn oil. From 30% to 32% of the dose remained in the stomach as ethyl acrylate 30 minutes after dosing at 100 mg/kg and 21%-27% was present 120 minutes after dosing. Corresponding values for the 200 mg/kg dose were 23%-24% at 30 minutes and 13%-16% at 120 minutes. No differences were observed between males and females with respect to decrease in non-protein thiols or to the disappearance of ethyl acrylate from the stomach (Appendix M).

Ethyl acrylate was measured in retro-orbital venous plexus blood at 15, 30, and 60 minutes and in portal venous blood at 15 and 30 minutes after a single gavage dose of 200 mg/kg ethyl acrylate in corn oil. No ethyl acrylate was found in any of the retro-orbital venous plexus blood samples (limit of detection was 1 μg/ml). All animals had detectable amounts of ethyl acrylate in portal venous blood at either 15 or 30 minutes after dosing. Concentrations up to 27 μg/ml were observed (Appendix M).

Animal Toxicity and Teratogenicity

Ethyl acrylate has low acute toxicity in laboratory animals. The oral LD_{50} in rats is approximately 1,020 mg/kg body weight (Pozzani et al., 1949). Following a 4-hour inhalation exposure, the LC_{50} for rats was between 1,000 and 2,000 ppm (Pozzani et al., 1949). The LD_{50} in male ICR mice given ethyl acrylate by intraperitoneal injection was reported to be 599 mg/kg body weight (Lawrence et al., 1972). In rabbits the dermal LD_{50} was 1,790 mg/kg body weight (Pozzani et al., 1949) and the minimum lethal oral dose was 280 to 420 mg/kg body weight (Treon et al., 1949).

Toxicity following repeated inhalation exposure to ethyl acrylate has been reported for rats, mice, guinea pigs, and rabbits. Exposure of rats to 540, 300, and 70 ppm of ethyl acrylate for up to 30 days produced mortality and pathologic changes in lungs, liver, and kidneys in the high and middle concentration groups (Pozzani et al., 1949). The 540 ppm exposure concentration was terminated after 19 exposure days because of high mortality. Eighteen of 30 rats exposed to 300 ppm of ethyl acrylate died prior to completion of the exposure regimen, while all 30 rats exposed to 70 ppm survived to termination of the study. Treatment-related histopathologic changes observed in rats that died consisted of pulmonary congestion, cloudy swelling and congestion of the liver, cloudy swelling of renal tubules, and excessive pigmentation of the spleen. Exposure to ethyl acrylate was associated with exacerbation of rat pneumonia; the renal and hepatic lesions were observed only in rats with pneumonia.

Fifty 7-hour daily exposures of rats, rabbits, and guinea pigs to 75 ppm of ethyl acrylate caused no indications of toxicity but higher concentrations produced mortality, pulmonary edema, and toxic degenerative changes in the heart, liver, and kidney (Treon et al., 1949). Body weight gain depression and degenerative, inflammatory, and metaplastic histopathologic changes in the nasal turbinates were seen in F344 rats and B6C3F$_1$ mice exposed to 75 or 225 ppm ethyl acrylate (30 6-hour per day exposures); no effects were seen at the 25 ppm level (Miller et al., 1980). Nasal cavity lesions were attributed to irritation produced by ethyl acrylate.

Oral administration of ethyl acrylate in corn oil to purebred beagles for two years at "dietary equivalent" dosage levels of 10, 100, or 300 to 1,000 ppm resulted in no treatment-related mortality, organ weight effects, or histopathologic tissue alterations (Borzelleca et al., 1964). Ethyl acrylate inhalation studies were conducted using one monkey each at 24.5, 26.2, 272, and 1,204 ppm (Treon et al., 1949). The monkey exposed to 1,204 ppm died after 2.2 days. The monkey exposed to 272 ppm for 28 days was lethargic and had weight loss and slight irritation of the mucous membranes. There were no signs of intoxication in animals exposed to 130 7-hour exposures at 26.2 and 24.5 ppm.

Pregnant Sprague-Dawley rats (33 per group) were exposed to air containing 0, 50, or 150 ppm of ethyl acrylate for 6 hours per day during days 6 through 15 of gestation (the period of major organogenesis). Maternal toxicity, as evidenced by decreased body weight gain, decreased food consumption, and increased water consumption, was noted among rats exposed to 150 ppm of ethyl acrylate. In the presence of maternal toxicity at 150 ppm, a slight but non-statistically significant increase in malformed fetuses was observed. At 50 ppm, there was neither maternal toxicity nor an adverse effect on the developing embryo or fetus in rats. Based on these data, inhalation of the ethyl acrylate vapors by rats at a concentration of 50 or 150 ppm during major organogenesis was not considered to be teratogenic (Murray et al., 1981).

Human Toxicity and Exposure

Ethyl acrylate is a strong irritant to the skin, eyes, mucous membranes, gastrointestinal tract and respiratory system (Sandmeyer and Kirwin, 1981). Prolonged exposure to 50-75 ppm produced drowsiness, headache, and nausea (Nemec and Bauer, 1978). Ethyl acrylate tested at 4% concentration in petrolatum produced sensitization reactions in 10 of 24 human volunteers (Opdyke, 1975). In the past, the primary route of consumer exposure was by ingestion of ethyl acrylate used as a direct food additive with maximum daily intakes estimated to range from 0.15 to 4.95 mg (NAS/NRC, 1972). The present more

limited use of ethyl acrylate as a flavoring agent (NAS/NRC, 1976) significantly reduces the extent of consumer exposure. Primary routes of potential exposure for workers in the plastics industry, laboratory, and health professions are dermal and inhalation. The workplace Threshold Limit Value is 5 ppm (ACGIH, 1982). The odor threshold for ethyl acrylate is 0.5 ppb (A.D. Little, 1968).

Mutagenicity and Carcinogenicity

Ethyl acrylate was tested with *Salmonella typhimurium* strains TA1535, TA1537, TA98, and TA100 and *Saccharomyces cerevisiae* strain D4 at concentrations of 0.001-5.0 μl/plate with and without a rat liver Aroclor induced microsomal enzyme preparation. Under conditions of the studies ethyl acrylate did not demonstrate mutagenic activity (Rosenthal and Smith, 1982; O'Neill and Scribner, 1979).

Ethyl acrylate was tested in a liquid suspension modification of the Ames test with and without a rat liver Aroclor induced microsomal enzyme preparation. Preliminary results with *Salmonella typhimurium* strain TA100 show a concentration dependent increase in revertants per survivors in the presence of the enzyme preparation. This was not, however, accompanied by an increase in revertants per ml (Rosenthal and Smith, 1982).

Ethyl acrylate (with or without metabolic activation) did not induce a mutagenic response in *Salmonella typhimurium* tester strains TA98, TA100, TA1535, and TA1537 (Appendix G). Structurally related methyl acrylate (with or without metabolic activation) was not mutagenic for *Salmonella typhimurium* G46, TA1535, TA100, C3076, TA1537, D3052, TA1538, TA98 or *Escherichia coli* WP2, or WP2 uvrA- (McMahon et al., 1979).

Ethyl acrylate was tested with L5178Y TK +/− Mouse Lymphoma Cells at concentrations up to 300 nl/ml with and 40 nl/ml without a rat liver Aroclor induced microsomal enzyme preparation. Without the microsomal enzyme preparation 30 nl produced a significant increase in mutation frequency with a 4-22% relative growth (survival). In the presence of the enzyme preparation 100-150 nl/ml were required to produce a significant increase in mutation frequency with a 14-50% relative growth (survival) (Rosenthal and Smith, 1982; Litton Bionetics, 1980).

No clear signs of toxicity or carcinogenicity were observed when groups of 25 male and 25 female Wistar rats were administered drinking water containing 6-7 or 60-70 ppm ethyl acrylate for 2 years, but depressions in body weight were observed in rats administered 2,000 ppm (Borzelleca et al., 1964). No compound-related histopathologic lesions, hematologic or urinary changes, or alterations in organ weight were reported in this study, but it has been noted that insufficient details on survival and pathologic examination were given (IARC, 1979).

Male and female F344 rats and B6C3F$_1$ mice were exposed for 6 hours per day to air containing 0, 25, or 75 ppm ethyl acrylate for 27 months. Additional groups of rats and mice were exposed to 225 ppm. Mean body weight gains of the 75 and 225 ppm exposure groups of rats and mice were significantly depressed during the first months of the study and remained depressed throughout the study. For both species the depression of weight gain in the 225 ppm groups was sufficiently great for the authors to judge the 225 ppm exposure to be a life-threatening concentration, and consequently, this exposure level was terminated after 6 months and animals were held for evaluation after 21 months of recovery. With the exception of depressed body weight gains, no toxicologically significant alterations in organ weight, hemograms, clinical chemistries, urinalysis, or pathology were observed. There was no increased incidence of tumors in any organ or tissue attributed to ethyl acrylate exposure (Miller et al., 1982).

For the 25 and 75 ppm exposed groups treatment-related histopathologic lesions were similar in rats and mice and were confined to the olfactory portion of the nasal cavity. These lesions included hyperplasia of basal or reserve cells in the olfactory mucosa with loss of overlying neurons, replacement of olfactory neuroepithelium by ciliated respiratory epithelium, and hyperplasia of submucosal glands. In terms of the distribution of nasal cavity lesions, the major effects were concentration-dependent with greater effects in the more anterior portions of the olfactory mucosa (Miller et al., 1982).

In rats the residual lesions of the 225 ppm "exposure-recovery" group, while also limited to the nasal olfactory region, were qualitatively different from the 25 and 75 ppm "continuous-exposed" rats and consisted of a diffuse atrophy of the olfactory epithelium with only a single layer of support (sustenticular) cells and a single layer of focally hyperplastic basal cells. In mice

changes in the 225 ppm "exposure-recovery" group were qualitatively similar to those in the 25 or 75 ppm groups (Miller et al., 1982).

The dermal carcinogenic potential of ethyl acrylate was assessed by applying 25 μl of undiluted ethyl acrylate to the backs of 40 C3H/HeJ male mice, 3 times per week, for their lifetime. Epidermal necrosis, dermatitis, dermal fibrosis, and hyperkeratosis were observed in several treated mice, but no skin or subcutaneous tumors were induced. The mean survival time for these mice was 408 days (Hengler and DePass, 1982).

Rationale for Testing

The Bioassay Program tested ethyl acrylate because of its high volume of production, the potential for chronic exposure of workers in the plastics and chemical industry as well as laboratory workers and dental and health professionals, and because of its use (now limited) as a direct food additive. Protocols of previous long-term studies (Borzelleca et al., 1964) did not conform to present day standards.

II. MATERIALS AND METHODS

CHEMICAL ANALYSES

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FOURTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

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Animal Maintenance

Clinical Examinations and Pathology

Data Recording and Statistical Methods

CHEMICAL ANALYSES

Ethyl acrylate was purchased in two lots from Rohm and Haas (Philadelphia, PA). The manufacturer listed no purity specifications but indicated the material contained 15 ppm of the monoethyl ether of hydroquinone as an inhibitor. Purity and identity analyses were conducted at Midwest Research Institute (Appendix I).

Gas chromatographic analysis of Lot No. 37201, which was used for the short-term and 13-week studies and for the first 7 months of the 2-year study, indicated a purity of approximately 99%. Lot No. 343029, which was used for the final 17 months of the 2-year study, was determined to be approximately 99.5% pure by gas chromatography.

Both lots of ethyl acrylate were stored at −20°C during the studies. Southern Research Institute periodically reanalyzed each lot throughout the study by vapor phase chromatography and infrared spectroscopy. No evidence of degradation was found.

DOSE PREPARATION

In the single-dose and the first 14-day study, ethyl acrylate was first dissolved in ethanol and then diluted with water to make the solution 25% ethanol in water. The lower doses were prepared by dilution of the highest dose with water. Ethyl acrylate in water was found to be stable for 24 hours at room temperature (Appendix J) and the dose mixtures for these two studies were prepared and used on the same day.

One percent ethyl acrylate in water was found to be relatively unstable for 1 week, losing up to 9% of the original concentration within 7 days (Appendix J). In addition, the maximum solubility of ethyl acrylate in water at room temperature was determined to be 1.6 ± 0.2% (w/v). Therefore, because of the instability of aqueous ethyl acrylate solutions and the relative insolubility in water compared to the dose levels required for the studies, corn oil was selected as the vehicle of choice for the remainder of the studies.

In the third 14-day study, the 13-week studies, and the 2-year study, the appropriate amounts of ethyl acrylate and Mazola® corn oil were mixed for 10 minutes in a beaker containing a magnetic stirring bar (Table 2). Midwest Research Institute determined that ethyl acrylate/corn oil solutions were stable for at least 8 days at room temperature (Appendix K). Once formulated, solutions were stored for no more than 16 days at 5°C. Results of analyses of stock solutions indicated that all analyzed formulations conformed to specifications (± 10% of theoretical values) (Appendix L).

TESTING CHRONOLOGY

Because of the unusual temporal sequence of prechronic tests, the testing chronology for ethyl acrylate is presented in Table 1. In subsequent sections of this report, each specific study will be designated as indicated in Tables 1 and 2.

TABLE 1. TESTING CHRONOLOGY FOR ETHYL ACRYLATE

Study	Species	Vehicle and Route	Date Study Began
Single-Dose	Rats and mice	Aqueous ethanol, gavage	August 1976
First 14-Day	Rats and mice	Aqueous ethanol, gavage	September 1976
First 13-Week	Rats and mice	Corn oil, gavage	February 1977
Second 14-Day	Rats and mice	Dosed water	June 1977
Second 13-Week	Mice only	Corn oil, gavage	October 1977
Third 14-Day	Rats and mice	Corn oil, gavage	May 1978
2-Year	Rats and mice	Corn oil, gavage	February 1979

SINGLE-DOSE STUDIES

Male and female F344/N rats and B6C3F$_1$ mice were obtained from the Frederick Cancer Research Center and held for 9 days (rats) or 8 days (mice) before the test began. Animals were approximately 5 weeks old when placed on the study.

Groups of five rats of each sex received a single gavage dose of ethyl acrylate (55, 110, 225, 450, or 900 mg/kg) in aqueous ethanol. Groups of five mice of each sex received doses of 110, 225, 450, 900, or 1,800 mg/kg in aqueous ethanol.

Animals were housed three per cage and received water and feed *ad libitum* during the observation period. Details of animal maintenance are presented in Table 2.

Animals were observed for mortality twice daily for 14 days.

FOURTEEN-DAY STUDIES

First Study

Male and female F344/N rats and B6C3F$_1$ mice were obtained from the Frederick Cancer Research Center and held for 8 days before the study began. Animals were approximately 5 weeks old when placed on the study.

Groups of five rats of each sex received ethyl acrylate (55, 110, 225, 450, or 900 mg/kg) in aqueous ethanol by gavage for 14 consecutive days. Groups of five mice of each sex received doses of 25, 55, 110, 225, or 450 mg/kg on the same schedule. Animals were housed five per cage and received water and feed *ad libitum*. Details of animal maintenance are presented in Table 2.

Second Study

Because of suggestive evidence of gastric mucosal irritation observed in the first 13-week corn oil gavage study, this second 14-day study was undertaken using dosed water as the route of administration. This alternate route was selected to allow substantial increase in the total dose of ethyl acrylate per animal without producing local irritation.

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Frederick Cancer Research Center and held in quarantine for 7 days before the study began. Groups of five rats of each sex received ethyl acrylate (0, 0.025, 0.05, 0.11, 0.22, or 0.45%) in drinking water for 14 consecutive days. Groups of five mice of each sex received dose solutions of 0, 0.013, 0.025, 0.05, 0.11, or 0.22% ethyl acrylate in drinking water on the same schedule. Animals were housed five per cage and received appropriately dosed water and feed *ad libitum*. Fresh dosed-water solutions were prepared at 3- or 4-day intervals at which time water consumption by cage during the preceeding interval was measured. Details of animal maintenance are presented in Table 2.

Third Study

Because of the absence of toxic effects in previous 14-day and 13-week studies, a third 14-day study was undertaken using higher doses of ethyl acrylate. Four-week-old male and female F344/N rats and B6C3F$_1$ mice were obtained from Harlan Industries and held for 14 days before the study began. Groups of five rats and mice of each sex received ethyl acrylate (0, 100, 200, 400, 600, or 800 mg/kg) in corn oil by gavage for 14 consecutive days. Animals were housed five per cage and received water and feed *ad libitum*. Details of animal maintenance are presented in Table 2.

Histologic examinations were conducted on the stomachs of rats administered 0, 100, 200, or 400 mg/kg and mice administered 0, 100, 200, 400, or 600 mg/kg. Stomachs from higher dosage groups had similar gross lesions to the rats administered 400 mg/kg and the mice administered 600 mg/kg of ethyl acrylate. Consequently, histologic examinations were not conducted on these higher dosage groups.

THIRTEEN-WEEK STUDIES

First Study

Thirteen-week studies were conducted to evaluate the cumulative toxicity of ethyl acrylate 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 Frederick Cancer Research Center, observed for 1 week, and assigned to cages by species and sex according to a table of random numbers. The 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 covered with spun-bonded polyester filter sheets (Table 2). Water and feed were available *ad libitum*.

Groups of 10 rats of each sex received ethyl acrylate (0, 7, 14, 28, 55, or 110 mg/kg) in corn oil by gavage, 5 days per week for 13 weeks. Groups of 10 mice of each sex received doses of 0, 1.5, 3, 6, 12, or 25 mg/kg on the same schedule.

Second Study

Three-to-four-week old mice of each sex were obtained from Charles River Breeding Laboratories and held for 16 days before the study began. Groups of 10 mice of each sex received ethyl acrylate (0, 12, 25, 50, or 100 mg/kg) in corn oil by gavage 5 days per week for 13 weeks. All other aspects of experimental design and animal maintenance were similar to those in the first 13-week study.

Animals were checked for mortality and signs of morbidity twice daily. Those animals that were 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. Necropsies were performed on animals that survived to the end of the study and on all animals found dead, unless precluded by autolysis or cannibalization. Tissues examined histopathologically are identified in Table 2. Tissues were fixed in formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin.

TWO-YEAR STUDIES

Study Design

Groups of 50 rats and 50 mice of each sex were administered 100 or 200 mg/kg body weight ethyl acrylate in corn oil by gavage 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

The male and female F344/N rats and B6C3F$_1$ (C57BL/6N × C3H/HeN MTV-) mice used in this study were produced under strict barrier conditions at the Charles River Breeding Laboratories, Portage, MI, under a contract to the 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 which were transferred from isolators to barrier maintained rooms. Animals were shipped to the testing laboratory at 4-5 weeks of age. The animals were quarantined at the testing facility for 2 weeks after which the health status of the animals was assessed by a complete pathology evaluation of a selected number of rats and mice. The rodents were placed on study at 7 weeks of age. Animal health status during the course of the 2-year study was monitored according to the protocols of the NTP Sentinel Animal Program (Appendix H).

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 a Bioassay Program supplier. 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. The potential genetic non-uniformity of mice in this study should be considered when making comparisons with historic control incidence data.

Animal Maintenance

Rats and mice were housed five per cage in polycarbonate cages (Table 2). Animals were assigned 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. Cages and bedding were replaced twice per week. Feed and water were available *ad libitum*.

The temperature in the animal rooms was 19°-26° C and the humidity was 27%-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 mortality and morbidity. Body weights were recorded once per 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 study were killed with 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. Tissues examined microscopically are identified in Table 2.

Necropsies were performed on all animals found dead and on those killed at the end of the study 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 hepatic 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 tissues were verified, and histotechniques were evaluated. All tumor diagnoses, target tissues, and tissues from a randomly selected 10% of the animals were evaluated by a pathologist. Slides of all target tissues and those on 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 Chairperson were reviewed blindly by PWG pathologists, who reached a consensus and compared their findings with the original diagnoses and quality assurance. When disagreements were found, the PWG sent the appropriate slides and their comments to the original pathologist for review. (This procedure has been described by Maronpot and Boorman, 1982.) 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 survival analyses are one-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 numbers of animals necropsied.

For the statistical analysis of tumor incidence data, two different methods of adjusting for intercurrent mortality were employed. Each used the classical methods 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 methods 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 necropsy 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 actually necropsied 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 the 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. All reported P values for tumor incidence 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 2. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS

Experimental Design	Single-Dose Studies	14-Day Studies	13-Week Studies	2-Year Studies
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
		First Study	**First Study**	
Doses	Rats: 55, 110, 225, 450, or 900 mg/kg body weight in aqueous ethanol by gavage (dose volume: 10 ml/kg) Mice: 110, 225, 450, 900, or 1800 mg/kg body weight in aqueous alcohol by gavage (dose volume: 10 ml/kg)	Rats: 55, 110, 225, 450, or 900 mg/kg in aqueous ethanol by gavage (dose volume: 10 ml/kg) Mice: 25, 55, 110, 225, or 450 mg/kg in aqueous ethanol (dose volume: 10 mg/kg).	Rats: 0, 7, 14, 28, 55, or 110 mg/kg body weight by gavage in corn oil (dose volume: 10 ml/kg) Mice: 0, 1.5, 3, 6, 12, or 25 mg/kg body weight by gavage in corn oil (dose volume: 10 ml/kg)	0, 100, or 200 mg/kg body weight by gavage in corn oil. Dose volume: rats: 5 ml/kg body weight; mice: 10 ml/kg body weight
		Second Study	**Second Study**	
		Rats: 0, 0.025, 0.05, 0.11, 0.22, or 0.45% in drinking water Mice: 0, 0.013, 0.025, 0.05, 0.11, or 0.22% in drinking water	Mice: 0, 12, 25, 50, or 100 mg/kg body weight in corn oil by gavage (dose volume: 10 ml/kg)	
		Third Study		
		Rats and Mice: 0, 100, 200, 400, 600, or 800 mg/kg in corn oil by gavage (dose volume: 5 ml/kg for rats an 10 ml/kg for mice)		
Duration of Dosing	Single dose	14 consecutive days	13 weeks (5 days per week)	103 weeks
Type and Frequency of Observations	Observed twice daily for mortality and morbidity; individual animal weights were measured at day 0 and day 15	Observed twice daily for clinical signs of toxicity; weighed on day 0 or 1 and on day 15	Observed twice daily for clinical signs of toxicity; weighed weekly	Observed twice daily for mortality and moribundity; weighed weekly for first 12 weeks and monthly thereafter

TABLE 2. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS (Continued)

Experimental Design	Single-Dose Studies	14-Day Studies	13-Week Studies	2-Year Studies
Necropsy and Histological Examination	The peritoneal cavities of mice in the top three dose groups were grossly examined	All animals were necropsied. No histopathologic examinations were performed except for stomachs in the third study	Necropsies performed on all animals; the following tissues examined histologically in all controls and high-dose groups:gross lesions, tissue masses, abnormal lymph nodes, skin, mandibular lymph nodes, mammary gland, salivary gland, thigh muscle, bone marrow, thymus, trachea, lungs and bronchi, heart, thyroid, parathyroid, esophagus, stomach, small intestine, cecum, colon, mesenteric lymph nodes, liver, pancreas, spleen, kidneys, urinary bladder, prostate/testes or ovaries/uterus, brain, and pituitary	Necropsies performed on all animals; following tissues examined histologically in all groups: tissue masses, gross lesions, abnormal lymph nodes, blood smears, mandibular or mesenteric lymph nodes, mammary gland, salivary gland, bone marrow, femur, thymus, trachea, lungs and bronchi, heart, thyroid, parathyroid, esophagus, stomach, small intestine, colon, liver, gallbladder (mice), pancreas, spleen, kidneys, adrenals, urinary bladder, prostate/testes or ovaries/uterus, brain, pituitary, eyes, ears, nasal cavity, larynx, sciatic nerve, rectum, thigh muscle, skin
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	Frederick Cancer Research Center (Frederick, MD)	First and second studies: Frederick Cancer Research Center Third study: Harlan Industries (Indianapolis, IN)	First study: Frederick Cancer Research Center Second study: Charles River Breeding Laboratories (Portage, MI)	Charles River Breeding Laboratories, (Portage, MI)

TABLE 2. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS (Continued)

Experimental Design	Single-Dose Studies	14-Day Studies	13-Week Studies	2-Year Studies
Time Held Before Start of Test	Rats: 9 days Mice: 8 days	First study: 8 days Second study: 7 days Third study: 14 days	First study: 7 days Second study: 16 days	2 weeks
Age When Placed on Study	5 weeks	5 weeks	5 weeks	7 weeks
Age When Killed	Killed on day 16	Killed on days 16 and 17	First study: killed on days 92 to 97 Second study: killed on days 92 to 94	Rats: 111 to 112 weeks Mice: 111 to 113 weeks
Method of Animal Distribution	Animals assigned by species and sex to cages according to a table of random numbers. Cages assigned to control and dose groups according to another table of random numbers	Same as single-dose study	Same as single-dose study	Same as single-dose study
Feed	Wayne Lab Blox®, Allied Mills, Inc. (Chicago, IL)	Same as single-dose study	Same as single-dose study	Wayne Lab Blox®
Bedding	Betta-Chips® heat-treated hardwood chips Northeastern Products Corp. (Warrensburg, NY)	Same as single-dose study	First study: same as single dose study Second study: Betta-Chips® for days 1-35. Sawdust, PWI, Inc., (Louisville, NY) for rest of study	Same as single-dose study
Water	Glass water bottles	Glass water bottles	Automatic watering system, Edstrom Automatic, (Waterford, WI)	Same as 13-week studies
Cages	Stainless steel Hahn Proofing and Steel Metal Co., (Birmingham, AL)	Polycarbonate, Lab Products, (Garfield, NJ); changed twice weekly	Same as 14-day studies	Same as 14-day studies
Cage Filters	Not stated	Spun-bonded polyester filter (Dupont 2024) Snow Filtration, (Cincinnati, OH)	Same as 14-day studies	Same as 14-day studies

TABLE 2. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS (Continued)

Experimental Design	Single-Dose Studies	14-Day Studies	13-Week Studies	2-Year Studies
Animals per Cage	Three	Five	Five	Five
Animal Room Environment	20°-24°C; 38%-42% relative humidity; 9 hours of fluorescent light per day; 15 room air changes per hour	21°-23°C; 40%-60% relative humidity; 12 hours of fluorescent light per day; 15 room air changes per hour	Same as 14-day studies	21°-24°C; 30%-60% relative humidity; 12 hours of fluorescent light per day; 15 room air changes per hour
Other Chemicals on Test in Same Room	Eugenol and allyl isothiocyanate	First study: eugenol, allyl isothiocyanate, and D-mannitol Second and third studies: none	None	None
Chemical Vehicle Mixture Preparation	Ethyl acrylate was added to ethanol and stirred. Sufficient distilled water was added to adjust the solution to 25% ethanol for high dose formulation. The lower doses were prepared by dilution of the highest dose with water alone. The two highest doses were cloudy while the remainder were clear.	First study: same as single dose study Second study: ethyl acrylate was pipetted into a known volume of rapidly stirred tap water to obtain the high dose formulation. Lower doses were prepared by dilution of the highest dose with water. Third study: ethyl acrylate was added (volume/volume) to corn oil and mixed with a magnetic stirrer. The high dose formulation was used as a stock solution from which lower doses were prepared by addition of corn oil.	Same as 14-day rerun	Same as 13-week study
Maximum Storage Time	Mixed on day of dosing	First and third studies: same as single dose study.	Gavage formulations prepared every 7 days	16 days
Storage Conditions		Second study: mixed every 3 to 4 days	Stored in amber bottles in the animal room	5°C

III. RESULTS

RATS

SINGLE-DOSE STUDIES

FOURTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Survival

Pathology and Statistical Analyses of Result

MICE

SINGLE-DOSE STUDIES

FOURTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

III. RESULTS: RATS—SINGLE-DOSE STUDIES

SINGLE-DOSE STUDIES

Rats receiving 900 mg/kg were inactive after dosing. One male rat receiving 900 mg/kg died. No other deaths occurred. Necropsies were not done on these rats.

FOURTEEN-DAY STUDIES

First Study

In the first study, ethyl acrylate was administered by gavage in aqueous ethanol. All rats receiving 900 mg/kg were dead within 24 hours (Table 3). Among animals surviving 14 days, all male and female rats receiving 225 or 450 mg/kg and 1/5 female rats receiving 110 mg/kg had thickened necrotic mucosa in the forestomach. Adhesions of the spleen and stomach to the peritoneum were found in 3/5 males and 2/4 females receiving 450 mg/kg. Rats receiving 450 mg/kg became slightly inactive by day 2 and remained inactive throughout the study.

Second Study

In the second 14-day study, ethyl acrylate was administered in the drinking water. Because of broken water bottles, clogged or leaking sipper tubes, animals playing with water rather than drinking it, and instability of ethyl acrylate in water, the data from this study are inaccurate and do not reflect the actual amount consumed. The only treatment-related effects were an apparent decreased water consumption and reddening of the mucosal surface of the duodenum in several of the treated rats. On the basis of this study, it was recommended that the route of administration be changed back to gavage.

Third Study

In the third 14-day study, ethyl acrylate was administered by gavage in corn oil. All animals survived (Table 4). In male rats receiving 800 mg/kg mean body weights were depressed 25% compared with those of controls. All rats receiving 600 or 800 mg/kg were inactive and had ruffled fur. A thickened stomach wall and abdominal adhesions were observed in 5/5 males and 5/5 females receiving 800 and 400 mg/kg, in 4/5 males and 5/5 females receiving 600 mg/kg, in 4/5 males and 4/5 females receiving 200 mg/kg, and in 1/5 males and 3/5 females receiving 100 mg/kg. Abdominal adhesions were seen in all rats that received 800 mg/kg and in 3/5 males and 4/5 females receiving 600 mg/kg. Histologically, ulcerative and nonulcerative inflammation of the forestomach was observed in 5/5 males and 4/5 females receiving 400 mg/kg. The inflammatory reaction was characterized by the presence of neutrophils, lymphocytes, and histiocytes in the mucosa and submucosa of the forestomach. Inflammatory lesions were not observed in forestomach sections from rats receiving 200 or 100 mg/kg.

TABLE 3. SURVIVAL AND MEAN BODY WEIGHTS OF RATS ADMINISTERED ETHYL ACRYLATE BY GAVAGE FOR 14 DAYS (FIRST STUDY)

Dose (mg/kg)	Survival *(a)*	Mean Body Weight (grams)		
		Initial	Final	Change *(b)*
MALES				
55	5/5	94.8 ± 1.6	143.8 ± 3.7	+49.0 ± 3.2
110	5/5	83.2 ± 4.4	127.0 ± 6.8	+43.8 ± 4.5
225	5/5	83.4 ± 5.1	136.0 ± 9.0	+52.6 ± 4.1
450	5/5	84.2 ± 3.9	121.2 ± 5.2	+37.0 ± 2.7
900	0/5	*(c)*	*(c)*	*(c)*
FEMALES				
55	5/5	76.8 ± 2.9	98.2 ± 3.1	+21.4 ± 4.9
110	5/5	77.6 ± 4.0	108.2 ± 3.3	+30.6 ± 1.6
225	5/5	73.4 ± 2.7	106.8 ± 3.3	+33.4 ± 0.9
450	4/5	84.5 ± 4.0	106.5 ± 2.1	+22.0 ± 3.6
900	0/5	*(c)*	*(c)*	*(c)*

(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) No data are presented due to the 100% mortality in this group.

TABLE 4. SURVIVAL AND MEAN BODY WEIGHTS OF RATS ADMINISTERED ETHYL ACRYLATE BY GAVAGE FOR 14 DAYS (THIRD STUDY)

Dose (mg/kg)	Survival *(a)*	Mean Body Weight (grams)			Final Body Weight Relative to Controls *(c)* (percent)
		Initial	Final	Change *(b)*	
MALES					
0	5/5	121.6 ± 8.8	168.2 ± 8.4	+46.6 ± 2.9	—
100	5/5	109.0 ± 6.6	162.8 ± 8.0	+53.8 ± 4.1	- 3
200	5/5	107.2 ± 5.1	164.6 ± 9.5	+57.4 ± 4.5	- 2
400	5/5	112.0 ± 6.4	160.2 ± 8.0	+48.2 ± 2.5	- 5
600	5/5	123.0 ± 6.8	152.8 ± 6.4	+29.8 ± 4.5	- 9
800	5/5	118.8 ± 9.4	125.6 ± 12.3	+ 6.8 ± 4.8	-25
FEMALES					
0	5/5	99.2 ± 5.0	122.4 ± 4.9	+23.2 ± 0.6	—
100	5/5	95.8 ± 2.4	113.2 ± 2.1	+17.4 ± 1.7	- 8
200	5/5	99.4 ± 3.9	119.6 ± 4.6	+20.2 ± 1.7	- 2
400	5/5	97.8 ± 4.3	120.2 ± 5.9	+22.4 ± 2.2	- 2
600	5/5	106.4 ± 3.8	120.6 ± 3.8	+14.2 ± 1.0	- 1
800	5/5	108.2 ± 3.7	111.6 ± 3.8	+ 3.4 ± 3.2	- 9

(a) Number surviving/number initially in the group.
(b) Mean weight change of the survivors of the group ± standard error of the mean.
(c) Weight of the dosed survivors relative to the survivors of the controls =

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

THIRTEEN-WEEK STUDIES

In the 13-week studies, ethyl acrylate was administered by gavage in corn oil. No dosed animals died during the studies, and mean body weights of dosed and control rats were essentially comparable (Table 5). The duodenum was reddened in 1/10 male rats receiving 110 mg/kg and blood vessels in the cardiac region of the stomach were prominent in 2/10 males receiving 110 mg/kg. No compound-related clinical signs were observed and no compound-related histopathologic effects were seen.

Because of the histopathologic effects (ulcerative and non-ulcerative inflammation) observed in the stomach at 400 mg/kg in the third 14-day study, gavage doses for rats in the 2-year studies were set at 100 and 200 mg/kg ethyl acrylate in corn oil, 5 days per week.

TABLE 5. SURVIVAL AND MEAN BODY WEIGHTS OF RATS ADMINISTERED ETHYL ACRYLATE BY GAVAGE FOR 13 WEEKS

Dose (mg/kg)	Survival *(a)*	Mean Body Weight (grams)			Final Body Weight Relative to Controls *(c)* (percent)
		Initial	Final	Change *(b)*	
MALES					
0	10/10	90.7 ± 2.9	331.0 ± 6.6	+240.3 ± 5.1	—
7	10/10	85.2 ± 4.4	317.1 ± 8.4	+231.9 ± 5.1	-4
14	10/10	82.9 ± 3.3	319.9 ± 8.4	+237.0 ± 6.9	-3
28	10/10	83.6 ± 3.4	310.0 ± 6.3	+226.4 ± 5.3	-6
55	10/10	89.7 ± 3.0	318.9 ± 7.4	+229.2 ± 5.6	-4
110	10/10	84.3 ± 3.8	323.5 ± 7.3	+239.2 ± 5.4	-2
FEMALES					
0	9/10	81.0 ± 1.7	198.6 ± 1.5	+117.6 ± 2.0	—
7	10/10	75.6 ± 3.1	193.7 ± 4.1	+118.1 ± 3.2	-2
14	10/10	79.5 ± 3.2	196.2 ± 3.2	+116.7 ± 0.6	-1
28	10/10	80.4 ± 2.9	201.8 ± 1.2	+121.4 ± 2.5	+2
55	10/10	78.6 ± 2.6	196.4 ± 2.7	+117.8 ± 2.1	-1
110	10/10	83.6 ± 2.0	206.7 ± 2.4	+123.1 ± 1.6	+4

(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 survivors relative to the survivors of the controls =

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

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Throughout the studies, mean body weights of high dose and vehicle control rats were comparable (Figure 1 and Table 6). No compound-related clinical signs were observed.

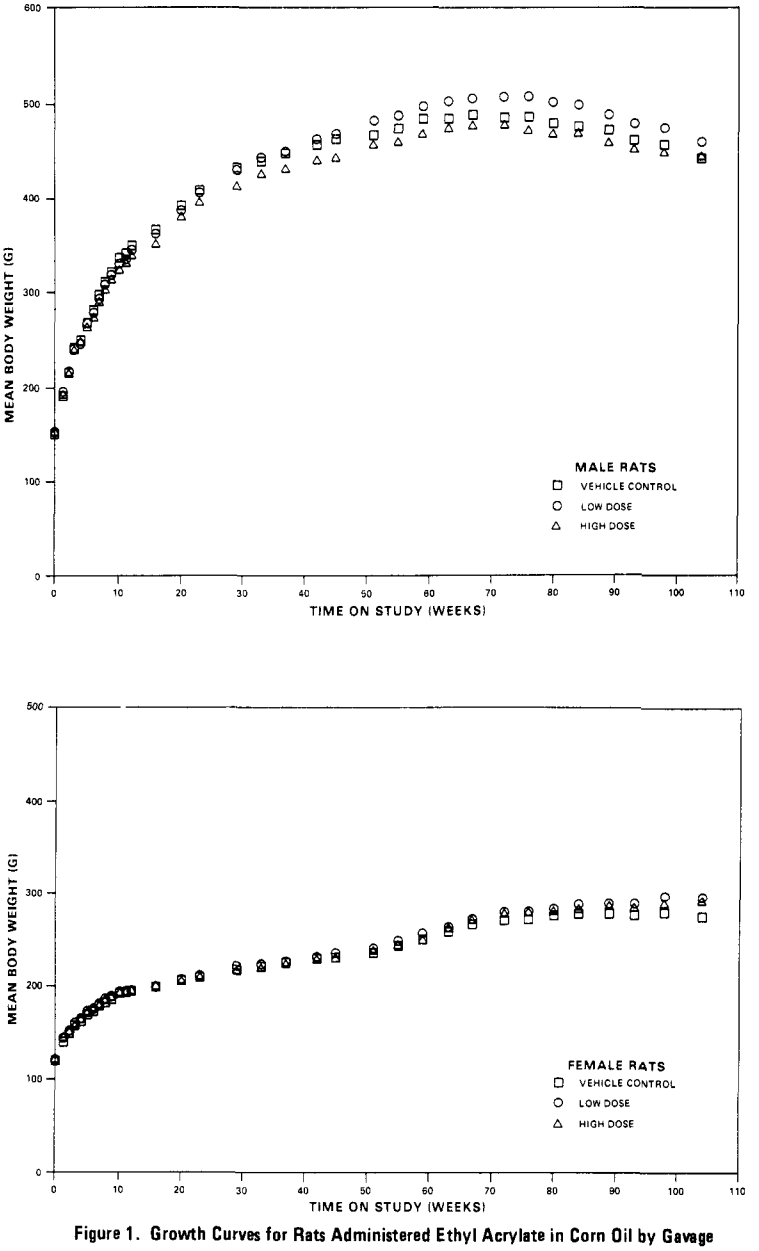


Figure 1. Growth Curves for Rats Administered Ethyl Acrylate in Corn Oil by Gavage

TABLE 6. MEAN BODY WEIGHTS (RELATIVE TO CONTROLS) OF RATS ADMINISTERED ETHYL ACRYLATE BY GAVAGE IN THE TWO-YEAR STUDIES

Week No.	Mean Body Weight (grams)			Mean Body Weights Relative to Controls *(a)* (Percent)	
	Vehicle Control	Low Dose	High Dose	Low Dose	High Dose
MALES					
0	151	153	153	+1	+1
1	191	196	193	+3	+1
20	393	388	379	-1	-4
42	459	465	443	+1	-3
63	487	504	476	+3	-2
80	483	503	470	+4	-3
104	444	462	446	+4	0
FEMALES					
0	120	121	122	+1	+2
1	139	143	144	+3	+4
20	206	208	206	+1	0
42	230	233	230	+1	0
63	259	264	263	+2	+2
80	276	284	281	+3	+2
104	276	297	294	+8	+7

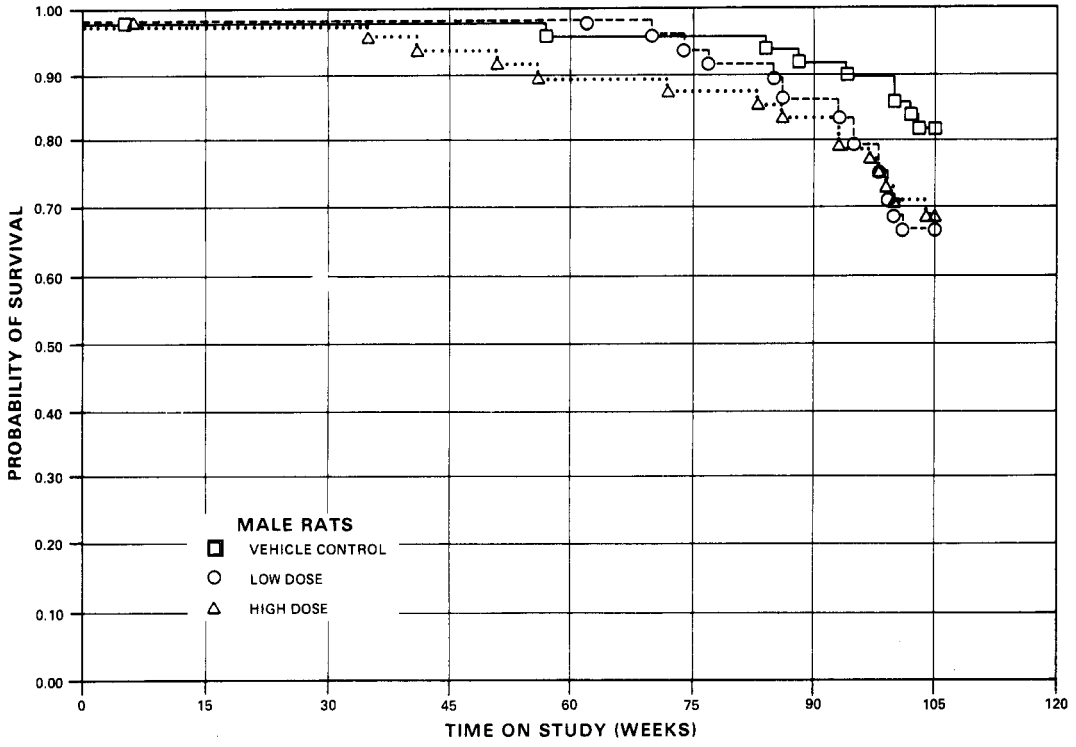
(a) Mean Body Weight Relative to Controls =

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

Survival

Estimates of the probabilities of survival of male and female rats administered ethyl acrylate by gavage at the doses of these studies, and those of the controls, are shown by the Kaplan and Meier curves in Figure 2. No significant differences in survival were observed between groups of the same sex. Two low dose males, one high dose male, and one high dose female were accidentally killed.

In male rats, 41/50 (82%) of the controls, 32/50 (64%) of the low dose, and 34/50 (68%) of the high dose group lived to the end of the study at 104-105 weeks. In female rats, 36/50 (72%) of the controls, 36/50 (72%) of the low dose, and 42/50 (84%) of the high dose group lived to the end of the study at 104-105 weeks. The survival incidences include one high dose male and one control female that died during the termination period of the study. For statistical purposes, these animals have been pooled with those killed at the end of the study.



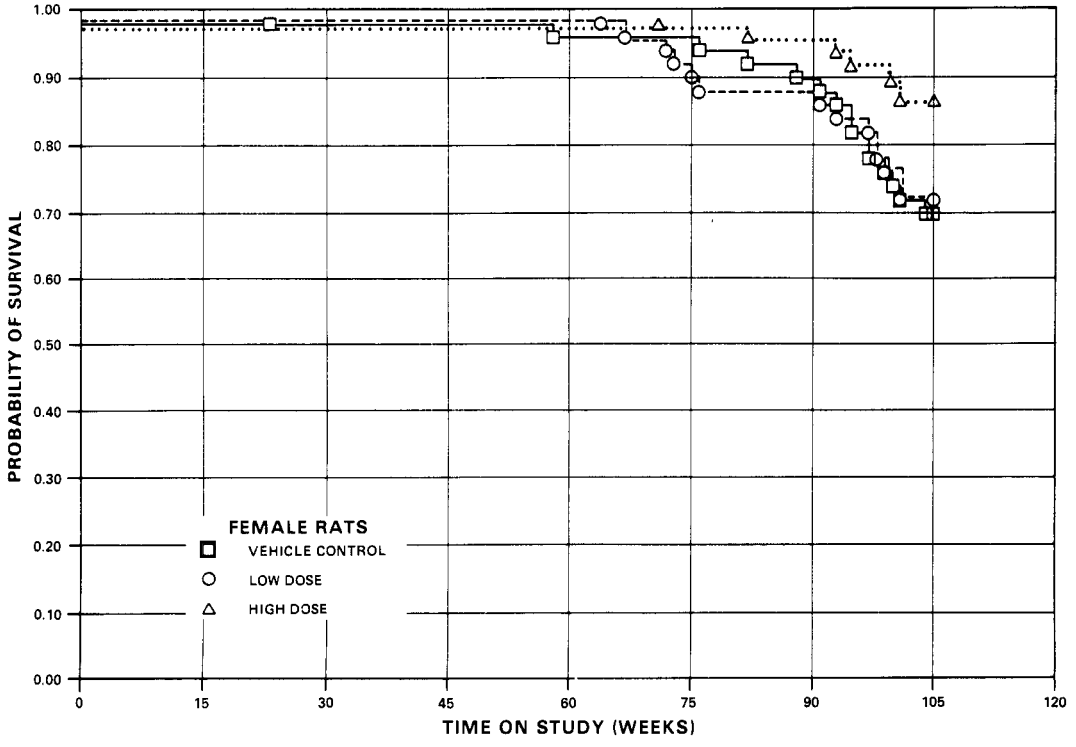


Figure 2. Survival Curves for Rats Administered Ethyl Acrylate in Corn Oil by Gavage

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 E. Appendix F, Tables F1 and F2, 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 the Materials and Methods (Data Recording and Statistical Methods) and Appendix F (footnotes).

Forestomach: Several nonneoplastic lesions were observed in male and female rats at dose-related incidences (Table 7). These lesions included inflammation, epithelial hyperplasia, and hyperkeratosis.

Squamous epithelial hyperplasia of the forestomach was characterized by increased basophilia and mitotic activity of the basal epithelium and an overall increase in the number of epithelial cells. Hyperkeratosis usually accompanied the hyperplasia. Increased cellularity of the squamous epithelium often resulted in a grossly wrinkled appearance of the mucosa. At times, the mucosa was disorganized to the extent that masses of keratin, cellular debris, food particles, and hair were trapped in epithelial invaginations within the wall of the forestomach. Foreign material (hair) was sometimes found in the submucosa adjacent to these masses and was often accompanied by an inflammatory reaction to the foreign material.

Statistically significant positive trends were observed in the incidences of male rats with squamous cell papillomas and squamous cell carcinomas (Table 8); the incidences in the dosed groups were significantly higher than those in the vehicle controls. The incidences of female rats with squamous cell papillomas occurred with a statistically significant positive trend; the incidences in the dosed groups were significantly higher (by the incidental tumor test) than those in the vehicle controls.

Lesions diagnosed as papillomas consisted of cauliflower shaped proliferations of squamous epithelial cells situated on a core or stalk of connective tissue. The lesions projected toward the lumen of the forestomach and were usually covered with thick layers of keratin. Carcinomas were characterized by invasion of the wall of the stomach by more anaplastic squamous epithelial cells. Aggregates or nodules of carcinomatous cells in the wall were often accompanied by fibrosis.

