NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 257

TOXICOLOGY AND CARCINOGENESIS STUDIES OF DIGLYCIDYL RESORCINOL ETHER (TECHNICAL GRADE)

(CAS NO. 101-90-6)

IN F344/N RATS AND B6C3F$_1$ MICE (GAVAGE STUDIES)

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

NATIONAL TOXICOLOGY PROGRAM

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

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

Special Note: This Technical Report was peer reviewed in public session and approved by the NTP Board of Scientific Counselors' Technical Reports Review Subcommittee on February 28, 1983 [see page 14]. Thereafter, 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 L.] Consequently, printing and distribution of this Technical Report have been delayed and the format differs from that of Technical Reports peer reviewed more recently. The categories of evidence of carcinogenicity adopted by the NTP in June 1983 were not used to evaluate these data. This final Technical Report supercedes all previous drafts of this report that have been distributed.

NTP TECHNICAL REPORT
ON THE

TOXICOLOGY AND CARCINOGENESIS STUDIES OF DIGLYCIDYL RESORCINOL ETHER (TECHNICAL GRADE)

(CAS NO. 101-90-6)

IN F344/N RATS AND B6C3F$_1$ MICE (GAVAGE STUDIES)

NATIONAL TOXICOLOGY PROGRAM
Box 12233
Research Triangle Park
North Carolina 27709

October 1986

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

NOTE TO THE READER

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

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

Comments and questions about the National Toxicology Program Technical Reports on Carcinogenesis 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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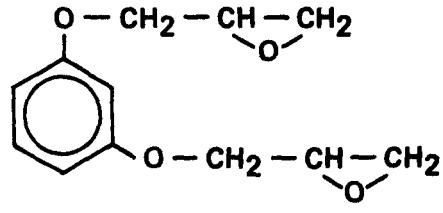

DIGLYCIDYL RESORCINOL ETHER

CAS NO. 101-90-6

$C_{12}H_{14}O_4$ Mol. Wt. 222.2

ABSTRACT

Toxicology and carcinogenesis studies of technical grade diglycidyl resorcinol ether (81% pure) were conducted by administering the chemical in corn oil by gavage to groups of 50 male and 50 female F344/N rats at doses of 25 or 50 mg/kg and to groups of 50 male and 50 female B6C3F$_1$ mice at doses of 50 or 100 mg/kg. A supplemental study of similar design in male and female rats (0 or 12 mg/kg) was started approximately 12 months later because of high mortality in the 50 mg/kg dose groups. Doses were administered five times per week for 103 weeks. Groups of 50 rats and 50 mice of each sex received corn oil by gavage on the same dosing schedule and served as vehicle controls.

Throughout most of the primary study, mean body weights of high dose male and female rats and female mice were lower than those of the corresponding vehicle controls. In the supplemental study, body weights of both sexes of the dosed rats were unaffected by administration of DGRE. Survival of dosed rats of each sex in the primary study was dose related and was shorter ($P<0.001$) than that of the vehicle controls. No high dose male rats and only 1/50 high dose female rats lived to the end of the study. Bronchopneumonia was the most frequent cause of early death among the rats and may have resulted from the animals' aspiration of corn oil containing diglycidyl resorcinol ether. Survival of the dosed male rats in the supplemental study was reduced ($P<0.005$) when compared to controls. There was no significant difference in survival between dosed and control female rats in the supplemental study. Survival of dosed and control mice was comparable but poorer in females, with 20/50 (40%) of the controls, 13/50 (26%) of the low dose, and 10/50 (20%) of the high dose groups alive at the end of 2 years. These early deaths were due to suppurative and necrotizing inflammation of the reproductive tract, possibly caused by a *Klebsiella sp.* infection.

The incidences of rats and mice with hyperkeratosis and hyperplasia of the forestomach were compound related. For rats and mice of each sex, incidences of animals with squamous cell papillomas, squamous cell carcinomas, or both occurred with statistically significant positive trends and the incidences in the dosed groups were significantly higher than those in the vehicle controls.

The significantly lower survival of rats in the high dose groups probably reduced the incidence of stomach neoplasms in these groups and was responsible for the numerous decreased overall tumor incidences observed in other organs in dosed groups relative to the controls.

An audit of the experimental data was conducted for the 2-year studies of diglycidyl resorcinol ether. No data discrepancies were found that influenced the final interpretations.

FORESTOMACH LESIONS IN F344/N RATS AND B6C3F$_1$ MICE

	Squamous Cell Papillomas			Squamous Cell Carcinomas		
	RATS					
	Vehicle Control	**25 mg/kg**	**50 mg/kg**	**Vehicle Control**	**25 mg/kg**	**50 mg/kg**
Males	0/50	17/50	6/49	0/50	38/50	4/49
Females	0/49	7/50	1/50	0/49	34/50	3/50
	MICE					
	Vehicle Control	**50 mg/kg**	**100 mg/kg**	**Vehicle Control**	**50 mg/kg**	**100 mg/kg**
Males	0/47	4/49	10/50	0/47	14/49	25/50
Females	0/47	5/49	10/49	0/47	12/49	23/49
	RATS (Supplemental Study)					
	Vehicle Control	**12 mg/kg**		**Vehicle Control**	**12 mg/kg**	
Males	0/50	16/50		0/50	39/50	
Females	0/50	19/50		0/50	27/50	

Under the conditions of these 2-year gavage studies, technical grade diglycidyl resorcinol ether caused hyperkeratosis and hyperplasia of the forestomach in rats and mice. DGRE was carcinogenic for male and female F344/N rats and for male and female B6C3F$_1$ mice, causing both benign and malignant neoplasms of the forestomach.

CONTRIBUTORS

The 2-year studies of diglycidyl resorcinol ether were conducted at EG&G Mason Research Institute under a subcontract to Tracor Jitco, Inc., the prime contractor for the Carcinogenesis Testing Program. The 2-year studies in rats were begun in April 1979 and completed in April 1981. The supplemental rat studies were started in April 1980 and completed in April 1982. The 2-year studies in mice were begun in March 1979 and completed in March 1981.

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The pathology report and selected slides of the primary study were evaluated on February 23, 1982 by the NTP Pathology Working Group, which was composed of:

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Review of the supplemental study in rats was conducted on December 10, 1982. Members of this Pathology Working Group included:

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SUMMARY OF PEER REVIEW COMMENTS ON THE CARCINOGENESIS STUDIES OF DIGLYCIDYL RESORCINOL ETHER

On 28 February 1983, the draft Technical Report on technical grade diglycidyl resorcinol ether underwent 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. Holland, a principal reviewer for the report on the carcinogenesis studies of diglycidyl resorcinol ether (DGRE), agreed with the conclusions, yet wondered what the significance might be of positive PVM titers in rats with regard to the treatment-related bronchopneumonia and to the quality of the animals used in these studies. He offered that there were two reported negative skin painting studies with DGRE. In view of the irritant properties of DGRE, he agreed with the NTP for giving this appropriate consideration in a well-written discussion that the forestomach tumors were likely to have resulted from an indirect or local toxic effect of DGRE. There was further discussion by Dr. Friess and Dr. Holland as to whether the forestomach tumors might have been due to secondary or irritant effects of DGRE as opposed to a specific chemical/tissue interaction. Dr. McConnell said more emphasis would be given to the irritant properties of DGRE.

As a second principal reviewer, Dr. Scala agreed with the conclusions. He faulted the poor quality of the animal husbandry and environmental controls at the laboratory performing these studies and cited the high virus titers in the animals used and the excessive temperature and humidity fluctuations. Further, the failure to kill some concurrent control animals at the time of large numbers of deaths in the test groups reflected poorly on laboratory management. As a third principal reviewer, Dr. Elashoff agreed with the conclusions. He asked whether the presence of 19% impurities in the test compound would restrict interpretability of the study. He agreed with the report that the high and early mortality in high dose rat groups in the primary study led to divergent or contradictory findings among statistical tests yielding confusing information.

Dr. E. McConnell, NTP, speculated that the bronchopneumonia was probably due to aspiration of food resulting from gastric dysfunction caused by the tumors. Dr. Holland said the technical grade nature of the compound should be clearly noted in the summary. Dr. Huff, NTP, indicated this would be given in the title.

Dr. Holland moved that the technical report on the carcinogenesis studies of diglycidyl resorcinol ether be accepted with revisions discussed. Dr. Elashoff seconded the motion and the report was approved unanimously by the Peer Review Panel.

I. INTRODUCTION

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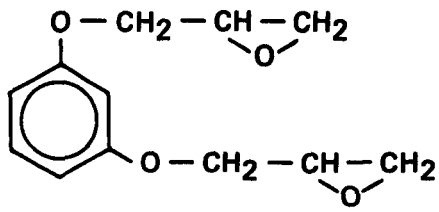

DIGLYCIDYL RESORCINOL ETHER

CAS NO. 101-90-6

$C_{12}H_{14}O_4$ Mol. Wt. 222.2

Diglycidyl resorcinol ether (DGRE), a pale yellow, translucent, amorphous solid at room temperature, has a density of d_4^{25} 1.21 and a refractive index of n_D^{25} 1.54. DGRE is used as a liquid spray epoxy resin, as a diluent in the production of other epoxy resins used in electrical, tooling, adhesive, and laminating applications, and as a curing agent for polysulfide rubber (IARC, 1976). Approximately 3,000 workers are exposed to DGRE (NIOSH, 1978). The quantity of DGRE produced in the United States is not known (USITC, 1981).

Single-dose oral LD_{50} values have been reported for male Long-Evans rats (2.2-3.0 g/kg) and male Webster mice (0.79-1.29 g/kg). The single-dose intraperitoneal LD_{50} values are considerably lower than the oral LD_{50} values: rats - 0.132-0.241 and mice - 0.183-0.324 g/kg (Hine et al., 1958).

Data on the metabolism, pharmacokinetics and tissue distribution of DGRE were not located in the literature.

An 8-hour exposure to air saturated with DGRE (exposure concentration not determined analytically) produced no deaths in rats and mice, but deaths occurred when rabbits received dermal applications totalling up to 1.2 g DGRE (IARC, 1976). Eye and skin irritation was observed in animals in these studies.

In monkeys, monthly intravenous injections (number of injections not specified) of 100 mg/kg-200 mg/kg body weight DGRE produced a progressive lowering of the leukocyte count (Hine and Rowe, 1963). DGRE produced a 27% inhibition of the growth of Walker carcinoma in rats (Hendry et al., 1951).

Diglycidyl resorcinol ether is a potential alkylating agent that may covalently bind to protein, RNA, or DNA if it is not detoxified by epoxide hydrase or conjugated to glutathione (Oesch, 1972; Boyland and Williams, 1965). The NTP found DGRE to be mutagenic in the *Salmonella typhimurium* (strains TA100 and TA1535) microbial mutagenicity assay, with or without metabolic activation; no mutagenic response was observed in strain TA1537 (Appendix G).

Papillomas of the skin were observed in C57BL mice receiving three dermal applications of DGRE per week (dose and duration not stated) (McCammon et al., 1957). This study cannot be evaluated, since the results were not fully reported. In a later study (Kotin and Falk, 1963), dermal applications of 16.6 mg administered three times per week produced only 1 skin tumor in the 14 C57BL mice that survived 8 months.

No skin tumors were observed in groups of 30 Swiss-Millerton mice administered 1% diglycidyl resorcinol ether in benzene by dermal application three times per week for a median survival time of 70 weeks (Van Duuren et al., 1965).

A two-year skin painting study of DGRE using C3Hf/Bd mice also failed to cause any skin neoplasms (Holland et al, 1981). In humans, dermal exposure to DGRE has produced burns and skin sensitization (Hine and Rowe, 1963). The latter authors suggested that the different responses in mice may be related to strain (of mice) differences.

Diglycidyl resorcinol ether was tested because of worker exposure and because previous tests for carcinogenicity were considered inadequate due to insufficient duration and reporting of results (IARC, 1976).

II. MATERIALS AND METHODS

CHEMICAL ANALYSES

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FOURTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Study Design

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Clinical Examinations and Pathology

Data Recording and Statistical Methods

CHEMICAL ANALYSES

Diglycidyl resorcinol ether (DGRE) was obtained from the Ciba-Geigy Corporation (Ardsley, NY) as Araldite ERE 1359 in a single lot (No. P-60002). Purity and identity analyses were conducted at Midwest Research Institute (MRI) (Appendix I). Elemental analyses for carbon and hydrogen agreed with theoretical values. The results of titration of the epoxide groups with *in situ* generated hydrogen iodide indicated a purity of 81.2%. Thin-layer chromatography by one system indicated five trace impurities. A second system indicated nine trace impurities and one slight trace impurity. By gas-liquid chromatography, 30 impurities were detected with a total area of approximately 14% of the major peak area. One of the impurities had an area that was 3.7% of the major peak area, and two groups of unresolved impurities had a combined area of 3.7% and 2.0% of the major peak area. The remaining impurities had a combined area of less than 4% of the major peak area. The identity of the impurities was not determined. The estimated purity of the bulk chemical by gas-liquid chromatography (GLC) is approximately 86%. However, the GLC purity estimation is based on the assumption that the detector response is identical for each component and all components elute from the column. Since the assumptions cannot be confirmed and the purity estimate by the specific epoxide titration procedure is less than the GLC estimate, the best estimate of purity is the 81.2% as determined by the epoxide titration. The infrared and nuclear magnetic resonance spectra were consistent with the structure, although small impurities were noted in the nuclear magnetic spectrum.

Bulk stability studies were carried out at MRI at -20°, 5°, 25°, and 60°C, for 2 weeks using the epoxide titration method. No decomposition was observed in any of the samples. At EG & G Mason Research Institute, DGRE was stored in the dark at 23°C in its original container. Results of repeated bulk chemical analyses at this laboratory throughout the study indicated that no notable changes occurred and confirmed that the material was stable.

DOSAGE PREPARATION

Corn oil was selected for the gavage vehicle and was analyzed monthly for peroxides. To improve the suspendability, DGRE was first dissolved in acetone before being added to corn oil. Stability studies established that the chemical was stable in this vehicle (4% acetone in corn oil) for 7 days at 25°C (Appendix J).

In subsequent studies, MRI found that a viable suspension could be prepared by initially warming the DGRE to 40°C and then adding the clear, liquefied chemical to the corn oil. After mixing, the suspension was homogenized with the aid of sonication. A separate stability study was not conducted for DGRE in corn oil without acetone.

During the 2-year study, the second method of dose preparation was used. Appropriate amounts of DGRE and corn oil were mixed and stored at 0° ± 5°C for no longer than 10 days. Before use, the suspension was warmed to room temperature and homogenized with a Bronson sonifier. Results of the chemical-vehicle analyses at EG & G Mason Research Institute indicated that the analyzed mixtures were properly formulated (Appendix K, Table K1). Dosage preparations had to be stirred continuously during sampling to insure that the preparation was homogeneous.

FOURTEEN-DAY STUDIES

Male and female F344/N rats and B6C3F$_1$ mice (C57BL/6N × C3H/HeN MTV$^-$) were obtained from Harlan Industries and held for approximately 3 weeks before the study began. Groups of five rats of each sex were administered DGRE in corn oil in 14 consecutive daily doses of 0, 190, 380, 750, 1,500, or 3,000 mg/kg body weight. Groups of five mice of each sex were administered doses of 0, 90, 190, 380, 750, or 1,500 mg/kg on the same schedule.

Details of animal maintenance are presented in Table 1. The rats and mice were observed twice daily for mortality. Necropsies were performed on all animals.

THIRTEEN-WEEK STUDIES

Thirteen-week studies were conducted to evaluate the 90-day cumulative toxicity of diglycidyl resorcinol ether and to determine the doses to be used in the 2-year study.

Four-week-old male and female F344/N rats and 5- to 6-week-old male and female B6C3F$_1$ mice were obtained from Harlan Industries, observed for 3 weeks, and then randomized by weight so that average cage weights were approximately equal for all animals of the same sex and species.

Groups of 10 rats of each sex were administered DGRE in corn oil by gavage, 5 days per week for 13 weeks, at doses of 0, 12.5, 25, 50, 100, or 200 mg/kg body weight. Groups of 10 mice of each sex were administered doses of 0, 25, 50, 100, 200, or 400 mg/kg on the same schedule. Details of animal maintenance are presented in Table 1.

Animals were checked for mortality and signs of morbidity twice daily. Those animals that were judged to be moribund were killed with carbon dioxide and necropsies were performed. Each animal was given a weekly clinical examination, including palpation for tissue masses or swelling. Body weight data were collected weekly.

At the end of the 13-week study, survivors were killed and necropsies were performed on these animals and on all animals found dead, unless precluded in whole or in part by autolysis or cannibalization. The following specimens were examined for the control and highest dose group of mice and for the control and two highest dosed groups of rats: gross lesions, tissue masses, abnormal lymph nodes, skin, mandibular lymph nodes, mammary gland, salivary gland, sternebrae, bone marrow, thymus, trachea, lungs and bronchi, heart, thyroid, parathyroid, esophagus, stomach, small intestine, colon, mesenteric lymph nodes, liver, gallbladder (mice), pancreas, spleen, kidneys, adrenals, urinary bladder, prostate/testes or ovaries/uterus, brain, pituitary, and spinal cord. Tissues were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin.

Because of chemical-related lesions found in the higher dose groups, histologic examinations were also performed on the stomachs of male and female rats that received 12.5, 25, or 50 mg/kg and of male and female mice that received 50, 100, or 200 mg/kg. The liver, kidneys, and testes of mice that received 200 mg/kg were examined histologically.

TWO-YEAR STUDIES

Study Design

Using the observations and results from the 13-week study, groups of 50 rats of each sex were administered diglycidyl resorcinol ether in corn oil by gavage 5 days per week for 103 weeks at doses of 0, 25, or 50 mg/kg body weight. Because of early deaths in the high dose male and female rats, a supplemental study using DGRE dose levels of 0 and 12 mg/kg was started 12 months after the primary study. Except for dose, the protocol of the supplemental study was identical to that of the primary study, including the use of the same batch of DGRE. Groups of 50 mice of each sex were administered 0, 50, or 100 mg/kg on the same schedule.

Source and Specifications of Test Animals

Weanling F344 rats and B6C3F$_1$ (C57BL/6N × C3H/HeN MTV$^-$) mice, which were barrier sustained and specific pathogen free, were produced at the Charles River Breeding Laboratories 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 are progeny of defined microbiologically associated parents which were transferred from isolators to barrier maintained rooms. Animals are shipped to the testing laboratory at 4-5 weeks of age. The animals are quarantined at the testing facility for 2-3 weeks, after which the health status of the animals is assessed by a complete pathology evaluation of a selected number of rats and mice. The rodents are placed on study at 6-8 weeks of age.

Five-week-old male and female F344/N rats and B6C3F$_1$ (C57BL/6N × C3H/HeN MTV$^-$) mice were obtained from Charles River Breeding Laboratories, observed for 3 weeks, and then 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.

The health of the animals used in this 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 1978 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 the C3H mice monitored were variant at one to three loci, indicating some heterogeneity in the C3H line. Nevertheless, the genome of this line is more homogeneous than those of randomly 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 these studies. The influence of the potential genetic nonuniformity in the hybrid mice on the test results is not known, but should not affect the validity of the studies since matched concurrent controls were included.

Animal Maintenance

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

Twelve changes of room air were provided per hour. Fluorescent lighting provided illumination 12 hours per day. The temperature in the animal rooms was 17°-32°C and the humidity was 20%-81%. The following variations in temperature and humidity were observed:

Temperature (°C)	Percent of Readings
<20	3.4
20-25.9	96.0
26-26.9	0.5
27-27.9	0
28-29	0.1
30-32	<0.1

Humidity (Percent)	Percent of Readings
20-29	10.2
30-39	13.1
40-59	39.5
≥60	37.2

Clinical Examinations and Pathology

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

Examinations for grossly visible lesions were performed on major tissues or organs. Tissues were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. The following were examined microscopically: tissue masses, abnormal lymph nodes, skin, mandibular or mesenteric lymph nodes, mammary gland, salivary gland, sternebrae, bone marrow, thymus, larynx, 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, and pituitary.

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

The classification of neoplastic nodules in the liver 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, neoplasms, and other slides about which the original and quality assurance pathologists disagreed were submitted to the Chairperson of the Pathology Working Group (PWG) for evaluation. Representative slides selected by the Chairperson were reviewed blindly by PWG pathologists, who reached a consensus and compared their findings with the original diagnoses. 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 the survival analyses are two-sided.

The incidence of neoplastic or nonneoplastic lesions has been given as the ratio of the number of animals bearing such lesions at a specific anatomic site to the number of animals in which that site was examined. In most instances, the denominators included only those animals for which that site was examined histologically. However, when macroscopic examination was required to detect lesions (e.g., skin or mammary tumors) prior to histologic sampling, or when lesions could have appeared at multiple sites (e.g., lymphomas), the denominators consist of the number of animals on which necropsies were performed.

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

The first method of analysis assumed that all tumors of a given type observed in animals dying before the end of the study were "fatal"; i.e., they either directly or indirectly caused the death of the animal. According to this approach, the proportions of tumor-bearing animals in the dosed and control groups were compared at each point in time at which an animal died with a tumor of interest. The denominators of these proportions were the total number of animals at risk in each group. These results, including the data from animals killed at the end of the study, were then combined by the Mantel-Haenszel 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 the following 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 1. EXPERIMENTAL DESIGN, ANIMAL MAINTENANCE, AND DOSE PREPARATION

	Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies *(a)*
Experimental Design			
Size of Test Groups	5 females and 5 males of each species	10 females and 10 males of each species	50 females and 50 males of each species
Doses	Rats: 0, 190, 380, 750, 1,500, or 3,000 mg/kg body weight in corn oil by gavage (dose volume: 5 ml/kg body weight)	Rats: 0, 12.5, 25, 50, 100, or 200 mg/kg body weight in corn oil by gavage (dose volume: 3 ml/kg)	Rats: 0, 25, or 50 mg/kg body wt in corn oil by gavage (dose volume: body weight) 3 ml/kg
	Mice: 0, 90, 190, 380, 750, or 1,500 mg/kg body weight in corn oil by gavage (dose volume: 5 ml/kg body weight)	Mice: 0, 25, 50, 100, 200, or 400 mg/kg body weight in corn oil by gavage (dose volume: 3 ml/kg)	Mice: 0, 50, or 100 mg/kg body weight in corn oil by gavage (dose volume: 3 ml/kg body weight) Supplemental Two-Year Studies Rats: 0 or 12 mg/kg body wt in corn oil by gavage
Duration of Dosing	14 consecutive days; killed on day 15	13 weeks (5 days per week)	103 weeks (5 days per week)
Type and Frequency of Observations	Observed twice daily for morbidity or mortality; initial and final individual body weights recorded	Observed twice daily for morbidity or mortality; animal weights measured weekly.	Observed twice daily for mortality or morbidity; weighed once weekly for first 12 weeks and monthly thereafter.
Necropsy and Histological Examination	Necropsies performed on all animals; stomachs from one rat and two mice examined histologically	Necropsies performed on all animals; following tissues examined in the two highest dose groups of rats and highest dose group of mice: tissue masses, gross lesions, skin, mandibular lymph nodes; mammary gland, salivary gland, bone marrow, sternebrae, thymus, trachea, lungs and bronchi, heart, thyroid, parathyroid, esophagus, stomach, small intestine, colon, liver, pancreas, gallbladder (mouse), spleen, kidneys, adrenals, mesenteric lymph notes, urinary bladder, prostate/testes, ovaries/uterus, brain, pituitary, and spinal cord (if grossly abnormal); histologic exam on stomach of rats administered 12.5, 25, or 50 mg/kg and of mice receiving	Necropsies performed on all animals; all groups received histopathologic exam including: tissue masses, gross lesions, abnormal lymph nodes, mandibular or mesenteric lymph nodes, mammary gland, salivary gland, sternebrae, bone marrow, thymus, trachea, larynx, lungs and bronchi, heart, thyroid, parathyroid, esophagus, stomach, small intestine, colon, liver, gallbladder (mouse only), pancreas, spleen, kidneys, adrenals, urinary bladder, prostate/testes or ovaries/uterus, brain, pituitary, and skin

TABLE 1. EXPERIMENTAL DESIGN, ANIMAL MAINTENANCE, AND DOSE PREPARATION (Continued)

	Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies *(a)*
Experimental Design			
Necropsy and Histological Examination (Continued)		50, 100, or 200 mg/kg; liver, kidneys, and testes examined histologically in mice administered 200 mg/kg	
Animals and Animal Maintenance			
Species	F344/N rats; B6C3F$_1$ mice	F344/N rats; B6C3F$_1$ mice	F344/N rats; B6C3F$_1$ mice
Animal Source	Harlan Industries (Indianapolis, IN)	Harlan Industries	Charles River, Portage, MI
Time Held Before Start of Test	Rats: 26 days; mice: 19 days	Rats and mice: 21 days	Rats: 25 days; mice: 21 days
Age When Placed on Study	Rats: 8 weeks; mice: 7 weeks	Rats: 7 weeks; mice: 8 to 9 weeks	Rats and mice: 8 to 9 weeks
Age When Killed	Rats: 10 weeks; Mice: 9 weeks	Rats: 20 weeks; mice: 21 to 22 weeks	Rats and Mice: 111 to 113 weeks
Method of Animal Distribution	Animals were distributed to cages so that average cage weights were approx. equal for all animals of same sex and species	Same as 14-day study	Animals were assigned to cages according to a table of random numbers; cages were assigned to dosed and control groups according to another table of random numbers
Feed	Wayne Laboratory Blox® Allied Mills (Chicago, IL)	Same as 14-day study	Same as 14-day study
Bedding	Hardwood chips: Aspen Bed® American Excelsior (Baltimore, MD)	Same as 14-day study	Same as 14-day study
Water	Glass bottles with rubber stoppers and stainless steel sipper tubes; changed twice weekly	Edstrom automatic watering system, Edstrom Industries (Waterford, WI)	Same as 13-week study
Cages	Polycarbonate	Same as 14-day study	Same as 14-day study
Cage Filters	Non-woven fiber filter Lab Products (Rochelle Park, NJ)	Same as 14-day study	Same as 14-day study
Animals Per Cage	Five	Same as 14-day study	Same as 14-day study

TABLE 1. EXPERIMENTAL DESIGN, ANIMAL MAINTENANCE, AND DOSE PREPARATION (Continued)

	Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies *(a)*
Animal Room Environment	Temperature and relative humidity not reported. 12 hrs of fluorescent light per day; 10 room air changes per hour.	18°-29°C (mean temperature: 22°C); 21%-70% relative humidity (mean 37.8%); 12 hours of fluorescent light per day; 10 room air changes per hour	17°-32°C (mean temperature: 22°C); 23%-81% relative humidity; mean humidity: 48% (rats) or 50% (mice) for first 21-22 months and then 60% (rats) or 61% (mice) for rest of studies; 12 hours of fluorescent light per day; 12 room air changes per hour
Other Chemicals on Test in Same Room	Not stated	None	None
Chemical/Vehicle Mixture Preparation	Diglycidyl resorcinol ether was liquefied by warming and mixed on a molar basis with corn oil in a stoppered graduated cylinder by manual inversion	Same as 14-day study	Diglycidyl resorcinol ether was liquified by warming to 40°C, added to corn oil on a weight/volume basis, and homogenized
Maximum Storage Time	Not stated	10 days	10 days
Storage Conditions	4°C	4°C	5°C

(a) Data for two-year supplemental studies were the same as for original studies except where noted.

III. RESULTS

RATS

FOURTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

MICE

FOURTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

FOURTEEN-DAY STUDIES

All males and females that received 750, 1,500, or 3,000 mg/kg and 2/5 males that received 380 mg/kg died before the end of the study (Table 2). All rats receiving 380 mg/kg and 2/5 males and 1/5 females receiving 190 mg/kg lost weight during the study. Clinical signs were not compound related.

Macroscopically observable effects were found in the kidney and stomachs of rats administered diglycidyl resorcinol ether (Table 3). The renal medullae were red and more prominent than usual. The forestomachs showed reddened mucosae and early development of small papillary-like growths. No histopathologic examinations were performed to further characterize these lesions.

TABLE 2. SURVIVAL AND MEAN BODY WEIGHT OF RATS ADMINISTERED DIGLYCIDYL RESORCINOL ETHER IN CORN OIL BY GAVAGE FOR 14 DAYS

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	156.4 ± 4.3	176.2 ± 7.1	+19.8 ± 3.0	—
190	5/5	156.2 ± 4.5	156.6 ± 4.5	+ 0.4 ± 1.4	-11
380	3/5	151.7 ± 2.6	136.0 ± 1.7	-15.7 ± 2.4	-23
750	0/5	*(d)*	*(d)*	*(d)*	*(d)*
1,500	0/5	*(d)*	*(d)*	*(d)*	*(d)*
3,000	0/5	*(d)*	*(d)*	*(d)*	*(d)*
Females					
0	5/5	118.0 ± 5.5	130.8 ± 7.3	+12.8 ± 1.9	—
190	5/5	117.4 ± 5.6	119.4 ± 6.2	+ 2.0 ± 0.8	- 9
380	5/5	117.8 ± 3.9	109.8 ± 5.4	- 8.0 ± 2.0	-16
750	0/5	*(d)*	*(d)*	*(d)*	*(d)*
1,500	0/5	*(d)*	*(d)*	*(d)*	*(d)*
3,000	0/5	*(d)*	*(d)*	*(d)*	*(d)*

(a) Number surviving/number per 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) Final Body Weight Relative to Controls =

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

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

TABLE 3. INCIDENCES OF SOME COMPOUND-RELATED EFFECTS IN RATS ADMINISTERED DIGLYCIDYL RESORCINOL ETHER IN CORN OIL BY GAVAGE FOR 14 DAYS

Dose (mg/kg)	Observation		
	Renal Medullae - Dark Red	Stomach - Reddened Mucosa	Stomach - Papillary Growths
Males			
0	0/5	0/5	0/5
190	0/5	0/5	0/5
380	2/5	2/5	1/5
750	3/5	5/5	0/5
1,500	5/5	5/5	0/5
3,000	0/5	5/5	0/5
Females			
0	0/5	0/5	0/5
190	0/5	0/5	5/5
380	0/5	0/5	4/5
750	5/5	5/5	0/5
1,500	5/5	4/5	0/5
3,000	5/5	2/5	0/5

THIRTEEN-WEEK STUDIES

One male that received 200 mg/kg died during week 8. (The cause of death was not determined, but the rat was emaciated.) Mean body weight was depressed 10% or more in males that received 100 mg/kg and in males and females that received 200 mg/kg (Table 4).

TABLE 4. SURVIVAL AND MEAN BODY WEIGHT OF RATS ADMINISTERED DIGLYCIDYL RESORCINOL ETHER IN CORN OIL 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	127.4 ± 2.6	323.0 ± 7.6	+195.6 ± 6.4	
12.5	10/10	128.3 ± 2.7	324.3 ± 5.2	+196.0 ± 5.2	0
25	10/10	128.6 ± 2.5	331.1 ± 3.6	+202.5 ± 3.5	+ 3
50	10/10	128.1 ± 2.7	316.6 ± 5.5	+188.5 ± 4.4	- 2
100	10/10	129.2 ± 2.7	292.1 ± 4.4	+162.9 ± 4.5	-10
200	9/10	128.4 ± 2.9	241.8 ± 2.2	+113.4 ± 2.4	-25
Females					
0	10/10	104.9 ± 2.0	185.7 ± 2.9	+ 80.8 ± 3.6	
12.5	10/10	104.9 ± 1.8	184.7 ± 2.3	+ 79.8 ± 2.9	- 1
25	10/10	104.5 ± 1.8	181.2 ± 2.7	+ 76.7 ± 2.3	- 2
50	10/10	105.2 ± 1.9	184.2 ± 3.4	+ 79.0 ± 4.1	- 1
100	10/10	105.3 ± 2.0	179.5 ± 2.8	+ 74.2 ± 3.2	- 3
200	10/10	105.0 ± 1.6	167.5 ± 3.6	+ 62.5 ± 2.8	-10

(a) Number surviving/number per 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) Final Body Weight Relative to Controls =

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

III. RESULTS: RATS—THIRTEEN-WEEK STUDIES

Compound-related lesions were observed in the forestomach (squamous cell papilloma, hyperkeratosis, and basal cell hyperplasia) and in the liver (minimal to mild centrilobular fatty metamorphosis). Chronic inflammation in the mesenteric lymph nodes (Table 5) was probably secondary to the inflammation or ulceration of the forestomach. Compared with the controls, the three male rats with fatty metamorphosis in the liver had decreased final body weights. However, lower mean body weight gains were also found in other male and female rats administered 200 mg/kg which did not show hepatic fatty metamorphosis.

At necropsy, the wall of the forestomach of rats was sometimes thickened and the mucosal surface contained small, white papillomatous nodules. When examined microscopically, some nodules were squamous papillomata, having localized acanthosis and papillary projections of the epidermis covered by thick layers of keratinized cells. The basal layer of the epithelium was hyperplastic, sometimes showing finger-like projections into the submucosa. Diffuse hyperkeratosis, focal basal cell hyperplasia, or both were usually present in the forestomach of rats without discrete squamous papillomata. In some rats that received 200 mg/kg, ulceration in the forestomach had completely eroded the epithelium and extended into the muscularis. A few rats without ulcers had circumscribed areas of inflammation in the stomach (Table 5).

Because of the mean body weight depression (relative to controls) observed at the higher doses, doses of 25 and 50 mg/kg diglycidyl resorcinol ether in corn oil were selected for both male and female rats in the 2-year study.

TABLE 5. LESIONS OBSERVED IN RATS ADMINISTERED DIGLYCIDYL RESORCINOL ETHER IN CORN OIL OIL BY GAVAGE FOR 13 WEEKS

		Dose (mg/kg)											
		Males(a)						Females(a)					
Site		**0**	**12.5**	**25**	**50**	**100**	**200**	**0**	**12.5**	**25**	**50**	**100**	**200**
Stomach	Inflammation	0	8	6	3	0	3	0	8	9	3	1	2
	Ulcer	0	0	0	0	0	4	0	0	0	1(b)	0	1
	Fibrosis	0	2	2	0	0	0	0	0	0	0	0	0
	Hyperkeratosis	0	1	1	7	9	7	0	0	0	1	9	7
	Basal cell hyperplasia	2	3	5	7	9	7	1	3	2	5	7	7
	Squamous papilloma	0	0	0	1	1	3	0	0	0	0	1	2
	No lesion seen	8	1	1	0	0	0	9	1	0	3	0	0
Lymph Node:	Inflammation	0	NE(c)	NE	NE	NE	7	0	NE	NE	NE	NE	4
Liver:	Fatty Metamorphosis, mild or slight	0	NE	NE	NE	NE	3	0	NE	NE	NE	NE	0

(a) Ten animals were examined in each dose group.

(b) Ulcer was shallow lesion of glandular stomach, not forestomach.

(c) NE = not examined.

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Throughout most of the primary study (after week 30), mean body weights of high dose rats of each sex were lower than those of the controls (Figure 1 and Table 6). Except for weeks 80 to 100, mean body weights of low dose males and females were comparable with those of the controls. Wheezing and respiratory distress were the only compound-related clinical signs observed. Body weight gain in the supplemental study was not affected by the administration of 12 mg/kg of DGRE (Figure 2 and Table 7).

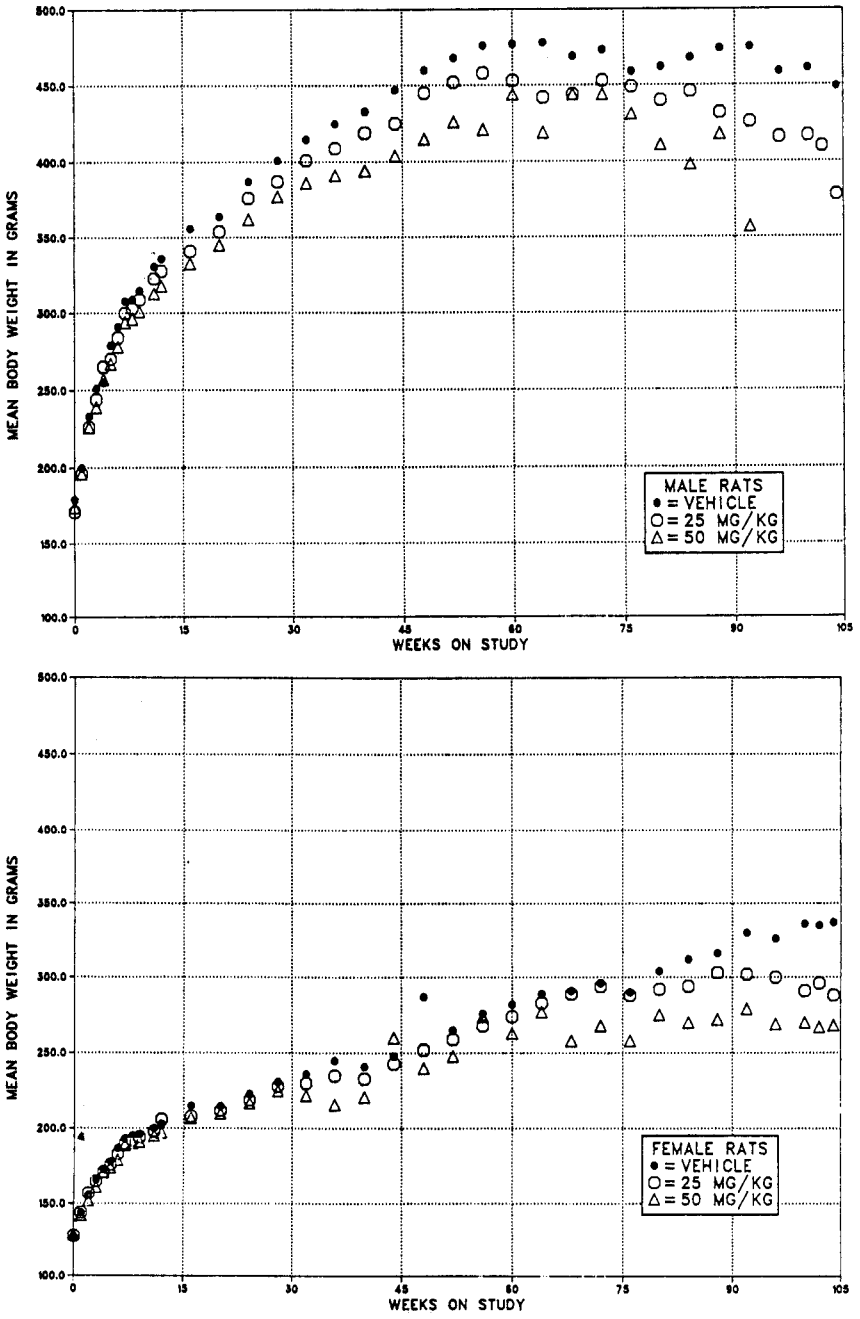

Figure 1. Growth Curves for Rats Administered Diglycidyl Resorcinol Ether in Corn Oil by Gavage

TABLE 6. MEAN BODY WEIGHTS OF RATS ADMINISTERED DIGLYCIDYL RESORCINOL ETHER IN CORN OIL BY GAVAGE FOR TWO YEARS

Weeks on Study	Vehicle Control		Low Dose			High Dose		
	Av. Wt. (grams)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of controls)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of controls)	No. of Survivors
MALE								
0	179	50	171	95.5	50	174	97.2	50
1	200	50	196	98.0	50	196	98.0	50
2	233	50	226	97.0	50	226	97.0	50
3	251	50	244	97.2	50	239	95.2	50
4	255	50	265	103.9	50	257	100.8	50
5	279	50	270	96.8	50	267	95.7	50
6	291	50	284	97.6	50	278	95.5	50
7	308	50	300	97.4	50	294	95.5	50
8	309	50	303	98.1	50	296	95.8	50
9	315	50	309	98.1	50	301	95.6	50
11	331	50	323	97.6	50	313	94.6	50
12	336	50	328	97.6	50	318	94.6	50
16	356	50	341	95.8	49	333	93.5	50
20	364	50	354	97.3	49	345	94.8	50
24	387	50	376	97.2	49	362	93.5	50
28	401	50	387	96.5	49	377	94.0	50
32	415	50	401	96.6	49	386	93.0	46
36	425	50	409	96.2	48	391	92.0	38
40	433	50	419	96.8	48	394	91.0	27
44	447	50	425	95.1	48	404	90.4	23
48	460	49	445	96.7	48	415	90.2	20
52	468	49	452	96.6	48	426	91.0	16
56	476	49	458	96.2	48	421	88.4	12
60	477	49	453	95.0	47	444	93.1	9
64	478	49	442	92.5	42	419	87.7	5
68	469	49	444	94.7	38	444	94.7	4
72	473	49	453	95.8	35	444	93.9	4
76	459	49	449	97.8	30	431	93.9	4
80	462	45	440	95.2	27	411	89.0	3
84	468	45	446	95.3	23	398	85.0	3
88	474	45	432	91.1	20	418	88.2	2
92	475	44	426	89.7	16	357	75.2	2
96	459	44	416	90.6	13	-	-	-
100	461	42	417	90.5	9	-	-	-
102	-	-	410	-	6	-	-	-
104	449	42	378	84.2	5	-	-	-
FEMALE								
0	127	50	128	100.8	50	129	101.6	50
1	144	50	144	100.0	50	142	98.6	50
2	156	50	157	100.6	50	152	97.4	50
3	166	50	165	99.4	50	161	97.0	50
4	173	50	171	98.8	50	171	98.8	50
5	178	50	176	98.9	50	174	97.8	50
6	187	50	183	97.9	50	179	95.7	50
7	193	50	190	98.4	50	189	97.9	50
8	195	50	192	98.5	50	190	97.4	50
9	196	50	194	99.0	50	191	97.4	50
11	200	50	198	99.0	50	195	97.5	50
12	203	50	206	101.5	50	197	97.0	50
16	215	50	208	96.7	50	207	96.3	50
20	215	50	212	98.6	50	210	97.7	50
24	223	50	219	98.2	50	217	97.3	50
28	231	50	228	98.7	50	225	97.4	47
32	236	50	230	97.5	50	222	94.1	40
36	245	50	235	95.9	50	216	88.2	26
40	241	50	233	96.7	50	221	91.7	16
44	248	50	243	98.0	49	260	104.8	11
48	287	50	252	87.8	45	240	83.6	7
52	265	50	259	97.7	42	248	93.6	7
56	276	50	268	97.1	42	274	99.3	4
60	282	50	274	97.2	41	263	93.3	4
64	289	50	283	97.9	39	277	95.8	2
68	291	50	289	99.3	37	258	88.7	2
72	296	50	294	99.3	36	268	90.5	2
76	290	50	288	99.3	36	258	89.0	2
80	304	49	292	96.1	35	275	90.5	2
84	312	47	294	94.2	34	270	86.5	2
88	316	46	303	95.9	29	272	86.1	2
92	330	44	302	91.5	26	279	84.5	1
96	326	39	300	92.0	25	269	82.5	1
100	336	37	291	86.6	19	270	80.4	1
102	335	37	296	88.4	17	267	79.7	1
104	337	36	288	85.5	16	268	79.5	1

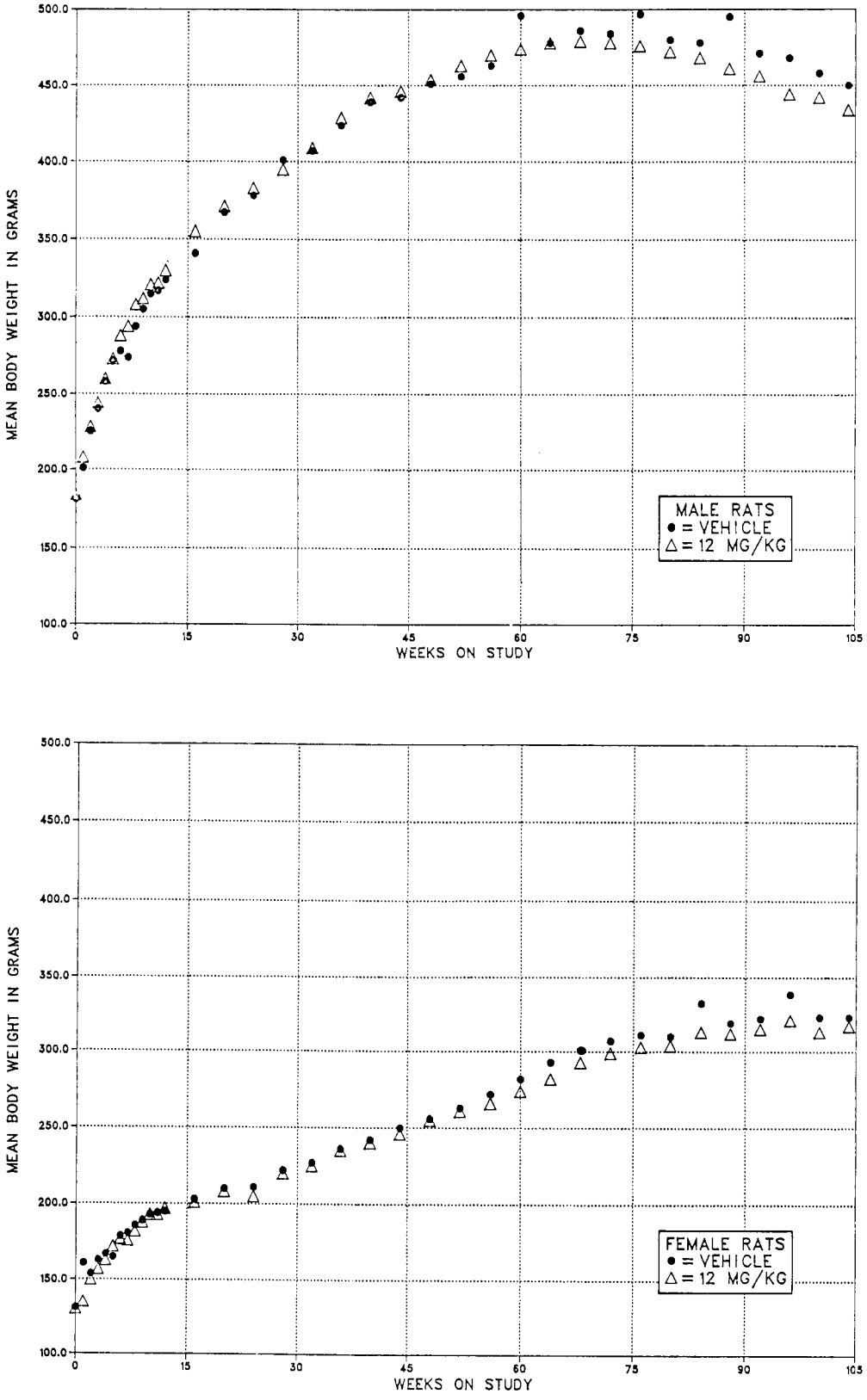

Figure 2. Growth Curves for Rats Administered Diglycidyl Resorcinol Ether by Gavage in the Supplemental Study

TABLE 7. MEAN BODY WEIGHTS OF RATS ADMINISTERED DIGLYCIDYL RESORCINOL ETHER IN CORN OIL BY GAVAGE IN THE SUPPLEMENTAL STUDY

	Weeks on Study	Vehicle Control		Dosed		
		Av. Wt. (grams)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of controls)	No. of Survivors
MALE						
	0	181	50	184	101.7	50
	1	201	50	208	103.5	50
	2	225	50	228	101.3	50
	3	240	50	244	101.7	50
	4	258	50	260	100.8	50
	5	272	50	273	100.4	50
	6	278	50	288	103.6	50
	7	274	50	294	107.3	50
	8	294	50	308	104.8	50
	9	305	50	312	102.3	50
	10	315	50	321	101.9	50
	11	317	50	322	101.6	50
	12	324	50	330	101.9	50
	16	341	50	355	104.1	50
	20	367	50	371	101.1	50
	24	378	50	383	101.3	50
	28	401	50	395	98.5	50
	32	407	50	409	100.5	50
	36	424	50	429	101.2	50
	40	439	50	442	100.7	50
	44	442	50	446	100.9	50
	48	451	50	454	100.7	50
	52	456	50	463	101.5	50
	56	463	50	470	101.5	50
	60	496	49	474	95.6	49
	64	478	48	478	100.0	48
	68	486	47	479	98.6	48
	72	484	46	478	98.8	48
	76	497	46	476	95.8	47
	80	480	46	472	98.3	45
	84	478	45	468	97.9	43
	88	495	43	461	93.1	41
	92	471	43	456	96.8	34
	96	468	42	444	94.9	32
	100	458	41	442	96.5	28
	104	450	39	434	96.4	23
FEMALE						
	0	131	50	130	99.2	50
	1	161	50	135	83.9	50
	2	154	50	150	97.4	50
	3	163	50	157	96.3	50
	4	167	50	163	97.6	50
	5	165	50	172	104.2	50
	6	179	50	177	98.9	50
	7	181	50	176	97.2	50
	8	186	50	182	97.8	50
	9	189	50	188	99.5	50
	10	193	50	193	100.0	50
	11	194	50	193	99.5	50
	12	195	50	197	101.0	50
	16	203	50	201	99.0	50
	20	210	50	208	99.0	50
	24	211	50	205	97.2	50
	28	222	49	220	99.1	50
	32	227	49	225	99.1	50
	36	236	49	235	99.6	50
	40	242	49	240	99.2	50
	44	250	49	246	98.4	50
	48	256	48	255	99.6	50
	52	263	48	261	99.2	50
	56	272	48	266	97.8	49
	60	282	48	274	97.2	49
	64	293	48	282	96.2	48
	68	301	48	293	97.3	47
	72	307	48	299	97.4	47
	76	311	47	303	97.4	45
	80	310	47	304	98.1	45
	84	333	46	313	94.0	44
	88	319	45	312	97.8	44
	92	322	43	315	97.8	42
	96	339	42	321	94.7	37
	100	323	40	313	96.9	37
	104	323	39	317	98.1	34

Survival

The probabilities of survival for male and female rats in this bioassay are shown by the Kaplan and Meier curves in Figure 3. The survival of male and female rats was significantly reduced ($P<0.001$) when compared with that for the controls, and the high dose group of each sex had significantly lower survival ($P<0.001$) than that in the low dose group.