TABLE 7. NUMBERS OF RATS WITH FORESTOMACH LESIONS

	Males			Females		
	Vehicle Control	Low Dose	High Dose	Vehicle Control	Low Dose	High Dose
No. of Animals						
Animals Examined	50	50	50	50	50	50
Hyperkeratosis	0	37	46	0	24	46
Epithelial Hyperplasia	1	41	46	0	34	49
Acute and or Chronic Inflammation	1	8	28	1	3	20
Squamous Cell Papilloma	1	15	29	1	6	9
Squamous Cell Carcinoma	0	5	12	0	0	2
Papilloma or Carcinoma	1	18	36	1	6	11

TABLE 8. ANALYSIS OF FORESTOMACH TUMORS IN RATS

	Vehicle Control	100 mg/kg	200 mg/kg
MALES			
Squamous Cell Papilloma			
Overall	1/50 (2%)	15/50 (30%)	29/50 (58%)
Adjusted	2.0%	35.7%	70.5%
Terminal	0/41 (0%)	6/32 (19%)	22/34 (65%)
Life Table Test	P<0.001	P<0.001	P<0.001
Incidental Tumor Test	P<0.001	P=0.001	P<0.001
Cochran-Armitage Trend Test	P<0.001		
Fisher Exact Test		P<0.001	P<0.001
Squamous Cell Carcinoma			
Overall	0/50 (0%)	5/50 (10%)	12/50 (24%)
Adjusted	0.0%	14.3%	32.7%
Terminal	0/41 (0%)	3/32 (9%)	10/34 (29%)
Life Table Test	P<0.001	P=0.019	P<0.001
Incidental Tumor Test	P<0.001	P=0.038	P<0.001
Cochran-Armitage Trend Test	P<0.001		
Fisher Exact Test		P=0.028	P<0.001
Squamous Cell Papilloma or Carcinoma			
Overall	1/50 (2%)	18/50 (36%)	36/50 (72%)
Adjusted	2.0%	42.1%	83.6%
Terminal	0/41 (0%)	8/32 (25%)	27/34 (79%)
Life Table Test	P<0.001	P<0.001	P<0.001
Incidental Tumor Test	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test	P<0.001		
Fisher Exact Test		P<0.001	P<0.001
FEMALES			
Squamous Cell Papilloma			
Overall	1/50 (2%)	6/50 (12%)	9/50 (18%)
Adjusted	2.2%	15.5%	19.8%
Terminal	0/36 (0%)	4/36 (11%)	6/42 (14%)
Life Table Test	P=0.018	P=0.063	P=0.021
Incidental Tumor Test	P=0.004	P=0.034	P=0.004
Cochran-Armitage Trend Test	P=0.008		
Fisher Exact Test		P=0.056	P=0.008
Squamous Cell Carcinoma			
Overall	0/50 (0%)	0/50 (0%)	2/50 (4%)
Adjusted	0.0%	0.0%	4.5%
Terminal	0/36 (0%)	0/36 (0%)	1/42 (2%)
Life Table Test	P=0.111	—	P=0.264
Incidental Tumor Test	P=0.813	—	P=0.204
Cochran-Armitage Trend Test	P=0.095		
Fisher Exact Test		—	P=0.247
Squamous Cell Papilloma or Carcinoma			
Overall	1/50 (2%)	6/50 (12%)	11/50 (22%)
Adjusted	2.2%	15.5%	23.8%
Terminal	0/36 (0%)	4/36 (11%)	7/42 (17%)
Life Table Test	P=0.005	P=0.063	P=0.008
Incidental Tumor Test	P<0.001	P=0.034	P<0.001
Cochran-Armitage Trend Test	P=0.002		
Fisher Exact Test		P=0.056	P=0.002

Pancreas: The combined incidence of benign and malignant acinar cell tumors in low dose male rats (4/50) was significantly higher than that in the vehicle controls (0/49) by the life table test (P=0.041). Of the four rats with acinar cell tumors, three had adenomas and one had a carcinoma. None were observed in the high dose group. Pancreatic acinar hyperplasia was not found in treated males.

Hematopoietic System: Mononuclear cell leukemia occurred in low dose male rats (6/50) at an incidence significantly higher than that in the vehicle controls (1/50) by the life table test (P=0.035); one of 50 was observed in a high dose male.

Eye: Retinopathy and cataracts were found at increased incidences in high dose males and low dose females (Table 9).

TABLE 9. NUMBERS OF RATS WITH RETINOPATHY OR CATARACTS

	Males			Females		
	Vehicle Control	Low Dose	High Dose	Vehicle Control	Low Dose	High Dose
Retinopathy	0/50	1/50	19/50	0/50	19/50	0/50
Cataracts	0/50	1/50	19/50	0/50	16/50	0/50

Negative Trends: Statistically significant negative trends were observed in male rats for overall incidences of benign adrenal pheochromocytomas (controls, 15/50; low dose, 13/49; high dose, 5/50) and basal cell tumors of the skin (controls, 3/50; low dose, 0/50; high dose, 0/50). Incidences of testicular interstitial cell tumors occurred with a negative trend (controls, 47/50; low dose, 45/50; high dose, 40/50), but this trend is not statistically significant when survival differences are taken into account (Appendix F, Table F1).

III. RESULTS: MICE—SINGLE-DOSE STUDIES

SINGLE-DOSE STUDIES

Four of five males and 3/5 females receiving 1,800 mg/kg were dead by day 2. No other compound-related deaths occurred. Necropsies were not done on these mice.

FOURTEEN-DAY STUDIES

First Study

In the first study, ethyl acrylate was administered by gavage in aqueous ethanol. Two animals died after dosing ceased but before other animals were killed: one male receiving 450 mg/kg died on day 15 and one female receiving 450 mg/kg died on day 17 (Table 10). A grossly thickened, rough mucosa in the forestomach was observed in 4/4 males and 4/5 females receiving 450 mg/kg. Weight changes were not clearly dose related.

TABLE 10. SURVIVAL AND MEAN BODY WEIGHTS OF MICE ADMINISTERED ETHYL ACRYLATE BY GAVAGE FOR 14 DAYS (FIRST STUDY)

Dose (mg/kg)	Survival *(a)*	Mean Body Weight (grams)		
		Initial	Final *(b)*	Change *(c)*
MALES				
25	5/5	22.0 ± 0.3	22.6 ± 0.2	+0.6 ± 0.2
55	5/5	20.4 ± 0.7	20.0 ± 1.9	-0.4 ± 1.5
110	5/5	21.2 ± 0.5	22.0 ± 0.6	+0.8 ± 1.0
225	5/5	21.0 ± 0.7	22.2 ± 1.0	+1.2 ± 0.4
450	4/5 *(d)*	21.3 ± 0.6	18.5 ± 1.6	-2.8 ± 1.7
FEMALES				
25	5/5	18.4 ± 0.7	17.8 ± 1.2	-0.6 ± 0.7
55	5/5	17.6 ± 0.5	17.4 ± 0.9	-0.2 ± 0.5
110	5/5	17.2 ± 0.4	18.0 ± 0.0	+0.8 ± 0.4
225	5/5	18.2 ± 0.4	17.8 ± 1.0	-0.4 ± 0.7
450	4/5 *(e)*	18.0 ± 0.6	18.0 ± 0.7	0.0 ± 0.5

(a) Number surviving/number initially in the group. All calculations are based on those animals surviving to the end of the study.
(b) Weight on day 15.
(c) Mean weight change of the survivors of the group.
(d) One animal died on day 15.
(e) One animal died on day 17.

Second Study

In the second 14-day study, ethyl acrylate was administered in the drinking water. Because of broken water bottles, clogged or leaking sipper tubes, animals playing with water rather than drinking it, and instability of ethyl acrylate in water, the data from this study are inaccurate and do not reflect the actual amount consumed. The only treatment-related effects were an apparent decreased water consumption and reddening of the mucosal surface of the duodenum in three of the treated mice. On the basis of this study, it was recommended that the route of administration be changed back to gavage.

Third Study

No compound-related deaths occurred during the third study in which ethyl acrylate was administered by gavage in corn oil. Mean body weight gains by dosed and control groups were comparable (Table 11). The forestomach was grossly thickened in all males receiving 200, 400, 600, or 800 mg/kg, in 1/5 males receiving 100 mg/kg, in all females receiving 400, 600, or 800 mg/kg, and in 1/5 females receiving 200 mg/kg. Multiple abdominal lesions were observed grossly in 2/5 males and 1/5 females receiving 800 mg/kg. Histologically, ulcerative inflammation in the forestomach was found in 4/4 males and 5/5 females administered 600 mg/kg and in 1/5 males administered 400 mg/kg. Mild, nonulcerative inflammation of the forestomach was seen in 2/5 males and 1/5 females receiving 400 mg/kg and in 1/5 females receiving 200 mg/kg. The inflammatory reaction was characterized by the presence of neutrophils, lymphocytes, and histiocytes in the mucosa and submucosa of the forestomach. Significant histologic lesions were not observed in the forestomachs of mice dosed with 200 or 100 mg/kg.

TABLE 11. SURVIVAL AND MEAN BODY WEIGHTS OF MICE ADMINISTERED ETHYL ACRYLATE BY GAVAGE FOR 14 DAYS (THIRD STUDY)

Dose (mg/kg)	Survival *(a)*	Mean Body Weight (grams)			Final Body Weight Relative to Controls *(c)* (percent)
		Initial	Final	Change *(b)*	
MALES					
0	5/5	22.0 ± 0.7	23.4 ± 0.5	+1.4 ± 0.4	—
100	5/5	21.2 ± 0.9	23.0 ± 1.0	+1.8 ± 0.2	-2
200	4/5	23.0 ± 0.7	23.8 ± 0.6	+0.8 ± 0.3	+2
400	5/5	21.2 ± 0.4	22.8 ± 0.6	+1.6 ± 0.2	-3
600	5/5	23.6 ± 0.5	24.8 ± 0.5	+1.2 ± 0.2	+6
800	5/5	23.0 ± 0.3	24.4 ± 0.8	+1.4 ± 0.7	+4
FEMALES					
0	5/5	17.4 ± 0.5	19.8 ± 0.7	+2.4 ± 0.5	—
100	5/5	17.8 ± 0.7	20.0 ± 0.6	+2.2 ± 0.2	+1
200	5/5	17.4 ± 0.5	19.8 ± 0.4	+2.4 ± 0.2	0
400	5/5	17.2 ± 0.4	18.8 ± 0.4	+1.6 ± 0.4	-5
600	5/5	18.6 ± 0.6	19.8 ± 1.2	+1.2 ± 1.1	0
800	5/5	16.0 ± 0.4	19.0 ± 0.4	+3.0 ± 0.5	-4

(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 survivors relative to the survivors of the controls ◘

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

THIRTEEN-WEEK STUDIES

Ethyl acrylate was administered by gavage in corn oil in two separate studies. In the first study, 2/10 females and 1/10 males receiving 25 mg/kg and 1/10 females receiving 6 mg/kg died (Table 12). The male mouse was accidentally killed. The cause of death of the female mice could not be determined. Mean body weight gains by dosed and control mice in the first study were comparable.

Since treatment-related effects were not observed in mice in the first study, a second study using higher doses was undertaken. No treatment-related deaths occurred in the second study. Mean body weight changes by dosed and control mice of each sex were not dose related (Table 13). As was the case in the first study, no compound-related gross or microscopic pathologic effects were observed.

Because of deaths observed at 450 mg/kg in the first 14-day study and histopathologic effects (ulcerative and non-ulcerative inflammation) seen at 400 mg/kg in the third 14-day study, doses for mice in the 2-year studies were set at 100 and 200 mg/kg ethyl acrylate.

TABLE 12. SURVIVAL AND MEAN BODY WEIGHTS OF MICE ADMINISTERED ETHYL ACRYLATE BY GAVAGE FOR 13 WEEKS (FIRST STUDY)

Dose (mg/kg)	Survival *(a)*	Mean Body Weight (grams)			Final Body Weight Relative to Controls *(c)* (percent)
		Initial	Final	Change *(b)*	
MALES					
0	10/10	19.5 ± 0.5	36.1 ± 1.2	+16.6 ± 1.1	—
1.5	10/10	19.8 ± 0.6	35.5 ± 1.4	+15.7 ± 1.2	-2
3	10/10	19.1 ± 0.4	36.1 ± 0.7	+17.0 ± 0.8	0
6	10/10	20.4 ± 0.4	35.2 ± 0.8	+14.8 ± 0.7	-2
12	10/10	19.3 ± 0.2	35.7 ± 1.4	+16.4 ± 1.3	-1
25	9/10 *(d)*	19.3 ± 0.3	35.9 ± 1.2	+16.6 ± 1.3	-1
FEMALES					
0	10/10	16.9 ± 0.3	25.8 ± 0.5	+ 8.9 ± 0.3	—
1.5	10/10	16.8 ± 0.2	25.9 ± 0.6	+ 9.1 ± 0.6	0
3	10/10	16.4 ± 0.4	26.4 ± 0.4	+10.0 ± 0.1	+2
6	9/10	16.4 ± 0.3	26.0 ± 0.4	+ 9.6 ± 0.3	+1
12	10/10	16.3 ± 0.3	25.6 ± 0.4	+ 9.3 ± 0.3	-1
25	8/10	16.8 ± 0.3	26.6 ± 0.6	+ 9.8 ± 0.5	+3

(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 survivors relative to the survivors of the controls ◘

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

(d) Accidental death.

TABLE 13. SURVIVAL AND MEAN BODY WEIGHTS OF MICE ADMINISTERED ETHYL ACRYLATE BY GAVAGE FOR 13 WEEKS (SECOND STUDY)

Dose (mg/kg)	Survival *(a)*	Mean Body Weight (grams)			Final Body Weight Relative to Controls *(c)* (percent)
		Initial	Final	Change *(b)*	
MALES					
0	9/10	23.0 ± 0.6	29.6 ± 1.2	+6.6 ± 0.8	—
12	8/10	24.9 ± 0.6	31.8 ± 0.7	+6.9 ± 0.5	+7
25	9/10	23.3 ± 0.4	30.6 ± 0.4	+7.3 ± 0.5	+3
50	9/10	24.1 ± 0.7	29.4 ± 0.9	+5.3 ± 0.3	-1
100	10/10	24.3 ± 0.5	31.1 ± 0.9	+6.8 ± 0.7	+5
FEMALES					
0	10/10	20.2 ± 0.2	26.3 ± 0.4	+6.1 ± 0.4	—
12	10/10	20.4 ± 0.3	26.2 ± 0.4	+5.8 ± 0.3	0
25	10/10	20.1 ± 0.4	27.2 ± 0.6	+7.1 ± 0.4	+3
50	10/10	20.3 ± 0.4	25.2 ± 0.5	+4.9 ± 0.5	-4
100	10/10	19.7 ± 0.7	24.9 ± 0.9	+5.2 ± 0.4	-5

(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 survivors relative to the survivors of the controls =

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

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of high dose and vehicle control mice of each sex were comparable (Figure 3 and Table 14). Mean body weights of low dose female mice were lower than those of the controls.

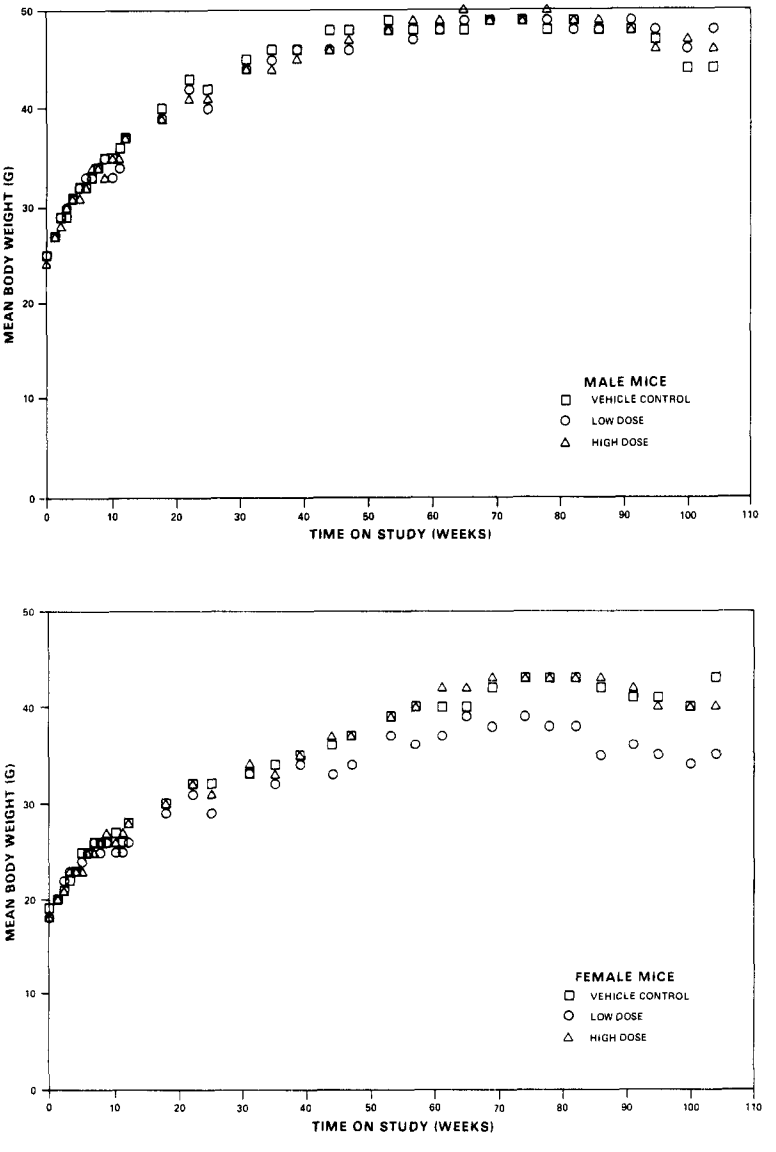


Figure 3. Growth Curves for Mice Administered Ethyl Acrylate in Corn Oil by Gavage

TABLE 14. MEAN BODY WEIGHTS (RELATIVE TO CONTROLS) OF MICE ADMINISTERED ETHYL ACRYLATE BY GAVAGE IN THE TWO-YEAR STUDIES

Week No.	Mean Body Weight (grams)			Mean Body Weights Relative to Controls *(a)* (Percent)	
	Vehicle Control	Low Dose	High Dose	Low Dose	High Dose
MALES					
0	25	25	24	0	-4
1	27	27	27	0	0
18	40	39	39	- 3	-3
39	46	46	45	0	-2
61	48	48	49	0	+2
82	49	48	49	- 2	0
100	44	46	47	+ 5	+7
104	44	48	46	+ 9	+5
FEMALES					
0	19	18	18	- 5	-5
1	20	20	20	0	0
18	30	29	30	- 3	0
39	35	34	35	- 3	0
61	40	37	42	- 8	+5
82	43	38	43	-12	0
100	40	34	40	-15	0
104	43	35	40	-19	-7

(a) Mean Body Weight Relative to Controls =

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

Survival

Estimates of the probabilities of survival of male and female mice administered ethyl acrylate by gavage at the doses used in this bioassay, and those of the controls, are shown by the Kaplan and Meier curves in Figure 4. No significant differences in survival were observed between any groups of the same sex. Three vehicle control, one low dose, and eight high dose males, and three vehicle control and three high dose females were accidentally killed.

In male mice, 28/50 (56%) of the controls, 36/50 (72%) of the low dose, and 30/50 (60%) of the high dose group lived to the termination period of the study at 104-105 weeks. In female mice, 27/50 (54%) of the controls, 35/50 (70%) of the low dose, and 26/50 (52%) of the high dose group lived to the termination period of the study at 104-105 weeks. The survival data include one control male that died during the termination period of the study. For purposes of statistical analysis, this animal was pooled with those killed at the end of the study.

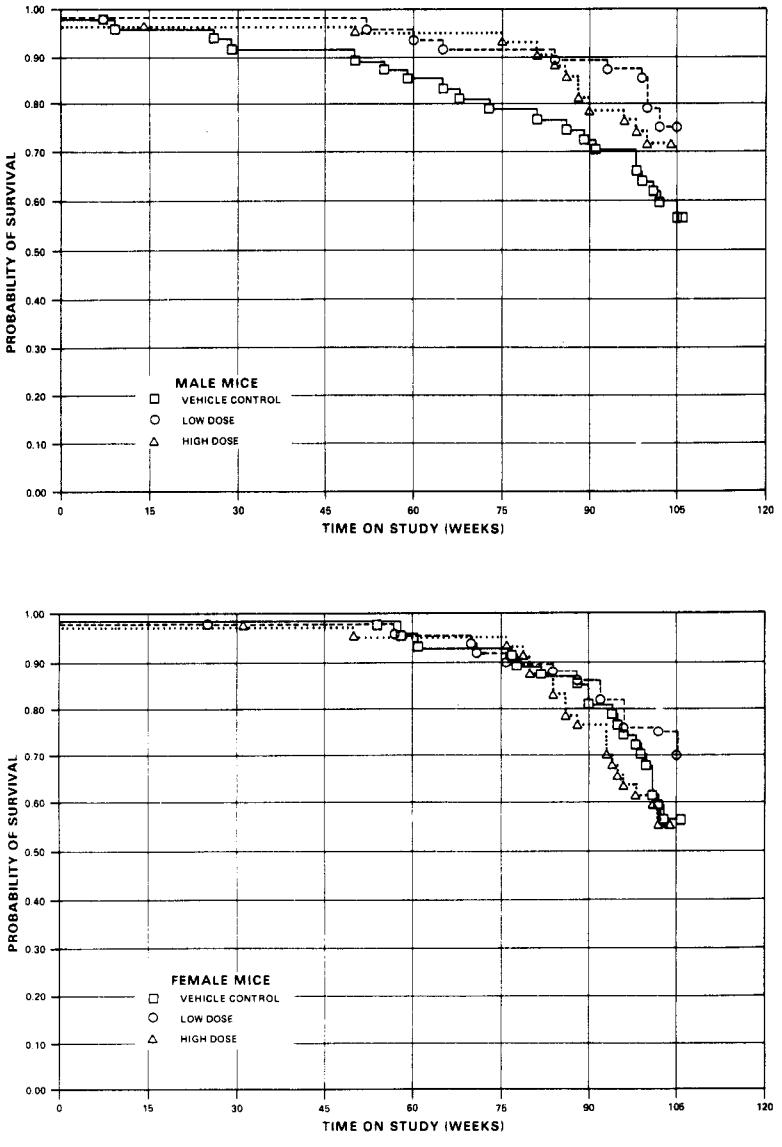


Figure 4. Survival Curves for Mice Administered Ethyl Acrylate in Corn Oil by Gavage

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 E. Appendix F, Tables F3 and F4, 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 the Materials and Methods (Data Recording and Statistical Methods) and Appendix F (footnotes).

Forestomach: The incidences of nonneoplastic lesions were dose related in both male and female mice (Table 15). These lesions included ulceration, inflammation, epithelial hyperplasia, and hyperkeratosis.

Statistically significant positive trends occurred in the incidences of male mice with squamous cell papillomas, squamous cell carcinomas, or either papillomas or carcinomas, and the incidences in the high dose group were significantly higher than those in the vehicle controls (Table 16). The combined incidences of female mice with squamous cell papillomas or carcinomas occurred with a statistically significant positive trend; the incidence in the high dose group was significantly higher than that in the vehicle controls.

Epithelial hyperplasia of the forestomach was manifested by increased cellular basophilia, elongation and proliferation of basilar cells with increased mitotic activity, and increased thickness of the squamous epithelium without folding of the underlying musculature. Mild epithelial down-growth was present in some cases. Epithelial hyperplasia was usually associated with variable degrees of hyperkeratosis.

Squamous cell papillomas were thin or wide-based papillary structures situated on the surface of the squamous mucosa. Most papillomas had a loose but vascular stroma covered by well differentiated squamous cells. Hyperkeratosis was extensive in most papillomas.

Squamous cell carcinomas were usually more pleomorphic, having cells with large vesicular nuclei and increased mitotic activity. Keratin pearl formation was common. Carcinomas invaded the wall of the stomach and often penetrated to the gastric serosa. Metastasis to surrounding organs and lymph nodes was observed. Squamous cell carcinomas frequently were characterized by variable degrees of surface ulceration.

TABLE 15. NUMBERS OF MICE WITH FORESTOMACH LESIONS

	Males			Females		
	Vehicle Control	Low Dose	High Dose	Vehicle Control	Low Dose	High Dose
Number of Animals Examined	48	47	50	50	49	48
Hyperkeratosis	0	19	28	2	14	32
Epithelial Hyperplasia	0	17	26	3	12	30
Acute and/or Chronic Inflammation	0	3	8	1	4	12
Ulceration	2	1	5	0	1	6
Squamous Cell Papilloma	0	4	9	1	4	5
Squamous Cell Carcinoma	0	2	5	0	1	2
Papilloma or Carcinoma	0	5	12	1	5	7

TABLE 16. ANALYSIS OF FORESTOMACH TUMORS IN MICE

	Vehicle Control	100 mg/kg	200 mg/kg
MALES			
Squamous Cell Papilloma			
Overall	0/48 (0%)	4/47 (9%)	9/50 (18%)
Adjusted	0.0%	10.5%	28.0%
Terminal	0/27 (0%)	3/36 (8%)	7/30 (23%)
Life Table Test	P=0.001	P=0.108	P=0.004
Incidental Tumor Test	P<0.001	P=0.109	P=0.002
Cochran-Armitage Trend Test	P=0.002		
Fisher Exact Test		P=0.056	P=0.002
Squamous Cell Carcinoma			
Overall	0/48 (0%)	2/47 (4%)	5/50 (10%)
Adjusted	0.0%	5.6%	14.7%
Terminal	0/27 (0%)	2/36 (6%)	2/30 (7%)
Life Table Test	P=0.017	P=0.303	P=0.040
Incidental Tumor Test	P=0.025	P=0.303	P=0.040
Cochran-Armitage Trend Test	P=0.019		
Fisher Exact Test		P=0.242	P=0.031
Squamous Cell Papilloma or Carcinoma			
Overall	0/48 (0%)	5/47 (11%)	12/50 (24%)
Adjusted	0.0%	13.2%	35.0%
Terminal	0/27 (0%)	4/36 (11%)	8/30 (27%)
Life Table Test	P<0.001	P=0.065	P<0.001
Incidental Tumor Test	P<0.001	P=0.066	P<0.001
Cochran-Armitage Trend Test	P<0.001		
Fisher Exact Test		P=0.026	P<0.001
FEMALES			
Squamous Cell Papilloma			
Overall	1/50 (2%)	4/49 (8%)	5/48 (10%)
Adjusted	3.7%	11.4%	17.3%
Terminal	1/27 (4%)	4/35 (11%)	3/26 (12%)
Life Table Test	P=0.062	P=0.264	P=0.091
Incidental Tumor Test	P=0.061	P=0.264	P=0.084
Cochran-Armitage Trend Test	P=0.072		
Fisher Exact Test		P=0.175	P=0.093
Squamous Cell Carcinoma			
Overall	0/50 (0%)	1/49 (2%)	2/48 (4%)
Adjusted	0.0%	2.3%	6.6%
Terminal	0/27 (0%)	0/35 (0%)	1/26 (4%)
Life Table Test	P=0.128	P=0.525	P=0.227
Incidental Tumor Test	P=0.156	P=0.455	P=0.214
Cochran-Armitage Trend Test	P=0.135		
Fisher Exact Test		P=0.495	P=0.237
Squamous Cell Papilloma or Carcinoma			
Overall	1/50 (2%)	5/49 (10%)	7/48 (15%)
Adjusted	3.7%	13.5%	23.1%
Terminal	1/27 (4%)	4/35 (11%)	4/26 (15%)
Life Table Test	P=0.018	P=0.166	P=0.028
Incidental Tumor Test	P=0.020	P=0.148	P=0.023
Cochran-Armitage Trend Test	P=0.022		
Fisher Exact Test		P=0.098	P=0.026

Ovaries, Uterus, Vagina, or Multiple Organs: Pyogenic infection of female genital organs occurred in mice but did not appear to be compound related (control, 11/50; low dose, 12/50; high dose, 11/50). The lesions occurred in some animals that died or were killed in a moribund condition before the end of the study (8 controls, 4 low dose, and 10 high dose animals), and they were the probable cause of death or moribundity in most cases. Specific lesions included suppurative inflammation and abscess formation in the ovaries, uterus, vagina, and on the abdominal cavity peritoneum. The disease was not observed until relatively late in the study (after week 86). To date, the etiologic agent has not been identified. Identical lesions observed in subsequent studies in the same laboratory have been attributed to *Klebsiella oxytoca* (although Koch's postulates have not been fulfilled).

Negative Trends: Statistically significant negative trends in tumor incidences are summarized in Table 17. Details for these tumor incidences can be found in Appendix F, Tables F3 and F4.

TABLE 17. NEGATIVE TRENDS IN OVERALL TUMOR INCIDENCES IN MICE

	Vehicle Control	100 mg/kg	200 mg/kg
MALES			
Liver:			
Carcinoma	12/49 (24%)	10/49 (20%)	3/50 (6%)
Adenoma or Carcinoma	17/49 (35%)	12/49 (24%)	6/50 (12%)
Thyroid:			
Follicular Cell Adenoma	4/49 (8%)	2/47 (4%)	0/49 (0%)
Follicular Cell Adenoma or Carcinoma	4/49 (8%)	3/47 (6%)	0/49 (0%)
Integumentary System:			
Sarcoma or Fibrosarcoma	3/49 (6%)	0/49 (0%)	0/50 (0%)
Hematopoietic System:			
Malignant Lymphocytic Lymphoma	7/49 (14%)	3/49 (6%)	1/50 (2%)
FEMALES			
Pituitary:			
Adenoma *(a)*	8/46 (17%)	2/47 (4%)	3/45 (7%)
Uterus:			
Endometrial Stromal Polyp *(a)*	4/50 (8%)	0/50 (0%)	1/50 (2%)

(a) Results of trend tests were not significant, but a significantly lower incidence ($P<0.05$) was observed in the low dose group.

IV. DISCUSSION AND CONCLUSIONS

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In the short-term testing phase of the ethyl acrylate studies there were three 14-day studies in addition to two mouse 13-week studies and one rat 13-week study. The reason for conducting several prechronic studies was to define a route of administration which would allow delivery of a sufficient amount of ethyl acrylate to produce systemic toxicity without producing severe irritation at the site of administration. Limited solubility, chemical instability of ethyl acrylate and technical difficulties mitigated against use of aqueous ethanol or drinking water administration. Ultimately, corn oil gavage was selected as the mode of administration for estimation of the maximum tolerated dose and for conduct of the 2-year studies. The data obtained from the various prechronic studies were somewhat variable and in some cases contradictory. Dosage selection for the 2-year studies was based primarily upon results obtained in the third 14-day studies.

The principal toxic effect of ethyl acrylate found in the acute and 14-day studies was confined to the forestomach of both sexes of rats and mice. There was no evidence of systemic toxicity in the 14-day studies. The most definitive prechronic study was the third 14-day study in which ethyl acrylate was administered by gavage in corn oil. In this study, histologic lesions in the forestomach included ulceration and inflammation with attendant epithelial hyperplasia and hyperkeratosis. These lesions were sufficiently severe to have been associated with abdominal cavity adhesions in a few cases. The lowest dosage in rats in which there were histologic forestomach lesions was 400 mg/kg. The lowest dosage producing histologic forestomach lesions in mice was 200 mg/kg where one of five females had the target tissue lesion. Similar target tissue effects were not observed in the 13-week studies where the highest dosage was 110 mg/kg for rats and 100 mg/kg for mice.

Doses of 100 and 200 mg/kg ethyl acrylate were selected for rats and mice in the 2-year studies because of the prevalence and severity of the forestomach lesions observed at the next higher (400 mg/kg) dosage in the third 14-day study. Weight gain and survival of dosed and control rats and mice in the 2-year studies were comparable with the exception of an unexplained decreased body weight gain in low dose female mice. The animals probably could not have tolerated higher doses because the severity of the stomach lesions indicate relatively toxic doses were used; a higher dose might have exacerbated this situation, significantly reducing survival.

In the rat and mouse 2-year studies, hyperkeratosis, hyperplasia, inflammation, and the occurrence of benign and malignant tumors of the forestomach mucosa were clearly associated with gavage administration of ethyl acrylate. Incidences of forestomach tumors in the vehicle controls were comparable to those of historic control groups in the Bioassay Program (Appendix E, Tables E1, E2, E5, and E6). In the 2-year studies, rats were gavaged with a lower volume per body weight (5 ml/kg) of corn oil than mice (10 ml/kg). Thus, the concentration of ethyl acrylate in the gavage solution for rats was twice that in the gavage solution for mice for each comparable dosage group. When the forestomach tumor data from rats and mice are compared on the basis of ethyl acrylate concentration rather than dosage, the response between the two species is similar (Table 18). This is also true for nonneoplastic stomach lesions (Tables 7 and 15). Consequently, the forestomach changes are more an effect of the delivered concentration of ethyl acrylate to the target tissue than the dose to the whole animal.

For high dose mice and for both low dose and high dose rats, there were more forestomach tumors in males than in females. This differential tumor response may reflect the larger volume of a given concentration of dosing solution administered to males compared to females. If so, the observed effect would be more related to the amount of ethyl acrylate delivered to the target tissue than to the dosage to the whole animal.

The observed tissue necrosis (ulceration and inflammation) and hyperplasia at the site of exposure (forestomach) is consistent with the known irritant properties of ethyl acrylate. Irritation occurred in the nasal cavity of F344 rats and $B6C3F_1$ mice in ethyl acrylate inhalation studies (Miller et al., 1980 and 1982) and on the skin of rabbits in ethyl acrylate dermal studies (Pozzani et al., 1949).

There was no evidence of toxicity induced by ethyl acrylate at sites other than the forestomach in the prechronic and two-year studies. While this may be attributed to unique sensitivity of the forestomach to ethyl acrylate, it is more probable that other tissues did not receive a comparable exposure to the parent chemical. Both forestomach and glandular stomach tissues metabolize ethyl acrylate and, when given by gavage in corn oil, ethyl acrylate remains in the

TABLE 18. COMPARISON OF FORESTOMACH TUMORS IN RATS AND MICE BASED ON ETHYL ACRYLATE CONCENTRATION *(a)* IN THE CORN OIL GAVAGE SOLUTION

	Squamous Cell Papilloma				Squamous Cell Carcinoma				Papilloma or Carcinoma			
	0%	1%	2%	4%	0%	1%	2%	4%	0%	1%	2%	4%
RATS												
Males	1/50	—	15/50	29/50	0/50	—	5/50	12/50	1/50	—	18/50	36/50
Females	1/50	—	6/50	9/50	0/50	—	0/50	2/50	1/50	—	6/50	11/50
MICE												
Males	0/48	4/47	9/50	—	0/48	2/47	5/50	—	0/48	5/47	12/50	—
Females	1/50	4/49	5/48	—	0/50	1/49	2/48	—	1/50	5/49	7/48	—

(a) 0% = vehicle controls; 1% = low dose mice (100 mg/kg); 2% = high dose mice (200 mg/kg) and low dose rats (100 mg/kg); 4% = high dose rats (200 mg/kg).
— = not applicable.

stomach for a time period sufficient to reduce tissue non-protein thiols (Appendix M). It is known that ethyl acrylate is readily hydrolyzed by esterases present in several tissues, including blood (Silver and Murphy, 1981; Miller et al., 1981). In our studies (Appendix M) ethyl acrylate was detected in portal venous blood after gavage in corn oil but was not detected in blood from the retro-orbital venous plexus. This suggests that following gavage dosing any absorbed ethyl acrylate is rapidly hydrolyzed in the blood and/or liver and does not circulate throughout the body. Consequently, it is believed that under the conditions of the present bioassay, the only tissue receiving significant exposure to ethyl acrylate was the stomach. Despite the sex-difference in occurrence of tumors in the 2-year study, there was no significant sex difference in the metabolism of ethyl acrylate by male and female F344 rats (Appendix M).

While the occurrence of forestomach tumors is clearly treatment-related, the design of these 2-year studies does not permit elucidation of the pathogenesis of these lesions. Most of the animals had both neoplastic and nonneoplastic lesions of the forestomach. A few animals had both squamous cell papillomas and carcinomas in addition to the nonneoplastic lesions. Since most of the forestomach tumors were found in animals killed at the end of the 2-year time period, it was not possible to clearly demonstrate a progression from hyperplasia to benign neoplasia to malignant neoplasia, although such a progression is suggested by the constellation of forestomach lesions observed. Indeed, the findings in these studies suggest a causative role of irritation in the genesis of forestomach tumors.

Based upon mutagenicity testing results (Rosenthal and Smith, 1982; Litton Bionetics, 1980; Appendix G), ethyl acrylate is genotoxic in some test systems. As a mutagen, ethyl acrylate could have produced the carcinogenic effect on the forestomach by direct interaction with cellular DNA. The high cell turnover which presumably resulted from repeated administration of necrogenic doses of ethyl acrylate to the forestomach would have increased the amount of replicating DNA at risk for mutational alteration. Alternatively, the presumed high cell turnover could have permitted enhancement of pre-existing potential for development of forestomach tumors.

The contention that the target tissue effects of ethyl acrylate observed in the 2-year gavage studies are more concentration dependent than dose dependent is supported by the concentration dependent nasal cavity response reported in an unpublished ethyl acrylate inhalation study (Miller et al., 1982). Metaplastic and hyperplastic lesions in the nasal cavity were observed in both rats and mice exposed for 27 months to 75 ppm ethyl acrylate. These lesions were more severe in the anterior portions of the olfactory nasal mucosa than in the posterior portions where direct exposure to ethyl acrylate would be less. In this inhalation study, male and female F344 rats and $B6C3F_1$ mice exposed to 25 and 75 ppm of ethyl acrylate for 27 months had no increased tumor incidences at any tissue site (Miller et al., 1982).

IV. DISCUSSION AND CONCLUSIONS

In a drinking water study no treatment-related nonneoplastic or neoplastic lesions were found in male or female Wistar rats given ethyl acrylate for 2 years (Borzelleca et al., 1964). Based upon average body weight and water consumption, the highest dose (2,000 ppm in drinking water) corresponded to approximately 170 or 120 mg ethyl acrylate per kilogram body weight per day for males or females, respectively. These dose levels are between the low and high doses used in the NTP two-year rat gavage study. Since the concentration of ethyl acrylate in the dosed drinking water was 0.2% versus 2% and 4% in corn oil in the NTP 2-year study, the discrepant results between the two rat studies may be attributed to the ethyl acrylate concentration differences. Other possible explanations include administration of ethyl acrylate in a bolus dose (gavage administration) versus prolonged daily administration (dosed water), instability of ethyl acrylate in the dosed water, and the differences in rat strains. Insufficient details of survival and pathologic examinations in the drinking water study (Borzelleca et al., 1964) preclude direct comparison with the NTP gavage study.

In a lifetime skin-painting study neither skin tumors nor tumors at distant sites were found after undiluted ethyl acrylate was applied to the skin of C3H/HeJ male mice (Hengler and DePass, 1982). Although epidermis and forestomach mucosa are composed of a similar type of epithelium, direct comparison of the skin-painting study with the 2-year carcinogenesis studies is problematic considering the probability of rapid evaporation of ethyl acrylate from the painted skin. The documentation of dermal inflammation, hyperplasia, and hyperkeratosis in some of the painted mice is indicative of an irritating effect of ethyl acrylate exposure. Since the mean survival time in the skin-painted mice was 408 days, less than an optimal number of mice were at risk for a significant time period to categorically state that ethyl acrylate is noncarcinogenic by the skin-painting route. In the 2-year gavage study, most tumors of the forestomach of mice were found at final sacrifice. The earliest forestomach tumor diagnoses found in mice not surviving to the end of the study were at week 92 for one female and week 99 for one male.

A marginal increase was observed in the incidence of pancreatic acinar cell adenomas or carcinomas in low dose male rats (controls, 0/49; low dose 4/50; P=0.041, life table test). This increase was not significant by the more appropriate incidental tumor test. Furthermore, this effect is not considered to be related to ethyl acrylate administration because acinar cell tumors were not observed in the high dose group. One male vehicle control rat had pancreatic acinar cell hyperplasia, but none of the males dosed with ethyl acrylate had hyperplasia of the exocrine pancreas.

The marginally increased incidence of mononuclear cell leukemia observed in low dose male rats is not considered an effect of treatment because of the absence of a dose response and because of an unusually low concurrent control incidence for this hematopoietic neoplasm.

Retinopathy and cataract formation occurred at increased incidences in male rats administered 200 mg/kg and in female rats administered 100 mg/kg in the 2-year studies. Retinal degeneration is known to be associated with exposure to high intensity light (Weibe et al., 1974). The groups of rats most affected were maintained in clear polycarbonate cages on the top level of the cage racks. Consequently, the affected groups were exposed to light of higher intensity than were the unaffected groups. Thus, increases in retinal degeneration and cataracts cannot be attributed to administration of ethyl acrylate.

Several tumors occurred in rats and mice with significantly ($P<0.05$) negative trends. The decrease in basal cell tumors of the integumentary system of male rats results from an atypically high incidence of this tumor in the vehicle controls (controls, 3/50; low dose, 0/50; high dose, 0/50). The historic incidence in male rats at this laboratory and for the entire Bioassay Program is less than 1% (Appendix E, Table E7). In light of the historic control incidence of pheochromocytomas of the adrenal gland in male F344/N rats at the performing laboratory (Appendix E, Table E8), the negative trend for overall incidence of pheochromocytoma observed in the 2-year study (control 15/50; low dose 13/49; high dose 5/50) is considered to be a result of administration of ethyl acrylate. The negative trend for interstitial cell tumors of the testes of male rats is not statistically significant when survival differences are taken into account.

In male mice, significant ($P<0.05$) negative trends were observed for hepatocellular carcinomas and for adenomas or carcinomas combined (Table 17). These trends are considered to be treatment related. The negative trend in the combined incidence of follicular cell tumors of the thyroid is statistically significant and, since the vehicle control incidence is consistent with the

historic control incidence at the performing laboratory (Appendix E, Table E9), this effect is considered compound associated. The negative trend for sarcomas or fibrosarcomas of the integumentary system is based upon three cases in controls versus none in the treated male mice, and as such, probably is not a consequence of orally administered ethyl acrylate. The negative trend for lymphocytic lymphoma is likely an effect of ethyl acrylate since the vehicle control incidence is similar to the historic control rate at this laboratory (Appendix E, Table E10).

In female mice, the significantly lower incidence of pituitary adenomas in the low dose group is probably biologically significant. The incidence of endometrial stromal polyps of the uterus is significant only in the low dose group and only by the life table test.

At the present time a mechanistic explanation for the occurrence of compound associated negative trends is lacking. The results of these studies clearly indicate that repeated gavage administration of ethyl acrylate leads to development of forestomach tumors in F344/N rats and $B6C3F_1$ mice. The evidence for carcinogenicity is unequivocal in both species and as such ethyl acrylate should be regarded as potentially carcinogenic for humans. However, judgments regarding potential human risk should be tempered by all available relevant facts. Humans are unlikely to be exposed repeatedly to high concentrations of ethyl acrylate because of its pungent and local irritating properties. No systemic toxicity was observed in the prechronic and chronic rodent studies. Furthermore, the odor threshold of 0.5 ppb for ethyl acrylate (A.D. Little, 1968) should signal exposure and thus would limit the extent (level and duration) of human exposure. Limited contemporary use of ethyl acrylate as a flavoring and fragrance minimizes the likelihood of significant consumer exposure. While chronic dermal and inhalation exposure to relatively low levels are realistic occupational hazards, chronic human exposure to ethyl acrylate by the oral route is unlikely.

In retrospect, current toxicological study design principles would dictate a different protocol for the conduct of studies to evaluate the potential carcinogenicity of ethyl acrylate. In particular, data on pharmacodynamic properties of ethyl acrylate would be used to devise dosing schedules and routes which would reflect current scientific standards for conducting carcinogenesis studies as well as attempting to more closely mimic human exposure.

Conclusions: Under the conditions of these studies, ethyl acrylate was carcinogenic for the forestomach of F344/N rats and $B6C3F_1$ mice, causing squamous cell carcinomas in male rats and male mice, squamous cell papillomas in male and female rats and male mice, and squamous cell papillomas or carcinomas (combined) in male and female rats and mice. Evidence for carcinogenicity was greater in males than in females. Ethyl acrylate also caused irritation of the forestomach mucosa in male and female rats and mice.

V. REFERENCES

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APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS ADMINISTERED ETHYL ACRYLATE IN CORN OIL BY GAVAGE

TABLE A1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS ADMINISTERED ETHYL ACRYLATE 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			
*MULTIPLE ORGANS	(50)	(50)	(50)
FIBROUS HISTIOCYTOMA, MALIGNANT		1 (2%)	
*SKIN	(50)	(50)	(50)
SQUAMOUS CELL PAPILLOMA	2 (4%)	2 (4%)	1 (2%)
BASAL-CELL TUMOR	1 (2%)		
KERATOACANTHOMA	1 (2%)	1 (2%)	
*SUBCUT TISSUE	(50)	(50)	(50)
BASAL-CELL TUMOR	2 (4%)		
KERATOACANTHOMA			1 (2%)
SARCOMA, NOS			1 (2%)
FIBROMA	3 (6%)	3 (6%)	2 (4%)
FIBROSARCOMA	1 (2%)	1 (2%)	2 (4%)
FIBROUS HISTIOCYTOMA, MALIGNANT		1 (2%)	
NEURILEMOMA	2 (4%)		
RESPIRATORY SYSTEM			
#LUNG	(50)	(50)	(50)
ISLET-CELL CARCINOMA, METASTATIC	1 (2%)		
ALVEOLAR/BRONCHIOLAR ADENOMA	3 (6%)	1 (2%)	1 (2%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	1 (2%)		1 (2%)
OSTEOSARCOMA, METASTATIC	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
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
MONOCYTIC LEUKEMIA	1 (2%)	6 (12%)	1 (2%)
CIRCULATORY SYSTEM			
*SUBCUT TISSUE	(50)	(50)	(50)
HEMANGIOSARCOMA		1 (2%)	
#LUNG	(50)	(50)	(50)
HEMANGIOSARCOMA, METASTATIC		1 (2%)	
DIGESTIVE SYSTEM			
#LIVER	(50)	(50)	(50)
NEOPLASTIC NODULE			1 (2%)
#PANCREAS	(49)	(50)	(49)
ADENOMA, NOS			1 (2%)
ACINAR-CELL ADENOMA		3 (6%)	
ACINAR-CELL CARCINOMA		1 (2%)	
#FORESTOMACH	(50)	(50)	(50)
SQUAMOUS CELL PAPILLOMA	1 (2%)	15 (30%)	29 (58%)
SQUAMOUS CELL CARCINOMA		5 (10%)	12 (24%)
SARCOMA, NOS			1 (2%)
#DUODENUM	(50)	(50)	(49)
CYSTADENOMA, NOS		1 (2%)	
#COLON	(48)	(50)	(50)
ADENOCARCINOMA, NOS	1 (2%)		
ADENOMATOUS POLYP, NOS	1 (2%)	1 (2%)	
CYSTADENOMA, NOS	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
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
TUBULAR-CELL ADENOCARCINOMA			1 (2%)
#URINARY BLADDER	(50)	(50)	(49)
TRANSITIONAL-CELL CARCINOMA		1 (2%)	
ENDOCRINE SYSTEM			
#PITUITARY	(48)	(50)	(48)
CARCINOMA,NOS		1 (2%)	
ADENOMA, NOS	12 (25%)	12 (24%)	13 (27%)
#ADRENAL	(50)	(49)	(50)
CORTICAL ADENOMA		1 (2%)	
PHEOCHROMOCYTOMA	15 (30%)	13 (27%)	5 (10%)
PHEOCHROMOCYTOMA, MALIGNANT			2 (4%)
#THYROID	(49)	(49)	(48)
FOLLICULAR-CELL CARCINOMA			1 (2%)
C-CELL ADENOMA	10 (20%)	4 (8%)	6 (13%)
C-CELL CARCINOMA	1 (2%)	1 (2%)	2 (4%)
#PANCREATIC ISLETS	(49)	(50)	(49)
ISLET-CELL ADENOMA	1 (2%)	2 (4%)	1 (2%)
ISLET-CELL CARCINOMA	4 (8%)	3 (6%)	1 (2%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
FIBROADENOMA	2 (4%)		3 (6%)
*PREPUTIAL GLAND	(50)	(50)	(50)
CARCINOMA,NOS	1 (2%)	2 (4%)	2 (4%)
#TESTIS	(50)	(50)	(50)
INTERSTITIAL-CELL TUMOR	47 (94%)	45 (90%)	40 (80%)

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
NERVOUS SYSTEM			
#BRAIN	(50)	(50)	(50)
ASTROCYTOMA	1 (2%)		
SPECIAL SENSE ORGANS			
*EYE	(50)	(50)	(50)
NEURILEMOMA		1 (2%)	
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*THORAX	(50)	(50)	(50)
OSTEOSARCOMA	1 (2%)		
*MEDIASTINUM	(50)	(50)	(50)
OSTEOSARCOMA, METASTATIC	1 (2%)		
*PERITONEUM	(50)	(50)	(50)
OSTEOSARCOMA		1 (2%)	
*MESENTERY	(50)	(50)	(50)
SARCOMA, NOS		1 (2%)	
MESOTHELIOMA, NOS	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
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
ADENOCARCINOMA, NOS		1 (2%)	
SARCOMA, NOS		1 (2%)	
FIBROUS HISTIOCYTOMA, METASTATIC		1 (2%)	
MESOTHELIOMA, MALIGNANT		2 (4%)	3 (6%)
TAIL			
SARCOMA, NOS	1		
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	2	4	6
MORIBUND SACRIFICE	7	12	9
SCHEDULED SACRIFICE			
TERMINAL SACRIFICE	41	32	33
DOSING ACCIDENT			
ACCIDENTALLY KILLED, NDA			
ACCIDENTALLY KILLED, NOS		2	2
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*	49	50	47
TOTAL PRIMARY TUMORS	118	135	134
TOTAL ANIMALS WITH BENIGN TUMORS	49	49	45
TOTAL BENIGN TUMORS	104	105	103
TOTAL ANIMALS WITH MALIGNANT TUMORS	12	26	22
TOTAL MALIGNANT TUMORS	13	30	30
TOTAL ANIMALS WITH SECONDARY TUMORS#	2	2	
TOTAL SECONDARY TUMORS	3	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 A2.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS ADMINISTERED ETHYL ACRYLATE 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)
KERATOACANTHOMA	1 (2%)	1 (2%)	
FIBROMA	1 (2%)		
*SUBCUT TISSUE	(50)	(50)	(50)
FIBROMA		1 (2%)	
SYNOVIAL SARCOMA	1 (2%)		
RESPIRATORY SYSTEM			
#LUNG	(50)	(50)	(50)
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (2%)	1 (2%)	3 (6%)
ALVEOLAR/BRONCHIOLAR CARCINOMA			1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
MONOCYTIC LEUKEMIA	5 (10%)	8 (16%)	7 (14%)

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(50)	(50)	(50)
NEOPLASTIC NODULE			1 (2%)
#FORESTOMACH	(50)	(50)	(50)
SQUAMOUS CELL PAPILLOMA	1 (2%)	6 (12%)	9 (18%)
SQUAMOUS CELL CARCINOMA			2 (4%)
URINARY SYSTEM			
#URINARY BLADDER	(50)	(50)	(49)
NEUROFIBROMA	1 (2%)		
ENDOCRINE SYSTEM			
#PITUITARY	(49)	(49)	(47)
CARCINOMA,NOS	2 (4%)	1 (2%)	
ADENOMA, NOS	20 (41%)	17 (35%)	17 (36%)
#ADRENAL	(50)	(50)	(50)
CORTICAL ADENOMA	1 (2%)		
PHEOCHROMOCYTOMA	3 (6%)	4 (8%)	5 (10%)
PHEOCHROMOCYTOMA, MALIGNANT		1 (2%)	
#THYROID	(50)	(49)	(48)
FOLLICULAR-CELL ADENOMA	1 (2%)		1 (2%)
FOLLICULAR-CELL CARCINOMA			1 (2%)
C-CELL ADENOMA	6 (12%)	7 (14%)	8 (17%)
C-CELL CARCINOMA	1 (2%)	4 (8%)	5 (10%)
#PANCREATIC ISLETS	(50)	(49)	(50)
ISLET-CELL ADENOMA		1 (2%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
ADENOMA, NOS	1 (2%)		
ADENOCARCINOMA, NOS	1 (2%)	1 (2%)	1 (2%)
FIBROADENOMA	13 (26%)	12 (24%)	11 (22%)
*CLITORAL GLAND	(50)	(50)	(50)
CARCINOMA,NOS	2 (4%)		
#UTERUS	(50)	(50)	(50)
ADENOCARCINOMA, NOS			2 (4%)
SARCOMA, NOS		1 (2%)	
ENDOMETRIAL STROMAL POLYP	17 (34%)	14 (28%)	18 (36%)
ENDOMETRIAL STROMAL SARCOMA			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
#OVARY	(50)	(50)	(49)
GRANULOSA-CELL TUMOR	2 (4%)		1 (2%)
NERVOUS SYSTEM			
#CEREBRUM	(50)	(50)	(50)
EPENDYMOMA		1 (2%)	
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
CARCINOMA,NOS	1 (2%)		
SARCOMA, NOS	1 (2%)		
FIBROSARCOMA	1 (2%)		
FOOT			
SQUAMOUS CELL PAPILLOMA		1	
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	6	5	2
MORIBUND SACRIFICE	9	9	5
SCHEDULED SACRIFICE			
TERMINAL SACRIFICE	35	36	42
DOSING ACCIDENT			
ACCIDENTALLY KILLED, NDA			
ACCIDENTALLY KILLED, NOS			1
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	44	44
TOTAL PRIMARY TUMORS	84	82	94
TOTAL ANIMALS WITH BENIGN TUMORS	35	38	38
TOTAL BENIGN TUMORS	67	65	72
TOTAL ANIMALS WITH MALIGNANT TUMORS	14	16	20
TOTAL MALIGNANT TUMORS	15	17	20
TOTAL ANIMALS WITH SECONDARY TUMORS#			
TOTAL SECONDARY TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	2		2
TOTAL UNCERTAIN TUMORS	2		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 A3.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR STUDY OF ETHYL ACRYLATE

VEHICLE CONTROL

ANIMAL NUMBER	0 0 1	0 0 2	0 0 3	0 0 4	0 0 5	0 0 6	0 0 7	0 0 8	0 0 9	0 1 0	0 1 1	0 1 2	0 1 3	0 1 4	0 1 5	0 1 6	0 1 7	0 1 8	0 1 9	0 2 0	0 2 1	0 2 2	0 2 3	0 2 4	0 2 5
WEEKS ON STUDY	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	0 8 4	1 0 5	1 0 5	1 0 5	0 0 5	1 0 5	1 0 5	1 0 5	1 0 5	0 8 8	1 0 3	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	0 5 7	1 0 5	0 9 4	1 0 5
INTEGUMENTARY SYSTEM																								
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL PAPILLOMA																							X	
BASAL-CELL TUMOR																								
KERATOACANTHOMA																								
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
BASAL-CELL TUMOR										X		X												
FIBROMA						X																		
FIBROSARCOMA																								
NEURILEMOMA																								
RESPIRATORY SYSTEM																								
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ISLET-CELL CARCINOMA, METASTATIC																								
ALVEOLAR/BRONCHIOLAR ADENOMA	X																							
ALVEOLAR/BRONCHIOLAR CARCINOMA																								
OSTEOSARCOMA, METASTATIC			X																					
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																								
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	+	+	-	+	+	-	+	+	+	+	+	+	+	+	+	+	+	-	-	+	+	-	+	+
CIRCULATORY SYSTEM																								
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																								
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
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL PAPILLOMA																					X			
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOCARCINOMA, NOS						X																		
ADENOMATOUS POLYP, NOS																								
CYSTADENOMA, NOS																								
URINARY SYSTEM																								
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																								
PITUITARY	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOMA, NOS				X								X			X	X	X	X			X	X		
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PHEOCHROMOCYTOMA				X				X			X		X			X	X	X						
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-CELL ADENOMA											X							X	X				X	
C-CELL CARCINOMA																					X			
PARATHYROID	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	-	-	+	+	+
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+
ISLET-CELL ADENOMA																						X	X	
ISLET-CELL CARCINOMA																								
REPRODUCTIVE SYSTEM																								
MAMMARY GLAND	N	N	+	+	+	+	+	+	N	+	+	+	N	+	+	N	N	+	+	+	+	+	N	+
FIBROADENOMA																								
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
CARCINOMA,NOS															X									
NERVOUS SYSTEM																								
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ASTROCYTOMA																								
BODY CAVITIES																								
PLEURA	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																					
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
OSTEOSARCOMA, METASTATIC			X																					
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
MESOTHELIOMA, NOS									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																								
TAIL																								
SARCOMA, NOS																								

+: 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	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 TISSUES TUMORS
WEEKS ON STUDY	105	105	105	105	105	105	105	105	104	105	105	105	105	100	105	105	105	105	105	105	100	105	102	105	105	
INTEGUMENTARY SYSTEM																										
SKIN	+	N	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
SQUAMOUS CELL PAPILLOMA																			X							2
BASAL-CELL TUMOR																										1
KERATOACANTHOMA																X										1
SUBCUTANEOUS TISSUE	+	N	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
BASAL-CELL TUMOR																										2
FIBROMA				X		X																				3
FIBROSARCOMA																			X							1
NEURILEMOMA									X							X										2
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ISLET-CELL CARCINOMA, METASTATIC											X															1
ALVEOLAR/BRONCHIOLAR ADENOMA															X				X							3
ALVEOLAR/BRONCHIOLAR CARCINOMA																							X			1
OSTEOSARCOMA, METASTATIC																										1
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
THYMUS	+	+	+	+	+	+	-	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	-	42
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SQUAMOUS CELL PAPILLOMA																										1
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	+	+	48
ADENOCARCINOMA, NOS																										1
ADENOMATOUS POLYP, NOS						X																				1
CYSTADENOMA, NOS														X												1
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	48
ADENOMA, NOS	X	X							X										X							12
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
PHEOCHROMOCYTOMA					X			X	X	X						X		X	X			X				15
THYROID	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-CELL ADENOMA			X		X				X									X	X					X		10
C-CELL CARCINOMA																										1
PARATHYROID	-	-	-	+	+	+	+	+	+	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	42
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ISLET-CELL ADENOMA													X													1
ISLET-CELL CARCINOMA									X		X															4
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	+	N	N	+	+	+	+	+	+	N	+	+	+	+	N	+	N	N	+	+	+	+	+	+	N	50*
FIBROADENOMA							X						X													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	X	X	X	X	X	X	47
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	N	50*
CARCINOMA,NOS																										1
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ASTROCYTOMA																X										1
BODY CAVITIES																										
PLEURA	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
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*
OSTEOSARCOMA, METASTATIC																										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	N	50*
MESOTHELIOMA, NOS																										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												1
TAIL																										
SARCOMA, NOS											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 TWO-YEAR STUDY OF ETHYL ACRYLATE

LOW DOSE

ANIMAL NUMBER	0011	0021	0031	0041	0051	0061	0071	0081	0091	0101	0111	0121	0131	0141	0151	0161	0171	0181	0191	0201	0211	0221	0231	0241	0251
WEEKS ON STUDY	057	077	051	062	055	055	051	055	055	055	055	055	055	099	055	095	093	051	055	063	077	051	085	055	055
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	N	+	+
SQUAMOUS CELL PAPILLOMA																								X	
KERATOACANTHOMA																									
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	N	+	+
FIBROMA																			X						
FIBROSARCOMA																									
FIBROUS HISTIOCYTOMA, MALIGNANT																						X			
HEMANGIOSARCOMA																									
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALVEOLAR/BRONCHIOLAR ADENOMA																									
HEMANGIOSARCOMA, METASTATIC																									
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ACINAR-CELL ADENOMA											X														
ACINAR-CELL CARCINOMA																									
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL PAPILLOMA			X												X		X							X	X
SQUAMOUS CELL CARCINOMA											X					X									
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CYSTADENOMA, NOS																									
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOMATOUS POLYP, NOS					X																				
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
TRANSITIONAL-CELL CARCINOMA														X											
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARCINOMA,NOS																									
ADENOMA, NOS				X							X				X	X									X
ADRENAL	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CORTICAL ADENOMA																						X			
PHEOCHROMOCYTOMA			X			X		X					X			X							X		
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+
C-CELL ADENOMA																			X			X			
C-CELL CARCINOMA																									
PARATHYROID	+	+	+	+	+	+	+	+	+	-	+	+	-	+	+	+	+	+	+	-	+	+	+	+	+
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ISLET-CELL ADENOMA							X																		
ISLET-CELL CARCINOMA					X																				
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	N	+	+	+	+	+	N	N	+	+	+	N	N	N	+	+	N	+	N	N	N	N	+	N
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	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																				
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
EYE	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	+	N	N	+	N	N	N	N	N
NEURILEMOMA																									
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
OSTEOSARCOMA																									
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
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
ADENOCARCINOMA, NOS																									
SARCOMA, NOS																	X								
FIBROUS HISTIOCYTOMA, MALIGNANT																						X			
FIBROUS HISTIOCYTOMA, METASTATIC																									
MESOTHELIOMA, MALIGNANT																					X				
MONOCYTIC LEUKEMIA		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
C NO TISSUE INFORMATION SUBMITTED; 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	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL TISSUES TUMORS
WEEKS ON STUDY	105	105	110	070	105	074	085	086	098	095	095	105	105	098	095	105	095	095	105	105	105	110	100	086	105	
INTEGUMENTARY SYSTEM																										
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SQUAMOUS CELL PAPILLOMA															X											2
KERATOACANTHOMA							X																			1
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
FIBROMA					X																		X			3
FIBROSARCOMA										X																1
FIBROUS HISTIOCYTOMA, MALIGNANT																										1
HEMANGIOSARCOMA																								X		1
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALVEOLAR/BRONCHIOLAR ADENOMA		X																								1
HEMANGIOSARCOMA, METASTATIC																								X		1
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
THYMUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	±	●	+	●	●	50
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
ACINAR-CELL ADENOMA		X											X													3
ACINAR-CELL CARCINOMA																								X		1
ESOPHAGUS	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SQUAMOUS CELL PAPILLOMA		X				X	X	X			X			X					X				X	X	X	15
SQUAMOUS CELL CARCINOMA					X																		X		X	5
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CYSTADENOMA, NOS		X																								1
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ADENOMATOUS POLYP, NOS																										1
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
TRANSITIONAL-CELL CARCINOMA																										1
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CARCINOMA,NOS																					X					1
ADENOMA, NOS			X	X				X					X	X	X			X								12
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
CORTICAL ADENOMA																										1
PHEOCHROMOCYTOMA			X		X		X		X										X			X			X	13
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-CELL ADENOMA										X															X	4
C-CELL CARCINOMA																			X							1
PARATHYROID	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–	+	–	–	+	+	+	+	+	+	–	41
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ISLET-CELL ADENOMA																				X						2
ISLET-CELL CARCINOMA												X	X													3
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	+	+	+	+	N	N	N	+	N	+	+	+	+	+	N	+	+	+	N	+	+	+	+	+	+	50
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	X	X	X	45
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	N	50
CARCINOMA,NOS															X											2
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
EYE	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												X														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	N	50
OSTEOSARCOMA						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	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
ADENOCARCINOMA, NOS							X							X												1
SARCOMA, NOS																										1
FIBROUS HISTIOCYTOMA, MALIGNANT																										1
FIBROUS HISTIOCYTOMA, METASTATIC																										1
MESOTHELIOMA, MALIGNANT																									X	2
MONOCYTIC LEUKEMIA											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 A3.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR STUDY OF ETHYL ACRYLATE

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	100	072	104	099	006	041	104	041	083	104	104	104	104	104	041	104	104	104	104	104	041	097	105	105	035
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	N	+	+	+	+
SQUAMOUS CELL PAPILLOMA																				X					
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	N	+	+	+	+
KERATOACANTHOMA									X																
SARCOMA, NOS																									X
FIBROMA										X															
FIBROSARCOMA															X							X			
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALVEOLAR/BRONCHIOLAR ADENOMA																									
ALVEOLAR/BRONCHIOLAR CARCINOMA																									
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+
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	N
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+
ADENOMA, NOS																									
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL PAPILLOMA	X		X	X		X	X	X	X		X	X		X	X	X	X	X	X	X	X	X		X	
SQUAMOUS CELL CARCINOMA			X							X	X		X			X					X				X	
SARCOMA, NOS																									
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
TUBULAR-CELL ADENOCARCINOMA																									
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOMA, NOS	X						X		X		X	X											X		
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PHEOCHROMOCYTOMA	X						X													X					
PHEOCHROMOCYTOMA, MALIGNANT										X			X												
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+
FOLLICULAR-CELL CARCINOMA																									
C-CELL ADENOMA	X													X						X		X	X		
C-CELL CARCINOMA															X										
PARATHYROID	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	-	+	+	-	+	+	+	+	+
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+
ISLET-CELL ADENOMA	X																								
ISLET-CELL CARCINOMA																									
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																							
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																									
MONOCYTIC LEUKEMIA				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 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 TISSUES TUMORS
WEEKS ON STUDY	105	061	105	105	105	105	105	105	105	105	105	086	105	051	105	056	105	098	093	093	104	006	105	105	105	
INTEGUMENTARY SYSTEM																										
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	50*
SQUAMOUS CELL PAPILLOMA																										1
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	50*
KERATOACANTHOMA																										1
SARCOMA, NOS																										1
FIBROMA										X																2
FIBROSARCOMA																										2
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALVEOLAR/BRONCHIOLAR ADENOMA																							X			1
ALVEOLAR/BRONCHIOLAR CARCINOMA													X													1
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
THYMUS	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
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
ADENOMA, NOS																							X			1
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	49
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SQUAMOUS CELL PAPILLOMA			X		X	X		X		X					X	X	X			X	X				X	29
SQUAMOUS CELL CARCINOMA					X	X					X		X	X					X							12
SARCOMA, NOS																					X					1
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
TUBULAR-CELL ADENOCARCINOMA											X															1
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	-	+	+	+	+	48
ADENOMA, NOS	X		X	X							X								X				X		X	13
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
PHEOCHROMOCYTOMA								X		X																5
PHEOCHROMOCYTOMA, MALIGNANT																										2
THYROID	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	48
FOLLICULAR-CELL CARCINOMA																										1
C-CELL ADENOMA									X								X									6
C-CELL CARCINOMA											X															2
PARATHYROID	+	-	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	-	+	+	+	44
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ISLET-CELL ADENOMA																										1
ISLET-CELL CARCINOMA											X															1
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	N	+	+	+	N	+	+	+	+	+	50*
FIBROADENOMA															X				X							3
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	N	50*
CARCINOMA,NOS																X										2
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*
MESOTHELIOMA, MALIGNANT					X							X							X							3
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 A4.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR STUDY OF ETHYL ACRYLATE

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	104	104	110	104	104	104	105	105	105	105	101	091	088	105	091	105	104	093	082	097	097	105	105	105	058
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+
KERATOACANTHOMA																									
FIBROMA																									
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+
SYNOVIAL SARCOMA											X														
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALVEOLAR/BRONCHIOLAR ADENOMA																				X					
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	+	+	+	+	+	+	+	+	+	-	+	+	-	+	+	+	-	-	-	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	X	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL PAPILLOMA																									
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NEUROFIBROMA																									
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-
CARCINOMA,NOS							X				X														
ADENOMA, NOS	X	X				X						X		X		X	X	X	X	X	X				
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CORTICAL ADENOMA																				X					
PHEOCHROMOCYTOMA																		X	X						
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FOLLICULAR-CELL ADENOMA																									
C-CELL ADENOMA						X												X							
C-CELL CARCINOMA								X																	
PARATHYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	-	+	-	-	
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+
ADENOMA, NOS																									
ADENOCARCINOMA, NOS																									
FIBROADENOMA			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	N
CARCINOMA,NOS																									
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOMETRIAL STROMAL POLYP	X	X	X			X	X					X			X	X					X				
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GRANULOSA-CELL TUMOR	X															X									
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
CARCINOMA,NOS																									
SARCOMA, NOS																									X
FIBROSARCOMA																									
MONOCYTIC LEUKEMIA														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: AMIMAL MISSING
B: NO NECROPSY PERFORMED

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

ANIMAL NUMBER / WEEKS ON STUDY	TOTAL TISSUES TUMORS
INTEGUMENTARY SYSTEM	
SKIN	50M
KERATOACANTHOMA	1
FIBROMA	1
SUBCUTANEOUS TISSUE	50M
SYNOVIAL SARCOMA	1
RESPIRATORY SYSTEM	
LUNGS AND BRONCHI	50
ALVEOLAR/BRONCHIOLAR ADENOMA	1
TRACHEA	50
HEMATOPOIETIC SYSTEM	
BONE MARROW	49
SPLEEN	50
LYMPH NODES	50
THYMUS	41
CIRCULATORY SYSTEM	
HEART	50
DIGESTIVE SYSTEM	
SALIVARY GLAND	50
LIVER	50
BILE DUCT	50
GALLBLADDER & COMMON BILE DUCT	50M
PANCREAS	50
ESOPHAGUS	50
STOMACH	50
SQUAMOUS CELL PAPILLOMA	1
SMALL INTESTINE	50
LARGE INTESTINE	49
URINARY SYSTEM	
KIDNEY	50
URINARY BLADDER	50
NEUROFIBROMA	1
ENDOCRINE SYSTEM	
PITUITARY	49
CARCINOMA,NOS	2
ADENOMA, NOS	20
ADRENAL	50
CORTICAL ADENOMA	1
PHEOCHROMOCYTOMA	3
THYROID	50
FOLLICULAR-CELL ADENOMA	1
C-CELL ADENOMA	6
C-CELL CARCINOMA	1
PARATHYROID	45
REPRODUCTIVE SYSTEM	
MAMMARY GLAND	50M
ADENOMA, NOS	1
ADENOCARCINOMA, NOS	1
FIBROADENOMA	13
PREPUTIAL/CLITORAL GLAND	50M
CARCINOMA,NOS	2
UTERUS	50
ENDOMETRIAL STROMAL POLYP	17
OVARY	50
GRANULOSA-CELL TUMOR	2
NERVOUS SYSTEM	
BRAIN	50
ALL OTHER SYSTEMS	
MULTIPLE ORGANS NOS	50M
CARCINOMA,NOS	1
SARCOMA, NOS	1
FIBROSARCOMA	1
MONOCYTIC LEUKEMIA	5

M ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
M: 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 TWO-YEAR STUDY OF ETHYL ACRYLATE

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	064	101	105	093	105	105	105	105	105	105	067	076	105	105	105	098	105	105	105	105	091	072	105	105	105
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
KERATOACANTHOMA																			X						
SUBCUTANEOUS TISSUE	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FIBROMA																									
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALVEOLAR/BRONCHIOLAR ADENOMA																				X					
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	+	-	+	+	+	+	-	+	-	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	-
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
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				X											X				X		
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARCINOMA,NOS																									
ADENOMA, NOS		X		X			X	X								X			X	X	X		X	X	
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PHEOCHROMOCYTOMA			X		X																				
PHEOCHROMOCYTOMA, MALIGNANT																									
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-CELL ADENOMA						X			X				X	X	X										
C-CELL CARCINOMA																			X						X
PARATHYROID	+	+	-	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+
PANCREATIC ISLETS	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ISLET-CELL ADENOMA																	X								
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOCARCINOMA, NOS					X																				
FIBROADENOMA		X	X											X			X								
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SARCOMA, NOS																				X					
ENDOMETRIAL STROMAL POLYP			X				X		X						X	X	X				X	X			
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
EPENDYMOMA																									
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
MONOCYTIC LEUKEMIA	X										X										X				
FOOT NOS																									
SQUAMOUS CELL PAPILLOMA																				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	105	105	105	105	105	105	105	105	105	105	097	105	073	105	105	105	105	105	098	105	101	105	075	099	105	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	50*	
KERATOACANTHOMA																									1	
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	X	+	+	N	+	50*
FIBROMA																										1
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALVEOLAR/BRONCHIOLAR ADENOMA																										1
TRACHEA	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
BONE MARROW	-	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
THYMUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
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	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SQUAMOUS CELL PAPILLOMA			X																		X					6
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	49
CARCINOMA,NOS											X															1
ADENOMA, NOS			X	X	X		X			X		X								X						17
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
PHEOCHROMOCYTOMA																		X				X				4
PHEOCHROMOCYTOMA, MALIGNANT																		X								1
THYROID	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-CELL ADENOMA													X												X	7
C-CELL CARCINOMA								X						X												4
PARATHYROID	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	-	+	+	+	44
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ISLET-CELL ADENOMA																										1
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
ADENOCARCINOMA, NOS																										1
FIBROADENOMA		X		X	X				X		X							X			X			X		12
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SARCOMA, NOS																										1
ENDOMETRIAL STROMAL POLYP		X	X		X												X		X	X						14
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
EPENDYMOMA													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*
MONOCYTIC LEUKEMIA			X						X									X				X	X			8
FOOT NOS																										
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 TWO-YEAR STUDY OF ETHYL ACRYLATE

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	04	10	04	04	04	82	04	04	04	71	04	01	04	04	04	01	04	05	05	05	05	05	05	05	05
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALVEOLAR/BRONCHIOLAR ADENOMA													X				X								
ALVEOLAR/BRONCHIOLAR CARCINOMA																								X	
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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	N
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL PAPILLOMA		X										X		X		X	X								
SQUAMOUS CELL CARCINOMA								X																	
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	-	+	+	+	+
ADENOMA, NOS		X		X	X			X	X			X	X	X	X								X		
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PHEOCHROMOCYTOMA		X																	X						
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+
FOLLICULAR-CELL ADENOMA																									
FOLLICULAR-CELL CARCINOMA					X		X		X		X									X					
C-CELL ADENOMA			X												X										
C-CELL CARCINOMA																									
PARATHYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	-
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	N	+	+	+	+	+
ADENOCARCINOMA, NOS																									
FIBROADENOMA	X								X			X										X			
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOCARCINOMA, NOS																									
ENDOMETRIAL STROMAL POLYP		X		X					X	X	X						X		X				X		
ENDOMETRIAL STROMAL SARCOMA																									
OVARY	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GRANULOSA-CELL TUMOR																									
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
MONOCYTIC LEUKEMIA						X						X				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 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	105	006	105	105	105	105	105	105	105	105	093	105	105	105	105	105	105	105	105	095	105	105	105	105	TISSUES TUMORS
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALVEOLAR/BRONCHIOLAR ADENOMA														X												3
ALVEOLAR/BRONCHIOLAR CARCINOMA																										1
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
THYMUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	49
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SQUAMOUS CELL PAPILLOMA						X	X	X				X														9
SQUAMOUS CELL CARCINOMA																					X					2
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LARGE INTESTINE	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
ADENOMA, NOS	X				X											X	X			X			X	X		17
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
PHEOCHROMOCYTOMA				X					X							X										5
THYROID	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
FOLLICULAR-CELL ADENOMA				X																						1
FOLLICULAR-CELL CARCINOMA																	X									1
C-CELL ADENOMA						X									X				X				X		X	8
C-CELL CARCINOMA																								X		5
PARATHYROID	+	+	–	+	+	+	+	+	–	+	+	–	+	+	+	+	+	+	+	+	–	–	–	+	–	41
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
ADENOCARCINOMA, NOS							X																			1
FIBROADENOMA				X				X								X	X			X		X	X			11
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ADENOCARCINOMA, NOS		X								X																2
ENDOMETRIAL STROMAL POLYP	X	X						X		X			X	X		X			X			X		X		18
ENDOMETRIAL STROMAL SARCOMA											X															1
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
GRANULOSA-CELL TUMOR																			X							1
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*
MONOCYTIC LEUKEMIA					X	X						X														7

* 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 NEOPLAMS IN MICE ADMINISTERED ETHYL ACRYLATE IN CORN OIL BY GAVAGE

TABLE B1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE ADMINISTERED ETHYL ACRYLATE IN CORN OIL BY GAVAGE

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS MISSING		1	
ANIMALS NECROPSIED	49	49	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	49	49	50
INTEGUMENTARY SYSTEM			
*MULTIPLE ORGANS	(49)	(49)	(50)
FIBROUS HISTIOCYTOMA, MALIGNANT			1 (2%)
*SKIN	(49)	(49)	(50)
PAPILLOMA, NOS	2 (4%)		
SQUAMOUS CELL PAPILLOMA			1 (2%)
KERATOACANTHOMA		1 (2%)	
FIBROMA		1 (2%)	
FIBROSARCOMA	1 (2%)		
*SUBCUT TISSUE	(49)	(49)	(50)
BASAL-CELL CARCINOMA			1 (2%)
SARCOMA, NOS	1 (2%)		
FIBROMA	1 (2%)	1 (2%)	
FIBROSARCOMA	1 (2%)		
NEURILEMOMA, MALIGNANT		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(48)	(49)	(50)
ADENOCARCINOMA, NOS, METASTATIC	1 (2%)		
HEPATOCELLULAR CARCINOMA, METAST	5 (10%)	2 (4%)	
ALVEOLAR/BRONCHIOLAR ADENOMA	5 (10%)	4 (8%)	1 (2%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	3 (6%)	2 (4%)	5 (10%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(49)	(49)	(50)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	6 (12%)	2 (4%)	1 (2%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)
MALIGNANT LYMPHOMA, MIXED TYPE	2 (4%)	1 (2%)	2 (4%)

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
LYMPHOCYTIC LEUKEMIA			1 (2%)
#MESENTERIC L. NODE	(49)	(48)	(50)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	1 (2%)	1 (2%)	
#PEYER'S PATCH	(48)	(47)	(47)
MALIGNANT LYMPHOMA, MIXED TYPE			1 (2%)
CIRCULATORY SYSTEM			
*MULTIPLE ORGANS	(49)	(49)	(50)
HEMANGIOSARCOMA			2 (4%)
#SPLEEN	(49)	(48)	(50)
HEMANGIOSARCOMA	1 (2%)	1 (2%)	1 (2%)
#LIVER	(49)	(49)	(50)
HEMANGIOSARCOMA		1 (2%)	
DIGESTIVE SYSTEM			
#LIVER	(49)	(49)	(50)
HEPATOCELLULAR ADENOMA	6 (12%)	5 (10%)	3 (6%)
HEPATOCELLULAR CARCINOMA	12 (24%)	10 (20%)	3 (6%)
#GASTRIC MUCOSA	(48)	(47)	(50)
ADENOCARCINOMA, NOS		1 (2%)	
#FORESTOMACH	(48)	(47)	(50)
SQUAMOUS CELL PAPILLOMA		4 (9%)	9 (18%)
SQUAMOUS CELL CARCINOMA		2 (4%)	5 (10%)
#SMALL INTESTINE	(48)	(47)	(47)
ADENOCARCINOMA, NOS		1 (2%)	1 (2%)
MUCINOUS ADENOCARCINOMA			1 (2%)
#DUODENUM	(48)	(47)	(47)
ADENOMATOUS POLYP, NOS		1 (2%)	
#JEJUNUM	(48)	(47)	(47)
ADENOCARCINOMA, NOS	1 (2%)	1 (2%)	
URINARY 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
ENDOCRINE SYSTEM			
#PITUITARY	(41)	(43)	(45)
ADENOMA, NOS	1 (2%)	1 (2%)	
#ADRENAL	(49)	(49)	(49)
CORTICAL ADENOMA			1 (2%)
PHEOCHROMOCYTOMA	1 (2%)	1 (2%)	
#THYROID	(49)	(47)	(49)
FOLLICULAR-CELL ADENOMA	4 (8%)	2 (4%)	
FOLLICULAR-CELL CARCINOMA		1 (2%)	
REPRODUCTIVE SYSTEM			
*PREPUTIAL GLAND	(49)	(49)	(50)
ADENOMA, NOS	1 (2%)		
#TESTIS	(49)	(49)	(49)
INTERSTITIAL-CELL TUMOR		1 (2%)	
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*HARDERIAN GLAND	(49)	(49)	(50)
CARCINOMA,NOS	1 (2%)		
ADENOMA, NOS	3 (6%)	2 (4%)	1 (2%)
MUSCULOSKELETAL SYSTEM			
*MUSCLE OF NECK	(49)	(49)	(50)
NEURILEMOMA, INVASIVE		1 (2%)	
BODY CAVITIES			
NONE			

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(49)	(49)	(50)
SQUAMOUS CELL CARCINOMA, METASTA			2 (4%)
MESOTHELIOMA, MALIGNANT		1 (2%)	
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATHa	10	6	5
MORIBUND SACRIFICE	10	6	7
SCHEDULED SACRIFICE			
TERMINAL SACRIFICE	27	36	30
DOSING ACCIDENT			
ACCIDENTALLY KILLED, NDA			
ACCIDENTALLY KILLED, NOS	3	1	8
ANIMAL MISSING		1	
ANIMAL MISSEXED			
OTHER CASES			
a INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	30	32	29
TOTAL PRIMARY TUMORS	54	50	42
TOTAL ANIMALS WITH BENIGN TUMORS	15	20	14
TOTAL BENIGN TUMORS	24	24	16
TOTAL ANIMALS WITH MALIGNANT TUMORS	23	21	22
TOTAL MALIGNANT TUMORS	30	26	26
TOTAL ANIMALS WITH SECONDARY TUMORS#	6	3	2
TOTAL SECONDARY TUMORS	6	3	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 B2.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE ADMINISTERED ETHYL ACRYLATE 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%)
RESPIRATORY SYSTEM			
*NASAL TURBINATE	(50)	(50)	(50)
OSTEOSARCOMA			1 (2%)
#LUNG	(50)	(50)	(49)
HEPATOCELLULAR CARCINOMA, METAST	1 (2%)		
ALVEOLAR/BRONCHIOLAR ADENOMA	2 (4%)	1 (2%)	1 (2%)
ALVEOLAR/BRONCHIOLAR CARCINOMA		1 (2%)	2 (4%)

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
MALIGNANT LYMPHOMA, NOS	1 (2%)		
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	4 (8%)	4 (8%)	3 (6%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	2 (4%)	2 (4%)	2 (4%)
MALIGNANT LYMPHOMA, MIXED TYPE	3 (6%)	6 (12%)	7 (14%)
LYMPHOCYTIC LEUKEMIA			1 (2%)
#SPLEEN	(50)	(49)	(50)
MALIGNANT LYMPHOMA, MIXED TYPE			1 (2%)
#MANDIBULAR L. NODE	(50)	(49)	(50)
MAST-CELL TUMOR		1 (2%)	
#INGUINAL LYMPH NODE	(50)	(49)	(50)
MAST-CELL TUMOR		1 (2%)	
#LIVER	(50)	(50)	(50)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	1 (2%)		
MALIGNANT LYMPHOMA, MIXED TYPE		1 (2%)	
CIRCULATORY SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
HEMANGIOSARCOMA			1 (2%)
#SPLEEN	(50)	(49)	(50)
HEMANGIOSARCOMA		1 (2%)	
#LIVER	(50)	(50)	(50)
HEMANGIOSARCOMA	1 (2%)		
#UTERUS	(50)	(50)	(50)
HEMANGIOSARCOMA	2 (4%)		

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			
#SALIVARY GLAND	(50)	(48)	(50)
SQUAMOUS CELL CARCINOMA		1 (2%)	
#LIVER	(50)	(50)	(50)
HEPATOCELLULAR ADENOMA	1 (2%)	1 (2%)	1 (2%)
HEPATOCELLULAR CARCINOMA	2 (4%)	2 (4%)	2 (4%)
#FORESTOMACH	(50)	(49)	(48)
SQUAMOUS CELL PAPILLOMA	1 (2%)	4 (8%)	5 (10%)
SQUAMOUS CELL CARCINOMA		1 (2%)	2 (4%)
#DUODENUM	(50)	(49)	(46)
ADENOCARCINOMA, NOS			1 (2%)
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
TUBULAR-CELL ADENOCARCINOMA	1 (2%)		
ENDOCRINE SYSTEM			
#PITUITARY	(46)	(47)	(45)
CARCINOMA,NOS	2 (4%)	4 (9%)	1 (2%)
ADENOMA, NOS	8 (17%)	2 (4%)	3 (7%)
MENINGIOMA	1 (2%)		
#ADRENAL	(50)	(50)	(48)
PHEOCHROMOCYTOMA		1 (2%)	
#THYROID	(48)	(46)	(49)
FOLLICULAR-CELL ADENOMA	4 (8%)	4 (9%)	1 (2%)
FOLLICULAR-CELL CARCINOMA	1 (2%)		
C-CELL CARCINOMA	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
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
ADENOCARCINOMA, NOS	1 (2%)	1 (2%)	2 (4%)
#UTERUS	(50)	(50)	(50)
LEIOMYOMA	1 (2%)		1 (2%)
ENDOMETRIAL STROMAL POLYP	4 (8%)		1 (2%)
#CERVIX UTERI	(50)	(50)	(50)
LEIOMYOSARCOMA	1 (2%)		
#UTERUS/ENDOMETRIUM	(50)	(50)	(50)
ADENOMA, NOS	1 (2%)		
ADENOCARCINOMA, NOS		1 (2%)	
#OVARY	(50)	(49)	(50)
GRANULOSA-CELL TUMOR	1 (2%)		1 (2%)
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*HARDERIAN GLAND	(50)	(50)	(50)
ADENOMA, NOS	1 (2%)	1 (2%)	
*EAR	(50)	(50)	(50)
SARCOMA, NOS	1 (2%)		
*ZYMBAL'S GLAND	(50)	(50)	(50)
ADENOMA, NOS	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
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA, METASTA			1 (2%)
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	8	4	7
MORIBUND SACRIFICE	12	11	14
SCHEDULED SACRIFICE			
TERMINAL SACRIFICE	27	35	26
DOSING ACCIDENT			
ACCIDENTALLY KILLED, NDA			
ACCIDENTALLY KILLED, NOS	3		3
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*	32	31	28
TOTAL PRIMARY TUMORS	50	42	41
TOTAL ANIMALS WITH BENIGN TUMORS	19	12	12
TOTAL BENIGN TUMORS	24	14	13
TOTAL ANIMALS WITH MALIGNANT TUMORS	20	21	22
TOTAL MALIGNANT TUMORS	25	26	27
TOTAL ANIMALS WITH SECONDARY TUMORS#	1		1
TOTAL SECONDARY TUMORS	1		1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	1	1	1
TOTAL UNCERTAIN TUMORS	1	2	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 B3.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR STUDY OF ETHYL ACRYLATE

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	099	089	105	073	105	105	099	091	105	105	098	105	105	105	105	098	105	051	007	028	105	061	105	105	105
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
PAPILLOMA, NOS			X																						
FIBROSARCOMA	X																								
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
SARCOMA, NOS																									
FIBROMA		X																							
FIBROSARCOMA																									
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	A	+	+	+	+
ADENOCARCINOMA, NOS, METASTATIC								X																	
HEPATOCELLULAR CARCINOMA, METASTA		X													X										
ALVEOLAR/BRONCHIOLAR ADENOMA			X											X		X									
ALVEOLAR/BRONCHIOLAR CARCINOMA										X															
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
HEMANGIOSARCOMA																									
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE										X															
THYMUS	+	+	+	+	+	+	+	+	-	+	+	+	+	+	-	+	+	+	+	-	A	+	+	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
HEPATOCELLULAR ADENOMA											X	X		X											
HEPATOCELLULAR CARCINOMA		X													X		X								X
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	+	N	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	N	A	+	N	+	+
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	-	+	+
ADENOCARCINOMA, NOS																									
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
ADENOMA, NOS																									
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
PHEOCHROMOCYTOMA																									
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
FOLLICULAR-CELL ADENOMA		X									X														
PARATHYROID	-	-	+	+	+	-	+	+	+	-	+	+	+	+	+	-	+	-	+	-	A	-	+	+	+
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	A	N	N	N	N
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	A	N	N	N	N
ADENOMA, NOS																									
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
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	A	N	N	N	N
CARCINOMA,NOS																									
ADENOMA, NOS			X													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	A	N	N	N	N
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE								X			X														
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) 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	106	109	086	059	106	116	106	106	106	026	106	101	065	106	106	108	061	106	106	106	055	061	081	102	050	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49*
PAPILLOMA, NOS																						X				2
FIBROSARCOMA																										1
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49*
SARCOMA, NOS																									X	1
FIBROMA																						X				1
FIBROSARCOMA																										1
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ADENOCARCINOMA, NOS, METASTATIC																										1
HEPATOCELLULAR CARCINOMA, METASTA																										5
ALVEOLAR/BRONCHIOLAR ADENOMA				X													X	X			X			X	5
ALVEOLAR/BRONCHIOLAR CARCINOMA									X										X							3
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMANGIOSARCOMA									X																	1
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE																										1
THYMUS	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	-	43
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEPATOCELLULAR ADENOMA						X		X												X						6
HEPATOCELLULAR CARCINOMA			X					X					X	X			X	X					X	X		12
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	49*
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	48
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ADENOCARCINOMA, NOS																								X		1
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	47
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	-	+	+	+	+	+	+	-	-	+	+	+	+	+	-	-	+	-	+	+	+	-	41
ADENOMA, NOS														X												1
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
PHEOCHROMOCYTOMA												X														1
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
FOLLICULAR-CELL ADENOMA	X																	X								4
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	49*
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
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	49*
ADENOMA, NOS						X																				1
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
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	49*
CARCINOMA,NOS					X																					1
ADENOMA, NOS						X																				3
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	49*
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	X		X			X																				6
MALIGNANT LYMPHOMA, MIXED TYPE				X																				X		2

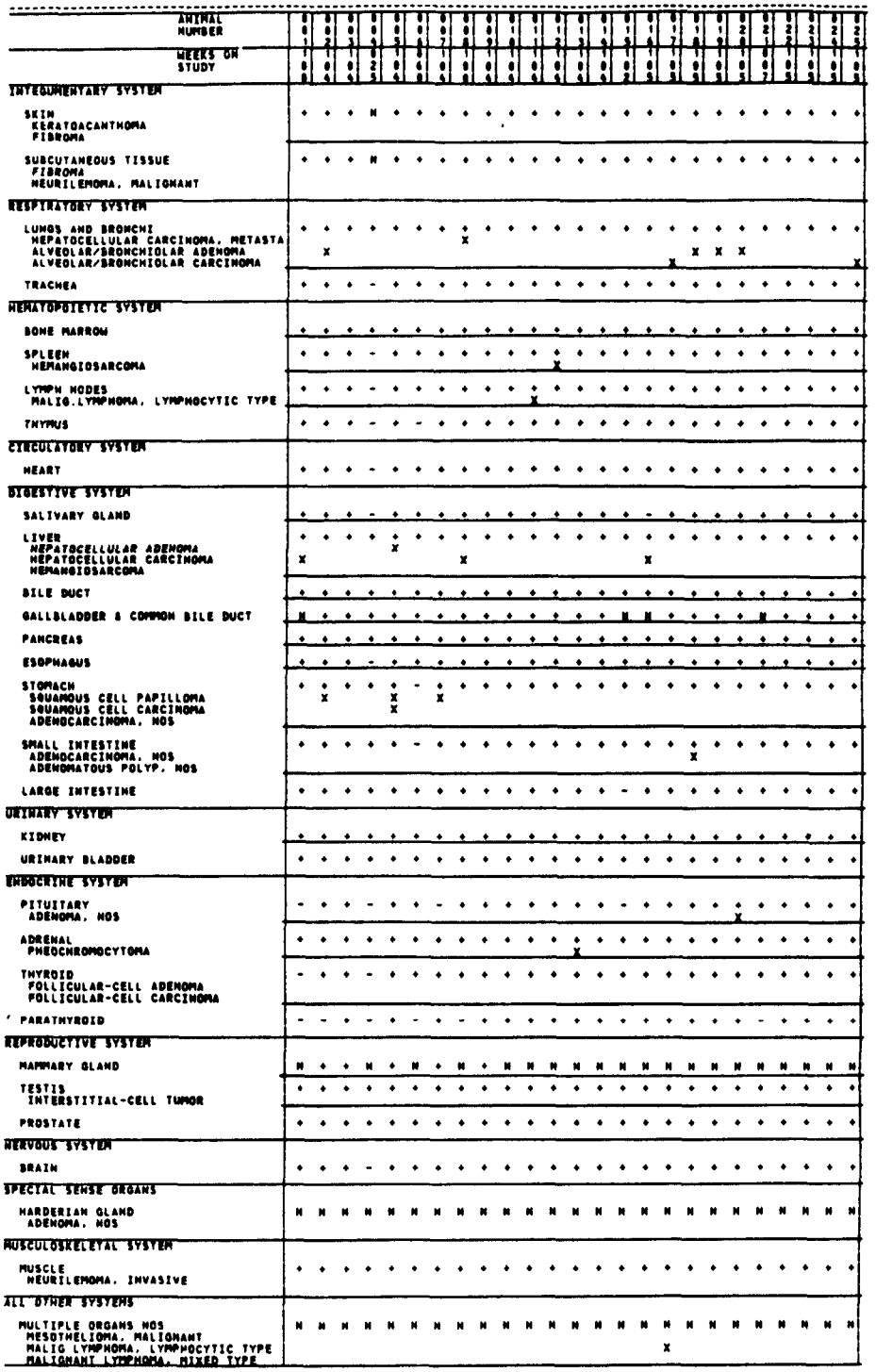
* ANIMALS NECROPSIED

+: 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 TWO-YEAR STUDY OF ETHYL ACRYLATE

LOW DOSE



\+ TISSUE EXAMINED MICROSCOPICALLY
\- REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X TUMOR INCIDENCE
N NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S ANIMAL MIS-SEXED
B 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	0267	0277	0291	0301	0312	0326	0333	0346	0352	0365	0377	0388	0391	0401	0411	0423	0439	0445	0455	0466	0477	0488	0491	0505	TOTAL
WEEKS ON STUDY	105	105	105	105	105	105	105	105	052	005	084	105	105	105	105	105	099	105	102	063	105	100	093	105	TISSUES TUMORS
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49M
KERATOACANTHOMA																						X			1
FIBROMA						X																			1
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49M
FIBROMA																			X						1
NEURILEMOMA, MALIGNANT																						X			1
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEPATOCELLULAR CARCINOMA, METASTA																							X		2
ALVEOLAR/BRONCHIOLAR ADENOMA																									4
ALVEOLAR/BRONCHIOLAR CARCINOMA																									2
TRACHEA	+	+	+	+	•	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	47
SPLEEN	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
HEMANGIOSARCOMA																									1
LYMPH NODES	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE																									1
THYMUS	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	45
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
LIVER	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEPATOCELLULAR ADENOMA	X										X	X		X											5
HEPATOCELLULAR CARCINOMA											X	X		X		X				X			X	X	10
HEMANGIOSARCOMA																			X						1
BILE DUCT	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
GALLBLADDER & COMMON BILE DUCT	N	+	+	+	+	+	M	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	49M
PANCREAS	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	48
ESOPHAGUS	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
STOMACH	+	+	+	+	+	+	M	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
SQUAMOUS CELL PAPILLOMA																		X	X						6
SQUAMOUS CELL CARCINOMA																	X								2
ADENOCARCINOMA, NOS																		X							1
SMALL INTESTINE	+	+	+	+	+	+	M	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	47
ADENOCARCINOMA, NOS																		X							2
ADENOMATOUS POLYP, NOS											X														1
LARGE INTESTINE	+	+	+	+	+	+	M	+	+	-	+	+	+	+	+	+	+	-	+	+	+	+	+	+	46
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY BLADDER	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	M	+	+	-	+	+	+	+	+	+	+	+	+	-	+	+	+	+	43
ADENOMA, NOS																									1
ADRENAL	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
PHEOCHROMOCYTOMA																									1
THYROID	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
FOLLICULAR-CELL ADENOMA		X			X																				2
FOLLICULAR-CELL CARCINOMA			X																						1
PARATHYROID	-	+	+	+	+	+	M	+	-	-	-	+	+	+	+	+	+	-	+	+	+	-	+	-	36
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	N	N	N	N	N	N	M	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	49M
TESTIS	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
INTERSTITIAL-CELL TUMOR														X											1
PROSTATE	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	M	+	+	+	+	•	+	+	+	+	+	+	+	+	+	+	+	+	48
SPECIAL SENSE ORGANS																									
HARDERIAN GLAND	N	N	N	N	N	N	M	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	49M
ADENOMA, NOS														X							X				2
MUSCULOSKELETAL SYSTEM																									
MUSCLE	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	49M
NEURILEMOMA, INVASIVE																						X			1
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	M	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	49M
MESOTHELIOMA, MALIGNANT																					X				1
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		X																							2
MALIGNANT LYMPHOMA, MIXED TYPE																			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 B3.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR STUDY OF ETHYL ACRYLATE