In male rats, 42/50 (84%) of the controls, 5/50 (10%) of the low dose, and 0/50 of the high dose group lived to the end of the study (104-105 weeks). In female rats, 37/50 (74%) of the controls, 16/50 (32%) of the low dose, and 1/50 (2%) of the high dose group lived to the end of the study. The survival data include one low dose male, one control female, and one low dose female that died during the termination of the study. For statistical purposes, these animals have been pooled with those killed at the end of the study. Most of the early deaths not related to tumor induction were attributable to bronchopneumonia.

The probabilities of survival of male and female rats in the supplemental study are shown by the Kaplan and Meier curves in Figure 4. Survival of the male dosed rats was significantly reduced ($P=0.003$) when compared with that of the controls. No significant difference in survival was observed between dosed and control female rats.

In male rats, 39/50 (78%) of the controls and 23/50 (46%) of the dosed group lived to the end of the study (104-105 weeks). In female rats, 39/50 (78%) of the controls and 35/50 (70%) of the dosed group lived to the end of the study. The survival data include one control male and one dosed female (moribund sacrifice) 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.

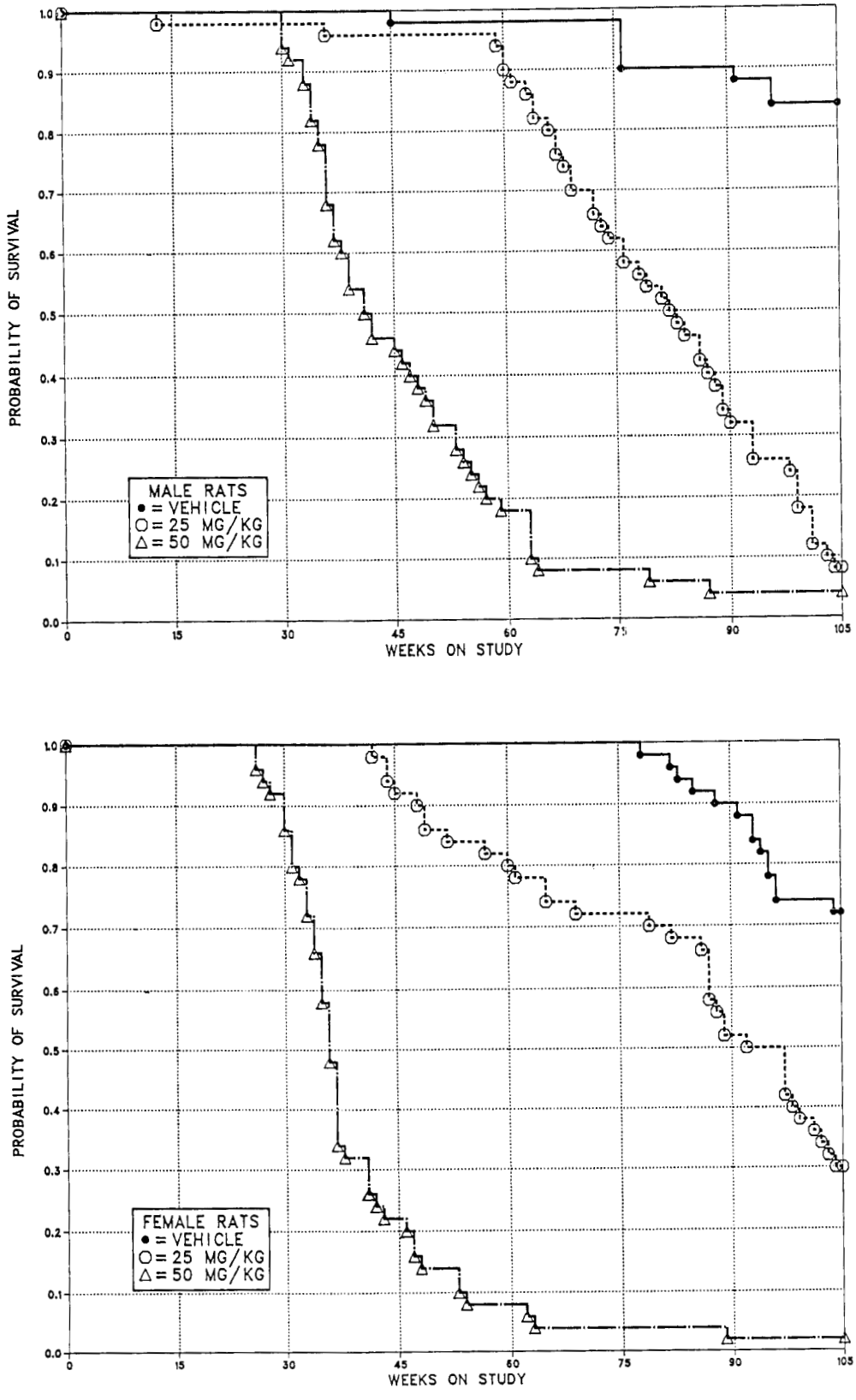

Figure 3. Survival Curves for Rats Administered Diglycidyl Resorcinol Ether in Corn Oil by Gavage

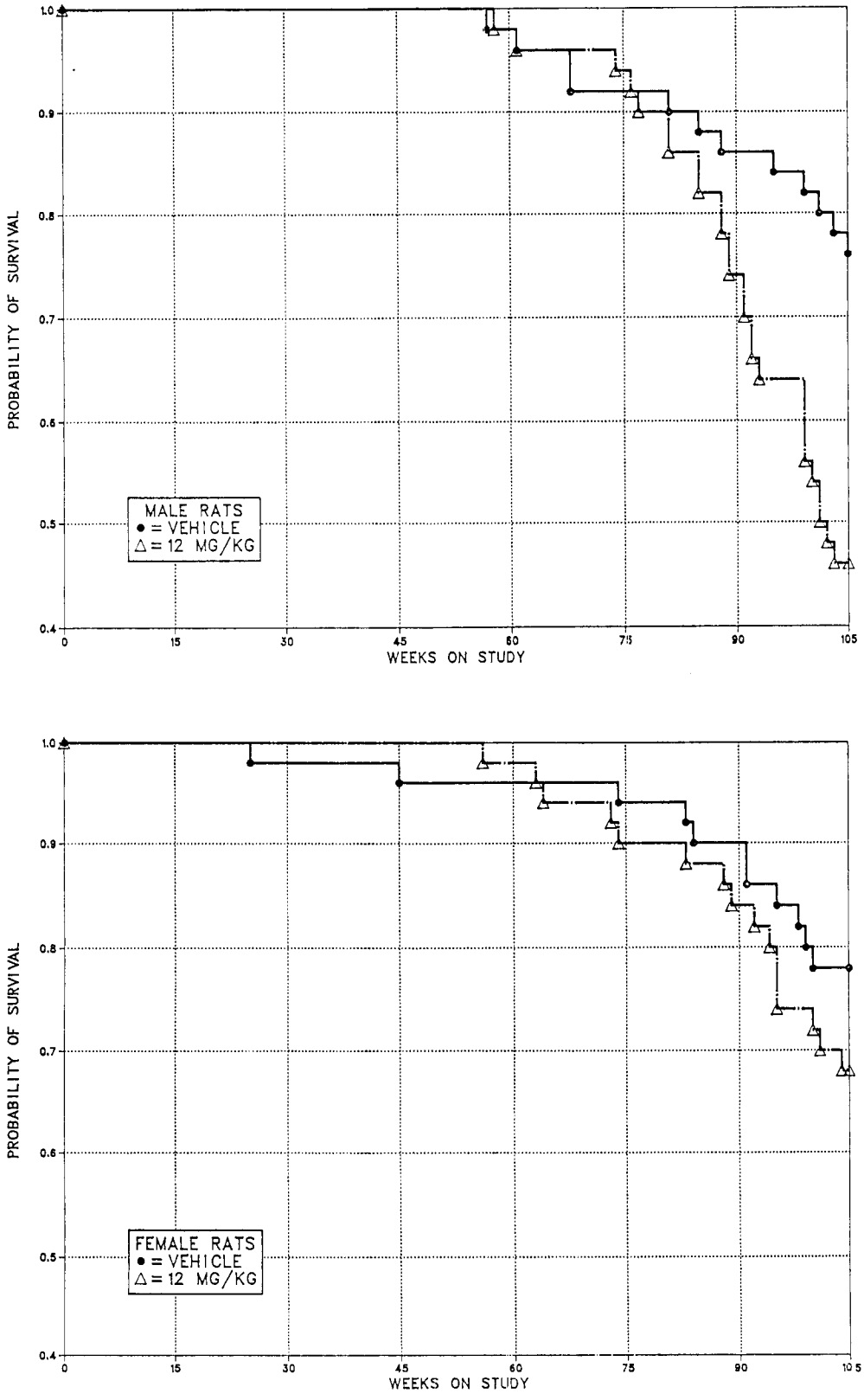

Figure 4. Survival Curves for Rats Administered Diglycidyl Resorcinol Ether by Gavage in the Supplemental Study

Pathology and Statistical Analyses of Results

Histopathologic findings on neoplasms in rats are summarized in Appendix A, Tables A1 and A2 (primary study) and Tables A5 and A6 (supplemental study); Appendix Tables A3 and A4 (primary study) and Tables A7 and A8 (supplemental study) 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 (primary study) and Tables C3 and C4 (supplemental study). Historical incidences of tumors in control animals are listed in Appendix F. Appendix E, Tables E1 and E2, (primary study) and Tables E5 and E6 (supplemental study) contain the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the groups. The statistical analyses used are discussed in chapter II (Data Recording and Statistical Methods) and Appendix E (footnotes).

The statistical analyses and interpretation of the tumor incidence data for rats in the primary study were complicated by the marked reduction in survival in dosed male and female rats when compared with that of the controls. No control animals were killed when the dosed animals were dying. Consequently, the incidental tumor test is of little or no value, since there is little overlapping of survival in dosed and control groups. This test was not performed for rats. In addition, the results of the life table and "unadjusted" analyses (i.e., the Fisher exact and Cochran-Armitage tests) were frequently contradictory. That is, the life table analysis often indicated a significant positive trend while the unadjusted analysis indicated a significant negative trend. These results were produced because life table analysis is sensitive to the time at which animals die with tumors. Thus, for these data life table analyses give more emphasis to tumors in the dosed groups (which generally occurred in animals dying early in the study) than to tumors in the controls (which generally occurred later in the study, when few dosed animals were alive for comparative purposes). Conversely, the unadjusted analysis compares only the overall tumor rates. These incidences are frequently lower in the dosed groups than in the controls because of the early deaths in the dosed groups.

Because of these problems, evidence of a positive effect by both life table and unadjusted analyses was considered necessary before an increase in tumor incidence was regarded as being related to chemical administration. These criteria would not apply when neoplasms are clearly recognized as the cause of death; life table analysis would be appropriate in this instance. The problems noted above did not apply to the supplemental study in which markedly reduced survival was not observed, and hence the usual analyses of tumor incidence data were employed.

Stomach: Diglycidyl resorcinol ether produced hyperkeratosis, hyperplasia, and neoplasms of the squamous epithelium of the forestomach in both the primary and the supplemental studies (Tables 8 and 9). The squamous epithelium of the esophagus and nasopharynx was hyperkeratotic in some rats, but no tumors were found.

Postmortem examination of the stomachs revealed numerous small rough nodules on the nonglandular mucosa that progressed in some animals to form large, white, fungiform masses which were occasionally ulcerated. The larger lesions involved adjacent tissues such as the spleen, pancreas, and lymph nodes. Histologically, the thickened mucosa showed intense hyperkeratosis that was usually accompanied by hyperplasia of the basal layers. Small nodules, diagnosed as squamous papillomas, were characterized by projections of hyperkeratotic epithelium supported by a fibrovascular core. These changes appeared to be identical to those found in the 13-week study.

In the larger masses, the basal cells developed hyperchromatism, pleomorphism, and parachromatin clearing—all signs of malignancy. The masses grew downward through the basement membrane into and through the muscularis mucosa in irregular strands and clumps, and keratin pearls were often produced. Both normal and abnormal mitotic figures were frequently observed. These lesions were diagnosed as squamous cell carcinomas. Metastases from these tumors were found in 14 low dose males, 1 high dose male, and 5 low dose females. Metastatic tumors were found in the regional lymph nodes, pancreas, liver, spleen, lungs, and brain.

TABLE 8. INCIDENCES OF F344/N RATS WITH HYPERPLASTIC AND NEOPLASTIC LESIONS OF THE STOMACH IN THE PRIMARY STUDY

	Males			Females		
	Vehicle Control	Low Dose	High Dose	Vehicle Control	Low Dose	High Dose
No. of Stomachs Examined	50	50	49	49	50	50
Basal Cell Hyperplasia	1	16	34	2	12	33
Hyperkeratosis	1	12	43	1	12	48
Squamous Cell Papilloma	0	17	6	0	7	1
Squamous Cell Carcinoma	0	38	4	0	34	3
Adenocarcinoma	0	1	0	0	0	0
Leiomyosarcoma	0	0	0	0	1	0
Carcinosarcoma	0	0	0	0	1	0
Total Number of Animals with Proliferative Stomach Lesions	1	49	49	2	50	50

TABLE 9. INCIDENCES OF F344/N RATS WITH HYPERPLASTIC AND NEOPLASTIC LESIONS OF THE FORESTOMACH IN THE SUPPLEMENTAL STUDY

	Males		Females	
	Vehicle Control	Dosed	Vehicle Control	Dosed
No. of Stomachs Examined	50	50	50	50
Basal Cell Hyperplasia	6	37	3	45
Basal Cell Carcinoma	0	0	0	1
Hyperkeratosis	0	38	0	46
Squamous Cell Papilloma	0	16	0	19
Squamous Cell Carcinoma	0	39	0	27
Total Number of Animals with Proliferative Stomach Lesions	6	48	3	48

Low and high dose male and female rats had statistically significant increased incidences of squamous cell papillomas and carcinomas, although the effects in the high dose groups were not as striking (Tables 10 and 11). The markedly increased number of early deaths in high dose male and female groups may explain the low incidences of benign and malignant neoplasms

TABLE 10. INCIDENCES OF NEOPLASMS OF THE STOMACH IN MALE RATS ADMINISTERED DIGLYCIDYL RESORCINOL ETHER IN CORN OIL BY GAVAGE FOR TWO YEARS

	Vehicle Control	25 mg/kg	50 mg/kg
Squamous Cell Papilloma			
Overall Incidence	0/50 (0%)	17/50 (34%)	6/49 (12%)
Adjusted Incidence *(a)*	0.0%	40.9%	33.5%
Terminal Incidence	0/42 (0%)	0/5 (0%)	0/0 (0%)
Life Table Test	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test	P=0.058		
Fisher Exact Test		P<0.001	P=0.012
Squamous Cell Carcinoma			
Overall Incidence	0/50 (0%)	38/50 (76%)	4/49 (8%)
Adjusted Incidence *(a)*	0.0%	100%	100%
Terminal Incidence	0/42 (0%)	5/5 (100%)	0/0 (0%)
Life Table Test	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test	P=0.199		
Fisher Exact Test		P<0.001	P=0.056

(a) Kaplan-Meier estimated tumor incidence at the end of the study after adjusting for intercurrent mortality.

TABLE 11. INCIDENCES OF NEOPLASMS OF THE FORESTOMACH IN FEMALE RATS ADMINISTERED DIGLYCIDYL RESORCINOL ETHER IN CORN OIL BY GAVAGE FOR TWO YEARS

	Vehicle Control	25 mg/kg	50 mg/kg
Squamous Cell Papilloma			
Overall Incidence	0/49 (0%)	7/50 (14%)	1/50 (2%)
Adjusted Incidence *(a)*	0.0%	24.2%	14.3%
Terminal Incidence	0/36 (0%)	1/16 (6%)	0/1 (0%)
Life Table Test	P<0.001	P=0.002	P=0.125
Cochran-Armitage Trend Test	P=0.421		
Fisher Exact Test		P=0.007	P=0.505
Squamous Cell Carcinoma			
Overall Incidence	0/49 (0%)	34/50 (68%)	3/50 (6%)
Adjusted Incidence *(a)*	0.0%	97.0%	100.0%
Terminal Incidence	0/36 (0%)	15/16 (94%)	1/1 (100%)
Life Table Test	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test	P=0.300		
Fisher Exact Test		P=0.001	P=0.125

(a) Kaplan-Meier estimated tumor incidence at the end of the study after adjusting for intercurrent mortality.

of the nonglandular stomach at this dose level. The supplemental study (12 mg/kg) also showed an extremely high rate of benign (males: 32%; females: 38%) and malignant (males: 78%; females: 54%) neoplasms in the forestomach (Tables 12 and 13). No benign or malignant neoplasms were observed in the control rats of either sex.

TABLE 12. INCIDENCES OF NEOPLASMS OF THE FORESTOMACH IN MALE RATS ADMINISTERED DIGLYCIDYL RESORCINOL ETHER IN CORN OIL BY GAVAGE FOR TWO YEARS IN THE SUPPLEMENTAL STUDY

	Vehicle Control	12 mg/kg
Squamous Cell Papilloma		
Overall Incidence	0/50 (0%)	16/50 (32%)
Adjusted Incidence *(a)*	0.0%	51.7%
Terminal Incidence	0/39 (0%)	10/23 (43%)
Life Table Test		P<0.001
Incidental Tumor Test		P<0.001
Fisher Exact Test		P<0.001
Squamous Cell Carcinoma		
Overall Incidence	0/50 (0%)	39/50 (78%)
Adjusted Incidence *(a)*	0.0%	92.8%
Terminal Incidence	0/39 (0%)	20/23 (87%)
Life Table Test		P<0.001
Incidental Tumor Test		P<0.001
Fisher Exact Test		P<0.001

(a) Kaplan-Meier estimated tumor incidence at the end of the study after adjusting for intercurrent mortality.

TABLE 13. INCIDENCES OF NEOPLASMS OF THE FORESTOMACH IN FEMALE RATS ADMINISTERED DIGLYCIDYL RESORCINOL ETHER IN CORN OIL BY GAVAGE FOR TWO YEARS IN THE SUPPLEMENTAL STUDY

	Vehicle Control	12 mg/kg
Squamous Cell Papilloma		
Overall Incidence	0/50 (0%)	19/50 (38%)
Adjusted Incidence *(a)*	0.0%	48.4%
Terminal Incidence	0/39 (0%)	15/35 (43%)
Life Table Test		P<0.001
Incidental Tumor Test		P<0.001
Fisher Exact Test		P<0.001
Squamous Cell Carcinoma		
Overall Incidence	0/50 (0%)	27/50 (54%)
Adjusted Incidence *(a)*	0.0%	64.0%
Terminal Incidence	0/39 (0%)	20/35 (57%)
Life Table Test		P<0.001
Incidental Tumor Test		P<0.001
Fisher Exact Test		P<0.001

(a) Kaplan-Meier estimated tumor incidence at the end of the study after adjusting for intercurrent mortality.

Lung: Bronchopneumonia was the most frequent cause of early death in rats (Table 14) and was characterized by patches of polymorphonuclear leukocytes in the alveoli of the lung, especially near the bronchi. Polymorphonuclear leukocytes also occurred in masses within bronchi and in the bronchial epithelium. In some rats, pulmonary vessels were dilated and showed perivascular edema. Microbiological examinations were not conducted on these rats. Pneumonia was not observed in the supplemental study.

TABLE 14. INCIDENCES OF BRONCHOPNEUMONIA IN F344/N RATS ADMINISTERED DIGLYCIDYL RESORCINOL ETHER IN CORN OIL BY GAVAGE FOR TWO YEARS

Dose (mg/kg)	Males	Females
0	2/50 (4%)	0/50 (0%)
25	17/49 (35%)	10/50 (20%)
50	26/50 (52%)	17/50 (34%)

Other Sites: In the primary study, several other types of neoplasms occurred in rats with overall incidences that were lower in the dosed groups than in the controls; these included adrenal pheochromocytoma, leukemia, pituitary adenoma, and thyroid C-cell tumors in males and females; lung adenoma, pancreatic islet cell tumors, and interstitial cell tumors of the testes in males; and mammary gland fibroadenomas and uterine tumors in females. None of these decreases were statistically significant when life table analyses were used, and they appeared to be related to the reduced survival observed in the dosed groups relative to those in the controls (Appendix G).

In the supplemental study, neurofibrosarcomas were observed at an increased incidence in dosed male rats (control, 0/50; dosed, 3/50), but the increase was not statistically significant. The incidence of C-cell tumors of the thyroid was significantly reduced in the dosed males compared to controls (control, 11/50; dosed, 3/50; $P<0.03$, incidental tumor and Fisher exact tests). In female rats, there was a statistically significant decrease ($P<0.05$) in the incidence of pheochromocytomas of the adrenal medulla in the dosed group (control, 5/50; dosed, 0/50).

FOURTEEN-DAY STUDIES

Five of five males and 4/5 females receiving 1,500 mg/kg and 2/5 males receiving 750 mg/kg died (Table 15). These deaths were attributed to administration of DGRE. Weight loss was observed in all mice that received 750 mg/kg or more and in 4/5 males and 1/5 females that received 380 mg/kg. Weight loss also occurred in mice in the 90 mg/kg groups (4 males and 5 females), but not in animals administered 190 mg/kg. Clinical signs were not compound related. Compound-related effects were observed grossly in the kidney (reddened medullae) and stomach (reddened mucosae) (Table 16). No histopathologic examinations were performed to further characterize these lesions.

TABLE 15. SURVIVAL AND MEAN BODY WEIGHT OF MICE ADMINISTERED DIGLYCIDYL RESORCINOL ETHER IN CORN OIL BY GAVAGE FOR 14 DAYS

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	23.6 ± 0.4	24.8 ± 0.8	+1.2 ± 0.4	—
90	4/5	23.6 ± 0.9	21.5 ± 1.4	-2.1 ± 1.3	-13
190	5/5	23.3 ± 0.7	25.9 ± 0.9	+2.6 ± 0.5	+ 4
380	5/5	23.6 ± 0.6	22.4 ± 0.8	-1.2 ± 0.6	-10
750	3/5	23.2 ± 1.1	18.3 ± 2.0	-4.9 ± 1.3	-26
1,500	0/5	*(d)*	*(d)*	*(d)*	
Females					
0	5/5	19.6 ± 0.4	21.4 ± 0.8	+1.8 ± 0.5	—
90	5/5	19.5 ± 0.5	18.8 ± 0.4	-0.7 ± 0.1	-12
190	5/5	19.4 ± 0.6	20.7 ± 0.6	+1.3 ± 0.2	- 3
380	5/5	19.3 ± 0.4	19.9 ± 0.6	+0.6 ± 0.3	- 7
750	5/5	19.4 ± 0.3	18.0 ± 0.8	-1.4 ± 0.6	-16
1,500	1/5	19.3 ± 0.0	17.2 ± 0.0	-2.1 ± 0.0	-20

(a) Number surviving/number per 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 change of the dosed survivors relative to the survivors of the controls =

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

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

TABLE 16. INCIDENCES OF COMPOUND-RELATED EFFECTS IN MICE ADMINISTERED DIGLYCIDYL RESORCINOL ETHER IN CORN OIL BY GAVAGE FOR 14 DAYS

Dose (mg/kg)	*Renal Medullae* - Red	*Glandular Stomach* - Reddened Mucosa	Forestomach - Papillary Growths
Males			
0	0/5	0/5	0/5
90	1/5	0/5	0/5
190	1/5	0/5	0/5
380	0/5	0/5	4/5
750	2/5	2/5	1/5
1,500	5/5	5/5	0/5
Females			
0	0/5	0/5	0/5
90	0/5	0/5	0/5
190	0/5	0/5	0/5
380	2/5	0/5	2/5
750	3/5	1/5	3/5
1,500	0/5	4/5	0/5

THIRTEEN-WEEK STUDIES

Nine of ten males and 7/10 females administered 400 mg/kg died; these deaths were considered to be compound related. Final mean body weight compared to controls was depressed 10-25% in groups that received 400 mg/kg (Table 17). Clinical signs were not compound related.

Compound-related lesions were found in the forestomach and liver of male and female mice (Table 18). The effects seen in the forestomach resembled those seen in the rats: squamous papillomata, diffuse hyperkeratosis, basal cell hyperplasia, and inflammation. Two females administered 400 mg/kg had mucosal ulcers of the forestomach.

Slight to mild focal tubular atrophy of the testes was seen in three mice that died during weeks 9 or 10. This lesion was not seen in mice that survived to the end of the study. The mean body weight of the male mice receiving 400 mg/kg was 26.0 g at week 8 (10 mice alive) and 27.4 g at week 9 (5 mice alive), whereas the mean body weights of all other groups of male mice for these same time periods ranged from 31.1 to 32.4 g. For these reasons, the testicular atrophy was interpreted as being a result of morbidity rather than a direct effect of DGRE administration.

Liver lesions were observed in the high dose mice only. Hepatic necrosis was focally extensive, involving large areas of the liver that were sharply demarcated from the nonnecrotic liver. Smaller, multiple areas of necrosis were seen in some mice. Minimal to mild fatty metamorphosis was observed in periportal areas of the liver, but only in animals that died.

Because of mortality at 400 mg/kg, depression in mean body weight gain in groups administered 200 or 400 mg/kg and because of lack of life threatening lesions at lower doses, doses of 50 and 100 mg/kg were selected for mice in the 2-year study of diglycidyl resorcinol ether.

TABLE 17. SURVIVAL AND MEAN BODY WEIGHT OF MICE ADMINISTERED DIGLYCIDYL RESORCINOL ETHER IN CORN OIL 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	22.1 ± 0.3	35.1 ± 0.8	+13.0 ± 0.7	
25	10 10	22.1 ± 0.4	35.6 ± 0.6	+13.5 ± 0.3	+ 1
50	10 10	21.6 ± 0.4	35.3 ± 0.8	+13.7 ± 0.5	+ 1
100	10 10	21.9 ± 0.5	34.0 ± 0.8	+12.1 ± 0.5	- 3
200	10 10	22.1 ± 0.3	32.7 ± 0.5	+10.6 ± 0.5	7
400	1 10	21.1 ± 0.0	26.5 ± 0.0	+ 5.4 ± 0.0	25
Females					
0	10 10	17.7 ± 0.5	24.8 ± 0.6	+ 7.1 ± 0.7	
25	10 10	18.1 ± 0.4	26.9 ± 0.9	+ 8.8 ± 0.7	+ 8
50	10 10	18.2 ± 0.3	25.4 ± 0.4	+ 7.2 ± 0.3	+ 2
100	10 10	18.4 ± 0.4	25.7 ± 0.7	+ 7.3 ± 0.5	+ 4
200	10 10	18.0 ± 0.2	25.2 ± 0.6	+ 7.2 ± 0.5	+ 2
400	3 10	19.1 ± 0.9	22.4 ± 0.9	+ 3.3 ± 0.5	10

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

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

(c) Body weight of the dosed survivors relative to the survivors of the controls =

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

TABLE 18. LESIONS OBSERVED IN MICE ADMINISTERED DIGLYCIDYL RESORCINOL ETHER IN CORN OIL BY GAVAGE FOR 13 WEEKS

		Males *(a)*						Females *(a)*					
Dose (mg/kg)		**0**	**25**	**50**	**100**	**200**	**400**	**0**	**25**	**50**	**100**	**200**	**400**
Stomach:	Inflammation	0	0	1	0	3	0	0	4	2	0	4	2
	Ulcer	0	0	0	0	0	0	0	0	0	0	0	2
	Basal cell hyperplasia	0	1	0	2	1	2	0	0	0	1	6	2
	Hyperkeratosis	0	0	1	7	4	8	0	0	3	7	8	5
	Squamous metaplasia	0	1	0	0	0	0	0	0	0	0	0	0
	Squamous papilloma	0	0	1	0	5	2	0	0	0	1	1	5
	Epidermal inclusion cyst	0	2	0	0	0	0	0	0	0	0	0	0
	No lesion seen	10	8	8	3	0	0	10	6	6	2	0	0
Liver:	Focal necrosis	0	NE*(b)*	NE	NE	0	5	0	NE	NE	NE	0	3
	Fatty metamorphosis	0	NE	NE	NE	0	3	0	NE	NE	NE	0	1
	Focal inflammation	1	NE	NE	NE	0	0	0	NE	NE	NE	0	0
Testis:	Focal tubular atrophy	0	NE	NE	NE	0	3						

(a) Ten animals were examined in each group
(b) NE = not examined

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of high dose female mice were lower than those of the controls after week 20 of the study (Figure 5 and Table 19). Mean body weights of high and low dose male mice and of low dose female mice were comparable with those of the controls. No compound-related clinical signs were observed.

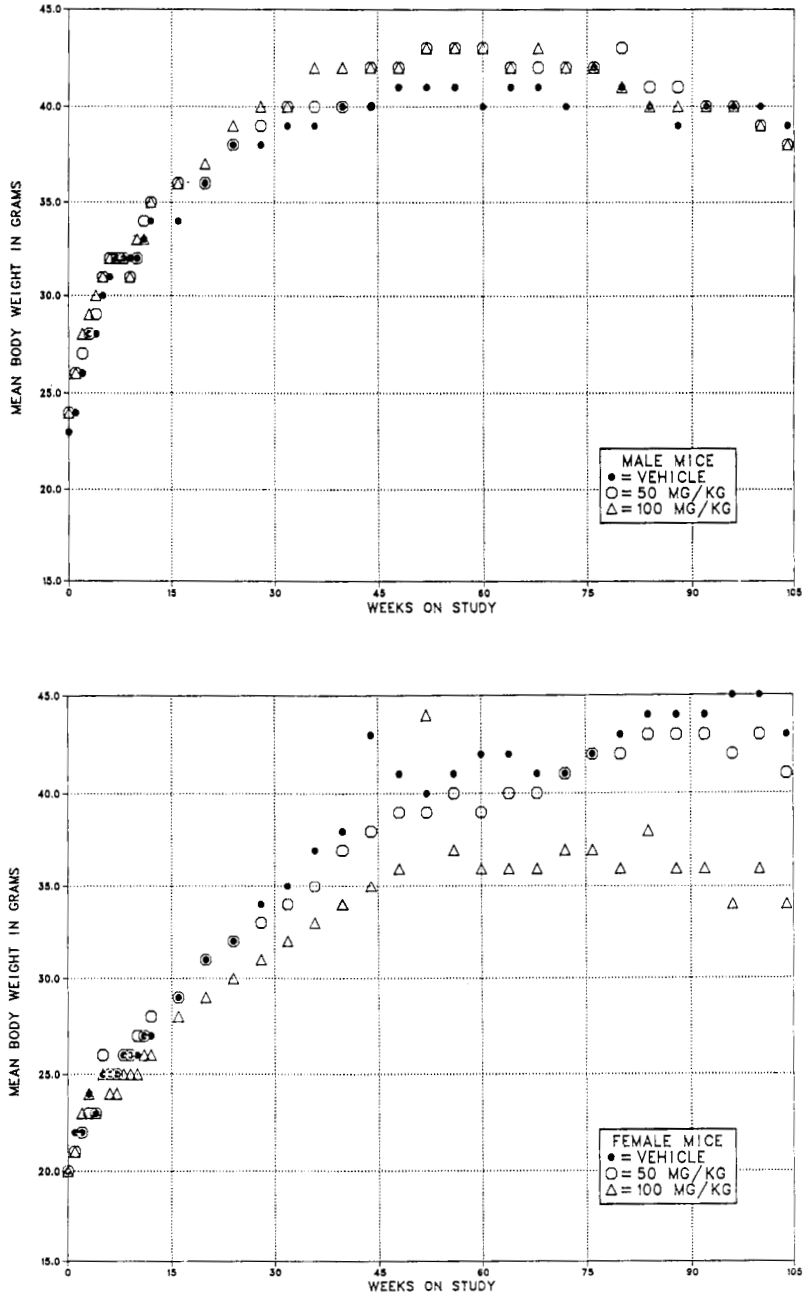

Figure 5. Growth Curves for Mice Administered Diglycidyl Resorcinol Ether in Corn Oil by Gavage

TABLE 19. MEAN BODY WEIGHTS OF MICE ADMINISTERED DIGLYCIDYL RESORCINOL ETHER IN CORN OIL BY GAVAGE FOR TWO YEARS

Weeks on Study	Vehicle Control		Low Dose			High Dose		
	Av. Wt. (grams)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of controls)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of controls)	No. of Survivors
MALE								
0	23	50	24	104.3	50	24	104.3	50
1	24	50	26	108.3	50	26	108.3	50
2	26	49	27	103.8	50	28	107.7	50
3	28	49	28	100.0	50	29	103.6	50
4	28	49	29	103.6	50	30	107.1	50
5	30	49	31	103.3	50	31	103.3	50
6	31	49	32	103.2	50	32	103.2	50
7	32	49	32	100.0	50	32	100.0	50
8	32	49	32	100.0	50	32	100.0	50
9	32	49	31	96.9	50	31	96.9	50
10	32	49	32	100.0	50	33	103.1	50
11	33	49	34	103.0	50	33	100.0	50
12	34	49	35	102.9	50	35	102.9	50
16	34	49	36	105.9	49	36	105.9	49
20	36	49	36	100.0	49	37	102.8	49
24	38	46	38	100.0	49	39	102.6	47
28	38	45	39	102.6	49	40	105.3	47
32	39	45	40	102.6	49	40	102.6	47
36	39	45	40	102.6	47	42	107.7	47
40	40	44	40	100.0	46	42	105.0	47
44	40	44	42	105.0	46	42	105.0	47
48	41	44	42	102.4	45	42	102.4	47
52	41	44	43	104.9	45	43	104.9	47
56	41	44	43	104.9	45	43	104.9	47
60	40	44	43	107.5	45	43	107.5	47
64	41	44	42	102.4	44	42	102.4	47
68	41	44	42	102.4	42	43	104.9	47
72	40	43	42	105.0	41	42	105.0	46
76	42	41	42	100.0	41	42	100.0	45
80	41	40	43	104.9	36	41	100.0	43
84	40	37	41	102.5	36	40	100.0	43
88	39	37	41	105.1	36	40	102.6	41
92	40	34	40	100.0	35	40	100.0	37
96	40	32	40	100.0	33	40	100.0	35
100	40	32	39	97.5	28	39	97.5	34
104	39	30	38	97.4	26	38	97.4	34
FEMALE								
0	20	50	20	100.0	50	20	100.0	50
1	22	50	21	95.5	50	21	95.5	50
2	22	50	22	100.0	47	23	104.5	50
3	24	50	23	95.8	47	24	100.0	50
4	23	50	23	100.0	47	23	100.0	50
5	25	50	26	104.0	47	25	100.0	50
6	25	50	25	100.0	47	24	96.0	50
7	25	50	25	100.0	47	24	96.0	50
8	26	50	26	100.0	47	25	96.2	50
9	26	50	26	100.0	47	25	96.2	50
10	26	50	27	103.8	47	25	96.2	50
11	27	50	27	100.0	47	26	96.3	50
12	27	50	28	103.7	47	26	96.3	50
16	29	50	29	100.0	47	28	96.6	50
20	31	50	31	100.0	47	29	93.5	50
24	32	50	32	100.0	47	30	93.8	50
28	34	50	33	97.1	47	31	91.2	50
32	35	49	34	97.1	47	32	91.4	50
36	37	49	35	94.6	47	33	89.2	50
40	38	49	37	97.4	47	34	89.5	50
44	43	48	38	88.4	47	35	81.4	50
48	41	48	39	95.1	47	36	87.8	50
52	40	48	39	97.5	47	44	110.0	50
56	41	48	40	97.6	47	37	90.2	49
60	42	48	39	92.9	47	36	85.7	49
64	42	47	40	95.2	46	36	85.7	49
68	41	47	40	97.6	40	36	87.8	49
72	41	44	41	100.0	38	37	90.2	46
76	42	39	42	100.0	36	37	88.1	45
80	43	36	42	97.7	33	36	83.7	44
84	44	34	43	97.7	29	38	86.4	33
88	44	32	43	97.7	26	36	81.8	27
92	44	29	43	97.7	25	36	81.8	23
96	45	26	42	93.3	21	34	75.6	20
100	45	24	43	95.6	19	36	80.0	11
104	43	20	41	95.3	14	34	79.1	10

Survival

The probabilities of survival for male and female mice in these studies are shown by the Kaplan and Meier curves in Figure 6. No significant differences in survival were observed between the dosed and control groups.

In male mice, 30/50 (60%) of the controls, 26/50 (52%) of the low dose, and 34/50 (68%) of the high dose group lived to the end of the study (104-105 weeks). In female mice, 20/50 (40%) of the controls, 13/50 (26%) of the low dose, and 10/50 (20%) of the high dose group lived to the end of the study. The survival data include one control and one low dose male 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. The major cause of death in dosed female mice was a necrosuppurative lesion of the ovary which spread to other areas of the abdominal cavity.

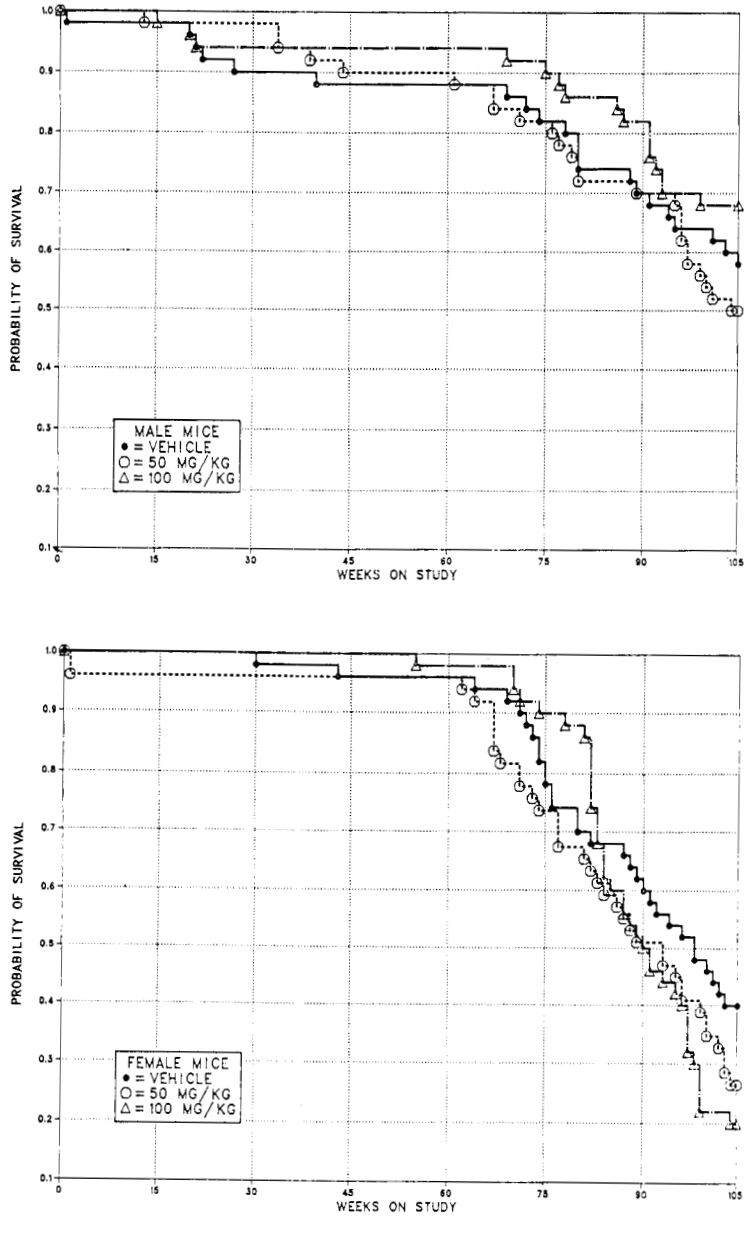

Figure 6. Survival Curves for Mice Administered Diglycidyl Resorcinol Ether in Corn Oil by Gavage

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 F. Appendix E, Tables E3 and E4, contain the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups. The statistical analyses used are discussed in chapter II (Data Recording and Statistical Methods) and Appendix E (footnotes).

Stomach: Hyperplastic and neoplastic lesions were observed at increased incidences in male and female mice (Table 20). Squamous cell papillomas and carcinomas and papillomatosis occurred in male and female mice with statistically significant positive trends and the incidences in the high dose groups were significantly higher than those in the controls (Tables 21 and 22).

The squamous cell papillomas were papillary growths of the epithelium and were supported by a narrow or broad fibrovascular stalk. They were covered by markedly thickened epithelium which was often heavily keratinized. Multiple lesions in the stomach of a single animal were referred to as papillomatosis. Squamous cell carcinomas were characterized by infiltrative growth into the submucosa and muscularis. The component cells varied in size and shape and many had indistinct margins. The cytoplasm was more eosinophilic than normal and, in some cells in the superficial layers, it contained keratohyalin granules. Nuclei were enlarged and contained coarse or stippled chromatin and one or two prominent nucleoli. Mitotic figures were present but not numerous. Keratin pearls were present in many of the carcinomas of different sizes. The lumina of the large pearls were filled with desquamated material, inflammatory cells, and necrotic debris. Nonkeratinizing squamous cell carcinomas were seen in the forestomach of a few mice. Areas of necrosis and hemorrhage were common in the large tumors. The morphology of the gastric neoplasms in mice was comparable to that obtained in rats.

In 4 low dose males, 10 high dose males, 1 low dose female, and 9 high dose females, the squamous cell carcinomas of the stomach had disseminated onto the serosal surfaces of the abdominal cavity and in some mice had metastasized to the lung (most common site), liver, lymph nodes, spleen, adrenal glands, heart, and kidneys.

TABLE 20. INCIDENCES OF HYPERPLASTIC AND NEOPLASTIC LESIONS IN THE STOMACH OF MICE ADMINISTERED DIGLYCIDYL RESORCINOL ETHER IN CORN OIL BY GAVAGE FOR TWO YEARS

	Males			Females		
	Vehicle Control	50 mg/kg	100 mg/kg	Vehicle Control	50 mg/kg	100 mg/kg
Number of stomachs evaluated	47	49	50	47	49	49
Diagnosis						
Hyperkeratosis	3	40	42	11	31	46
Hyperplasia	1	30	37	3	25	26
Squamous cell papilloma or papillomatosis *(a)*	0	4	10	0	5	10
Squamous cell carcinoma	0	14	25	0	12	23
Adenocarcinoma	0	0	1	0	0	0

(a) Papillomatosis is a term used by the contractor pathologist to describe multiple papillomas in the stomach of a single animal.

TABLE 21. INCIDENCES OF STOMACH LESIONS IN MALE MICE ADMINISTERED DIGLYCIDYL RESORCINOL ETHER IN CORN OIL BY GAVAGE FOR TWO YEARS

	Vehicle Control	50 mg/kg	100 mg/kg
Squamous Cell Papilloma or Papillomatosis			
Overall Incidence	0/47 (0%)	4/49 (8%)	10/50 (20%)
Adjusted Incidence *(a)*	0.0%	14.0%	29.4%
Terminal Incidence	0/30 (0%)	3/26 (12%)	10/34 (29%)
Life Table Test	P=0.001	P=0.051	P=0.002
Incidental Tumor Test	P=0.001	P=0.041	P=0.002
Cochran-Armitage Trend Test	P=0.001		
Fisher Exact Test		P=0.064	P=0.001
Squamous Cell Carcinoma			
Overall Incidence	0/47 (0%)	14/49 (29%)	25/50 (50%)
Adjusted Incidence *(a)*	0.0%	40.7%	55.5%
Terminal Incidence	0/30 (0%)	7/26 (27%)	14/34 (41%)
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

(a) Kaplan-Meier estimated tumor incidence at the end of the study after adjusting for intercurrent mortality.