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	104	100	075	041	101	115	104	084	104	104	084	041	104	010	096	104	104	025	081	104	104	088	100	104	104
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL PAPILLOMA	X																								
SUBCUTANEOUS TISSUE	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
BASAL-CELL CARCINOMA																									
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALVEOLAR/BRONCHIOLAR ADENOMA															X					X					
ALVEOLAR/BRONCHIOLAR CARCINOMA																									
TRACHEA	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMANGIOSARCOMA																									
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	+	+	+	+	+	+	+	+	-	+	+	+	+	+	-	+	+	+	-	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR ADENOMA									X																
HEPATOCELLULAR CARCINOMA		X																		X					
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	+	N	+	+	N	+	+	N	+	+	+	+	+	+	+	+	N	+	+	+	N	+	+	+	+
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL PAPILLOMA									X			X			X					X					X
SQUAMOUS CELL CARCINOMA									X		X									X					
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+
ADENOCARCINOMA, NOS							X																		
MUCINOUS ADENOCARCINOMA							X																		
MALIGNANT LYMPHOMA, MIXED TYPE																									
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	-	+	+	+	+	+	+	+	+	+	+	+	-	+	-	+	+	+	+	+	+	+	+
ADRENAL	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CORTICAL ADENOMA											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
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																									
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
SQUAMOUS CELL CARCINOMA, METASTAT											X														
FIBROUS HISTIOCYTOMA, MALIGNANT																									
HEMANGIOSARCOMA			X																			X			
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE								X																	
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																									
MALIGNANT LYMPHOMA, MIXED TYPE																									
LYMPHOCYTIC 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 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	086	104	104	050	104	104	081	104	104	104	104	024	104	104	023	104	091	104	104	104	104	090	104	104	104	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50M
SQUAMOUS CELL PAPILLOMA																										1
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50M
BASAL-CELL CARCINOMA																								X		1
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALVEOLAR/BRONCHIOLAR ADENOMA														X												1
ALVEOLAR/BRONCHIOLAR CARCINOMA		X									X			X												5
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMANGIOSARCOMA									X																	1
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
THYMUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+		46
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEPATOCELLULAR ADENOMA																			X				X			3
HEPATOCELLULAR CARCINOMA				X																						3
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	N	+	N	+	+	N	N	+	+	+	+	+	+	+	N	+	+	+	+	+	+	N	+	+	+	50M
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SQUAMOUS CELL PAPILLOMA						X			X														X			9
SQUAMOUS CELL CARCINOMA		X																				X				5
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	-	+	+	+	+	+	+	+	+	47
ADENOCARCINOMA, NOS																										1
MUCINOUS ADENOCARCINOMA																										1
MALIGNANT LYMPHOMA, MIXED TYPE							X																			1
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	+	+	+	+	+	+	+	45
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
CORTICAL ADENOMA																										1
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
PARATHYROID	+	-	-	+	+	-	+	+	-	-	-	+	+	-	+	-	+	+	+	+	-	-	+	+	*	29
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	50M
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
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	50M
ADENOMA, 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	50M
SQUAMOUS CELL CARCINOMA, METASTAT																						X				2
FIBROUS HISTIOCYTOMA, MALIGNANT	X																									1
HEMANGIOSARCOMA																										2
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE																										1
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																						X				1
MALIGNANT LYMPHOMA, MIXED TYPE										X				X												2
LYMPHOCYTIC LEUKEMIA												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 B4.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR STUDY OF ETHYL ACRYLATE

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	105	105	105	094	103	096	095	095	105	090	090	090	082	090	096	096	096	091	086	087	087	077
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR CARCINOMA, METASTA				X																					
ALVEOLAR/BRONCHIOLAR ADENOMA					X		X																		
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR ADENOMA																									
HEPATOCELLULAR CARCINOMA				X																					
HEMANGIOSARCOMA																X									
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE																						X			
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	+	+	+	N	+	+	N	+	+	+	+	+	+	+	+	N	+	+	+	+	N
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL PAPILLOMA																									
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
TUBULAR-CELL ADENOCARCINOMA			X																						
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+
CARCINOMA,NOS																							X		
ADENOMA, NOS					X				X	X									X		X				
MENINGIOMA													X												
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FOLLICULAR-CELL ADENOMA	X						X												X						
FOLLICULAR-CELL CARCINOMA																				X					
C-CELL CARCINOMA																									
PARATHYROID	-	-	-	+	-	+	-	+	+	+	-	+	-	-	-	-	+	+	-	+	+	+	+	+	-
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOCARCINOMA, NOS																					X				
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOMA, NOS																									
LEIOMYOMA			X																						
LEIOMYOSARCOMA																									
ENDOMETRIAL STROMAL POLYP			X				X																		
HEMANGIOSARCOMA																X									
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GRANULOSA-CELL TUMOR																									
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
SARCOMA, NOS												X													
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
ADENOMA, NOS																					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
MALIGNANT LYMPHOMA, NOS											X					X		X							
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE								X																	
MALIG.LYMPHOMA, HISTIOCYTIC TYPE									X											X	X				
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 B4. FEMALE MICE: 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 TISSUES TUMORS
WEEKS ON STUDY	106	106	106	110	106	106	101	058	090	106	097	100	098	102	088	106	104	106	106	106	106	106	054	106	078	
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEPATOCELLULAR CARCINOMA, METASTA																										1
ALVEOLAR/BRONCHIOLAR ADENOMA																										2
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	−	+	+	+	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	49
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
THYMUS	+	+	+	+	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	47
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEPATOCELLULAR ADENOMA																								X		1
HEPATOCELLULAR CARCINOMA																										2
HEMANGIOSARCOMA																										1
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE																										1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	N	50M
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
STOMACH	+	+	+	+	+	+	+	+	+	•	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SQUAMOUS CELL PAPILLOMA	X																									1
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	49
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
TUBULAR-CELL ADENOCARCINOMA																										1
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	46
CARCINOMA,NOS										X																2
ADENOMA, NOS			X									X						X								8
MENINGIOMA																										1
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
THYROID	+	+	+	+	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	48
FOLLICULAR-CELL ADENOMA										X																4
FOLLICULAR-CELL CARCINOMA										X																1
C-CELL CARCINOMA																										1
PARATHYROID	+	−	−	−	+	+	−	−	−	−	+	−	−	+	−	−	+	−	−	−	+	−	−	+	+	22
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50M
ADENOCARCINOMA, NOS																										1
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ADENOMA, NOS													X													1
LEIOMYOMA																										1
LEIOMYOSARCOMA																		X								1
ENDOMETRIAL STROMAL POLYP						X			X																	4
HEMANGIOSARCOMA									X																	2
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GRANULOSA-CELL TUMOR						X																				1
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	50M
ADENOMA, NOS																										1
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	50M
SARCOMA, NOS																										1
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	N	50M
ADENOMA, NOS																										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	50M
MALIGNANT LYMPHOMA, NOS							X																			1
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE								X																		4
MALIG.LYMPHOMA, HISTIOCYTIC TYPE															X											2
MALIGNANT LYMPHOMA, MIXED TYPE																										3

M 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 TWO-YEAR STUDY OF ETHYL ACRYLATE

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	104	104	104	076	025	071	104	104	070	104	104	104	105	105	105	102	105	092	102	102	105	105	105	104	105
INTEGUMENTARY SYSTEM																									
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SARCOMA, NOS						X																			
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALVEOLAR/BRONCHIOLAR ADENOMA																									
ALVEOLAR/BRONCHIOLAR CARCINOMA																									
TRACHEA	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMANGIOSARCOMA														X											
LYMPH NODES	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MAST-CELL TUMOR																									
THYMUS	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+
SQUAMOUS CELL CARCINOMA																X									
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR ADENOMA		X																							
HEPATOCELLULAR CARCINOMA																X									
MALIGNANT LYMPHOMA, MIXED TYPE	X																								
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	N	N	+	+	N	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+
PANCREAS	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL PAPILLOMA												X												X	
SQUAMOUS CELL CARCINOMA																		X							
SMALL INTESTINE	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+
CARCINOMA,NOS												X							X						
ADENOMA, NOS														X											
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PHEOCHROMOCYTOMA																									
THYROID	+	+	+	+	-	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+
FOLLICULAR-CELL ADENOMA								X				X													
PARATHYROID	+	+	-	+	-	+	-	-	-	+	-	-	+	-	-	+	+	+	+	+	-	+	-	-	
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	N	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	
ADENOCARCINOMA, NOS																									
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOCARCINOMA, NOS																									
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																									
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
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE												X				X						X	X		
MALIG.LYMPHOMA, HISTIOCYTIC TYPE									X				X												
MALIGNANT LYMPHOMA, MIXED TYPE										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 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 TISSUES TUMORS
WEEKS ON STUDY	105	105	092	105	105	105	096	105	057	096	096	105	105	105	105	105	105	105	105	105	105	105	105	088	105	
INTEGUMENTARY SYSTEM																										
SUBCUTANEOUS TISSUE SARCOMA, NOS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50* 1
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI ALVEOLAR/BRONCHIOLAR ADENOMA ALVEOLAR/BRONCHIOLAR CARCINOMA	+	+	+	+	+	+	+	+	+	+	+	+	+ X	+	+	+	+	+	+	+	+	+	+	+	+ X	50 1 1
TRACHEA	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPLEEN HEMANGIOSARCOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49 1
LYMPH NODES MAST-CELL TUMOR	+	+ Xa	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49 1
THYMUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND SQUAMOUS CELL CARCINOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48 1
LIVER HEPATOCELLULAR ADENOMA HEPATOCELLULAR CARCINOMA MALIGNANT LYMPHOMA, MIXED TYPE	+	+	+	+	+	+ X	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50 1 2 1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	50*
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
STOMACH SQUAMOUS CELL PAPILLOMA SQUAMOUS CELL CARCINOMA	+	+	+	+	+ X	+	+	+	+	+	+	+	+ X	+	+	+	+	+	+	+	+	+	+	+	+	49 4 1
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
PITUITARY CARCINOMA,NOS ADENOMA, NOS	+ X	+	+	+	+	+	+	+	-	+	+	+ X	+	+	+	+	+	+ X	+	+	+	+	+	+	+	47 4 2
ADRENAL PHEOCHROMOCYTOMA	+	+	+ X	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50 1
THYROID FOLLICULAR-CELL ADENOMA	+	+	+	+	+	+	+	+	+	+	-	+	-	+	+	+ X	+	+	+	+	+ X	+	+	+	+	46 4
PARATHYROID	-	-	+	-	+	-	+	+	+	+	-	-	-	+	-	+	+	+	+	+	+	+	-	+	-	28
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND ADENOCARCINOMA, NOS	+	+	+	+	+	+	+	+ X	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50* 1
UTERUS ADENOCARCINOMA, NOS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+ X	+	+	+	+	+	50 1
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
HARDERIAN GLAND ADENOMA, NOS	N	N	N	N	N	N	N	N	N	N	N X	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50* 1
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS MALIG.LYMPHOMA, LYMPHOCYTIC TYPE MALIG.LYMPHOMA, HISTIOCYTIC TYPE MALIGNANT LYMPHOMA, MIXED TYPE	N	N	N	N	N	N	N X	N	N	N X	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50* 4 2 6

* ANIMALS NECROPSIED
a: MULTIPLE OCCURENCE OF MORPHOLOGY

+: 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 TWO-YEAR STUDY OF ETHYL ACRYLATE

HIGH DOSE

ANIMAL NUMBER	0011	0012	0013	0014	0015	0016	0017	0018	0019	0020	0111	0112	0113	0114	0115	0116	0117	0118	0119	0120	0211	0212	0213	0214	0215
WEEKS ON STUDY	094	088	104	102	091	102	095	104	080	091	096	104	104	104	104	104	101	104	104	104	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
SUBCUTANEOUS TISSUE SARCOMA, NOS	+	+ X	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI ALVEOLAR/BRONCHIOLAR ADENOMA ALVEOLAR/BRONCHIOLAR CARCINOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NASAL CAVITY OSTEOSARCOMA	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
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN MALIGNANT LYMPHOMA, MIXED TYPE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+ X	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER HEPATOCELLULAR ADENOMA HEPATOCELLULAR CARCINOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+ X	+ X	+	+	+	+	+	+	+	+	+
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+
PANCREAS	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH SQUAMOUS CELL PAPILLOMA SQUAMOUS CELL CARCINOMA	+	+	+ X	+	+	+	+ X	+	+	+	+	+	+	+	+	+	+ X	+ X	+	+	+	+ X	+	+	+
SMALL INTESTINE ADENOCARCINOMA, NOS	+	+ X	+	+	-	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY CARCINOMA,NOS ADENOMA, NOS	+	+	-	+	-	+	+	+	+	+	+	+ X	+	+	+	+	+	+	+	+	+	+	+	+	+ X
ADRENAL	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYROID FOLLICULAR-CELL ADENOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PARATHYROID	+	+	+	+	+	+	+	+	+	-	-	+	-	+	+	-	+	-	-	-	-	+	-	-	+
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND ADENOCARCINOMA, NOS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+ X	+	+	+	+	+ X
UTERUS LEIOMYOMA ENDOMETRIAL STROMAL POLYP	+	+	+	+	+	+	+	+	+ X	+	+	+	+	+ X	+	+	+	+	+	+	+	+	+	+	+
OVARY GRANULOSA-CELL TUMOR	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS SQUAMOUS CELL CARCINOMA, METASTAT HEMANGIOSARCOMA MALIG.LYMPHOMA, LYMPHOCYTIC TYPE MALIG.LYMPHOMA, HISTIOCYTIC TYPE MALIGNANT LYMPHOMA, MIXED TYPE LYMPHOCYTIC LEUKEMIA	N X	N X	N	N	N	N	N X	N	N	N X	N	N	N	N	N	N X	N	N X	N	N	N	N X	N	N	N 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	0262	0278	0298	0304	0311	0321	0331	0346	0358	0363	0375	0388	0390	0411	0421	0434	0441	0453	0467	0478	0489	0501	TOTAL
WEEKS ON STUDY	1040	1080	1084	1040	1040	0791	1094	1041	1084	0993	0995	1041	1086	0404	1041	1044	1044	0850	0767	1041	0932	0988	TISSUES TUMORS
INTEGUMENTARY SYSTEM																							
SUBCUTANEOUS TISSUE SARCOMA, NOS	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	50M 1
RESPIRATORY SYSTEM																							
LUNGS AND BRONCHI ALVEOLAR/BRONCHIOLAR ADENOMA ALVEOLAR/BRONCHIOLAR CARCINOMA	+	+	+	+	+	+	+ X	+	+	+	+	+	+	+ X	+	+	+	+	+	+	+ X	+	49 1 2
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
NASAL CAVITY OSTEOSARCOMA	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+ X	N	N	N	50M 1
HEMATOPOIETIC SYSTEM																							
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPLEEN MALIGNANT LYMPHOMA, MIXED TYPE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50 1
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
THYMUS	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	-	+	48
CIRCULATORY SYSTEM																							
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																							
SALIVARY GLAND	+	+	•	+	•	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LIVER HEPATOCELLULAR ADENOMA HEPATOCELLULAR CARCINOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+ X	+	+	+	+	+	+	+	50 1 2
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	+	+	+	+	+	+	N	+	N	+	+	+	+	+	+	+	N	N	50M
PANCREAS	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
STOMACH SQUAMOUS CELL PAPILLOMA SQUAMOUS CELL CARCINOMA	+	+	-	+	+	+	+	+	+	+ X	+	+	+	+	+	+	+ X	+	+	+	-	+	48 5 2
SMALL INTESTINE ADENOCARCINOMA, NOS	+	+	-	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	46 1
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																							
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																							
PITUITARY CARCINOMA,NOS ADENOMA, NOS	+	+	+	+	+	+	+	+	+	+	+	+	+	+ X	+	+	+ X	-	+	+	-	+	45 1 3
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	48
THYROID FOLLICULAR-CELL ADENOMA	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+ X	+	+	+	+	+	+	+	49 1
PARATHYROID	+	-	+	+	+	+	-	+	-	-	-	-	+	-	+	+	+	+	+	-	+	+	31
REPRODUCTIVE SYSTEM																							
MAMMARY GLAND ADENOCARCINOMA, NOS	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	50M 2
UTERUS LEIOMYOMA ENDOMETRIAL STROMAL POLYP	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50 1 1
OVARY GRANULOSA-CELL TUMOR	+	+	+	+	+ X	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50 1
NERVOUS SYSTEM																							
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ALL OTHER SYSTEMS																							
MULTIPLE ORGANS NOS SQUAMOUS CELL CARCINOMA, METASTAT HEMANGIOSARCOMA MALIG.LYMPHOMA, LYMPHOCYTIC TYPE MALIG.LYMPHOMA, HISTIOCYTIC TYPE MALIGNANT LYMPHOMA, MIXED TYPE LYMPHOCYTIC LEUKEMIA	N	N X	N	N	N	N	N	N	N X	N X	N	N	N	N	N	N	N X	N	N	N	N X	N X	50M 1 1 3 2 7 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 C

SUMMARY OF THE INCIDENCE ON NONNEOPLASTIC LESIONS IN RATS ADMINISTERED ETHYL ACRYLATE IN CORN OIL BY GAVAGE

TABLE C1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS ADMINISTERED ETHYL ACRYLATE 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%)		
FIBROSIS, FOCAL	1 (2%)		1 (2%)
ALOPECIA			1 (2%)
*SUBCUT TISSUE	(50)	(50)	(50)
NECROSIS, FAT	1 (2%)		
RESPIRATORY SYSTEM			
#LUNG/BRONCHUS	(50)	(50)	(50)
HEMORRHAGE	1 (2%)		
#LUNG	(50)	(50)	(50)
FOREIGN BODY, NOS		1 (2%)	
LYMPHOCYTIC INFLAMMATORY INFILTR		1 (2%)	
INFLAMMATION, ACUTE SUPPURATIVE		1 (2%)	
INFLAMMATION, FOCAL GRANULOMATOU		1 (2%)	
PROTEINOSIS, ALVEOLAR			1 (2%)
HYPERPLASIA, ADENOMATOUS	1 (2%)		
HYPERPLASIA, ALVEOLAR EPITHELIUM	3 (6%)		3 (6%)
HEMATOPOIETIC SYSTEM			
#SPLEEN	(50)	(50)	(50)
INFARCT, NOS		1 (2%)	
HEMOSIDEROSIS	28 (56)	22 (44)	16 (32)
HEMATOPOIESIS	1 (2%)	1 (2%)	2 (4%)
#SPLENIC CAPSULE	(50)	(50)	(50)
CYST, NOS		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
#LIVER	(50)	(50)	(50)
LEUKOCYTOSIS, NOS			1 (2%)
CIRCULATORY SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
PERIARTERITIS		1 (2%)	
*MEDIASTINUM	(50)	(50)	(50)
PERIARTERITIS	1 (2%)		
#MANDIBULAR L. NODE	(50)	(50)	(49)
LYMPHANGIECTASIS			3 (6%)
#PANCREATIC L.NODE	(50)	(50)	(49)
LYMPHANGIECTASIS		2 (4%)	6 (12%)
#MESENTERIC L. NODE	(50)	(50)	(49)
LYMPHANGIECTASIS			4 (8%)
#HEART	(50)	(50)	(50)
THROMBOSIS, NOS	1 (2%)	1 (2%)	1 (2%)
INFLAMMATION, ACUTE SUPPURATIVE			1 (2%)
INFLAMMATION, CHRONIC FOCAL	1 (2%)		
FIBROSIS		2 (4%)	
FIBROSIS, FOCAL	26 (52%)	27 (54%)	20 (40%)
*MESENTERIC ARTERY	(50)	(50)	(50)
PERIARTERITIS		1 (2%)	
DIGESTIVE SYSTEM			
#LIVER	(50)	(50)	(50)
CYST, NOS			1 (2%)
CYSTIC DUCTS		1 (2%)	
INFLAMMATION, ACUTE/CHRONIC			1 (2%)
INFLAMMATION, CHRONIC FOCAL			1 (2%)
NECROSIS, FOCAL	1 (2%)	1 (2%)	
NECROSIS, HEMORRHAGIC			1 (2%)
NECROSIS, ZONAL			1 (2%)
CYTOPLASMIC VACUOLIZATION		2 (4%)	1 (2%)
FOCAL CELLULAR CHANGE	1 (2%)	5 (10%)	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
CYTOLOGIC ALTERATION, NOS		3 (6%)	
HYPERPLASIA, NOS		1 (2%)	
ANGIECTASIS	1 (2%)		
#BILE DUCT	(50)	(50)	(50)
HYPERPLASIA, NOS	26 (52%)	32 (64%)	30 (60%)
HYPERPLASIA, FOCAL	2 (4%)	2 (4%)	4 (8%)
#PANCREAS	(49)	(50)	(49)
INFLAMMATION, NECROTIZING			1 (2%)
INFLAMMATION, ACUTE/CHRONIC			1 (2%)
ATROPHY, NOS	2 (4%)	1 (2%)	
ATROPHY, FOCAL	4 (8%)	5 (10%)	2 (4%)
HYPERPLASIA, FOCAL	1 (2%)		
#PANCREATIC ACINUS	(49)	(50)	(49)
ATROPHY, NOS			1 (2%)
#ESOPHAGEAL SUBMUCOSA	(49)	(49)	(49)
HEMORRHAGE			1 (2%)
#STOMACH	(50)	(50)	(50)
ULCER, NOS		1 (2%)	
INFLAMMATION, ACUTE		1 (2%)	
INFLAMMATION, ACUTE SUPPURATIVE			1 (2%)
HYPERPLASIA, EPITHELIAL		1 (2%)	
#GASTRIC MUCOSA	(50)	(50)	(50)
INFLAMMATION, ACUTE FOCAL	1 (2%)		
#FORESTOMACH	(50)	(50)	(50)
FOREIGN BODY, NOS			10 (20%)
ULCER, NOS	2 (4%)	2 (4%)	1 (2%)
INFLAMMATION, ACUTE SUPPURATIVE		1 (2%)	1 (2%)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)	2 (4%)	14 (28%)
INFLAMMATION, CHRONIC		3 (6%)	9 (18%)
INFLAMMATION, CHRONIC FOCAL		2 (4%)	4 (8%)
HYPERPLASIA, EPITHELIAL	1 (2%)	41 (82%)	46 (92%)
HYPERKERATOSIS		37 (74%)	46 (92%)
#COLON	(48)	(50)	(50)
ULCER, NOS	2 (4%)		
INFLAMMATION, ACUTE/CHRONIC		1 (2%)	
PARASITISM		1 (2%)	
*RECTUM	(50)	(50)	(50)
PARASITISM		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
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
HYDRONEPHROSIS		1 (2%)	
CYST, NOS			1 (2%)
LYMPHOCYTIC INFLAMMATORY INFILTR		2 (4%)	
NEPHROPATHY	12 (24%)	23 (46%)	16 (32%)
HEMOSIDEROSIS		1 (2%)	1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(48)	(50)	(48)
CYST, NOS	2 (4%)	3 (6%)	
HEMORRHAGE		1 (2%)	1 (2%)
HEMOSIDEROSIS		3 (6%)	2 (4%)
HYPERPLASIA, NOS			1 (2%)
HYPERPLASIA, FOCAL			2 (4%)
ANGIECTASIS	7 (15%)	12 (24%)	12 (25%)
#ADRENAL	(50)	(49)	(50)
ANGIECTASIS	1 (2%)	4 (8%)	3 (6%)
#ADRENAL CORTEX	(50)	(49)	(50)
CYTOPLASMIC VACUOLIZATION	2 (4%)	3 (6%)	4 (8%)
FOCAL CELLULAR CHANGE	1 (2%)		1 (2%)
CYTOLOGIC ALTERATION, NOS		1 (2%)	
ANGIECTASIS		1 (2%)	
#ADRENAL MEDULLA	(50)	(49)	(50)
HYPERPLASIA, NOS	1 (2%)	1 (2%)	
HYPERPLASIA, FOCAL	1 (2%)	3 (6%)	8 (16%)
#THYROID	(49)	(49)	(48)
CYSTIC FOLLICLES	5 (10%)	12 (24%)	13 (27%)
DEGENERATION, CYSTIC		2 (4%)	2 (4%)
HYPERPLASIA, CYSTIC	1 (2%)	1 (2%)	2 (4%)
HYPERPLASIA, C-CELL	3 (6%)	3 (6%)	
HYPERPLASIA, FOLLICULAR-CELL	1 (2%)	3 (6%)	1 (2%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
CYSTIC DUCTS	9 (18%)	12 (24%)	14 (28%)

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ADENOSIS			1 (2%)
*PREPUTIAL GLAND	(50)	(50)	(50)
CYSTIC DUCTS	4 (8%)	3 (6%)	4 (8%)
HEMORRHAGE		1 (2%)	
INFLAMMATION, ACUTE SUPPURATIVE	1 (2%)	1 (2%)	3 (6%)
INFLAMMATION, ACUTE/CHRONIC			2 (4%)
INFLAMMATION, CHRONIC		1 (2%)	
INFLAMMATION, CHRONIC FOCAL	1 (2%)		
#PROSTATE	(50)	(50)	(50)
INFLAMMATION, ACUTE SUPPURATIVE	4 (8%)	5 (10%)	6 (12%)
HYPERPLASIA, CYSTIC			1 (2%)
#TESTIS	(50)	(50)	(50)
NECROSIS, NOS	1 (2%)		
ATROPHY, NOS	2 (4%)		3 (6%)
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*EYE	(50)	(50)	(50)
RETINOPATHY		1 (2%)	19 (38%)
CATARACT		1 (2%)	19 (38%)
*HARDERIAN GLAND	(50)	(50)	(50)
HEMORRHAGE	2 (4%)		
*EAR CANAL	(50)	(50)	(50)
CYST, NOS			1 (2%)
*MIDDLE EAR	(50)	(50)	(50)
CYST, NOS		1 (2%)	
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*MEDIASTINUM	(50)	(50)	(50)
FOREIGN BODY, NOS		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
*MESENTERY	(50)	(50)	(50)
INFLAMMATION, CHRONIC			1 (2%)
NECROSIS, FAT	1 (2%)	1 (2%)	2 (4%)
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
HEMOSIDEROSIS			1 (2%)
FOOT			
FIBROSIS, FOCAL	1		
CALLUS	5	6	3
SOLE OF FOOT			
CALLUS	1		
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED			2

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

TABLE C2.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS ADMINISTERED ETHYL ACRYLATE 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%)		
INFLAMMATION, ACUTE FOCAL		1 (2%)	
INFLAMMATION, ACUTE SUPPURATIVE	1 (2%)		
INFLAMMATION, ACUTE/CHRONIC		1 (2%)	
ALOPECIA			1 (2%)
RESPIRATORY SYSTEM			
#LUNG	(50)	(50)	(50)
PNEUMONIA, LIPID	1 (2%)		
INFLAMMATION, PYOGRANULOMATOUS		1 (2%)	
HYPERPLASIA, ALVEOLAR EPITHELIUM	1 (2%)	1 (2%)	
HISTIOCYTOSIS			1 (2%)
HEMATOPOIETIC SYSTEM			
#SPLEEN	(50)	(50)	(50)
HEMOSIDEROSIS	35 (70%)	33 (66%)	29 (58%)
#MEDIASTINAL L.NODE	(50)	(50)	(50)
HEMOSIDEROSIS		1 (2%)	
#THYMUS	(41)	(45)	(48)
CYST, NOS		2 (4%)	
HEMORRHAGE			1 (2%)
CIRCULATORY SYSTEM			
#MANDIBULAR L. NODE	(50)	(50)	(50)
LYMPHANGIECTASIS			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
#PANCREATIC L.NODE	(50)	(50)	(50)
LYMPHANGIECTASIS		1 (2%)	2 (4%)
#MESENTERIC L. NODE	(50)	(50)	(50)
LYMPHANGIECTASIS		1 (2%)	
#HEART	(50)	(50)	(50)
LYMPHOCYTIC INFLAMMATORY INFILTR		1 (2%)	
INFLAMMATION, ACUTE/CHRONIC			1 (2%)
FIBROSIS, FOCAL	5 (10%)	11 (22%)	11 (22%)
DIGESTIVE SYSTEM			
#LIVER	(50)	(50)	(50)
HEMORRHAGE	1 (2%)		1 (2%)
LYMPHOCYTIC INFLAMMATORY INFILTR		1 (2%)	
SCAR			1 (2%)
NECROSIS, NOS		1 (2%)	
NECROSIS, FOCAL	2 (4%)		
HEMOSIDEROSIS			1 (2%)
CYTOPLASMIC VACUOLIZATION		2 (4%)	1 (2%)
FOCAL CELLULAR CHANGE	1 (2%)	1 (2%)	1 (2%)
HYPERPLASIA, NOS		1 (2%)	1 (2%)
#BILE DUCT	(50)	(50)	(50)
HYPERPLASIA, NOS	13 (26%)	28 (56%)	26 (52%)
HYPERPLASIA, FOCAL			6 (12%)
#PANCREAS	(50)	(49)	(50)
ATROPHY, FOCAL	7 (14%)	7 (14%)	6 (12%)
#ESOPHAGUS	(50)	(49)	(49)
INFLAMMATION, ACUTE/CHRONIC		1 (2%)	
#ESOPHAGEAL MUSCULARI	(50)	(49)	(49)
INFLAMMATION, ACUTE SUPPURATIVE			1 (2%)
#FORESTOMACH	(50)	(50)	(50)
FOREIGN BODY, NOS			11 (22%)
ULCER, NOS			1 (2%)
INFLAMMATION, ACUTE SUPPURATIVE		1 (2%)	
INFLAMMATION, ACUTE/CHRONIC	1 (2%)	2 (4%)	12 (24%)
INFLAMMATION, CHRONIC			4 (8%)

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
INFLAMMATION, CHRONIC FOCAL			4 (8%)
HYPERPLASIA, NOS		1 (2%)	
HYPERPLASIA, EPITHELIAL		34 (68%)	49 (98%)
HYPERKERATOSIS		24 (48%)	46 (92%)
#DUODENUM	(50)	(50)	(50)
INFLAMMATION, CHRONIC		1 (2%)	
#COLON	(49)	(50)	(49)
INFLAMMATION, ACUTE FOCAL		2 (4%)	
PARASITISM		2 (4%)	1 (2%)
*RECTUM	(50)	(50)	(50)
INFLAMMATION, ACUTE FOCAL		1 (2%)	
PARASITISM		1 (2%)	2 (4%)
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
HYDRONEPHROSIS		1 (2%)	
CYST, NOS	1 (2%)		
LYMPHOCYTIC INFLAMMATORY INFILTR		1 (2%)	
NEPHROPATHY	2 (4%)	2 (4%)	1 (2%)
HEMOSIDEROSIS	1 (2%)		
#URINARY BLADDER	(50)	(50)	(49)
INFLAMMATION, CHRONIC FOCAL	1 (2%)		
HYPERPLASIA, EPITHELIAL	1 (2%)		
HYPERPLASIA, STROMAL	1 (2%)		
ENDOCRINE SYSTEM			
#PITUITARY	(49)	(49)	(47)
CYST, NOS	3 (6%)	9 (18%)	3 (6%)
HEMORRHAGE	1 (2%)		
HEMOSIDEROSIS		9 (18%)	
HYPERPLASIA, NOS			1 (2%)
HYPERPLASIA, FOCAL		2 (4%)	
ANGIECTASIS	20 (41%)	21 (43%)	15 (32%)
#ADRENAL	(50)	(50)	(50)
CYST, NOS		1 (2%)	1 (2%)
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
ANGIECTASIS		1 (2%)	
#ADRENAL CORTEX	(50)	(50)	(50)
CYTOPLASMIC VACUOLIZATION		4 (8%)	6 (12%)
FOCAL CELLULAR CHANGE	5 (10%)		1 (2%)
ANGIECTASIS			3 (6%)
#ADRENAL MEDULLA	(50)	(50)	(50)
LYMPHOCYTIC INFLAMMATORY INFILTR		1 (2%)	
HYPERPLASIA, FOCAL	1 (2%)		1 (2%)
#THYROID	(50)	(49)	(48)
THYROGLOSSAL DUCT CYST		1 (2%)	
CYSTIC FOLLICLES	1 (2%)	1 (2%)	4 (8%)
INFLAMMATION, CHRONIC		1 (2%)	
HYPERPLASIA, C-CELL			1 (2%)
HYPERPLASIA, FOLLICULAR-CELL		1 (2%)	3 (6%)
ANGIECTASIS		1 (2%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
CYSTIC DUCTS	35 (70%)	36 (72%)	34 (68%)
ADENOSIS	7 (14%)	7 (14%)	10 (20%)
*PREPUTIAL GLAND	(50)	(50)	(50)
CYSTIC DUCTS		1 (2%)	
*CLITORAL GLAND	(50)	(50)	(50)
CYSTIC DUCTS	2 (4%)	1 (2%)	
INFLAMMATION, ACUTE SUPPURATIVE	1 (2%)		
INFLAMMATION, ACUTE/CHRONIC	1 (2%)	1 (2%)	
INFLAMMATION, CHRONIC	1 (2%)		
*VAGINA	(50)	(50)	(50)
POLYPOID HYPERPLASIA	1 (2%)		
#UTERUS	(50)	(50)	(50)
HYDROMETRA	1 (2%)		
HEMORRHAGE	1 (2%)	1 (2%)	1 (2%)
INFLAMMATION, ACUTE SUPPURATIVE	2 (4%)	1 (2%)	
HYPERPLASIA, FOCAL			1 (2%)
#UTERUS/ENDOMETRIUM	(50)	(50)	(50)
HYPERPLASIA, CYSTIC	1 (2%)	8 (16%)	10 (20%)

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#OVARY	(50)	(50)	(49)
CYST, NOS	2 (4%)	2 (4%)	4 (8%)
NERVOUS SYSTEM			
#BRAIN	(50)	(50)	(50)
HEMORRHAGE	1 (2%)	1 (2%)	
SPECIAL SENSE ORGANS			
*EYE	(50)	(50)	(50)
INFLAMMATION, ACUTE SUPPURATIVE		1 (2%)	
RETINOPATHY		19 (38%)	
CATARACT		16 (32%)	
MUSCULOSKELETAL SYSTEM			
*SKULL	(50)	(50)	(50)
HYPEROSTOSIS	1 (2%)		
*MUSCLE OF TRUNK	(50)	(50)	(50)
FIBROSIS			1 (2%)
BODY CAVITIES			
*MEDIASTINUM	(50)	(50)	(50)
HEMORRHAGE			1 (2%)
NECROSIS, FAT		1 (2%)	
*MESENTERY	(50)	(50)	(50)
NECROSIS, FAT	7 (14%)	5 (10%)	9 (18%)
ALL OTHER SYSTEMS			
FOOT			
INFLAMMATION, ACUTE/CHRONIC	1	2	
INFLAMMATION, CHRONIC		4	4
INFLAMMATION, CHRONIC FOCAL			1
FIBROSIS, FOCAL	2		
CALLUS	14	20	21
SOLE OF FOOT			
CALLUS	3		
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED			

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

APPENDIX D

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE ADMINISTERED ETHYL ACRYLATE IN CORN OIL BY GAVAGE

TABLE D1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE ADMINISTERED ETHYL ACRYLATE IN CORN OIL BY GAVAGE

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS MISSING		1	
ANIMALS NECROPSIED	49	49	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	49	49	50
INTEGUMENTARY SYSTEM			
*SKIN	(49)	(49)	(50)
ULCER, NOS	1 (2%)		
ULCER, FOCAL	1 (2%)		
INFLAMMATION, SUPPURATIVE	1 (2%)		
INFLAMMATION, ACUTE FOCAL	1 (2%)		
INFLAMMATION, CHRONIC	3 (6%)	5 (10%)	2 (4%)
INFLAMMATION, CHRONIC FOCAL		1 (2%)	1 (2%)
FIBROSIS	1 (2%)		
HYPERPLASIA, BASAL CELL	2 (4%)		
*SUBCUT TISSUE	(49)	(49)	(50)
FOREIGN BODY, NOS		1 (2%)	
REACTION, FOREIGN BODY			1 (2%)
INFLAMMATION, PYOGRANULOMATOUS		1 (2%)	
INFECTION, FUNGAL		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(48)	(49)	(50)
ASPIRATION, NOS			1 (2%)
ATELECTASIS			1 (2%)
CONGESTION, NOS		2 (4%)	2 (4%)
LYMPHOCYTIC INFLAMMATORY INFILTR		4 (8%)	
PNEUMONIA, LIPID	1 (2%)	1 (2%)	
PNEUMONIA, ASPIRATION		1 (2%)	1 (2%)
INFLAMMATION, FOCAL GRANULOMATOU	2 (4%)	2 (4%)	2 (4%)
CHOLESTEROL DEPOSIT		1 (2%)	
PIGMENTATION, NOS		1 (2%)	1 (2%)
ALVEOLAR MACROPHAGES	2 (4%)	3 (6%)	
HYPERPLASIA, ADENOMATOUS	3 (6%)	3 (6%)	6 (12%)
HYPERPLASIA, ALVEOLAR EPITHELIUM	1 (2%)	1 (2%)	
#LUNG/ALVEOLI	(48)	(49)	(50)
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			
*MULTIPLE ORGANS	(49)	(49)	(50)
HYPERPLASIA, LYMPHOID	1 (2%)		
#BONE MARROW	(49)	(47)	(49)
ATROPHY, NOS		2 (4%)	
MYELOFIBROSIS		1 (2%)	
#SPLEEN	(49)	(48)	(50)
HEMATOMA, NOS			1 (2%)
ANGIECTASIS		1 (2%)	
HYPERPLASIA, LYMPHOID		1 (2%)	
HEMATOPOIESIS	3 (6%)	3 (6%)	2 (4%)
#MESENTERIC L. NODE	(49)	(48)	(50)
ANGIECTASIS		1 (2%)	
HYPERPLASIA, LYMPHOID			1 (2%)
#INGUINAL LYMPH NODE	(49)	(48)	(50)
HYPERPLASIA, NOS		1 (2%)	
#PEYER'S PATCH	(48)	(47)	(47)
HYPERPLASIA, LYMPHOID		2 (4%)	1 (2%)
CIRCULATORY SYSTEM			
*SUBCUT TISSUE	(49)	(49)	(50)
LYMPHANGIECTASIS	1 (2%)	1 (2%)	1 (2%)
#MANDIBULAR L. NODE	(49)	(48)	(50)
LYMPHANGIECTASIS		1 (2%)	
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(49)	(47)	(50)
CYSTIC DUCTS			1 (2%)
#LIVER	(49)	(49)	(50)
CYST, NOS	1 (2%)		1 (2%)
LYMPHOCYTIC INFLAMMATORY INFILTR	2 (4%)		
INFLAMMATION, SUPPURATIVE			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
ABSCESS, NOS			1 (2%)
INFLAMMATION, CHRONIC FOCAL	1 (2%)		
FIBROSIS, FOCAL	1 (2%)		
NECROSIS, NOS	1 (2%)		1 (2%)
NECROSIS, FOCAL			1 (2%)
NECROSIS, COAGULATIVE	1 (2%)	2 (4%)	
NECROSIS, ISCHEMIC			1 (2%)
NUCLEAR ENLARGEMENT	1 (2%)		
CYTOPLASMIC VACUOLIZATION	2 (4%)	2 (4%)	
FOCAL CELLULAR CHANGE	1 (2%)		1 (2%)
#LIVER/CENTRILOBULAR	(49)	(49)	(50)
DEGENERATION, NOS	1 (2%)		
#BILE DUCT	(49)	(49)	(50)
CYST, NOS		1 (2%)	
#PANCREAS	(49)	(48)	(50)
ATROPHY, NOS			1 (2%)
#ESOPHAGUS	(49)	(48)	(49)
ULCER, FOCAL	1 (2%)		
#GASTRIC MUCOSA	(48)	(47)	(50)
DIVERTICULUM		1 (2%)	
CYST, NOS		2 (4%)	
HYPERPLASIA, FOCAL		1 (2%)	
#GASTRIC SUBMUCOSA	(48)	(47)	(50)
CYST, NOS			1 (2%)
#FORESTOMACH	(48)	(47)	(50)
ULCER, FOCAL	2 (4%)	1 (2%)	5 (10%)
INFLAMMATION, ACUTE/CHRONIC		2 (4%)	5 (10%)
INFLAMMATION, CHRONIC		1 (2%)	3 (6%)
REACTION, FOREIGN BODY			1 (2%)
HYPERPLASIA, EPITHELIAL		17 (36%)	26 (52%)
HYPERPLASIA, PAPILLARY		1 (2%)	2 (4%)
HYPERKERATOSIS		19 (40%)	28 (56%)
#SMALL INTESTINE	(48)	(47)	(47)
AMYLOIDOSIS		1 (2%)	
URINARY SYSTEM			
#KIDNEY	(49)	(49)	(50)
HYDRONEPHROSIS	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
GLOMERULONEPHRITIS, NOS		1 (2%)	
LYMPHOCYTIC INFLAMMATORY INFILTR	5 (10%)	13 (27%)	10 (20%)
INFLAMMATION, CHRONIC		2 (4%)	
NEPHROPATHY		2 (4%)	
CYTOPLASMIC VACUOLIZATION	1 (2%)		
METAPLASIA, OSSEOUS	1 (2%)		
#KIDNEY/CORTEX	(49)	(49)	(50)
CYTOPLASMIC VACUOLIZATION	1 (2%)		
#KIDNEY/PELVIS	(49)	(49)	(50)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)		
#URINARY BLADDER	(47)	(49)	(50)
INFLAMMATION, ACUTE SUPPURATIVE	1 (2%)		
INFLAMMATION, CHRONIC	1 (2%)		
HYPERPLASIA, EPITHELIAL	1 (2%)		
ENDOCRINE SYSTEM			
#PITUITARY	(41)	(43)	(45)
CYST, NOS	1 (2%)		
HYPERPLASIA, FOCAL	1 (2%)		
#ADRENAL CORTEX	(49)	(49)	(49)
DEGENERATION, NOS	1 (2%)		
CYTOLOGIC ALTERATION, NOS			1 (2%)
#ADRENAL MEDULLA	(49)	(49)	(49)
CYTOPLASMIC VACUOLIZATION	1 (2%)		
#THYROID	(49)	(47)	(49)
CYSTIC FOLLICLES		2 (4%)	1 (2%)
LYMPHOCYTIC INFLAMMATORY INFILTR		1 (2%)	
DEGENERATION, CYSTIC	2 (4%)	1 (2%)	1 (2%)
HYPERPLASIA, CYSTIC	2 (4%)	2 (4%)	
#THYROID FOLLICLE	(49)	(47)	(49)
HYPERPLASIA, EPITHELIAL		3 (6%)	1 (2%)
HYPERPLASIA, CYSTIC		3 (6%)	2 (4%)
#PARATHYROID	(37)	(36)	(29)
CYST, NOS		1 (3%)	

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM			
*PREPUTIAL GLAND	(49)	(49)	(50)
RETENTION OF CONTENT	1 (2%)		
CYSTIC DUCTS	6 (12%)	2 (4%)	1 (2%)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)		
INFLAMMATION, SUPPURATIVE		1 (2%)	
INFLAMMATION, ACUTE SUPPURATIVE		1 (2%)	
INFLAMMATION, CHRONIC	2 (4%)		
INFLAMMATION, CHRONIC SUPPURATIV	1 (2%)		
#PROSTATE	(49)	(49)	(50)
INFLAMMATION, CHRONIC SUPPURATIV		1 (2%)	
#TESTIS	(49)	(49)	(49)
GRANULOMA, SPERMATIC		1 (2%)	
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*EYE	(49)	(49)	(50)
RETINOPATHY	1 (2%)		
PHTHISIS BULBI		1 (2%)	
*EYE/CRYSTALLINE LENS	(49)	(49)	(50)
CATARACT	1 (2%)		
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*MEDIASTINUM	(49)	(49)	(50)
INFLAMMATION, SUPPURATIVE	3 (6%)		
INFLAMMATION, CHRONIC		1 (2%)	
REACTION, FOREIGN BODY	5 (10%)		

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
*PERITONEUM	(49)	(49)	(50)
INFLAMMATION, ACUTE SUPPURATIVE			1 (2%)
*PLEURAL CAVITY	(49)	(49)	(50)
REACTION, FOREIGN BODY			1 (2%)
*PLEURA	(49)	(49)	(50)
INFLAMMATION, SUPPURATIVE	1 (2%)		
REACTION, FOREIGN BODY	2 (4%)		
*MESENTERY	(49)	(49)	(50)
HEMORRHAGE			1 (2%)
STEATITIS			1 (2%)
INFLAMMATION, CHRONIC SUPPURATIV		1 (2%)	
INFLAMMATION, PYOGRANULOMATOUS	1 (2%)		
NECROSIS, FAT	2 (4%)		2 (4%)
ALL OTHER SYSTEMS			
OMENTUM			
STEATITIS		2	1
REACTION, FOREIGN BODY		1	
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	5	1	6
ANIMAL MISSING/NO NECROPSY		1	
AUTOLYSIS/NO NECROPSY	1		