TABLE 22. INCIDENCES OF STOMACH LESIONS IN FEMALE MICE ADMINISTERED DIGLYCIDYL RESORCINOL ETHER IN CORN OIL BY GAVAGE FOR TWO YEARS

	Vehicle Control	50 mg/kg	100 mg/kg
Squamous Cell Papilloma or Papillomatosis			
Overall Incidence	0/47 (0%)	5/49 (10%)	10/49 (20%)
Adjusted Incidence *(a)*	0.0%	33.4%	73.1%
Terminal Incidence	0/20 (0%)	4/13 (31%)	7/10 (70%)
Life Table Test	P<0.001	P=0.009	P<0.001
Incidental Tumor Test	P<0.001	P=0.009	P<0.001
Cochran-Armitage Trend Test	P=0.001		
Fisher Exact Test		P=0.031	P=0.001
Squamous Cell Carcinoma			
Overall Incidence	0/47 (0%)	12/49 (24%)	23/49 (47%)
Adjusted Incidence *(a)*	0.0%	53.3%	70.5%
Terminal Incidence	0/20 (0%)	4/13 (31%)	2/10 (20%)
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

(a) Kaplan-Meier estimated tumor incidence at the end of the study after adjusting for intercurrent mortality.

Liver: While pairwise comparisons were not significant (P>0.05), positive trends occurred in the incidences of female mice with hepatocellular carcinomas (Table 23). The incidences in the high dose group were significantly higher by the life table test than those in the controls. The incidences of females with either adenomas or carcinomas had a significant positive trend; and the pairwise comparison between the high dose group and the controls was significant by the life table test.

TABLE 23. INCIDENCES OF LIVER TUMORS IN FEMALE MICE ADMINISTERED DIGLYCIDYL RESORCINOL ETHER IN CORN OIL BY GAVAGE FOR TWO YEARS

	Vehicle Control	50 mg/kg	100 mg/kg
Hepatocellular Adenoma			
Tumor Rates			
Overall Incidence	3/48 (6%)	0/50 (0%)	5/49 (10%)
Adjusted Incidence	15.8%	0.0%	31.0%
Terminal Incidence	3/19 (16%)	0/13 (0%)	2/10 (20%)
Life Table Test	P=0.105	P=0.191N	P=0.135
Incidental Tumor Test	P=0.184	P=0.191N	P=0.253
Cochran-Armitage Trend Test	P=0.259		
Fisher Exact Test		P=0.114N	P=0.369
Hepatocellular Carcinoma			
Overall Incidence	0/48 (0%)	1/50 (2%)	3/49 (6%)
Adjusted Incidence	0.0%	6.3%	25.0%
Terminal Incidence	0/19 (0%)	0/13 (0%)	2/10 (20%)
Life Table Test	P=0.019	P=0.446	P=0.041
Incidental Tumor Test	P=0.047	P=0.581	P=0.073
Cochran-Armitage Trend Test	P=0.061		
Fisher Exact Test		P=0.510	P=0.125
Hepatocellular Adenoma or Carcinoma			
Overall Incidence	3/48 (6%)	1/50 (2%)	7/49 (14%)
Adjusted Incidence	15.8%	6.2%	43.4%
Terminal Incidence	3/19 (16%)	0/13 (0%)	3/10 (30%)
Life Table Test	P=0.019	P=0.437N	P=0.030
Incidental Tumor Test	P=0.061	P=0.370N	P=0.089
Cochran-Armitage Trend Test	P=0.093		
Fisher Exact Test		P=0.294N	P=0.167

Ovary: The ovaries were enlarged and filled with a viscous yellow exudate in 17/50 control, 12/50 low dose, and 15/50 high dose females. Ovarian tissue was not macroscopically recognizable in many of these masses. Microscopically, a mantle of neutrophils, macrophages, and fibrosis surrounded the multiple abscesses. Extensive adhesions were present between the mass and the omentum. Neutrophils, lymphocytes, and plasma cells were present in the adjacent adipose tissue. Fibrinoid exudate was disseminated both in the abdominal and thoracic cavities. Overall, necrotizing inflammation was found in the abdominal cavity, ovary, uterus, or multiple organs in 18/30 vehicle control, 18/36 low dose, and 16/40 high dose females that died before the end of the study. Although microbiologic examinations were not performed on mice in this study, *Klebsiella oxytoca* has been isolated from mice that had similar lesions in other studies performed at the same laboratory.

Kidney: Mineralization was found in the kidneys of 8/50 control males, 18/50 low dose males, and 30/50 high dose males. The mineralization was minimal and the distribution was multifocal, being located primarily in the cortex. The foci were small, ranging from the size of one or two renal tubular epithelial cells to the size of a tubule.

Hematopoietic System: Malignant lymphocytic lymphomas, malignant lymphomas of mixed types, and malignant lymphomas of all types occurred in female mice with negative dose-related trends (Table 24). The incidence of all types of malignant lymphomas was significantly lower in the high dose group than in the controls.

TABLE 24. INCIDENCES OF LYMPHOMAS IN FEMALE MICE ADMINISTERED DIGLYCIDYL RESORCINOL ETHER IN CORN OIL BY GAVAGE FOR TWO YEARS

	Vehicle Control	50 mg/kg	100 mg/kg
Malignant Lymphoma, Lymphocytic Type			
Overall Incidence	3/50 (6%)	2/50 (4%)	0/50 (0%)
Adjusted Incidence *(a)*	11.4%	10.2%	0.0%
Terminal Incidence	1/20 (5%)	0/13 (0%)	0/10 (0%)
Life Table Trend	P=0.155N	P=0.621N	P=0.212N
Incidental Tumor Test	P=0.036N	P=0.487N	P=0.079N
Cochran-Armitage Trend Test	P=0.082N		
Fisher Exact Test		P=0.500N	P=0.122N
Malignant Lymphoma, Mixed Type			
Overall Incidence	4/50 (8%)	3/50 (6%)	0/50 (0%)
Adjusted Incidence *(a)*	20.0%	16.4%	0.0%
Terminal Incidence	4/20 (20%)	1/13 (8%)	0/10 (0%)
Life Table Test	P=0.161N	P=0.618	P=0.175N
Incidental Tumor Test	P=0.096N	P=0.606N	P=0.175N
Cochran-Armitage Trend Test	P=0.049N		
Fisher Exact Test		P=0.500N	P=0.059N
Malignant Lymphoma, All Malignant			
Overall Incidence	17/50 (34%)	9/50 (18%)	3/50 (6%)
Adjusted Incidence *(a)*	55.6%	43.0%	24.0%
Terminal Incidence	8/20 (40%)	3/13 (23%)	2/10 (20%)
Life Table Test	P=0.014N	P=0.246N	P=0.018N
Incidental Tumor Test	P<0.001N	P=0.064N	P=0.003N
Cochran-Armitage Trend Test	P<0.001N		
Fisher Exact Test		P=0.055N	P<0.001N

(a) Kaplan-Meier estimated tumor incidence at the end of the study after adjusting for intercurrent mortality.

Subcutaneous Tissue: Fibroma, fibrosarcoma, or sarcoma, NOS (combined) occurred in male mice with a statistically significant negative trend (Table 25).

TABLE 25. INCIDENCES OF SUBCUTANEOUS FIBROMA, FIBROSARCOMA, OR SARCOMA, NOS (COMBINED) IN MALE MICE ADMINISTERED DIGLYCIDYL RESORCINOL ETHER IN CORN OIL BY GAVAGE FOR TWO YEARS

	Vehicle Control	50 mg/kg	100 mg/kg
Overall Incidence	11/50 (22%)	6/50 (12%)	3/50 (6%)
Adjusted Incidence *(a)*	31.9%	19.8%	8.8%
Terminal Incidence	7/30 (23%)	4/26 (15%)	3/34 (9%)
Life Table Test	P=0.010N	P=0.211N	P=0.014N
Incidental Tumor Test	P=0.010N	P=0.151N	P=0.017N
Cochran-Armitage Trend Test	P=0.014N		
Fisher Exact Test		P=0.144N	P=0.021N

(a) Kaplan-Meier estimated tumor incidence at the end of the study after adjusting for intercurrent mortality.

IV. DISCUSSION AND CONCLUSIONS

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Diglycidyl resorcinol ether (DGRE) was administered in corn oil by gavage to male and female F344/N rats and $B6C3F_1$ mice at the following doses:

	14-Day Study	13-Week Study
Rats:	0, 190, 380, 750, 1500, or 3,000 mg/kg	0, 12.5, 25, 50, 100, or 200 mg/kg
Mice:	0, 90, 190, 380, 750, or 1,500 mg/kg	0, 25, 50, 100, 200, or 400 mg/kg
	2-Year Study	**Supplemental 2-Year Study**
Rats:	0, 25, or 50 mg/kg	0 or 12 mg/kg
Mice:	0, 50, or 100 mg/kg	none

Administration of DGRE to rats and mice caused marked toxicity at the sites of direct contact (i.e., the esophagus and stomach). In most cases, the stomach lesions seen in animals dying in the 14-day and 13-week studies were not severe enough to produce death. The presence of macroscopic lesions in the kidney of rats and mice in the 14-day studies suggests absorption of DGRE, but the exact cause of death was not apparent.

The dose-related decreases in survival for rats in the 2-year studies indicate that the high dose was toxic. However, a significant gastric tumor response was observed even in the high dose group, which showed decreased survival. The doses appeared to be reasonable on the basis of the data from the 13-week studies. No biologically significant decreases in weight gain or survival were observed in the 13-week studies at the doses selected for the 2-year study. Although doses of 25 or 50 mg/kg produced stomach lesions when administered for 13 weeks, they were not severe enough to suggest that they would be life threatening in the 2-year studies. Additionally, survival of rats in the 2-year studies was not affected until week 30. Therefore, even a 6-month study would likely have supported the doses selected for the 2-year studies. Despite the reduced survival, the 2-year studies are considered valid since neoplasms observed in the nonglandular stomach were related to DGRE administration. Also a very high rate of gastric neoplasia was observed in both sexes of rats in the supplemental study, which was conducted at one-half of the low dose used in the primary study.

Decreases in mean body weight gain were observed in high dose male rats (after week 25) and in high dose female rats (after week 35) on the 2-year studies. The differences in weight gain between low dose and control males and between low dose and control females were not seen until after week 80. The weight reductions in the low dose groups were not life threatening. Since food consumption was not measured, the differences in weight gain cannot be definitely attributed to either the toxic effects of DGRE or to reduced feed consumption or to both.

Decreased survival was dose-related in rats administered DGRE. Deaths in the high dose groups began at week 30. Fifty percent of the male rats were dead by week 40 and fifty percent of the female rats were dead by week 35. The increase in mortality occurred later in the low dose groups; deaths began at week 45 in females and week 60 in males. However, 50% of the males were still alive at week 80 and 50% of the females were alive at week 90. Thus, at least half of the low dose rats lived longer than 18 months.

Bronchopneumonia was the major cause of death in rats in the 2-year studies, and was found in approximately one third of the high dose females and one half of the high dose males. A large number of low dose rats also died from this infection. The lesion is not consistent with chemical pneumonitis, and the suppurative nature of the lesion suggests that it was bacterial in origin. While microbiological cultures were not conducted, the pulmonary lesions were not characteristic of *Mycoplasma sp.* infection (chronic respiratory disease). Also, chronic respiratory disease is a highly infectious disease, and one would expect more control rats to have had bronchopneumonia if a mycoplasmosis was present in the study animals. The NTP Pathology Working Group, during its review of the bronchopneumonia lesions, observed the presence of foreign material in the lung. They speculated that the stomach lesions (see below) may have caused problems in swallowing, with resultant inhalation of food particles. The presence of a PVM titer in the serum of sentinel animals in the same animal room has to be considered in relation to the etiology of the bronchopneumonia. This possibility was discounted because PVM is not known to cause pulmonary disease

in rats. Whatever the etiology of the bronchopneumonia, the animals' pathologic response or susceptibility to infection appeared to be influenced (directly or indirectly) by their exposure to DGRE.

In mice, only the high dose female group had a decrease in body weight gain. First noticed at week 20, the decrease was never great enough to be considered life threatening, and the cause could not be determined.

Survival in dosed and control mice was comparable although lower than that normally seen in other corn oil vehicle controls in the Bioassay Program. The increase in mortality was attributed to a pyogenic infection which appeared to originate in the ovary. The infection occasionally became systemic but was usually localized to the abdominal cavity. Abscessation and suppurative peritonitis were characteristic of the infection. The etiology is not known. Identical lesions observed in subsequent studies at the same laboratory have been attributed to *Klebsiella oxytoca* (although Koch's postulates have not been fulfilled). In all of these studies, the disease was not observed until after week 60.

The stratified squamous epithelium that lines the proximal alimentary tract was the primary target tissue affected in rats and mice administered DGRE. In the single dose, 14-day, and 13-week studies the animals showed inflammation, ulceration, and hyperplasia of the nonglandular stomach (forestomach) and, to a lesser degree, of the esophagus. Some animals had inflammation in the lymph nodes draining these tissues.

Similar inflammatory and proliferative lesions were seen in rats and mice in the 2-year studies. In addition, a high incidence of benign and malignant neoplasms, some of which showed metastasis, was observed in the nonglandular stomach of male and female rats and mice in both the primary and the supplemental study (Table 26).

Similar lesions have been observed in the skin of mice that received repeated dermal applications of DGRE, and subcutaneous tumors have been reported in rats at the site of subcutaneous injection (McCammon et al., 1957).

The forestomach of the mouse and rat is often a target organ for chemical carcinogens, particularly when the chemical is administered by oral intubation. The squamous-lined forestomach (nonglandular stomach) is the proximal 2/3 of the stomach, immediately adjacent to the esophagus, and is sharply demarcated from the distal glandular stomach. The latter is composed of columnar secretory epithelium similar to that of

TABLE 26. INCIDENCES OF FORESTOMACH TUMORS IN RATS AND MICE ADMINISTERED DIGLYCIDYL RESORCINOL ETHER IN CORN OIL BY GAVAGE IN THE PRIMARY AND SUPPLEMENTAL STUDIES

	Squamous Cell Papillomas				Squamous Cell Carcinomas			
	Vehicle Control	12 mg/kg *(a)*	25 mg/kg	50 mg/kg	Vehicle Control	12 mg/kg *(a)*	25 mg/kg	50 mg/kg
Rats								
Males	0/100 *(b)*	16/50	17/50	6/49	0/100 *(b)*	39/50	38/50	4/49
Females	0/99 *(b)*	19/50	7/50	1/50	0/99 *(b)*	27/50	34/50	3/50
			50 mg/kg	100 mg/kg			50 mg/kg	100 mg/kg
Mice								
Males	0/47		4/49	10/50	0/47		14/49	25/50
Females	0/47		5/49	10/49	0/47		12/49	23/49

(a) Dose administered to rats in the supplemental study.

(b) Represents combined incidence of the primary and supplemental studies.

many (or most) higher mammals, including man. Humans, in common with many other non-rodent mammals, have no direct counterpart of the rodent forestomach, except possibly the squamous epithelium at the squamocolumnar junction of the cardiac portion of the stomach, which can be a site for either squamous cell carcinoma or adenocarcinoma.

The glandular portion of the rodent stomach is rarely a site of carcinogenesis in untreated animals or those given chemical carcinogens. Gastric adenocarcinomas are, however, frequent in humans in certain countries of the world, including Japan and Chile, for example. In the United States, these neoplasms used to occur more frequently; but during the past 50 years, the incidence has, for as yet unknown reasons, decreased both in the U.S. and in some European countries. Conversely, carcinoma of the human esophagus is increasing in the United States. In many respects, the rodent forestomach more closely resembles the human esophagus than the human stomach.

The results of these studies of DGRE provide an opportunity to observe the sequence of stages that occur during the pathogenesis of this malignant neoplasm in the rodent forestomach. In both rats and mice, the earliest changes were basal cell hyperplasia, hyperkeratosis, and acanthosis of surface epithelium. As the hyperplastic process progressed, papillary structures (papillomas) were observed, yet there was no invasion of the submucosa or other evidence of malignancy. As the benign neoplasia progressed towards carcinoma, the component cells showed increasing degrees of atypia and invasive potential, in some animals invading through all layers of the stomach wall to the serosa, and in some cases extending to other intraabdominal structures and metastasizing to distant organs such as the lungs and liver. The process was clearly a function of time.

From the foregoing discussion, DGRE appears to be toxic to stratified squamous epithelium by direct contact. This may (McCammon et al., 1957) or may not (Holland et al., 1981) include skin as well as the esophagus and forestomach (this study). It appears that the lesions clearly associated with DGRE toxicity are local irritation, hyperplasia, and neoplasia.

Presumably direct contact is required because tissues of the same type but distant to the site of exposure, i.e. oral cavity, did not show lesions. However, this may also be a function of dose and concentration since the amount at the site of application would be considerably higher than that present at a site that required transport via the blood. The presence of renal and hepatic lesions, albeit of lesser severity, would suggest that DGRE is absorbed to some degree.

Another observation was the lack of lesions in the glandular portion of the stomach and proximal small intestine. The concentration of DGRE would have been the same in these areas as in the nonglandular stomach. The presence of a layer of mucous, buffering systems, and/or a difference in local pH may play a role in explaining this observation.

Further evidence for the potential carcinogenicity of DGRE is provided by positive mutagenic responses in *Salmonella typhimurium*, strains TA100 and TA1535 with and without activation (Appendix G). In addition, most monoglycidyl and diglycidyl ethers have been found to be mutagenic in *S. typhimurium* (Wade et al., 1978; Pullin and Legator, 1977).

Compound-related incidences of fatty metamorphosis of the liver in male rats and mice and necrosis of the liver in mice were seen in the 13-week studies. However, these lesions were seen only in some of the high dose animals that lost weight or had reductions in weight gain, and were considered to be the result of debilitation rather than a direct effect of the chemical.

Statistically significant positive trends were observed in the incidences of female mice with hepatocellular carcinomas (life table and incidental tumor tests) and hepatocellular adenomas and carcinomas combined (life table test). However, the incidences in the high dose groups were significant only by the life table test and the incidences in the dosed groups were lower than those observed in comparable control groups at the same laboratory. Thus, these tumors were probably not related to administration of DGRE. No increased incidences of hepatocellular neoplasms were observed in F344/N rats.

Macroscopic examination of the kidney revealed dose-related reddening of the renal medullae in rats and mice in the 14-day studies. While no renal lesions were seen in rats and mice administered DGRE for 13 weeks, an increased

incidence of mineralization was found in male mice in the 2-year studies. The morphology of the lesion was comparable in dosed and control mice. Administration of DGRE was considered to exacerbate the development of this lesion in aging animals, although the severity of the lesion was not considered life threatening. No primary neoplasms were observed in the kidneys of dosed rats or mice.

Several types of neoplasms occurred at reduced incidences in dosed rats (relative to control incidences): pheochromocytomas, leukemia, lymphomas, pituitary adenomas, C-cell neoplasms of the thyroid, interstitial cell tumors of the testes, neoplasms of the uterus, and fibroadenomas of the mammary gland. Since the reduced incidences were not statistically significant by life table analysis, the reductions were attributed to reduced survival.

Conclusions: Under the conditions of these 2-year gavage studies, technical grade diglycidyl resorcinol ether caused hyperkeratosis and hyperplasia of the forestomach in rats and mice. DGRE was carcinogenic for male and female F344/N rats and for male and female B6C3F$_1$ mice, causing both benign and malignant neoplasms of the forestomach.

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V. REFERENCES

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APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS ADMINISTERED DIGLYCIDYL RESORCINOL ETHER IN CORN OIL BY GAVAGE

TABLE A1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS ADMINISTERED DIGLYCIDYL RESORCINOL ETHER IN CORN OIL BY GAVAGE

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
SQUAMOUS CELL PAPILLOMA	1 (2%)		
BASAL-CELL CARCINOMA	1 (2%)		
SEBACEOUS ADENOCARCINOMA	1 (2%)		
KERATOACANTHOMA	1 (2%)	1 (2%)	
*SUBCUT TISSUE	(50)	(50)	(50)
FIBROMA	1 (2%)	2 (4%)	
FIBROSARCOMA		1 (2%)	
LIPOMA	1 (2%)	1 (2%)	
NEUROFIBROMA	1 (2%)		
RESPIRATORY SYSTEM			
#TRACHEA	(50)	(49)	(49)
SQUAMOUS CELL PAPILLOMA		1 (2%)	
#LUNG	(50)	(49)	(50)
ALVEOLAR/BRONCHIOLAR ADENOMA	3 (6%)		
ALVEOLAR/BRONCHIOLAR CARCINOMA	1 (2%)	1 (2%)	
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
MALIGNANT LYMPHOMA, NOS	1 (2%)		
MYELOMONOCYTIC LEUKEMIA	4 (8%)	2 (4%)	
LEUKEMIA,MONONUCLEAR CELL	1 (2%)		
#SPLEEN	(50)	(50)	(48)
SQUAMOUS CELL CARCINOMA, METASTA		1 (2%)	
#CELIAC LYMPH NODE	(49)	(47)	(47)
SQUAMOUS CELL CARCINOMA, METASTA		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
#MESENTERIC L. NODE	(49)	(47)	(47)
SQUAMOUS CELL CARCINOMA, METASTA		1 (2%)	
#LUNG	(50)	(49)	(50)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	1 (2%)		
CIRCULATORY SYSTEM			
*SUBCUT TISSUE	(50)	(50)	(50)
HEMANGIOSARCOMA		1 (2%)	
DIGESTIVE SYSTEM			
#LIVER	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA, INVASIV		1 (2%)	
SQUAMOUS CELL CARCINOMA, METASTA		3 (6%)	
NEOPLASTIC NODULE	1 (2%)	1 (2%)	
#PANCREAS	(49)	(44)	(47)
ACINAR-CELL ADENOMA	1 (2%)		
ACINAR-CELL CARCINOMA	1 (2%)		
#STOMACH	(50)	(50)	(49)
SQUAMOUS CELL PAPILLOMA		17 (34%)	6 (12%)
SQUAMOUS CELL CARCINOMA		38 (76%)	4 (8%)
ADENOCARCINOMA, NOS		1 (2%)	
#JEJUNUM	(50)	(49)	(47)
ADENOCARCINOMA, NOS		1 (2%)	1 (2%)
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
TUBULAR-CELL ADENOCARCINOMA	1 (2%)		
ENDOCRINE SYSTEM			
#PITUITARY	(49)	(48)	(47)
CARCINOMA,NOS		1 (2%)	
ADENOMA, NOS	17 (35%)	8 (17%)	2 (4%)

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#ADRENAL	(50)	(50)	(50)
CORTICAL ADENOMA	2 (4%)		
PHEOCHROMOCYTOMA	11 (22%)	4 (8%)	
PHEOCHROMOCYTOMA, MALIGNANT	1 (2%)		
#ADRENAL MEDULLA	(50)	(50)	(50)
GANGLIONEUROMA	1 (2%)		
#THYROID	(47)	(47)	(46)
FOLLICULAR-CELL ADENOMA		1 (2%)	
C-CELL ADENOMA	3 (6%)		
C-CELL CARCINOMA	1 (2%)		
#PANCREATIC ISLETS	(49)	(44)	(47)
ISLET-CELL ADENOMA	2 (4%)	1 (2%)	
ISLET-CELL CARCINOMA	3 (6%)		
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
FIBROADENOMA	2 (4%)		
*PREPUTIAL GLAND	(50)	(50)	(50)
CARCINOMA,NOS	1 (2%)	1 (2%)	
#TESTIS	(50)	(49)	(50)
INTERSTITIAL-CELL TUMOR	47 (94%)	39 (80%)	11 (22%)
NERVOUS SYSTEM			
#BRAIN	(50)	(50)	(49)
GLIOMA, NOS	1 (2%)		
SPECIAL SENSE ORGANS			
*EAR	(50)	(50)	(50)
NEUROFIBROSARCOMA		2 (4%)	
MUSCULOSKELETAL SYSTEM			
NONE			

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
BODY CAVITIES			
*ABDOMINAL CAVITY	(50)	(50)	(50)
NEUROFIBROSARCOMA, METASTATIC		1 (2%)	
*PERITONEUM	(50)	(50)	(50)
MESOTHELIOMA, NOS		1 (2%)	
*MESENTERY	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA, METASTA		1 (2%)	
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA, METASTA		8 (16%)	1 (2%)
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	5	36	45
MORIBUND SACRIFICE	3	10	5
SCHEDULED SACRIFICE			
TERMINAL SACRIFICE	42	4	
DOSING ACCIDENT			
ACCIDENTALLY KILLED, NDA			
ACCIDENTALLY KILLED, NOS			
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	49	16
TOTAL PRIMARY TUMORS	114	126	24
TOTAL ANIMALS WITH BENIGN TUMORS	49	47	16
TOTAL BENIGN TUMORS	94	75	19
TOTAL ANIMALS WITH MALIGNANT TUMORS	17	41	5
TOTAL MALIGNANT TUMORS	19	49	5
TOTAL ANIMALS WITH SECONDARY TUMORS#		16	1
TOTAL SECONDARY TUMORS		17	1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	1	2	
TOTAL UNCERTAIN TUMORS	1	2	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

TABLE A2.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS ADMINISTERED DIGLYCIDYL RESORCINOL ETHER 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)
TRICHOEPITHELIOMA	1 (2%)		
RESPIRATORY SYSTEM			
#LUNG	(50)	(50)	(50)
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (2%)	1 (2%)	
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
MYELOMONOCYTIC LEUKEMIA	5 (10%)	2 (4%)	
LEUKEMIA,MONONUCLEAR CELL	1 (2%)	2 (4%)	
#CELIAC LYMPH NODE	(49)	(47)	(50)
SQUAMOUS CELL CARCINOMA, METASTA		1 (2%)	
CIRCULATORY SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
HEMANGIOSARCOMA		1 (2%)	
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(50)	(50)	(50)
ADENOMA, NOS		1 (2%)	
#LIVER	(50)	(50)	(50)
NEOPLASTIC NODULE	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
#PANCREAS	(50)	(46)	(47)
SQUAMOUS CELL CARCINOMA, METASTA		1 (2%)	
#STOMACH	(49)	(50)	(50)
SQUAMOUS CELL PAPILLOMA		7 (14%)	1 (2%)
SQUAMOUS CELL CARCINOMA		34 (68%)	3 (6%)
LEIOMYOSARCOMA		1 (2%)	
CARCINOSARCOMA		1 (2%)	
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#PITUITARY	(50)	(49)	(47)
CARCINOMA,NOS	1 (2%)	1 (2%)	
ADENOMA, NOS	18 (36%)	8 (16%)	1 (2%)
#ADRENAL	(50)	(48)	(49)
CORTICAL ADENOMA	1 (2%)	2 (4%)	
CORTICAL CARCINOMA	1 (2%)		
PHEOCHROMOCYTOMA	3 (6%)		
PHEOCHROMOCYTOMA, MALIGNANT		1 (2%)	
#THYROID	(50)	(47)	(41)
FOLLICULAR-CELL ADENOMA	1 (2%)		
C-CELL ADENOMA	2 (4%)		
C-CELL CARCINOMA	1 (2%)		
#PARATHYROID	(22)	(17)	(23)
ADENOMA, NOS	1 (5%)		
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
ADENOCARCINOMA, NOS	2 (4%)		
FIBROADENOMA	18 (36%)	8 (16%)	
*CLITORAL GLAND	(50)	(50)	(50)
CARCINOMA,NOS		2 (4%)	

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#UTERUS	(50)	(50)	(50)
ADENOCARCINOMA, NOS	1 (2%)		
LEIOMYOSARCOMA	1 (2%)		
ENDOMETRIAL STROMAL POLYP	11 (22%)	7 (14%)	1 (2%)
ENDOMETRIAL STROMAL SARCOMA	1 (2%)		
#CERVIX UTERI	(50)	(50)	(50)
LEIOMYOMA	2 (4%)		
#UTERUS/ENDOMETRIUM	(50)	(50)	(50)
ADENOCARCINOMA, NOS		2 (4%)	
#OVARY	(49)	(50)	(50)
GRANULOSA-CELL TUMOR	1 (2%)		
NERVOUS SYSTEM			
#BRAIN	(50)	(50)	(50)
GLIOMA, NOS	1 (2%)		
ASTROCYTOMA	1 (2%)		
NEUROFIBROSARCOMA		1 (2%)	
SPECIAL SENSE ORGANS			
*EAR	(50)	(50)	(50)
NEUROFIBROSARCOMA		1 (2%)	
*ZYMBAL'S GLAND	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA	1 (2%)		
MUSCULOSKELETAL SYSTEM			
*SKELETAL MUSCLE	(50)	(50)	(50)
RHABDOMYOSARCOMA	1 (2%)		
BODY CAVITIES			
*PERITONEUM	(50)	(50)	(50)
ENDOMETRIAL STROMAL SARCOMA, MET	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
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA, METASTA	1 (2%)	3 (6%)	
ADENOCARCINOMA, NOS, METASTATIC	1 (2%)		
CARCINOSARCOMA, METASTATIC		1 (2%)	
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	8	32	47
MORIBUND SACRIFICE	6	3	2
SCHEDULED SACRIFICE			
TERMINAL SACRIFICE	36	15	1
DOSING ACCIDENT			
ACCIDENTALLY KILLED, NDA			
ACCIDENTALLY KILLED, NOS			
ANIMAL MISSING			
ANIMAL MISSEXED			
OTHER CASES			

@ INCLUDES AUTOLYZED ANIMALS
* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	46	41	6
TOTAL PRIMARY TUMORS	79	83	6
TOTAL ANIMALS WITH BENIGN TUMORS	38	25	3
TOTAL BENIGN TUMORS	59	34	3
TOTAL ANIMALS WITH MALIGNANT TUMORS	18	37	3
TOTAL MALIGNANT TUMORS	18	49	3
TOTAL ANIMALS WITH SECONDARY TUMORS#	3	6	
TOTAL SECONDARY TUMORS	3	6	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	2		
TOTAL UNCERTAIN TUMORS	2		
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

TABLE A3.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR STUDY OF DIGLYCIDYL RESORCINOL ETHER

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	104	096	105	076	091	104	104	105	104	104	076	104	104	104	105	104	104	104	104	104	105	104	104
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+
SQUAMOUS CELL PAPILLOMA								X																	
BASAL-CELL CARCINOMA																									
SEBACEOUS ADENOCARCINOMA						X																			
KERATOACANTHOMA																									
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+
FIBROMA									X																
LIPOMA																									
NEUROFIBROMA		X																							
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALVEOLAR/BRONCHIOLAR ADENOMA																									
ALVEOLAR/BRONCHIOLAR CARCINOMA																									
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE																								X	
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	+	+	+	-	+	-	-	-	-	+	+	+	-	-	-	+	-	+	+	-	+	+	+	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NEOPLASTIC NODULE			X																						
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+
ACINAR-CELL ADENOMA																									
ACINAR-CELL CARCINOMA																									
ESOPHAGUS	-	+	+	-	+	+	+	-	-	+	+	+	+	+	+	+	+	+	-	-	+	+	-	+	-
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
TUBULAR-CELL ADENOCARCINOMA																									
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOMA, NOS	X							X			X	X							X	X	X	X			
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CORTICAL ADENOMA																			X						
PHEOCHROMOCYTOMA								X									X		X		X			X	
PHEOCHROMOCYTOMA, MALIGNANT													X												
GANGLIONEUROMA					X																				
THYROID	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	-	+	+	+	+	+	+	+
C-CELL ADENOMA			X																					X	
C-CELL CARCINOMA								X																	
PARATHYROID	-	-	+	+	-	-	+	-	-	-	+	-	-	+	+	-	+	-	-	-	-	-	-	-	+
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+
ISLET-CELL ADENOMA																									
ISLET-CELL CARCINOMA								X			X												X		
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
FIBROADENOMA									X										X						
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
INTERSTITIAL-CELL TUMOR		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GLIOMA, 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																									
MYELOMONOCYTIC LEUKEMIA				X										X											
LEUKEMIA,MONONUCLEAR CELL																									

+: 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
WEEKS ON STUDY	104	104	104	076	104	045	105	105	051	105	105	105	096	105	051	105	105	051	105	051	076	105	105	105	105	TISSUES / TUMORS
INTEGUMENTARY SYSTEM																										
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	50*
SQUAMOUS CELL PAPILLOMA																						X				1
BASAL-CELL CARCINOMA																										1
SEBACEOUS ADENOCARCINOMA																										1
KERATOACANTHOMA				X																						1
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	50*
FIBROMA																										1
LIPOMA				X																						1
NEUROFIBROMA																										1
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALVEOLAR/BRONCHIOLAR ADENOMA								X	X	X																3
ALVEOLAR/BRONCHIOLAR CARCINOMA	X																									1
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE																										1
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
THYMUS	+	+	-	+	+	+	+	+	+	-	-	-	+	-	+	+	+	-	+	+	+	+	+	+	-	33
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NEOPLASTIC NODULE																										1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ACINAR-CELL ADENOMA													X													1
ACINAR-CELL CARCINOMA										X																1
ESOPHAGUS	-	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	40
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LARGE INTESTINE	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
TUBULAR-CELL ADENOCARCINOMA			X																							1
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ADENOMA, NOS	X						X	X	X				X			X	X	X		X						17
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CORTICAL ADENOMA																				X						2
PHEOCHROMOCYTOMA												X	X				X			X		X			X	11
PHEOCHROMOCYTOMA, MALIGNANT																										1
GANGLIONEUROMA																										1
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	47
C-CELL ADENOMA																				X						3
C-CELL CARCINOMA																										1
PARATHYROID	-	-	-	-	-	+	+	-	-	+	-	+	-	+	-	+	-	-	-	-	-	-	+	-	-	15
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ISLET-CELL ADENOMA			X																X							2
ISLET-CELL CARCINOMA																										3
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	50*
FIBROADENOMA																										2
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
INTERSTITIAL-CELL TUMOR	X	X	X	X	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	47
PROSTATE	-	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	45
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
GLIOMA, 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*
MALIGNANT LYMPHOMA, NOS														X												1
MYELOMONOCYTIC LEUKEMIA			X																			X				4
LEUKEMIA,MONONUCLEAR CELL										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 DIGLYCIDYL RESORCINOL ETHER

LOW DOSE

ANIMAL NUMBER	0012	0028	0036	0044	0055	0066	0077	0088	0091	0104	0116	0121	0132	0145	0156	0163	0178	0186	0197	0201	0212	0223	0234	0245
WEEKS ON STUDY	104	104	074	064	090	068	076	011	104	066	061	059	082	089	060	083	088	076	079	067	061	098	104	093
INTEGUMENTARY SYSTEM																								
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	N	+	N	+	+	+
KERATOACANTHOMA										X														
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	N	+	N	+	+	+
FIBROMA	X																							
FIBROSARCOMA																								
LIPOMA																							X	
HEMANGIOSARCOMA																								
RESPIRATORY SYSTEM																								
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+
ALVEOLAR/BRONCHIOLAR CARCINOMA																								
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+
SQUAMOUS CELL PAPILLOMA																								
HEMATOPOIETIC SYSTEM																								
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL CARCINOMA, METASTAT																					X			
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL CARCINOMA, METASTAT													X										X	
THYMUS	+	-	+	+	-	+	-	+	-	+	+	+	-	-	+	-	-	+	+	-	+	-	+	-
CIRCULATORY SYSTEM																								
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+
DIGESTIVE SYSTEM																								
SALIVARY GLAND	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	-	+	+	-	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL CARCINOMA, INVASIVE					X																			
SQUAMOUS CELL CARCINOMA, METASTAT																								
NEOPLASTIC NODULE														X										
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
PANCREAS	+	+	+	+	+	+	+	+	-	+	-	+	-	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	-	-	-	+	-	-	+	+	-
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL PAPILLOMA			X			X	X			X			X		X					X	X	X		
SQUAMOUS CELL CARCINOMA	X	X	X	X	X	X	X	X	X		X		X	X		X	X		X	X	X	X		X
ADENOCARCINOMA, NOS																								
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOCARCINOMA, NOS													X											
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																								
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																								
PITUITARY	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+
CARCINOMA,NOS																								
ADENOMA, NOS	X							X		X			X	X									X	
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PHEOCHROMOCYTOMA														X										
THYROID	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+
FOLLICULAR-CELL ADENOMA	X																							
PARATHYROID	-	+	+	+	+	-	+	+	-	+	+	+	-	+	-	+	+	-	-	-	-	-	-	-
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	-	+	-	+	-	+	+	+	+	+	+	+	+	+	+	+
ISLET-CELL ADENOMA																								
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
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																								
EAR	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
NEUROFIBROSARCOMA									X															
BODY CAVITIES																								
PERITONEUM	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
MESOTHELIOMA, NOS																								
NEUROFIBROSARCOMA, METASTATIC																								
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
SQUAMOUS CELL CARCINOMA, METASTAT																								
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
SQUAMOUS CELL CARCINOMA, METASTAT														X		X	X				X			
MYELOMONOCYTIC LEUKEMIA																								

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

TABLE A3. MALE RATS: TUMOR PATHOLOGY (CONTINUED) 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	104	086	073	013	099	099	069	110	089	093	093	067	087	084	086	031	072	063	060	097	081	110	072	064	077	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
KERATOACANTHOMA																										1
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
FIBROMA																				X						2
FIBROSARCOMA																				X						1
LIPOMA																			X							1
HEMANGIOSARCOMA																										1
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ALVEOLAR/BRONCHIOLAR CARCINOMA								X																		1
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SQUAMOUS CELL PAPILLOMA										X																1
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SQUAMOUS CELL CARCINOMA, METASTAT																										1
LYMPH NODES	+	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	47
SQUAMOUS CELL CARCINOMA, METASTAT																										2
THYMUS	+	+	+	–	+	–	+	–	–	+	–	+	–	+	+	+	+	+	+	+	+	+	–	+		32
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SQUAMOUS CELL CARCINOMA, INVASIVE																										1
SQUAMOUS CELL CARCINOMA, METASTAT						X				X											X					3
NEOPLASTIC NODULE																										1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	–	+	–	–	+	+	+	+	+	+	+	+	+	44
ESOPHAGUS	+	+	+	+	+	+	–	+	+	–	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	40
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SQUAMOUS CELL PAPILLOMA			X				X		X				X					X	X					X	X	17
SQUAMOUS CELL CARCINOMA	X	X			X	X	X	X		X	X		X	X		X	X	X		X	X	X		X	X	38
ADENOCARCINOMA, NOS												X														1
SMALL INTESTINE	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ADENOCARCINOMA, NOS																										1
LARGE INTESTINE	+	+	+	+	+	+	+	–	–	+	+	+	+	–	+	–	+	+	+	–	+	+	+	+	–	44
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
CARCINOMA,NOS										X								X								1
ADENOMA, NOS												X														8
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
PHEOCHROMOCYTOMA					X			X											X							4
THYROID	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
FOLLICULAR-CELL ADENOMA																										1
PARATHYROID	+	–	–	–	–	–	–	–	–	+	+	–	+	+	+	–	+	–	–	–	–	+	+	–	+	22
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	–	+	–	–	+	+	+	+	+	+	+	+	+	44
ISLET-CELL ADENOMA											X															1
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	50*
TESTIS	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
INTERSTITIAL-CELL TUMOR	X	X	X	X	X	X		X			X		X	X		X	X			X	X	X	X		X	39
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	48
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
CARCINOMA,NOS																										1
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
EAR	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	50*
NEUROFIBROSARCOMA																		X								2
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*
MESOTHELIOMA, NOS									X																	1
NEUROFIBROSARCOMA, METASTATIC																		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*
SQUAMOUS CELL CARCINOMA, METASTAT										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*
SQUAMOUS CELL CARCINOMA, METASTAT								X			X			X											X	8
MYELOMONOCYTIC LEUKEMIA	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 A3.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR STUDY OF DIGLYCIDYL RESORCINOL ETHER

HIGH DOSE

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	0 4 2	0 5 7	0 5 1	0 6 7	0 8 7	0 3 9	0 3 0	0 4 8	0 4 8	0 5 3	0 5 5	0 6 3	0 6 7	0 3 6	0 6 4	0 6 5	0 5 0	0 3 4	0 5 3	0 6 7	0 4 1	0 6 3	0 6 5	0 6 1	0 6 4
RESPIRATORY SYSTEM																								
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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			X					X									
SQUAMOUS CELL CARCINOMA					X				X										X					
SMALL INTESTINE	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+
ADENOCARCINOMA, NOS															X									
LARGE INTESTINE	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																								
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																								
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+
ADENOMA, NOS									X															
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
INTERSTITIAL-CELL TUMOR		X			X				X	X	X							X	X					
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																								
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+
ALL OTHER SYSTEMS																								
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
SQUAMOUS CELL CARCINOMA, METASTAT																								

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
$: 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 / WEEKS ON STUDY	0267 0313	0278 0333	0299 0333	0307 0381	0317 0493	0322 0377	0337 0377	0341 0373	0352 0391	0356 0494	0375 0566	0386 0566	0389 0636	0401 0636	0411 0593	0423 0991	0434 0963	0446 0961	0455 0963	0466 0963	0478 0641	0488 0630	0491 0402	0505 0553	TOTAL TISSUES / TUMORS
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
LYMPH NODES	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	-	+	+	+	47
THYMUS	+	-	+	+	+	+	+	-	-	-	+	+	-	-	+	-	-	+	-	-	-	+	+	-	+	34
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	48
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	50*
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	47
ESOPHAGUS	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	-	+	-	-	+	+	37
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SQUAMOUS CELL PAPILLOMA								X							X			X							6
SQUAMOUS CELL CARCINOMA			X																						4
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	47
ADENOCARCINOMA, NOS																									1
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	-	+	47
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	-	+	+	47
ADENOMA, NOS																					X				2
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	-	+	+	+	+	+	+	46
PARATHYROID	+	+	-	-	-	+	-	-	-	+	-	+	-	-	-	-	-	-	-	-	-	+	-	-	20
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	+	N	N	N	50*
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
INTERSTITIAL-CELL TUMOR			X											X		X		X							11
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	49
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
SQUAMOUS CELL CARCINOMA, METASTAT			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 A4.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR STUDY OF DIGLYCIDYL RESORCINOL ETHER

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	096	105	083	105	082	093	105	104	105	105	095	105	105	105	105	105	105	095	105	091
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
TRICHOEPITHELIOMA																									
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALVEOLAR/BRONCHIOLAR ADENOMA																									
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARCINOMA,NOS												X													
ADENOMA, NOS			X	X							X		X	X	X		X		X	X			X		X
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CORTICAL ADENOMA																									
CORTICAL CARCINOMA																									
PHEOCHROMOCYTOMA																									
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FOLLICULAR-CELL ADENOMA																									
C-CELL ADENOMA			X																						
C-CELL CARCINOMA																		X							
PARATHYROID	+	-	-	-	-	-	+	-	+	+	-	+	+	+	-	+	-	+	+	-	-	-	-	-	-
ADENOMA, NOS												X													
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	N	N	+	+	N	+	N	N	N	+	N	+	+	N	+	N	N	+	N	+	+	N	+	N
ADENOCARCINOMA, NOS					X																X				
FIBROADENOMA	X			X			X				X		X	X		X			X		X			X	
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOCARCINOMA, NOS																									
LEIOMYOMA				X																					
LEIOMYOSARCOMA																									
ENDOMETRIAL STROMAL POLYP									X							X	X					X	X		
ENDOMETRIAL STROMAL SARCOMA								X																	
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GRANULOSA-CELL TUMOR																				X					
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	·	+	+	+	+	+	+	+	+	+	+	+	+	+
GLIOMA, NOS																									
ASTROCYTOMA						X																			
SPECIAL SENSE ORGANS																									
ZYMBAL'S GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
SQUAMOUS CELL CARCINOMA																									
MUSCULOSKELETAL SYSTEM																									
MUSCLE	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
RHABDOMYOSARCOMA	X																								
BODY CAVITIES																									
PERITONEUM	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ENDOMETRIAL STROMAL SARCOMA, META								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
SQUAMOUS CELL CARCINOMA, METASTAT																									
ADENOCARCINOMA, NOS, METASTATIC																									
MYELOMONOCYTIC LEUKEMIA										X									X						
LEUKEMIA,MONONUCLEAR CELL																									

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

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

ANIMAL NUMBER	0212	0227	0228	0230	0310	0311	0312	0315	0316	0317	0318	0319	0320	0321	0322	0323	0324	0325	0326	0327	0328	0329	0330	0331	0332	0333	0334	0335	0336	0337	0338	0339	0340	0341	0342	0343	0344	0345	0346	0347	0348	0349	0350	TOTAL TISSUES TUMORS
WEEKS ON STUDY	105	088	051	093	005	005	005	005	078	005	005	005	051	051	051	005	005	005	005	005	005	005	005	005	005	005	005	005	005	005	005	005	005	005	005	005	005	005	005	005	005	005	005	
INTEGUMENTARY SYSTEM																																												
SKIN	+	+	+	+	+	+	+	+	•	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
TRICHOEPITHELIOMA										X																																		1
RESPIRATORY SYSTEM																																												
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALVEOLAR/BRONCHIOLAR ADENOMA																																												1
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																																												
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LYMPH NODES	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
THYMUS	+	+	+	+	+	+	+	+	–	–	+	+	+	–	+	+	+	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	36
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	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ESOPHAGUS	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
URINARY SYSTEM																																												
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																																												
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CARCINOMA,NOS																																												1
ADENOMA, NOS								X		X															X		X	X		X	X												18
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CORTICAL ADENOMA													X	X																														1
CORTICAL CARCINOMA																																												1
PHEOCHROMOCYTOMA								X																																				3
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
FOLLICULAR-CELL ADENOMA																																												1
C-CELL ADENOMA																									X																			2
C-CELL CARCINOMA																																												1
PARATHYROID	–	+	+	–	–	–	+	–	–	+	–	–	+	–	–	–	–	+	+	+	+	+	+	+	–	+																		22
ADENOMA, NOS																																												1
REPRODUCTIVE SYSTEM																																												
MAMMARY GLAND	+	N	N	+	N	N	N	+	N	N	N	N	N	N	+	N	N	N	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ADENOCARCINOMA, NOS																					X	X		X	X																		2
FIBROADENOMA	X			X					X																																			18
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ADENOCARCINOMA, NOS										X																																		1
LEIOMYOMA																					X																							2
LEIOMYOSARCOMA																																												1
ENDOMETRIAL STROMAL POLYP					X		X	X											X	X																								11
ENDOMETRIAL STROMAL SARCOMA																																													1
OVARY	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
GRANULOSA-CELL TUMOR																																													1
NERVOUS SYSTEM																																												
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GLIOMA, NOS		X																																										1
ASTROCYTOMA																																													1
SPECIAL SENSE ORGANS																																												
ZYMBAL'S GLAND	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50
SQUAMOUS CELL CARCINOMA			X																																									1
MUSCULOSKELETAL SYSTEM																																												
MUSCLE	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	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50
RHABDOMYOSARCOMA																																												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	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50
ENDOMETRIAL STROMAL SARCOMA, META																																												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	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50
SQUAMOUS CELL CARCINOMA, METASTAT			X																																									1
ADENOCARCINOMA, NOS, METASTATIC										X																																			1
MYELOMONOCYTIC LEUKEMIA	X										X										X																								5
LEUKEMIA,MONONUCLEAR CELL							X																																						1

N 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 DIGLYCIDYL RESORCINOL ETHER

LOW DOSE

ANIMAL NUMBER	0012	0013	0046	0055	0064	0077	0088	0091	0101	0112	0132	0144	0155	0166	0178	0189	0201	0222	0223	0244	0255
WEEKS ON STUDY	104	088	104	065	004	004	097	041	065	021	061	044	048	069	104	089	041	071	079	011	087	049	042
RESPIRATORY SYSTEM																							
LUNGS AND BRONCHI ALVEOLAR/BRONCHIOLAR ADENOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																							
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES SQUAMOUS CELL CARCINOMA, METASTAT	+	+	+	+	+	+	+	+	+	+	-	+	-	+	+	+	+	+	+	+	+	+	+
THYMUS	+	+	+	+	-	+	+	+	+	+	-	+	+	+	+	+	-	+	+	-	-	+	-	+
CIRCULATORY SYSTEM																							
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																							
SALIVARY GLAND ADENOMA, NOS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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 SQUAMOUS CELL CARCINOMA, METASTAT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL PAPILLOMA											X	X				X			X			X		
SQUAMOUS CELL CARCINOMA	X	X	X	X		X	X	X	X	X	X						X	X		X	X	X	X	
LEIOMYOSARCOMA							X																	
CARCINOSARCOMA																								
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																							
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																							
PITUITARY	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARCINOMA,NOS																								
ADENOMA, NOS		X								X		X							X		X			
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+
CORTICAL ADENOMA															+									
PHEOCHROMOCYTOMA, MALIGNANT															X	+								
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+
PARATHYROID	-	-	-	-	-	-	+	+	+	+	-	+	-	+	+	-	-	-	-	+	+	-	-	-	+
REPRODUCTIVE SYSTEM																							
MAMMARY GLAND	+	+	N	+	N	N	+	N	+	+	N	N	N	+	N	N	N	N	N	N	N	N	+	+
FIBROADENOMA				X			X																	
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
CARCINOMA,NOS										X														
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOCARCINOMA, NOS						X																		
ENDOMETRIAL STROMAL POLYP							X									X								
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																							
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NEUROFIBROSARCOMA																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	02601	02701	02801	02901	03001	03101	03201	03301	03401	03501	03601	03701	03801	03901	04001	04101	04201	04301	04401	04501	04601	04701	04801	04901	05001	TOTAL TISSUES TUMORS
WEEKS ON STUDY	104	104	099	097	097	098	055	088	086	094	104	086	045	082	104	097	103	041	098	044	044	041	060	092	052	
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	X	+	+	+	+	+	+	+	+	50
ALVEOLAR/BRONCHIOLAR ADENOMA																										1
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LYMPH NODES	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
SQUAMOUS CELL CARCINOMA, METASTAT		X																								1
THYMUS	+	+	+	+	+	+	+	+	+	+	-	+	+	-	+	+	+	+	+	+	+	+	+	-	+	41
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ADENOMA, NOS									X																	1
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	+	+	+	+	+	+	+	+	+	+	+	+	-	-	+	-	+	+	+	+	+	+	+	+	+	46
SQUAMOUS CELL CARCINOMA, METASTAT	X																									1
ESOPHAGUS	+	+	+	+	+	-	+	+	+	+	+	+	+	-	+	+	+	-	+	+	+	-	+	+		45
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SQUAMOUS CELL PAPILLOMA																								X		7
SQUAMOUS CELL CARCINOMA	X	X	X	X	X	X		X	X		X	X		X	X		X	X	X		X	X	X			34
LEIOMYOSARCOMA																										1
CARCINOSARCOMA																X										1
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	48
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
CARCINOMA,NOS					X																					1
ADENOMA, NOS		X				X																	X			6
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	48
CORTICAL ADENOMA																								X		2
PHEOCHROMOCYTOMA, MALIGNANT																										1
THYROID	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	47
PARATHYROID	-	-	+	-	-	-	+	-	-	-	-	-	-	-	+	+	+	+	+	-	-	-	-	-	-	17
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	+	+	+	+	+	+	N	+	+	N	N	N	N	+	+	+	N	N	+	N	N	N	N	N	N	50*
FIBROADENOMA	X	X	X		X				X						X											8
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
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ADENOCARCINOMA, NOS															X											2
ENDOMETRIAL STROMAL POLYP		X							X	X										X			X			7
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NEUROFIBROSARCOMA																										1
SPECIAL SENSE ORGANS																										
EAR	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
NEUROFIBROSARCOMA																										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*
SQUAMOUS CELL CARCINOMA, METASTAT				X											X											3
CARCINOSARCOMA, METASTATIC																X										1
HEMANGIOSARCOMA																										1
MYELOMONOCYTIC LEUKEMIA																								X		2
LEUKEMIA,MONONUCLEAR CELL		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 A4.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR STUDY OF DIGLYCIDYL RESORCINOL ETHER

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	026	031	047	032	036	033	037	041	028	033	031	033	030	042	048	038	037	035	030	043	037	031	030	035	027
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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																									
SQUAMOUS CELL CARCINOMA														X											
SMALL INTESTINE	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+
ADENOMA, NOS																									
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+
THYROID	+	-	+	+	+	+	+	+	-	+	-	+	+	+	+	+	+	+	-	+	+	+	+	+	+
PARATHYROID	+	-	-	+	-	-	-	-	-	+	-	-	-	-	-	-	+	-	-	-	-	-	-	+	+
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	N	+	N	N	N	N	N	N	+	N	N	N	+	+	N	N	+	N	N	N	N	+	N	+	N
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOMETRIAL STROMAL POLYP						X																			
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
EAR	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
NEUROFIBROSARCOMA						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
SQUAMOUS CELL CARCINOMA, METASTAT																				X					
CARCINOSARCOMA, METASTATIC																									
HEMANGIOSARCOMA	X																								
MYELOMONOCYTIC LEUKEMIA									X																
LEUKEMIA, MONONUCLEAR CELL																									

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

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

ANIMAL NUMBER / WEEKS ON STUDY	0026 034	0027 046	0028 036	0029 051	0031 037	0032 035	0033 034	0034 041	0035 037	0036 056	0037 056	0038 036	0039 036	0040 037	0041 035	0042 041	0043 037	0044 031	0045 063	0046 071	0047 062	0048 053	0049 041	0050 089	0051 026	TOTAL TISSUES / TUMORS
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
THYMUS	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	-	+	+	-	+	+	+	+	-	+	36
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	47
ESOPHAGUS	+	-	+	+	+	-	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	37
STOMACH	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SQUAMOUS CELL PAPILLOMA					X																					1
SQUAMOUS CELL CARCINOMA																			X					X		3
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	47
LARGE INTESTINE	+	+	+	-	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
ADENOMA, NOS																X										1
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
THYROID	+	+	+	-	-	+	+	-	+	+	-	+	+	+	+	+	+	+	-	+	+	+	+	+	+	41
PARATHYROID	+	+	+	-	-	+	+	-	+	+	-	+	+	+	+	+	+	-	-	+	+	-	-	+	+	23
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	+	N	N	N	N	+	+	N	N	+	N	N	N	+	N	N	N	N	N	N	N	N	N	+	+	50#
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOMETRIAL STROMAL POLYP																										1
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

\# 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 A5.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS ADMINISTERED DIGLYCIDYL RESORCINOL ETHER IN CORN OIL BY GAVAGE (SUPPLEMENTAL STUDY)

	VEHICLE CONTROL	TEST
ANIMALS INITIALLY IN STUDY	50	50
ANIMALS NECROPSIED	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50
INTEGUMENTARY SYSTEM		
*SKIN	(50)	(50)
SQUAMOUS CELL CARCINOMA	1 (2%)	1 (2%)
TRICHOEPITHELIOMA		2 (4%)
KERATOACANTHOMA	2 (4%)	2 (4%)
*SUBCUT TISSUE	(50)	(50)
SARCOMA, NOS	1 (2%)	
FIBROMA	4 (8%)	3 (6%)
FIBROSARCOMA	1 (2%)	
LIPOMA		1 (2%)
NEUROFIBROSARCOMA		3 (6%)
RESPIRATORY SYSTEM		
#LUNG	(50)	(50)
SQUAMOUS CELL CARCINOMA, METASTA		1 (2%)
ALVEOLAR/BRONCHIOLAR ADENOMA	2 (4%)	2 (4%)
HEMATOPOIETIC SYSTEM		
*MULTIPLE ORGANS	(50)	(50)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		1 (2%)
LEUKEMIA,MONONUCLEAR CELL	6 (12%)	6 (12%)
#SPLEEN	(49)	(50)
SQUAMOUS CELL CARCINOMA, INVASIV		1 (2%)
#LYMPH NODE	(50)	(48)
SQUAMOUS CELL CARCINOMA, METASTA		1 (2%)
CIRCULATORY SYSTEM		
*SUBCUT TISSUE	(50)	(50)
HEMANGIOMA	1 (2%)	

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

TABLE A5. MALE RATS: NEOPLASMS (CONTINUED)

	VEHICLE CONTROL	TEST
#HEART	(50)	(50)
NEURILEMOMA		1 (2%)
DIGESTIVE SYSTEM		
#LIVER	(50)	(50)
NEOPLASTIC NODULE	1 (2%)	
HEPATOCELLULAR CARCINOMA		1 (2%)
#PANCREAS	(49)	(46)
ACINAR-CELL ADENOMA	1 (2%)	1 (2%)
#FORESTOMACH	(50)	(50)
SQUAMOUS CELL PAPILLOMA		16 (32%)
SQUAMOUS CELL CARCINOMA		39 (78%)
URINARY SYSTEM		
#KIDNEY	(50)	(50)
TUBULAR-CELL ADENOMA		1 (2%)
SARCOMA, NOS	1 (2%)	
ENDOCRINE SYSTEM		
#PITUITARY INTERMEDIA	(50)	(48)
ADENOMA, NOS	1 (2%)	1 (2%)
#ANTERIOR PITUITARY	(50)	(48)
CARCINOMA,NOS		2 (4%)
ADENOMA, NOS	17 (34%)	14 (29%)
#ADRENAL	(50)	(49)
CORTICAL ADENOMA	1 (2%)	
CORTICAL CARCINOMA		1 (2%)
PHEOCHROMOCYTOMA	1 (2%)	
#ADRENAL MEDULLA	(50)	(49)
PHEOCHROMOCYTOMA	10 (20%)	10 (20%)
PHEOCHROMOCYTOMA, MALIGNANT	1 (2%)	3 (6%)
NEUROBLASTOMA		1 (2%)
#THYROID	(50)	(50)
FOLLICULAR-CELL ADENOMA		1 (2%)

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

TABLE A5. MALE RATS: NEOPLASMS (CONTINUED)

	VEHICLE CONTROL	TEST
FOLLICULAR-CELL CARCINOMA		1 (2%)
C-CELL ADENOMA	9 (18%)	1 (2%)
C-CELL CARCINOMA	2 (4%)	2 (4%)
#PANCREATIC ISLETS	(49)	(46)
ISLET-CELL ADENOMA	3 (6%)	1 (2%)
ISLET-CELL CARCINOMA	1 (2%)	1 (2%)
REPRODUCTIVE SYSTEM		
*MAMMARY GLAND	(50)	(50)
ADENOCARCINOMA, NOS	1 (2%)	
FIBROADENOMA	3 (6%)	
*PREPUTIAL GLAND	(50)	(50)
CARCINOMA,NOS	1 (2%)	3 (6%)
SQUAMOUS CELL CARCINOMA	1 (2%)	
ADENOMA, NOS	1 (2%)	1 (2%)
#TESTIS	(50)	(48)
INTERSTITIAL-CELL TUMOR	47 (94%)	45 (94%)
NERVOUS SYSTEM		
#BRAIN	(50)	(49)
SQUAMOUS CELL CARCINOMA, METASTA	1 (2%)	
NEURILEMOMA, MALIGNANT		1 (2%)
SPECIAL SENSE ORGANS		
*ZYMBAL'S GLAND	(50)	(50)
CARCINOMA,NOS		1 (2%)
SQUAMOUS CELL CARCINOMA	1 (2%)	
ADENOMA, NOS		1 (2%)
MUSCULOSKELETAL SYSTEM		
*BONE	(50)	(50)
OSTEOSARCOMA	1 (2%)	
BODY CAVITIES		
NONE		

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

TABLE A5. MALE RATS: NEOPLASMS (CONTINUED)

	VEHICLE CONTROL	TEST
ALL OTHER SYSTEMS		
*MULTIPLE ORGANS	(50)	(50)
SQUAMOUS CELL CARCINOMA, INVASIV		1 (2%)
SQUAMOUS CELL CARCINOMA, METASTA		5 (10%)
DIAPHRAGM		
SQUAMOUS CELL CARCINOMA, METASTA		1
OMENTUM		
SQUAMOUS CELL CARCINOMA, METASTA		2
ANIMAL DISPOSITION SUMMARY		
ANIMALS INITIALLY IN STUDY	50	50
NATURAL DEATH	7	8
MORIBUND SACRIFICE	5	19
SCHEDULED SACRIFICE		
TERMINAL SACRIFICE	38	23
DOSING ACCIDENT		
ACCIDENTALLY KILLED, NDA		
ACCIDENTALLY KILLED, NOS		
ANIMAL MISSING		
ANIMAL MISSEXED		
OTHER CASES		
TUMOR SUMMARY		
TOTAL ANIMALS WITH PRIMARY TUMORS*	49	49
TOTAL PRIMARY TUMORS	123	171
TOTAL ANIMALS WITH BENIGN TUMORS	47	47
TOTAL BENIGN TUMORS	103	104
TOTAL ANIMALS WITH MALIGNANT TUMORS	17	47
TOTAL MALIGNANT TUMORS	19	67
TOTAL ANIMALS WITH SECONDARY TUMORS#	1	12
TOTAL SECONDARY TUMORS	1	12
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	1	
TOTAL UNCERTAIN TUMORS	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 A6.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS ADMINISTERED DIGLYCIDYL RESORCINOL ETHER IN CORN OIL BY GAVAGE (SUPPLEMENTAL STUDY)

	VEHICLE CONTROL	TEST
ANIMALS INITIALLY IN STUDY	50	50
ANIMALS NECROPSIED	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50
INTEGUMENTARY SYSTEM		
*SUBCUT TISSUE	(50)	(50)
FIBROMA	1 (2%)	
FIBROSARCOMA	1 (2%)	
LIPOMA		1 (2%)
RESPIRATORY SYSTEM		
#LUNG	(50)	(50)
CARCINOMA, NOS, METASTATIC		1 (2%)
ADENOCARCINOMA, NOS, METASTATIC	1 (2%)	
PHEOCHROMOCYTOMA, METASTATIC	1 (2%)	
HEMATOPOIETIC SYSTEM		
*MULTIPLE ORGANS	(50)	(50)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	2 (4%)	
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (2%)	
LEUKEMIA,MONONUCLEAR CELL	5 (10%)	6 (12%)
#PANCREATIC L.NODE	(49)	(50)
SQUAMOUS CELL CARCINOMA, METASTA		1 (2%)
#LUMBAR LYMPH NODE	(49)	(50)
SQUAMOUS CELL CARCINOMA, METASTA		1 (2%)
#UTERUS/ENDOMETRIUM	(50)	(50)
DECIDUOMA		1 (2%)
CIRCULATORY SYSTEM		
*PULMONARY ARTERY	(50)	(50)
PHEOCHROMOCYTOMA, METASTATIC	1 (2%)	

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

TABLE A6. FEMALE RATS: NEOPLASMS (CONTINUED)

	VEHICLE CONTROL	TEST
DIGESTIVE SYSTEM		
#SALIVARY GLAND	(50)	(50)
SQUAMOUS CELL CARCINOMA, METASTA		1 (2%)
#LIVER	(50)	(50)
NEOPLASTIC NODULE	2 (4%)	2 (4%)
HEPATOCELLULAR CARCINOMA		1 (2%)
#PANCREAS	(50)	(49)
SQUAMOUS CELL CARCINOMA, METASTA		1 (2%)
#STOMACH	(50)	(50)
SQUAMOUS CELL PAPILLOMA		1 (2%)
#FORESTOMACH	(50)	(50)
SQUAMOUS CELL PAPILLOMA		19 (38%)
SQUAMOUS CELL CARCINOMA		27 (54%)
BASAL-CELL CARCINOMA		1 (2%)
URINARY SYSTEM		
#KIDNEY	(50)	(50)
TUBULAR-CELL ADENOMA		1 (2%)
LIPOMA		1 (2%)
#URINARY BLADDER	(48)	(49)
TRANSITIONAL-CELL PAPILLOMA		1 (2%)
ENDOCRINE SYSTEM		
#PITUITARY	(50)	(50)
ADENOMA, NOS		1 (2%)
CRANIOPHARYNGIOMA		1 (2%)
#PITUITARY INTERMEDIA	(50)	(50)
ADENOMA, NOS	1 (2%)	1 (2%)
#ANTERIOR PITUITARY	(50)	(50)
CARCINOMA,NOS	2 (4%)	3 (6%)
ADENOMA, NOS	16 (32%)	24 (48%)
#ADRENAL	(50)	(50)
CORTICAL ADENOMA	1 (2%)	2 (4%)

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

TABLE A6. FEMALE RATS: NEOPLASMS (CONTINUED)

	VEHICLE CONTROL	TEST
#ADRENAL MEDULLA	(50)	(50)
PHEOCHROMOCYTOMA	5 (10%)	
PHEOCHROMOCYTOMA, MALIGNANT	1 (2%)	
#THYROID	(50)	(50)
C-CELL ADENOMA	5 (10%)	4 (8%)
C-CELL CARCINOMA		1 (2%)
#PANCREATIC ISLETS	(50)	(49)
ISLET-CELL CARCINOMA		1 (2%)
REPRODUCTIVE SYSTEM		
*MAMMARY GLAND	(50)	(50)
ADENOCARCINOMA, NOS		2 (4%)
FIBROADENOMA	17 (34%)	20 (40%)
*CLITORAL GLAND	(50)	(50)
CARCINOMA,NOS	2 (4%)	2 (4%)
ADENOMA, NOS	1 (2%)	1 (2%)
*VAGINA	(50)	(50)
SQUAMOUS CELL CARCINOMA		1 (2%)
#UTERUS	(50)	(50)
ADENOCARCINOMA, NOS	1 (2%)	
LEIOMYOMA	1 (2%)	
ENDOMETRIAL STROMAL POLYP	12 (24%)	11 (22%)
ENDOMETRIAL STROMAL SARCOMA	3 (6%)	3 (6%)
#UTERUS/ENDOMETRIUM	(50)	(50)
ADENOMA, NOS		2 (4%)
ADENOCARCINOMA, NOS	2 (4%)	1 (2%)
#UTERUS/MYOMETRIUM	(50)	(50)
LEIOMYOSARCOMA		1 (2%)
#OVARY	(50)	(48)
FIBROMA	1 (2%)	
NERVOUS SYSTEM		
#BRAIN	(50)	(50)
CARCINOMA, NOS, INVASIVE		1 (2%)

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

TABLE A6. FEMALE RATS: NEOPLASMS (CONTINUED)

	VEHICLE CONTROL	TEST
SPECIAL SENSE ORGANS		
*ZYMBAL'S GLAND	(50)	(50)
CARCINOMA,NOS		1 (2%)
MUSCULOSKELETAL SYSTEM		
NONE		
BODY CAVITIES		
NONE		
ALL OTHER SYSTEMS		
*MULTIPLE ORGANS	(50)	(50)
SQUAMOUS CELL CARCINOMA, METASTA		2 (4%)
ANIMAL DISPOSITION SUMMARY		
ANIMALS INITIALLY IN STUDY	50	50
NATURAL DEATH	6	6
MORIBUND SACRIFICE	5	10
SCHEDULED SACRIFICE		
TERMINAL SACRIFICE	39	34
DOSING ACCIDENT		
ACCIDENTALLY KILLED, NDA		
ACCIDENTALLY KILLED, NOS		
ANIMAL MISSING		
ANIMAL MISSEXED		
OTHER CASES		

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

TABLE A6. FEMALE RATS: NEOPLASMS (CONTINUED)

	VEHICLE CONTROL	TEST
TUMOR SUMMARY		
TOTAL ANIMALS WITH PRIMARY TUMORS*	45	49
TOTAL PRIMARY TUMORS	83	145
TOTAL ANIMALS WITH BENIGN TUMORS	39	42
TOTAL BENIGN TUMORS	61	91
TOTAL ANIMALS WITH MALIGNANT TUMORS	18	38
TOTAL MALIGNANT TUMORS	20	51

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

TABLE A6. FEMALE RATS: NEOPLASMS (CONTINUED)

	VEHICLE CONTROL	TEST
TUMOR SUMMARY		
TOTAL ANIMALS WITH SECONDARY TUMORS#	2	7
TOTAL SECONDARY TUMORS	3	8
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	2	3
TOTAL UNCERTAIN TUMORS	2	3
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 A7.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR STUDY OF DIGLYCIDYL RESORCINOL ETHER (SUPPLEMENTAL STUDY)

VEHICLE CONTROL

ANIMAL NUMBER	051	052	053	054	055	056	057	058	059	060	061	062	063	064	065	066	067	068	069	070	071	072	073	074	075
WEEKS ON STUDY	103	068	105	105	061	105	105	081	105	105	105	105	105	105	105	068	105	105	105	105	105	105	105	105	105
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL CARCINOMA																									
KERATOACANTHOMA																									
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+
SARCOMA, NOS					X																				X
FIBROMA																									
FIBROSARCOMA																									
HEMANGIOMA																									
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALVEOLAR/BRONCHIOLAR ADENOMA								X													X				
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	-	+	-	-	+	+	-	+	-	-	-	-	+	+	+	+	+	-	+	+	+	+	+	+	-
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NEOPLASTIC NODULE				X																					
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+
ACINAR-CELL ADENOMA																									
ESOPHAGUS	+	+	+	+	+	-	-	+	+	-	-	-	+	+	-	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	-	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	X	+	+	+	+	+	+	+	+
SARCOMA, NOS																									
URINARY BLADDER	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOMA, NOS	X					X				X		X	X					X		X	X	X	X		
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CORTICAL ADENOMA							X																		
PHEOCHROMOCYTOMA			X						X		X				X			X							
PHEOCHROMOCYTOMA, MALIGNANT																					X				
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-CELL ADENOMA	X								X	X			X												
C-CELL CARCINOMA															X										
PARATHYROID	-	-	+	-	-	-	-	-	-	+	+	+	+	-	+	-	-	+	+	-	+	-	-	-	-
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+
ISLET-CELL ADENOMA																							X		
ISLET-CELL CARCINOMA																									
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	+	+	N	+	N	+
ADENOCARCINOMA, NOS																					X				
FIBROADENOMA																									X
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
INTERSTITIAL-CELL TUMOR	X	X	X	X		X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	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																	
SQUAMOUS CELL CARCINOMA																									
ADENOMA, NOS													X												
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL CARCINOMA, METASTAT																									
SPECIAL SENSE ORGANS																									
ZYMBAL'S GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
SQUAMOUS CELL CARCINOMA																									
MUSCULOSKELETAL SYSTEM																									
BONE	N	+	N	N	+	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N
OSTEOSARCOMA																									
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
LEUKEMIA,MONONUCLEAR CELL	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 A7. MALE RATS: TUMOR PATHOLOGY (CONTINUED) VEHICLE CONTROL

ANIMAL NUMBER	0076	0078	0079	0080	0081	0082	0083	0084	0085	0086	0087	0088	0089	0090	0091	0092	0093	0094	0095	0096	0097	0098	0099	0100	TOTAL
WEEKS ON STUDY	105	088	105	101	105	105	105	105	105	105	105	099	105	105	085	095	105	105	105	105	105	105	105	057	TISSUES TUMORS
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SQUAMOUS CELL CARCINOMA					X																				1
KERATOACANTHOMA												X									X				2
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SARCOMA, NOS																									1
FIBROMA									X			X	X												4
FIBROSARCOMA													X												1
HEMANGIOMA								X																	1
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALVEOLAR/BRONCHIOLAR ADENOMA																									2
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPLEEN	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
THYMUS	+	+	+	+	+	-	-	-	-	+	+	+	+	+	+	-	-	+	+	+	-	-	-	-	29
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NEOPLASTIC NODULE																									1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ACINAR-CELL ADENOMA																				X					1
ESOPHAGUS	+	+	-	+	+	+	-	-	-	+	+	+	+	+	+	-	-	+	-	+	-	-	-	+	33
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LARGE INTESTINE	+	+	+	+	+	+	-	-	+	+	+	-	+	+	-	-	+	-	+	+	+	+	+	+	42
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SARCOMA, NOS																									1
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ADENOMA, NOS			X	X		X				X					X		X					X	X		18
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CORTICAL ADENOMA																									1
PHEOCHROMOCYTOMA			X		X		X											X							11
PHEOCHROMOCYTOMA, MALIGNANT					X																				1
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-CELL ADENOMA					X			X									X	X				X			9
C-CELL CARCINOMA																							X		2
PARATHYROID	+	+	+	+	-	-	-	-	-	-	-	-	-	+	-	-	-	-	-	+	+	-	+	-	17
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ISLET-CELL ADENOMA							X			X															3
ISLET-CELL CARCINOMA																X									1
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	N	+	+	+	N	N	N	N	N	+	+	N	N	N	+	+	N	+	+	+	N	+	N	50
ADENOCARCINOMA, NOS												X								X					1
FIBROADENOMA																									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	X	X	X	X	+	47
PROSTATE	+	+	+	+	+	+	+	+	-	+	+	+	-	+	+	+	-	+	+	+	-	+	-	+	44
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50
CARCINOMA,NOS																					X				1
SQUAMOUS CELL CARCINOMA																									1
ADENOMA, NOS																									1
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SQUAMOUS CELL CARCINOMA, METASTAT																X									1
SPECIAL SENSE ORGANS																									
ZYMBAL'S GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	50
SQUAMOUS CELL CARCINOMA																X									1
MUSCULOSKELETAL SYSTEM																									
BONE	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	50
OSTEOSARCOMA		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	50
LEUKEMIA,MONONUCLEAR CELL								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 A7.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR STUDY OF DIGLYCIDYL RESORCINOL ETHER (SUPPLEMENTAL STUDY)

TEST

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	093	101	085	091	104	104	104	104	089	104	092	099	104	074	099	104	101	043	104	104	058	061	104	104	089
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL CARCINOMA		X																							
TRICHOEPITHELIOMA																									
KERATOACANTHOMA																									
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+
FIBROMA																									
LIPOMA																								X	
NEUROFIBROSARCOMA	X																								
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL CARCINOMA, METASTAT																			X						
ALVEOLAR/BRONCHIOLAR ADENOMA								X		X															
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL CARCINOMA, INVASIVE																									
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL CARCINOMA, METASTAT																			X						
THYMUS	-	-	+	+	+	+	+	-	+	+	+	-	+	+	+	+	+	+	-	-	+	-	-	-	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NEURILEMOMA										X															
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR CARCINOMA									X																
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	-	+	-	+	+	+
ACINAR-CELL ADENOMA																									
ESOPHAGUS	-	-	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	-	+	-	+	+	-	-	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL PAPILLOMA					X	X	X					X				X		X					X	X	
SQUAMOUS CELL CARCINOMA	X	X	X	X		X	X	X			X	X	X			X	X	X	X	X			X	X	X
SQUAMOUS CELL CARCINOMA, METASTAT											X														
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-
LARGE INTESTINE	+	+	+	+	+	-	+	+	+	+	+	+	-	+	-	+	+	+	+	+	+	+	+	+	-
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
TUBULAR-CELL ADENOMA										X															
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	-	+	-
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARCINOMA,NOS																									
ADENOMA, NOS		X				X	X									X				X				X	
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CORTICAL CARCINOMA										X															
PHEOCHROMOCYTOMA		X										X				X									
PHEOCHROMOCYTOMA, MALIGNANT								X		X													X		
NEUROBLASTOMA																			X						
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FOLLICULAR-CELL ADENOMA																	X								
FOLLICULAR-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	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	
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																									
ADENOMA, NOS																									
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NEURILEMOMA, MALIGNANT																						X			
SPECIAL SENSE ORGANS																									
ZYMBAL'S GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
CARCINOMA,NOS																									
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, INVASIVE																									X
SQUAMOUS CELL CARCINOMA, METASTAT				X													X								
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE																									
LEUKEMIA,MONONUCLEAR CELL	X								X			X		X											
DIAPHRAGM NOS																									
SQUAMOUS CELL CARCINOMA, METASTAT																									

+: 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 A7. MALE RATS: TUMOR PATHOLOGY (CONTINUED) TEST

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	118	088	104	085	092	104	081	104	104	102	088	104	104	104	104	076	091	104	081	104	099	099	100	104	077	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	50
SQUAMOUS CELL CARCINOMA													X													1
TRICHOEPITHELIOMA					X																					2
KERATOACANTHOMA																X		X								2
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	X	+	+	+	+	+	+	X	X	+	N	+	+	50
FIBROMA																										3
LIPOMA																										1
NEUROFIBROSARCOMA								X			X															3
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SQUAMOUS CELL CARCINOMA, METASTAT																										1
ALVEOLAR/BRONCHIOLAR ADENOMA																										2
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	48
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SQUAMOUS CELL CARCINOMA, INVASIVE					X																					1
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	+	+	+	48
SQUAMOUS CELL CARCINOMA, METASTAT																										1
THYMUS	+	–	–	–	–	+	–	+	–	–	–	–	–	–	–	+	+	–	+	–	+	–	–	+	–	24
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NEURILEMOMA																										1
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	49
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEPATOCELLULAR CARCINOMA																										1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	46
ACINAR-CELL ADENOMA									X																	1
ESOPHAGUS	+	–	+	–	–	–	–	+	–	–	+	–	–	–	–	–	+	+	–	+	–	+	–	–	+	27
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SQUAMOUS CELL PAPILLOMA	X			X							X		X						X	X			X	X	X	16
SQUAMOUS CELL CARCINOMA	X	X	X		X	X		X	X	X		X	X	X	X	X	X	X		X	X	X	X	X	X	39
SQUAMOUS CELL CARCINOMA, METASTAT										X																2
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	45
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
TUBULAR-CELL ADENOMA																										1
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
CARCINOMA,NOS													X											X		2
ADENOMA, NOS					X	X	X	X	X					X			X				X	X				15
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	49
CORTICAL CARCINOMA																										1
PHEOCHROMOCYTOMA			X			X				X			X	X							X	X				10
PHEOCHROMOCYTOMA, MALIGNANT																										3
NEUROBLASTOMA																										1
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
FOLLICULAR-CELL ADENOMA																										1
FOLLICULAR-CELL CARCINOMA																								X		1
PARATHYROID	+	–	–	+	–	–	–	–	–	–	–	–	–	–	–	+	–	–	+	+	+	+	+	+	+	16
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	46
ISLET-CELL ADENOMA																										1
ISLET-CELL CARCINOMA																										1
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	N	N	+	N	N	N	N	+	N	+	+	N	N	N	N	N	N	N	N	N	+	N	N	N	N	50
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
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	45
PROSTATE	+	–	+	+	–	+	+	+	+	–	–	–	+	–	+	+	–	+	+	–	+	–	+	+	+	36
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										X			X					X				3
ADENOMA, NOS																										1
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
NEURILEMOMA, MALIGNANT																										1
SPECIAL SENSE ORGANS																										
ZYMBAL'S GLAND	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	+	N	N	N	+	N	N	N	N	N	50
CARCINOMA,NOS																X				X						1
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	50
SQUAMOUS CELL CARCINOMA, INVASIVE																										1
SQUAMOUS CELL CARCINOMA, METASTAT			X																		X	X				5
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE							X																			1
LEUKEMIA,MONONUCLEAR CELL													X												X	6
DIAPHRAGM NOS																										
SQUAMOUS CELL CARCINOMA, METASTAT		X																								1

N 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 A8.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR STUDY OF DIGLYCIDYL RESORCINOL ETHER (SUPPLEMENTAL STUDY)

VEHICLE CONTROL

ANIMAL NUMBER	051	052	053	054	055	056	057	058	059	060	061	062	063	064	065	066	067	068	069	070	071	072	073	074	075
WEEKS ON STUDY	105	105	083	105	095	105	091	105	105	105	105	099	105	105	105	105	105	105	105	105	105	105	105	105	105
INTEGUMENTARY SYSTEM																									
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FIBROMA																							X		
FIBROSARCOMA																				X					
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOCARCINOMA, NOS, METASTATIC													X												
PHEOCHROMOCYTOMA, METASTATIC							X																		
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+
THYMUS	+	+	+	+	+	+	+	-	-	-	-	+	+	+	+	+	+	+	-	+	-	-	-	-	-
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
BLOOD VESSELS	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
PHEOCHROMOCYTOMA, METASTATIC							X																		
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NEOPLASTIC NODULE																									
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	-	+	+	+	+	+	+	-	-	-	-	+	+	+	+	+	+	+	-	+	+	-	-	-	-
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARCINOMA,NOS										X															
ADENOMA, NOS	X	X	X					X		X		X		X			X								X
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CORTICAL ADENOMA														X											
PHEOCHROMOCYTOMA							X																		
PHEOCHROMOCYTOMA, MALIGNANT							X																		
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-CELL ADENOMA				X																					X
PARATHYROID	+	+	-	+	-	+	-	-	-	-	-	+	-	-	+	+	-	-	+	+	+	-	-	+	+
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	N	+	+	+	+	N	+	+	N	N	+	+	+	+	+	+	+	+	+	N	+	N	N	+	N
FIBROADENOMA		X		X			X				X								X					X	
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
CARCINOMA,NOS																									
ADENOMA, NOS																		X							
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOCARCINOMA, NOS		X									X		X												
LEIOMYOMA			X		X	X		X	X					X			X	X							
ENDOMETRIAL STROMAL POLYP																									
ENDOMETRIAL STROMAL SARCOMA																									
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FIBROMA																					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
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE																									
MALIG.LYMPHOMA, HISTIOCYTIC TYPE					X																				
LEUKEMIA,MONONUCLEAR CELL						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 A8. FEMALE RATS: TUMOR PATHOLOGY (CONTINUED) VEHICLE CONTROL

ANIMAL NUMBER	0746	0747	0748	0749	0750	0801	0802	0803	0804	0805	0806	0807	0808	0809	0810	0811	0812	0813	0814	0815	0816	0817	0818	0819	0820	TOTAL
WEEKS ON STUDY	1 0 5	1 0 5	1 0 5	0 9 1	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	0 9 8	1 0 5	1 0 4	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	0 2 5	1 0 5	0 7 4	1 0 0	1 0 5	1 0 5	#ISSUES TUMORS
INTEGUMENTARY SYSTEM																										
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
FIBROMA																										1
FIBROSARCOMA																										1
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ADENOCARCINOMA, NOS, METASTATIC																										1
PHEOCHROMOCYTOMA, METASTATIC																										1
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	49
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
THYMUS	+	+	+	+	+	-	-	-	-	+	+	+	+	+	+	+	+	-	+	+	+	~	+	+	-	34
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
BLOOD VESSELS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50
PHEOCHROMOCYTOMA, METASTATIC																										1
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NEOPLASTIC NODULE														X					X							2
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	+	+	+	-	-	-	-	-	-	+	+	+	+	+	-	+	+	+	+	+	+	+	+	-	+	32
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	48
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CARCINOMA,NOS																			X							2
ADENOMA, NOS							X		X		X	X			X	X	X					X				17
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CORTICAL ADENOMA																										1
PHEOCHROMOCYTOMA																X	X			X					X	5
PHEOCHROMOCYTOMA, MALIGNANT																										1
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-CELL ADENOMA																			X		X				X	5
PARATHYROID	~	-	-	+	-	-	-	+	-	+	+	-	+	-	+	+	-	-	+	-	+	+	-	-	+	23
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	+	+	+	N	+	+	+	+	N	N	+	N	N	N	+	+	+	+	+	N	N	+	+	N	N	50
FIBROADENOMA	X	X	X		X	X	X	X			X				X		X						X			17
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	X																							2
ADENOMA, NOS																										1
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ADENOCARCINOMA, NOS																									X	3
LEIOMYOMA		X			X										X				X					X		1
ENDOMETRIAL STROMAL POLYP												X									X					12
ENDOMETRIAL STROMAL SARCOMA																										3
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
FIBROMA																										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
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE				X																			X			2
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																										1
LEUKEMIA,MONONUCLEAR CELL								X											X					X		5

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

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

TABLE A8.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR STUDY OF DIGLYCIDYL RESORCINOL ETHER (SUPPLEMENTAL STUDY)

TEST

ANIMAL NUMBER	001	002	003	005	006	007	008	009	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	092	104	083	104	041	104	104	104	073	104	064	104	104	045	088	046	089	104	104	011	104	104	104
INTEGUMENTARY SYSTEM																							
SUBCUTANEOUS TISSUE LIPOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																							
LUNGS AND BRONCHI CARCINOMA, NOS, METASTATIC	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
TRACHEA	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																							
BONE MARROW	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES SQUAMOUS CELL CARCINOMA, METASTAT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	+	-	-	+	-	-	+	+	-	+	+	+	+	+	-	+	-	+	-	-	+	-	+
CIRCULATORY SYSTEM																							
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																							
SALIVARY GLAND SQUAMOUS CELL CARCINOMA, METASTAT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER NEOPLASTIC NODULE HEPATOCELLULAR CARCINOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
																				X			
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
PANCREAS SQUAMOUS CELL CARCINOMA, METASTAT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	-	-	+	-	-	+	-	+	+	+	+	+	+	+	+	-	+	-	-	+	-	-
STOMACH SQUAMOUS CELL PAPILLOMA SQUAMOUS CELL CARCINOMA BASAL-CELL CARCINOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
		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											
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																							
KIDNEY TUBULAR-CELL ADENOMA LIPOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
																					X		
URINARY BLADDER TRANSITIONAL-CELL PAPILLOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																							
PITUITARY CARCINOMA,NOS ADENOMA, NOS CRANIOPHARYNGIOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
												X											
	X	X		X		X					X		X	X		X				X	X	X	X
															X								
ADRENAL CORTICAL ADENOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYROID C-CELL ADENOMA C-CELL CARCINOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
														X									
								X									X						
PARATHYROID	+	+	+	+	+	+	-	-	+	+	-	-	+	-	+	-	-	+	+	-	-	+	-
PANCREATIC ISLETS ISLET-CELL CARCINOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MAMMARY GLAND ADENOCARCINOMA, NOS FIBROADENOMA	+	+	N	+	N	+	+	N	N	+	N	N	+	+	+	+	N	+	+	N	+	+	+
							X																
		X		X		X	X							X					X		X	X	X
PREPUTIAL/CLITORAL GLAND CARCINOMA,NOS ADENOMA, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
						X				X													
VAGINA SQUAMOUS CELL CARCINOMA	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
UTERUS ADENOMA, NOS ADENOCARCINOMA, NOS LEIOMYOSARCOMA ENDOMETRIAL STROMAL POLYP ENDOMETRIAL STROMAL SARCOMA DECIDUOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	X	+	+	+	+	+	+	+	+
																	X						
											X												
	X			X	X		X								X					X			
OVARY	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																							
BRAIN CARCINOMA, NOS, INVASIVE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																							
ZYMBAL'S GLAND CARCINOMA,NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ALL OTHER SYSTEMS																							
MULTIPLE ORGANS NOS SQUAMOUS CELL CARCINOMA, METASTAT LEUKEMIA,MONONUCLEAR CELL	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
							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 A8. FEMALE RATS: TUMOR PATHOLOGY (CONTINUED) TEST

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	104	104	104	104	095	074	104	104	104	101	104	094	104	095	104	105	104	105	063	104	095	095	105	056	105	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
LIPOMA											X															1
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CARCINOMA, NOS, METASTATIC						X																				1
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SQUAMOUS CELL CARCINOMA, METASTAT			X										X													2
THYMUS	+	+	-	-	+	+	-	-	+	-	+	+	+	+	+	-	-	-	+	-	+	+	+	+	+	30
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SQUAMOUS CELL CARCINOMA, METASTAT																		X								1
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NEOPLASTIC NODULE					X				X																	2
HEPATOCELLULAR CARCINOMA																										1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
PANCREAS	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SQUAMOUS CELL CARCINOMA, METASTAT													X													1
ESOPHAGUS	+	+	-	-	+	+	-	-	+	+	+	+	+	-	-	-	-	-	-	-	+	-	+	+	-	27
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SQUAMOUS CELL PAPILLOMA					X			X	X			X								X	X	X	X			20
SQUAMOUS CELL CARCINOMA	X	X		X			X			X	X	X	X	X	X		X	X		X		X			X	27
BASAL-CELL CARCINOMA																										1
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LARGE INTESTINE	+	+	+	+	+	+	-	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	46
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
TUBULAR-CELL ADENOMA																		X								1
LIPOMA																										1
URINARY BLADDER	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
TRANSITIONAL-CELL PAPILLOMA																				X						1
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CARCINOMA,NOS														X								X				3
ADENOMA, NOS	X	X					X	X			X				X	X	X	X			X	X	X2		X	25
CRANIOPHARYNGIOMA																										1
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CORTICAL ADENOMA																X									X	2
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-CELL ADENOMA									X						X											4
C-CELL CARCINOMA																										1
PARATHYROID	+	+	-	-	-	+	-	-	+	+	+	-	+	-	+	+	+	+	-	+	+	-	+	+	-	29
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ISLET-CELL CARCINOMA							X																			1
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	+	+	+	+	+	N	+	N	+	+	+	+	+	+	N	+	N	+	N	+	+	+	+	N	N	50*
ADENOCARCINOMA, NOS																							X			2
FIBROADENOMA	X	X		X	X		X		X					X				X				X	X			20
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																										2
ADENOMA, NOS																									X	1
VAGINA	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
SQUAMOUS CELL CARCINOMA			X																							1
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ADENOMA, NOS		X																								2
ADENOCARCINOMA, NOS																										1
LEIOMYOSARCOMA																										1
ENDOMETRIAL STROMAL POLYP	X				X	X	X										X				X					11
ENDOMETRIAL STROMAL SARCOMA																			X					X		3
DECIDUOMA		X																								1
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	48
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CARCINOMA, NOS, INVASIVE														X												1
SPECIAL SENSE ORGANS																										
ZYMBAL'S GLAND	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
CARCINOMA,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*
SQUAMOUS CELL CARCINOMA, METASTAT							X			X																2
LEUKEMIA,MONONUCLEAR CELL																X				X	X					6

* ANIMALS NECROPSIED

a: MULTIPLE OCCURENCE OF MORPHOLOGY

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

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

APPENDIX B

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE ADMINISTERED DIGLYCIDYL RESORCINOL ETHER IN CORN OIL BY GAVAGE

TABLE B1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE ADMINISTERED DIGLYCIDYL RESORCINOL ETHER 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	3 (6%)		
FIBROMA	4 (8%)	3 (6%)	1 (2%)
FIBROSARCOMA	4 (8%)	3 (6%)	2 (4%)
RESPIRATORY SYSTEM			
#LUNG	(50)	(50)	(49)
SQUAMOUS CELL CARCINOMA, METASTA		2 (4%)	2 (4%)
HEPATOCELLULAR CARCINOMA, METAST		3 (6%)	2 (4%)
ALVEOLAR/BRONCHIOLAR ADENOMA	6 (12%)	2 (4%)	8 (16%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
MALIGNANT LYMPHOMA, NOS		2 (4%)	4 (8%)
MALIG.LYMPHOMA, UNDIFFER-TYPE	1 (2%)		
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	2 (4%)	1 (2%)	
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (2%)	3 (6%)	
MALIGNANT LYMPHOMA, MIXED TYPE			1 (2%)
#SPLEEN	(47)	(49)	(48)
SQUAMOUS CELL CARCINOMA, METASTA		1 (2%)	
#LYMPH NODE	(43)	(44)	(47)
SQUAMOUS CELL CARCINOMA, METASTA		1 (2%)	3 (6%)
SARCOMA, NOS, METASTATIC		1 (2%)	
MALIGNANT LYMPHOMA, NOS			1 (2%)
#LIVER	(49)	(50)	(50)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (2%)		

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#PEYER'S PATCH	(45)	(44)	(45)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (2%)		
CIRCULATORY SYSTEM			
*SUBCUT TISSUE	(50)	(50)	(50)
HEMANGIOMA	1 (2%)		
#SPLEEN	(47)	(49)	(48)
HEMANGIOMA		1 (2%)	1 (2%)
ANGIOSARCOMA			1 (2%)
#LYMPH NODE	(43)	(44)	(47)
HEMANGIOMA		2 (5%)	
#LIVER	(49)	(50)	(50)
HEMANGIOMA		1 (2%)	
ANGIOSARCOMA		1 (2%)	
DIGESTIVE SYSTEM			
#LIVER	(49)	(50)	(50)
NEOPLASM, NOS, UNC PRIM OR META		1 (2%)	
SQUAMOUS CELL CARCINOMA, INVASIV		1 (2%)	
SQUAMOUS CELL CARCINOMA, METASTA		2 (4%)	2 (4%)
HEPATOCELLULAR ADENOMA	7 (14%)	7 (14%)	5 (10%)
HEPATOCELLULAR CARCINOMA	7 (14%)	11 (22%)	6 (12%)
*GALLBLADDER	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA, INVASIV		1 (2%)	
#PANCREAS	(45)	(47)	(49)
SQUAMOUS CELL CARCINOMA, INVASIV		1 (2%)	1 (2%)
#STOMACH	(47)	(49)	(50)
NEOPLASM, NOS, UNC PRIM OR META		1 (2%)	
PAPILLOMATOSIS		1 (2%)	1 (2%)
SQUAMOUS CELL PAPILLOMA		3 (6%)	9 (18%)
SQUAMOUS CELL CARCINOMA		14 (29%)	25 (50%)
ADENOCARCINOMA, NOS			1 (2%)
#GASTRIC SUBMUCOSA	(47)	(49)	(50)
SARCOMA, NOS		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
#JEJUNUM	(45)	(44)	(45)
ADENOCARCINOMA, NOS			1 (2%)
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#ADRENAL	(47)	(50)	(48)
SQUAMOUS CELL CARCINOMA, INVASIV			1 (2%)
SQUAMOUS CELL CARCINOMA, METASTA			1 (2%)
ADENOMA, NOS	1 (2%)		
PHEOCHROMOCYTOMA	1 (2%)		3 (6%)
#THYROID	(46)	(49)	(47)
FOLLICULAR-CELL ADENOMA	1 (2%)	1 (2%)	
REPRODUCTIVE SYSTEM			
*PREPUTIAL GLAND	(50)	(50)	(50)
ADENOMA, NOS			1 (2%)
*SEMINAL VESICLE	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA, INVASIV		1 (2%)	
NERVOUS SYSTEM			
#BRAIN	(49)	(49)	(50)
SQUAMOUS CELL CARCINOMA, METASTA		1 (2%)	
SPECIAL SENSE ORGANS			
*HARDERIAN GLAND	(50)	(50)	(50)
ADENOMA, NOS	3 (6%)	2 (4%)	2 (4%)
MUSCULOSKELETAL 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
BODY CAVITIES			
*ABDOMINAL CAVITY	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA, INVASIV		1 (2%)	2 (4%)
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA, INVASIV		2 (4%)	6 (12%)
SQUAMOUS CELL CARCINOMA, METASTA			4 (8%)
ADIPOSE TISSUE			
SQUAMOUS CELL CARCINOMA, INVASIV			1
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	16	21	13
MORIBUND SACRIFICE	5	4	3
SCHEDULED SACRIFICE			
TERMINAL SACRIFICE	29	25	34
DOSING ACCIDENT			
ACCIDENTALLY KILLED, NDA			
ACCIDENTALLY KILLED, NOS			
ANIMAL MISSING			
ANIMAL MISSEXED			
OTHER CASES			