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

TABLE D2.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE ADMINISTERED ETHYL ACRYLATE 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)
STEATITIS		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(50)	(50)	(49)
ASPIRATION, NOS	1 (2%)		
CONGESTION, NOS	2 (4%)	1 (2%)	
EDEMA, NOS		1 (2%)	
BRONCHOPNEUMONIA, FOCAL		1 (2%)	
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)	4 (8%)	1 (2%)
PNEUMONIA, LIPID	1 (2%)		2 (4%)
PNEUMONIA, ASPIRATION		1 (2%)	1 (2%)
INFLAMMATION, FOCAL GRANULOMATOU		2 (4%)	1 (2%)
ADHESION, NOS			1 (2%)
CHOLESTEROL DEPOSIT			1 (2%)
HYPERPLASIA, ADENOMATOUS	3 (6%)	6 (12%)	4 (8%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
HYPERPLASIA, LYMPHOID	4 (8%)		3 (6%)
HEMATOPOIESIS	1 (2%)		1 (2%)
#BONE MARROW	(49)	(50)	(50)
ATROPHY, NOS	1 (2%)		
MYELOFIBROSIS	2 (4%)	2 (4%)	5 (10%)
HYPERPLASIA, GRANULOCYTIC	1 (2%)		
#SPLEEN	(50)	(49)	(50)
NECROSIS, 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
HEMOSIDEROSIS	1 (2%)		
HYPERPLASIA, LYMPHOID	1 (2%)	1 (2%)	1 (2%)
HEMATOPOIESIS	6 (12%)	3 (6%)	8 (16%)
#MANDIBULAR L. NODE	(50)	(49)	(50)
PIGMENTATION, NOS	1 (2%)		
#BRONCHIAL LYMPH NODE	(50)	(49)	(50)
HYPERPLASIA, NOS		1 (2%)	
#PANCREATIC L.NODE	(50)	(49)	(50)
HYPERPLASIA, LYMPHOID			1 (2%)
#LUMBAR LYMPH NODE	(50)	(49)	(50)
HEMORRHAGE			1 (2%)
#LUNG	(50)	(50)	(49)
HYPERPLASIA, LYMPHOID			1 (2%)
#LIVER	(50)	(50)	(50)
LEUKOCYTOSIS, NOS	4 (8%)	2 (4%)	3 (6%)
HEMATOPOIESIS			1 (2%)
#OMENTUM	(50)	(49)	(48)
HYPERPLASIA, LYMPHOID	1 (2%)		
#THYMUS	(47)	(48)	(48)
HYPERPLASIA, LYMPHOID	2 (4%)		
CIRCULATORY SYSTEM			
#MYOCARDIUM	(50)	(50)	(50)
INFLAMMATION, ACUTE/CHRONIC		1 (2%)	
#ENDOCARDIUM	(50)	(50)	(50)
INFLAMMATION, ACUTE SUPPURATIVE	1 (2%)		
#OVARY	(50)	(49)	(50)
THROMBUS, FIBRIN			1 (2%)
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(50)	(48)	(50)
CYST, 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
LYMPHOCYTIC INFLAMMATORY INFILTR		1 (2%)	
#LIVER	(50)	(50)	(50)
LYMPHOCYTIC INFLAMMATORY INFILTR	7 (14%)		1 (2%)
INFLAMMATION, SUPPURATIVE			1 (2%)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)		
NECROSIS, NOS	1 (2%)		1 (2%)
NECROSIS, FOCAL			1 (2%)
NECROSIS, ZONAL		1 (2%)	
CYTOPLASMIC VACUOLIZATION	1 (2%)		
FOCAL CELLULAR CHANGE		2 (4%)	1 (2%)
#PANCREAS	(50)	(49)	(48)
CYSTIC DUCTS		1 (2%)	
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)		
INFLAMMATION, CHRONIC		1 (2%)	
ATROPHY, NOS	2 (4%)	1 (2%)	1 (2%)
#STOMACH	(50)	(49)	(48)
INFLAMMATION, ACUTE SUPPURATIVE		1 (2%)	
#GASTRIC MUCOSA	(50)	(49)	(48)
CYST, NOS		1 (2%)	
METAPLASIA, SQUAMOUS	1 (2%)		
#FORESTOMACH	(50)	(49)	(48)
MINERALIZATION			1 (2%)
ULCER, FOCAL		1 (2%)	6 (13%)
INFLAMMATION, SUPPURATIVE			2 (4%)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)	3 (6%)	5 (10%)
INFLAMMATION, CHRONIC		1 (2%)	4 (8%)
INFLAMMATION, CHRONIC SUPPURATIV			1 (2%)
HYPERPLASIA, NOS			1 (2%)
HYPERPLASIA, EPITHELIAL	3 (6%)	12 (24%)	30 (63%)
HYPERPLASIA, PAPILLARY			2 (4%)
HYPERKERATOSIS	2 (4%)	14 (29%)	32 (67%)
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
CYST, NOS		1 (2%)	
GLOMERULONEPHRITIS, NOS			1 (2%)
LYMPHOCYTIC INFLAMMATORY INFILTR	22 (44%)	11 (22%)	8 (16%)
INFLAMMATION, CHRONIC	1 (2%)	1 (2%)	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
NEPHROPATHY		1 (2%)	1 (2%)
AMYLOIDOSIS	1 (2%)	1 (2%)	
#RENAL PAPILLA	(50)	(50)	(50)
NECROSIS, NOS	1 (2%)		
#KIDNEY/TUBULE	(50)	(50)	(50)
NECROSIS, NOS			1 (2%)
#KIDNEY/PELVIS	(50)	(50)	(50)
LYMPHOCYTIC INFLAMMATORY INFILTR		1 (2%)	
#URINARY BLADDER	(49)	(50)	(49)
LYMPHOCYTIC INFLAMMATORY INFILTR			1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(46)	(47)	(45)
HYPERPLASIA, NOS			1 (2%)
HYPERPLASIA, FOCAL	1 (2%)	1 (2%)	1 (2%)
ANGIECTASIS	5 (11%)	6 (13%)	2 (4%)
#ADRENAL	(50)	(50)	(48)
HEMORRHAGE			1 (2%)
CYTOPLASMIC VACUOLIZATION			1 (2%)
ANGIECTASIS		1 (2%)	
#ADRENAL CORTEX	(50)	(50)	(48)
CYST, NOS	1 (2%)		
FOCAL CELLULAR CHANGE			1 (2%)
#ADRENAL MEDULLA	(50)	(50)	(48)
CYST, NOS		1 (2%)	
#THYROID	(48)	(46)	(49)
CYSTIC FOLLICLES	2 (4%)		2 (4%)
LYMPHOCYTIC INFLAMMATORY INFILTR			1 (2%)
INFLAMMATION, SUPPURATIVE	1 (2%)		
DEGENERATION, CYSTIC	3 (6%)	3 (7%)	6 (12%)
HYPERPLASIA, CYSTIC		2 (4%)	2 (4%)
HYPERPLASIA, FOLLICULAR-CELL	1 (2%)		
#THYROID FOLLICLE	(48)	(46)	(49)
HYPERPLASIA, EPITHELIAL		2 (4%)	

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, CYSTIC	4 (8%)		
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
CYSTIC DUCTS	6 (12%)	6 (12%)	4 (8%)
*MAMMARY LOBULE	(50)	(50)	(50)
HYPERPLASIA, NOS	1 (2%)		
*VAGINA	(50)	(50)	(50)
INFLAMMATION, SUPPURATIVE	1 (2%)		
INFLAMMATION, ACUTE SUPPURATIVE			1 (2%)
#UTERUS	(50)	(50)	(50)
INFLAMMATION, ACUTE SUPPURATIVE	1 (2%)		4 (8%)
#UTERUS/ENDOMETRIUM	(50)	(50)	(50)
INFLAMMATION, SUPPURATIVE	1 (2%)	7 (14%)	1 (2%)
INFLAMMATION, ACUTE SUPPURATIVE		1 (2%)	
ABSCESS, NOS	1 (2%)		
HYPERPLASIA, CYSTIC	42 (84%)	45 (90%)	43 (86%)
HYPERPLASIA, ADENOMATOUS		1 (2%)	
#OVARY	(50)	(49)	(50)
MINERALIZATION			1 (2%)
CYST, NOS	2 (4%)	2 (4%)	
CYSTIC FOLLICLES	4 (8%)	8 (16%)	2 (4%)
MULTILOCULAR CYST			1 (2%)
HEMORRHAGE	1 (2%)		1 (2%)
HEMATOMA, NOS			1 (2%)
HEMORRHAGIC CYST	2 (4%)		
LYMPHOCYTIC INFLAMMATORY INFILTR			1 (2%)
INFLAMMATION, ACUTE SUPPURATIVE	1 (2%)		4 (8%)
INFLAMMATION, CHRONIC SUPPURATIV	1 (2%)		
ABSCESS, CHRONIC	2 (4%)	2 (4%)	1 (2%)
HEMOSIDEROSIS		1 (2%)	1 (2%)
NERVOUS SYSTEM			
#BRAIN/MENINGES	(50)	(50)	(49)
LYMPHOCYTIC INFLAMMATORY INFILTR	2 (4%)	1 (2%)	
#BRAIN	(50)	(50)	(49)
EPIDERMAL INCLUSION CYST			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
PERIVASCULAR CUFFING		1 (2%)	
DEGENERATION, NOS			1 (2%)
#CEREBELLUM	(50)	(50)	(49)
STATUS SPONGIOSUS	1 (2%)		
SPECIAL SENSE ORGANS			
*MIDDLE EAR	(50)	(50)	(50)
INFLAMMATION, SUPPURATIVE	1 (2%)		
MUSCULOSKELETAL SYSTEM			
*BONE	(50)	(50)	(50)
FIBROUS OSTEODYSTROPHY	10 (20%)	3 (6%)	5 (10%)
BODY CAVITIES			
*MEDIASTINUM	(50)	(50)	(50)
FOREIGN BODY, NOS	2 (4%)		
*ABDOMINAL WALL	(50)	(50)	(50)
ABSCESS, CHRONIC			1 (2%)
*PERITONEUM	(50)	(50)	(50)
INFLAMMATION, SUPPURATIVE		1 (2%)	
INFLAMMATION, ACUTE SUPPURATIVE			1 (2%)
INFLAMMATION, CHRONIC SUPPURATIV			1 (2%)
*PLEURAL CAVITY	(50)	(50)	(50)
REACTION, FOREIGN BODY			1 (2%)
*MEDIASTINAL PLEURA	(50)	(50)	(50)
INFLAMMATION, ACUTE/CHRONIC			1 (2%)
*MESENTERY	(50)	(50)	(50)
HEMORRHAGIC CYST	1 (2%)		
STEATITIS	1 (2%)		
NECROSIS, FAT		1 (2%)	
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
INFLAMMATION, ACUTE SUPPURATIVE	4 (8%)	2 (4%)	4 (8%)
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	1		

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

APPENDIX E

HISTORICAL INCIDENCES OF TUMORS IN F344/N RATS AND B6C3F$_1$ MICE RECEIVING CORN OIL BY GAVAGE

TABLE E1. HISTORICAL INCIDENCE OF STOMACH TUMORS IN MALE F344/N RATS RECEIVING CORN OIL BY GAVAGE *(a)*

Laboratory	Incidence	Site	Diagnosis
Battelle	1/100	Cardiac stomach	Squamous cell papilloma
Hazleton	0/50		
Gulf South	1/268	Stomach, NOS	Squamous cell papilloma
	1/268	Stomach, NOS	Squamous cell carcinoma
Litton	0/125		
Mason	1/125	Forestomach	Squamous cell papilloma
Papanicolaou	0/50		
Southern	1/249	Forestomach	Squamous cell papilloma
Total	5/967 (0.5%)		

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

TABLE E2. HISTORICAL INCIDENCE OF STOMACH TUMORS IN FEMALE F344/N RATS RECEIVING CORN OIL BY GAVAGE *(a)*

Laboratory	Incidence	Site	Diagnosis
Battelle	0/99		
Hazleton	0/50		
Gulf South	1/276	Stomach, NOS	Squamous cell carcinoma
Litton	1/127	Stomach, NOS	Squamous cell papilloma
Mason	0/123		
Papanicolaou	0/49		
Southern	1/249	Stomach, NOS	Squamous cell papilloma
	1/249	Gastric mucosa	Squamous cell papilloma
	1/249	Forestomach	
Squamous cell papilloma			
Total	5/973 (0.5%)		

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

TABLE E3. HISTORICAL INCIDENCE OF PANCREATIC ACINAR CELL ADENOMAS IN MALE F344/N RATS RECEIVING CORN OIL BY GAVAGE *(a)*

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

(a) Date 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 E4. HISTORICAL INCIDENCE OF LIVER TUMORS IN MALE B6C3F$_1$ MICE RECEIVING CORN OIL BY GAVAGE *(a)*

Laboratory	Adenoma	Carcinoma	Adenoma or Carcinoma
Battelle	12/100 (12.0%)	27/100 (27.0%)	35/100 (35.0%)
Gulf South	33/240 (13.8%)	48/240 (20.0%)	80/240 (33.3%)
Litton	6/119 (5.0%)	18/119 (15.1%)	24/119 (20.2%)
Mason	21/149 (14.1%)	22/149 (14.8%)	43/149 (28.9%)
Papanicolaou	3/48 (6.3%)	8/48 (16.7%)	11/48 (22.9%)
Southern	24/248 (9.7%)	64/248 (25.8%)	83/248 (33.5%)
Total	99/904 (11.0%)	187/904 (20.7%)	276/904 (30.5%)
Overall Historical Range			
High	10/48	18/50	22/50
Low	0/50	4/48	7/50

(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 E5 HISTORICAL INCIDENCE OF STOMACH TUMORS IN MALE B6C3F1 MICE RECEIVING CORN OIL BY GAVAGE *(a)*

Laboratory	Incidence	Site	Diagnosis
Battelle	0/100		
Gulf South	1/224	Stomach, NOS	Papilloma, NOS
Litton	1/117	Forestomach	Papilloma, NOS
Mason	0/146		
Papanicolaou	1/48	Stomach, NOS	Squamous cell carcinoma
Southern	1/246	Stomach, NOS	Squamous cell papilloma
	1/246	Stomach, NOS	Squamous cell carcinoma
Total	5/881 (0.6%)		

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

TABLE E6 HISTORICAL INCIDENCE OF STOMACH TUMORS IN FEMALE B6C3F1 MICE RECEIVING CORN OIL BY GAVAGE *(a)*

Laboratory	Incidence	Site	Diagnosis
Battelle	0/99		
Gulf South	2/245	Stomach, NOS	Squamous cell papilloma
	1/245	Stomach, NOS	Adenocarcinoma, NOS
Litton	0/116		
Mason	1/147	Stomach, NOS	Papillomatosis
Papanicolaou	0/47		
Southern	1/247	Gastric mucosa	Squamous cell papilloma
	1/247	Gastric mucosa	Adenoma, NOS
	1/247	Gastric mucosa	Adenocarcinoma, NOS
	1/247	Forestomach	Squamous cell papilloma
Total	8/901 (0.9%)		

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

TABLE E7. HISTORICAL INCIDENCE OF INTEGUMENTARY BASAL CELL TUMORS IN MALE F344/N RATS RECEIVING CORN OIL BY GAVAGE *(a)*

	Skin		Subcutaneous	
Laboratory	**Tumor**	**Carcinoma**	**Tumor**	**Carcinoma**
Battelle	0/100	1/100	0/100	0/100
Gulf South	0/294	0/294	0/294	0/294
Hazleton	0/50	1/50	0/50	0/50
Litton	0/130	0/130	1/130	0/130
Mason	0/125	1/125	0/125	0/125
Papanicolaou	0/50	0/50	0/50	0/50
Southern	3/250	0/250	2/250	0/250
Total	3/999 (0.3%)	3/999 (0.3%)	3/999 (0.3%)	0/999 (0%)

(a) Data as of November 30, 1981. The greatest incidence observed was 3/50, comprised of 1 skin and 2 subcutaneous basal cell tumors in one group of 50 animals.

TABLE E8. HISTORICAL INCIDENCE OF ADRENAL TUMORS IN MALE F344/N RATS RECEIVING CORN OIL BY GAVAGE *(a)*

Laboratory	**Pheochromocytoma**
Battelle	14/99 (14.1%)
Gulf South	24/289 (8.3%)
Hazleton	8/50 (16.0%)
Litton	19/128 (14.8%)
Mason	25/125 (20.0%)
Papanicolaou	3/45 (6.7%)
Southern	60/250 (24.0%)
Total	153/986 (15.5%)
SD *(b)*	8.74%
Overall Historical Range	
High	16/50
Low	2/46

(a) Data as the November 30, 1981 for studies of at least 104 weeks.
(b) Standard deviation. Range and SD are presented for groups of at least 35 animals.

TABLE E9. HISTORICAL INCIDENCE OF THYROID TUMORS IN MALE B6C3F$_1$ MICE RECEIVING CORN OIL BY GAVAGE *(a)*

Laboratory	Follicular Cell Adenoma	Follicular Cell Carcinoma	F-Cell Adenoma or Carcinoma
Battelle	1/83 (1%)	0/83 (0%)	1/83 (1%)
Gulf South	3/206 (1%)	0/206 (0%)	3/206 (1%)
Litton	2/115 (2%)	0/115 (0%)	2/115 (2%)
Mason	1/138 (1%)	1/138 (1%)	2/138 (1%)
Papanicolaou	0/50 (0%)	0/50 (0%)	0/50 (0%)
Southern	17/244 (7%)	0/244 (0%)	17/244 (7%)
Total	24/836 (2.9%)	1/836 (0.1%)	25/836 (3%)
SD *(b)*	3.42%	0.54%	3.44%
Overall Historical Range			
High	5/47	1/45	5/47
Low	0/50	0/50	0/50

(a) Data as of November 30, 1981 for studies of at least 104 weeks.
(b) Standard deviation. Range and SD are presented for groups of 35 or more animals.

TABLE E10. HISTORICAL INCIDENCE OF HEMATOPOIETIC TUMORS IN MALE B6C3F$_1$ MICE RECEIVING CORN OIL BY GAVAGE *(a)*

Laboratory	Lymphocytic Lymphoma	Lymphoma, All Malignant	Lymphoma or Leukemia
Battelle	9/100 (9%)	13/100 (13%)	13/100 (13%)
Gulf South	0/241 (0%)	20/241 (8%)	28/241 (12%)
Litton	2/120 (2%)	18/120 (15%)	19/120 (16%)
Mason	2/150 (1%)	21/150 (14%)	21/150 (14%)
Papanicolaou	2/50 (4%)	11/50 (22%)	11/50 (22%)
Southern	17/249 (7%)	28/249 (11%)	28/249 (11%)
Total	32/910 (3.5%)	111/910 (12.2%)	120/910 (13.2%)
SD *(b)*	4.64%	5.19%	6.73%
Overall Historical Range			
High	7/49	11/50	15/48
Low	0/50	1/48	1/48

(a) Data as of November 30, 1981 for studies of at least 104 weeks.
(b) Standard deviation. Range and SD are presented for groups of 35 or more animals.

APPENDIX F

ANALYSIS OF PRIMARY TUMORS IN RATS AND MICE

TABLE F1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS

	Vehicle Control	100 mg/kg	200 mg/kg
Skin: Squamous Cell Papilloma or Keratoacanthoma			
Tumor Rates			
Overall *(a)*	3/50 (6%)	3/50 (6%)	1/50 (2%)
Adjusted *(b)*	7.0%	8.4%	2.9%
Terminal *(c)*	2/41 (5%)	2/32 (6%)	1/34 (3%)
Statistical Tests *(d)*			
Life Table	P=0.316N	P=0.555	P=0.381N
Incidental Tumor Test	P=0.282N	P=0.662	P=0.340N
Cochran-Armitage Trend Test	P=0.238N		
Fisher Exact Test		P=0.661	P=0.309N
Skin or Subcutaneous Tissue: Squamous Cell Papilloma or Keratoacanthoma			
Tumor Rates			
Overall *(a)*	3/50 (6%)	3/50 (6%)	2/50 (4%)
Adjusted *(b)*	7.0%	8.4%	5.3%
Terminal *(c)*	2/41 (5%)	2/32 (6%)	1/34 (3%)
Statistical Tests *(d)*			
Life Table	P=0.501N	P=0.555	P=0.585N
Incidental Tumor Test	P=0.460N	P=0.662	P=0.534N
Cochran-Armitage Trend Test	P=0.412N		
Fisher Exact Test		P=0.661	P=0.500N
Skin or Subcutaneous Tissue: Basal Cell Tumor			
Tumor Rates			
Overall *(a)*	3/50 (6%)	0/50 (0%)	0/50 (0%)
Adjusted *(b)*	6.9%	0.0%	0.0%
Terminal *(c)*	2/41 (5%)	0/32 (0%)	0/34 (0%)
Statistical Tests *(d)*			
Life Table	P=0.054N	P=0.163N	P=0.158N
Incidental Tumor Test	P=0.041N	P=0.114N	P=0.134N
Cochran-Armitage Trend Test	P=0.037N		
Fisher Exact Test		P=0.121N	P=0.121N
Subcutaneous Tissue: Fibroma			
Tumor Rates			
Overall *(a)*	3/50 (6%)	3/50 (6%)	2/50 (4%)
Adjusted *(b)*	6.9%	9.0%	5.9%
Terminal *(c)*	2/41 (5%)	2/32 (6%)	2/34 (6%)
Statistical Tests *(d)*			
Life Table	P=0.506N	P=0.554	P=0.582N
Incidental Tumor Test	P=0.472N	P=0.662	P=0.568N
Cochran-Armitage Trend Test	P=0.412N		
Fisher Exact Test		P=0.661	P=0.500N
Subcutaneous Tissue: Sarcoma or Fibrosarcoma			
Tumor Rates			
Overall *(a)*	1/50 (2%)	1/50 (2%)	3/50 (6%)
Adjusted *(b)*	2.4%	3.1%	7.5%
Terminal *(c)*	1/41 (2%)	1/32 (3%)	1/34 (3%)
Statistical Tests *(d)*			
Life Table	P=0.169	P=0.706	P=0.258
Incidental Tumor Test	P=0.298	P=0.706	P=0.418
Cochran-Armitage Trend Test	P=0.202		
Fisher Exact Test		P=0.753	P=0.309

TABLE F1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS (Continued)

	Vehicle Control	100 mg/kg	200 mg/kg
Lung: Alveolar/Bronchiolar Adenoma			
Tumor Rates			
Overall *(a)*	3/50 (6%)	1/50 (2%)	1/50 (2%)
Adjusted *(b)*	7.3%	3.1%	2.9%
Terminal *(c)*	3/41 (7%)	1/32 (3%)	1/34 (3%)
Statistical Tests *(d)*			
Life Table	P=0.261N	P=0.397N	P=0.374N
Incidental Tumor Test	P=0.261N	P=0.397N	P=0.374N
Cochran-Armitage Trend Test	P=0.202N		
Fisher Exact Test		P=0.309N	P=0.309N
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Tumor Rates			
Overall *(a)*	4/50 (8%)	1/50 (2%)	2/50 (4%)
Adjusted *(b)*	9.8%	3.1%	5.9%
Terminal *(c)*	4/41 (10%)	1/32 (3%)	2/34 (6%)
Statistical Tests *(d)*			
Life Table	P=0.314N	P=0.261N	P=0.426N
Incidental Tumor Test	P=0.314N	P=0.261N	P=0.426N
Cochran-Armitage Trend Test	P=0.238N		
Fisher Exact Test		P=0.181N	P=0.339N
Hematopoietic System: Monocytic (Mononuclear Cell) Leukemia			
Tumor Rates			
Overall *(a)*	1/50 (2%)	6/50 (12%)	1/50 (2%)
Adjusted *(b)*	2.2%	15.8%	2.8%
Terminal *(c)*	0/41 (0%)	2/32 (6%)	0/34 (0%)
Statistical Tests *(d)*			
Life Table	P=0.489	P=0.035	P=0.707
Incidental Tumor Test	P=0.555N	P=0.149	P=0.730N
Cochran-Armitage Trend Test	P=0.588		
Fisher Exact Test		P=0.056	P=0.753
Pancreas: Acinar Cell Adenoma			
Tumor Rates			
Overall *(a)*	0/49 (0%)	3/50 (6%)	0/49 (0%)
Adjusted *(b)*	0.0%	9.4%	0.0%
Terminal *(c)*	0/41 (0%)	3/32 (9%)	0/34 (0%)
Statistical Tests *(d)*			
Life Table	P=0.584	P=0.081	*(e)*
Incidental Tumor Test	P=0.584	P=0.081	*(e)*
Cochran-Armitage Trend Test	P=0.640		
Fisher Exact Test		P=0.125	*(e)*
Pancreas: Acinar Cell Adenoma or Carcinoma			
Tumor Rates			
Overall *(a)*	0/49 (0%)	4/50 (8%)	0/49 (0%)
Adjusted *(b)*	0.0%	11.5%	0.0%
Terminal *(c)*	0/41 (0%)	3/32 (9%)	0/34 (0%)
Statistical Tests *(d)*			
Life Table	P=0.562	P=0.041	*(e)*
Incidental Tumor Test	P=0.616	P=0.066	*(e)*
Cochran-Armitage Trend Test	P=0.622		
Fisher Exact Test		P=0.061	*(e)*

TABLE F1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS (Continued)

	Vehicle Control	100 mg/kg	200 mg/kg
Forestomach: Squamous Cell Papilloma			
Tumor Rates			
Overall *(a)*	1/50 (2%)	15/50 (30%)	29/50 (58%)
Adjusted *(b)*	2.0%	35.7%	70.5%
Terminal *(c)*	0/41 (0%)	6/32 (19%)	22/34 (65%)
Statistical Tests *(d)*			
Life Table	P<0.001	P<0.001	P<0.001
Incidental Tumor Test	P<0.001	P=0.001	P<0.001
Cochran-Armitage Trend Test	P<0.001		
Fisher Exact Test		P<0.001	P<0.001
Forestomach: Squamous Cell Carcinoma			
Tumor Rates			
Overall *(a)*	0/50 (0%)	5/50 (10%)	12/50 (24%)
Adjusted *(b)*	0.0%	14.3%	32.7%
Terminal *(c)*	0/41 (0%)	3/32 (9%)	10/34 (29%)
Statistical Tests *(d)*			
Life Table	P<0.001	P=0.019	P<0.001
Incidental Tumor Test	P<0.001	P=0.038	P<0.001
Cochran-Armitage Trend Test	P<0.001		
Fisher Exact Test		P=0.028	P<0.001
Forestomach: Squamous Cell Papilloma or Carcinoma			
Tumor Rates			
Overall *(a)*	1/50 (2%)	18/50 (36%)	36/50 (72%)
Adjusted *(b)*	2.0%	42.1%	83.6%
Terminal *(c)*	0/41 (0%)	8/32 (25%)	27/34 (79%)
Statistical Tests *(d)*			
Life Table	P<0.001	P<0.001	P<0.001
Incidental Tumor Test	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test	P<0.001		
Fisher Exact Test		P<0.001	P<0.001
Colon: Adenocarcinoma, Cystadenoma or Adenomatous Polyp			
Tumor Rates			
Overall *(a)*	3/48 (6%)	1/50 (2%)	0/50 (0%)
Adjusted *(b)*	6.7%	3.1%	0.0%
Terminal *(c)*	1/40 (3%)	1/32 (3%)	0/34 (0%)
Statistical Tests *(d)*			
Life Table	P=0.087N	P=0.382N	P=0.160N
Incidental Tumor Test	P=0.056N	P=0.241N	P=0.109N
Cochran-Armitage Trend Test	P=0.056N		
Fisher Exact Test		P=0.293N	P=0.114N
Pituitary: Adenoma			
Tumor Rates			
Overall *(a)*	12/48 (25%)	12/50 (24%)	13/48 (27%)
Adjusted *(b)*	27.5%	29.7%	35.6%
Terminal *(c)*	9/40 (23%)	6/32 (19%)	10/33 (30%)
Statistical Tests *(d)*			
Life Table	P=0.270	P=0.402	P=0.301
Incidental Tumor Test	P=0.356	P=0.365N	P=0.389
Cochran-Armitage Trend Test	P=0.453		
Fisher Exact Test		P=0.547N	P=0.500

TABLE F1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS (Continued)

	Vehicle Control	100 mg/kg	200 mg/kg
Pituitary: Adenoma or Carcinoma			
Tumor Rates			
Overall *(a)*	12/48 (25%)	13/50 (26%)	13/48 (27%)
Adjusted *(b)*	27.5%	32.4%	35.6%
Terminal *(c)*	9/40 (23%)	7/32 (22%)	10/33 (30%)
Statistical Tests *(d)*			
Life Table	P=0.267	P=0.313	P=0.301
Incidental Tumor Test	P=0.351	P=0.471N	P=0.389
Cochran-Armitage Trend Test	P=0.454		
Fisher Exact Test		P=0.547	P=0.500
Adrenal: Pheochromocytoma (Benign)			
Tumor Rates			
Overall *(a)*	15/50 (30%)	13/49 (27%)	5/50 (10%)
Adjusted *(b)*	35.7%	34.6%	14.3%
Terminal *(c)*	14/41 (34%)	8/31 (26%)	4/34 (12%)
Statistical Tests *(d)*			
Life Table	P=0.045N	P=0.455	P=0.037N
Incidental Tumor Test	P=0.026N	P=0.546N	P=0.028N
Cochran-Armitage Trend Test	P=0.011N		
Fisher Exact Test		P=0.437N	P=0.011N
Adrenal: Pheochromocytoma (Benign or Malignant)			
Tumor Rates			
Overall *(a)*	15/50 (30%)	13/49 (27%)	7/50 (14%)
Adjusted *(b)*	35.7%	34.6%	20.0%
Terminal *(c)*	14/41 (34%)	8/31 (26%)	6/34 (18%)
Statistical Tests *(d)*			
Life Table	P=0.119N	P=0.455	P=0.115N
Incidental Tumor Test	P=0.081N	P=0.546N	P=0.095N
Cochran-Armitage Trend Test	P=0.038N		
Fisher Exact Test		P=0.437N	P=0.045N
Thyroid: C-Cell Adenoma			
Tumor Rates			
Overall *(a)*	10/49 (20%)	4/49 (8%)	6/48 (13%)
Adjusted *(b)*	25.0%	12.9%	16.5%
Terminal *(c)*	10/40 (25%)	4/31 (13%)	4/34 (12%)
Statistical Tests *(d)*			
Life Table	P=0.250N	P=0.168N	P=0.326N
Incidental Tumor Test	P=0.225N	P=0.168N	P=0.287N
Cochran-Armitage Trend Test	P=0.160N		
Fisher Exact Test		P=0.074N	P=0.219N
Thyroid: C-Cell Adenoma or Carcinoma			
Tumor Rates			
Overall *(a)*	11/49 (22%)	5/49 (10%)	8/48 (17%)
Adjusted *(b)*	27.5%	15.3%	22.1%
Terminal *(c)*	11/40 (28%)	4/31 (13%)	6/34 (18%)
Statistical Tests *(d)*			
Life Table	P=0.387N	P=0.202N	P=0.458N
Incidental Tumor Test	P=0.346N	P=0.171N	P=0.418N
Cochran-Armitage Trend Test	P=0.261N		
Fisher Exact Test		P=0.085N	P=0.323N

TABLE F1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS (Continued)

	Vehicle Control	100 mg/kg	200 mg/kg
Pancreatic Islets: Islet Cell Carcinoma			
Tumor Rates			
Overall *(a)*	4/49 (8%)	3/50 (6%)	1/49 (2%)
Adjusted *(b)*	9.3%	9.4%	2.9%
Terminal *(c)*	3/41 (7%)	3/32 (9%)	1/34 (3%)
Statistical Tests *(d)*			
Life Table	P=0.195N	P=0.625N	P=0.242N
Incidental Tumor Test	P=0.178N	P=0.571N	P=0.216N
Cochran-Armitage Trend Test	P=0.132N		
Fisher Exact Test		P=0.489N	P=0.181N
Pancreatic Islets: Islet Cell Adenoma or Carcinoma			
Tumor Rates			
Overall *(a)*	5/49 (10%)	5/50 (10%)	2/49 (4%)
Adjusted *(b)*	11.7%	15.6%	5.7%
Terminal *(c)*	4/41 (10%)	5/32 (16%)	1/34 (3%)
Statistical Tests *(d)*			
Life Table	P=0.271N	P=0.476	P=0.305N
Incidental Tumor Test	P=0.237N	P=0.524	P=0.250N
Cochran-Armitage Trend Test	P=0.177N		
Fisher Exact Test		P=0.617N	P=0.218N
Mammary Gland: Fibroadenoma			
Tumor Rates			
Overall *(a)*	2/50 (4%)	0/50 (0%)	3/50 (6%)
Adjusted *(b)*	4.9%	0.0%	8.2%
Terminal *(c)*	2/41 (5%)	0/32 (0%)	2/34 (6%)
Statistical Tests *(d)*			
Life Table	P=0.330	P=0.294N	P=0.420
Incidental Tumor Test	P=0.347	P=0.294N	P=0.449
Cochran-Armitage Trend Test	P=0.390		
Fisher Exact Test		P=0.247N	P=0.500
Testis: Interstitial Cell Tumor			
Tumor Rates			
Overall *(a)*	47/50 (94%)	45/50 (90%)	40/50 (80%)
Adjusted *(b)*	97.9%	97.8%	97.6%
Terminal *(c)*	40/41 (98%)	31/32 (97%)	33/34 (97%)
Statistical Tests *(d)*			
Life Table	P=0.408	P=0.060	P=0.485
Incidental Tumor Test	P=0.286N	P=0.556N	P=0.423N
Cochran-Armitage Trend Test	P=0.023N		
Fisher Exact Test		P=0.357N	P=0.036N
All Sites: Malignant Mesothelioma			
Tumor Rates			
Overall *(a)*	1/50 (2%)	2/50 (4%)	3/50 (6%)
Adjusted *(b)*	2.4%	5.2%	7.9%
Terminal *(c)*	1/41 (2%)	1/32 (3%)	1/34 (3%)
Statistical Tests *(d)*			
Life Table	P=0.179	P=0.438	P=0.248
Incidental Tumor Test	P=0.206	P=0.618	P=0.291
Cochran-Armitage Trend Test	P=0.222		
Fisher Exact Test		P=0.500	P=0.309

TABLE F1. 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 exact tests compare directly the overall incidence rates. A negative trend or lower incidence is indicated by (N).
(e) No tumors observed in dosed or control groups.

TABLE F2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS

	Vehicle Control	100 mg/kg	200 mg/kg
Lung: Alveolar/Bronchiolar Adenoma			
Tumor Rates			
Overall *(a)*	1/50 (2%)	1/50 (2%)	3/50 (6%)
Adjusted *(b)*	2.4%	2.8%	7.1%
Terminal *(c)*	0/36 (0%)	1/36 (3%)	3/42 (7%)
Statistical Tests *(d)*			
Life Table	P=0.245	P=0.758N	P=0.357
Incidental Tumor Test	P=0.213	P=0.746	P=0.305
Cochran-Armitage Trend Test	P=0.202		
Fisher Exact Test		P=0.753	P=0.309
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Tumor Rates			
Overall *(a)*	1/50 (2%)	1/50 (2%)	4/50 (8%)
Adjusted *(b)*	2.4%	2.8%	9.5%
Terminal *(c)*	0/36 (0%)	1/36 (3%)	4/42 (10%)
Statistical Tests *(d)*			
Life Table	P=0.134	P=0.758N	P=0.227
Incidental Tumor Test	P=0.114	P=0.746	P=0.189
Cochran-Armitage Trend Test	P=0.101		
Fisher Exact Test		P=0.753	P=0.181
Hematopoietic System: Monocytic (Mononuclear Cell) Leukemia			
Tumor Rates			
Overall *(a)*	5/50 (10%)	8/50 (16%)	7/50 (14%)
Adjusted *(b)*	13.9%	18.4%	15.1%
Terminal *(c)*	5/36 (14%)	4/36 (11%)	3/42 (7%)
Statistical Tests *(d)*			
Life Table	P=0.423	P=0.282	P=0.480
Incidental Tumor Test	P=0.227	P=0.378	P=0.312
Cochran-Armitage Trend Test	P=0.330		
Fisher Exact Test		P=0.277	P=0.380
Forestomach: Squamous Cell Papilloma			
Tumor Rates			
Overall *(a)*	1/50 (2%)	6/50 (12%)	9/50 (18%)
Adjusted *(b)*	2.2%	15.5%	19.8%
Terminal *(c)*	0/36 (0%)	4/36 (11%)	6/42 (14%)
Statistical Tests *(d)*			
Life Table	P=0.018	P=0.063	P=0.021
Incidental Tumor Test	P=0.004	P=0.034	P=0.004
Cochran-Armitage Trend Test	P=0.008		
Fisher Exact Test		P=0.056	P=0.008
Forestomach: Squamous Cell Papilloma or Carcinoma			
Tumor Rates			
Overall *(a)*	1/50 (2%)	6/50 (12%)	11/50 (22%)
Adjusted *(b)*	2.2%	15.5%	23.8%
Terminal *(c)*	0/36 (0%)	4/36 (11%)	7/42 (17%)
Statistical Tests *(d)*			
Life Table	P=0.005	P=0.063	P=0.008
Incidental Tumor Test	P<0.001	P=0.034	P<0.001
Cochran-Armitage Trend Test	P=0.002		
Fisher Exact Test		P=0.056	P=0.002

TABLE F2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS (Continued)

	Vehicle Control	100 mg/kg	200 mg/kg
Pituitary: Adenoma			
Tumor Rates			
Overall *(a)*	20/49 (41%)	17/49 (35%)	17/47 (36%)
Adjusted *(b)*	46.0%	43.0%	41.2%
Terminal *(c)*	13/36 (36%)	13/35 (37%)	15/39 (38%)
Statistical Tests *(d)*			
Life Table	P=0.215N	P=0.380N	P=0.245N
Incidental Tumor Test	P=0.401N	P=0.497N	P=0.434N
Cochran-Armitage Trend Test	P=0.355N		
Fisher Exact Test		P=0.339N	P=0.399N
Pituitary: Adenoma or Carcinoma			
Tumor Rates			
Overall *(a)*	22/49 (45%)	18/49 (37%)	17/47 (36%)
Adjusted *(b)*	49.7%	44.4%	41.2%
Terminal *(c)*	14/36 (39%)	13/35 (37%)	15/39 (38%)
Statistical Tests (d)			
Life Table	P=0.121N	P=0.316N	P=0.141N
Incidental Tumor Test	P=0.268N	P=0.423N	P=0.289N
Cochran-Armitage Trend Test	P=0.219N		
Fisher Exact Test		P=0.269N	P=0.254N
Adrenal: Pheochromocytoma			
Tumor Rates			
Overall *(a)*	3/50 (6%)	4/50 (8%)	5/50 (10%)
Adjusted *(b)*	6.6%	11.1%	11.5%
Terminal *(c)*	0/36 (0%)	4/36 (11%)	4/42 (10%)
Statistical Tests *(d)*			
Life Table	P=0.365	P=0.491	P=0.425
Incidental Tumor Test	P=0.240	P=0.401	P=0.237
Cochran-Armitage Trend Test	P=0.290		
Fisher Exact Test		P=0.500	P=0.357
Thyroid: C-Cell Adenoma			
Tumor Rates			
Overall *(a)*	6/50 (12%)	7/49 (14%)	8/48 (17%)
Adjusted *(b)*	15.2%	18.9%	20.0%
Terminal *(c)*	4/36 (11%)	6/35 (17%)	8/40 (20%)
Statistical Tests *(d)*			
Life Table	P=0.410	P=0.480	P=0.466
Incidental Tumor Test	P=0.357	P=0.527	P=0.405
Cochran-Armitage Trend Test	P=0.303		
Fisher Exact Test		P=0.484	P=0.355
Thyroid: C-Cell Carcinoma			
Tumor Rates			
Overall *(a)*	1/50 (2%)	4/49 (8%)	5/48 (10%)
Adjusted *(b)*	2.8%	11.4%	12.5%
Terminal *(c)*	1/36 (3%)	4/35 (11%)	5/40 (13%)
Statistical Tests *(d)*			
Life Table	P=0.105	P=0.170	P=0.128
Incidental Tumor Test	P=0.105	P=0.170	P=0.128
Cochran-Armitage Trend Test	P=0.072		
Fisher Exact Test		P=0.175	P=0.093

TABLE F2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS (Continued)

	Vehicle Control	100 mg/kg	200 mg/kg
Thyroid: C-Cell Adenoma or Carcinoma			
Tumor Rates			
Overall *(a)*	7/50 (14%)	11/49 (22%)	13/48 (27%)
Adjusted *(b)*	17.8%	30.1%	32.5%
Terminal *(c)*	5/36 (14%)	10/35 (29%)	13/40 (33%)
Statistical Tests *(d)*			
Life Table	P=0.137	P=0.201	P=0.159
Incidental Tumor Test	P=0.110	P=0.228	P=0.127
Cochran-Armitage Trend Test	P=0.071		
Fisher Exact Test		P=0.204	P=0.087
Mammary Gland: Fibroadenoma			
Tumor Rates			
Overall *(a)*	13/50 (26%)	12/50 (24%)	11/50 (22%)
Adjusted *(b)*	30.9%	29.9%	25.5%
Terminal *(c)*	8/36 (22%)	8/36 (22%)	10/42 (24%)
Statistical Tests *(d)*			
Life Table	P=0.236N	P=0.500N	P=0.275N
Incidental Tumor Test	P=0.419N	P=0.551	P=0.456N
Cochran-Armitage Trend Test	P=0.363N		
Fisher Exact Test		P=0.500N	P=0.408N
Uterus: Endometrial Stromal Polyp			
Tumor Rates			
Overall *(a)*	17/50 (34%)	14/50 (28%)	18/50 (36%)
Adjusted *(b)*	39.9%	34.3%	40.7%
Terminal *(c)*	11/36 (31%)	10/36 (28%)	16/42 (38%)
Statistical Tests *(d)*			
Life Table	P=0.437N	P=0.345N	P=0.466N
Incidental Tumor Test	P=0.437	P=0.364N	P=0.480
Cochran-Armitage Trend Test	P=0.458		
Fisher Exact Test		P=0.333N	P=0.500
Uterus: Endometrial Stromal Polyp or Sarcoma			
Tumor Rates			
Overall *(a)*	17/50 (34%)	14/50 (28%)	19/50 (38%)
Adjusted *(b)*	39.9%	34.3%	43.0%
Terminal *(c)*	11/36 (31%)	10/36 (28%)	17/42 (40%)
Statistical Tests *(d)*			
Life Table	P=0.512N	P=0.345N	P=0.539N
Incidental Tumor Test	P=0.360	P=0.364N	P=0.404
Cochran-Armitage Trend Test	P=0.375		
Fisher Exact Test		P=0.333N	P=0.418

(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 exact tests compare directly the overall incidence rates. A negative trend or lower incidence is indicated by (N).

TABLE F3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE

	Vehicle Control	100 mg/kg	200 mg/kg
Skin or Subcutaneous Tissue: Sarcoma or Fibrosarcoma			
Tumor Rates			
Overall *(a)*	3/49 (6%)	0/49 (0%)	0/50 (0%)
Adjusted *(b)*	8.2%	0.0%	0.0%
Terminal *(c)*	0/27 (0%)	0/36 (0%)	0/30 (0%)
Statistical Tests *(d)*			
Life Table	P=0.034N	P=0.091N	P=0.129N
Incidental Tumor Test	P=0.039N	P=0.237N	P=0.112N
Cochran-Armitage Trend Test	P=0.036N		
Fisher Exact Test		P=0.121N	P=0.117N
Lung: Alveolar/Bronchiolar Adenoma			
Tumor Rates			
Overall *(a)*	5/48 (10%)	4/49 (8%)	1/50 (2%)
Adjusted *(b)*	16.9%	11.1%	3.3%
Terminal *(c)*	4/27 (15%)	4/36 (11%)	1/30 (3%)
Statistical Tests *(d)*			
Life Table	P=0.056N	P=0.335N	P=0.085N
Incidental Tumor Test	P=0.081N	P=0.399N	P=0.127N
Cochran-Armitage Trend Test	P=0.072N		
Fisher Exact Test		P=0.487N	P=0.093N
Lung: Alveolar/Bronchiolar Carcinoma			
Tumor Rates			
Overall *(a)*	3/48 (6%)	2/49 (4%)	5/50 (10%)
Adjusted *(b)*	11.1%	5.6%	16.0%
Terminal *(c)*	3/27 (11%)	2/36 (6%)	4/30 (13%)
Statistical Tests *(d)*			
Life Table	P=0.305	P=0.369N	P=0.407
Incidental Tumor Test	P=0.284	P=0.369N	P=0.371
Cochran-Armitage Trend Test	P=0.292		
Fisher Exact Test		P=0.490N	P=0.381
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Tumor Rates			
Overall *(a)*	8/48 (17%)	6/49 (12%)	5/50 (10%)
Adjusted *(b)*	27.7%	16.7%	16.0%
Terminal *(c)*	7/27 (26%)	6/36 (17%)	4/30 (13%)
Statistical Tests *(d)*			
Life Table	P=0.166N	P=0.193N	P=0.220N
Incidental Tumor Test	P=0.218N	P=0.233N	P=0.304N
Cochran-Armitage Trend Test	P=0.203N		
Fisher Exact Test		P=0.371N	P=0.250N
Hematopoietic System: Malignant Lymphoma, Lymphocytic Type			
Tumor Rates			
Overall *(a)*	7/49 (14%)	3/49 (6%)	1/50 (2%)
Adjusted *(b)*	22.1%	8.3%	2.6%
Terminal *(c)*	4/27 (15%)	3/36 (8%)	0/30 (0%)
Statistical Tests *(d)*			
Life Table	P=0.012N	P=0.076N	P=0.031N
Incidental Tumor Test	P=0.009N	P=0.149N	P=0.017N
Cochran-Armitage Trend Test	P=0.016N		
Fisher Exact Test		P=0.159N	P=0.028N

TABLE F3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE (Continued)

	Vehicle Control	100 mg/kg	200 mg/kg
Hematopoietic System: Malignant Lymphoma, Mixed Type			
Tumor Rates			
Overall *(a)*	2/49 (4%)	1/49 (2%)	3/50 (6%)
Adjusted *(b)*	5.8%	2.6%	9.1%
Terminal *(c)*	0/27 (0%)	0/36 (0%)	2/30 (7%)
Statistical Tests *(d)*			
Life Table	P=0.416	P=0.424N	P=0.524
Incidental Tumor Test	P=0.294	P=0.524N	P=0.385
Cochran-Armitage Trend Test	P=0.407		
Fisher Exact Test		P=0.500N	P=0.510
Hematopoietic System: Malignant Lymphoma, All Types			
Tumor Rates			
Overall *(a)*	9/49 (18%)	4/49 (8%)	5/50 (10%)
Adjusted *(b)*	26.6%	10.7%	14.6%
Terminal *(c)*	4/27 (15%)	3/36 (8%)	3/30 (10%)
Statistical Tests *(d)*			
Life Table	P=0.116N	P=0.052N	P=0.174N
Incidental Tumor Test	P=0.122N	P=0.114N	P=0.182N
Cochran-Armitage Trend Test	P=0.133N		
Fisher Exact Test		P=0.116N	P=0.183N
Hematopoietic System: Malignant Lymphoma or Leukemia			
Tumor Rates			
Overall *(a)*	9/49 (18%)	4/49 (8%)	6/50 (12%)
Adjusted *(b)*	26.6%	10.7%	16.6%
Terminal *(c)*	4/27 (15%)	3/36 (8%)	3/30 (10%)
Statistical Tests *(d)*			
Life Table	P=0.199N	P=0.052N	P=0.266N
Incidental Tumor Test	P=0.200N	P=0.114N	P=0.270N
Cochran-Armitage Trend Test	P=0.215N		
Fisher Exact Test		P=0.116N	P=0.274N
Circulatory System: Hemangiosarcoma			
Tumor Rates			
Overall *(a)*	1/49 (2%)	2/49 (4%)	3/50 (6%)
Adjusted *(b)*	3.7%	5.3%	8.4%
Terminal *(c)*	1/27 (4%)	1/36 (3%)	1/30 (3%)
Statistical Tests *(d)*			
Life Table	P=0.239	P=0.597	P=0.336
Incidental Tumor Test	P=0.167	P=0.605	P=0.233
Cochran-Armitage Trend Test	P=0.229		
Fisher Exact Test		P=0.500	P=0.316
Liver: Adenoma			
Tumor Rates			
Overall *(a)*	6/49 (12%)	5/49 (10%)	3/50 (6%)
Adjusted *(b)*	21.0%	13.1%	10.0%
Terminal *(c)*	5/27 (19%)	4/36 (11%)	3/30 (10%)
Statistical Tests *(d)*			
Life Table	P=0.148N	P=0.314N	P=0.197N
Incidental Tumor Test	P=0.147N	P=0.390N	P=0.220N
Cochran-Armitage Trend Test	P=0.186N		
Fisher Exact Test		P=0.500N	P=0.233N

TABLE F3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE (Continued)

	Vehicle Control	100 mg/kg	200 mg/kg
Liver: Carcinoma			
Tumor Rates			
Overall *(a)*	12/49 (24%)	10/49 (20%)	3/50 (6%)
Adjusted *(b)*	34.8%	23.6%	8.7%
Terminal *(c)*	6/27 (22%)	5/36 (14%)	1/30 (3%)
Statistical Tests *(d)*			
Life Table	P=0.009N	P=0.199N	P=0.013N
Incidental Tumor Test	P=0.013N	P=0.484N	P=0.014N
Cochran-Armitage Trend Test	P=0.010N		
Fisher Exact Test		P=0.405N	P=0.010N
Liver: Adenoma or Carcinoma			
Tumor Rates			
Overall *(a)*	17/49 (35%)	12/49 (24%)	6/50 (12%)
Adjusted *(b)*	48.8%	28.5%	18.2%
Terminal *(c)*	10/27 (37%)	7/36 (19%)	4/30 (13%)
Statistical Tests *(d)*			
Life Table	P=0.005N	P=0.058N	P=0.008N
Incidental Tumor Test	P=0.006N	P=0.160N	P=0.008N
Cochran-Armitage Trend Test	P=0.006N		
Fisher Exact Test		P=0.188N	P=0.007N
Forestomach: Squamous Cell Papilloma			
Tumor Rates			
Overall *(a)*	0/48 (0%)	4/47 (9%)	9/50 (18%)
Adjusted *(b)*	0.0%	10.5%	28.0%
Terminal *(c)*	0/27 (0%)	3/36 (8%)	7/30 (23%)
Statistical Tests *(d)*			
Life Table	P=0.001	P=0.108	P=0.004
Incidental Tumor Test	P<0.001	P=0.109	P=0.002
Cochran-Armitage Trend Test	P=0.002		
Fisher Exact Test		P=0.056	P=0.002
Forestomach: Squamous Cell Carcinoma			
Tumor Rates			
Overall *(a)*	0/48 (0%)	2/47 (4%)	5/50 (10%)
Adjusted *(b)*	0.0%	5.6%	14.7%
Terminal *(c)*	0/27 (0%)	2/36 (6%)	2/30 (7%)
Statistical Tests *(d)*			
Life Table	P=0.017	P=0.303	P=0.040
Incidental Tumor Test	P=0.025	P=0.303	P=0.040
Cochran-Armitage Trend Test	P=0.019		
Fisher Exact Test		P=0.242	P=0.031
Forestomach: Squamous Cell Papilloma or Carcinoma			
Tumor Rates			
Overall *(a)*	0/48 (0%)	5/47 (11%)	12/50 (24%)
Adjusted *(b)*	0.0%	13.2%	35.0%
Terminal *(c)*	0/27 (0%)	4/36 (11%)	8/30 (27%)
Statistical Tests *(d)*			
Life Table	P=0.001	P=0.065	P 0.001
Incidental Tumor Test	P<0.001	P=0.066	P<0.001
Cochran-Armitage Trend Test	P<0.001		
Fisher Exact Test		P=0.026	P<0.001

TABLE F3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE (Continued)

	Vehicle Control	100 mg/kg	200 mg/kg
Small Intestine: Adenomatous Polyp or Adenocarcinoma			
Tumor Rates			
Overall *(a)*	1/48 (2%)	3/47 (6%)	1/47 (2%)
Adjusted *(b)*	3.4%	8.3%	3.3%
Terminal *(c)*	0/27 (0%)	3/36 (8%)	1/30 (3%)
Statistical Tests *(d)*			
Life Table	P=0.583N	P=0.412	P=0.745N
Incidental Tumor Test	P=0.615	P=0.418	P=0.718
Cochran-Armitage Trend Test	P=0.602		
Fisher Exact Test		P=0.301	P=0.747
Thyroid: Follicular Cell Adenoma			
Tumor Rates			
Overall *(a)*	4/49 (8%)	2/47 (4%)	0/49 (0%)
Adjusted *(b)*	12.8%	5.6%	0.0%
Terminal *(c)*	2/27 (7%)	2/36 (6%)	0/30 (0%)
Statistical Tests *(d)*			
Life Table	P=0.028N	P=0.226N	P=0.061N
Incidental Tumor Test	P=0.032N	P=0.323N	P=0.068N
Cochran-Armitage Trend Test	P=0.038N		
Fisher Exact Test		P=0.359N	P=0.059N
Thyroid: Follicular Cell Adenoma or Carcinoma			
Tumor Rates			
Overall *(a)*	4/49 (8%)	3/47 (6%)	0/49 (0%)
Adjusted *(b)*	12.8%	8.3%	0.0%
Terminal *(c)*	2/27 (7%)	3/36 (8%)	0/30 (0%)
Statistical Tests *(d)*			
Life Table	P=0.037N	P=0.357N	P=0.061N
Incidental Tumor Test	P=0.041N	P=0.467N	P=0.068N
Cochran-Armitage Trend Test	P=0.050N		
Fisher Exact Test		P=0.524N	P=0.059N
Harderian Gland: Adenoma			
Tumor Rates			
Overall *(a)*	3/49 (6%)	2/49 (4%)	1/50 (2%)
Adjusted *(b)*	11.1%	5.6%	2.9%
Terminal *(c)*	3/27 (11%)	2/36 (6%)	0/30 (0%)
Statistical Tests *(d)*			
Life Table	P=0.189N	P=0.369N	P=0.278N
Incidental Tumor Test	P=0.172N	P=0.369N	P=0.244N
Cochran-Armitage Trend Test	P=0.216N		
Fisher Exact Test		P=0.500N	P=0.301N
Harderian Gland: Adenoma or Carcinoma			
Tumor Rates			
Overall *(a)*	4/49 (8%)	2/49 (4%)	1/50 (2%)
Adjusted *(b)*	14.8%	5.6%	2.9%
Terminal *(c)*	4/27 (15%)	2/36 (6%)	0/30 (3%)
Statistical Tests *(d)*			
Life Table	P=0.091N	P=0.212N	P=0.156N
Incidental Tumor Test	P=0.084N	P=0.212N	P=0.134N
Cochran-Armitage Trend Test	P=0.114N		
Fisher Exact Test		P=0.339N	P=0.175N

TABLE F3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE (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 exact tests compare directly the overall incidence rates. A negative trend or lower incidence is indicated by (N).