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	31	40	41
TOTAL PRIMARY TUMORS	44	62	73
TOTAL ANIMALS WITH BENIGN TUMORS	19	18	24
TOTAL BENIGN TUMORS	24	23	31
TOTAL ANIMALS WITH MALIGNANT TUMORS	20	32	32
TOTAL MALIGNANT TUMORS	20	37	42
TOTAL ANIMALS WITH SECONDARY TUMORS#		10	14
TOTAL SECONDARY TUMORS		18	25
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			
TOTAL UNCERTAIN TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC		1	
TOTAL UNCERTAIN TUMORS		2	

* 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 DIGLYCIDYL RESORCINOL ETHER 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	49	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA		1 (2%)	
BASAL-CELL CARCINOMA	1 (2%)		
*SUBCUT TISSUE	(50)	(50)	(50)
SARCOMA, NOS		1 (2%)	
FIBROSARCOMA	2 (4%)		
RESPIRATORY SYSTEM			
#LUNG	(49)	(50)	(50)
SQUAMOUS CELL CARCINOMA, METASTA			4 (8%)
BASAL-CELL CARCINOMA, METASTATIC	1 (2%)		
HEPATOCELLULAR CARCINOMA, METAST		1 (2%)	
ALVEOLAR/BRONCHIOLAR ADENOMA	3 (6%)	3 (6%)	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	6 (12%)	1 (2%)	3 (6%)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	3 (6%)	2 (4%)	
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)	
MALIGNANT LYMPHOMA, MIXED TYPE	4 (8%)	2 (4%)	
*HEMATOPOIETIC SYSTEM	(50)	(50)	(50)
MALIGNANT LYMPHOMA, NOS	1 (2%)		
#SPLEEN	(48)	(48)	(49)
SQUAMOUS CELL CARCINOMA, METASTA			1 (2%)
MALIGNANT LYMPHOMA, NOS	1 (2%)	1 (2%)	
#LYMPH NODE	(46)	(44)	(44)
SQUAMOUS CELL CARCINOMA, METASTA			2 (5%)
MALIGNANT LYMPHOMA, NOS	1 (2%)		
#PEYER'S PATCH	(41)	(44)	(39)
MALIGNANT LYMPHOMA, NOS	1 (2%)	1 (2%)	
#KIDNEY	(48)	(50)	(50)
MALIGNANT LYMPHOMA, MIXED TYPE		1 (2%)	
CIRCULATORY SYSTEM			
NONE			

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
#LIVER	(48)	(50)	(49)
SQUAMOUS CELL CARCINOMA, METASTA			1 (2%)
HEPATOCELLULAR ADENOMA	3 (6%)		5 (10%)
HEPATOCELLULAR CARCINOMA		1 (2%)	3 (6%)
#PANCREAS	(46)	(44)	(45)
SQUAMOUS CELL CARCINOMA, INVASIV		1 (2%)	1 (2%)
#STOMACH	(47)	(49)	(49)
PAPILLOMATOSIS		3 (6%)	5 (10%)
SQUAMOUS CELL PAPILLOMA		2 (4%)	5 (10%)
SQUAMOUS CELL CARCINOMA		12 (24%)	23 (47%)
URINARY SYSTEM			
#KIDNEY	(48)	(50)	(50)
SQUAMOUS CELL CARCINOMA, METASTA			1 (2%)
#URINARY BLADDER	(48)	(49)	(50)
SQUAMOUS CELL CARCINOMA, INVASIV		1 (2%)	
ENDOCRINE SYSTEM			
#PITUITARY	(39)	(40)	(37)
ADENOMA, NOS	7 (18%)	7 (18%)	3 (8%)
#ADRENAL	(47)	(43)	(47)
ADENOMA, NOS	2 (4%)		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
PHEOCHROMOCYTOMA		1 (2%)	
#THYROID	(45)	(45)	(42)
FOLLICULAR-CELL ADENOMA	1 (2%)	1 (2%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
ADENOMA, NOS	1 (2%)		
ADENOCARCINOMA, NOS			1 (2%)
#UTERUS	(49)	(50)	(49)
SARCOMA, NOS	2 (4%)		
ENDOMETRIAL STROMAL POLYP		2 (4%)	1 (2%)
#OVARY	(33)	(41)	(40)
SQUAMOUS CELL CARCINOMA, INVASIV			3 (8%)
PAPILLARY CYSTADENOMA, NOS		1 (2%)	
LUTEOMA		1 (2%)	
SERTOLI-CELL TUMOR	1 (3%)		
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*HARDERIAN GLAND	(50)	(50)	(50)
CARCINOMA,NOS	1 (2%)		
ADENOMA, NOS	2 (4%)		2 (4%)
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*ABDOMINAL CAVITY	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA, INVASIV			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
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA, INVASIV		3 (6%)	9 (18%)
SQUAMOUS CELL CARCINOMA, METASTA		1 (2%)	3 (6%)
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	25	33	34
MORIBUND SACRIFICE	5	3	6
SCHEDULED SACRIFICE			
TERMINAL SACRIFICE	20	13	10
DOSING ACCIDENT			
ACCIDENTALLY KILLED, NDA			
ACCIDENTALLY KILLED, NOS		1	
ANIMAL MISSING			
ANIMAL MISSEXED			
OTHER CASES			
@ INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	28	27	38
TOTAL PRIMARY TUMORS	43	45	54
TOTAL ANIMALS WITH BENIGN TUMORS	13	16	17
TOTAL BENIGN TUMORS	20	21	24
TOTAL ANIMALS WITH MALIGNANT TUMORS	21	19	28
TOTAL MALIGNANT TUMORS	23	24	30
TOTAL ANIMALS WITH SECONDARY TUMORS#	1	5	14
TOTAL SECONDARY TUMORS	1	7	26
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			
TOTAL UNCERTAIN TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

TABLE B3.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR STUDY OF DIGLYCIDYL RESORCINOL ETHER

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	080	105	040	105	094	072	074	105	105	101	101	105	022	021	021	105	088	105	105	105	105
INTEGUMENTARY SYSTEM																									
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	N	+	+	+	+	+	+
SARCOMA, NOS		X																							
FIBROMA																				X		X			
FIBROSARCOMA									X																
HEMANGIOMA													X												
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALVEOLAR/BRONCHIOLAR ADENOMA			X																	X				X	
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+
SPLEEN	+	+	+	+	+	+	-	+	+	+	+	+	+	+	A	+	+	+	-	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	+	+	+	+	-	+	+	+	+	A	+	+	-	-	+	+	+	+	+	+
THYMUS	+	+	+	+	-	+	-	+	-	-	-	+	-	-	A	-	-	-	-	+	-	-	-	-	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR ADENOMA	X				X							X											X		
HEPATOCELLULAR CARCINOMA										X				X		X							X		
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			X																						
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	+	+	+	+	+	N	N	+	+	+	N	+	N	N	N	+	N	+	+	+	+
PANCREAS	+	+	+	+	+	+	+	+	+	-	+	+	+	+	A	+	+	+	-	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	-	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	-	+	-	+	+	+	+
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																						X			
LARGE INTESTINE	-	+	+	+	+	+	+	-	+	+	+	+	+	+	A	+	+	+	-	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	-	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	-	+	+	-	+	+	+	+
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	-	+	+	+	+	+	+
ADENOMA, NOS				X																					
PHEOCHROMOCYTOMA																									
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	-	-	+	-	+	+	+	+
FOLLICULAR-CELL ADENOMA	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	N	N	M	N	N	N
TESTIS	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	-	-	+	+	-	+	+	+
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
HARDERIAN GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ADENOMA, NOS																				X					X
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, UNDIFFER-TYPE					X																				
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE																					X				
MALIG.LYMPHOMA, HISTIOCYTIC 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 / WEEKS ON STUDY	026 105	027 105	028 105	029 105	030 105	031 078	032 105	033 088	034 105	035 045	036 089	037 105	038 020	039 105	040 105	041 069	042 071	043 095	044 105	045 091	046 105	047 051	048 080	049 103	050 105	TOTAL TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SARCOMA, NOS				X																				X		3
FIBROMA														X	X											4
FIBROSARCOMA								X										X					X			4
HEMANGIOMA																										1
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALVEOLAR/BRONCHIOLAR ADENOMA									X															X	X	6
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
LYMPH NODES	+	+	+	+	+	+	+	+	-	+	+	+	-	+	+	+	+	+	+	+	+	+	+	-	+	43
THYMUS	+	+	+	+	-	-	+	+	+	+	-	-	+	-	+	-	-	-	+	-	+	+	-	-	+	23
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	49
HEPATOCELLULAR ADENOMA		X												X	X											7
HEPATOCELLULAR CARCINOMA											X									X					X	7
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																										1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	49
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	+	N	+	+	N	+	N	+	N	+	+	N	N	+	+	+	+	+	N	N	+	50
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	-	+	+	+	45
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	48
STOMACH	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	+	45
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																										1
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	+	44
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	-	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	-	+	+		44
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	47
ADENOMA, NOS				X																						1
PHEOCHROMOCYTOMA																										1
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
FOLLICULAR-CELL ADENOMA																										1
PARATHYROID	+	+	+	-	+	+	+	+	+	-	-	+	-	+	+	-	+	-	+	+	+	+	+	+	+	36
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50
TESTIS	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	-	+	+	+	+	+	+	-	-	+	45
PROSTATE	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	44
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	50
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	50
MALIG.LYMPHOMA, UNDIFFER-TYPE																										1
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	X																									2
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																										1

N 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 DIGLYCIDYL RESORCINOL ETHER

LOW DOSE

ANIMAL NUMBER	00101	00201	00301	00401	00501	00601	00701	00801	00901	01001	01101	01201	01301	01401	01501	01601	01701	01801	01901	02001	02101	02201	02301	02401	02501
WEEKS ON STUDY	07 1	10 5	10 5	10 4	09 6	10 5	10 5	10 0	09 7	03 4	10 5	08 0	10 5	10 5	03 4	10 5	10 5	07 7	08 0	10 3	10 5	10 5	10 5	08 9	10 5
INTEGUMENTARY SYSTEM																									
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+
FIBROMA																									
FIBROSARCOMA												X							X				X		
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL CARCINOMA, METASTAT																									
HEPATOCELLULAR CARCINOMA, METASTA					X			X																	
ALVEOLAR/BRONCHIOLAR ADENOMA																			X						
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL CARCINOMA, METASTAT									X																
HEMANGIOMA												X													
LYMPH NODES	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	-	+
SQUAMOUS CELL CARCINOMA, METASTAT																									
SARCOMA, NOS, METASTATIC				X																					
HEMANGIOMA							X																		
THYMUS	-	-	+	-	-	+	+	-	-	-	+	-	+	-	-	-	+	-	-	-	-	-	+	-	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	-	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	:	+	+	+	+	+	+	+	+	+	+
NEOPLASM, NOS, UNC PRIM OR META																		X							
SQUAMOUS CELL CARCINOMA, INVASIVE																						X			
SQUAMOUS CELL CARCINOMA, METASTAT									X																
HEPATOCELLULAR ADENOMA			X				X				X														
HEPATOCELLULAR CARCINOMA					X	X		X					X	X			X				X				
HEMANGIOMA																									
ANGIOSARCOMA																									
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	N	+	+	+	N	+	+	N	+	N	+	+	+	+	N	+	+	N	N	N	+	+	+	N	+
SQUAMOUS CELL CARCINOMA, INVASIVE									X																
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+
SQUAMOUS CELL CARCINOMA, INVASIVE									X																
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+
STOMACH	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NEOPLASM, NOS, UNC PRIM OR META																		X							
PAPILLOMATOSIS							+																		
SQUAMOUS CELL PAPILLOMA						X																		X	
SQUAMOUS CELL CARCINOMA		X						X	X												X	X	X	X	
SARCOMA, NOS				X												X									
SMALL INTESTINE	+	+	+	+	+	+	+	-	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	-	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	-	+	-	+	-	+	+	+
ADRENAL	+	+	+	+	+	+	•	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYROID	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FOLLICULAR-CELL ADENOMA																									
PARATHYROID	-	-	-	+	+	+	+	-	-	-	-	-	+	+	-	+	+	+	-	-	-	+	-	+	+
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SEMINAL VESICLE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL CARCINOMA, INVASIVE																									
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+
SQUAMOUS CELL CARCINOMA, METASTAT																									
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
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
SQUAMOUS CELL CARCINOMA, INVASIVE																									
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, INVASIVE																								X	
MALIGNANT LYMPHOMA, NOS							X																		
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE																									
MALIG.LYMPHOMA, HISTIOCYTIC 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) LOW DOSE

ANIMAL NUMBER	0026	0027	0028	0029	0030	0031	0032	0033	0034	0035	0036	0037	0038	0039	0040	0041	0042	0043	0044	0045	0046	0047	0048	0049	0050	TOTAL
WEEKS ON STUDY	105	105	076	105	105	097	101	067	105	105	067	096	065	079	105	061	085	044	099	093	095	096	085	105		TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50M
FIBROMA										X					X											3
FIBROSARCOMA																									X	3
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+,	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SQUAMOUS CELL CARCINOMA, METASTAT																			X	X						2
HEPATOCELLULAR CARCINOMA, METASTA							X																			3
ALVEOLAR/BRONCHIOLAR ADENOMA				X																						2
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	49
SQUAMOUS CELL CARCINOMA, METASTAT																										1
HEMANGIOMA																										1
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	-	+	+	+	+	+	+	-	44
SQUAMOUS CELL CARCINOMA, METASTAT																			X							1
SARCOMA, NOS, METASTATIC																										1
HEMANGIOMA							X																			2
THYMUS	+	+	-	+	+	-	-	+	-	-	-	-	-	-	-	+	+	-	-	-	-	-	-	-	-	15
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NEOPLASM, NOS, UNC PRIM OR META																										1
SQUAMOUS CELL CARCINOMA, INVASIVE																										1
SQUAMOUS CELL CARCINOMA, METASTAT												X														2
HEPATOCELLULAR ADENOMA				X					X			X			X											7
HEPATOCELLULAR CARCINOMA		X			X		X																		X	11
HEMANGIOMA																								X		1
ANGIOSARCOMA																		X								1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	+	+	N	+	+	N	+	N	+	+	+	N	+	N	+	+	+	N	+	N	+	N	N	N	+	50M
SQUAMOUS CELL CARCINOMA, INVASIVE																										1
PANCREAS	+	+	+	+	•	+	+	+	+	+	+	-	+	+	+	+	+	-	+	+	+	+	+	+	+	47
SQUAMOUS CELL CARCINOMA, INVASIVE																										1
ESOPHAGUS	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
NEOPLASM, NOS, UNC PRIM OR META																										1
PAPILLOMATOSIS																										1
SQUAMOUS CELL PAPILLOMA													X													3
SQUAMOUS CELL CARCINOMA	X		X		X							X							X	X	X					14
SARCOMA, NOS																										2
SMALL INTESTINE	+	+	+	+	+	-	+	+	+	+	+	-	+	+	+	+	+	-	+	+	+	-	+	+	+	44
LARGE INTESTINE	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	46
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	-	+	+	+	+	+	-	+	+	+	+	+	+	+	-	+	+	-	+	+	+	+	42
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
FOLLICULAR-CELL ADENOMA	X																									1
PARATHYROID	+	+	+	-	+	-	-	+	-	+	+	-	+	-	+	+	+	-	-	+	+	+	-	-	-	26
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50M
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	-	-	+	-	+	+	+	+	+	+	+	+	-	+	46
SEMINAL VESICLE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50M
SQUAMOUS CELL CARCINOMA, INVASIVE												X														1
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	•	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SQUAMOUS CELL CARCINOMA, METASTAT												X														1
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																									2
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	50M
SQUAMOUS CELL CARCINOMA, INVASIVE												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, INVASIVE																			X							2
MALIGNANT LYMPHOMA, NOS				X																						2
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		X																								1
MALIG.LYMPHOMA, HISTIOCYTIC TYPE										X				X												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 B3.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR STUDY OF DIGLYCIDYL RESORCINOL ETHER

HIGH DOSE

ANIMAL NUMBER	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	1104	1104	1104	1104	0911	0924	1008	1104	1104	1104	1104	1104	1104	0911	1104	1104	0211	0115	1104	1104	1104	1104	0911	0807
INTEGUMENTARY SYSTEM																								
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+
FIBROMA							X																	
FIBROSARCOMA																								
RESPIRATORY SYSTEM																								
LUNGS AND BRONCHI	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL CARCINOMA, METASTAT								X																
HEPATOCELLULAR CARCINOMA, METASTA													X								X			
ALVEOLAR/BRONCHIOLAR ADENOMA	X	X		X			X															X		
TRACHEA	+	+	+	+	+	+	+	+	•	+	+	+	+	+	+	+	•	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																								
BONE MARROW	+	+	+	+	-	+	-	+	+	+	+	+	+	-	-	+	-	+	-	+	+	+	+	+
SPLEEN	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+
HEMANGIOMA																								
ANGIOSARCOMA																						X		
LYMPH NODES	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	~	+	+	+	+	+	-	+
SQUAMOUS CELL CARCINOMA, METASTAT							X			X														
MALIGNANT LYMPHOMA, NOS																					X			
THYMUS	-	+	-	+	-	-	-	-	+	-	-	+	+	+	-	-	+	~	-	+	+	+	+	-	-
CIRCULATORY SYSTEM																								
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																								
SALIVARY GLAND	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL CARCINOMA, METASTAT														X										
HEPATOCELLULAR ADENOMA																						X		
HEPATOCELLULAR CARCINOMA										X			X		X						X			
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	+	N	+	+	N	N	+	+	+	+	+	+	+	N	+	+	+	N	+	+	N	+	N	+
PANCREAS	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL CARCINOMA, INVASIVE																								
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	~	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PAPILLOMATOSIS																								
SQUAMOUS CELL PAPILLOMA										X		X	X									X		
SQUAMOUS CELL CARCINOMA			X	X	X	X	X	X		X				X	X				X				X	
ADENOCARCINOMA, NOS																								
SMALL INTESTINE	+	+	+	+	+	-	+	+	+	+	+	+	+	-	+	+	+	-	+	+	+	+	+	+
ADENOCARCINOMA, NOS															X									
LARGE INTESTINE	-	+	+	+	-	-	+	+	+	+	+	+	+	-	+	+	+	-	+	+	+	+	+	+
URINARY SYSTEM																								
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																								
PITUITARY	+	+	+	-	-	-	+	+	-	+	+	+	-	+	+	+	+	-	+	+	+	+	+	+
ADRENAL	+	+	+	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL CARCINOMA, INVASIVE																								
SQUAMOUS CELL CARCINOMA, METASTAT							X																	
PHEOCHROMOCYTOMA																						X		
THYROID	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+
PARATHYROID	+	-	+	-	-	-	-	+	-	+	+	+	-	-	+	-	-	-	+	+	+	-	+	-	+
REPRODUCTIVE SYSTEM																								
MAMMARY GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
TESTIS	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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
ADENOMA, NOS																								
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
ADENOMA, NOS												X									X			
BODY CAVITIES																								
PERITONEUM	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
SQUAMOUS CELL CARCINOMA, INVASIVE					X																			
ALL OTHER SYSTEMS																								
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
SQUAMOUS CELL CARCINOMA, INVASIVE							X	X						X										
SQUAMOUS CELL CARCINOMA, METASTAT																								
MALIGNANT LYMPHOMA, NOS											X										X			
MALIGNANT LYMPHOMA, MIXED TYPE							X																	
ADIPOSE TISSUE																								
SQUAMOUS CELL CARCINOMA, INVASIVE										X														

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

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

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL TISSUES TUMORS
WEEKS ON STUDY	104	104	075	104	104	104	077	105	104	069	105	020	093	105	105	105	093	105	105	099	105	105	105	105	078	
INTEGUMENTARY SYSTEM																										
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	50M
FIBROMA																										1
FIBROSARCOMA															X				X							2
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SQUAMOUS CELL CARCINOMA, METASTAT			X																							2
HEPATOCELLULAR CARCINOMA, METASTA																										2
ALVEOLAR/BRONCHIOLAR ADENOMA				X									X										X			8
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	−	+	+	+	+	41
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
HEMANGIOMA																							+			1
ANGIOSARCOMA																							X			1
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
SQUAMOUS CELL CARCINOMA, METASTAT			X																							3
MALIGNANT LYMPHOMA, NOS																										1
THYMUS	+	+	−	+	+	−	+	−	−	+	−	−	+	−	+	−	−	+	−	−	+	+	+	+	−	23
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SQUAMOUS CELL CARCINOMA, METASTAT													X													2
HEPATOCELLULAR ADENOMA	X		X																					X	X	5
HEPATOCELLULAR CARCINOMA							X	X																		6
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	N	+	+	+	+	+	N	+	+	N	+	N	N	+	+	N	N	+	N	+	N	+	+	N	+	50M
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SQUAMOUS CELL CARCINOMA, INVASIVE																				X						1
ESOPHAGUS	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	−	+	+	+	+	−	+	+	+	+	46
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
PAPILLOMATOSIS															X											1
SQUAMOUS CELL PAPILLOMA				X						X						X		X						X		9
SQUAMOUS CELL CARCINOMA	X		X		X	X	X	X						X		X	X	X	X	X	X				X	25
ADENOCARCINOMA, NOS					X																					1
SMALL INTESTINE	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	45
ADENOCARCINOMA, NOS																										1
LARGE INTESTINE	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	−	+	+	−	+	+	+	+	+	+	41
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
PITUITARY	−	−	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
SQUAMOUS CELL CARCINOMA, INVASIVE							X																			1
SQUAMOUS CELL CARCINOMA, METASTAT																										1
PHEOCHROMOCYTOMA										X								X							3
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	47
PARATHYROID	+	+	−	+	−	−	−	−	−	−	+	+	+	+	−	−	−	+	−	−	−	−	−	+		22
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50M
TESTIS	+	+	+	+	•	+	+	+	−	+	+	+	+	+	+	+	+	+	•	+	+	+	+	+	+	48
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	−	+	−	+	+	+	+	+	45
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	50M
ADENOMA, NOS								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																										2
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	50M
SQUAMOUS CELL CARCINOMA, INVASIVE						X																				2
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, INVASIVE			X														X								X	6
SQUAMOUS CELL CARCINOMA, METASTAT							X										X			X					X	4
MALIGNANT LYMPHOMA, NOS				X												X										4
MALIGNANT LYMPHOMA, MIXED TYPE																										1
ADIPOSE TISSUE																										
SQUAMOUS CELL CARCINOMA, INVASIVE																										1

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 DIGLYCIDYL RESORCINOL ETHER

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	101	074	105	105	096	088	073	105	098	098	064	074	105	087	092	105	105	105	080	082	103	105	105	102
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+
BASAL-CELL CARCINOMA																									
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+
FIBROSARCOMA		X																							
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
BASAL-CELL CARCINOMA, METASTATIC																									
ALVEOLAR/BRONCHIOLAR ADENOMA							X		X																
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	-	+	+	+	-	+	+	+	+	-	-	+	+	+	+	+	+	+	-	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MALIGNANT LYMPHOMA, NOS																			X						
LYMPH NODES	+	+	+	+	+	+	+	+	-	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MALIGNANT LYMPHOMA, NOS																									
THYMUS	+	-	-	-	+	-	+	-	+	-	-	-	-	+	-	-	+	+	+	-	-	-	+	+	-
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR ADENOMA									X																
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	+	+	N	+	+	N	N	+	+	+	+	+	+	:	N	+	+	+	+	+	+	N	+	+	N
PANCREAS	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	-	+	+	+	+	+	+	+	-	+	+	+	-	+	+	+	+	+	+	-	+	+	-
MALIGNANT LYMPHOMA, NOS																					X				
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+
ADENOMA, NOS	X								X					X	X								X		
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOMA, NOS																+									
THYROID	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	-	+	+	+	-
FOLLICULAR-CELL ADENOMA				X																					
PARATHYROID	-	-	-	-	-	+	+	+	+	+	-	-	+	-	-	+	+	-	+	+	-	-	+	-	-
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	N	+	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	+	N	N	+	N	N
ADENOMA, NOS																							X		
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SARCOMA, NOS																		X						X	
OVARY	+	+	-	+	-	+	+	+	+	-	+	+	+	+	-	+	+	-	+	-	+	+	-	+	-
SERTOLI-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
CARCINOMA,NOS																									
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
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE							X				X														
MALIGNANT LYMPHOMA, MIXED TYPE				X										X		X									
HEMATOPOIETIC SYSTEM																									
MALIGNANT LYMPHOMA, NOS																						X			

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

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

ANIMAL NUMBER	0226	0227	0229	0230	0311	0312	0313	0314	0315	0316	0317	0318	0319	0410	0411	0412	0413	0414	0415	0416	0417	0418	0419	0420	TOTAL
WEEKS ON STUDY	1105	0766	1105	0775	0630	0795	0851	0751	0772	1105	0901	1010	1105	1105	1105	0954	0889	0766	0669	0671	1005	0990	0880	0743	TISSUES TUMORS
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	50
BASAL-CELL CARCINOMA																								X	1
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	50
FIBROSARCOMA														X											2
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	49
BASAL-CELL CARCINOMA, METASTATIC																								X	1
ALVEOLAR/BRONCHIOLAR ADENOMA													X												3
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	A	+	+	+	+	-	-	41
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	-	+	+	+	+	+	48
MALIGNANT LYMPHOMA, NOS																									1
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	~	+	+	+	+	+	A	+	+	+	+	+	+	46
MALIGNANT LYMPHOMA, NOS																				X					1
THYMUS	-	-	-	-	-	-	+	-	-	-	-	+	-	+	-	+	-	-	A	-	-	+	-	-	-	15
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	-	+	+	+	+	+	+	+	+	+	-	+	+	+	A	+	+	+	+	+	+	47
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	47
LIVER	+	+	+	+		+	+	+	+	+	+	+	+	+	-	+	+	A	+	+	+	+	+	+	48
HEPATOCELLULAR ADENOMA			X													X									3
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	A	+	+	+	+	+	+	48
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	N	+	+	+	N	+	+	+	+	+	N	+	N	+	N	N	N	N	+	+	N	50
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	A	-	+	+	+	+	+	46
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	-	A	-	+	+	+	+	+	46
STOMACH	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	A	-	+	+	+	+	+	47
SMALL INTESTINE	+	+	+	+	-	+	+	+	+	+	+	+	+	+	-	+	+	A	-	+	+	+	+	+	41
MALIGNANT LYMPHOMA, NOS																									1
LARGE INTESTINE	+	+	+	+	-	-	+	+	+	+	+	+	+	+	-	+	+	A	-	+	+	-	+	+	43
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	A	+	+	+	+	+	+	48
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	A	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																									
PITUITARY	-	+	+	-	-	+	+	+	-	+	+	-	+	+	-	+	+	A	+	-	+	+	-	+	39
ADENOMA, NOS								X								X									7
ADRENAL	+	+	+	+	-	+	+	+	+	+	+	+	+	+	-	+	+	A	+	+	+	+	+	+	47
ADENOMA, NOS											X														2
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	A	+	+	+	+	+	+	45
FOLLICULAR-CELL ADENOMA																									1
PARATHYROID	+	+	+	+	-	+	-	-	-	+	-	-	+	+	-	+	-	A	-	+	-	+	-	+	24
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	50
ADENOMA, NOS																									1
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	49
SARCOMA, NOS																									2
OVARY	+	+	+	-	+	-	+	+	+	+	-	+	+	+	-	+	-	-	A	-	+	+	+	-	33
SERTOLI-CELL TUMOR			X																						1
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	A	+	+	+	+	+	+	47
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	50
CARCINOMA,NOS			X																						1
ADENOMA, NOS								X																	2
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50
MALIGNANT LYMPHOMA, NOS					X				X			X			X	X									6
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE							X																		3
MALIGNANT LYMPHOMA, MIXED TYPE								X																	4
HEMATOPOIETIC SYSTEM																									
MALIGNANT LYMPHOMA, NOS																									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 DIGLYCIDYL RESORCINOL ETHER

LOW DOSE

ANIMAL NUMBER	0011	0012	0013	0014	0015	0016	0017	0018	0019	0111	0112	0113	0114	0115	0116	0117	0118	0119	0120	0121	0122	0123	0124	0125
WEEKS ON STUDY	095	077	093	089	083	011	099	071	103	105	077	074	105	077	081	088	067	067	086	102	115	064	096	104	115
INTEGUMENTARY SYSTEM																								
SKIN	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL CARCINOMA																								
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SARCOMA, NOS																								
RESPIRATORY SYSTEM																								
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR CARCINOMA, METASTA									X															
ALVEOLAR/BRONCHIOLAR ADENOMA				X									X				X							
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																								
BONE MARROW	+	+	+	+	+	+	-	+	+	+	+	+	-	+	+	+	+	+	+	-	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+
MALIGNANT LYMPHOMA, NOS																								X
LYMPH NODES	+	+	+	+	+	+	+	-	+	+	+	+	+	+	-	-	+	+	+	+	+	+	+	+
THYMUS	-	-	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-	+	-	-	+	+
CIRCULATORY SYSTEM																								
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																								
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR CARCINOMA									X															
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	N	N	+	N	N	N	N	N	N	+	+	N	+	+	N	N	N	N	N	+	N	+	N	+
PANCREAS	+	+	+	-	+	+	+	+	+	+	+	+	+	+	-	+	+	+	-	+	+	+	+	+
SQUAMOUS CELL CARCINOMA, INVASIVE																								
ESOPHAGUS	+	-	+	+	+	+	+	+	+	-	+	+	+	+	-	+	-	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+
PAPILLOMATOSIS										X														
SQUAMOUS CELL PAPILLOMA				X																				X
SQUAMOUS CELL CARCINOMA	X								X											X	X	X		
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	-	+	-	+	+	+
MALIGNANT LYMPHOMA, NOS																								
LARGE INTESTINE	+	+	+	+	+	+	-	+	+	+	+	+	+	+	-	+	+	+	-	+	-	+	+	+
URINARY SYSTEM																								
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MALIGNANT LYMPHOMA, MIXED TYPE	X																							
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL CARCINOMA, INVASIVE																								
ENDOCRINE SYSTEM																								
PITUITARY	+	+	+	-	-	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	-	+
ADENOMA, NOS			X							X		X	X						X			X		
ADRENAL	+	+	-	+	+	-	+	+	+	+	+	+	+	+	-	+	+	+	-	+	+	+	+	+
PHEOCHROMOCYTOMA																								
THYROID	+	-	+	+	+	+	+	+	+	+	+	+	+	+	-	+	-	+	+	+	-	+	+	+
FOLLICULAR-CELL ADENOMA													X											
PARATHYROID	-	-	-	-	+	-	+	+	+	+	-	+	-	+	-	+	-	-	-	+	-	+	+	+
REPRODUCTIVE SYSTEM																								
MAMMARY GLAND	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	+	N	N	N	N	N	N	N
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOMETRIAL STROMAL POLYP																								
OVARY	+	+	-	-	+	+	+	+	+	+	-	-	+	+	-	+	+	+	-	+	+	+	+	+
PAPILLARY CYSTADENOMA, NOS																							X	
LUTEOMA																								
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
SQUAMOUS CELL CARCINOMA, INVASIVE																					X			
SQUAMOUS CELL CARCINOMA, METASTAT																					X			
MALIGNANT LYMPHOMA, NOS																			X					
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE																							X	
MALIG.LYMPHOMA, HISTIOCYTIC TYPE					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 B4. FEMALE MICE: TUMOR PATHOLOGY (CONTINUED) LOW DOSE

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL
WEEKS ON STUDY	001	015	073	103	101	105	082	105	087	105	105	105	105	093	071	084	096	105	001	105	062	100	068	067	067	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
SKIN	+	+	+	+	+	+	+	+	+	+	+	+ X	+	+	+	+	+	N	+	+	+	+	+	+	50*	
SQUAMOUS CELL CARCINOMA												X													1	
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	50*	
SARCOMA, NOS				X																					1	
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
HEPATOCELLULAR CARCINOMA, METASTA																									1	
ALVEOLAR/BRONCHIOLAR ADENOMA																									3	
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46	
SPLEEN	+	•	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	•	-	+	+	+	+	48	
MALIGNANT LYMPHOMA, NOS																									1	
LYMPH NODES	-	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	44	
THYMUS	-	+	+	+	-	+	-	+	-	-	+	+	-	-	-	-	+	-	-	-	-	-	+	-	14	
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
HEPATOCELLULAR CARCINOMA																									1	
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
GALLBLADDER & COMMON BILE DUCT	N	+	N	+	N	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	N	+	N	N	50*
PANCREAS	+	+	-	+	-	+	+	+	+ X	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	44
SQUAMOUS CELL CARCINOMA, INVASIVE																										1
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46	
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+ X	+	+	+	+	+	+	+	+	+	+	+	49	
PAPILLOMATOSIS		X											X												3	
SQUAMOUS CELL PAPILLOMA																									2	
SQUAMOUS CELL CARCINOMA				X	X				X	X		X						X				X			12	
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+ X	+	+	+	-	+	-	+	+	+	+	-	+	+	44	
MALIGNANT LYMPHOMA, NOS																									1	
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	-	+	+	+	+	+	+	+	44	
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
MALIGNANT LYMPHOMA, MIXED TYPE																									1	
URINARY BLADDER	+	+	-	+	+	+	+	+	+ X	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
SQUAMOUS CELL CARCINOMA, INVASIVE																									1	
ENDOCRINE SYSTEM																										
PITUITARY	-	+	-	+	-	+	-	+	+	+	+	+	+	-	+	+	+	+ X	-	+	+	+	+	+	40	
ADENOMA, NOS																		X							7	
ADRENAL	+	+	-	+	-	+	+	+	+	+	+	+	+	+	+	-	+ X	+	+	+	+	+	+	+	43	
PHEOCHROMOCYTOMA																	X								1	
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	45	
FOLLICULAR-CELL ADENOMA																									1	
PARATHYROID	-	-	+	+	+	-	+	+	-	+	+	+	-	+	+	-	-	+	-	+	-	-	-	+	26	
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	50*	
UTERUS	+	+	+	+	+	+	+	+	+	•	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
ENDOMETRIAL STROMAL POLYP				X						X															2	
OVARY	+	+	+	+	-	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	41	
PAPILLARY CYSTADENOMA, NOS																									1	
LUTEOMA																		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	50*	
SQUAMOUS CELL CARCINOMA, INVASIVE																						X			3	
SQUAMOUS CELL CARCINOMA, METASTAT																									1	
MALIGNANT LYMPHOMA, NOS																									1	
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE																X									2	
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																									1	
MALIGNANT LYMPHOMA, MIXED TYPE					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 B4.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR STUDY OF DIGLYCIDYL RESORCINOL ETHER

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	078	105	105	082	082	084	074	105	098	082	090	082	082	091	081	099	104	070	105	105	105	082	096	081	084
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL CARCINOMA, METASTAT				X																					
ALVEOLAR/BRONCHIOLAR ADENOMA																									
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+
SQUAMOUS CELL CARCINOMA, METASTAT																									
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	−	+	+	+
SQUAMOUS CELL CARCINOMA, METASTAT																									
THYMUS	+	+	−	−	+	−	+	+	−	−	−	−	−	−	−	−	−	−	+	+	−	−	−		
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+
SQUAMOUS CELL CARCINOMA, METASTAT																			X						
HEPATOCELLULAR ADENOMA								X											X	X					
HEPATOCELLULAR CARCINOMA									X																
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+
GALLBLADDER & COMMON BILE DUCT	+	+	+	N	+	+	+	+	N	+	N	N	N	N	+	N	N	N	+	+	+	N	+	N	N
PANCREAS	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	−	+	+	+
SQUAMOUS CELL CARCINOMA, INVASIVE												X													
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	−	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+
PAPILLOMATOSIS																			X		X				
SQUAMOUS CELL PAPILLOMA								X		X														X	
SQUAMOUS CELL CARCINOMA			X	X		X			X		X	X		X	X	X	X			X			X		
SMALL INTESTINE	+	+	+	−	+	+	+	+	−	+	+	+	+	+	−	−	+	−	+	+	+	−	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	−	−	+	+	+	−	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL CARCINOMA, METASTAT												X													
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+	−	+	+	+	+	+	−	+
ADENOMA, NOS		X	X								X														
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	−	+	+	+
ADENOMA, NOS																			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	+
ADENOCARCINOMA, NOS																									X
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+
ENDOMETRIAL STROMAL POLYP								X																	
OVARY	+	−	+	+	+	+	+	+	+	−	+	+	+	+	−	+	+	+	+	+	+	−	+	−	−
SQUAMOUS CELL CARCINOMA, INVASIVE						X						X													
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																									
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
SQUAMOUS CELL CARCINOMA, INVASIVE																									
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, INVASIVE				X					X		X														
SQUAMOUS CELL CARCINOMA, METASTAT																									
MALIGNANT LYMPHOMA, 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 B4. FEMALE 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	097	099	095	099	070	105	091	097	083	081	097	097	083	101	084	055	087	087	105	089	088	071	099	093		TISSUES TUMORS
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SQUAMOUS CELL CARCINOMA, METASTAT		X																	X						X	4
ALVEOLAR/BRONCHIOLAR ADENOMA																				X					X	2
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
BONE MARROW	-	+	+	+	+	+	-	+	+	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	45
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SQUAMOUS CELL CARCINOMA, METASTAT																								X		1
LYMPH NODES	+	-	-	+	+	+	+	-	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	44
SQUAMOUS CELL CARCINOMA, METASTAT							X																		X	2
THYMUS	-	-	-	-	-	+	-	-	-	-	-	-	-	+	-	-	-	-	+	-	-	+	-	-		11
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SQUAMOUS CELL CARCINOMA, METASTAT																								X		1
HEPATOCELLULAR ADENOMA								X		X														X		5
HEPATOCELLULAR CARCINOMA																										3
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	+	+	N	N	N	N	+	N	+	+	+	N	N	+	+	+	N	+	+	+	N	50*
PANCREAS	+	+	+	-	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
SQUAMOUS CELL CARCINOMA, INVASIVE																										1
ESOPHAGUS	-	+	+	+	+	+	-	+	-	+	+	+	+	+	-	+	+	+	+	+	+	+	-	+	+	43
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
PAPILLOMATOSIS												X		X					X							5
SQUAMOUS CELL PAPILLOMA						X														X						5
SQUAMOUS CELL CARCINOMA		X	X	X			X		X						X		X	X			X			X	X	23
SMALL INTESTINE	+	-	-	+	-	+	+	+	-	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	39
LARGE INTESTINE	-	+	-	+	-	+	-	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SQUAMOUS CELL CARCINOMA, METASTAT																										1
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
PITUITARY	+	-	+	+	-	-	-	-	+	-	+	+	+	+	+	-	+	+	+	+	+	-	+	+	-	37
ADENOMA, NOS																										3
ADRENAL	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
ADENOMA, NOS																										1
THYROID	-	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	-	+	-		42
PARATHYROID	-	-	-	+	-	-	-	-	+	-	+	+	+	-	-	+	-	+	+	+	+	-	+	+		24
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
ADENOCARCINOMA, NOS																										1
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOMETRIAL STROMAL POLYP																										1
OVARY	+	+	+	+	+	+	-	+	+	+	+	+	-	+	+	-	-	+	+	+	+	+	+	+	+	40
SQUAMOUS CELL CARCINOMA, INVASIVE			X																							3
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
HARDERIAN GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
ADENOMA, NOS													X		X											2
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*
SQUAMOUS CELL CARCINOMA, INVASIVE			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*
SQUAMOUS CELL CARCINOMA, INVASIVE		X		X			X								X				X							9
SQUAMOUS CELL CARCINOMA, METASTAT			X												X								X			3
MALIGNANT LYMPHOMA, NOS	X					X								X												3

* ANIMALS NECROPSIED

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

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

APPENDIX C

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS ADMINISTERED DIGLYCIDYL RESORCINOL ETHER IN CORN OIL BY GAVAGE

TABLE C1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS ADMINISTERED DIGLYCIDYL RESORCINOL ETHER IN CORN OIL BY GAVAGE

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
ULCER, NOS	1 (2%)		
*SUBCUT TISSUE	(50)	(50)	(50)
EPIDERMAL INCLUSION CYST	1 (2%)		
INFLAMMATION, GRANULOMATOUS		1 (2%)	
RESPIRATORY SYSTEM			
*LARYNX	(50)	(50)	(50)
INFLAMMATION, ACUTE			1 (2%)
INFLAMMATION, ACUTE FOCAL			1 (2%)
HYPERKERATOSIS			1 (2%)
#TRACHEA	(50)	(49)	(49)
INFLAMMATION, ACUTE		2 (4%)	
INFLAMMATION, ACUTE/CHRONIC		2 (4%)	
INFLAMMATION, CHRONIC	1 (2%)		
HYPERKERATOSIS		2 (4%)	1 (2%)
#LUNG/BRONCHIOLE	(50)	(49)	(50)
METAPLASIA, NOS	2 (4%)	1 (2%)	
#LUNG	(50)	(49)	(50)
CONGESTION, NOS			1 (2%)
EDEMA, NOS		1 (2%)	1 (2%)
HEMORRHAGE			1 (2%)
BRONCHOPNEUMONIA, NOS	2 (4%)	17 (35%)	26 (52%)
INFLAMMATION, INTERSTITIAL		1 (2%)	
GRANULOMA, FOREIGN BODY		1 (2%)	
METAPLASIA, OSSEOUS		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
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(48)	(49)	(50)
FIBROSIS, FOCAL		1 (2%)	
HYPERPLASIA, NOS	2 (4%)	8 (16%)	1 (2%)
HYPERPLASIA, HEMATOPOIETIC		5 (10%)	
HYPERPLASIA, ERYTHROID		1 (2%)	
#SPLEEN	(50)	(50)	(48)
CONGESTION, NOS	1 (2%)		
INFARCT, NOS		1 (2%)	
HEMOSIDEROSIS		1 (2%)	7 (15%)
LYMPHOID DEPLETION			1 (2%)
HEMATOPOIESIS	3 (6%)	10 (20%)	
#SPLENIC CAPSULE	(50)	(50)	(48)
HEMORRHAGE	1 (2%)		
#SPLENIC FOLLICLES	(50)	(50)	(48)
ATROPHY, NOS		1 (2%)	
#LYMPH NODE	(49)	(47)	(47)
INFLAMMATION, CHRONIC		1 (2%)	
#MANDIBULAR L. NODE	(49)	(47)	(47)
CONGESTION, NOS	1 (2%)		
#MEDIASTINAL L.NODE	(49)	(47)	(47)
CONGESTION, NOS		1 (2%)	
CIRCULATORY SYSTEM			
#LYMPH NODE	(49)	(47)	(47)
LYMPHANGIECTASIS		1 (2%)	
#CELIAC LYMPH NODE	(49)	(47)	(47)
LYMPHANGIECTASIS		1 (2%)	
#MESENTERIC L. NODE	(49)	(47)	(47)
LYMPHANGIECTASIS	1 (2%)	1 (2%)	
#HEART	(50)	(49)	(50)
THROMBUS, MURAL		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
#HEART/ATRIUM	(50)	(49)	(50)
THROMBOSIS, NOS			1 (2%)
#MYOCARDIUM	(50)	(49)	(50)
DEGENERATION, NOS	48 (96%)	40 (82%)	30 (60%)
*PULMONARY ARTERY	(50)	(50)	(50)
CALCIFICATION, NOS	1 (2%)		
*MESENTERIC ARTERY	(50)	(50)	(50)
PERIARTERITIS	1 (2%)		
HYPERTROPHY, NOS			1 (2%)
*MESENTERY	(50)	(50)	(50)
LYMPHANGIECTASIS			1 (2%)
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(50)	(47)	(48)
DILATATION/DUCTS		1 (2%)	
FIBROSIS		1 (2%)	
#LIVER	(50)	(50)	(50)
HERNIA, NOS	3 (6%)	1 (2%)	
CONGESTION, NOS		4 (8%)	16 (32%)
CONGESTION, CHRONIC PASSIVE		2 (4%)	3 (6%)
CHOLANGIOFIBROSIS	3 (6%)	3 (6%)	
DEGENERATION, NOS			1 (2%)
NECROSIS, FOCAL		3 (6%)	4 (8%)
METAMORPHOSIS FATTY	18 (36%)	21 (42%)	4 (8%)
BASOPHILIC CYTO CHANGE	10 (20%)	3 (6%)	
FOCAL CELLULAR CHANGE		1 (2%)	
CLEAR-CELL CHANGE	5 (10%)		
ANGIECTASIS		1 (2%)	
#LIVER/CENTRILOBULAR	(50)	(50)	(50)
NECROSIS, NOS		2 (4%)	
#BILE DUCT	(50)	(50)	(50)
DILATATION, NOS	1 (2%)		
HYPERPLASIA, NOS	29 (58%)		
#PANCREAS	(49)	(44)	(47)
INFLAMMATION, CHRONIC	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
FIBROSIS		1 (2%)	
FIBROSIS, FOCAL	7 (14%)	1 (2%)	3 (6%)
ATROPHY, FOCAL	1 (2%)		
#ESOPHAGUS	(40)	(40)	(37)
INFLAMMATION, ACUTE NECROTIZING			1 (3%)
HYPERKERATOSIS			4 (11%)
#STOMACH	(50)	(50)	(49)
EPIDERMAL INCLUSION CYST		1 (2%)	
ULCER, NOS	2 (4%)	4 (8%)	2 (4%)
INFLAMMATION, ACUTE	1 (2%)		
HYPERPLASIA, BASAL CELL	1 (2%)	16 (32%)	34 (69%)
HYPERKERATOSIS	1 (2%)	12 (24%)	43 (88%)
ACANTHOSIS			1 (2%)
#GASTRIC SUBMUCOSA	(50)	(50)	(49)
GRANULATION, TISSUE		1 (2%)	
#JEJUNAL MUCOUS MEMBR	(50)	(49)	(47)
NECROSIS, NOS		1 (2%)	
#COLON	(48)	(44)	(47)
PARASITISM	8 (17%)		3 (6%)
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
CYST, NOS	2 (4%)		
INFLAMMATION, ACUTE FOCAL		1 (2%)	
INFLAMMATION, CHRONIC FOCAL		1 (2%)	
NEPHROSIS, NOS	45 (90%)	31 (62%)	7 (14%)
CALCIFICATION, FOCAL		4 (8%)	6 (12%)
#KIDNEY/TUBULE	(50)	(50)	(50)
PIGMENTATION, NOS		1 (2%)	
#KIDNEY/PELVIS	(50)	(50)	(50)
HYPERPLASIA, EPITHELIAL	2 (4%)		
#URINARY BLADDER	(50)	(50)	(50)
CALCULUS,UNKN GROSS OR MICRO	1 (2%)	2 (4%)	4 (8%)
HEMORRHAGE		1 (2%)	
INFLAMMATION, CHRONIC FOCAL	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
HYPERPLASIA, EPITHELIAL		1 (2%)	
*URETHRA	(50)	(50)	(50)
HYPERPLASIA, EPITHELIAL		1 (2%)	
*PROSTATIC URETHRA	(50)	(50)	(50)
CALCULUS,UNKN GROSS OR MICRO		1 (2%)	
ENDOCRINE SYSTEM			
#PITUITARY	(49)	(48)	(47)
CYST, NOS	1 (2%)	4 (8%)	1 (2%)
HEMORRHAGIC CYST	1 (2%)	1 (2%)	
HYPERPLASIA, FOCAL	3 (6%)	5 (10%)	1 (2%)
HYPERPLASIA, DIFFUSE	1 (2%)		
VASCULARIZATION	2 (4%)	1 (2%)	
#ADRENAL CORTEX	(50)	(50)	(50)
DEGENERATION, LIPOID		1 (2%)	
CYTOPLASMIC VACUOLIZATION	6 (12%)	20 (40%)	3 (6%)
HYPERTROPHY, NOS		1 (2%)	
HYPERPLASIA, FOCAL	1 (2%)		
#ADRENAL MEDULLA	(50)	(50)	(50)
HYPERPLASIA, NOS	8 (16%)	5 (10%)	
#THYROID	(47)	(47)	(46)
CYSTIC FOLLICLES	1 (2%)		
HYPERPLASIA, C-CELL	2 (4%)	2 (4%)	
#PANCREATIC ISLETS	(49)	(44)	(47)
HYPERPLASIA, NOS		1 (2%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
GALACTOCELE		1 (2%)	
#PROSTATE	(45)	(48)	(49)
CALCULUS,UNKN GROSS OR MICRO		1 (2%)	
INFLAMMATION, FOCAL			1 (2%)
INFLAMMATION, ACUTE	2 (4%)	3 (6%)	
INFLAMMATION, ACUTE FOCAL		1 (2%)	

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ABSCESS, NOS	1 (2%)		
INFLAMMATION, ACUTE/CHRONIC	1 (2%)	1 (2%)	1 (2%)
INFLAMMATION, CHRONIC	1 (2%)		
HYPERPLASIA, NOS	1 (2%)		
HYPERPLASIA, FOCAL	2 (4%)	3 (6%)	
*SEMINAL VESICLE	(50)	(50)	(50)
ATROPHY, NOS	2 (4%)	1 (2%)	1 (2%)
#TESTIS	(50)	(49)	(50)
ATROPHY, NOS	5 (10%)	5 (10%)	2 (4%)
ATROPHY, FOCAL	1 (2%)		
HYPERPLASIA, INTERSTITIAL CELL	4 (8%)	7 (14%)	13 (26%)
#TESTIS/TUBULE	(50)	(49)	(50)
ATROPHY, FOCAL	1 (2%)		1 (2%)
NERVOUS SYSTEM			
#SUBARACHNOID SPACE	(50)	(50)	(49)
HEMORRHAGE			1 (2%)
#BRAIN	(50)	(50)	(49)
HYDROCEPHALUS, NOS	1 (2%)	1 (2%)	
HEMORRHAGE		1 (2%)	
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*ABDOMINAL CAVITY	(50)	(50)	(50)
ABSCESS, NOS		1 (2%)	
NECROSIS, FAT		1 (2%)	
*PERITONEUM	(50)	(50)	(50)
INFLAMMATION, CHRONIC		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
*PERICARDIUM	(50)	(50)	(50)
INFLAMMATION, ACUTE			1 (2%)
*MESENTERY	(50)	(50)	(50)
HEMORRHAGIC CYST		1 (2%)	
NECROSIS, FAT	1 (2%)	1 (2%)	
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
INFARCT, NOS		1 (2%)	
CALCIFICATION, FOCAL		2 (4%)	
ATROPHY, NOS		3 (6%)	1 (2%)
HYPERKERATOSIS			2 (4%)
SPECIAL MORPHOLOGY SUMMARY			
NONE			

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

TABLE C2.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS ADMINISTERED DIGLYCIDYL RESORCINOL ETHER 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			
NONE			
RESPIRATORY SYSTEM			
#TRACHEA	(50)	(50)	(49)
HYPERKERATOSIS		5 (10%)	2 (4%)
#LUNG/BRONCHIOLE	(50)	(50)	(50)
METAPLASIA, NOS	1 (2%)	2 (4%)	
#LUNG	(50)	(50)	(50)
ASPIRATION, NOS		2 (4%)	2 (4%)
CONGESTION, NOS	1 (2%)		
EDEMA, NOS			1 (2%)
BRONCHOPNEUMONIA, NOS		10 (20%)	17 (34%)
PNEUMONIA, CHRONIC MURINE			1 (2%)
GRANULOMA, NOS		1 (2%)	
GRANULOMA, FOREIGN BODY		2 (4%)	
REACTION, FOREIGN BODY		1 (2%)	
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(50)	(50)	(49)
HYPEROSTOSIS	1 (2%)		
HYPERPLASIA, NOS		4 (8%)	
HYPERPLASIA, HEMATOPOIETIC	1 (2%)	2 (4%)	
#SPLEEN	(50)	(50)	(50)
ACCESSORY STRUCTURE		1 (2%)	
CONGESTION, NOS		1 (2%)	
FIBROSIS, FOCAL	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
HEMOSIDEROSIS	3 (6%)	3 (6%)	11 (22%)
HEMATOPOIESIS	2 (4%)	9 (18%)	1 (2%)
#MANDIBULAR L. NODE	(49)	(47)	(50)
HYPERPLASIA, NOS		1 (2%)	
#MEDIASTINAL L.NODE	(49)	(47)	(50)
CONGESTION, NOS	1 (2%)		
CIRCULATORY SYSTEM			
#CELIAC LYMPH NODE	(49)	(47)	(50)
LYMPHANGIECTASIS		2 (4%)	
#MYOCARDIUM	(50)	(50)	(50)
DEGENERATION, NOS	30 (60%)	25 (50%)	12 (24%)
#KIDNEY/PELVIS	(50)	(50)	(50)
THROMBUS, ORGANIZED	1 (2%)		
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(50)	(50)	(50)
DILATATION/DUCTS	1 (2%)		
HYPERPLASIA, NOS	1 (2%)	1 (2%)	
#LIVER	(50)	(50)	(50)
HERNIA, NOS	4 (8%)	3 (6%)	
CONGESTION, NOS		3 (6%)	
CONGESTION, CHRONIC PASSIVE	1 (2%)	2 (4%)	
INFLAMMATION, ACUTE FOCAL		1 (2%)	
CHOLANGIOFIBROSIS	4 (8%)		
NECROSIS, FOCAL	2 (4%)		3 (6%)
METAMORPHOSIS FATTY	6 (12%)	10 (20%)	7 (14%)
BASOPHILIC CYTO CHANGE	27 (54%)	16 (32%)	2 (4%)
ANGIECTASIS	1 (2%)		
#BILE DUCT	(50)	(50)	(50)
CYST, NOS		1 (2%)	
HYPERPLASIA, NOS		4 (8%)	
#PANCREAS	(50)	(46)	(47)
FIBROSIS, FOCAL	6 (12%)	3 (7%)	

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ATROPHY, NOS	1 (2%)		
#ESOPHAGUS	(44)	(45)	(37)
HYPERKERATOSIS			1 (3%)
#STOMACH	(49)	(50)	(50)
EPIDERMAL INCLUSION CYST		5 (10%)	
ULCER, NOS	1 (2%)	1 (2%)	3 (6%)
INFLAMMATION, ACUTE SUPPURATIVE			1 (2%)
HYPERPLASIA, BASAL CELL	2 (4%)	12 (24%)	33 (66%)
HYPERKERATOSIS	1 (2%)	12 (24%)	48 (96%)
#GASTRIC MUCOSA	(49)	(50)	(50)
ABSCESS, NOS		1 (2%)	1 (2%)
#COLON	(48)	(48)	(47)
PARASITISM	6 (13%)	5 (10%)	3 (6%)
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
HYDRONEPHROSIS	1 (2%)		
NEPHROSIS, NOS	28 (56%)	15 (30%)	
CALCIFICATION, FOCAL	6 (12%)	12 (24%)	12 (24%)
#KIDNEY/TUBULE	(50)	(50)	(50)
PIGMENTATION, NOS		1 (2%)	
#URINARY BLADDER	(50)	(50)	(49)
INFLAMMATION, ACUTE		1 (2%)	
ENDOCRINE SYSTEM			
#PITUITARY	(50)	(49)	(47)
CYST, NOS	12 (24%)	13 (27%)	2 (4%)
HEMORRHAGE		1 (2%)	
HEMORRHAGIC CYST	3 (6%)		
INFARCT, FOCAL		1 (2%)	
HYPERPLASIA, FOCAL	5 (10%)	3 (6%)	1 (2%)
ANGIECTASIS			1 (2%)
VASCULARIZATION	2 (4%)	5 (10%)	
DYSPLASIA, NOS	1 (2%)		
#ADRENAL	(50)	(48)	(49)
HEMORRHAGE			1 (2%)

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#ADRENAL CORTEX	(50)	(48)	(49)
DEGENERATION, LIPOID	1 (2%)		
CYTOPLASMIC VACUOLIZATION	3 (6%)	15 (31%)	2 (4%)
ATROPHY, NOS	1 (2%)		
HYPERPLASIA, NOS	1 (2%)		
HYPERPLASIA, FOCAL	1 (2%)		
#ADRENAL MEDULLA	(50)	(48)	(49)
HYPERPLASIA, NOS	5 (10%)	8 (17%)	
HYPERPLASIA, FOCAL	1 (2%)		
#THYROID	(50)	(47)	(41)
INFLAMMATION, CHRONIC FOCAL			1 (2%)
HYPERPLASIA, C-CELL	5 (10%)		
#PARATHYROID	(22)	(17)	(23)
HYPERPLASIA, NOS	1 (5%)		
#PANCREATIC ISLETS	(50)	(46)	(47)
HYPERPLASIA, NOS	1 (2%)		
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
GALACTOCELE	6 (12%)	4 (8%)	
*CLITORAL GLAND	(50)	(50)	(50)
HYPERPLASIA, NOS	1 (2%)		
#UTERUS	(50)	(50)	(50)
DILATATION, NOS	1 (2%)	5 (10%)	
#UTERUS/ENDOMETRIUM	(50)	(50)	(50)
HEMATOMA, NOS	1 (2%)		
HYPERPLASIA, CYSTIC	6 (12%)	2 (4%)	
#ENDOMETRIAL GLAND	(50)	(50)	(50)
CYST, NOS	1 (2%)		
#OVARY	(49)	(50)	(50)
CYST, NOS	2 (4%)		1 (2%)
NERVOUS SYSTEM			
#SUBARACHNOID SPACE	(50)	(50)	(50)
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
#BRAIN	(50)	(50)	(50)
HYDROCEPHALUS, NOS	2 (4%)	2 (4%)	
HEMORRHAGE	1 (2%)		
SPECIAL SENSE ORGANS			
*EYE	(50)	(50)	(50)
HEMORRHAGE		1 (2%)	
*EYE/RETINA	(50)	(50)	(50)
DEGENERATION, NOS		1 (2%)	
*HARDERIAN GLAND	(50)	(50)	(50)
INFLAMMATION, FOCAL		1 (2%)	
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*ABDOMINAL CAVITY	(50)	(50)	(50)
NECROSIS, FAT	1 (2%)	2 (4%)	1 (2%)
*MESENTERY	(50)	(50)	(50)
NECROSIS, FAT	2 (4%)		
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
CONGESTION, NOS			2 (4%)
CALCIFICATION, FOCAL	2 (4%)		1 (2%)
HYPERKERATOSIS		1 (2%)	
SPECIAL MORPHOLOGY SUMMARY			
NONE			

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

TABLE C3.
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS ADMINISTERED DIGLYCIDYL RESORCINOL ETHER IN CORN OIL BY GAVAGE (SUPPLEMENTAL STUDY)

	VEHICLE CONTROL	TEST
ANIMALS INITIALLY IN STUDY	50	50
ANIMALS NECROPSIED	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50
INTEGUMENTARY SYSTEM		
*SKIN	(50)	(50)
EPIDERMAL INCLUSION CYST	2 (4%)	1 (2%)
*SUBCUT TISSUE	(50)	(50)
CYST, NOS	1 (2%)	
ANGIECTASIS	1 (2%)	
RESPIRATORY SYSTEM		
#LUNG/BRONCHIOLE	(50)	(50)
METAPLASIA, NOS	4 (8%)	1 (2%)
#LUNG	(50)	(50)
CONGESTION, NOS		1 (2%)
INFLAMMATION, ACUTE FOCAL		1 (2%)
GRANULOMA, FOREIGN BODY	1 (2%)	
HEMATOPOIETIC SYSTEM		
*MULTIPLE ORGANS	(50)	(50)
HEMATOPOIESIS		1 (2%)
#BONE MARROW	(50)	(48)
FIBROSIS	1 (2%)	
HYPERPLASIA, NOS	5 (10%)	12 (25%)
HYPERPLASIA, HEMATOPOIETIC	1 (2%)	4 (8%)
#SPLEEN	(49)	(50)
FIBROSIS, FOCAL	1 (2%)	
ADHESION, NOS		1 (2%)
INFARCT, NOS	1 (2%)	

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

TABLE C3. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	TEST
LYMPHOID DEPLETION		1 (2%)
HEMATOPOIESIS	1 (2%)	4 (8%)
#LYMPH NODE	(50)	(48)
PLASMACYTOSIS		1 (2%)
#MANDIBULAR L. NODE	(50)	(48)
CONGESTION, NOS		1 (2%)
ABSCESS, NOS	1 (2%)	
INFLAMMATION, CHRONIC		1 (2%)
#MEDIASTINAL L.NODE	(50)	(48)
CONGESTION, NOS		2 (4%)
HYPERPLASIA, NOS		1 (2%)
PLASMACYTOSIS		3 (6%)
#MESENTERIC L. NODE	(50)	(48)
CONGESTION, NOS		1 (2%)
INFLAMMATION, CHRONIC		1 (2%)
#PEYER'S PATCH	(50)	(49)
HYPERPLASIA, LYMPHOID	1 (2%)	
CIRCULATORY SYSTEM		
#MEDIASTINAL L.NODE	(50)	(48)
LYMPHANGIECTASIS	1 (2%)	
#LUNG	(50)	(50)
PERIVASCULITIS	1 (2%)	
#HEART	(50)	(50)
THROMBUS, MURAL	1 (2%)	
FIBROSIS, FOCAL		1 (2%)
#MYOCARDIUM	(50)	(50)
DEGENERATION, NOS	43 (86%)	41 (82%)
#SALIVARY GLAND	(49)	(49)
LYMPHANGIECTASIS		1 (2%)
#LIVER	(50)	(50)
PERIVASCULITIS	2 (4%)	

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

TABLE C3. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	TEST
DIGESTIVE SYSTEM		
#SALIVARY GLAND	(49)	(49)
ATROPHY, NOS	1 (2%)	
#LIVER	(50)	(50)
HERNIA, NOS	1 (2%)	2 (4%)
CONGESTION, NOS	1 (2%)	
PETECHIA		1 (2%)
INFLAMMATION, FOCAL		2 (4%)
INFLAMMATION, ACUTE FOCAL		1 (2%)
CHOLANGIOFIBROSIS		1 (2%)
NECROSIS, FOCAL	3 (6%)	4 (8%)
METAMORPHOSIS FATTY	24 (48%)	17 (34%)
CYTOPLASMIC CHANGE, NOS	2 (4%)	2 (4%)
BASOPHILIC CYTO CHANGE	12 (24%)	15 (30%)
CLEAR-CELL CHANGE	2 (4%)	1 (2%)
#BILE DUCT	(50)	(50)
HYPERPLASIA, NOS	26 (52%)	21 (42%)
#PANCREAS	(49)	(46)
INFLAMMATION, CHRONIC		3 (7%)
FIBROSIS		5 (11%)
FIBROSIS, FOCAL	3 (6%)	7 (15%)
#PANCREATIC ACINUS	(49)	(46)
HYPERPLASIA, FOCAL		1 (2%)
#STOMACH	(50)	(50)
INFLAMMATION, CHRONIC FOCAL	1 (2%)	
#GASTRIC SUBMUCOSA	(50)	(50)
FIBROSIS		1 (2%)
#FORESTOMACH	(50)	(50)
EPIDERMAL INCLUSION CYST		4 (8%)
ULCER, NOS		6 (12%)
ABSCESS, NOS		1 (2%)
HYPERPLASIA, BASAL CELL	6 (12%)	37 (74%)
HYPERKERATOSIS		38 (76%)
#COLON	(42)	(45)
PARASITISM	5 (12%)	1 (2%)

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

TABLE C3. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	TEST
URINARY SYSTEM		
#KIDNEY	(50)	(50)
CONGESTION, NOS	1 (2%)	
INFLAMMATION, ACUTE FOCAL	1 (2%)	
INFLAMMATION, CHRONIC	1 (2%)	
INFLAMMATION, CHRONIC FOCAL	1 (2%)	
SCAR	1 (2%)	
NEPHROPATHY	44 (88%)	42 (84%)
NEPHROSIS, NOS		1 (2%)
NEPHROSIS, CHOLEMIC	1 (2%)	
CALCIFICATION, FOCAL	3 (6%)	1 (2%)
#KIDNEY/TUBULE	(50)	(50)
DYSPLASIA, NOS	1 (2%)	
#URINARY BLADDER	(49)	(47)
CALCULUS,UNKN GROSS OR MICRO	1 (2%)	
CALCULUS,GROSS OBSERVATION ONLY		1 (2%)
INFLAMMATION, FOCAL	1 (2%)	
INFLAMMATION, CHRONIC FOCAL	3 (6%)	2 (4%)
NECROSIS, HEMORRHAGIC		1 (2%)
HYPERPLASIA, EPITHELIAL		1 (2%)
ENDOCRINE SYSTEM		
#PITUITARY	(50)	(48)
ANGIECTASIS	1 (2%)	
#PITUITARY INTERMEDIA	(50)	(48)
HYPERPLASIA, FOCAL	1 (2%)	
#ANTERIOR PITUITARY	(50)	(48)
CYST, NOS		1 (2%)
HEMORRHAGIC CYST		1 (2%)
HYPERPLASIA, FOCAL	4 (8%)	8 (17%)
#ADRENAL CORTEX	(50)	(49)
CYTOPLASMIC VACUOLIZATION	3 (6%)	6 (12%)
HYPERPLASIA, NOS		1 (2%)
HYPERPLASIA, FOCAL	4 (8%)	
DYSPLASIA, NOS	1 (2%)	
#ADRENAL MEDULLA	(50)	(49)
HYPERPLASIA, NOS	10 (20%)	7 (14%)

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

TABLE C3. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	TEST
#THYROID	(50)	(50)
FOLLICULAR CYST, NOS	1 (2%)	
HYPERPLASIA, C-CELL	12 (24%)	8 (16%)
#PANCREATIC ISLETS	(49)	(46)
HYPERPLASIA, NOS		1 (2%)
REPRODUCTIVE SYSTEM		
*MAMMARY GLAND	(50)	(50)
GALACTOCELE	1 (2%)	
LACTATION	1 (2%)	4 (8%)
*PREPUTIAL GLAND	(50)	(50)
DILATATION, NOS	1 (2%)	1 (2%)
ABSCESS, NOS	1 (2%)	
INFLAMMATION, CHRONIC	1 (2%)	
#PROSTATE	(44)	(36)
INFLAMMATION, NOS	1 (2%)	
INFLAMMATION, ACUTE	1 (2%)	3 (8%)
INFLAMMATION, ACUTE FOCAL	1 (2%)	
INFLAMMATION, ACUTE NECROTIZING		1 (3%)
INFLAMMATION, CHRONIC	4 (9%)	3 (8%)
ATROPHY, NOS	8 (18%)	7 (19%)
HYPERPLASIA, FOCAL		1 (3%)
*SEMINAL VESICLE	(50)	(50)
INFARCT, NOS	1 (2%)	
ATROPHY, NOS	31 (62%)	26 (52%)
HYPERPLASIA, FOCAL	1 (2%)	
#TESTIS	(50)	(48)
NECROSIS, FOCAL	1 (2%)	
NECROSIS, FAT	1 (2%)	
INFARCT, NOS	1 (2%)	
ATROPHY, NOS	9 (18%)	8 (17%)
HYPERPLASIA, INTERSTITIAL CELL	1 (2%)	4 (8%)
NERVOUS SYSTEM		
#BRAIN	(50)	(49)
HYDROCEPHALUS, NOS		1 (2%)

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

TABLE C3. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	TEST
HEMORRHAGE		1 (2%)
SPECIAL SENSE ORGANS		
*EYE/CRYSTALLINE LENS	(50)	(50)
CATARACT		1 (2%)
MUSCULOSKELETAL SYSTEM		
NONE		
BODY CAVITIES		
*PELVIC PERITONEAL CA	(50)	(50)
ABSCESS, NOS	1 (2%)	
*PELVIS	(50)	(50)
HEMORRHAGIC CYST		1 (2%)
ALL OTHER SYSTEMS		
*MULTIPLE ORGANS	(50)	(50)
CALCIFICATION, NOS	1 (2%)	
CALCIFICATION, FOCAL		1 (2%)
OMENTUM		
NECROSIS, FAT	6	2
SPECIAL MORPHOLOGY SUMMARY		
NONE		

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

TABLE C4.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS ADMINISTERED DIGLYCIDYL RESORCINOL ETHER IN CORN OIL BY GAVAGE (SUPPLEMENTAL STUDY)

	VEHICLE CONTROL	TEST
ANIMALS INITIALLY IN STUDY	50	50
ANIMALS NECROPSIED	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50
INTEGUMENTARY SYSTEM		
*SKIN	(50)	(50)
EPIDERMAL INCLUSION CYST		1 (2%)
FIBROSIS	1 (2%)	
*SUBCUT TISSUE	(50)	(50)
INFLAMMATION, ACUTE	1 (2%)	
GRANULATION, TISSUE	1 (2%)	
RESPIRATORY SYSTEM		
#LUNG/BRONCHIOLE	(50)	(50)
METAPLASIA, NOS	1 (2%)	1 (2%)
#LUNG	(50)	(50)
ASPIRATION, NOS		1 (2%)
CONGESTION, NOS		2 (4%)
BRONCHOPNEUMONIA, NOS		1 (2%)
GRANULOMA, FOREIGN BODY		1 (2%)
HEMATOPOIETIC SYSTEM		
*MULTIPLE ORGANS	(50)	(50)
HEMATOPOIESIS		1 (2%)
#BONE MARROW	(49)	(48)
FIBROSIS, FOCAL	1 (2%)	
HYPERPLASIA, NOS	6 (12%)	6 (13%)
HYPERPLASIA, HEMATOPOIETIC		1 (2%)
#SPLEEN	(50)	(50)
HEMOSIDEROSIS	1 (2%)	3 (6%)

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

TABLE C4. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	TEST
LYMPHOID DEPLETION	6 (12%)	3 (6%)
HEMATOPOIESIS	3 (6%)	4 (8%)
#MANDIBULAR L. NODE	(49)	(50)
CONGESTION, NOS	1 (2%)	
PLASMACYTOSIS	1 (2%)	
#MEDIASTINAL L.NODE	(49)	(50)
CONGESTION, NOS	1 (2%)	2 (4%)
PLASMACYTOSIS	1 (2%)	
#MESENTERIC L. NODE	(49)	(50)
INFLAMMATION, CHRONIC	1 (2%)	
HEMOSIDEROSIS		1 (2%)
#LIVER	(50)	(50)
HEMATOPOIESIS	1 (2%)	
CIRCULATORY SYSTEM		
#LUMBAR LYMPH NODE	(49)	(50)
LYMPHANGIECTASIS	1 (2%)	1 (2%)
#MESENTERIC L. NODE	(49)	(50)
LYMPHANGIECTASIS	1 (2%)	
#MYOCARDIUM	(50)	(50)
DEGENERATION, NOS	40 (80%)	36 (72%)
DIGESTIVE SYSTEM		
#LIVER	(50)	(50)
HERNIA, NOS		2 (4%)
CYST, NOS		1 (2%)
INFLAMMATION, FOCAL		1 (2%)
INFLAMMATION, ACUTE FOCAL		1 (2%)
ABSCESS, NOS		1 (2%)
FIBROSIS, FOCAL		1 (2%)
ADHESION, NOS		1 (2%)
METAMORPHOSIS FATTY	6 (12%)	6 (12%)
BASOPHILIC CYTO CHANGE	39 (78%)	39 (78%)
FOCAL CELLULAR CHANGE		1 (2%)
#LIVER/CENTRILOBULAR	(50)	(50)
NECROSIS, NOS	1 (2%)	

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

TABLE C4. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	TEST
#BILE DUCT	(50)	(50)
CYST, NOS	1 (2%)	
HYPERPLASIA, NOS	20 (40%)	18 (36%)
#PANCREAS	(50)	(49)
DILATATION/DUCTS		1 (2%)
FIBROSIS, FOCAL	8 (16%)	5 (10%)
#PANCREATIC ACINUS	(50)	(49)
HYPERPLASIA, FOCAL	1 (2%)	
#ESOPHAGUS	(32)	(27)
HYPERKERATOSIS		1 (4%)
#STOMACH	(50)	(50)
HYPERKERATOSIS		1 (2%)
#FORESTOMACH	(50)	(50)
EPIDERMAL INCLUSION CYST		5 (10%)
ULCER, NOS		6 (12%)
ABSCESS, NOS		1 (2%)
ULCER, PERFORATED	1 (2%)	
HYPERPLASIA, BASAL CELL	3 (6%)	45 (90%)
HYPERKERATOSIS		46 (92%)
#ILEUM	(50)	(50)
PARASITISM	1 (2%)	
#COLON	(48)	(46)
PARASITISM	3 (6%)	3 (7%)
URINARY SYSTEM		
#KIDNEY	(50)	(50)
CONGESTION, NOS	2 (4%)	
NEPHROPATHY	26 (52%)	18 (36%)
NEPHROSIS, CHOLEMIC	1 (2%)	3 (6%)
CALCIFICATION, FOCAL	15 (30%)	13 (26%)
#KIDNEY/CORTEX	(50)	(50)
MULTIPLE CYSTS		1 (2%)
#KIDNEY/PELVIS	(50)	(50)
INFLAMMATION, CHRONIC		1 (2%)

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

TABLE C4. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	TEST
#URINARY BLADDER	(48)	(49)
CALCULUS,GROSS OBSERVATION ONLY		1 (2%)
INFLAMMATION, CHRONIC		1 (2%)
INFLAMMATION, CHRONIC FOCAL	2 (4%)	4 (8%)
HYPERPLASIA, EPITHELIAL	1 (2%)	1 (2%)
#U.BLADDER/SUBMUCOSA	(48)	(49)
INFLAMMATION, CHRONIC FOCAL		1 (2%)
ENDOCRINE SYSTEM		
#PITUITARY	(50)	(50)
CYST, NOS		1 (2%)
MULTIPLE CYSTS		1 (2%)
HEMORRHAGIC CYST	1 (2%)	
VASCULARIZATION	1 (2%)	
#PITUITARY INTERMEDIA	(50)	(50)
HEMORRHAGIC CYST	1 (2%)	
#ANTERIOR PITUITARY	(50)	(50)
CYST, NOS	1 (2%)	1 (2%)
MULTIPLE CYSTS	1 (2%)	
HEMORRHAGIC CYST	3 (6%)	1 (2%)
HYPERPLASIA, FOCAL	5 (10%)	4 (8%)
ANGIECTASIS	1 (2%)	
#ADRENAL	(50)	(50)
NECROSIS, NOS		1 (2%)
#ADRENAL CORTEX	(50)	(50)
HEMORRHAGIC CYST	1 (2%)	
DEGENERATION, LIPOID	3 (6%)	4 (8%)
CYTOPLASMIC CHANGE, NOS	2 (4%)	
CYTOPLASMIC VACUOLIZATION	8 (16%)	10 (20%)
HYPERPLASIA, FOCAL		1 (2%)
DYSPLASIA, NOS	2 (4%)	1 (2%)
#ADRENAL MEDULLA	(50)	(50)
HYPERPLASIA, NOS	5 (10%)	1 (2%)
#THYROID	(50)	(50)
FOLLICULAR CYST, NOS		1 (2%)

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

TABLE C4. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	TEST
INFLAMMATION, CHRONIC	1 (2%)	
HYPERPLASIA, C-CELL	8 (16%)	10 (20%)
REPRODUCTIVE SYSTEM		
*MAMMARY GLAND	(50)	(50)
GALACTOCELE	13 (26%)	15 (30%)
LACTATION	13 (26%)	16 (32%)
#UTERUS	(50)	(50)
DILATATION, NOS	1 (2%)	
ABSCESS, NOS	1 (2%)	
#UTERUS/ENDOMETRIUM	(50)	(50)
CYST, NOS		1 (2%)
HYPERPLASIA, NOS	1 (2%)	
HYPERPLASIA, CYSTIC	3 (6%)	1 (2%)
#UTERUS/MYOMETRIUM	(50)	(50)
ABSCESS, NOS	1 (2%)	
#FALLOPIAN TUBE	(50)	(50)
INFLAMMATION, ACUTE	1 (2%)	
#OVARY	(50)	(48)
CYST, NOS	7 (14%)	4 (8%)
CONGESTION, NOS		1 (2%)
INFLAMMATION, ACUTE	1 (2%)	1 (2%)
NERVOUS SYSTEM		
#BRAIN	(50)	(50)
HYDROCEPHALUS, NOS	1 (2%)	3 (6%)
HEMORRHAGE	1 (2%)	
SPECIAL SENSE ORGANS		
*EYE/CRYSTALLINE LENS	(50)	(50)
CATARACT	1 (2%)	
MUSCULOSKELETAL SYSTEM		
NONE		

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

TABLE C4. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	TEST
BODY CAVITIES		
*PLEURA	(50)	(50)
INFLAMMATION, NOS		1 (2%)
*MESENTERY	(50)	(50)
NECROSIS, FAT		1 (2%)
ALL OTHER SYSTEMS		
*MULTIPLE ORGANS	(50)	(50)
CONGESTION, NOS		1 (2%)
CALCIFICATION, FOCAL	1 (2%)	
OMENTUM		
NECROSIS, FAT	4	2
SPECIAL MORPHOLOGY SUMMARY		
NONE		

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

APPENDIX D

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE ADMINISTERED DICLYCIDYL RESORCINOL ETHER IN CORN OIL BY GAVAGE

TABLE D1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE ADMINISTERED DIGLYCIDYL RESORCINOL ETHER IN CORN OIL BY GAVAGE

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
INFLAMMATION, NOS	2 (4%)		1 (2%)
NECROSIS, NOS	2 (4%)		
HYPERKERATOSIS	1 (2%)		
ACANTHOSIS	1 (2%)		
*SUBCUT TISSUE	(50)	(50)	(50)
MINERALIZATION	1 (2%)		
INFLAMMATION, NOS	1 (2%)		2 (4%)
INFLAMMATION, NECROTIZING	1 (2%)		
INFLAMMATION, ACUTE/CHRONIC	1 (2%)	1 (2%)	
NECROSIS, NOS	1 (2%)	1 (2%)	
METAPLASIA, OSSEOUS	1 (2%)		
RESPIRATORY SYSTEM			
#LUNG/BRONCHUS	(50)	(50)	(49)
INFLAMMATION, NOS		1 (2%)	
INFLAMMATION, FOCAL		1 (2%)	
#LUNG	(50)	(50)	(49)
MINERALIZATION	1 (2%)		1 (2%)
HEMORRHAGE	1 (2%)		
BRONCHOPNEUMONIA, NOS			1 (2%)
INFLAMMATION, NOS	6 (12%)	8 (16%)	6 (12%)
INFLAMMATION, FOCAL		1 (2%)	
INFLAMMATION, ACUTE	1 (2%)	5 (10%)	3 (6%)
INFLAMMATION, ACUTE FOCAL			1 (2%)
INFLAMMATION, ACUTE/CHRONIC			1 (2%)
INFLAMMATION, GRANULOMATOUS	1 (2%)		
HYPERPLASIA, EPITHELIAL			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	(50)	(50)	(50)
HEMATOPOIESIS		2 (4%)	3 (6%)
#BONE MARROW	(49)	(48)	(41)
HEMATOPOIESIS		1 (2%)	3 (7%)
#SPLEEN	(47)	(49)	(48)
INFLAMMATION, NOS	1 (2%)		
NECROSIS, NOS	1 (2%)		
NECROSIS, FOCAL	1 (2%)		
ATROPHY, NOS			1 (2%)
LYMPHOID DEPLETION		5 (10%)	4 (8%)
HYPERPLASIA, LYMPHOID	1 (2%)		2 (4%)
HEMATOPOIESIS	22 (47%)	29 (59%)	35 (73%)
#LYMPH NODE	(43)	(44)	(47)
HEMORRHAGE			1 (2%)
INFLAMMATION, NOS	1 (2%)	2 (5%)	
INFLAMMATION, ACUTE			1 (2%)
LYMPHOID DEPLETION		1 (2%)	1 (2%)
ANGIECTASIS	12 (28%)	8 (18%)	14 (30%)
PLASMACYTOSIS	3 (7%)	1 (2%)	6 (13%)
HYPERPLASIA, RETICULUM CELL	3 (7%)	1 (2%)	2 (4%)
HYPERPLASIA, LYMPHOID	7 (16%)		2 (4%)
HEMATOPOIESIS	14 (33%)	8 (18%)	19 (40%)
#LIVER	(49)	(50)	(50)
HEMATOPOIESIS	3 (6%)	4 (8%)	2 (4%)
CIRCULATORY SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
PERIVASCULITIS	1 (2%)		
#LYMPH NODE	(43)	(44)	(47)
THROMBOSIS, NOS			1 (2%)
#HEART	(50)	(50)	(50)
MINERALIZATION	1 (2%)		2 (4%)
ENDOCARDITIS, BACTERIAL		1 (2%)	
INFLAMMATION, NOS		2 (4%)	

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
INFLAMMATION, ACUTE	1 (2%)	1 (2%)	1 (2%)
INFLAMMATION, ACUTE/CHRONIC			1 (2%)
FIBROSIS		1 (2%)	
#MYOCARDIUM	(50)	(50)	(50)
DEGENERATION, NOS	2 (4%)	1 (2%)	1 (2%)
#LIVER	(49)	(50)	(50)
THROMBOSIS, NOS		1 (2%)	
#STOMACH	(47)	(49)	(50)
PERIVASCULITIS			1 (2%)
DIGESTIVE SYSTEM			
*INTESTINAL TRACT	(50)	(50)	(50)
INFLAMMATION, ACUTE NECROTIZING	1 (2%)		
#LIVER	(49)	(50)	(50)
MINERALIZATION	1 (2%)		
INFLAMMATION, NECROTIZING			1 (2%)
INFLAMMATION, ACUTE			1 (2%)
FIBROSIS			1 (2%)
NECROSIS, NOS		2 (4%)	
NECROSIS, FOCAL	1 (2%)	4 (8%)	4 (8%)
NECROSIS, ISCHEMIC	4 (8%)	4 (8%)	6 (12%)
METAMORPHOSIS FATTY	5 (10%)	6 (12%)	5 (10%)
ANGIECTASIS	1 (2%)		
#LIVER/CENTRILOBULAR	(49)	(50)	(50)
NECROSIS, NOS		1 (2%)	
*GALLBLADDER	(50)	(50)	(50)
INFLAMMATION, NOS			1 (2%)
INFLAMMATION, ACUTE			1 (2%)
HYPERPLASIA, EPITHELIAL		1 (2%)	
#BILE DUCT	(49)	(50)	(50)
HYPERPLASIA, NOS		1 (2%)	
#PANCREATIC ACINUS	(45)	(47)	(49)
ATROPHY, FOCAL	1 (2%)		1 (2%)
#ESOPHAGUS	(48)	(48)	(46)
HYPERKERATOSIS		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
ACANTHOSIS		1 (2%)	
#STOMACH	(47)	(49)	(50)
MINERALIZATION	1 (2%)	1 (2%)	
INFLAMMATION, NOS	1 (2%)	11 (22%)	17 (34%)
INFLAMMATION, ACUTE	1 (2%)		1 (2%)
INFLAMMATION, ACUTE/CHRONIC		9 (18%)	5 (10%)
INFLAMMATION, CHRONIC		1 (2%)	
NECROSIS, NOS		13 (27%)	19 (38%)
NECROSIS, FOCAL	1 (2%)		1 (2%)
HYPERPLASIA, EPITHELIAL	1 (2%)	30 (61%)	37 (74%)
HYPERPLASIA, BASAL CELL		1 (2%)	
HYPERKERATOSIS	3 (6%)	40 (82%)	42 (84%)
ACANTHOSIS		1 (2%)	
METAPLASIA, INTESTINAL			1 (2%)
#GASTRIC MUCOSA	(47)	(49)	(50)
HYPERPLASIA, FOCAL		2 (4%)	
HYPERPLASIA, ADENOMATOUS	1 (2%)		
#GASTRIC SEROSA	(47)	(49)	(50)
INFLAMMATION, NECROTIZING	1 (2%)		
#PEYER'S PATCH	(45)	(44)	(45)
HYPERPLASIA, NOS	14 (31%)	4 (9%)	6 (13%)
#JEJUNUM	(45)	(44)	(45)
HYPERPLASIA, ADENOMATOUS		1 (2%)	
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
MINERALIZATION	8 (16%)	18 (36%)	30 (60%)
INFLAMMATION, NOS			1 (2%)
INFLAMMATION, ACUTE		1 (2%)	1 (2%)
INFLAMMATION, CHRONIC	1 (2%)		
FIBROSIS, DIFFUSE		1 (2%)	
NEPHROPATHY	8 (16%)	8 (16%)	14 (28%)
METAMORPHOSIS FATTY			1 (2%)
#RENAL PAPILLA	(50)	(50)	(50)
MINERALIZATION			1 (2%)
NECROSIS, NOS	1 (2%)		
#KIDNEY/TUBULE	(50)	(50)	(50)
DEGENERATION, NOS		1 (2%)	

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
NECROSIS, FOCAL			1 (2%)
#URINARY BLADDER	(47)	(48)	(49)
EDEMA, NOS		1 (2%)	
INFLAMMATION, NOS		1 (2%)	
INFLAMMATION, ACUTE/CHRONIC	1 (2%)		
*PROSTATIC URETHRA	(50)	(50)	(50)
HYPERPLASIA, EPITHELIAL			1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(44)	(42)	(40)
HYPERPLASIA, FOCAL	1 (2%)		
#ADRENAL	(47)	(50)	(48)
HYPERPLASIA, NOS	16 (34%)	11 (22%)	16 (33%)
#ADRENAL CORTEX	(47)	(50)	(48)
HYPERTROPHY, FOCAL	5 (11%)	3 (6%)	3 (6%)
#ADRENAL MEDULLA	(47)	(50)	(48)
HYPERPLASIA, NOS	6 (13%)	6 (12%)	2 (4%)
HYPERPLASIA, FOCAL		1 (2%)	
#THYROID	(46)	(49)	(47)
INFLAMMATION, CHRONIC	1 (2%)		
REPRODUCTIVE SYSTEM			
*PENIS	(50)	(50)	(50)
MINERALIZATION	1 (2%)		
EPIDERMAL INCLUSION CYST	1 (2%)		
HYPERPLASIA, EPITHELIAL	1 (2%)		
*PREPUTIAL GLAND	(50)	(50)	(50)
MINERALIZATION	1 (2%)	1 (2%)	
INFLAMMATION, NOS	1 (2%)	1 (2%)	
INFLAMMATION, NECROTIZING	1 (2%)		
INFLAMMATION, ACUTE/CHRONIC			1 (2%)
INFLAMMATION, CHRONIC SUPPURATIV			1 (2%)
NECROSIS, NOS		1 (2%)	1 (2%)
#PROSTATE	(44)	(46)	(45)
INFLAMMATION, NOS	2 (5%)	2 (4%)	

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
INFLAMMATION, ACUTE		1 (2%)	
*SEMINAL VESICLE	(50)	(50)	(50)
INFLAMMATION, NOS		2 (4%)	
INFLAMMATION, ACUTE		2 (4%)	
#TESTIS	(45)	(49)	(48)
MINERALIZATION	4 (9%)	4 (8%)	
SPERMATOCELE	1 (2%)		
INFLAMMATION, NOS		1 (2%)	
ATROPHY, NOS	2 (4%)		1 (2%)
#TESTIS/TUBULE	(45)	(49)	(48)
DEGENERATION, NOS	1 (2%)		
ATROPHY, FOCAL		3 (6%)	2 (4%)
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*PERITONEUM	(50)	(50)	(50)
INFLAMMATION, NOS			1 (2%)
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
INFLAMMATION, NOS	1 (2%)		
OMENTUM			
MINERALIZATION		2	1

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
STEATITIS			1
NECROSIS, FAT		2	1
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	1	3	1
AUTO/NECROPSY/HISTO PERF	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 DIGLYCIDYL RESORCINOL ETHER 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	49	50	50
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE	(50)	(50)	(50)
INFLAMMATION, NECROTIZING	2 (4%)		2 (4%)
ABSCESS, NOS	1 (2%)		
NECROSIS, NOS	1 (2%)		
RESPIRATORY SYSTEM			
#TRACHEA	(49)	(50)	(50)
INFLAMMATION, FOCAL		1 (2%)	
#LUNG/BRONCHUS	(49)	(50)	(50)
INFLAMMATION, ACUTE		1 (2%)	1 (2%)
INFLAMMATION, ACUTE FOCAL			1 (2%)
#LUNG	(49)	(50)	(50)
MINERALIZATION			1 (2%)
HEMORRHAGE	1 (2%)		
BRONCHOPNEUMONIA, NOS		1 (2%)	4 (8%)
INFLAMMATION, NOS	7 (14%)	9 (18%)	12 (24%)
INFLAMMATION, HEMORRHAGIC	1 (2%)		
INFLAMMATION, NECROTIZING	3 (6%)		
INFLAMMATION, ACUTE	4 (8%)	7 (14%)	10 (20%)
HYPERPLASIA, EPITHELIAL	1 (2%)	2 (4%)	
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
HEMATOPOIESIS	5 (10%)	5 (10%)	6 (12%)
#BONE MARROW	(41)	(46)	(45)
HYPERPLASIA, 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
MYELOFIBROSIS			1 (2%)
HYPERPLASIA, HEMATOPOIETIC		2 (4%)	3 (7%)
HEMATOPOIESIS			2 (4%)
#SPLEEN	(48)	(48)	(49)
NECROSIS, NOS		1 (2%)	1 (2%)
LYMPHOID DEPLETION	8 (17%)	3 (6%)	9 (18%)
HEMATOPOIESIS	30 (63%)	26 (54%)	29 (59%)
#LYMPH NODE	(46)	(44)	(44)
HEMORRHAGE			1 (2%)
INFLAMMATION, NOS	8 (17%)	4 (9%)	6 (14%)
ABSCESS, NOS	1 (2%)	1 (2%)	
NECROSIS, NOS		2 (5%)	
LYMPHOID DEPLETION	1 (2%)	4 (9%)	2 (5%)
ANGIECTASIS	1 (2%)	2 (5%)	2 (5%)
PLASMACYTOSIS	5 (11%)	5 (11%)	4 (9%)
HYPERPLASIA, RETICULUM CELL	1 (2%)	1 (2%)	2 (5%)
HYPERPLASIA, LYMPHOID	1 (2%)		2 (5%)
HEMATOPOIESIS	11 (24%)	8 (18%)	9 (20%)
#LIVER	(48)	(50)	(49)
HEMATOPOIESIS	16 (33%)	17 (34%)	7 (14%)
#THYMUS	(15)	(14)	(11)
ABSCESS, NOS		1 (7%)	
CIRCULATORY SYSTEM			
#LYMPH NODE	(46)	(44)	(44)
THROMBOSIS, NOS		1 (2%)	
#HEART	(47)	(50)	(50)
MINERALIZATION		1 (2%)	
ENDOCARDITIS, BACTERIAL	1 (2%)		1 (2%)
INFLAMMATION, NOS	3 (6%)	2 (4%)	
INFLAMMATION, ACUTE			1 (2%)
#MYOCARDIUM	(47)	(50)	(50)
DEGENERATION, NOS	2 (4%)	4 (8%)	2 (4%)
*ARTERY	(50)	(50)	(50)
PERIVASCULITIS			1 (2%)