TABLE F4. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE

	Vehicle Control	100 mg/kg	200 mg/kg
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Tumor Rates			
Overall *(a)*	2/50 (4%)	2/50 (4%)	3/49 (6%)
Adjusted *(b)*	6.2%	5.1%	10.8%
Terminal *(c)*	1/27 (4%)	1/35 (3%)	2/26 (8%)
Statistical Tests *(d)*			
Life Table	P=0.372	P=0.632N	P=0.463
Incidental Tumor Test	P=0.418	P=0.668	P=0.472
Cochran-Armitage Trend Test	P=0.398		
Fisher Exact Test		P=0.691	P=0.490
Hematopoietic System: Malignant Lymphoma, Lymphocytic Type			
Tumor Rates			
Overall *(a)*	5/50 (10%)	4/50 (8%)	3/50 (6%)
Adjusted *(b)*	15.4%	10.2%	9.8%
Terminal *(c)*	3/27 (11%)	2/35 (6%)	2/26 (8%)
Statistical Tests *(d)*			
Life Table	P=0.307N	P=0.382N	P=0.384N
Incidental Tumor Test	P=0.315N	P=0.523N	P=0.437N
Cochran-Armitage Trend Test	P=0.290N		
Fisher Exact Test		P=0.500N	P=0.357N
Hematopoietic System: Malignant Lymphoma, Mixed Type			
Tumor Rates			
Overall *(a)*	3/50 (6%)	7/50 (14%)	8/50 (16%)
Adjusted *(b)*	10.0%	17.6%	23.7%
Terminal *(c)*	2/27 (7%)	3/35 (9%)	3/26 (12%)
Statistical Tests *(d)*			
Life Table	P=0.066	P=0.269	P=0.088
Incidental Tumor Test	P=0.079	P=0.088	P=0.110
Cochran-Armitage Trend Test	P=0.083		
Fisher Exact Test		P=0.159	P=0.100
Hematopoietic System: Malignant Lymphoma, All Types			
Tumor Rates			
Overall *(a)*	11/50 (22%)	13/50 (26%)	13/50 (26%)
Adjusted *(b)*	31.2%	30.5%	35.7%
Terminal *(c)*	5/27 (19%)	6/35 (17%)	5/26 (19%)
Statistical Tests *(d)*			
Life Table	P=0.315	P=0.553N	P=0.350
Incidental Tumor Test	P=0.323	P=0.256	P=0.397
Cochran-Armitage Trend Test	P=0.364		
Fisher Exact Test		P=0.408	P=0.408
Hematopoietic System: Malignant Lymphoma or Leukemia			
Tumor Rates			
Overall *(a)*	11/50 (22%)	13/50 (26%)	14/50 (28%)
Adjusted *(b)*	31.2%	30.5%	37.0%
Terminal *(c)*	5/27 (19%)	6/35 (17%)	5/26 (19%)
Statistical Tests *(d)*			
Life Table	P=0.245	P=0.553N	P=0.279
Incidental Tumor Test	P=0.275	P=0.256	P=0.348
Cochran-Armitage Trend Test	P=0.283		
Fisher Exact Test		P=0.408	P=0.322

TABLE F4. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE (Continued)

	Vehicle Control	100 mg/kg	200 mg/kg
Circulatory System: Hemangiosarcoma			
Tumor Rates			
Overall *(a)*	3/50 (6%)	1/50 (2%)	1/50 (2%)
Adjusted *(b)*	8.3%	2.9%	3.3%
Terminal *(c)*	1/27 (4%)	1/35 (3%)	0/26 (0%)
Statistical Tests *(d)*			
Life Table	P=0.217N	P=0.253N	P=0.339N
Incidental Tumor Test	P=0.163N	P=0.294N	P=0.235N
Cochran-Armitage Trend Test	P=0.202N		
Fisher Exact Test		P=0.309N	P=0.309N
Liver: Adenoma or Carcinoma			
Tumor Rates			
Overall *(a)*	3/50 (6%)	3/50 (6%)	3/50 (6%)
Adjusted *(b)*	11.1%	8.2%	11.5%
Terminal *(c)*	3/27 (11%)	2/35 (6%)	3/26 (12%)
Statistical Tests *(d)*			
Life Table	P=0.571	P=0.537N	P=0.648
Incidental Tumor Test	P=0.565	P=0.609N	P=0.648
Cochran-Armitage Trend Test	P=0.583		
Fisher Exact Test		P=0.661	P=0.661
Forestomach: Squamous Cell Papilloma			
Tumor Rates			
Overall *(a)*	1/50 (2%)	4/49 (8%)	5/48 (10%)
Adjusted *(b)*	3.7%	11.4%	17.3%
Terminal *(c)*	1/27 (4%)	4/35 (11%)	3/26 (12%)
Statistical Tests *(d)*			
Life Table	P=0.062	P=0.264	P=0.091
Incidental Tumor Test	P=0.061	P=0.264	P=0.084
Cochran-Armitage Trend Test	P=0.072		
Fisher Exact Test		P=0.175	P=0.093
Forestomach: Squamous Cell Papilloma or Carcinoma			
Tumor Rates			
Overall *(a)*	1/50 (2%)	5/49 (10%)	7/48 (15%)
Adjusted *(b)*	3.7%	13.5%	23.1%
Terminal *(c)*	1/27 (4%)	4/35 (11%)	4/26 (15%)
Statistical Tests *(d)*			
Life Table	P=0.018	P=0.166	P=0.028
Incidental Tumor Test	P=0.020	P=0.148	P=0.023
Cochran-Armitage Trend Test	P=0.022		
Fisher Exact Test		P=0.098	P=0.026
Pituitary: Adenoma			
Tumor Rates			
Overall *(a)*	8/46 (17%)	2/47 (4%)	3/45 (7%)
Adjusted *(b)*	27.5%	5.7%	12.0%
Terminal *(c)*	6/26 (23%)	2/35 (6%)	3/25 (12%)
Statistical Tests *(d)*			
Life Table	P=0.053N	P=0.017N	P=0.117N
Incidental Tumor Test	P=0.059N	P=0.031N	P=0.119N
Cochran-Armitage Trend Test	P=0.057N		
Fisher Exact Test		P=0.042N	P=0.105N

TABLE F4. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE (Continued)

	Vehicle Control	100 mg/kg	200 mg/kg
Pituitary: Carcinoma			
Tumor Rates			
Overall *(a)*	2/46 (4%)	4/47 (9%)	1/45 (2%)
Adjusted *(b)*	7.7%	11.0%	4.0%
Terminal *(c)*	2/26 (8%)	3/35 (9%)	1/25 (4%)
Statistical Tests *(d)*			
Life Table	P=0.416N	P=0.476	P=0.514N
Incidental Tumor Test	P=0.432N	P=0.392	P=0.514N
Cochran-Armitage Trend Test	P=0.415N		
Fisher Exact Test		P=0.349	P=0.508N
Pituitary: Adenoma or Carcinoma			
Tumor Rates			
Overall *(a)*	10/46 (22%)	6/47 (13%)	4/45 (9%)
Adjusted *(b)*	34.7%	16.6%	16.0%
Terminal *(c)*	8/26 (31%)	5/35 (14%)	4/25 (16%)
Statistical Tests *(d)*			
Life Table	P=0.050N	P=0.077N	P=0.085N
Incidental Tumor Test	P=0.058N	P=0.141N	P=0.087N
Cochran-Armitage Trend Test	P=0.055N		
Fisher Exact Test		P=0.192N	P=0.079N
Thyroid: Follicular Cell Adenoma or Carcinoma			
Tumor Rates			
Overall *(a)*	4/48 (8%)	4/46 (9%)	1/49 (2%)
Adjusted *(b)*	13.5%	12.1%	3.8%
Terminal *(c)*	3/27 (11%)	4/33 (12%)	1/26 (4%)
Statistical Tests *(d)*			
Life Table	P=0.149N	P=0.539N	P=0.198N
Incidental Tumor Test	P=0.152N	P=0.600N	P=0.195N
Cochran-Armitage Trend Test	P=0.142N		
Fisher Exact Test		P=0.619	P=0.175N
Uterus: Endometrial Stromal Polyp			
Tumor Rates			
Overall *(a)*	4/50 (8%)	0/50 (0%)	1/50 (2%)
Adjusted *(b)*	12.1%	0.0%	2.3%
Terminal *(c)*	2/27 (7%)	0/35 (0%)	0/26 (0%)
Statistical Tests *(d)*			
Life Table	P=0.087N	P=0.046N	P=0.204N
Incidental Tumor Test	P=0.063N	P=0.073N	P=0.136N
Cochran-Armitage Trend Test	P=0.082N		
Fisher Exact Test		P=0.059N	P=0.181N

(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 exact tests compare directly the overall incidence rates. A negative trend or lower incidence is indicated by (N).

APPENDIX G

MUTAGENESIS RESULTS FOR ETHYL ACRYLATE IN *SALMONELLA TYPHIMURIUM*

APPENDIX G

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

All chemicals are tested and evaluated as unknown compounds in four *Salmonella typhimurium* tester strains (TA98, TA100, TA1535 and TA1537) (Ames, et al., 1975). Exogenous metabolic activation is provided by 9000 X g liver supernatant (S-9) fractions from Aroclor-1254® induced male Sprague-Dawley rats and male Syrian hamsters. A preincubation modification (Yahagi, et al., 1975) of the Salmonella test is used; the test chemical is incubated with the tester strain, and either an S-9 plus cofactor mix or buffer, for 20 min. at 37° C prior to the addition of soft agar and plating on minimal agar plates for detection of induced mutants. Each test consists of a concurrent positive control, solvent control and at least 5 doses of test chemical, the high dose limited by toxicity or solubility, but not exceeding 10.0 mg per plate.

Each chemical is tested, in triplicate, at 5 doses, along with positive and solvent controls in the absence of exogenous metabolic activation (NA), in the presence of rat liver S-9 (RLI), and hamster liver S-9 (HLI). The entire test series or only those tests which yielded a positive response are repeated at least one week after the initial test.

A positive response is defined as a reproducible, dose-related increase in histidine-indepedent (revertant) colonies. An equivocal response is either a non-dose-related increase or a response that is not reproducible.

All tester strains measure point (gene) mutations. TA1535 is reverted by mutagens that produce base-pair substitution mutations. TA100 is a derivative of TA1535 and is responsive to base-hemical is tested, in triplicate, at 5 doses, along with positive and solvent controls in the absence of exogenous metabolic activation (NA), in the presence of rat liver S-9 (RLI), and hamster liver S-9 (HLI). The entire test series or only those testpair substitution mutagens and some classes of mutagens that produce frameshift mutations. Strains TA98 and TA1537 are both responsive to frameshift mutagens, but exhibit different sensitivities to different chemical classes.

B. DEFINITION OF TERMS AND ABBREVIATIONS USED ON DATA SHEETS

Solvent: Chemicals are dissolved in appropriate solvents and then added to the suspension culture; e.g., DMSO: dimethyl sulfoxide. O-Dose is the DMSO-solvent control

Dose: Dose is expressed in micrograms (μg)/plate.

Mutagenic Response: The chemicals are tested in triplicate (A, B, and C) for each dose. The numbers listed under each column indicate the number of revertant colonies/plate. Abbreviations following the numbers are as follows:

P - The chemical formed a precipitate at the concentration indicated.
S - The chemical at that concentration was slightly toxic.
T - The chemical was toxic.
C - The plate was contaminated.

C. RESULTS

Tests were done using the same lot of ethyl acrylate as was used in the two-year studies. See Tables G1-G8.

TABLE G1. RESULTS OF MUTAGENICITY TESTS OF ETHYL ACRYLATE IN *SALMONELLA TYPHIMURIUM* TA98 PERFORMED AT SRI INTERNATIONAL

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 *(c)*									
0.0 *(d)*	17	20	25	21 ± 2.3	0.0	20	21	16	19 ± 1.5
100.0	25	20	17	21 ± 2.3	100.0	9	18	18	15 ± 3.0
333.0	15	18	17	17 ± 0.9	333.0	13	12	18	14 ± 1.9
1,000.0	27	26	16	23 ± 3.5	1,000.0	14	14	17	15 ± 1.0
3,333.0	15	16	16	16 ± 0.3	3,333.0	14	15	20	16 ± 1.9
10,000.0	0T	5S	0T	5	1,000.0	0T	0T	0T	
B. Preincubation with Aroclor-1254® Induced Sprague-Dawley Rat Liver S-9 Preparation *(c)*									
0.0 *(d)*	36	36	32	35 ± 1.3	0.0 *(d)*	42	56	48	49 ± 4.1
100.0	27	25	28	27 ± .9	100.0	56	56	40	51 ± 5.3
333.0	36	30	20	29 ± 4.7	333.0	40	57	41	46 ± 5.5
1,000.0	24	25	17	22 ± 2.5	1,000.0	27	41	31	33 ± 4.2
3,333.0	31	36	27	31 ± 2.6	3,333.0	26	20	31	26 ± 3.2
10,000.0	1S	3S	9S	4 ± 2.4	10,000.0	0T	0T	0T	
C. Preincubation with Aroclor-1254® Induced Syrian Hamster Liver S-9 Preparation *(c)*									
0.0 *(d)*	43	39	31	38 ± 3.5	0.0 *(d)*	37	31	25	31 ± 3.5
100.0	39	39	27	35 ± 4.0	100.0	37	36	20	31 ± 5.5
333.0	27	32	19	26 ± 3.8	333.0	25	39	30	31 ± 4.1
1,000.0	26	26	27	26 ± 0.3	1,000.0	25	48	33	35 ± 6.7
3,333.0	41	38	28	36 ± 3.9	3,333.0	25	36	18	26 ± 5.2
10,000.0	2S	0T	0T	2	10,000.0	0T	31	0T	31

(a) Measured in triplicate
(b) Retest was 2 weeks after initial test
(c) T = chemical was toxic; S = chemical was slightly toxic
(d) Water solvent control

TABLE G2. RESULTS OF MUTAGENICITY TESTS OF ETHYL ACRYLATE IN *SALMONELLA TYPHIMURIUM* TA98 PERFORMED AT CASE WESTERN RESERVE UNIVERSITY

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)*	27	26	15	23 ± 3.8	0.0 *(c)*	23	29	30	27 ± 2.2
100.0	26	17	14	19 ± 3.6	33.0	28	29	28	28 ± 0.3
333.0	23	33	23	26 ± 3.3	100.0	23	31	33	29 ± 3.1
1,000.0	32	20	25	26 ± 3.5	333.0	32	22	32	29 ± 3.3
3,333.0	20	19	24	21 ± 1.5	1,000.0	24	31	27	27 ± 2.0
10,000.0	0	0	0	0 ± 0.0	3,333.0	25	34	30	30 ± 2.6
B. Preincubation with Aroclor-1254® Induced Sprague-Dawley Rat Liver S-9 Preparation									
0.0 *(c)*	34	18	35	29 ± 5.5	0.0 *(c)*	30	29	35	31 ± 1.9
100.0	40	25	32	32 ± 4.3	33.0	35	36	35	35 ± .3
333.0	39	27	36	34 ± 3.6	100.0	35	37	26	33 ± 3.4
1,000.0	27	21	38	29 ± 5.0	333.0	25	36	37	33 ± 3.8
3,333.0	36	38	33	36 ± 1.5	1,000.0	35	31	28	31 ± 2.0
10,000.0	0	0	0	0 ± 0.0	3,333.0	39	34	29	34 ± 2.9
C. Preincubation with Aroclor-1254® Induced Syrian Hamster Liver S-9 Preparation									
0.0 *(c)*	33	24	28	28 ± 2.6	0.0 *(c)*	28	36	28	31 ± 2.7
100.0	45	30	26	34 ± 5.8	33.0	30	28	40	33 ± 3.7
333.0	20	23	25	23 ± 1.5	100.0	37	26	34	32 ± 3.3
1,000.0	26	22	27	25 ± 1.5	333.0	25	36	30	30 ± 3.2
3,333.0	29	24	39	31 ± 4.4	1,000.0	25	35	28	29 ± 3.0
10,000.0	0	0	0	0 ± 0.0	3,333.0	34T	44	39	39 ± 2.9

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

TABLE G3. RESULTS OF MUTAGENICITY TESTS OF ETHYL ACRYLATE IN *SALMONELLA TYPHIMURIUM* TA100 PERFORMED AT SRI INTERNATIONAL

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 *(c)*									
0.0 *(d)*	130	172	161	154 ± 12.6	0.0 *(d)*	165	171	174	170 ± 2.6
100.0	127	104	141	124 ± 10.8	100.0	153	114	143	137 ± 11.7
333.0	135	100	123	119 ± 10.3	333.0	142	113	134	130 ± 8.6
1,000.0	115	135	148	133 ± 9.6	1,000.0	137	127	131	132 ± 2.9
3,333.0	80	116	108	101 ± 10.9	3,333.0	153	137	159	150 ± 6.6
10,000.0	0T	0T	0T		1,000.0	78S	0T	75S	76 ± 1.5
B. Preincubation with Aroclor-1254® Induced Sprague-Dawley Rat Liver S-9 Preparation *(c)*									
0.0 *(d)*	135	149	134	139 ± 4.8	0.0 *(d)*	131	149	131	137 ± 6.0
100.0	112	128	113	118 ± 5.2	100.0	103	135	110	116 ± 9.7
333.0	130	116	131	126 ± 4.8	333.0	112	130	134	125 ± 6.8
1,000.0	160	117	141	139 ± 12.4	1,000.0	115	122	112	116 ± 3.0
3,333.0	128	116	114	119 ± 4.4	3,333.0	124	149	101	125 ± 13.9
10,000.0	0T	0T	0T		10,000.0	0T	0T	0T	
C. Preincubation with Aroclor-1254® Induced Syrian Hamster Liver S-9 Preparation *(c)*									
0.0 *(d)*	134	173	173	160 ± 13.0	0.0 *(d)*	139	138	153	143 ± 4.8
100.0	125	160	125	137 ± 11.7	100.0	117	113	123	118 ± 2.9
333.0	137	113	129	126 ± 7.1	333.0	123	127	131	127 ± 2.3
1,000.0	152	126	128	135 ± 8.4	1,000.0	123	129	136	129 ± 3.8
3,333.0	151	137	109	132 ± 12.3	3,333.0	125	135	135	132 ± 3.3
10,000.0	20S	0T	0T	20	10,000.0	96	102	52	83 ± 15.8

(a) Measured in triplicate
(b) Retest was 2 weeks after initial test
(c) T = chemical was toxic; S = chemical was slightly toxic
(d) Water solvent control

TABLE G4. RESULTS OF MUTAGENICITY TESTS OF ETHYL ACRYLATE IN *SALMONELLA TYPHIMURIUM* TA100 PERFORMED AT CASE WESTERN RESERVE UNIVERSITY

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 *(c)*									
0.0 *(d)*	91	75	81	82 ± 4.7	0.0 *(d)*	89	89	86	88 ± 1.0
100.0	116	100	115	110 ± 5.2	33.0	100	107	101	103 ± 2.2
333.0	104	92	95	97 ± 3.6	100.0	92	116	105	104 ± 6.9
1,000.0	84	84	112	93 ± 9.3	333.0	125	101	102	109 ± 7.8
3,333.0	90	99	86	92 ± 3.8	1,000.0	51T	0	105	52 ± 52.5
10,000.0	0	0	0	0 ± 0.0	3,333.0	0T	0	0T	0
B. Preincubation with Aroclor-1254® Induced Sprague-Dawley Rat Liver S-9 Preparation *(c)*									
0.0 *(d)*	85	107	84	92 ± 7.5	0.0 *(d)*	143	118	119	127 ± 8.2
100.0	143	172	171	162 ± 9.5	33.0	182	180	190	184 ± 3.1
333.0	143	129	130	134 ± 4.5	100.0	212	191	200	201 ± 6.1
1,000.0	129	176	92	132 ± 24.3	333.0	213	213	190	205 ± 7.7
3,333.0	143	133	86	121 ± 17.6	1,000.0	135	122	111	123 ± 6.9
10,000.0	0	0	0	0 ± 0.0	3,333.0	98T	97T	112	112
C. Preincubation with Aroclor-1254® Induced Syrian Hamster Liver S-9 Preparation *(c)*									
0.0 *(d)*	77	83	76	79 ± 2.2	0.0 *(d)*	132	134	131	132 ± 0.9
100.0	132	143	160	145 ± 8.1	33.0	184	203	183	190 ± 6.5
333.0	119	106	131	119 ± 7.2	100.0	219	199	207	208 ± 5.8
1,000.0	123	99	94	105 ± 9.0	333.0	215	198	160	191 ± 16.3
3,333.0	153	142	133	143 ± 5.8	1,000.0	178	185	171	178 ± 4.0
10,000.0	0	0	0	0 ± 0.0	3,333.0	117	102	100	106 ± 5.4

(a) Measured in triplicate
(b) Retest was 2 weeks after initial test
(c) T = chemical was toxic; S = chemical was slightly toxic
(d) Water solvent control

TABLE G5. RESULTS OF MUTAGENICITY TESTS OF ETHYL ACRYLATE IN *SALMONELLA TYPHIMURIUM* TA 1535 PERFORMED AT SRI INTERNATIONAL

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 *(c)*									
0.0 *(d)*	27	38	37	34 ± 3.5	0.0 *(d)*	13	31	33	26 ± 6.4
100.0	16	19	21	19 ± 1.5	100.0	28	35	32	32 ± 2.0
333.0	9	17	17	14 ± 2.7	333.0	32	49	37	39 ± 5.0
1,000.0	7	24	19	17 ± 5.0	1,000.0	24	42	29	32 ± 5.4
3,333.0	19	20	14	18 ± 1.9	3,333.0	28	39	31	33 ± 3.3
10,000.0	0T	1S	0T	1	10,000.0	0T	0	0T	0
B. Preincubation with Aroclor-1254® Induced Sprague-Dawley Rat Liver S-9 Preparation *(c)*									
0.0 *(d)*	17	8	7	11 ± 3.2	0.0 *(d)*	24	14	15	18 ± 3.2
100.0	4	6	7	6 ± .9	100.0	16	4	9	10 ± 3.5
333.0	6	8	3	6 ± 1.5	333.0	15	13	14	14 ± 0.6
1,000.0	8	5	8	7 ± 1.0	1,000.0	14	14	20	16 ± 2.0
3,333.0	12	4	9	8 ± 2.3	3,333.0	9	25	14	16 ± 4.7
10,000.0	1S	0T	0T	1	10,000.0	0T	7S	0T	7
C. Preincubation with Aroclor-1254® Induced Syrian Hamster Liver S-9 Preparation *(c)*									
0.0 *(d)*	7	12	14	11 ± 2.1	0.0 *(d)*	5	12	12	10 ± 2.3
100.0	7	8	4	6 ± 1.2	100.0	14	14	14	14 ± 0.0
333.0	5	4	8	6 ± 1.2	333.0	7	8	14	10 ± 2.2
1,000.0	4	6	6	5 ± 0.7	1,000.0	7	5	16	9 ± 3.4
3,333.0	8	9	4	7 ± 1.5	3,333.0	5	5	5	5 ± 0.0
10,000.0	0T	0T	0T		10,000.0	0T	0T	0T	

(a) Measured in triplicate
(b) Retest was 2 weeks after initial test
(c) T = chemical was toxic; S = chemical was slightly toxic
(d) Water solvent control

TABLE G6. RESULTS OF MUTAGENICITY TESTS OF ETHYL ACRYLATE IN *SALMONELLA TYPHIMURIUM* TA1535 PERFORMED AT CASE WESTERN RESERVE UNIVERSITY

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)*	4	2	6	4 ± 1.2	0.0 *(c)*	7	9	10	9 ± 0.9
100.0	2	4	5	4 ± 0.9	33.0	5	8	6	6 ± 0.9
333.0	12	6	6	8 ± 2.0	100.0	7	11	5	8 ± 1.8
1,000.0	7	6	7	7 ± 0.6	333.0	7	9	7	8 ± 0.7
3,333.0	8	4	5	6 ± 1.2	,000.0	10	6	8	8 ± 0.2
10,000.0	3	5	4	4 ± 0.6	3,333.0	0	0	0	0 ± 0.0
B. Preincubation with Aroclor-1254® Induced Sprague-Dawley Rat Liver S-9 Preparation									
0.0 *(c)*	4	7	9	7 ± 1.5	0.0 *(c)*	6	8	14	9 ± 2.4
100.0	3	5	8	5 ± 1.5	33.0	9	8	15	11 ± 2.2
333.0	9	8	9	9 ± 0.3	100.0	9	11	6	9 ± 1.5
1,000.0	13	12	5	10 ± 2.5	333.0	13	13	9	12 ± 1.3
3,333.0	8	6	9	8 ± 0.9	1,000.0	18	12	17	16 ± 1.9
10,000.0	2	0	0	1 ± 0.7	3,333.0	0	2	1	1 ± 0.6
C. Preincubation with Aroclor-1254® Induced Syrian Hamster Liver S-9 Preparation									
0.0 *(c)*	7	12	14	11 ± 2.1	0.0 *(c)*	3	7	12	7 ± 2.6
100.0	7	8	4	6 ± 1.2	33.0	21	13	11	15 ± 3.1
333.0	5	4	8	6 ± 1.2	100.0	14	7	10	10 ± 2.0
1,000.0	4	6	6	5 ± 0.7	333.0	8	8	8	8 ± 0.0
3,333.0	8	9	4	7 ± 1.5	1,000.0	8	6	27	14 ± 6.7
10,000.0	0T	0T	0T		3,333.0	0	3	0	1 ± 1.0

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

TABLE G7. RESULTS OF MUTAGENICITY TESTS OF ETHYL ACRYLATE IN *SALMONELLA TYPHIMURIUM* TA1537 PERFORMED AT SRI INTERNATIONAL

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 *(c)*									
0.0 *(d)*	12	8	7	9 ± 1.5	0.0 *(d)*	3	5	7	5 ± 1.2
100.0	6	7	4	6 ± 0.9	100.0	12	6	6	8 ± 2.0
333.0	7	7	5	6 ± 0.7	333.0	7	13	8	7 ± 1.9
1,000.0	4	5	2	4 ± 0.9	1,000.0	8	4	8	7 ± 1.3
3,333.0	3	4	2	3 ± 0.6	3,333.0	8	8	8	8 ± 0.0
10,000.0	1S	0T	0T	1	10,000.0	13S	4S	0T	8 ± 4.5
B. Preincubation with Aroclor-1254® Induced Sprague-Dawley Rat Liver S-9 Preparation *(c)*									
0.0 *(d)*	12	9	7	9 ± 1.5	0.0 *(d)*	18	12	13	14 ± 1.9
100.0	15	8	12	12 ± 2.0	100.0	17	12	6	12 ± 3.2
333.0	8	6	9	8 ± 0.9	333.0	13	7	15	12 ± 2.4
1,000.0	5	7	12	8 ± 2.1	1,000.0	9	9	7	11 ± 2.1
3,333.0	8	6	8	7 ± 0.7	3,333.0	14	12	7	11 ± 2.1
10,000.0	0T	0T	0T	1	10,000.0	4S	0T	9	6 ± 2.6
C. Preincubation with Aroclor-1254® Induced Syrian Hamster Liver S-9 Preparation *(c)*									
0.0 *(d)*	7	9	8	8 ± 0.6	0.0 *(d)*	6	3	4	4 ± 0.9
100.0	12	7	7	9 ± 1.7	100.0	15	7	9	10 ± 2.4
333.0	13	8	5	9 ± 2.3	333.0	6	8	8	7 ± 0.7
1,000.0	14	7	7	9 ± 2.3	1,000.0	9	7	17	11 ± 3.1
3,333.0	8	12	4	8 ± 2.3	3,333.0	6	3	4	4 ± 0.9
10,000.0	0T	3S	0T	3	10,000.0	5S	0T	2S	3 ± 1.5

(a) Measured in triplicate
(b) Retest was 2 weeks after initial test
(c) T = chemical was toxic; S = chemical was slightly toxic
(d) Water solvent control

TABLE G8. RESULTS OF MUTAGENICITY TESTS OF ETHYL ACRYLATE IN *SALMONELLA TYPHIMURIUM* TA1537 PERFORMED AT CASE WESTERN RESERVE UNIVERSITY

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)*	6	12	7	8 ± 1.9	0.0 *(c)*	10	8	13	10 ± 1.5
100.0	2	14	13	10 ± 3.8	33.0	6	6	5	6 ± 0.3
333.0	9	6	4	6 ± 1.5	100.0	6	7	8	7 ± 0.6
1,000.0	10	8	5	8 ± 1.5	333.0	5	7	9	7 ± 1.2
3,333.0	5	4	3	4 ± 0.6	1,000.0	10	14	10	11 ± 1.3
10,000.0	0	0	0		3,333.0	0	0	0	0 ± 0.0
B. Preincubation with Aroclor-1254® Induced Sprague-Dawley Rat Liver S-9 Preparation									
0.0 *(c)*	4	3	6	5 ± 0.9	0.0 *(c)*	7	3	12	7 ± 2.6
100.0	8	6	12	9 ± 1.8	33.0	11	12	10	11 ± 0.6
333.0	11	10	9	10 ± 0.6	100.0	4	6	8	6 ± 1.2
1,000.0	12	12	10	11 ± 0.7	333.0	10	9	5	8 ± 1.5
3,333.0	14	10	10	11 ± 1.7	1,000.0	12	16	10	13 ± 1.8
10,000.0	0	0	0		3,333.0	0	2	1	1 ± 0.6
C. Preincubation with Aroclor-1254® Induced Syrian Hamster Liver S-9 Preparation									
0.0 *(c)*	11	17	12	13 ± 1.9	0.0 *(c)*	10	15	10	12 ± 1.7
100.0	12	12	9	11 ± 1.0	33.0	11	10	9	10 ± 0.6
333.0	9	13	5	9 ± 2.3	100.0	6	3	8	6 ± 1.5
1,000.0	9	10	13	11 ± 1.2	333.0	10	14	8	11 ± 1.8
3,333.0	0	12	12	8 ± 4.0	1,000.0	12	10	9	10 ± 0.9
10,000.0	0	0	0		3,333.0	0	0	0	

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

APPENDIX H

SENTINEL ANIMAL SEROLOGY DATA FOR THE ETHYL ACRYLATE BIOASSAY

APPENDIX H

A. METHODS

Rodents used in the Bioassay Program of the National Toxicology Program are produced in optimally clean facilities to eliminate potential pathogens that may affect test results. The Sentinel Animal Program is part of the monitoring of animal health that occurs during the toxicologic evaluation of chemical compounds. Under this program the disease state of the rodents in the Bioassay Program is monitored via viral serology on serum from extra (sentinel) animals in the test rooms. These animals are untreated, and both these animals and the test animals are subject to the identical environmental conditions. The sentinel animals come from the same production source and weanling groups as the animals used for the bioassays of chemical compounds.

Fifteen $B6C3F_1$ mice of both sexes and 15 F344/N rats of both sexes are selected at the time of randomization and allocation of the animals to the various study groups. Five animals of each designated sentinel group are killed at 6, 12, and 18 months on study. Data from animals surviving 24 months are collected from 5/50 randomly selected control animals of each sex and species. The blood from each animal is collected, allowed to clot, and the serum is harvested. The serum is cooled on ice and shipped to Microbiological Associates' Comprehensive Animal Diagnostic Service for determination of the viral titers. The following tests are performed:

	Hemagglutination Inhibition	Complement Fixation	Elisa*
Mice	PVM (Pneumonia virus of mice) Reo 3 (Reovirus 3) GDVII (Theiler's encephalomyelitis virus) Poly (Polyoma virus) Sendai (Sendai virus)** MVM (Minute virus of mice) Ectro (Ectromelia virus)	M. Ad. (Mouse adenovirus) LCM (Lymphocytic choriomeningitis virus) Sendai (Sendai virus)**	MHV (Mouse hepatitis virus)
Rats	PVM (Pneumonia virus of mice) Sendai (Sendai virus)** KRV (Kilham rat virus) H-1 (Toolan's H-1 virus)	RCV (Rat corona virus) Sendai (Sendai virus)**	

* Elisa = Enzyme-linked immunosorbent assay

** Sendai virus is determined either by hemagglutination or by a complement fixation.

B. RESULTS

See Table H1 and H2.

TABLE H1. MURINE VIRUS ANTIBODY DETERMINATIONS FOR RATS IN THE TWO-YEAR STUDY

Sample No.	Sex	Hemagglutination Inhibition				Complement Fixation	
		PVM	KRV	H-1	Sendai	RCV	Sendai
SIX MONTHS							
1	M	--	--	--		--	80
2	M	--	--	--		--	20
3	M	--	--	--		*(a)*	*(a)*
4	M	--	--	--		--	80
5	M	--	--	--		--	80
6	F	--	--	--		--	80
7	F	--	--	--		--	80
8	F	--	--	--		--	80
9	F	--	--	--		--	80
10	F	--	--	--		--	80
TWELVE MONTHS							
10	M	--	--	--		--	20
11	M	--	--	--		--	80
12	M	--	--	--		--	40
13	M	--	--	--		--	40
14	M	--	--	--		--	40
15	F	--	--	--		--	80
16	F	--	--	--		--	80
17	F	--	--	--		--	80
18	F	--	--	--		--	40
19	F	--	--	--		--	40
EIGHTEEN MONTHS							
1	M	--	--	--		--	40
2	M	--	--	--		--	80
3	M	--	--	--		--	40
4	M	--	--	--		--	80
5	F	--	--	--		--	160
6	F	--	--	--		--	160
7	F	--	--	--		--	80
8	F	--	--	--		--	40
9	F	--	--	--		--	320
TWENTY-FOUR MONTHS							
1	M	--	--	--	--	--	
2	M	--	--	--	10	--	
3	M	--	--	--	--	--	
4	M	--	--	--	10	--	
5	M	--	--	--	--	--	
6	F	--	--	--	40	--	
7	F	--	--	--	80	--	
8	F	--	--	--	20	--	
9	F	--	--	--	20	--	
10	F	--	--	--	80	--	
Significant Titer		20	20	20	10	10	10

(a) Anticomplimentary serum

TABLE H2. MURINE VIRUS ANTIBODY DETERMINATIONS FOR MICE IN THE TWO-YEAR STUDY

Sample Number	Sex	Hemagglutination Inhibition							Complement Fixation			
		PVM	Reo 3	GDVII	Poly	MVM	Ectro	Sendai	Sendai	M. Ad	MHV	LCM
SIX MONTHS												
12	M	--	--	--	--	--	--		(b)	--	--	--
13	M	--	--	--	--	--	--		20	--	--	(b)
14	M	--	--	--	--	--	(a)		(c)	--	(c)	(b)
15	M	--	--	--	--	--	--		40	--	--	(c)
17	F	--	--	--	--	--	--		40	--	--	(b)
18	F	--	--	--	--	--	--		20	--	--	(b)
19	F	--	--	--	--	--	--		40	--	--	(b)
TWELVE MONTHS												
1	M	--	--	--	--	--	--		10	--	--	--
2	M	--	--	--	--	--	--		40	--	--	--
3	M	--	--	--	--	--	--		--	--	--	--
4	M	--	--	--	--	--	--		20	--	--	--
5	F	--	--	--	--	--	--		40	--	--	--
6	F	--	--	--	--	--	--		20	--	--	--
7	F	--	--	--	--	--	--		80	--	--	--
8	F	--	(a)	(a)	--	--	--		40	--	--	--
9	F	--	--	--	--	--	--		80	--	--	--
EIGHTEEN MONTHS												
10	F	--	--	--	--	--	--		20	--	--	(d)
11	F	--	--	--	--	--	--		40	--	--	--
12	F	--	--	--	--	--	--		40	--	--	--
13	F	--	--	--	--	--	--		20	(c)	--	(c)
14	F	--	--	--	--	--	--		20	--	--	--
TWENTY-FOUR MONTHS												
1	M	--	--	--	--	--	--	--		--	--	(c)
2	M	--	--	--	--	--	--	--		--	--	--
3	M	--	--	--	--	--	--	--		--	--	--
4	M	--	--	--	--	--	--	10		--	--	--
5	M	--	--	--	--	--	--	--		--	--	--
6	F	--	--	--	--	--	--	--		(c)	(c)	(c)
7	F	--	--	--	(a)	--	--	(a)		--	(c)	(c)
8	F	--	--	--	(a)	--	--	--		--	--	--
9	F	--	--	--	--	--	--	(a)		--	--	--
10	F	--	--	(a)	(a)	--	--	--		--	--	--
Significant Titer		20	20	20	20	20	20		10	10	10	10

(a) Serum agglutinates red blood cells
(b) Serum reacts with control antigen
(c) Anticomplimentary serum
(d) Tested by the indirect fluorescent antibody method for LCM - Negative

APPENDIX I
ANALYSIS OF ETHYL ACRYLATE

APPENDIX I

A. ELEMENTAL ANALYSIS

Element	C	H	O
Theory	59.98	8.05	31.96
Determined			
Lot No. 37201	59.98	7.88	
	59.82	7.90	
Lot No. 343029			
	60.00	8.08	31.81
	59.85	8.23	31.62

B. WATER ANALYSIS (Karl Fischer)

Lot No. 37201	0.040 ± 0.009 (δ)%
Lot No. 343029	0.077 ± 0.005 (δ)%

C. BOILING POINT

Determined	Literature Value
Lot No. 37201	
95°C at 746.3 mm (visual, micro boiling point) 95-99°C at 746 mm (Dupont 900 DTA)	100°C at 760 mm (Arens et al., 1962)

D. INDEX OF REFRACTION

Determined	Literature Value
Lot No. 37201	
n_D^{12} : 1.4063 ± 0.003 (δ)	$n_D^{19.4}$: 1.4059 (Rappoport, 1967)

E. DENSITY

Determined	Literature Value
Lot No. 37201	
d_4^{21} : 0.9157 at 21°C	d_4^{15} : 0.9136 (Rappoport, 1967)

F. VAPOR-PHASE CHROMATOGRAPHY

Lot No. 37201

Instrument: Bendix 2500
Detector: Flame ionization

1. System 1

   Column: 10% Carbowax 20M-TPA, 1.8 m x 4 mm I.D.
   Oven Temperature Program: 60°C to 100°C at 10°C/min, with 5 min initial hold
   Results: Major peak and one impurity before the major peak

APPENDIX I

Peak	Retention Time (min)	Retention Time (Relative to Ethyl Acrylate)	Area (Percent Relative to Ethyl Acrylate)
1	2.4	0.86	0.82
2	2.8	1.00	100

2. System 2

Column: Chromosorb 102, 1.8 m x 4 mm I.D.
Oven Temperature Program: 2 min at 75°C, then 75° to 200°C at 10°C/min
Results: Major peak and no impurities with areas 0.1% or greater

Peak	Retention Time (min)	Retention Time (Relative to Ethyl Acrylate)	Area (Percent Relative to Ethyl Acrylate)
1	21.5	1.00	100

Lot No. 343029

Instrument: VA3700
Detector: Flame ionization
Inlet Temperature: 180°C
Detector Temperature: 250°C
Carrier Gas: Nitrogen

1. System 1

Column: 10% Carbowax 20M-TPA on 80/100 Chromosorb W (AW); 1.8 m x 4 mm I.D., glass
Carrier Flow Rate: 70 cc/min
Oven Temperature Program: 50°C for 5 min, then 50° to 200°C at 5°C/min
Samples Injected: Neat liquid (4μl) and solutions of 1.0% and 0.5% ethyl acrylate in o-dichlorobenzene to quantitate the major peak and check for detector overload.
Results: Major peak and four impurities.

Peak	Retention Time (min)	Retention Time (Relative to Ethyl Acrylate)	Area (Percent Relative to Major Peak Area)
1	2.2	0.50	0.14
2	3.6	0.82	0.08
3	4.4	1.00	100
4	9.4	2.14	0.02
5	10.8	2.45	0.02

2. System 2

Column: 80/100 Carbopack C/0.1% SP1000; 1.8 m x 4 mm I.D., glass
Carrier Flow Rate: 70 cc/min
Oven Temperature Program: 50°C for 5 min, then 50° to 200°C at 10°C/min
Samples Injected: Neat liquid (3 μl) and solutions of 1.0% and 0.5% (v/v) ethyl acrylate in methylene chloride to quantitate the major peak and check for detector overload.
Results: Major peak and four impurities.