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
*INTESTINAL TRACT	(50)	(50)	(50)
CONGESTION, PASSIVE		1 (2%)	
HEMORRHAGE		1 (2%)	
INFLAMMATION, NECROTIZING	1 (2%)		
#LIVER	(48)	(50)	(49)
HEMORRHAGE		1 (2%)	1 (2%)
INFLAMMATION, NOS		1 (2%)	
INFLAMMATION, NECROTIZING			1 (2%)
FIBROSIS, FOCAL	1 (2%)		
NECROSIS, NOS	1 (2%)	1 (2%)	
NECROSIS, FOCAL	6 (13%)	7 (14%)	5 (10%)
NECROSIS, ISCHEMIC	1 (2%)	5 (10%)	4 (8%)
NECROSIS, FIBRINOID	1 (2%)		
NECROSIS, HEMORRHAGIC		2 (4%)	
METAMORPHOSIS FATTY	5 (10%)	3 (6%)	3 (6%)
BASOPHILIC CYTO CHANGE			1 (2%)
FOCAL CELLULAR CHANGE	1 (2%)	1 (2%)	1 (2%)
ANGIECTASIS			1 (2%)
*GALLBLADDER	(50)	(50)	(50)
INFLAMMATION, NOS		1 (2%)	
#PANCREAS	(46)	(44)	(45)
INFLAMMATION, NECROTIZING			1 (2%)
INFLAMMATION, ACUTE/CHRONIC			1 (2%)
#PANCREATIC ACINUS	(46)	(44)	(45)
ATROPHY, NOS			3 (7%)
ATROPHY, FOCAL	1 (2%)		
#STOMACH	(47)	(49)	(49)
MINERALIZATION	1 (2%)	1 (2%)	1 (2%)
INFLAMMATION, NOS	3 (6%)	6 (12%)	9 (18%)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)	2 (4%)	7 (14%)
INFLAMMATION, CHRONIC	1 (2%)	1 (2%)	
NECROSIS, NOS	1 (2%)	4 (8%)	12 (24%)
NECROSIS, FOCAL	2 (4%)		2 (4%)
HYPERPLASIA, EPITHELIAL	3 (6%)	25 (51%)	26 (53%)
HYPERKERATOSIS	11 (23%)	31 (63%)	46 (94%)
ACANTHOSIS		1 (2%)	3 (6%)
METAPLASIA, INTESTINAL			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
#PEYER'S PATCH	(41)	(44)	(39)
HYPERPLASIA, NOS	8 (20%)	3 (7%)	2 (5%)
URINARY SYSTEM			
#KIDNEY	(48)	(50)	(50)
MINERALIZATION	1 (2%)	4 (8%)	2 (4%)
INFLAMMATION, NOS	3 (6%)	4 (8%)	
INFLAMMATION, NECROTIZING	1 (2%)	1 (2%)	
INFLAMMATION, ACUTE	2 (4%)		
INFLAMMATION, ACUTE FOCAL		1 (2%)	
INFLAMMATION, ACUTE/CHRONIC	1 (2%)	1 (2%)	2 (4%)
INFLAMMATION, CHRONIC			1 (2%)
NEPHROPATHY	9 (19%)	16 (32%)	11 (22%)
GLOMERULOSCLEROSIS, NOS		2 (4%)	
#RENAL PAPILLA	(48)	(50)	(50)
MINERALIZATION		1 (2%)	1 (2%)
NECROSIS, NOS	2 (4%)	2 (4%)	2 (4%)
#KIDNEY/TUBULE	(48)	(50)	(50)
DEGENERATION, NOS			1 (2%)
#URINARY BLADDER	(48)	(49)	(50)
INFLAMMATION, NOS	2 (4%)		2 (4%)
ENDOCRINE SYSTEM			
#PITUITARY	(39)	(40)	(37)
DILATATION, NOS	2 (5%)	1 (3%)	2 (5%)
HYPERPLASIA, FOCAL		1 (3%)	1 (3%)
#ADRENAL	(47)	(43)	(47)
DILATATION, NOS			1 (2%)
HYPERPLASIA, NOS	25 (53%)	21 (49%)	23 (49%)
#ADRENAL CORTEX	(47)	(43)	(47)
HYPERTROPHY, FOCAL		1 (2%)	
#THYROID	(45)	(45)	(42)
HYPERPLASIA, FOLLICULAR-CELL		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
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
GALACTOCELE			1 (2%)
#UTERUS	(49)	(50)	(49)
HYDROMETRA	5 (10%)	8 (16%)	6 (12%)
HEMORRHAGE	1 (2%)		
INFLAMMATION, NOS	3 (6%)	4 (8%)	6 (12%)
PYOMETRA			1 (2%)
INFLAMMATION, NECROTIZING	7 (14%)	2 (4%)	5 (10%)
INFLAMMATION, ACUTE		1 (2%)	
ABSCESS, NOS	1 (2%)		
NECROSIS, FOCAL	1 (2%)		
#UTERUS/ENDOMETRIUM	(49)	(50)	(49)
INFLAMMATION, NOS	2 (4%)		
HYPERPLASIA, NOS	5 (10%)	3 (6%)	10 (20%)
HYPERPLASIA, CYSTIC	15 (31%)	6 (12%)	5 (10%)
#OVARY	(33)	(41)	(40)
MINERALIZATION			1 (3%)
INFLAMMATION, NECROTIZING	4 (12%)	5 (12%)	5 (13%)
ABSCESS, NOS		1 (2%)	
INFLAMMATION, ACUTE/CHRONIC	1 (3%)		1 (3%)
INFLAMMATION, CHRONIC			1 (3%)
ANGIECTASIS			1 (3%)
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
*COSTOCHONDRAL SYNCHO	(50)	(50)	(50)
INFLAMMATION, NECROTIZING			1 (2%)
*SKELETAL MUSCLE	(50)	(50)	(50)
INFLAMMATION, NECROTIZING		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
BODY CAVITIES			
*THORACIC CAVITY	(50)	(50)	(50)
INFLAMMATION, NECROTIZING	2 (4%)	3 (6%)	2 (4%)
INFLAMMATION, FIBRINOID	1 (2%)		1 (2%)
*ABDOMINAL CAVITY	(50)	(50)	(50)
HEMORRHAGE	1 (2%)		
INFLAMMATION, NECROTIZING	13 (26%)	12 (24%)	8 (16%)
INFLAMMATION, ACUTE NECROTIZING			1 (2%)
ABSCESS, NOS	1 (2%)	3 (6%)	2 (4%)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)		
FIBROSIS	3 (6%)	3 (6%)	2 (4%)
NECROSIS, NOS			1 (2%)
*PERITONEUM	(50)	(50)	(50)
INFLAMMATION, NOS	13 (26%)	7 (14%)	12 (24%)
INFLAMMATION, NECROTIZING			1 (2%)
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
INFLAMMATION, NOS	2 (4%)	4 (8%)	2 (4%)
INFLAMMATION, NECROTIZING	1 (2%)	1 (2%)	1 (2%)
ADIPOSE TISSUE			
INFLAMMATION, NECROTIZING		1	
OMENTUM			
MINERALIZATION		1	
NECROSIS, FAT		1	
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED		6	1
AUTO/NECROPSY/NO HISTO	1		

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

APPENDIX E

ANALYSES OF PRIMARY TUMORS IN RATS AND MICE ADMINISTERED DIGLYCIDYL RESORCINOL ETHER IN CORN OIL BY GAVAGE

TABLE E1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS

	Vehicle Control	25 mg/kg	50 mg/kg
Lung: Alveolar/Bronchiolar Adenoma			
Tumor Rates			
Overall *(a)*	3/50 (6%)	0/49 (0%)	0/50 (0%)
Adjusted *(b)*	7.1%	0.0%	0.0%
Terminal *(c)*	3/42 (7%)	0/5 (0%)	0/0
Statistical Tests *(d)*			
Life Table	P=0.635N	P=0.635N	*(e)*
Cochran-Armitage Trend Test	P=0.038N		
Fisher Exact Test		P=0.125N	P=0.122N
Lung: Alveolar/Bronchiolar Carcinoma			
Overall *(a)*	1/50 (2%)	1/49 (2%)	0/50 (0%)
Hematopoietic System: Myelomonocytic Leukemia			
Tumor Rates			
Overall *(a)*	4/50 (8%)	2/50 (4%)	0/50 (0%)
Adjusted *(b)*	8.8%	26.7%	0.0%
Terminal *(c)*	2/42 (5%)	1/5 (20%)	0/0
Statistical Tests *(d)*			
Life Table	P=0.393	P=0.356	P=0.946N
Cochran-Armitage Trend Test	P=0.037N		
Fisher Exact Test		P=0.339N	P=0.059N
Hematopoietic System: All Leukemia			
Tumor Rates			
Overall *(a)*	5/50 (10%)	2/50 (4%)	0/50 (0%)
Adjusted *(b)*	11.1%	26.7%	0.0%
Terminal *(c)*	3/42 (7%)	1/5 (20%)	0/0
Statistical Tests *(d)*			
Life Table	P=0.438	P=0.404	P=0.946N
Cochran-Armitage Trend Test	P=0.016N		
Fisher Exact Test		P=0.218N	P=0.029N
Stomach: Squamous Cell Papilloma			
Tumor Rates			
Overall *(a)*	0/50 (0%)	17/50 (34%)	6/49 (12%)
Adjusted *(b)*	0.0%	40.9%	33.5%
Terminal *(c)*	0/42 (0%)	0/5 (0%)	0/0
Statistical Tests *(d)*			
Life Table	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test	P=0.058		
Fisher Exact Test		P<0.001	P=0.012
Stomach: Squamous Cell Carcinoma			
Tumor Rates			
Overall *(a)*	0/50 (0%)	38/50 (76%)	4/49 (8%)
Adjusted *(b)*	0.0%	100%	100%
Terminal *(c)*	0/42 (0%)	5/5 (100%)	0/0
Statistical Tests *(d)*			
Life Table	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test	P=0.199		
Fisher Exact Test		P<0.001	P=0.056

TABLE E1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS (Continued)

	Vehicle Control	25 mg/kg	50 mg/kg
Pituitary: Adenoma			
Tumor Rates			
Overall *(a)*	17/49 (35%)	8/48 (17%)	2/47 (4%)
Adjusted *(b)*	40.5%	56.3%	60.0%
Terminal *(c)*	17/42 (40%)	2/5 (40%)	0/0
Statistical Tests *(d)*			
Life Table	P<0.001	P=0.015	P<0.001
Cochran-Armitage Trend Test	P<0.001N		
Fisher Exact Test		P=0.036N	P<0.001N
Pituitary: Carcinoma			
Overall *(a)*	0/49 (0%)	1/48 (2%)	0/47 (0%)
Adrenal: Pheochromocytoma			
Tumor Rates			
Overall *(a)*	11/50 (22%)	4/50 (8%)	0/50 (0%)
Adjusted *(b)*	26.2%	27.5%	0.0%
Terminal *(c)*	11/42 (26%)	0/5 (0%)	0/0
Statistical Tests *(d)*			
Life Table	P=0.202	P=0.164	*(e)*
Cochran-Armitage Trend Test	P<0.001N		
Fisher Exact Test		P=0.045N	P<0.001N
Adrenal: Malignant Pheochromocytoma			
Overall *(a)*	1/50 (2%)	0/50 (0%)	0/50 (0%)
Thyroid: C-Cell Adenoma			
Tumor Rates			
Overall *(a)*	3/47 (6%)	0/47 (0%)	0/46 (0%)
Adjusted *(b)*	7.7%	0.0%	0.0%
Terminal *(c)*	3/39 (8%)	0/4 (0%)	0/0
Statistical Tests *(d)*			
Life Table	P=0.674N	P=0.674N	*(e)*
Cochran-Armitage Trend Test	P=0.038N		
Fisher Exact Test		P=0.121N	P=0.125N
Thyroid: C-Cell Adenonoma or Carcinoma			
Tumor Rates			
Overall *(a)*	4/47 (9%)	0/47 (0%)	0/46 (0%)
Adjusted *(b)*	10.3%	0.0%	0.0%
Terminal *(c)*	4/39 (10%)	0/4 (0%)	0/0 (0%)
Statistical Tests *(d)*			
Life Table	P=0.590N	P=0.590N	*(e)*
Cochran-Armitage Trend Test	P=0.015N		
Fisher Exact Test		P=0.059N	P=0.061N
Pancreatic Islets: Islet Cell Carcinoma			
Tumor Rates			
Overall *(a)*	3/49 (6%)	0/44 (0%)	0/47 (0%)
Adjusted *(b)*	7.3%	0.0%	0.0%
Terminal *(c)*	3/41 (7%)	0/4 (0%)	0/0
Statistical Tests *(d)*			
Life Table	P=0.686N	P=0.686N	*(e)*
Cochran-Armitage Trend Test	P=0.042N		
Fisher Exact Test		P=0.142N	P=0.129N

TABLE E1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS (Continued)

	Vehicle Control	25 mg/kg	50 mg/kg
Pancreatic Islets: Islet Cell Adenoma			
Overall *(a)*	2/49 (4%)	1/44 (2%)	0/47 (0%)
Testis: Interstitial Cell Tumor			
Tumor Rates			
Overall *(a)*	47/50 (94%)	39/49 (80%)	11/50 (22%)
Adjusted *(b)*	95.9%	100.0%	100.0%
Terminal *(c)*	40/42 (95%)	5/5 (100%)	0/0
Statistical Tests *(d)*			
Life Table	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test	P<0.001N		
Fisher Exact Test		P=0.033N	P<0.001N

(a) Number of tumor bearing animals/number of animals examined at the site.

(b) Kaplan-Meier estimated tumor incidence at the end of the study 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 meaningful comparison is possible. All tumors in controls were observed in animals that died or were killed after the last high-dose animal died.

TABLE E2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS

	Vehicle Control	25 mg/kg	50 mg/kg
Hematopoietic System: Myelomonocytic Leukemia			
Tumor Rates			
Overall *(a)*	5/50 (10%)	2/50 (4%)	0/50 (0%)
Adjusted *(b)*	12.6%	7.7%	0.0%
Terminal *(c)*	4/37 (11%)	0/16 (0%)	0/1 (0%)
Statistical Tests *(d)*			
Life Table	P=0.468N	P=0.533N	P=0.836N
Cochran-Armitage Trend Test	P=0.016N		
Fisher Exact Test		P=0.218N	P=0.029N
Hematopoietic System: All Leukemia			
Tumor Rates			
Overall *(a)*	6/50 (12%)	4/50 (8%)	0/50 (0%)
Adjusted *(b)*	15.3%	17.6%	0.0%
Terminal *(c)*	5/37 (14%)	1/16 (6%)	0/1 (0%)
Statistical Tests *(d)*			
Life Table	P=0.542	P=0.463	P=0.801N
Cochran-Armitage Trend Test	P=0.014N		
Fisher Exact Test		P=0.371N	P=0.014N
Stomach: Squamous Cell Papilloma			
Tumor Rates			
Overall *(a)*	0/49 (0%)	7/50 (14%)	1/50 (2%)
Adjusted *(b)*	0.0%	24.2%	14.3%
Terminal *(c)*	0/36 (0%)	1/16 (6%)	0/1 (0%)
Statistical Tests *(d)*			
Life Table	P<0.001	P=0.002	P=0.125
Cochran-Armitage Trend Test	P=0.421		
Fisher Exact Test		P=0.007	P=0.505
Stomach: Squamous Cell Carcinoma			
Tumor Rates			
Overall *(a)*	0/49 (0%)	34/50 (68%)	3/50 (6%)
Adjusted *(b)*	0.0%	97.0%	100.0%
Terminal *(c)*	0/36 (0%)	15/16 (94%)	1/1 (100%)
Statistical Tests *(d)*			
Life Table	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test	P=0.300		
Fisher Exact Test		P<0.001	P=0.125
Pituitary: Adenoma			
Tumor Rates			
Overall *(a)*	18/50 (36%)	8/49 (16%)	1/47 (2%)
Adjusted *(b)*	43.4%	42.5%	4.2%
Terminal *(c)*	14/37 (38%)	5/15 (33%)	0/1 (0%)
Statistical Tests *(d)*			
Life Table	P=0.519	P=0.595N	P=0.650
Cochran-Armitage Trend Test	P<0.001N		
Fisher Exact Test		P=0.022N	P<0.001N

TABLE E2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS (Continued)

	Vehicle Control	25 mg/kg	50 mg/kg
Pituitary: Carcinoma			
Overall *(a)*	1/50 (2%)	1/49 (2%)	0/47 (0%)
Adrenal: Pheochromocytoma			
Tumor Rates			
Overall *(a)*	3/50 (6%)	0/48 (0%)	0/49 (0%)
Adjusted *(b)*	8.1%	0.0%	0.0%
Terminal *(c)*	3/37 (8%)	0/16 (0%)	0/1 (0%)
Statistical Tests *(d)*			
Life Table	P=0.282N	P=0.301N	P=0.941N
Cochran-Armitage Trend Test	P=0.039N		
Fisher Exact Test		P=0.129N	P=0.125N
Adrenal: Malignant Pheochromocytoma			
Overall *(a)*	0/50 (0%)	1/48 (2%)	0/49 (0%)
Thyroid: C-Cell Adenoma or Carcinoma			
Tumor Rates			
Overall *(a)*	3/50 (6%)	0/47 (0%)	0/41 (0%)
Adjusted *(b)*	8.1%	0.0%	0.0%
Terminal *(c)*	3/37 (8%)	0/16 (0%)	0/1 (0%)
Statistical Tests *(d)*			
Life Table	P=0.282N	P=0.301N	P=0.941N
Cochran-Armitage Trend Test	P=0.048N		
Fisher Exact Test		P=0.134N	P=0.162N
Mammary Gland: Fibroadenoma			
Tumor Rates			
Overall *(a)*	18/50 (36%)	8/50 (16%)	0/50 (0%)
Adjusted *(b)*	43.5%	39.2%	0.0%
Terminal *(c)*	14/37 (38%)	5/16 (31%)	0/1 (0%)
Statistical Tests *(d)*			
Life Table	P=0.384N	P=0.522N	P=0.528N
Cochran-Armitage Trend Test	P<0.001N		
Fisher Exact Test		P=0.020N	P<0.001N
Uterus: Endometrial Stromal Polyp			
Tumor Rates			
Overall *(a)*	11/50 (22%)	7/50 (14%)	1/50 (2%)
Adjusted *(b)*	27.1%	26.9%	2.6%
Terminal *(c)*	8/37 (22%)	3/16 (19%)	0/1 (0%)
Statistical Tests *(d)*			
Life Table	P=0.376	P=0.438	P=0.624
Cochran-Armitage Trend Test	P=0.002N		
Fisher Exact Test		P=0.218N	P=0.002N

(a) Number of tumor bearing animals number of animals examined at the site.
(b) Kaplan-Meier estimated tumor incidence at the end of the study 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 E3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE

	Vehicle Control	50 mg/kg	100 mg/kg
Subcutaneous Tissue: Fibroma			
Tumor Rates			
Overall *(a)*	4/50 (8%)	3/50 (6%)	1/50 (2%)
Adjusted *(b)*	13.3%	11.5%	2.9%
Terminal *(c)*	4/30 (13%)	3/26 (12%)	1/34 (3%)
Statistical Tests *(d)*			
Life Table	P=0.106N	P=0.580N	P=0.142N
Incidental Tumor Test	P=0.106N	P=0.580N	P=0.142N
Cochran-Armitage Trend Test	P=0.133N		
Fisher Exact Test		P=0.500N	P=0.181N
Subcutaneous Tissue: Fibrosarcoma			
Tumor Rates			
Overall *(a)*	4/50 (8%)	3/50 (6%)	2/50 (4%)
Adjusted *(b)*	11.3%	8.9%	5.9%
Terminal *(c)*	1/30 (3%)	1/26 (4%)	2/34 (6%)
Statistical Tests *(d)*			
Life Table	P=0.235N	P=0.527N	P=0.301N
Incidental Tumor Test	P=0.254N	P=0.496N	P=0.351N
Cochran-Armitage Trend Test	P=0.264N		
Fisher Exact Test		P=0.500N	P=0.339N
Subcutaneous Tissue: Sarcoma, NOS			
Tumor Rates			
Overall *(a)*	3/50 (6%)	0/50 (0%)	0/50 (0%)
Adjusted *(b)*	9.7%	0.0%	0.0%
Terminal *(c)*	2/30 (7%)	0/26 (0%)	0/34 (0%)
Statistical Tests *(d)*			
Life Table	P=0.036N	P=0.151N	P=0.103N
Incidental Tumor Test	P=0.031N	P=0.090N	P=0.124N
Cochran-Armitage Trend Test	P=0.037N		
Fisher Exact Test		P=0.122N	P=0.122N
Subcutaneous Tissue: Fibroma, Fibrosarcoma or Sarcoma, NOS			
Tumor Rates			
Overall *(a)*	11/50 (22%)	6/50 (12%)	3/50 (6%)
Adjusted *(b)*	31.9%	19.8%	8.8%
Terminal *(c)*	7/30 (23%)	4/26 (15%)	3/34 (9%)
Statistical Tests *(d)*			
Life Table	P=0.010N	P=0.211N	P=0.014N
Incidental Tumor Test	P=0.010N	P=0.151N	P=0.017N
Cochran-Armitage Trend Test	P=0.014N		
Fisher Exact Test		P=0.144N	P=0.021N
Lung: Alveolar/Bronchiolar Adenoma			
Tumor Rates			
Overall *(a)*	6/50 (12%)	2/50 (4%)	8/49 (16%)
Adjusted *(b)*	19.4%	6.4%	22.7%
Terminal *(c)*	5/30 (17%)	1/26 (4%)	7/34 (21%)
Statistical Tests *(d)*			
Life Table	P=0.396	P=0.183N	P=0.481
Incidental Tumor Test	P=0.359	P=0.153N	P=0.437
Cochran-Armitage Trend Test	P=0.301		
Fisher Exact Test		P=0.135N	P=0.371

TABLE E3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE (Continued)

	Vehicle Control	50 mg/kg	100 mg/kg
Hematopoietic System: Malignant Lymphoma, Histiocytic Type			
Tumor Rates			
Overall *(a)*	3/50 (6%)	3/50 (6%)	0/50 (0%)
Adjusted *(b)*	8.9%	8.5%	0.0%
Terminal *(c)*	2/30 (7%)	1/26 (4%)	0/34 (0%)
Statistical Tests *(d)*			
Life Table	P=0.091N	P=0.621	P=0.103N
Incidental Tumor Test	P=0.091N	P=0.662	P=0.108N
Cochran-Armitage Trend Test	P=0.101N		
Fisher Exact Test		P=0.661N	P=0.122N
Hematopoietic System: Lymphoma, All Malignant			
Tumor Rates			
Overall *(a)*	6/50 (12%)	6/50 (12%)	6/50 (12%)
Adjusted *(b)*	16.7%	19.5%	17.6%
Terminal *(c)*	3/30 (10%)	4/26 (15%)	6/34 (18%)
Statistical Tests *(d)*			
Life Table	P=0.474N	P=0.550	P=0.537N
Incidental Tumor Test	P=0.491N	P=0.538	P=0.553N
Cochran-Armitage Trend Test	P=0.561		
Fisher Exact Test		P=0.620N	P=0.620N
Circulatory System: Hemangioma			
Tumor Rates			
Overall *(a)*	1/50 (2%)	4/50 (8%)	1/50 (2%)
Adjusted *(b)*	3.3%	14.8%	2.9%
Terminal *(c)*	1/30 (3%)	3/26 (12%)	1/34 (3%)
Statistical Tests *(d)*			
Life Table	P=0.550N	P=0.139	P=0.734N
Incidental Tumor Test	P=0.569N	P=0.188	P=0.734N
Cochran-Armitage Trend Test	P=0.601		
Fisher Exact Test		P=0.181	P=0.753N
Liver: Adenoma			
Tumor Rates			
Overall *(a)*	7/49 (14%)	7/50 (14%)	5/50 (10%)
Adjusted *(b)*	22.0%	25.3%	12.8%
Terminal *(c)*	6/30 (20%)	6/26 (23%)	3/34 (9%)
Statistical Tests *(d)*			
Life Table	P=0.252N	P=0.517	P=0.304N
Incidental Tumor Test	P=0.249N	P=0.539	P=0.284N
Cochran-Armitage Trend Test	P=0.312N		
Fisher Exact Test		P=0.597N	P=0.366N
Liver: Carcinoma			
Tumor Rates			
Overall *(a)*	7/49 (14%)	11/50 (22%)	6/50 (12%)
Adjusted *(b)*	20.1%	37.6%	16.6%
Terminal *(c)*	4/30 (13%)	8/26 (31%)	5/34 (15%)
Statistical Tests *(d)*			
Life Table	P=0.350N	P=0.155	P=0.409N
Incidental Tumor Test	P=0.369N	P=0.232	P=0.400N
Cochran-Armitage Trend Test	P=0.428N		
Fisher Exact Test		P=0.232	P=0.484N

TABLE E3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE (Continued)

	Vehicle Control	50 mg/kg	100 mg/kg
Liver: Adenoma or Carcinoma			
Tumor Rates			
Overall *(a)*	13/49 (27%)	18/50 (36%)	11/50 (22%)
Adjusted *(b)*	37.0%	59.7%	28.5%
Terminal *(c)*	9/30 (30%)	14/26 (54%)	8/34 (24%)
Statistical Tests *(d)*			
Life Table	P=0.246N	P=0.107	P=0.293N
Incidental Tumor Test	P=0.253N	P=0.161	P=0.262N
Cochran-Armitage Trend Test	P=0.345N		
Fisher Exact Test		P=0.212	P=0.386N
Stomach: Squamous Cell Papilloma or Papillomatosis			
Tumor Rates			
Overall *(a)*	0/47 (0%)	4/49 (8%)	10/50 (20%)
Adjusted *(b)*	0.0%	14.0%	29.4%
Terminal *(c)*	0/30 (0%)	3/26 (12%)	10/34 (29%)
Statistical Tests *(d)*			
Life Table	P=0.001	P=0.051	P=0.002
Incidental Tumor Test	P=0.001	P=0.041	P=0.002
Cochran-Armitage Trend Test	P=0.001		
Fisher Exact Test		P=0.064	P=0.001
Stomach: Squamous Cell Carcinoma			
Tumor Rates			
Overall *(a)*	0/47 (0%)	14/49 (29%)	25/50 (50%)
Adjusted *(b)*	0.0%	40.7%	55.5%
Terminal *(c)*	0/30 (0%)	7/26 (27%)	14/34 (41%)
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
Stomach: Papillomatosis, Squamous Cell Papilloma or Carcinoma			
Tumor Rates			
Overall *(a)*	0/47 (0%)	17/49 (35%)	33/50 (66%)
Adjusted *(b)*	0.0%	50.0%	73.3%
Terminal *(c)*	0/30 (0%)	10/26 (38%)	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
Adrenal: Pheochromocytoma			
Tumor Rates			
Overall *(a)*	1/47 (2%)	0/50 (0%)	3/48 (6%)
Adjusted *(b)*	3.3%	0.0%	7.9%
Terminal *(c)*	1/30 (3%)	0/26 (0%)	2/34 (6%)
Statistical Tests *(d)*			
Life Table	P=0.209	P=0.529N	P=0.346
Incidental Tumor Test	P=0.201	P=0.529N	P=0.340
Cochran-Armitage Trend Test	P=0.178		
Fisher Exact Test		P=0.485N	P=0.316

TABLE E3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE (Continued)

	Vehicle Control	50 mg/kg	100 mg/kg
Harderian Gland: Adenoma			
Tumor Rates			
Overall *(a)*	3/50 (6%)	2/50 (4%)	2/50 (4%)
Adjusted *(b)*	10.0%	7.7%	5.9%
Terminal *(c)*	3/30 (10%)	2/26 (8%)	2/34 (6%)
Statistical Tests *(d)*			
Life Table	P=0.353N	P=0.566N	P=0.442N
Incidental Tumor Test	P=0.353N	P=0.566N	P=0.442N
Cochran-Armitage Trend Test	P=0.406N		
Fisher Exact Test		P=0.500N	P=0.500N

(a) Number of tumor bearing animals/number of animals examined at the site.

(b) Kaplan-Meier estimated tumor incidence at the end of the study 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 E4. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE

	Vehicle Control	50 mg/kg	100 mg/kg
Lung: Alveolar/Bronchiolar Adenoma			
Tumor Rates			
Overall *(a)*	3/49 (6%)	3/50 (6%)	2/50 (4%)
Adjusted *(b)*	12.7%	14.5%	13.9%
Terminal *(c)*	2/20 (10%)	1/13 (8%)	1/10 (10%)
Statistical Tests *(d)*			
Life Table	P=0.558	P=0.510	P=0.651
Incidental Tumor Test	P=0.382N	P=0.532	P=0.570N
Cochran-Armitage Trend Test	P=0.402N		
Fisher Exact Test		P=0.652N	P=0.491N
Hematopoietic System: Malignant Lymphoma, Lymphocytic Type			
Tumor Rates			
Overall *(a)*	3/50 (6%)	2/50 (4%)	0/50 (0%)
Adjusted *(b)*	11.4%	10.2%	0.0%
Terminal *(c)*	1/20 (5%)	0/13 (0%)	0/10 (0%)
Statistical Tests *(d)*			
Life Table	P=0.155N	P=0.621N	P=0.212N
Incidental Tumor Test	P=0.036N	P=0.487N	P=0.079N
Cochran-Armitage Trend Test	P=0.082N		
Fisher Exact Test		P=0.500N	P=0.122N
Hematopoietic System: Malignant Lymphoma, Mixed Type			
Tumor Rates			
Overall *(a)*	4/50 (8%)	3/50 (6%)	0/50 (0%)
Adjusted *(b)*	20.0%	16.4%	0.0%
Terminal *(c)*	4/20 (20%)	1/13 (8%)	0/10 (0%)
Statistical Tests *(d)*			
Life Table	P=0.161N	P=0.618	P=0.175N
Incidental Tumor Test	P=0.096N	P=0.606N	P=0.175N
Cochran-Armitage Trend Test	P=0.049N		
Fisher Exact Test		P=0.500N	P=0.059N
Hematopoietic System: Lymphoma, All Malignant			
Tumor Rates			
Overall *(a)*	17/50 (34%)	9/50 (18%)	3/50 (6%)
Adjusted *(b)*	55.6%	43.0%	24.0%
Terminal *(c)*	8/20 (40%)	3/13 (23%)	2/10 (20%)
Statistical Tests *(d)*			
Life Table	P=0.014N	P=0.246N	P=0.018N
Incidental Tumor Test	P<0.001N	P=0.064N	P=0.003N
Cochran-Armitage Trend Test	P<0.001N		
Fisher Exact Test		P=0.055N	P<0.001N
Liver: Adenoma			
Tumor Rates			
Overall *(a)*	3/48 (6%)	0/50 (0%)	5/49 (10%)
Adjusted *(b)*	15.8%	0.0%	31.0%
Terminal *(c)*	3/19 (16%)	0/13 (0%)	2/10 (20%)
Statistical Tests *(d)*			
Life Table	P=0.105	P=0.191N	P=0.135
Incidental Tumor Test	P=0.184	P=0.191N	P=0.253
Cochran-Armitage Trend Test	P=0.259		
Fisher Exact Test		P=0.114N	P=0.369

TABLE E4. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE (Continued)

	Vehicle Control	50 mg/kg	100 mg/kg
Liver: Carcinoma			
Tumor Rates			
Overall *(a)*	0/48 (0%)	1/50 (2%)	3/49 (6%)
Adjusted *(b)*	0.0%	6.2%	25.0%
Terminal *(c)*	0/19 (0%)	0/13 (0%)	2/10 (20%)
Statistical Tests *(d)*			
Life Table	P=0.019	P=0.446	P=0.041
Incidental Tumor Test	P=0.047	P=0.581	P=0.073
Cochran-Armitage Trend Test	P=0.061		
Fisher Exact Test		P=0.510	P=0.125
Liver: Adenoma or Carcinoma			
Tumor Rates			
Overall *(a)*	3/48 (6%)	1/50 (2%)	7/49 (14%)
Adjusted *(b)*	15.8%	6.2%	43.4%
Terminal *(c)*	3/19 (16%)	0/13 (0%)	3/10 (30%)
Statistical Tests *(d)*			
Life Table	P=0.019	P=0.437N	P=0.030
Incidental Tumor Test	P=0.061	P=0.370N	P=0.089
Cochran-Armitage Trend Test	P=0.093		
Fisher Exact Test		P=0.294N	P=0.167
Stomach: Squamous Cell Papilloma or Papillomatosis			
Tumor Rates			
Overall *(a)*	0/47 (0%)	5/49 (10%)	10/49 (12%)
Adjusted *(b)*	0.0%	33.4%	73.1%
Terminal *(c)*	0/20 (0%)	4/13 (31%)	7/10 (70%)
Statistical Tests *(d)*			
Life Table	P<0.001	P=0.009	P<0.001
Incidental Tumor Test	P<0.001	P=0.009	P<0.001
Cochran-Armitage Trend Test	P=0.001		
Fisher Exact Test		P=0.031	P=0.001
Stomach: Squamous Cell Carcinoma			
Tumor Rates			
Overall *(a)*	0/47 (0%)	12/49 (24%)	23/49 (47%)
Adjusted *(b)*	0.0%	53.3%	70.5%
Terminal *(c)*	0/20 (0%)	4/13 (31%)	2/10 (20%)
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
Stomach: Papillomatosis, Squamous Cell Papilloma or Carcinoma			
Tumor Rates			
Overall *(a)*	0/47 (0%)	17/49 (35%)	33/49 (67%)
Adjusted *(b)*	0.0%	75.1%	96.7%
Terminal *(c)*	0/20 (0%)	8/13 (62%)	9/10 (90%)
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

TABLE E4. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE (Continued)

	Vehicle Control	50 mg/kg	100 mg/kg
Pituitary: Adenoma			
Tumor Rates			
Overall *(a)*	7/39 (18%)	7/40 (18%)	3/37 (8%)
Adjusted *(b)*	35.3%	35.6%	25.2%
Terminal *(c)*	6/18 (33%)	3/13 (23%)	2/9 (22%)
Statistical Tests *(d)*			
Life Table	P=0.427N	P=0.391	P=0.473N
Incidental Tumor Test	P=0.259N	P=0.521	P=0.334N
Cochran-Armitage Trend Test	P=0.149N		
Fisher Exact Test		P=0.595N	P=0.177N

(a) Number of tumor bearing animals/number of animals examined at the site.

(b) Kaplan-Meier estimated tumor incidence at the end of the study after adjusting for intercurrent mortality.

(c) Observed tumor incidence at terminal kill.

(d) Beneath the control incidence are the P-values associated with the trend test. Beneath the dosed group incidence are the P-values corresponding to pairwise comparisons between that dosed group and the controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as non-fatal. The Cochran-Armitage and Fisher's exact tests compare directly the overall incidence rates. A negative trend or lower incidence is indicated by (N).

TABLE E5. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE SUPPLEMENTAL STUDY

	Vehicle Control	Dosed *(a)*
Subcutaneous Tissue: Fibroma		
Tumor Rates		
Overall *(b)*	4/50 (8%)	3/50 (6%)
Adjusted *(c)*	9.9%	10.7%
Terminal *(d)*	3/39 (8%)	2/23 (9%)
Statistical Tests *(e)*		
Life Table		P=0.589
Incidental Tumor Test		P=0.543N
Fisher Exact Test		P=0.500N
Subcutaneous Tissue: Neurofibrosarcoma		
Tumor Rates		
Overall *(b)*	0/50 (0%)	3/50 (6%)
Adjusted *(c)*	0.0%	9.5%
Terminal *(d)*	0/39 (0%)	1/23 (4%)
Statistical Tests *(e)*		
Life Table		P=0.078
Incidental Tumor Test		P=0.213
Fisher Exact Test		P=0.121
Hematopoietic System: All Leukemias		
Tumor Rates		
Overall *(b)*	6/50 (12%)	6/50 (12%)
Adjusted *(c)*	14.2%	16.1%
Terminal *(d)*	3/39 (8%)	1/23 (4%)
Statistical Tests *(e)*		
Life Table		P=0.400
Incidental Tumor Test		P=0.376N
Fisher Exact Test		P=0.620N
Hematopoietic System: All Lymphomas or Leukemias		
Tumor Rates		
Overall *(b)*	6/50 (12%)	7/50 (14%)
Adjusted *(c)*	14.2%	18.0%
Terminal *(d)*	3/39 (8%)	1/23 (4%)
Statistical Tests *(e)*		
Life Table		P=0.298
Incidental Tumor Test		P=0.431N
Fisher Exact Test		P=0.500
Hematopoietic System: Leukemia, Mononuclear Cell		
Tumor Rates		
Overall *(b)*	6/50 (12%)	6/50 (12%)
Adjusted *(c)*	14.2%	16.1%
Terminal *(d)*	3/39 (8%)	1/23 (4%)
Statistical Tests *(e)*		
Life Table		P=0.400
Incidental Tumor Test		P=0.376N
Fisher Exact Test		P=0.620N

TABLE E5. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE SUPPLEMENTAL STUDY (Continued)

	Vehicle Control	Dosed *(a)*
Forestomach: Squamous Cell Papilloma		
Tumor Rates		
Overall *(b)*	0/50 (0%)	16/50 (32%)
Adjusted *(c)*	0.0%	51.7%
Terminal *(d)*	0/39 (0%)	10/23 (43%)
Statistical Tests *(e)*		
Life Table		P<0.001
Incidental Tumor Test		P<0.001
Fisher Exact Test		P<0.001
Forestomach: Squamous Cell Carcinoma		
Tumor Rates		
Overall *(b)*	0/50 (0%)	39/50 (78%)
Adjusted *(c)*	0.0%	92.8%
Terminal *(d)*	0/39 (0%)	20/23 (87%)
Statistical Tests *(e)*		
Life Table		P<0.001
Incidental Tumor Test		P<0.001
Fisher Exact Test		P<0.001
Anterior Pituitary: Adenoma, NOS		
Tumor Rates		
Overall *(b)*	17/50 (34%)	14/48 (29%)
Adjusted *(c)*	41.3%	47.0%
Terminal *(d)*	15/39 (38%)	8/22 (36%)
Statistical Tests *(e)*		
Life Table		P=0.233
Incidental Tumor Test		P=0.538N
Fisher Exact Test		P=0.384N
Adrenal Medulla: Pheochromocytoma		
Tumor Rates		
Overall *(b)*	10/50 (20%)	10/49 (20%)
Adjusted *(c)*	25.0%	36.1%
Terminal *(d)*	9/39 (23%)	6/23 (26%)
Statistical Tests *(e)*		
Life Table		P=0.167
Incidental Tumor Test		P=0.399
Fisher Exact Test		P=0.579
Adrenal Medulla: Pheochromocytoma, Malignant		
Tumor Rates		
Overall *(b)*	1/50 (2%)	3/49 (6%)
Adjusted *(c)*	2.4%	13.0%
Terminal *(d)*	0/39 (0%)	3/23 (13%)
Statistical Tests *(e)*		
Life Table		P=0.151
Incidental Tumor Test		P=0.231
Fisher Exact Test		P=0.301

TABLE E5. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE SUPPLEMENTAL STUDY (*Continued*)

	Vehicle Control	Dosed *(a)*
Adrenal: All Sites: Pheochromocytoma		
Tumor Rates		
Overall *(b)*	11/50 (22%)	10/49 (20%)
Adjusted *(c)*	27.5%	36.1%
Terminal *(d)*	10/39 (26%)	6/23 (26%)
Statistical Tests *(e)*		
Life Table		P=0.221
Incidental Tumor Test		P=0.478
Fisher Exact Test		P=0.521N
Adrenal: All Sites: Pheochromocytoma or Pheochromocytoma, Malignant		
Tumor Rates		
Overall *(b)*	11/50 (22%)	13/49 (27%)
Adjusted *(c)*	27.5%	47.4%
Terminal *(d)*	10/39 (26%)	9/23 (39%)
Statistical Tests *(e)*		
Life Table		P=0.050
Incidental Tumor Test		P=0.155
Fisher Exact Test		P=0.385
Thyroid: C-Cell Adenoma		
Tumor Rates		
Overall *(b)*	9/50 (18%)	1/50 (2%)
Adjusted *(c)*	21.4%	3.6%
Terminal *(d)*	6/39 (15%)	0/23 (0%)
Statistical Tests *(e)*		
Life Table		P=0.060N
Incidental Tumor Test		P=0.005N
Fisher Exact Test		P=0.008N
Thyroid: C-Cell Adenoma or Carcinoma		
Tumor Rates		
Overall *(b)*	11/50 (22%)	3/50 (6%)
Adjusted *(c)*	26.1%	11.2%
Terminal *(d)*	8/39 (21%)	1/23 (4%)
Statistical Tests *(e)*		
Life Table		P=0.145N
Incidental Tumor Test		P=0.016N
Fisher Exact Test		P=0.021N
Pancreatic Islets: Islet-Cell Adenoma		
Tumor Rates		
Overall *(b)*	3/49 (6%)	1/46 (2%)
Adjusted *(c)*	7.9%	3.2%
Terminal *(d)*	3/38 (8%)	0/22 (0%)
Statistical Tests *(e)*		
Life Table		P=0.490N
Incidental Tumor Test		P=0.389N
Fisher Exact Test		P=0.333N

TABLE E5. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE SUPPLEMENTAL STUDY (Continued)

	Vehicle Control	Dosed *(a)*
Pancreatic Islets: Islet-Cell Adenoma or Carcinoma		
Tumor Rates		
Overall *(b)*	4/49 (8%)	2/46 (4%)
Adjusted *(c)*	10.0%	7.3%
Terminal *(d)*	3/38 (8%)	0/22 (0%)
Statistical Tests *(e)*		
Life Table		P=0.588N
Incidental Tumor Test		P=0.293N
Fisher Exact Test		P=0.370N
Mammary Gland: All Tumors		
Tumor Rates		
Overall *(b)*	4/50 (8%)	0/50 (0%)
Adjusted *(c)*	10.3%	0.0%
Terminal *(d)*	4/39 (10%)	0/23 (0%)
Statistical Tests *(e)*		
Life Table		P=0.148N
Incidental Tumor Test		P=0.148N
Fisher Exact Test		P=0.059N
Mammary Gland: Fibroadenoma		
Tumor Rates		
Overall *(b)*	3/50 (6%)	0/50 (0%)
Adjusted *(c)*	7.7%	0.0%
Terminal *(d)*	3/39 (8%)	0/23 (0%)
Statistical Tests *(e)*		
Life Table		P=0.228N
Incidental Tumor Test		P=0.228N
Fisher Exact Test		P=0.122N
Preputial Gland: Carcinoma, NOS		
Tumor Rates		
Overall *(b)*	1/50 (2%)	3/50 (6%)
Adjusted *(c)*	2.2%	8.4%
Terminal *(d)*	0/39 (0%)	0/23 (0%)
Statistical Tests *(e)*		
Life Table		P=0.257
Incidental Tumor Test		P=0.689N
Fisher Exact Test		P=0.309
Testis: Interstitial-Cell Tumor		
Tumor Rates		
Overall *(b)*	47/50 (94%)	45/48 (94%)
Adjusted *(c)*	100%	97.8%
Terminal *(d)*	39/39 (100%)	22/23 (96%)
Statistical Tests *(e)*		
Life Table		P=0.002
Incidental Tumor Test		P=0.636
Fisher Exact Test		P=0.642N

TABLE E5. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE SUPPLEMENTAL STUDY (Continued)

(a) The dosed group received doses of 12 mg/kg of diglycidyl resorcinol ether by gavage.
(b) Number of tumor bearing animals/number of animals examined at the site.
(c) Kaplan-Meier estimated tumor incidence at the end of the study after adjusting for intercurrent mortality.
(d) Observed tumor incidence at terminal kill.
(e) Beneath the dosed group incidence is the P-value corresponding to the pairwise comparison between the 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 Fisher's exact test compares directly the overall incidence rates. A negative trend or lower incidence is indicated by (N).

TABLE E6. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE SUPPLEMENTAL STUDY

	Vehicle Control	Dosed *(a)*
Hematopoietic System: All Leukemias		
Tumor Rates		
Overall *(b)*	5/50 (10%)	6/50 (12%)
Adjusted *(c)*	12.8%	16.4%
Terminal *(d)*	5/39 (13%)	5/35 (14%)
Statistical Tests *(e)*		
Life Table		P=0.427
Incidental Tumor Test		P=0.456
Fisher Exact Test		P=0.500
Hematopoietic System: All Lymphomas		
Tumor Rates		
Overall *(b)*	3/50 (6%)	0/50 (0%)
Adjusted *(c)*	6.9%	0.0%
Terminal *(d)*	0/39 (0%)	0/35 (0%)
Statistical Tests *(e)*		
Life Table		P=0.137N
Incidental Tumor Test		P=0.072N
Fisher Exact Test		P=0.122N
Hematopoietic System: All Lymphomas or Leukemias		
Tumor Rates		
Overall *(b)*	8/50 (16%)	6/50 (12%)
Adjusted *(c)*	18.8%	16.4%
Terminal *(d)*	5/39 (13%)	5/35 (14%)
Statistical Tests *(e)*		
Life Table		P=0.465N
Incidental Tumor Test		P=0.380N
Fisher Exact Test		P=0.387N
Hematopoietic System: Leukemia, Mononuclear Cell		
Tumor Rates		
Overall *(b)*	5/50 (10%)	6/50 (12%)
Adjusted *(c)*	12.8%	16.4%
Terminal *(d)*	5/39 (13%)	5/35 (14%)
Statistical Tests *(e)*		
Life Table		P=0.427
Incidental Tumor Test		P=0.456
Fisher Exact Test		P=0.500
Liver: Neoplastic Nodule, Hepatocellular Carcinoma		
Tumor Rates		
Overall *(b)*	2/50 (4%)	3/50 (6%)
Adjusted *(c)*	5.1%	7.9%
Terminal *(d)*	2/39 (5%)	1/35 (3%)
Statistical Tests *(e)*		
Life Table		P=0.457
Incidental Tumor Test		P=0.544
Fisher Exact Test		P=0.500

TABLE E6. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE SUPPLEMENTAL STUDY (Continued)

	Vehicle Control	Dosed *(a)*
Forestomach: Squamous Cell Papilloma		
Tumor Rates		
Overall *(b)*	0/50 (0%)	19/50 (38%)
Adjusted *(c)*	0.0%	48.4%
Terminal *(d)*	0/39 (0%)	15/35 (43%)
Statistical Tests *(e)*		
Life Table		P<0.001
Incidental Tumor Test		P<0.001
Fisher Exact Tests		P<0.001
Forestomach: Squamous Cell Carcinoma		
Tumor Rates		
Overall *(b)*	0/50 (0%)	27/50 (54%)
Adjusted *(c)*	0.0%	64.0%
Terminal *(d)*	0/39 (0%)	20/35 (57%)
Statistical Tests *(e)*		
Life Table		P<0.001
Incidental Tumor Test		P<0.001
Fisher Exact Tests		P<0.001
Anterior Pituitary: Adenoma, NOS		
Tumor Rates		
Overall *(b)*	16/50 (32%)	24/50 (48%)
Adjusted *(c)*	36.9%	59.6%
Terminal *(d)*	12/39 (31%)	19/35 (54%)
Statistical Tests *(e)*		
Life Table		P=0.043
Incidental Tumor Test		P=0.050
Fisher Exact Test		P=0.076
Anterior Pituitary: Carcinoma, NOS		
Tumor Rates		
Overall *(b)*	2/50 (4%)	3/50 (6%)
Adjusted *(c)*	5.1%	8.1%
Terminal *(d)*	2/39 (5%)	2/35 (6%)
Statistical Tests *(e)*		
Life Table		P=0.454
Incidental Tumor Test		P=0.497
Fisher Exact Test		P=0.500
Adrenal Medulla: Pheochromocytoma		
Tumor Rates		
Overall *(b)*	5/50 (10%)	0/50 (0%)
Adjusted *(c)*	12.3%	0.0%
Terminal *(d)*	4/39 (10%)	0/35 (0%)
Statistical Tests *(e)*		
Life Table		P=0.044N
Incidental Tumor Test		P=0.042N
Fisher Exact Test		P=0.029N

TABLE E6. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE SUPPLEMENTAL STUDY (Continued)

	Vehicle Control	Dosed *(a)*
Thyroid: C-Cell Adenoma		
Tumor Rates		
Overall *(b)*	5/50 (10%)	4/50 (8%)
Adjusted *(c)*	12.8%	11.4%
Terminal *(d)*	5/39 (13%)	4/35 (11%)
Statistical Tests *(e)*		
Life Table		P=0.568N
Incidental Tumor Test		P=0.568N
Fisher Exact Test		P=0.500N
Thyroid: C-Cell Adenoma or Carcinoma		
Tumor Rates		
Overall *(b)*	5/50 (10%)	5/50 (10%)
Adjusted *(c)*	12.8%	14.3%
Terminal *(d)*	5/39 (13%)	5/35 (14%)
Statistical Tests *(e)*		
Life Table		P=0.562
Incidental Tumor Test		P=0.562
Fisher Exact Test		P=0.630N
Mammary Gland: Fibroadenoma		
Tumor Rates		
Overall *(b)*	17/50 (34%)	20/50 (40%)
Adjusted *(c)*	41.3%	51.0%
Terminal *(d)*	15/39 (38%)	16/35 (46%)
Statistical Tests *(e)*		
Life Table		P=0.215
Incidental Tumor Test		P=0.272
Fisher Exact Test		P=0.339
Uterus: Endometrial Stromal Polyp		
Tumor Rates		
Overall *(b)*	12/50 (24%)	11/50 (22%)
Adjusted *(c)*	28.1%	26.9%
Terminal *(d)*	9/39 (23%)	6/35 (17%)
Statistical Tests *(e)*		
Life Table		P=0.585
Incidental Tumor Test		P=0.437N
Fisher Exact Test		P=0.500N
Uterus: Endometrial Stromal Sarcoma		
Tumor Rates		
Overall *(b)*	3/50 (6%)	3/50 (6%)
Adjusted *(c)*	6.9%	6.2%
Terminal *(d)*	1/39 (3%)	0/35 (0%)
Statistical Tests *(e)*		
Life Table		P=0.641
Incidental Tumor Test		P=0.282N
Fisher Exact Test		P=0.661N

TABLE E6. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE SUPPLEMENTAL STUDY (Continued)

	Vehicle Control	Dosed *(a)*
Uterus: Endometrial Stromal Polyp or Sarcoma		
Tumor Rates		
Overall *(b)*	15/50 (30%)	14/50 (28%)
Adjusted *(c)*	33.5%	31.4%
Terminal *(d)*	10/39 (26%)	6/35 (17%)
Statistical Tests *(e)*		
Life Table		P=0.566
Incidental Tumor Test		P=0.257N
Fisher Exact Test		P=0.500N

(a) The dosed group received doses of 12 mg/kg of diglycidyl resorcinol ether by gavage.
(b) Number of tumor bearing animals/number of animals examined at the site.
(c) Kaplan-Meier estimated tumor incidence at the end of the study after adjusting for intercurrent mortality.
(d) Observed tumor incidence at terminal kill.
(e) Beneath the dosed group incidence is the P-value corresponding to the pairwise comparison between the 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 Fisher's exact test compares directly the overall incidence rates. A negative trend or lower incidence is indicated by (N).

APPENDIX F

HISTORICAL INCIDENCES OF TUMORS IN VEHICLE CONTROL RATS AND MICE

TABLE F1. 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
Gulf South	1/269	Stomach, NOS	Squamous cell papilloma
	1/269	Stomach, NOS	Squamous cell carcinoma
Litton	0/147		
Mason	1/200	Forestomach	Squamous cell papilloma
Papanicolaou	0/50		
Southern	1/299	Forestomach	Squamous cell papilloma
Total	5/1065 (0.5%)		

(a) Data as of March 16, 1983

TABLE F2. HISTORICAL INCIDENCE OF STOMACH TUMORS IN FEMALE F344/N RATS RECEIVING CORN OIL BY GAVAGE

Laboratory	Incidence	Site	Diagnosis
Battelle	0/99		
Gulf South	1/276	Stomach, NOS	Squamous cell carcinoma
Litton	1/150	Stomach, NOS	Squamous cell papilloma
Mason	0/199		
Papanicolaou	0/50		
Southern	1/299	Stomach	Squamous cell papilloma
	1/299	Gastric mucosa	Squamous cell papilloma
	1/299	Forestomach	Squamous cell papilloma
Total	5/1073 (0.5%)		

(a) Data as of March 16, 1983

TABLE F3. HISTORICAL INCIDENCE OF STOMACH TUMORS IN MALE B6C3F$_1$ MICE RECEIVING CORN OIL BY GAVAGE

Laboratory	Incidence	Site	Diagnosis
Battelle	0/100		
Gulf South	1/224	Stomach, NOS	Papilloma, NOS
Litton	1/147	Forestomach	Papilloma, NOS
	1/147	Stomach, NOS	Squamous cell papilloma
Mason	1/196	Forestomach	Squamous cell carcinoma
Papanicolaou	1/48	Stomach, NOS	Squamous cell carcinoma
Southern	1/296	Stomach, NOS	Squamous cell papilloma
	1/296	Stomach, NOS	Squamous cell carcinoma
Total	7/1011 (0.7%)		

(a) Data as of March 16, 1983

TABLE F4. HISTORICAL INCIDENCE OF STOMACH TUMORS IN FEMALE B6C3F$_1$ MICE RECEIVING CORN OIL BY GAVAGE

Laboratory	Incidence	Site	Diagnosis
Battelle	0/99		
Gulf South	2/245	Stomach, NOS	Squamous cell papilloma
	1/245	Stomach, NOS	Adenocarcinoma, NOS
Litton	0/145		
Mason	0/197		
Papanicolaou	0/47		
Southern	1/297	Gastric mucosa	Squamous cell papilloma
	1/297	Gastric mucosa	Adenoma, NOS
	1/297	Forestomach	Squamous cell papilloma
Total	6/1030 (0.6%)		

(a) Data as of March 16, 1983

TABLE F5. HISTORICAL INCIDENCE OF LIVER TUMORS IN FEMALE B6C3F$_1$ MICE RECEIVING CORN OIL BY GAVAGE

Laboratory	Adenoma	Carcinoma	Adenoma or Carcinoma
Battelle	4/98 (4.1%)	3/98 (3.1%)	6/98 (6.1%)
Gulf South	16/334 (4.8%)	11/334 (3.3%)	27/334 (8.1%)
Litton	4/148 (2.7%)	3/148 (2.0%)	7/148 (4.7%)
Mason	10/198 (5.1%)	7/198 (3.5%)	17/198 (8.6%)
Papanicolaou	2/48 (4.2%)	2/48 (4.2%)	4/48 (8.3%)
Southern	11/300 (3.7%)	7/300 (2.3%)	18/300 (6.0%)
Total	47/1126 (4.2%)	33/1126 (2.9%)	79/1126 (7.0%)
SD *(b)*	2.45%	2.22%	3.28%
Overall Historical Range			
High	5/50	4/50	7/50
Low	0/50	0/50	1/50

(a) Data as of March 16, 1983 for studies of at least 104 weeks.
(b) Standard deviation. Range and SD are presented for groups of 35 or more animals.

APPENDIX G

SALMONELLA/MICROSOME MUTAGENICITY TEST SYSTEM

APPENDIX G

Diglycidyl resorcinol ether (DGRE) was tested and evaluated blind in each of the four tester strains of *Salmonella typhimurium* using a preincubation modification (Yahagi et al., 1975) of the *Salmonella* assay (Ames et al., 1975). Strains of TA98 and TA1537 are more sensitive to chemicals that express frameshift mutagenic activity; strains TA100 and TA1535 are more sensitive to chemicals that cause base-pair substitutions.

DGRE was solubilized in dimethylsulfoxide (DMSO) and was incubated with the tester strains in suspension culture (20 minutes at 37°C). Soft agar was added and the mixture was plated to detect induced mutants. Exogeneous metabolic activation was provided by liver S-9 preparations from Aroclor-1254 induced Sprague-Dawley rats and Syrian hamsters. Coded chemicals were tested at 5 doses in triplicate in each strain and were retested at least 1 week later.

TABLE G1. RESULTS OF MUTAGENICITY TESTS OF DIGLYCIDYL RESORCINOL ETHER IN *SALMONELLA TYPHIMURIUM* TA98

Dose (μg/plate)	Number of Revertants per Plate — Initial Test A	B	C	Mean ± SE	Dose (μg/plate)	Retest A	B	C	Mean ± SE
A. No Activation									
0.0	19	24	19	21 ± 1.7					
3.3	21	20	19	20 ± 0.6					
10.0	23	23	22	23 ± 0.3					
33.0	22	27	20	23 ± 2.1					
100.0	26S	23S	19S	23 ± 2.0					
333.0	19S	21S	15S	18 ± 1.8					
B. Preincubation with Aroclor-1254 Induced Sprague-Dawley Rat Liver S-9 Preparation									
0	26S	25S	14S	22 ± 3.8	0	26	31	27	28 ± 1.5
33	22S	22S	27S	24 ± 1.7	33	34	35	40	36 ± 1.9
100	24S	24S	23S	24 ± .3	100	37	37	32	35 ± 1.7
333	20S	22S	22S	21 ± .7	333	38	28	48	38 ± 5.8
1000	281T	19S	15S	17 ± 2.0	1000	11S	13S	5S	10 ± 2.4
2000	28T	32T	94T	—	2000	50T	308T	55T	—
C. Preincubation with Aroclor-1254 Induced Syrian Hamster Liver S-9 Preparation									
0	32	33	21	29 ± 3.8					
33	35	50	37	41 ± 4.7					
100	32	37	25	31 ± 3.5					
333	30	44	39	38 ± 4.1					
1000	26S	21S	17S	21 ± 2.6					
2000	28T	14S	27S	20 ± 6.5					

T = chemical was toxic; S = chemical was slightly toxic

TABLE G2. RESULTS OF MUTAGENICITY TESTS OF DIGLYCIDYL RESORCINOL ETHER IN *SALMONELLA TYPHIMURIUM* TA100

Dose (μg/plate)	Number of Revertants per Plate — Initial Test A	B	C	Mean ± SE	Dose (μg/plate)	Retest A	B	C	Mean ± SE
A. No Activation									
0.0	131	140	124	132 ± 4.6	0.0	160	195	178	178 ± 10.1
3.3	176	143	165	161 ± 9.7	1.0	191	188	201	193 ± 3.9
10.0	235	238	239	237 ± 1.2	3.3	213	234	199	215 ± 10.2
33.0	375	379	376	377 ± 1.2	10.0	277	260	273	270 ± 5.1
100.0	538S	583S	527S	549 ± 17.1	33.3	376	377	416	390 ± 13.2
333.0	448S	455S	571S	491 ± 39.9	100.0	557S	543S	542S	547 ± 4.8
B. Preincubation with Aroclor-1254 Induced Sprague-Dawley Rat Liver S-9 Preparation									
0	99	101	106	102 ± 2.1	0	171	174	195	180 ± 7.5
33	154	118	121	131 ± 11.5	10	174	169	145	163 ± 9.0
100	133	140	133	135 ± 2.3	100	185	194	200	193 ± 4.4
333	252	236	265	251 ± 8.4	333	248S	241S	243S	244 ± 2.1
1000	535S	509S	470S	505 ± 18.9	667	315S	266S	307S	296 ± 15.2
2000	762S	764S	580T	763 ± 1.0	1000	539S	374T	557S	548 ± 9.0
C. Preincubation with Aroclor-1254 Induced Syrian Hamster Liver S-9 Preparation									
0	150	116	127	131 ± 10.0	0	193	219	191	201 ± 9.0
33	121	134	150	135 ± 8.4	10	198	208	198	201 ± 3.3
100	158	155	140	151 ± 5.6	100	197	187	206	197 ± 5.5
333	210	205	240	218 ± 10.9	333	277S	213S	261S	250 ± 19.2
1000	244S	281S	244S	256 ± 12.3	1000	212S	182S	232S	209 ± 14.5
2000	1275S	1261S	705T	1268 ± 7.0	1500	442T	391T	420T	—

T = chemical was toxic; S = chemical was slightly toxic

TABLE G3. RESULTS OF MUTAGENICITY TESTS OF DIGLYCIDYL RESORCINOL ETHER IN *SALMONELLA TYPHIMURIUM* TA1535

Dose (μg/plate)	Number of Revertants per Plate — Initial Test A	B	C	Mean ± SE	Dose (μg/plate)	Retest A	B	C	Mean ± SE
A. No Activation									
0.0	28	25	23	25 ± 1.5	0.0	25	25	31	27 ± 2.0
3.3	42	30	37	36 ± 3.5	1.0	24	24	25	24 ± 0.3
10.0	49	44	53	49 ± 2.6	3.3	34	26	25	28 ± 2.8
33.0	88	101	93	94 ± 3.8	10.0	42	39	41	41 ± 0.9
100.0	136S	142S	130S	136 ± 3.5	33.0	81	77	63	74 ± 5.5
333.0	61S	70S	91S	74 ± 8.9	100.0	143	137	102	127 ±12.8
B. Preincubation with Aroclor-1254 Induced Sprague-Dawley Rat Liver S-9 Preparation									
0	10	10	14	11 ± 1.3	0.0	12	13	8	11 ± 1.5
33	14	19	23	19 ± 2.6	10.0	9	13	16	13 ±12.0
100	35	50	54	46 ± 5.8	100.0	36	36	42	38 ± 2.0
333	105	89	84	93 ± 6.3	333.0	78	61	64	68 ± 5.2
1000	564S	536S	620S	573 ± 24.7	667.0	141S	138S	155S	145 ± 5.2
2000	656S	629S	671T	642 ± 13.5	1000.0	181S	177S	178S	179 ± 1.2
C. Preincubation with Aroclor-1254 Induced Syrian Hamster Liver S-9 Preparation									
0	9	21	11	14 ± 3.7	0.0	11	8	10	10 ± 0.9
33	11	14	10	12 ± 1.2	33.0	13	9	7	10 ± 1.8
100	13	14	11	13 ± 0.9	100.0	11	13	8	11 ± 1.5
333	27	25	26	26 ± 0.6	333.0	38	23	20	27 ± 5.6
1000	79S	133S	142S	118 ± 19.7	667.0	44S	44S	52S	47 ± 2.7
2000	719S	742T	573T	719 —	1000.0	68S	60S	63S	64 ± 2.3

T = chemical was toxic; S = chemical was slightly toxic

TABLE G4. RESULTS OF MUTAGENICITY TESTS OF DIGLYCIDYL RESORCINOL ETHER IN *SALMONELLA TYPHIMURIUM* TA1537

Dose (μg/plate)	Number of Revertants per Plate Initial Test A	B	C	Mean ± SE
A. No Activation				
0.0	3	10	12	8 ± 2.7
3.3	4	8	5	6 ± 1.2
10.0	8	8	4	7 ± 1.3
33.0	13	5	11	10 ± 2.4
100.0	13S	12S	5S	10 ± 2.5
333.0	3S	6S	7S	5 ± 1.2
B. Preincubation with Aroclor-1254 Induced Sprague-Dawley Rat Liver S-9 Preparation				
0	6	12	9	9 ± 1.7
33	9	20	9	13 ± 3.7
100	12	4	13	10 ± 2.8
333	7	9	15	10 ± 2.4
1000	5S	13S	9S	9 ± 2.3
2000	8S	6S	13S	9 ± 2.1
C. Preincubation with Aroclor-1254 Induced Syrian Hamster Liver S-9 Preparation				
0	12	10	7	10 ± 1.5
33	7	8	9	8 ± 0.6
100	14	9	12	12 ± 1.5
333	15	11	10	12 ± 1.5
1000	14S	12S	9S	12 ± 1.5
2000	8S	6S	8S	7 ± 0.7

T = chemical was toxic; S = chemical was slightly toxic

APPENDIX H

NTP SENTINEL ANIMAL PROGRAM

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 periodic 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 and clotted and the serum is separated. The serum is diluted 1:5 with buffered saline and shipped to the Murine Virus Diagnostic Laboratory of Microbiological Associates for determination of the viral titers. The following tests are performed:

	Hemagglutination Inhibition	Complement Fixation	Elisa
Mice	PVM (Pneumonia Virus of Mice) Adenovirus) Reo 3 (Reovirus, Type I) GDVII (Strain of Murine Encephalomyelitis Virus) Poly (Polyoma Virus) Sendai (Sendai Virus) MVM (Minute Virus of Mice) Ectro (Infectious Ectromelia Virus of Mice)	M. Ad. (Mouse Virus) LCM (Lymphocytic Choriomeningitis Virus of Mice)	MHV (Mouse Hepatitis
Rats	PVM (Pneumonia Virus of Mice) Sendai (Sendai Virus) KRV (Kilham Rat Virus) H-1 (Toolan's H-1 Virus)	RCV (Rat Corona Virus)	

B. RESULTS

See Tables H1, H2, H3

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
SIX MONTHS						
1	M	80	—	—	—	—
2	M	80	—	—	—	—
3	M	80	—	—	—	—
4	M	80	—	—	—	—
5	M	80	—	—	—	—
1	F	80	—	—	—	—
2	F	80	—	—	—	—
3	F	80	—	—	—	—
4	F	80	—	—	—	—
5	F	80	—	—	—	—
TWELVE MONTHS						
21	M	40	—	—	80	—
22	M	40	—	—	20	—
23	M	80	80	—	40	—
24	M	20	—	—	40	—
25	M	80	—	—	—	—
21	F	80	—	—	—	—
22	F	80	—	—	20	10
23	F	80	—	—	—	20
24	F	80	—	—	—	10
25	F	80	—	—	—	10
EIGHTEEN MONTHS						
26	M	20	80	—	40	—
27	M	10	80	—	80	—
28	M	—	40	—	40	—
29	M	20	20	—	20	—
30	M	20	20	—	20	—
26	F	80	—	—	—	—
27	F	40	—	—	—	—
28	F	80	—	—	—	—
29	F	80	—	—	—	—
30	F	80	—	—	—	—
TWENTY-FOUR MONTHS						
5	M	80	—	—	10	—
10	M	80	—	—	10	—
17	M	80	—	—	—	—
23	M	80	—	—	—	—
44	M	80	—	—	—	—
9	F	80	—	—	—	—
18	F	80	—	—	—	—
21	F	80	—	—	—	—
22	F	80	—	—	—	—
31	F	80	—	—	20	—
Significant Titer	20	20	20	10	10	

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

Sample No.	Sex	Hemagglutination Inhibition						Complement Fixation			
		PVM	Reo 3	GDVII	Poly	MVM	Ectro	Sendai	M. Ad	MHV	LCM
SIX MONTHS											
1	M	—	—	—	—	—	—	—	—	—	—
2	M	—	—	—	—	20	—	—	—	—	—
4	M	—	—	—	—	20	—	—	—	—	—
1	F	—	—	—	—	—	—	—	—	—	—
2	F	—	—	—	—	—	—	—	—	—	—
3	F	—	—	—	—	—	—	—	—	—	—
4	F	—	—	—	—	—	—	—	—	—	—
5	F	—	—	—	—	—	—	—	—	—	—
TWELVE MONTHS											
6	M	*(a)*	—	*(a)*	—	—	—	—	—	—	—
7	M	40	—	—	—	—	—	—	—	—	—
8	M	*(a)*	—	—	—	*(a)*	—	—	—	—	—
9	M	80	—	—	—	—	—	—	—	—	—
10	M	20	—	20	—	—	—	—	—	—	—
7	F	—	—	—	—	—	—	—	—	—	—
8	F	—	—	—	—	*(a)*	—	—	—	—	—
EIGHTEEN MONTHS											
11	M	—	—	—	—	—	—	—	—	—	—
12	M	—	—	—	—	—	—	—	—	—	*(b)*
15	M	—	—	—	*(c)*	—	—	—	—	—	—
11	F	—	—	—	—	—	—	—	—	—	—
12	F	—	—	—	*(c)*	*(c)*	—	*(a)*	—	—	—
13	F	—	—	—	—	—	—	—	—	—	—
14	F	—	—	—	—	—	—	—	—	—	*(d)*
15	F	—	—	—	*(c)*	*(c)*	—	*(d)*	—	—	*(b)*
TWENTY-FOUR MONTHS											
12	M	10	—	—	—	—	—	—	—	—	—
6	M	10	—	—	—	—	—	—	—	—	—
24	M	40	—	—	—	—	—	—	—	—	—
39	M	—	—	—	—	—	—	—	—	—	—
4	F	—	—	—	—	—	—	—	—	—	—
39	F	10	—	—	—	—	—	—	—	—	—
26	F	—	—	—	—	—	—	—	*(d)*	*(d)*	*(d)*
35	F	—	—	—	—	—	—	—	—	—	—
19	F	—	—	—	—	—	—	—	*(d)*	*(d)*	*(d)*
Significant Titer		20	20	20	20	20	20	10	10	10	10

(a) Insufficient serum
(b) Serum reacts with control antigen
(c) Serum agglutinates red blood cells
(d) Anticomplimentary serum

TABLE H3. MURINE VIRUS ANTIBODY DETERMINATIONS FOR RATS IN THE SUPPLEMENTAL STUDY

		Hemagglutination Inhibition				Complement Fixation	
Sample No.	Sex	PVM	KRV	H-1	Sendai	RCV	Sendai
SIX MONTHS							
16	M	80	1280-	—	NT	20	—
17	M	80	—	—	NT	10	—
18	M	80	—	—	NT	20	—
19	M	80	—	—	NT	20	—
20	M	80	—	—	NT	—	—
16	F	80	—	—	NT	20	—
17	F	80	—	—	NT	—	—
18	F	80	40	—	NT	—	—
19	F	80	—	—	NT	—	—
20	F	80	80	—	NT	10	—
TWELVE MONTHS							
21	M	40	—	—	80	—	—
22	M	40	—	—	20	—	—
23	M	80	80	—	40	—	—
24	M	20	—	—	40	—	—
25	M	80	—	—	—	—	—
21	F	80	—	—	—	—	—
22	F	80	—	—	20	10	—
23	F	80	—	—	—	20	—
24	F	80	—	—	—	10	—
25	F	80	—	—	—	10	—
EIGHTEEN MONTHS							
26	M	20	80	—	40	—	—
27	M	10	80	—	80	—	—
28	M	—	40	—	40	—	—
29	M	20	80	—	20	—	—
30	M	20	80	—	20	—	—
26	F	80	—	—	—	—	—
27	F	40	—	—	—	—	—
28	F	80	—	—	—	—	—
29	F	80	—	—	—	—	—
30	F	80	—	—	—	—	—
TWENTY-FOUR MONTHS							
74	M	—	—	—	—	—	—
94	M	—	—	—	—	—	—
96	M	—	—	—	—	—	—
89	M	10	—	—	—	—	—
82	M	—	—	—	—	—	—
59	F	10	10	—	—	—	—
73	F	40	—	—	—	—	—
63	F	40	—	—	—	—	—
76	F	80	—	—	—	—	—
56	F	20	—	—	—	—	—
Significant Titer		20	20	20	10	10	

NT = Not tested.

APPENDIX I

ANALYSIS OF DIGLYCIDYL RESORCINOL ETHER AT MIDWEST RESEARCH INSTITUTE

APPENDIX I

A. ELEMENTAL ANALYSIS

Element	C	H
Theory	64.85	6.35
Determined	64.71 64.57	6.37 6.48

B. WATER ANALYSIS (Karl Fischer)

Diglycidyl resorcinol ether reacts with Karl Fischer reagent. Water analysis was therefore not conducted.

C. TITRATION OF EPOXIDE GROUPS WITH IN SITU GENERATED HI (Jay, 1964)

81.2 ± 0.4 (δ)%

Weight per Epoxy Equivalent (epoxy equivalent number):

136.8 ± 0.7 (δ) (Annual Book of ASTM Standards)

D. INDEX OF REFRACTION

Determined

n_D^{20} = 1.5423 ± 0.0002 (δ)

Literature Values

n_D^{20} = 1.541 (Hawley, 1971)

E. DENSITY

d_{20}^{25} = 1.213 ± 0.001 (δ) g/ml

d_4^{25} =1.21 g/ml (Hawley, 1971)

F. THIN-LAYER CHROMATOGRAPHY

Plates: Silica Gel 60, F254

Amount Spotted: 100 and 300 μg, 10 μg/μl

Ref. Standard: m-Toluidine

Visualization: Ultraviolet light (254 and 366 nm); Potassium ferricyanide; ferric chloride (Egon Stahl Reagent No. 111) (Stahl, 1969), then spraying with 2N HCl

System 1: Benzene:Methanol (85:15)

R_f: 0.86 (major); 0.80 (trace); 0.74 (trace); 0.71 (trace, E.S. No. 111 only); 0.64 (trace); 0.52 (trace, E.S. No. 111 only)

R_{st}: 1.13, 1.05, 0.97, 0.93 0.84, 0.69

System 2: Ethyl acetate:Chloroform (75:25)

R_f: 0.78 (major); 0.71 (trace) 0.64 (slight trace); 0.62 (trace, E.S. No. 111 only); 0.56 (trace, E.S. No. 111 only); 0.50 (trace, E.S. No. 111 only); 0.25 (trace); (trace, E.S. No. 111 only); (trace, E.S. No. 111 only); 0.02 (trace, E.S. No. 111 only); origin (trace)

R_{st}: 0.99, 0.90, 0.81, 0.78, 0.71, 0.63, 0.32, 0.22, 0.16, 0.02. origin

G. VAPOR-PHASE CHROMATOGRAPHY

Instrument: Varian 3700 with CDS 111 Microprocessor
Column: 3% OV-17 on 80/100 mesh Supelcoport, 1.8 m x 2 mm I.D., glass, silanized
Detection: Flame ionization
Inlet temperature: 220°C
Detector temperature: 270°C
Oven temperature program: 50°C, 5 min; 50 to 250°C at 10°C/min
Sample injected: 3.5μl of a 10 mg/ml solution in methanol and 3.5μl of a 5 mg/ml solution in methanol to check for overloading.
Results: Major peak and 30 impurities. Two of the impurities had areas of 3.71% and 0.90%, respectively, of the major peak. An unresolved group of four other impurities had a total area of 3.66%, and another pair of unresolved impurities had a total area of 2.04% of the major peak. The remaining 22 impurities had a combined area of less than 4% of the major peak area.

Peak	Retention Time (min)	Retention Time (Relative to Diglycidyl Resorcinol Ether)	Area (Percent) of Diglycidyl Resorcinol Ether
1	7.42	0.346	0.47
2	7.49	0.350	0.05
3	7.56	0.353	0.03
4	7.61	0.355	0.03
5	7.67	0.358	0.08
6	7.81	0.365	0.10
7	8.01	0.374	0.66
8	9.36	0.437	0.02
9	9.42	0.440	0.16
10	9.86	0.460	0.10
11	10.20	0.476	0.03
12	10.54	0.492	0.14
13	10.90	0.509	0.15
14	12.38	0.578	0.39
15	13.45	0.628	0.18
16	14.21	0.663	3.71
17	16.46	0.768	0.04
18	20.09	0.938	0.04
19	20.38	0.951	0.26
20	20.81	0.972	0.22
21	21.42	1.000	100.00
22	21.92	1.023	
23	22.32 unresolved	1.042	3.66 total
24	22.61 peaks	1.056	
25	22.90	1.069	
26	24.37	1.138	0.09
27	25.09 unresolved	1.171	2.04 total
28	25.44 peaks	1.188	
29	26.00	1.214	0.90
30	26.77	1.250	0.22
31	33.04	1.542	0.12

APPENDIX I

H. SPECTRAL DATA

(1) Infrared

Consistent with literature spectrum (Lee and Neville, 1967)

Instrument: Beckman IR-12
Cell: Thin film between silver chloride plates
Results: See Figure 7

(2) Ultraviolet/Visible

No literature reference found

Instrument: Cary 118

No absorbance between 350 and 800 nm (visible region) at a concentration of 0.1 mg/ml.

Solvent: Methanol

λ max(nm)	ϵ max
279.8	1917 ± 10 (δ)
273.3	2129 ± 11 (δ)

(3) Nuclear Magnetic Resonance

No literature reference found.

Instrument: Varian HA-100

Solvent: $CDCl_3$ with internal tetramethylsilane

Assignments: (See Figure 8)

Chemical Shift (δ)	Coupling Constant
(a) dd, 2.57 ppm,	J_{ab} = 4.5 Hz,
(b) dd, 2.73 ppm,	J_{ac} = 2.5 Hz;
(c) m, 3.18 ppm,	J_{bc} = 5 Hz;
(d) dd, 3.72 ppm,	J_{cd} = 6 Hz, J_{ce} = 3 HZ
(e) dd, 4.06 ppm,	J_{de} = 11 Hz
(f) m, 6.28-6.62 ppm,	
(g) m, 7.04 ppm,	
(h) m, 2.18-2.20 ppm (impurity)	
(i) m, 2.31 ppm (impurity)	

Integration Ratios:

(a)	1.61,	(b)	1.93,	(c)	1.93,
(d)	2.48,	(e)	2.14,	(f)	2.90,
(g)	0.97,	(h)	0.24,	(i)	0.16

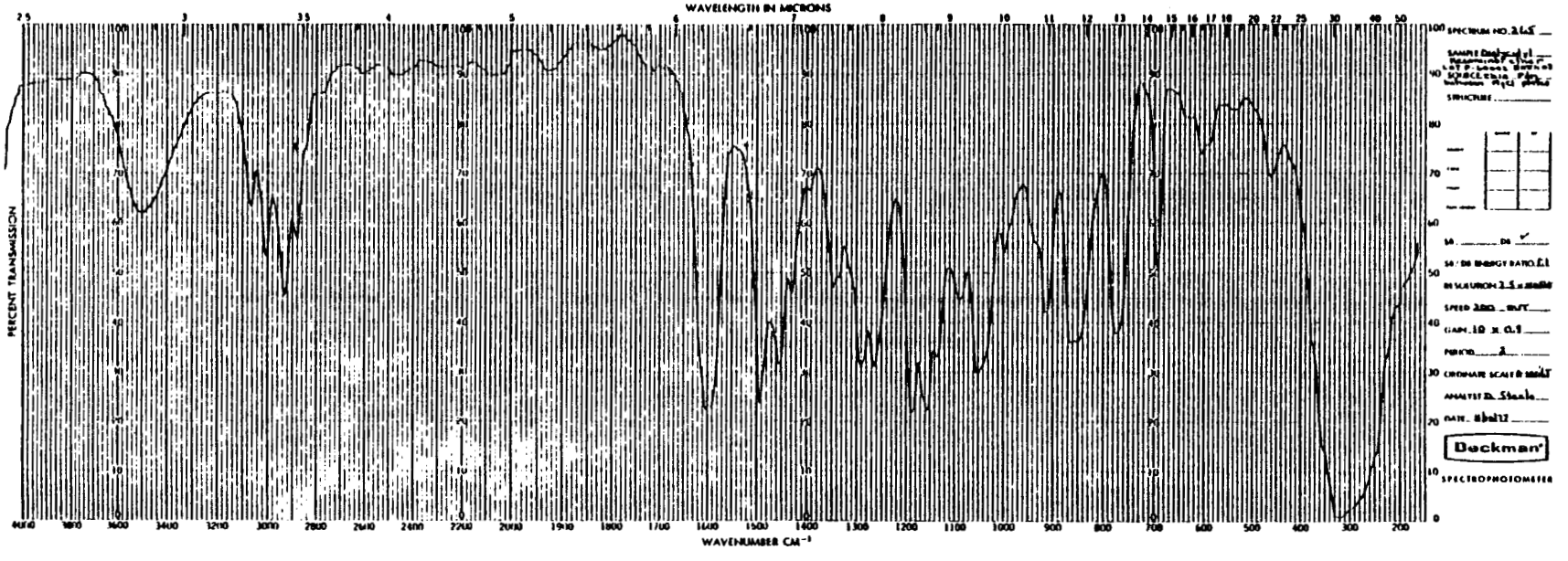

Figure 7. Infrared Absorption Spectrum of Diglycidyl Resorcinol Ether (Lot No. P-60002)

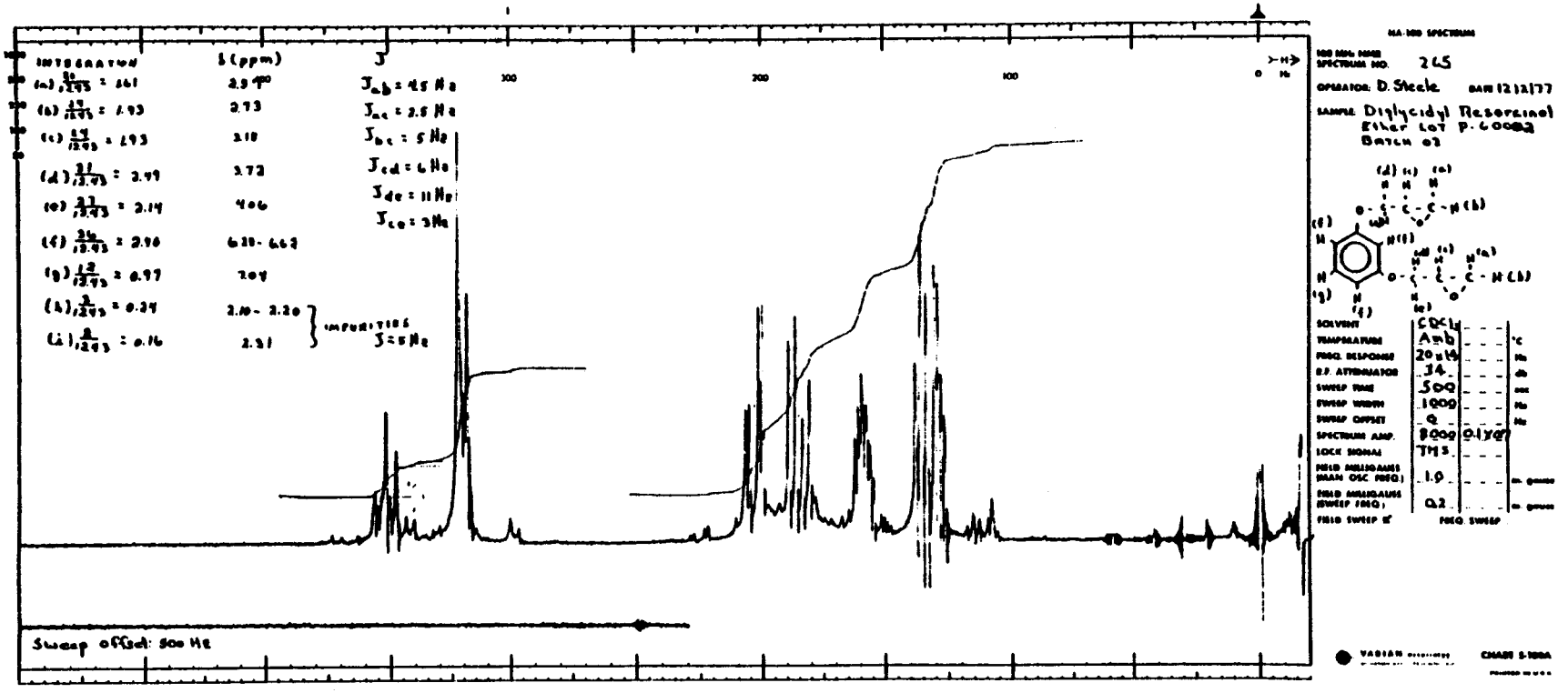

Figure 8. Nuclear Magnetic Resonance Spectrum of Diglycidyl Resorcinol Ether (Lot No. P-60002)

APPENDIX J

ANALYSIS OF DIGLYCIDYL RESORCINOL ETHER IN CORN OIL FOR STABILITY OF DIGLYCIDYL RESORCINOL ETHER

APPENDIX J

A. SAMPLE PREPARATION AND STORAGE

Diglycidyl resorcinol ether, by itself, does not suspend well in corn oil. Therefore, 2.485 ± 0.001 g of the chemical was dissolved in 2 ml of reagent grade acetone in a 50-ml volumetric flask; corn oil was added, with periodic shaking, to bring the volume of the mixture to the 50-ml mark. The mixture was placed in an ultrasonic vibratory bath for 10 minutes, with brief manual shaking every 2 minutes. This produced a uniform suspension of concentrations 49.70 ± 0.02 mg/ml, which remained visually homogeneous for a minimum of 4 hours.

As soon as the suspension had been prepared, eight accurately weighed 1.64-g aliquots were removed and sealed in separate 60-ml septum vials (Microsep F-138 gas chromatography septa with Teflon® film facing, from Canton Biomedical Products, Inc.; aluminum crimp seals from Wheaton Scientific Company, Inc.). Duplicate aliquots were used as initial, or zero-time samples and for storage at 1, 6, and 7 days, respectively.

B. SAMPLE EXTRACTION AND ANALYSIS

Extracting solvent containing an internal reference standard was prepared by weighing 0.7585 ± 0.0001 g of dibutyl phthalate, transferring to a 1-liter volumetric flask, and diluting to the mark with absolute methanol. The concentration of reference standard was 0.7585 ± 0.0001 mg/ml.

To extract each sample aliquot, the septum vial was rehomogenized by brief shaking and treatment in an ultrasonic vibrating bath for 5 minutes; the vial was opened, and 50 ml of the extracting solvent was added by volumetric pipette, and the vial immediately resealed. The corn oil/methanol mixture was manually shaken for 1 minute and centrifuged for 5 minutes. A portion of the clear, methanolic supernatant solution (5 ml) was then transferred to an 8.5ml septum vial for subsequent analysis by the gas chromatographic system outlined below.

Instrument: Bendix 2500 with Hewlett-Packard 3380A Automatic Integrator
Column: 3% OV-17 on 80/100 mesh Supelcoport, 1.8 m x 2 mm I.D., glass, silanized
Detection: Flame ionization
Temperatures: Inlet, 225° C
Oven, 180° C isothermal
Detector: 275° C
Carrier gas: Nitrogen; flow rate, 30 cc/min.
Volume of solution injection: 4 μl
Retection times: Test chemical, 9.5 min.
Reference standard, 7.8 min.

C. QUALITY CONTROL PROTOCOLS

Analyses were performed in duplicate using dibutyl phthalate as an internal reference standard. Recovery studies (zero-time samples) were performed in duplicate at the same concentration level as the test samples, both at the start and at the end of the 7-day period. Gas chromatographic linearity was determined with standard solutions in methanol at 1.84, 1.53, and 1.23 mg/ml concentrations for the diglycidyl resorcinol ether and 0.94, 0.78, and 0.62 mg/ml for the internal reference. The least squares plot correlation coefficients were 0.999 for both the test chemical and the internal reference (effectively 1.0, linear).

Several gas chromatographic and nuclear magnetic resonance checks were made in order to demonstrate that diglycidyl resorcinol ether does not react or decompose under conditions of this study. The chemical is stable.

D. RESULTS

Storage Time (Days)	Average Percent Chemical Found in Chemical/Vehicle Mixtures *(a, b)*
1	4.98 ± 0.05 *(c)*
6	4.87 ± 0.05
7	4.93 ± 0.05

(a) Zero-time recovery yield, 100.0 ± 0.3%
(b) Theoretical concentration of chemical in corn oil, 4.970 ± 0.002%
(c) The error values in this table are standard deviations obtained in the instrumental measurements of the test solutions, propagated by standard numerical methods in the calculation of the tabulated quantities.

E. CONCLUSION

Diglycidyl resorcinol ether mixed with corn oil to form a suspension as described above at a 5% dose level is stable for a period of 7 days when stored at 25°C, protected from exposure to direct light.

APPENDIX K

PREPARATION OF CHEMICAL/VEHICLE MIXTURES AND ANALYSIS OF DIGLYCIDYL RESORCINOL ETHER IN CORN OIL FOR CONCENTRATION OF DIGLYCIDYL RESORCINOL ETHER

APPENDIX K

A. GAVAGE PREPARATION PROCEDURE

A quantity of DGRE was melted by warming the chemical in a 40°C water bath, and a 2.5-g portion of the clear liquefied chemical was transferred to a 200-ml centrifuge bottle and mixed with 44.2 g of corn oil. No acetone was used. The mixture was homogenized using a Brinkman Polytron® homogenizer set at low speed for 1 minute. Air bubbles incorporated in the suspension during homogenization were removed by drawing a vacuum on the bottle with an aspirator while agitating the contents periodically for 2-3 minutes. The resulting mixture was visually homogeneous and appeared to remain stable for up to 2 hours. This combination of chemical and corn oil produced 50.0 ml of suspension containing DGRE at a concentration of 50.0 mg/ml.

B. PROCEDURE FOR ANALYSIS OF DGRE/CORN OIL MIXTURES

One-milliliter aliquots of the sample vials were extracted with 10 ml of methanol containing 0.7 g/ml of dibutyl phthalate as an internal standard. A reference calibration plot was prepared from spiked samples which were extracted in the same manner. The supernatant solutions were analyzed by VPC-FID at 210° on a 6 ft. x 1/4 in. x 2 mm I.D. glass column packed with SP2250 on 100/120 Supelcoport.

C. RESULTS

See Table K1.

TABLE K1. ANALYSIS OF CHEMICAL/VEHICLE MIXTURES

Date Mixed	Week Used	Concentration of Diglycidyl Resorcinol Ether in Corn Oil for Target Concentration *(a)*			
		4 mg/ml	8 mg/ml	17 mg/ml	33 mg/ml
03/12/79	3/15			19.6	29.6
05/22/79	5/25				31.8
05/25/79	5/30		7.8	15.8	
07/10/79	7/13		6.8	18.5	34.5
09/25/79	9/27		7.4	17.5	31.5
					(30.6) *(b)*
10/24/79	10/26		7.5	16.3	32.0
01/22/80	1/24		7.5	16.5	31.3
03/04/80	3/6		7.3	15.8	33.5
05/20/80	5/22	3.8	7.3	15.8	29.8
07/22/80	7/25	3.7	7.7	16.0	30.5
				(16.9) *(b)*	
09/09/80	9/11	4.4	7.8	15.8	36.3
10/14/80	10/16	3.6		16.1	34.0
10/20/80	10/21		8.5		
01/06/81	Not used	3.8 *(b)*			
01/08/81	1/10	4.0	7.8	16.3	32.0
01/27/81	1/29	3.8	7.4	16.0	33.8
03/24/81	4/2	3.9	7.4	16.0	
				(17.5) *(b)*	
Mean (mg/ml)		3.9	7.6	16.6	32.4
Standard deviation		0.3	0.4	1.2	2.0
Coefficient of variation (%)		6.7	5.2	7.0	6.0
Range (mg/ml)		3.6-4.4	6.8-8.5	15.8-19.6	29.6-36.3
Number of samples		7	13	14	13

(a) The data presented are the average of the results of duplicate analyses.
(b) Results of referee analyses at MRI.

APPENDIX L

DATA AUDIT SUMMARY

DATA AUDIT SUMMARY

The experimental records and pathology materials for the 2-year toxicology and carcinogenesis studies of diglycidyl resorcinol ether in rats and mice were audited for completeness, consistency, and accuracy. This study was performed at EG and G Mason Research Institute, Worcester, MA, under a subcontract with Tracor Jitco from the National Cancer Institute. The study was conducted from March 1979 to April 1982 and was initiated prior to the requirement of compliance to Good Laboratory Practice standards by NTP in October 1981. The audit was conducted August 20-31, 1984, at the NTP Archives, Rockville, MD, and involved the following Dynamac personnel: C. Dippel, M.S.; F. Garner, D.V.M.; J. Konz, M.S.P.H.; J. Plautz, M.S.; Ronald Ramsey, B.S.; Ronald Schueler, D.V.M.; C. Sexsmith, B.S.; and P. Wennerberg, D.V.M. Additional participants were: A. Grant (NTP), S. Corson (Pathology Associates, Inc.), and R. Joftes, (NTP).

The audit consisted of an in-depth review of the data and pathology materials collected during the conduct of the study as well as review of the correspondence, laboratory final report, and Draft Technical Report. For the in-life toxicology data, this review involved examination of 100% of the records on animal receipt and husbandry, mortality, environmental conditions, sentinel animals, and dosing and examination of body weight and clinical observation data for 10% of the animals. In the review of the chemistry data, all of the records were examined pertaining to receipt and use of the test chemical, analysis of the bulk chemical and dose solutions by the contract laboratory, and characterization of the bulk chemical and analysis of the dose solutions by the reference laboratory. The audit of the pathology materials included review of 100% of the Individual Animal Data Records (IADRs) for completeness and correlation between gross and microscopic diagnoses, examination of the wet tissues of 10% of the animals for unidentified lesions and correct identification, correlation of slides and tissue blocks for 6 of 10 sex-groups, and verification of the reported histopathology on a 10% sample of the animals.

Several minor problems were noted in the study's documentation. Records of the quarantine and randomization of animals were not available for review and clinical observation data were limited by infrequent and nondetailed entries. No overall record of mortalities was maintained in-life; IADRs were used as the primary record of mortality. Comparison of the available in-life records with the IADRs found several discrepancies in dates and modes of death. Several animals were identified as having possible errors in disposition codes. Review of the environmental data found that air temperature in the animal room was not well maintained during the first 9 months of the study; many daily high temperatures were recorded as being 80° F or more. Low humidities were also recorded frequently during 3 months of the initial study and during the latter half of the supplementary study. There was no evidence that the environmental conditions resulted in mortality or morbidity. Review of the draft Technical Report found all of the procedures and body weight data accurately reported; some errors were noted in the reporting of the sentinel animal data.

A review of the data showed that the chemical was received, prepared into dosing mixtures, and reanalyzed as required. Data were not present for the corn oil peroxide analysis and the infrared identity analysis.

Minor discrepancies and inconsistencies were noted during the review of the pathology materials and included a few missing slides and questionable slide/block matches, several discrepancies between gross and microscopic diagnoses and several animals could not definitely be identified due to torn ears. All of the discrepancies in target tissues were resolved and did not affect the incidence of proliferative lesions. In addition, 10 mice had possible disposition code errors because their deaths were likely a result of gavage trauma.

Although some problems and discrepancies were identified as discussed in the audit report, these were adequately resolved or were determined not to affect the outcome of the study. In conclusion, the data examined in this audit are considered adequate to meet the objectives of the study.

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