Peak	Retention Time (min)	Retention Time (Relative to Ethyl Acrylate)	Area (Percent Relative to Major Peak Area)
1	7.8	0.58	0.12
2	12.2	0.91	0.06
3	13.4	1.00	100
4 (shoulder)	13.7	1.02	0.01
5	19.7	1.47	0.02

G. SPECTRAL DATA

(1) Infrared

Spectra consistent with literature spectrum (Sadtler Standard Spectra)

Lot No. 37201

Instrument: Beckman IR-12
Cell: Neat, sodium chloride plates
Results: See Figure 5

Lot No. 343029

Instrument: Beckman IR-12
Cell: Thin film between silver chloride plates
Results: See Figure 6

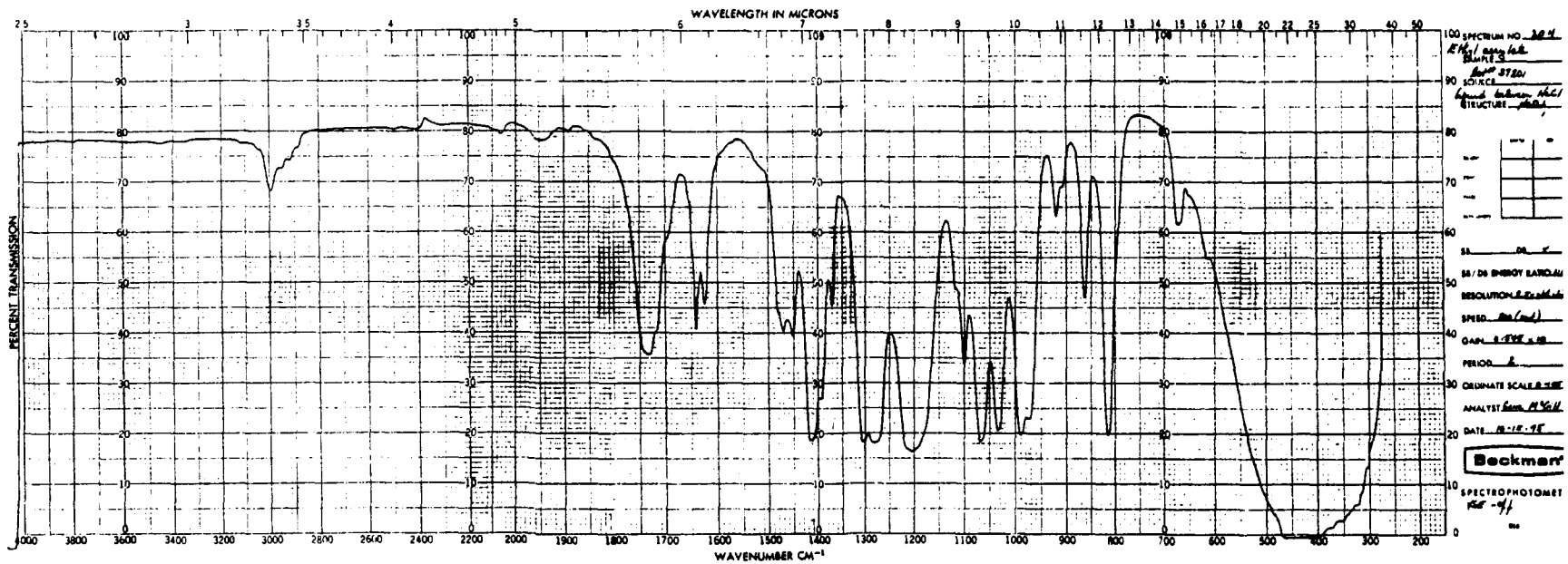


Figure 5. Infrared Absorption Spectrum of Ethyl Acrylate (Lot No. 37201)

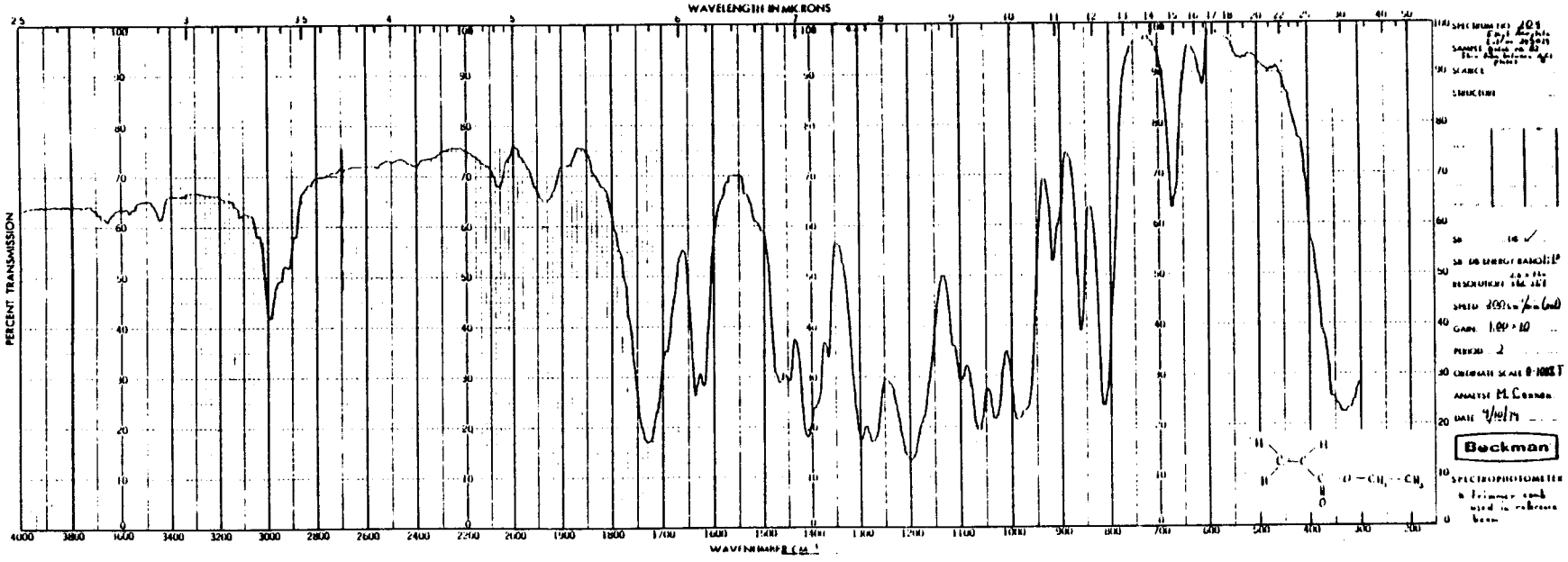


Figure 6. Infrared Absorption Spectrum of Ethyl Acrylate (Lot No. 343029)

(2) Ultraviolet/Visible — No literature values found

Lot No. 37201

Instrument: Cary 118
No absorbance between 350 and 800 nm (visible range).
No maximum between 207 and 350 nm (ultraviolet range), but a gradual increase in absorbance toward the short wavelength end of the spectrum.
Concentration: 1 mg/ml
Solvent: 95% Ethanol

Lot No. 343029

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

λ max(nm)	ϵ
242 (shoulder on absorbance rise to solvent cutoff)	92 ± 2 (δ)

Solvent: Methanol

(3) Nuclear Magnetic Resonance — Identical to literature spectrum (Arata et al., 1962 and Sadtler Standard Spectra)

Lot No. 37201

Instrument: Varian HA-100
Solvent: $CDCl_3$ with internal tetramethylsilane

Assignments (see Figure 7):

(a) t, δ 2.27 ppm
(b) q, δ 4.22 ppm
(c) d^2, δ 5.82 ppm
(d) d^2, δ 6.14 ppm
(e) d^2, δ 6.46 ppm

cde (AMX pattern):

J^{ce} = 3 cps
J^{de} = 17 cps
J^{cd} = 10 cps

Integration Ratios:

(a) 3.08
(b) 2.10
(c) 0.93
(d) 0.99
(e) 0.89

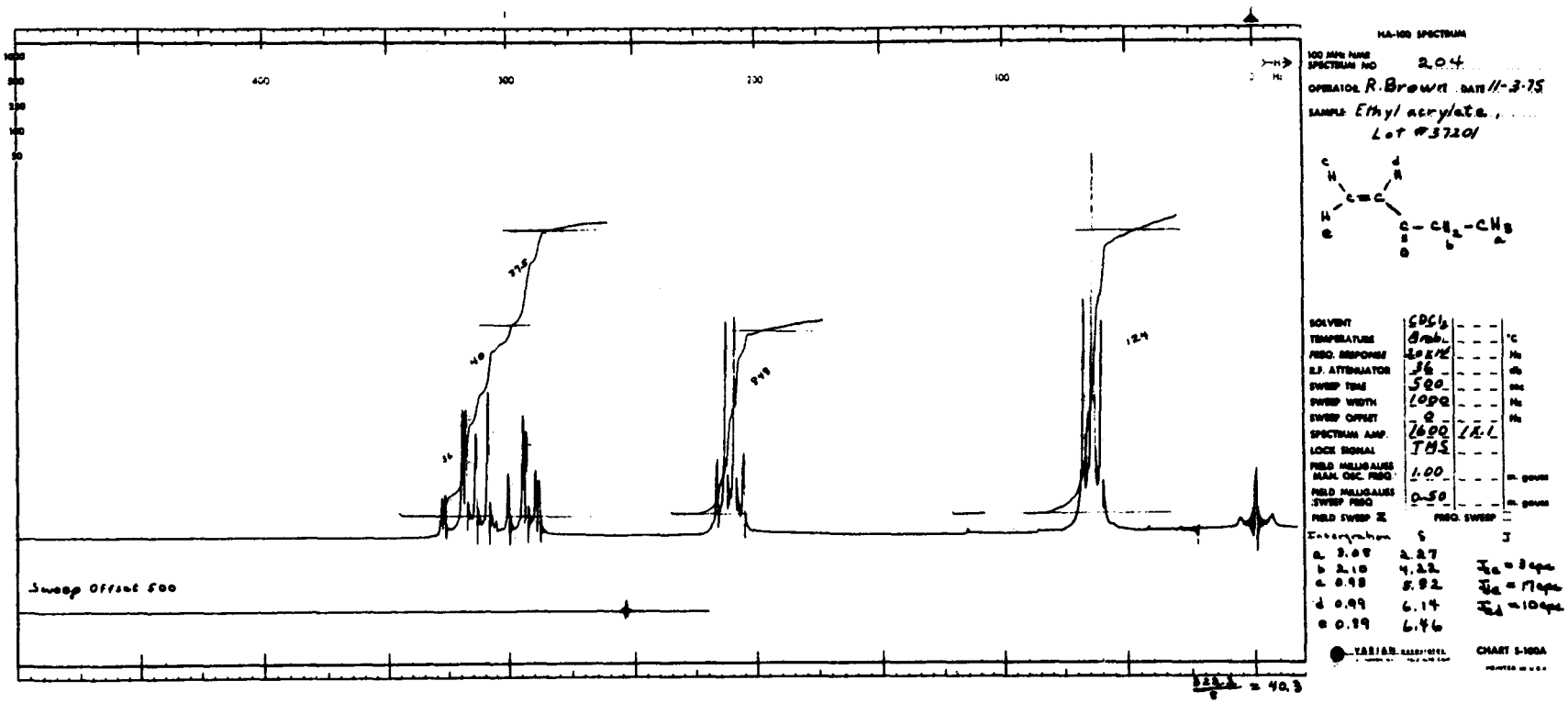


Figure 7. Nuclear Magnetic Resonance Spectrum of Ethyl Acrylate (Lot No. 37201)

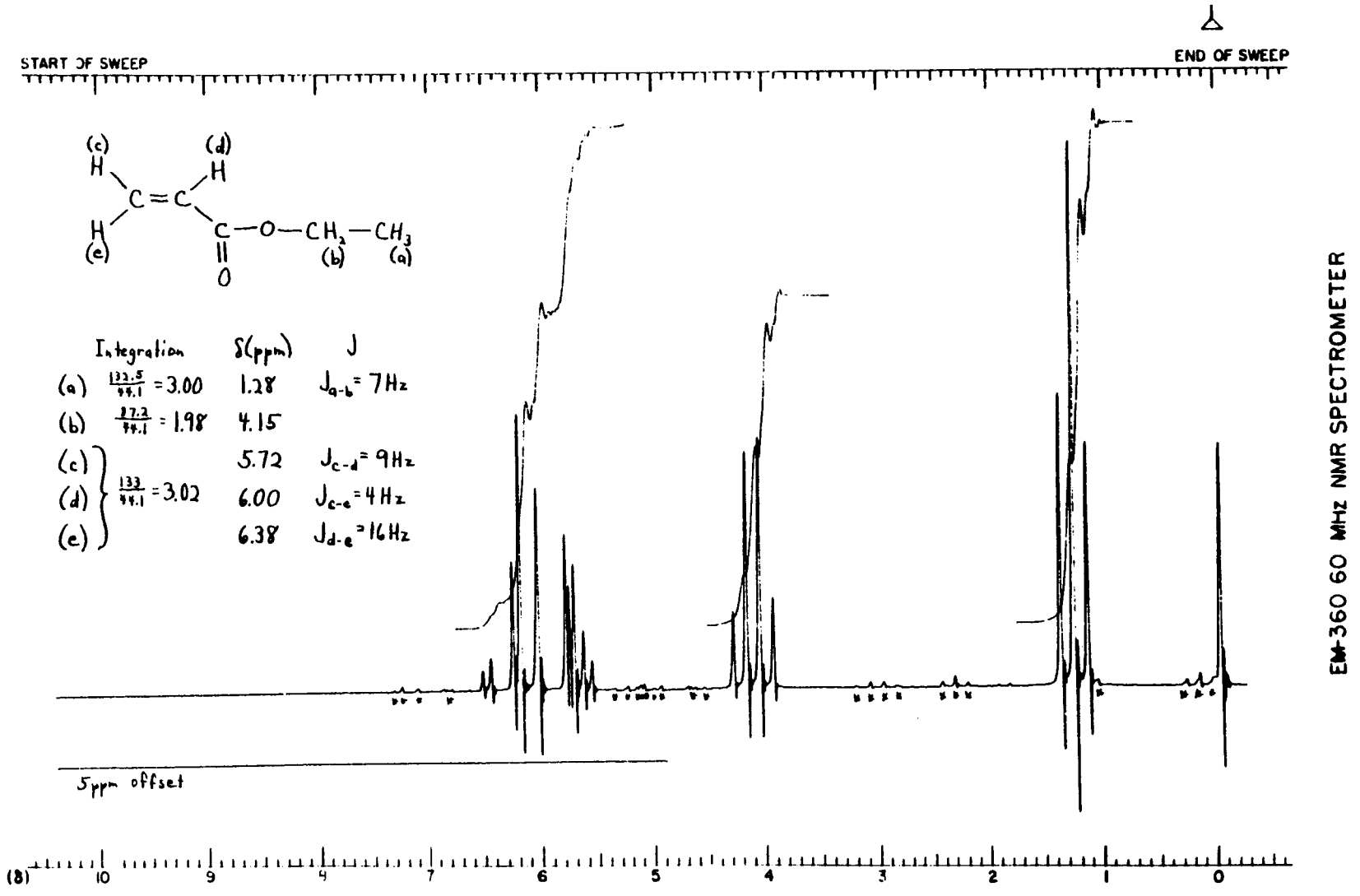


Figure 8. Nuclear Magnetic Resonance Spectrum of Ethyl Acrylate (Lot No. 343029)

APPENDIX I

Lot No. 343029

Instrument: Varian EM-360A
Solvent: Carbon tetrachloride with internal tetramethylsilane

Assignments (see Figure 8):
(a) t, δ 1.28 ppm, J_{a-b} = 7 Hz
(b) q, δ 4.15 ppm
(c) d of d, δ 5.72 ppm, J_{c-d} = 9 Hz, J_{c-e} ◻ 4 Hz
(d) d of d, δ 6.00 ppm, J_{d-e} = 16 Hz
(e) d of d, δ 6.38 ppm

Integration Ratios:
(a) 3.00
(b) 1.98
(c)
(d) } 3.02
(e)

Spectrum consistent with literature reference. (Arata et al., 1962 and Sadtler Standard Spectra)

APPENDIX J

ANALYSIS OF ETHYL ACRYLATE IN WATER FOR STABILITY OF ETHYL ACRYLATE

APPENDIX J

A. AQUEOUS SOLUTION FOR GAVAGE

1. Mixing and Storage: A 1% (v/v) solution of ethyl acrylate in water was prepared. The solution was stored for 24 hours at room temperature, and aliquots were removed for assay at various intermediate time intervals.

2. Analysis and Results: Analysis was by the vapor-phase chromatographic system described below. The aqueous solution aliquots from the storage sample were extracted with chloroform (1:1, single extraction). The chloroform extracts were injected into the VPC instrument.

Instrument: Tracor MT-220
Column: 3% OV-1 on 80/100 Supelcoport, 1.8 m x 4 mm, glass
Detection: Flame ionization
Temperatures: Inlet, 231°C; oven, 40°C, isothermal; detector, 285°C
Retention Time: 2.25 min

Time (hours)	Compound Recovered	Average Percent Compound Recovered
0.0	100.45	
0.067	99.78	99.64 ± 0.89
0.117	98.68	
4.433	96.7	
4.500	95.7	97.3 ± 2.5
4.567	95.8	
4.633	100.9	
5.667	99.1	
5.733	103.7	100.8 ± 2.0
5.800	100.3	
5.867	100.00	
22.000	99.4	
22.067	104.0	100.6 ± 2.7
22.133	101.1	
22.200	97.8	
24.833	100.2	
24.150	100.0	101.2 ± 2.2
24.217	104.5	
24.283	100.0	

There is no significant difference between the analyses at various times over the 24-hour stability test period.

B. CONCLUSION

Ethyl acrylate is stable in water solution over a period of 24 hours at room temperature.

APPENDIX K

ANALYSIS OF ETHYL ACRYLATE IN CORN OIL FOR STABILITY OF ETHYL ACRYLATE MIDWEST RESEARCH INSTITUTE

APPENDIX K

A. SAMPLE PREPARATION: A 1% (w/v) sample solution of ethyl acrylate in corn oil was prepared for each day of the study as follows: 10 ml of corn oil was transferred into a 50 ml Hypo-vial, the vial was sealed, and then approximately 95 mg of ethyl acrylate (exactly measured for each sample) was added via a 100 µl syringe. The samples were shaken and stored at room temperature from 1 to 8 days.

B. EXTRACTION AND ANALYSIS: Each sample was extracted with 20 ml of methanol, which was injected into the sample vial via a 10 ml syringe. Samples for analysis were withdrawn directly from the top (methanol) layer in the vial and analyzed by vapor-phase chromatography, using the following system:

Instrument: Bendix 2500 with Hewlett-Packard 3380A Automatic Integrator
Column: Chromosorb 102, 100/120 mesh, glass, 1.8 m x 4 mm I.D.
Detection: Flame ionization
Oven temperature: 190°C, isothermal
Detector temperature: 219°C
Inlet temperature: 181°C
Retention time of compound: 10.1 min

End of Day	Average Percent in Chemical/Vehicle Mixture *(a)*
1	0.96 ± 0.05
2	0.98 ± 0.05
4	0.97 ± 0.05
7	1.02 ± 0.05
8	1.00 ± 0.05

(a) Corrected for an average spiked recovery yield of 79.4%. Theoretical percent in chemical/vehicle mixture, 0.962.

C. CONCLUSION: Ethyl acrylate mixed with corn oil is stable for 8 days at room temperature.

APPENDIX L

ANALYSIS OF ETHYL ACRYLATE IN CORN OIL FOR CONCENTRATIONS OF ETHYL ACRYLATE

APPENDIX L

Samples were received as corn oil mixtures. The samples were extracted with methanol and analyzed by vapor phase chromatography. Chromatographic conditions were as follows:

Column: 3% OV-1 on 80/100 Supelcoport,
1.8 m x 4 mm, glass
Detection: Flame ionization
Temperature : Inlet, 170°C; oven, ambient air; detector, 270°C
Retention time: 2.3 min
Injection size: 1 µl

The gavage samples were compared to reference standards of ethyl acrylate prepared volume/volume in corn oil and then extracted with methanol in the same manner as the samples. No recovery correction was applied to the samples, since samples and reference standards were treated in the same manner.

TABLE L1. ANALYSIS OF ETHYL ACRYLATE IN CORN OIL

Date Mixed	Week Used	Concentration (a) of Ethyl Acrylate in Corn Oil for Target Concentration 1%	2%	4%
2/16/79	2/19/79		1.76	
3/19/79	3/26/79			3.80
4/13/79	4/23/79		1.98	
5/11/79	5/21/79			4.00
6/08/79	6/18/79		1.84	
			(1.99, b)	
7/06/79	7/16/79			4.18
8/03/79	8/10/79		1.86	
8/31/79	9/1/79			3.77
9/28/79	10/05/79		1.98	
10/26/79	11/02/79			4.27
11/30/79	12/07/79		2.10	
12/21/79	12/22/79			3.86
				(3.87, b)
1/18/80	1/28/80		2.09	3.93
2/15/80	2/16/80	0.989	1.90	
3/07/80	3/08/80		1.94	3.72
4/11/80	4/12/80	1.04	1.92	
5/09/80	5/10/80		2.01	3.92
5/11/80	5/12/80			4.18
6/06/80	6/07/80	0.971	2.00	
		(1.05, b)		
7/04/80	7/05/80		2.00	3.86
8/01/80	8/02/80	0.958	1.94	
8/29/80	8/30/80		1.93	3.65
9/26/80	9/27/80	0.989	1.80	
10/24/80	10/25/80		2.02	3.88
11/21/80	11/27/80	0.92	1.94	
12/19/80	12/20/80		2.01	4.07
				(3.99, b)
1/16/81	1/17/81	0.902	2.00	
1/21/81	1/22/81		2.04	
Mean (%)		0.967	1.96	3.94
Standard deviation		0.046	0.088	0.184
Coefficient of variation (%)		4.78	4.49	4.67
Range (%)		0.902 - 1.04	1.76 - 2.10	3.65 - 4.27

(a) The data presented are the average of the results of duplicate analyses.
(b) Midwest referee analysis

APPENDIX M

METABOLISM OF ETHYL ACRYLATE IN THE STOMACHS OF MALE AND FEMALE F344 RATS

RTI/2227/00-02P Date: December 1982

Project Report No. 2

Metabolism of Ethyl Acrylate in the Stomachs of Male and Female Fischer 344 Rats

Dates of Study: November - December 1982

Contract No. N01-ES-1-5007

Pharmacokinetics of Xenobiotics

Submitted to:

National Institute of Environmental Health Sciences
P. O. Box 12874
Research Triangle Park, N.C. 27709

Prepared by:

A. Robert Jeffcoat, Ph.D.
Assistant Director for Bioorganic Chemistry
Chemistry and Life Sciences Group

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List of Tables and Figures

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1.0 Abstract

Ethyl acrylate (EtOAcry) was metabolized in vitro by blood, forestomach tissue, glandular stomach tissue and stomach contents from both male and female Fischer 344 rats. The metabolism fitted first order kinetics with respect to EtOAcry in all cases although the metabolism of EtOAcry by blood appears to be more complex. Average half lives were 14 and 12 min (male, female) in blood, 76 and 96 min in forestomach tissue, 67 and 66 min in glandular stomach tissue, and 53 and 73 min in stomach contents. Differences between males and females were not significant (t test, $\alpha = 0.05$).

Concentrations of non-protein thiols in the forestomach and glandular stomach were substantially reduced 30 and 120 min after a single oral doses of either 100 mg/kg or 200 mg/kg of EtOAcry in corn oil. In the forestomach, non-protein thiol concentrations after a 100 mg/kg dose were about 30% of the concentration in control animals at 30 min while at 120 min and at both 30 and 120 min after the 200 mg/kg dose concentrations were 13-17% of the control values. Concentrations of non-protein thiols in the glandular stomach were 48-56% and 33-41% of controls following the 100 mg/kg and 200 mg/kg doses, respectively. Thirty minutes after the 100 mg/kg dose of EtOAcry, 29-30 percent of the dose remained in the stomach as parent compound, 16-20 percent at 120 min. Corresponding values after the 200 mg/kg dose were 38-40 percent at 30 min and 25-34 percent at 120 min. No differences were observed between males and females with respect to decrease in non-protein thiols or to the disappearance of EtOAcry from the stomach.

Ethyl acrylate was found in blood from the portal vein at concentrations up to 27 μg/mL in all animals dosed with 200 mg/kg of EtOAcry, but not in intraoccular blood (limit of detection was 1 μg/mL). Samples were taken 15 and 30 min after dosing.

2.0 Materials and Methods

2.1 Animals

Source. Fischer 344 (F344) rats were purchased from Charles River Breeders (Kingston, NY). The rats were examined for signs of disease or abnormality upon arrival and quarantined at least 10 days before they were used in a study. Animal weights at the time they were in studies are shown in Table 1.

Diet. Animals were fed Certified Purina Rat Chow and furnished water ad libitum.

Housing. Animals were housed in polypropylene cages (3-4 per cage). While participating in a study, animals were housed one per cage.

2.2 Xenobiotic

The test compound, ethyl acrylate (2-propenoic acid ethyl ester, $C_5H_8O_2$, CAS # 140-88-5) was supplied by NIEHS (Rohm and Haas Lot No. 343029, Batch 02). The ^{1}H-NMR of this material (Figure 1) was consistent with that contained in the NTP Technical Report on the Carcinogenesis Bioassay of Ethyl Acrylate (NIH Publication No. 82-2515). Chromatography of the ethyl acrylate by GC on a Carbopack C/0.3% Carbowax 20 M column showed less than 1% chemical impurities (cf. Figure 2).

2.3 In Vitro Metabolism

For incubations with forestomach and glandular stomach tissue and stomach contents, animals (3 males, 3 females) were sacrificed by cervical dislocation and their stomachs removed. Each stomach was opened and the contents removed with a spatula. The stomach was then divided into the forestomach and the glandular stomach. The tissues were homogenized in 0.1 M sodium phosphate buffer, pH 7.4, containing 4 mM sodium EDTA, by

Table 1. Weights and Doses of Animals

Rat ID	Sex	Weight (g)	Dose (mg/kg) of Ethyl Acrylate
31-R	M	223	189
31-B	M	246	188
31-W	F	167	187
31-O	F	164	183
31-G	M	249	189
31-Y	F	167	193
46-O	F	166	188
34-R	M	229	188
34-B	M	253	190
34-W	F	177	186
34-O	F	172	186
34-G	M	246	191
34-Y	F	156	192
38-R	M	256	102
38-B	M	242	105
38-W	F	173	106
38-O	F	168	102
38-G	M	221	104
38-Y	F	167	105
46-W	F	170	106
40-R	M	252	104
40-B	M	251	103
40-W	F	159	101
40-D	F	169	100
40-G	M	237	106
40-Y	F	171	102
47-R	M	257	0
47-B	M	226	0
47-W	F	174	0
47-O	F	166	0
47-G	M	267	0
47-Y	F	171	0
62-R	M	243	197
62-B	M	250	198
62-W	F	208	196
62-O	F	198	205
62-G	M	256	206
62-Y	F	186	171
62-Z	F	123	198
64-R	M	254	207
64-B	M	258	200
64-W	F	194	202
64-O	F	199	197
64-G	M	243	201
64-Y	F	194	201

Figure 1. Proton Magnetic Resonance Spectrum of Ethyl Acrylate

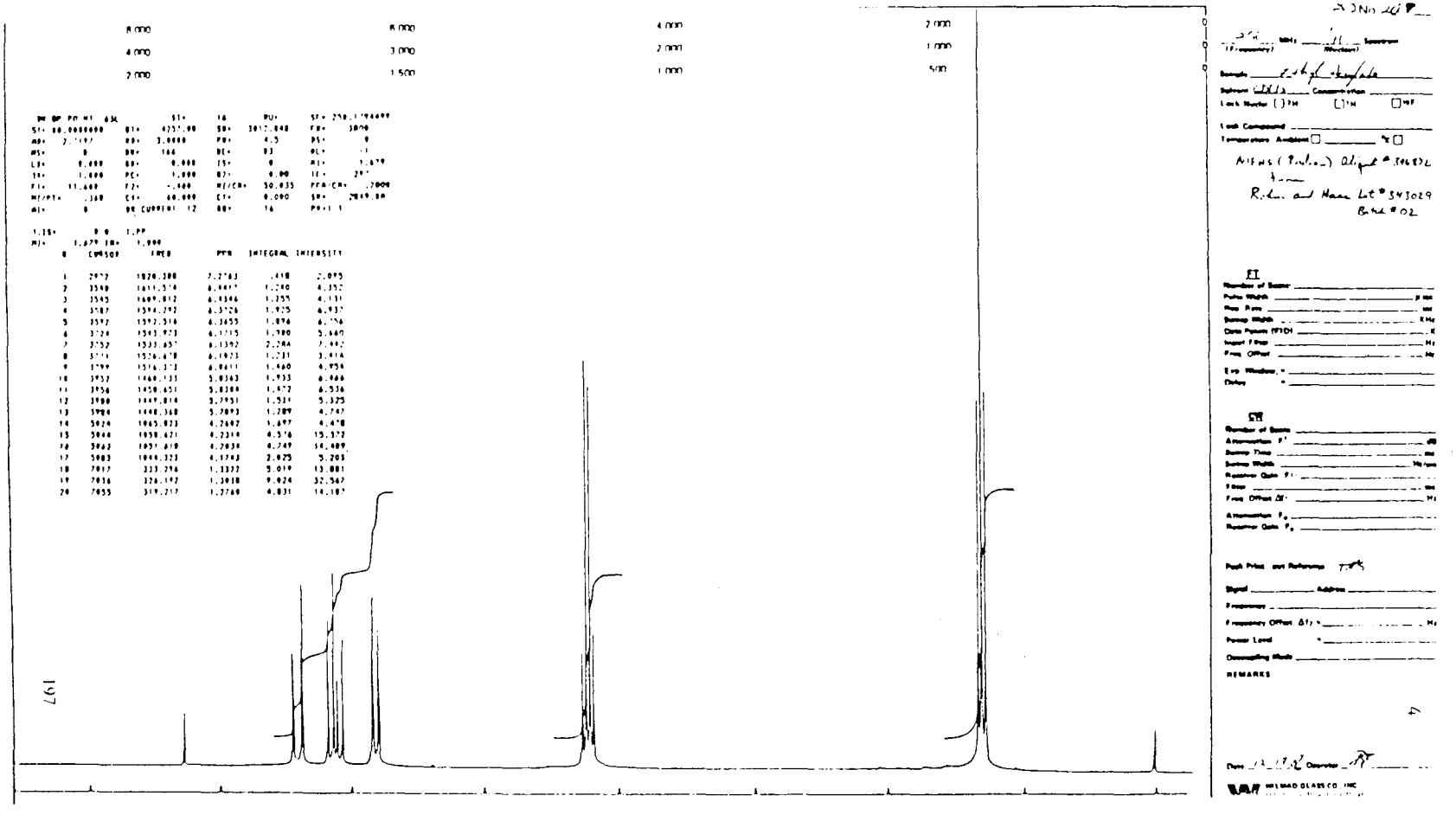
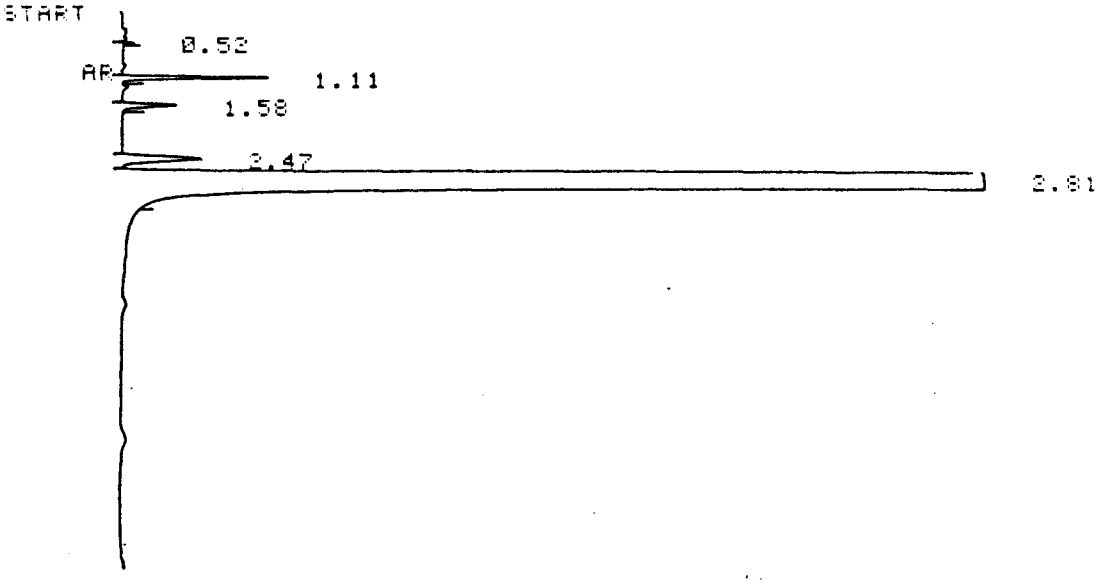


Figure 2. Gas Chromatogram of Ethyl Acrylate

Instrument: Hewlett-Packard 5840A
Column: 2 mm ID x 6 ft silylated glass packed wit
0.3 % Carbowax on Carbopack C
Mobile Phase: Nitrogen at 18.5 mL/min
Detection: FID
Oven Temperature: 135 °C, isothermal
Injector Temperature: 200 °C
Detector Temperature: 200 °C
Retention Time of Ethyl Acrylate: 2.81 min

Purity of Ethyl Acrylate: 99.8%



HP RUN # 526 DEC/20/82 TIME 13:05:37
AREA %

RT	AREA	AREA %
1.11	484	0.082
1.58	218	0.037
2.47	495	0.084
2.81	588500	99.797

use of a Polytron homogenizer (Brinkman Instruments, Westbury, NY) to yield a homogenate containing 40 mg of wet tissue per mL. Stomach contents were likewise homogenized in water to give a homogenate containing 100 mg of the stomach contents per mL. A 5 mL aliquot of each homogenate was transferred to a teflon-faced septum capped 20 mL vial and warmed to 37°C in a Dubnoff shaking water bath. Ethyl acrylate (150 μg) as a 5 mg/mL solution in water was added to each tissue aliquot. At 5, 20, 35, 50 and 65 min, 200 μL aliquots of the incubation mixture were transferred to 0.5 dram vials capped with teflon-faced septums. An aqueous solution (50 μL) containing 1 mg of 1,4-dioxane, the internal standard, per mL was then added to each vial. After mixing for a few seconds using a vortex mixer, 1 μL of the solution was withdrawn and chromatographed by GC using conditions shown in Figure 3. All transfers were made through the septum caps using glass micro syringes with teflon tipped plungers. The elapsed time between taking the aliquot from the incubation mixture and injection onto the gas chromatographed was less than 30 sec.

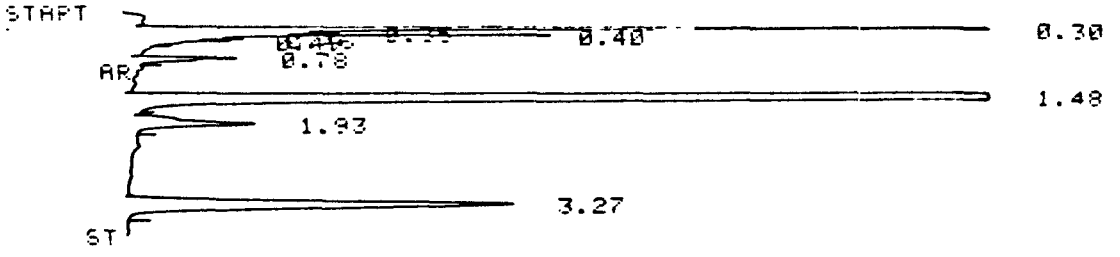
Samples of blood for determination of the half-life of ethyl acrylate in this fluid were collected from anesthetized (pentobarbital) animals by cardiac puncture. Each aliquot (1 mL) of blood was diluted with 4 mL of phosphate buffer (described above). After warming the diluted blood to 37°C, 0.5 mg of ethyl acrylate was added. Incubations were otherwise carried out as described for the stomach tissues. Aliquots were removed for analysis at 1.5, 5.5, 10, 15, 20 and 25 min.

2.4 Reaction of Ethyl Acrylate with non-Protein SH (Thiol) Groups

Animals (3 male, 3 female for each dose level and sacrifice time) were given single oral doses by gavage of either 200 mg/kg ethyl acrylate

Figure 3. Gas Chromatogram of Incubation Mixture of Ethyl Acrylate with Rat Forestomach Homogenate

Instrument: Hewlett-Packard 5840A
Column: 2 mm ID x 6 ft silylated glass packed with
0.3 % Carbowax on Carbopack C
Mobile Phase: Nitrogen at 18.5 mL/min
Detection: FID
Oven Temperature: 130 °C, isothermal
Injector Temperature: 200 °C
Detector Temperature: 200 °C
Retention Time of Ethyl Acrylate: 3.27 min
Internal Standard: 1,4-Dioxane
Retention Time of the Internal Standard: 1.48 min



HP RUN # 318 DEC/09/82 TIME 14:45:01
AREA %

RT	AREA	AREA %
1.48	32450	88.422
1.93	804	2.191
3.27	3445	9.387

For the [ethyl acrylate] range of 2-100 µg/mL

$$[\text{ethyl acrylate}]\ (\mu g/mL) = 213\ \frac{\text{area of ethyl acrylate}}{\text{area of 1,4-dioxane}} + 0.529$$

linear correlation coefficient = 0.998

as a 4 percent solution in corn oil or 100 mg/kg ethyl acrylate as a 2 percent solution in corn oil. Animals were killed by cervical dislocation at 30 or 120 min after dosing. Their stomachs were rapidly removed. The majority of the stomach contents were then squeezed out. The forestomach and glandular stomach from each rat was separated, opened, and washed successively in five 3 mL portions of ethyl ether. The ether washes were combined with the "squeezed out" stomach contents and mixed well. An aliquot of this mixture (200 μL) was transferred to a 0.5 dram vial containing the internal standard (50 μL of a 9 mg/mL solution of ethyl butyrate in chloroform). Ethyl acrylate was measured in the resulting solution by GC using the conditions shown in Figure 4.

Non-protein thiols were measured in forestomach and glandular stomach tissue by the method of Sedlak and Lindsay (1968). Tissues from control animals were obtained 30 min following a single oral dose of corn oil.

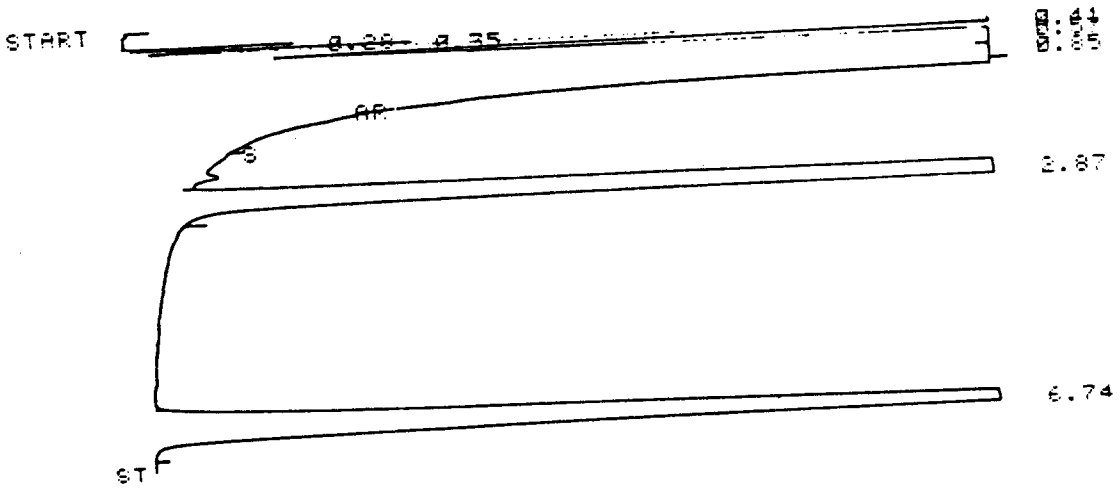
2.5 Measurement of Ethyl Acrylate in Blood Following a Single Oral Dose of Xenobiotic

Animals were administered single oral doses (gavage) of 200 mg/kg ethyl acrylate as a 4% solution in corn oil. The animals were then sedated with 50 mg/kg pentabarbital. To determine the concentration of ethyl acrylate in general circulation, 50 μL intraoccular blood samples were obtained at 15, 30 and 60 min. The blood was immediately transferred to a vial which contained 100 μL of a 0.125 mg/mL aqueous solution of the iternal standard, 1,4-dioxane. Aliquots of this solution were then assayed for ethyl acrylate by the system shown in Figure 3.

To determine the concentration of ethyl acrylate in the portal vein, venous punctures were made into the exposed vein at 15 and 30 min

Figure 4. Gas Chromatogram of Stomach Contents 30 min after a Single Oral Dose of Ethyl Acrylate (200 mg/kg)

Instrument: Hewlett-Packard 5840A
Column: 2 mm ID x 6 ft silylated glass packed with 0.3 % Carbowax on Carbopack C
Mobile Phase: Nitrogen at 18.5 mL/min
Detection: FID
Oven Temperature: 135 °C, isothermal
Injector Temperature: 200 °C
Detector Temperature: 200 °C
Retention Time of Ethyl Acrylate: 2.87 min
Internal Standard: Ethyl Butyrate
Retention Time of the Internal Standard: 6.74 min



HP RUN # 474 DEC/15/82 TIME 13:28:05
AREA %

RT	AREA	AREA %
2.87	152300	86.786
6.74	23190	13.214

For [ethyl acrylate] concentrations in the extract of stomach contents of 0.12 - 2.0 mg/mL

$$[\text{ethyl acrylate}]\ (\text{mg/mL}) = 0.267 \frac{\text{Area of Ethyl Acrylate}}{\text{Area of Ethyl Butyrate}} - 0.028$$

Linear correlation coefficient = 0.999

after dosing. Aliquots (50 μL) of blood were obtained and analyzed as described above.

3.0 Results and Discussion

3.1 Metabolism of Ethyl Acrylate in vitro

Ethyl acrylate is metabolized by homogenates of the forestomach, glandular stomach and the stomach contents. Half-lives of ethyl acrylate, present initially in concentrations of 0.75 μg/mg wet tissue and 0.30 μg/mg stomach contents, are shown in Table 2. The disappearance of ethyl acrylate was first order with respect to ethyl acrylate in all cases, with correlation coefficients of a linear least-squares fit of log [ethyl acrylate] vs. time of >0.98 for all tissue homogenates and >0.96 for all stomach contents. The concentration of ethyl acrylate in buffer remained constant over the same time interval (0-65 min). There was no significant difference between sexes in half-lives or in the slopes of the linear regression best fit lines (t test) at an α level of 0.05. Analysis of covariance of the data revealed no sex effect; however a sex x time effect ($p = 0.012$) was found for the stomach contents data. Further work with additional animals, which may reduce the variance observed in the present study, would be necessary to determine if real differences in in vitro metabolism exist between sexes.

Metabolism of ethyl acrylate in vitro by blood is much faster than by the tissue homogenates. At an initial concentration of 0.5 mg of ethyl acrylate per mL of blood, the average half-life for 3 males was 14.0 ± 2.1 (SD) min and that for 2 females was 11.8 ± 2.3 (range) min. Correlation coefficients of the linear least squeares fit of log [ethyl acrylate] vs. time was >0.97, although it is obvious that the data thus plotted still exhibits some curvature (cf. Figures A7-All in the Appendix).

Table 2. Metabolism of Ethyl Acrylate by Homogenates of Forestomach, Glandular Stomach and Stomach Contents[a]

Rat	Sex[b]	Forestomach $t_{1/2}$ (min)	Glandular Stomach $t_{1/2}$ (min)[c]	Stomach Contents $t_{1/2}$ (min)[d]
22-1	M	66	42	41
24-1	M	71	46	64
25-1	M	92	102	53
Mean (± SD)		76 ± 14	67 ± 31	53 ± 12
26-1	F	123	62	59
28-1	F	92	80	62
27-1	F	72	56	97
Mean (± SD)		96 ± 26	66 ± 12	73 ± 21

a. Half-life estimates from least-squares linear regression line of log [ethyl acrylate] vs. time. Measurements made at 5, 20, 35, 50 and 65 min. Data for individual animals is included in the Appendix as Figures A1-A6.

b. M = Male, F = Female.

c. Incubations were conducted for 65 min at 37°C with 40 mg/mL of wet tissue and 30 µg/mL of ethyl acrylate in 0.1 molar aqueous sodium phosphate, pH 7.4, 4 mM sodium EDTA.

d. Incubations were conducted for 65 min at 37°C with 100 mg/mL of stomach contents and 30 µg/mL of ethyl acrylate in distilled water.

3.2 Depletion of non-Protein Thiols (NP-SH) by Ethyl Acrylate

Miller et al (1981) have reported that ethyl acrylate reacts with non-protein thiols in vitro. Therefore we investigated the reaction of ethyl acrylate with non-protein thiols (NP-SH) in forestomach and glandular stomach in vivo following a single oral dose of 200 mg/kg and 100 mg/kg. These results are shown in Table 3. Concentrations of NP-SH were reduced in both the forestomach and glandular stomach by ethyl acrylate. At 120 min after dosing at either dose level and 30 min after dosing at 200 mg/kg, concentrations of NP-SH were 13-17% of control values in the forestomach. Concentrations of ca twice this amount were found 30 min after the 100 mg/kg dose. NP-SH concentrations in the glandular stomach were somewhat higher. There appears to be no significant difference in the depletion of NP-SH between sexes. The rates of recovery of NP-SH in the stomach tissues could not be determined from our data and would require analysis of samples taken at much longer time periods.

The percentage of the ethyl acrylate dose remaining in the stomachs of the animals in this study was also measured (cf. Table 4). After 30 min 29-40% of the dose was still in the stomach as the parent xenobiotic. These values decreased somewhat over the next 90 min, but assuming that 100% was in the stomachs originally, these decreases are much less than that which occurred during the first 30 min. Again, there appears to be no sex difference in the amount of ethyl acrylate in the stomachs at these time periods.

3.3 Concentrations of Ethyl Acrylate in Blood Following a Single Oral Dose

Ethyl acrylate was measured in intraoccular blood at 15, 30 and 60 min and in portal venous blood at 15 and 30 min following a single oral dose of 200 mg/kg of ethyl acrylate. No ethyl acrylate was found in any

Table 3. Concentration of non-Protein Thiols in Forestomach and Glandular Stomach Tissues following a Single Oral Dose of Ethyl Acrylate

	Values are in % of Controls[a,b]			
Dose (mg/kg):	100[c]		200[d]	
Time (min):	30	120	30	120
Forestomach				
Males	26 ± 8	16 ± 1	17 ± 6	13 ± 5
Females	34 ± 4	15 ± 2	17 ± 3	15 ± 7
Glandular Stomach				
Males	54 ± 3	56 ± 3	41 ± 4	37 ± 3
Females	48 ± 8	52 ± 3	38 ± 4	33 ± 4

a. Average ± SD from 3 animals. Data for individual animals are included in the Appendix as Table A1.

b. Average concentration of non-protein thiols in control animals were:

Forestomach, males: 3.5 ± 1.2 n mole/mg wet tissue
Forestomach, females: 2.8 ± 0.1 n mole/mg wet tissue
Glandular Stomach, males: 2.9 ± 0.1 n mole/mg wet tissue
Glandular Stomach, females: 3.2 ± 0.2 n mole/mg wet tissue

c. Dose given orally by gavage as a 2% solution in corn oil.

d. Dose given orally by gavage as a 4% solution in corn oil.

Table 4. Amount of Ethyl Acrylate Remaining in the Stomach Following a Single Oral Dose of Ethyl Acrylate.

Values are in Percent Dose[a]

Dose (mg/kg):	100[b]		200[c]	
Time (min):	30	120	30	120
Males	29 ± 9	16 ± 5	38 ± 10	34 ± 6
Females	30 ± 5	20 ± 3	40 ± 10	25 ± 6

a. Average ± SD from 3 animals. Data for individual animals is included in the Appendix, Table A2.

b. Dose given orally by gavage as a 2% solution in corn oil.

c. Dose given orally by gavage as a 4% solution in corn oil.

of the intraoccular blood samples (limit of detection was ca 1 μg/mL). Concentrations of ethyl acrylate in portal venous blood are shown in Table 5. Concentrations of up to 27 μg/mL blood were observed. Four of the six animals (2 males and 2 females) had detectable amounts of ethyl acrylate in portal vein blood 15 min after dosing and all animals had detectable amounts 30 min after dosing.

4.0 References

R. R. Miller, J. A. Ayers, L. W. Rampy and M. J. McKenna, Fundam. Appl. Toxicol. 1, 410-414 (1981).

J. Sedlak and R. H. Lindsay, Anal. Biochem. 25, 192-205 (1968).

Table 5. Concentrations of Ethyl Acrylate in Portal Venous Blood Following a Single Oral Dose

Values are µg/mL

Rat	Sex	15 min	30 min
65-1	M	4	12
65-2	M	ND	4
65-5	M	4	D
65-3	F	ND	D
65-4	F	27	18
65-6	F	5	15

D - ethyl acrylate was detected. Its concentration was ca. 1-4 µg/mL blood, but could not be accurately measured.

ND - ethyl acrylate was not detected in this sample (detection limit was ca. 1 µg/mL blood).

Table A1. Concentration of Non-protein Thiols in Forestomach (FS) and Glandular Stomach (GS) Homogenates Following a Single Oral Dose of Ethyl Acrylate

Animal Code	Sex	Stomach Tissue	Non-Protein Thiol Concentration (mM)[a]				
			Control	100 mg/kg Dose		200 mg/kg Dose	
				30 min	120 min	30 min	120 min
R	M	FS	0.362	0.0852	0.0613	0.0520	0.0421
		GS	0.260	0.147	0.154	0.118	0.103
B	M	FS	0.392	0.0751	0.0560	0.0467	0.0387
		GS	0.278	0.151	0.146	0.104	0.0940
G	M	FS	0.195	0.0686	0.0304	0.0458	0.0368
		GS	0.264	0.133	0.145	0.109	0.102
W	F	FS	b	0.0868	0.0336	0.0431	0.0361
		GS	0.298	0.126	0.144	0.120	0.0836
O	F	FS	0.240	0.0728	0.0357	0.0479	0.0212
		GS	0.268	0.153	0.144	0.108	0.0988
Y	F	FS	0.260	0.100	0.0426	0.0341	0.0571
		GS	0.300	0.138	0.161	0.0974	0.101

[a]Calculated as glutathione.

[b]Sample was lost.

Table A2. Ethyl Acrylate (EtOAcry) Remaining in Stomachs of Aminals Given 100 and .200 mg/kg Oral Doses

Dose (mg/kg)	Time (min)	Sex	Rat #	EtOAcry in Stomach mg	% Dose	Average % Dose ± SD
100	30	M	40 R	10.2	38.7	
		M	40 B	6.28	24.2	28.6 ± 8.8
		M	40 G	5.73	22.8	
		F	40 O	4.85	28.5	
		F	40 W	4.18	26.1	30.0 ± 4.9
		F	40 Y	6.18	35.5	
100	120	M	38 R	3.04	11.6	
		M	38 B	5.46	21.6	16.1 ± 5.1
		M	38 G	3.50	15.2	
		F	38 W	3.12	17.0	
		F	38 Y	3.86	21.9	20.5 ± 3.0
		F	38 O	3.89	22.6	
200	30	M	31 R	16.5	39.0	
		M	31 G	12.9	27.4	37.5 ± 9.5
		M	31 B	21.3	46.2	
		F	31 Y	16.0	49.7	
		F	31 W	9.06	29.0	39.9 ± 10.4
		F	31 O	12.3	40.9	
200	120	M	34 R	16.4	38.1	
		M	34 B	13.2	27.4	34.1 ± 5.8
		M	34 G	17.2	36.7	
		F	34 W	11.3	34.2	
		F	34 O	7.42	23.2	25.4 ± 6.1
		F	34 Y	7.19	24.0	
		F	46 O	6.23	20.0	

Figure A1. Plots of the logs of the ethyl acrylate concentrations vs. time for the in vitro incubation of ethyl acrylate with forestomach, glandular stomach, and stomach contents homogenates for rat 22-1 (male).

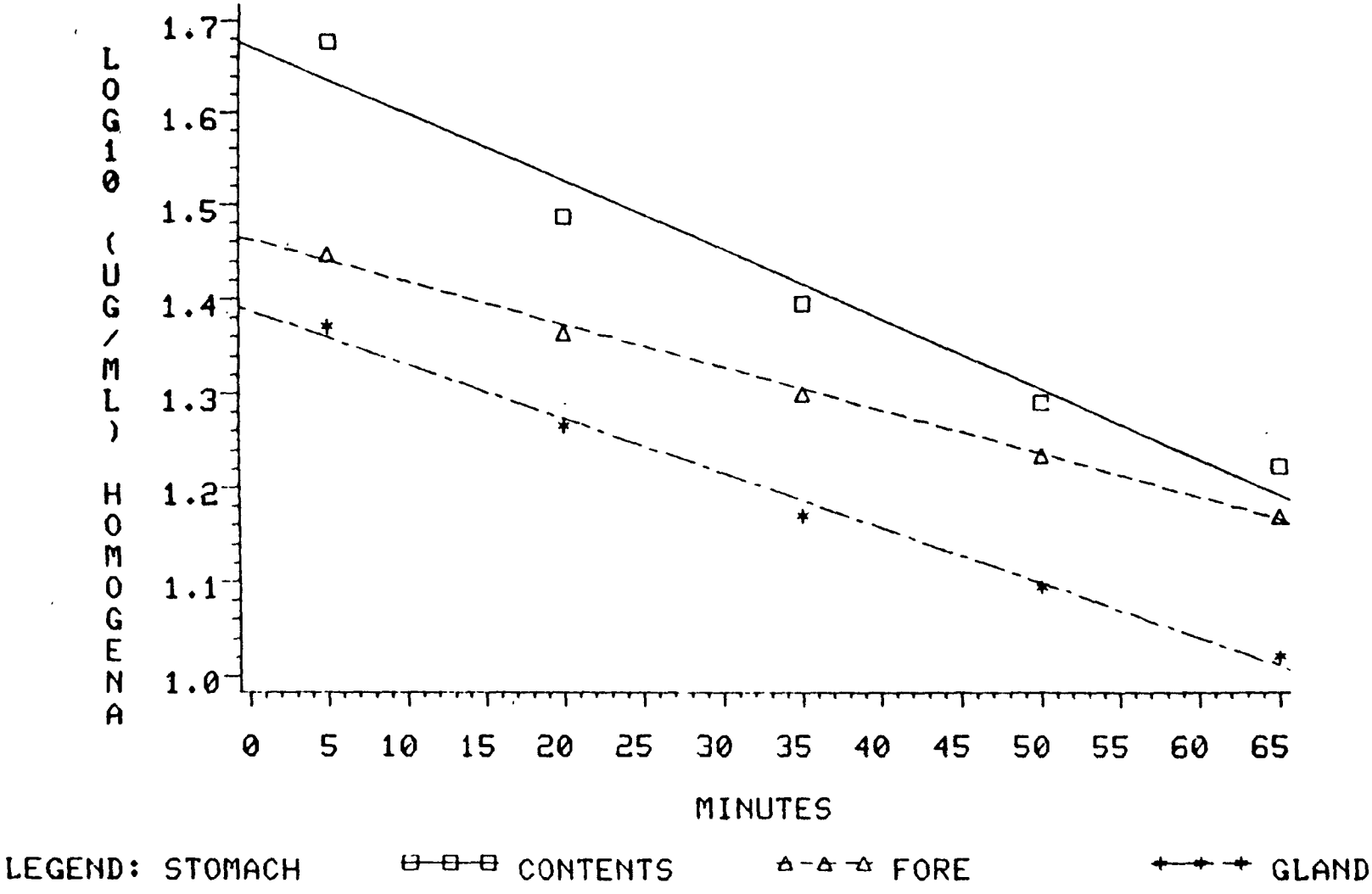


Figure A2. Plots of the logs of the ethyl acrylate concentrations vs. time for the in vitro incubation of ethyl acrylate with forestomach, glandular stomach, and stomach contents homogenates for rat 24-1 (male).

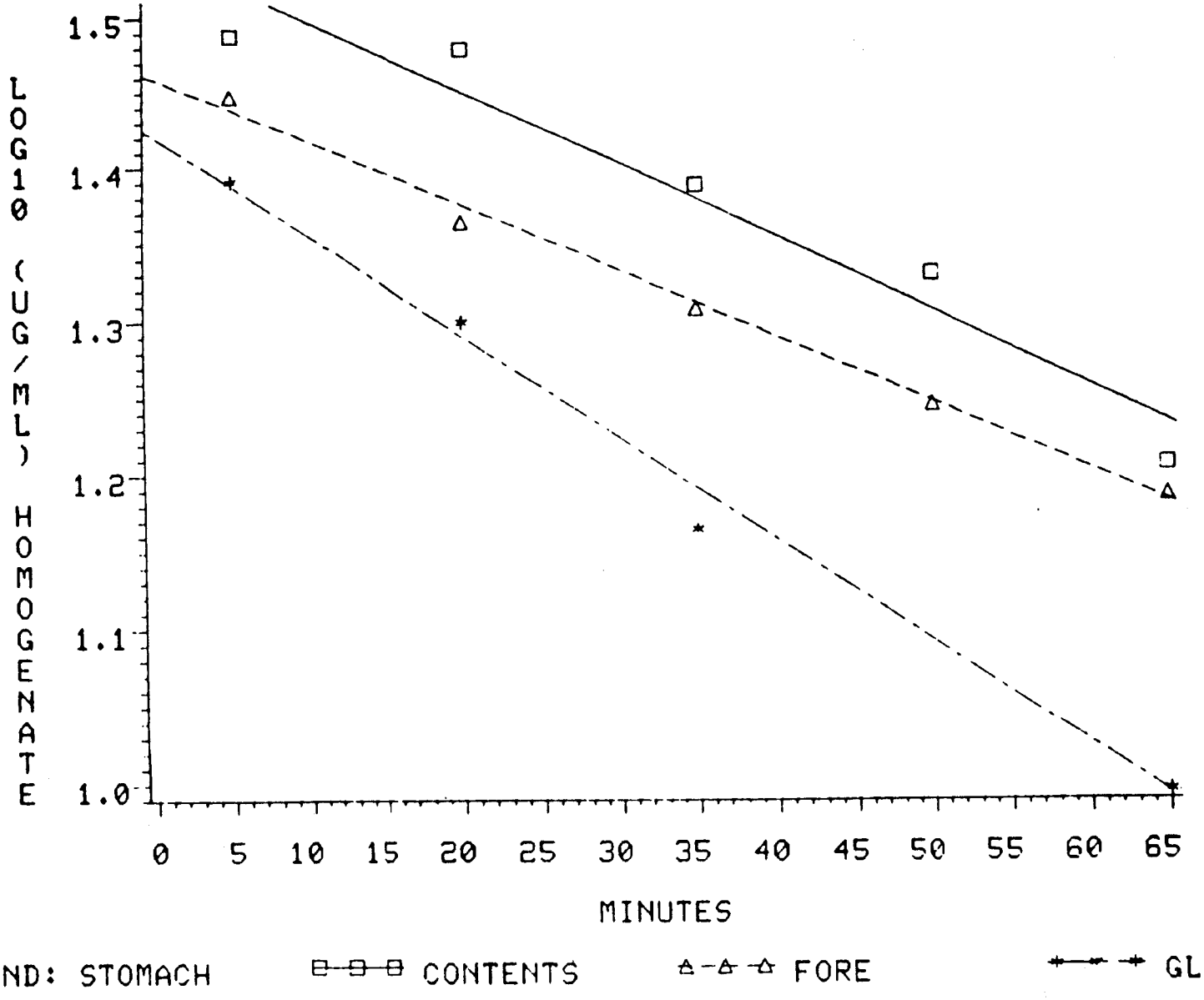


Figure A3. Plots of the logs of the ethyl acrylate concentrations vs. time for the in vitro incubation of ethyl acrylate with forestomach, glandular stomach, and stomach contents homogenates for rat 25-1 (male).

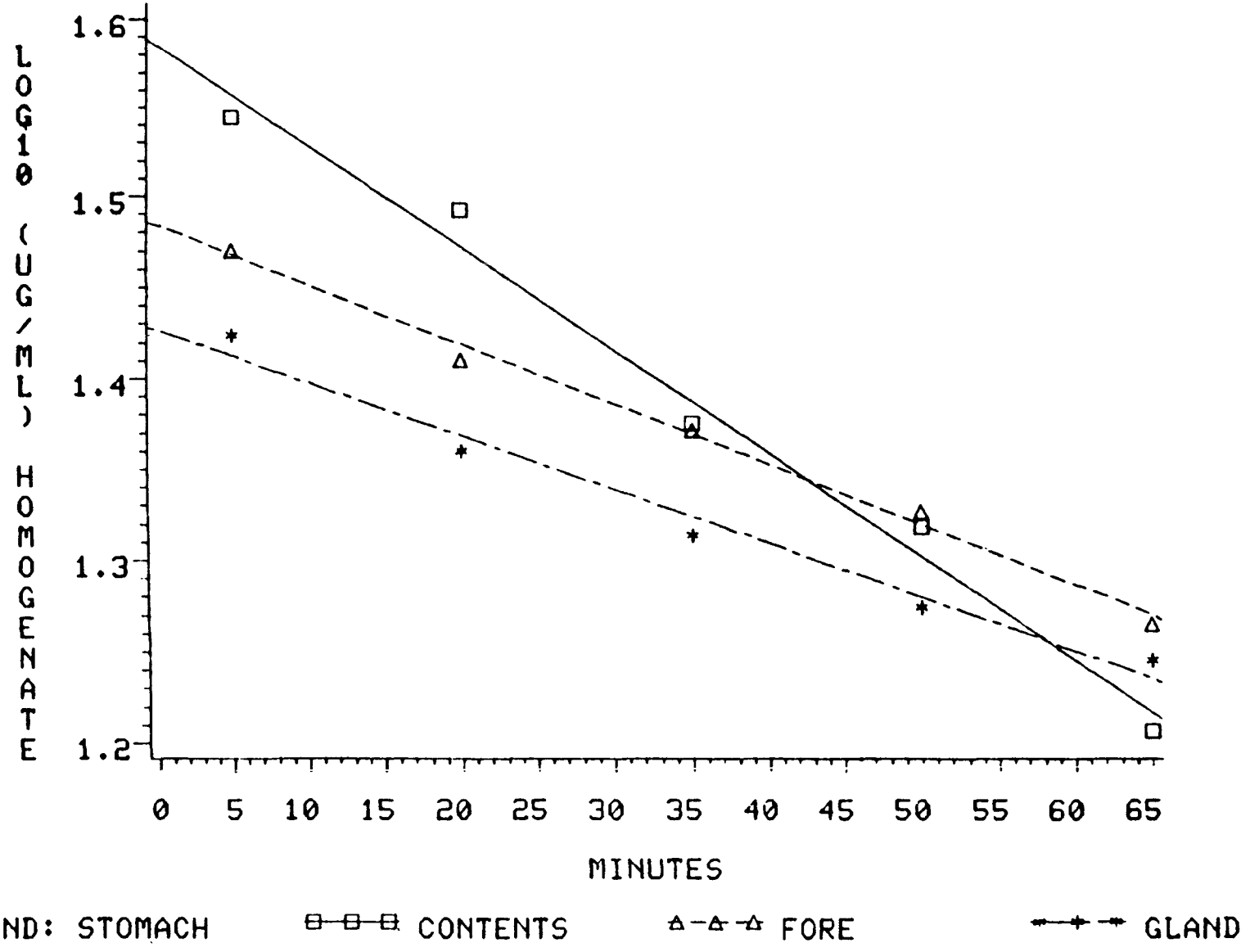


Figure A4. Plots of the logs of the ethyl acrylate concentrations vs. time for the in vitro incubation of ethyl acrylate with forestomach, glandular stomach, and stomach contents homogenates for rat 26-1 (female).

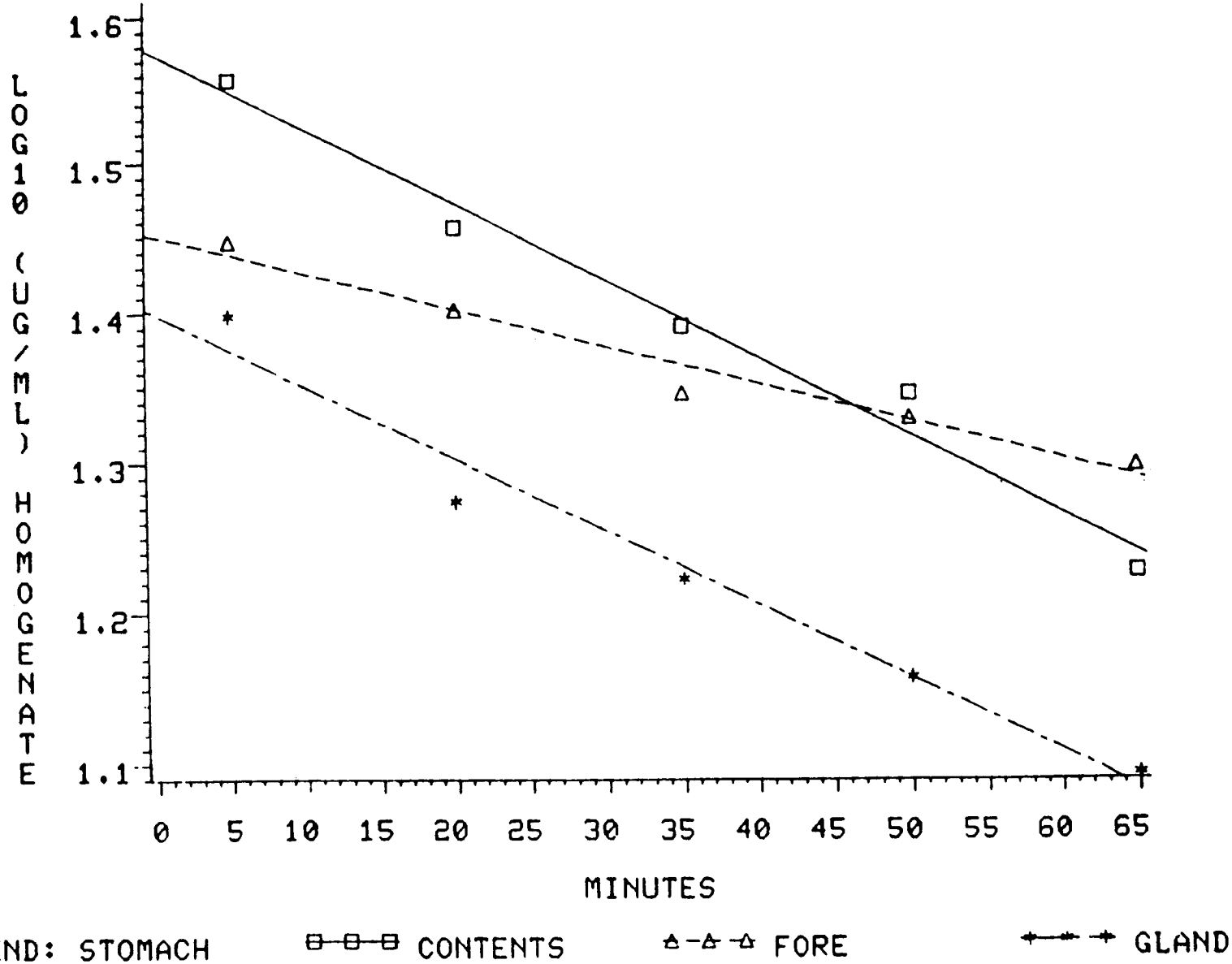


Figure A 5. Plots of the logs of the ethyl acrylate concentrations vs. time for the in vitro incubation of ethyl acrylate with forestomach, glandular stomach, and stomach contents homogenates for rat 27-1 (female).

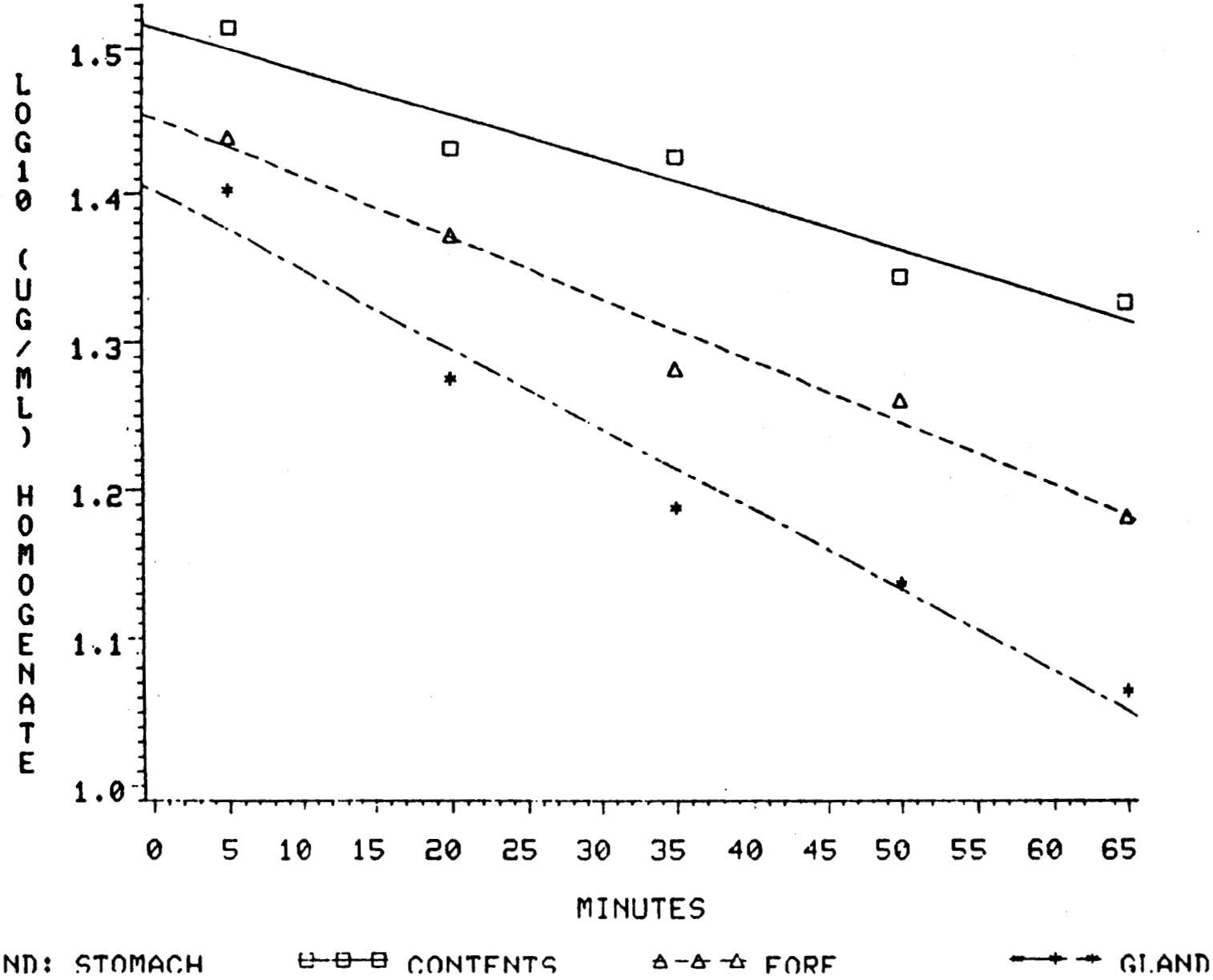


Figure A6. Plots of the logs of the ethyl acrylate concentrations vs. time for the in vitro incubation of ethyl acrylate with forestomach, glandular stomach, and stomach contents homogenates for rat 28-1 (female).

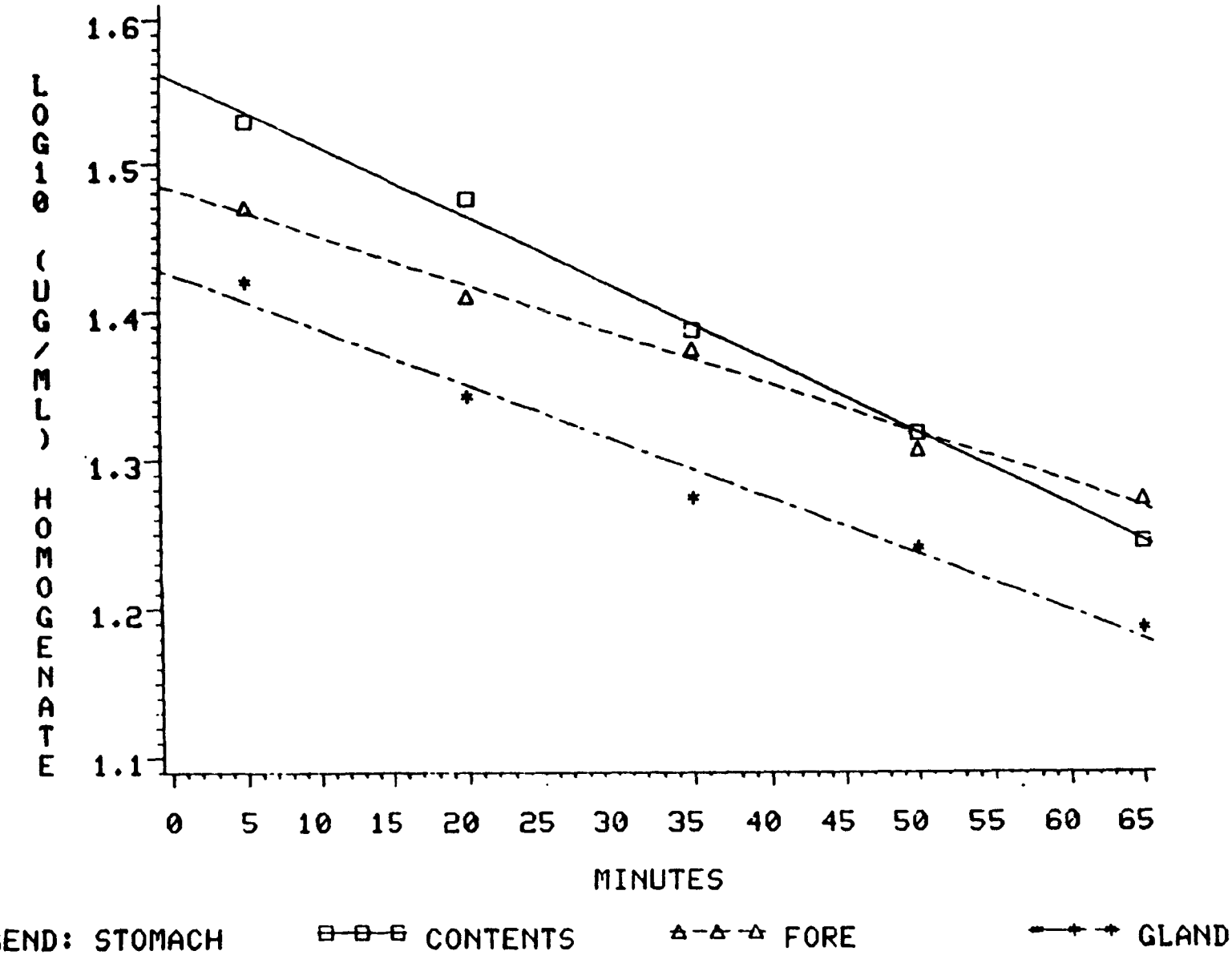


Figure A7. Plot of the log of the ethyl acrylate concentration vs. time for the in vitro incubation of ethyl acrylate with whole blood from rat 57-1 (male).

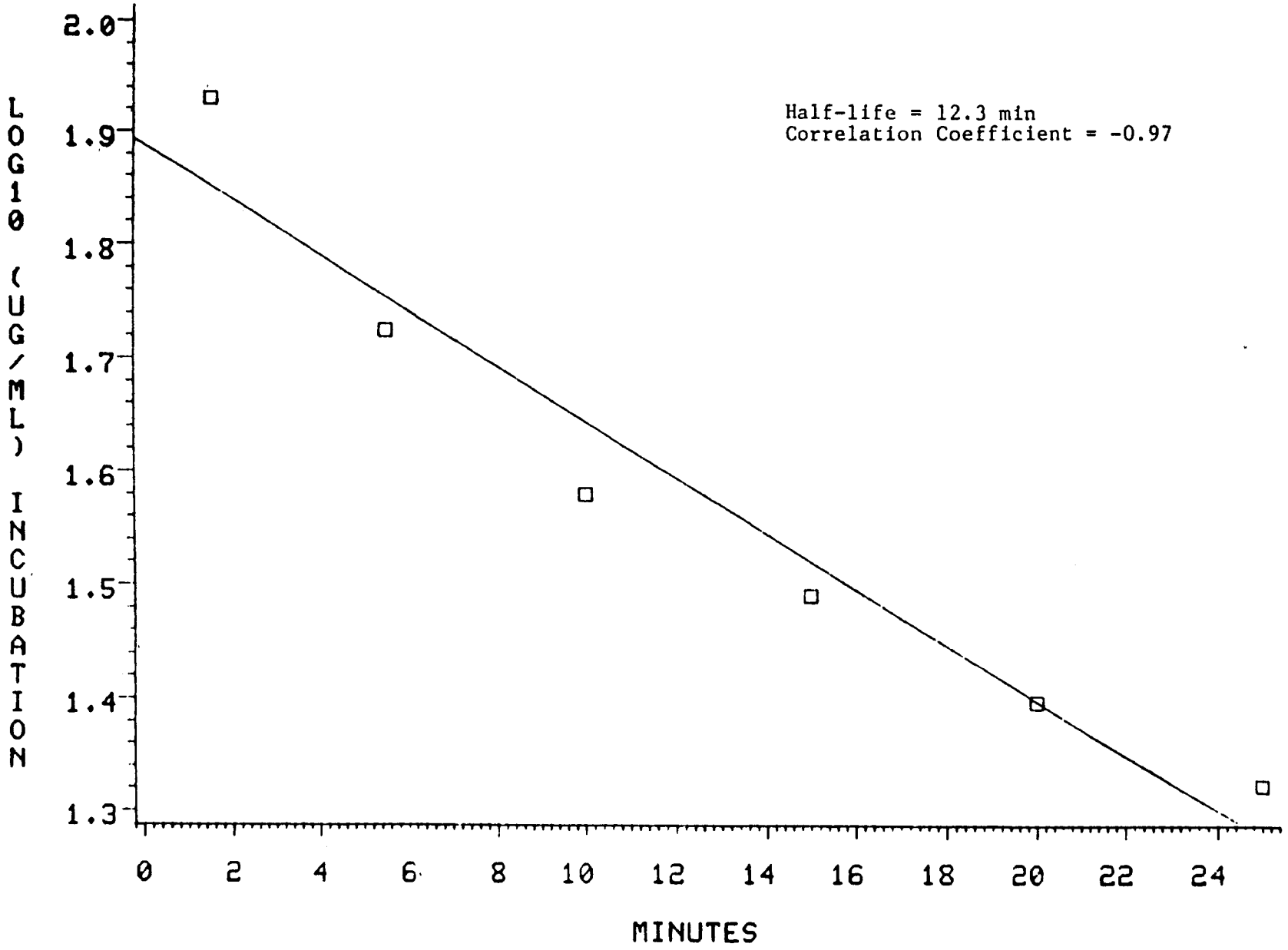


Figure A8. Plot of the log of the ethyl acrylate concentration vs. time for the in vitro incubation of ethyl acrylate with whole blood from rat 68-1 (male).

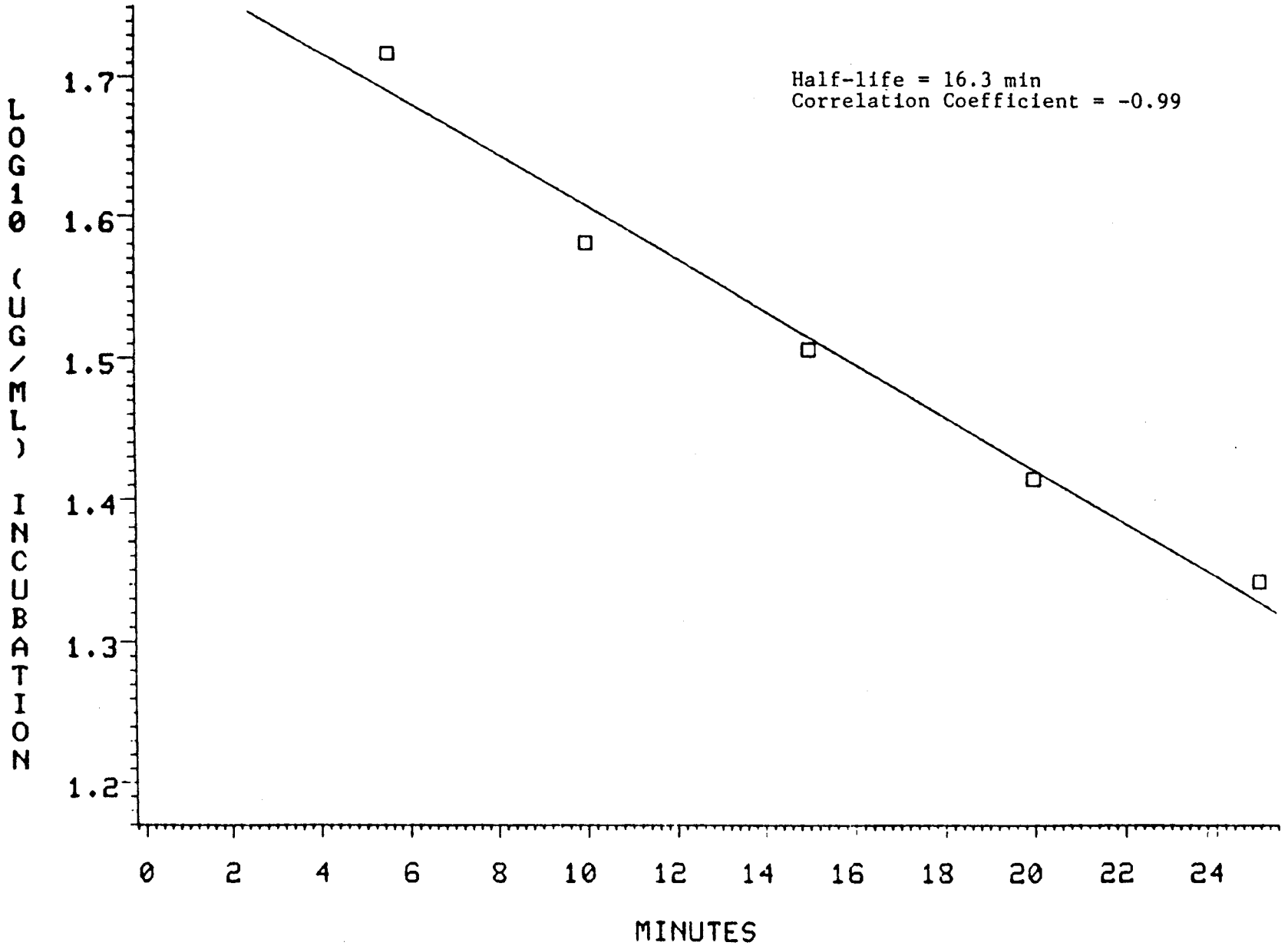


Figure A9. Plot of the log of the ethyl acrylate concentration vs. time for the in vitro incubation of ethyl acrylate with whole blood from rat 76-1 (male).

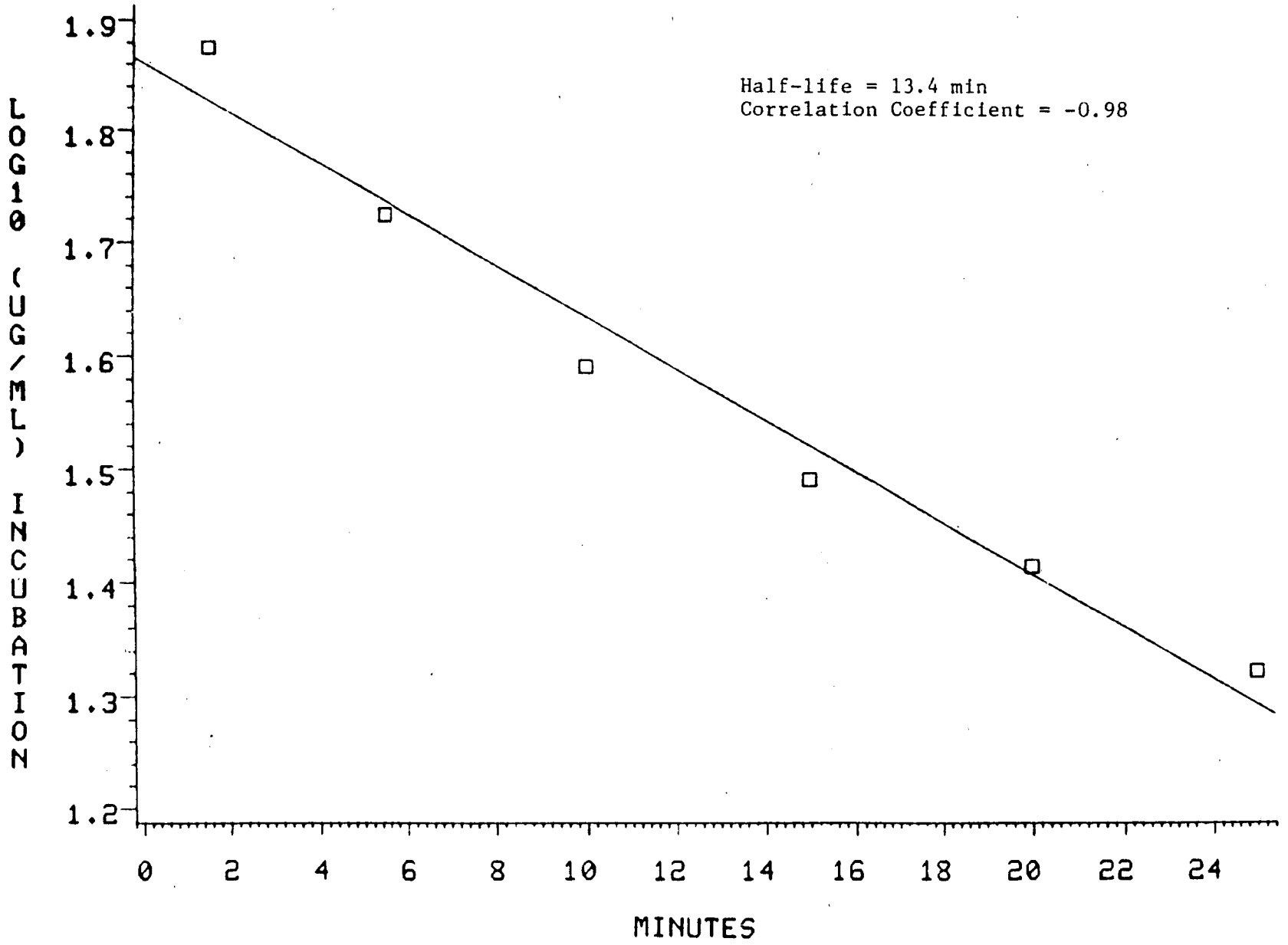


Figure A10. Plot of the log of the ethyl acrylate concentration vs. time for the in vitro incubation of ethyl acrylate with whole blood from rat 56-2 (male).

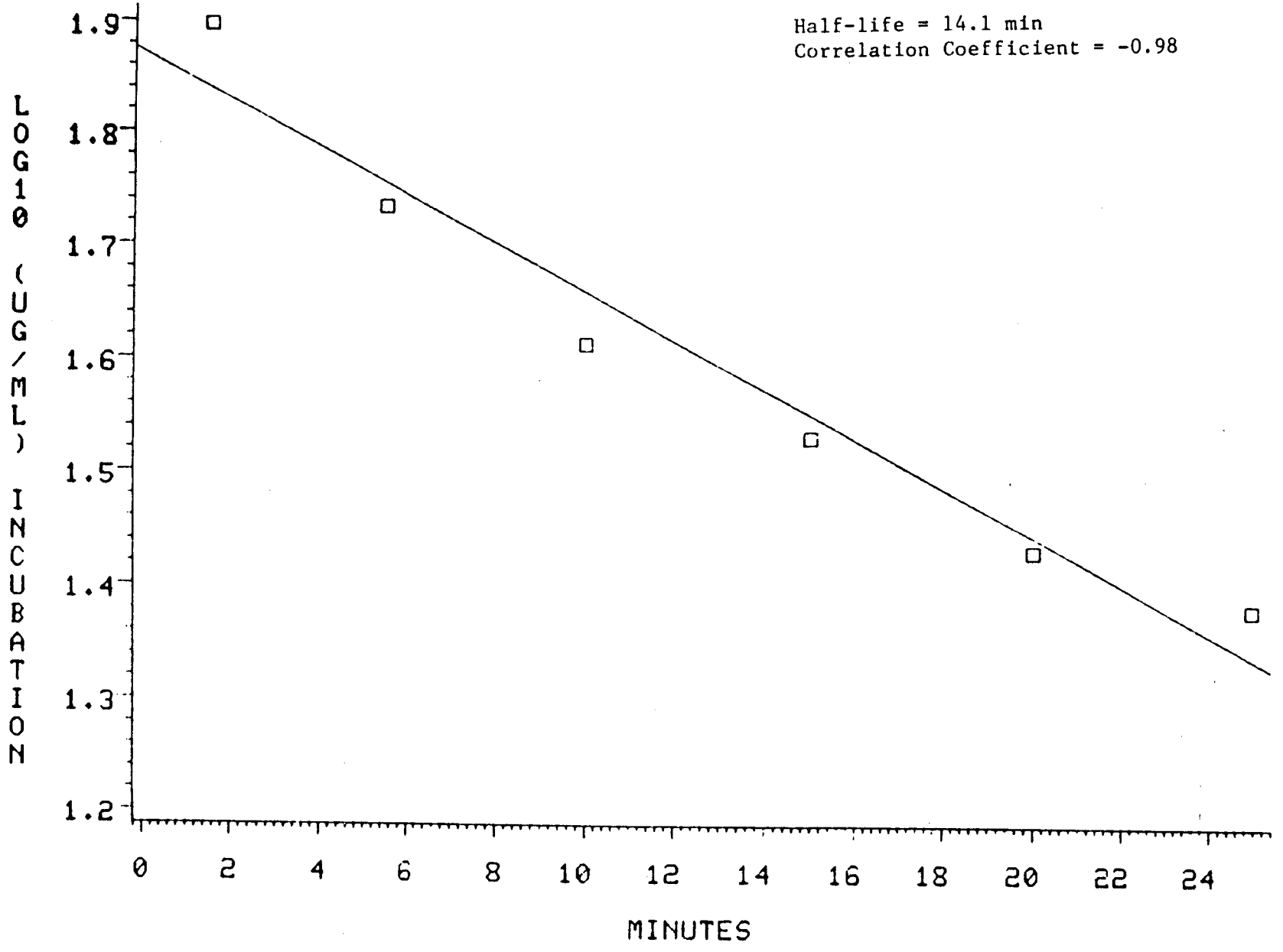
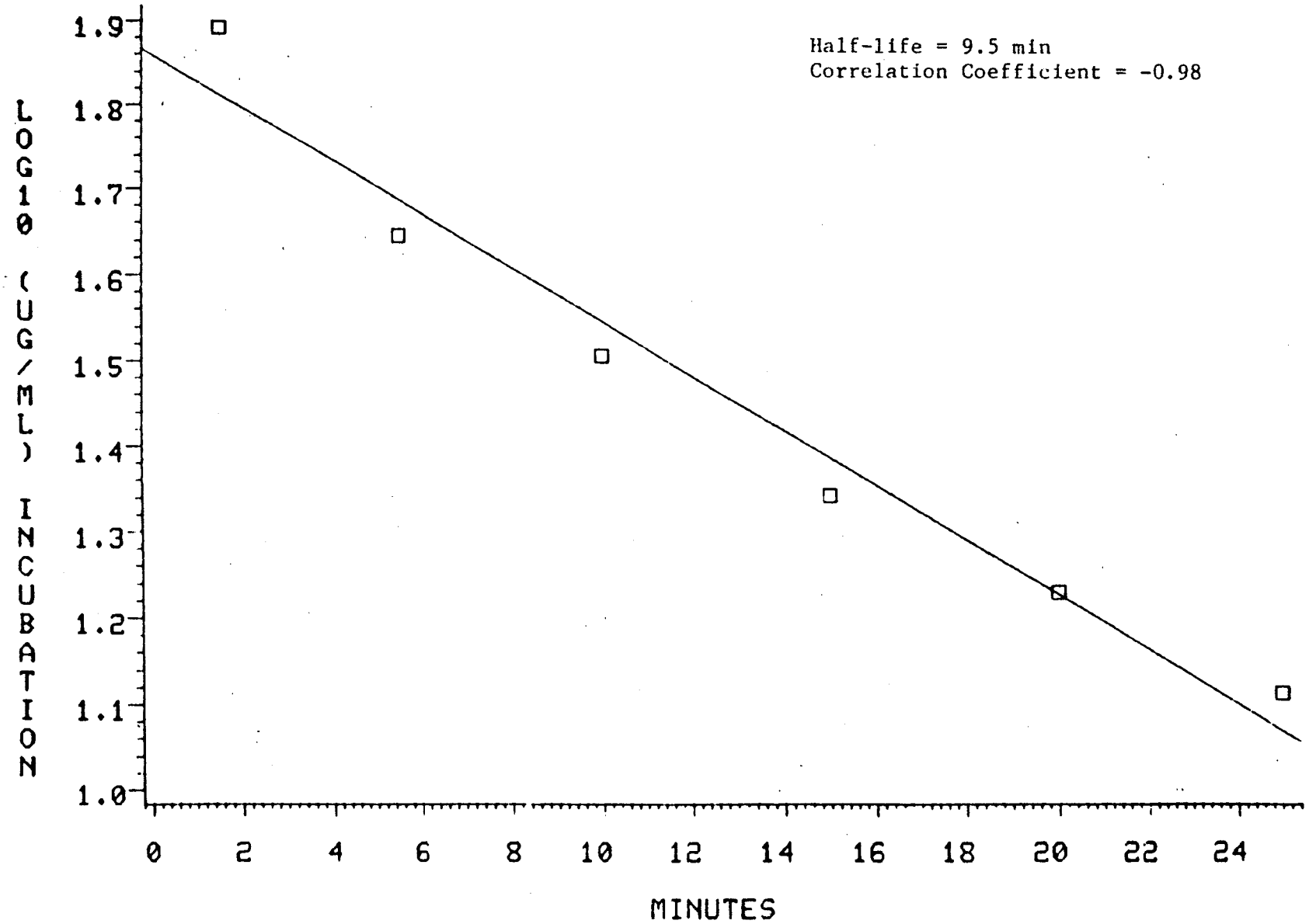


Figure A11. Plot of the log of the ethyl acrylate concentration vs. time for the in vitro incubation of ethyl acrylate with whole blood from rat 69-2 (male).



APPENDIX N

DATA AUDIT SUMMARY

APPENDIX N

The experimental data, documents, pathology materials, and draft Technical Report for the 2-year carcinogenesis studies of ethyl acrylate in rats and mice were audited for consistency, completeness, and accuracy. The animal exposures were conducted at Southern Research Institute from February 1979 to February 1981 before the NTP required compliance with Good Laboratory Practice Regulations in October 1981. The audit was conducted in May and October 1985 at the NTP Archives, Research Triangle Park, North Carolina, by the following personnel from ImmuQuest Laboratories, Inc., and Pathology Associates, Inc.: P.H. Errico, M.A.; L.H. Brennecke, D.V.M.; K.M. Witkin, Ph.D.; C.S. Reese; and S. Corson, HT (ASCP).

The full report of the audit is on file at the NIEHS, Research Triangle Park, North Carolina. The audit involved a review of the data records on body weight, clinical observations, dosing, and necropsy and pathology materials for a randomly selected 10% of the animals in each species, sex, and dose group. All of the chemistry and mortality data were examined. A slide/block match was conducted for all animals in the high dose and vehicle control groups.

All documentation required for the audit was available for review except quarantine records. No discrepancies were noted between the final in-life clinical observations and the Individual Animal Data Records (IADRs) for rats and mice. One high dose male rat, two vehicle control and one high dose male mouse, and one vehicle control female mouse listed as "natural deaths" in the IADRs may have died from gavage-related trauma, as indicated by the presence of blood or oil in the thoracic cavity. All of the IADRs were examined to ensure that each lesion noted at necropsy was followed by an appropriate comment or microscopic diagnosis. For all rats and mice combined, a total of 22 potential discrepancies between necropsy observation and microscopic diagnosis were noted for the target organ (forestomach). The wet tissues and/or slides for each of these were examined with the following results: one vehicle control male rat, one low dose male rat, and one low dose male mouse had potential forestomach lesions. Because the incidences of neoplasms of the forestomach were already strongly dose related, NTP staff decided that these three potential lesions would not affect the interpretation of the studies, and they were not pursued further.

In conclusion, the data audit revealed no significant findings concerning the conduct or documentation of the experiments that would influence the interpretation of the studies. A few other minor errors were noted in the draft Technical Report and were corrected in the final Report.

* U. S. GOVERNMENT PRINTING OFFICE: 1987-181-296:41284