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TOXICOLOGY AND CARCINOGENESIS STUDIES OF GLYCIDOL

(CAS NO. 556-52-5)

IN F344/N RATS AND B6C3F$_1$ MICE

(GAVAGE STUDIES)

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

NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS STUDIES OF GLYCIDOL

(CAS NO. 556-52-5)

IN F344/N RATS AND B6C3F$_1$ MICE

(GAVAGE STUDIES)

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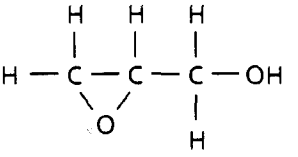

GLYCIDOL

CAS No. 556-52-5

$C_3H_6O_2$ Molecular weight 74.1

Synonyms: 2,3-epoxy-1-propanol

ABSTRACT

Glycidol is a viscous liquid that is used as a stabilizer in the manufacture of vinyl polymers, as an additive for oil and synthetic hydraulic fluids, and as a diluent in some epoxy resins. Toxicology and carcinogenesis studies were conducted by administering glycidol (94% pure, containing 1.2% 3-methoxy-1,2-propanediol, 0.4% 3-chloro-1,2-propanediol, 2.8% diglycidyl ether, and 1.1% 2,6-dimethanol-1,4-dioxane) in water by gavage to groups of F344/N rats and $B6C3F_1$ mice of each sex for 16 days, 13 weeks, or 2 years. Genetic toxicology studies were conducted in *Salmonella typhimurium*, Chinese hamster ovary (CHO) cells, *Drosophila melanogaster*, and the bone marrow of male $B6C3F_1$ mice.

Sixteen-Day Studies: Glycidol doses for groups of five rats or five mice of each sex ranged from 37.5 to 600 mg/kg; vehicle controls received distilled water. All rats that received 600 mg/kg died between days 3 and 13. Edema and degeneration of the epididymal stroma, atrophy of the testis, and granulomatous inflammation of the epididymis occurred in males that received 300 mg/kg.

All mice that received 600 mg/kg and two males and two females that received 300 mg/kg died by day 4 of the studies. Focal demyelination in the medulla and thalamus of the brain occurred in all female mice that received 300 mg/kg.

Thirteen-Week Studies: Doses for groups of 10 rats ranged from 25 to 400 mg/kg, and doses for groups of 10 mice ranged from 19 to 300 mg/kg; vehicle controls received distilled water. All rats that received 400 mg/kg died by week 2; three males and one female that received 200 mg/kg died during weeks 11-12. Final mean body weights of male rats that received 50, 100, or 200 mg/kg were 96%-85% that of vehicle controls; final mean body weights of female rats receiving the same doses were 94%-89% that of vehicle controls. Sperm count and sperm motility were reduced in male rats that received 100 or 200 mg/kg. Necrosis of the cerebellum, demyelination in the medulla of the brain, tubular degeneration and/or necrosis of the kidney, lymphoid necrosis of the thymus, and testicular atrophy and/or degeneration occurred in rats that received 400 mg/kg.

All mice that received 300 mg/kg died by week 2; deaths of mice that received 150 mg/kg occurred during weeks 4-8 for males and weeks 1-5 for females. Mean body weights of chemically exposed mice surviving to the end of the studies were generally 90%-94% those of vehicle controls. Sperm count and sperm motility were reduced in dosed male mice. Compound-related histopathologic lesions included demyelination of the brain in males and females that received 150 or 300 mg/kg, testicular atrophy in males at all doses, and renal tubular cell degeneration in male mice that received 300 mg/kg.

Based on reduced survival, reduced weight gain, and histopathologic lesions in the brain and kidney in rats that received 200 or 400 mg/kg and on reduced survival and histopathologic lesions of the

brain in mice that received 150 or 300 mg/kg, doses selected for the 2-year studies of glycidol were 37.5 and 75 mg/kg for rats and 25 and 50 mg/kg for mice.

Body Weights and Survival in the Two-Year Studies: Mean body weights of chemically exposed male rats generally ranged from 80% to 94% of those of vehicle controls, and mean body weights of chemically exposed female rats were from 90% to 97% of those of vehicle controls. Mean body weights of chemically exposed male mice were similar to those of vehicle controls; mean body weights of chemically exposed female mice were 79%-95% of those of vehicle controls. Virtually all male and female rats that received glycidol died or were killed in a moribund condition as a result of the early induction of neoplastic disease (final survival--male: vehicle control, 16/50; low dose, 0/50; high dose, 0/50; female: 28/50; 4/50; 0/50). Survival of vehicle control male rats was lower than that usually observed; however, specific causes of deaths could not be determined. The survival of male mice and low dose female mice was similar to that of vehicle controls; survival of female mice that received 50 mg/kg was lower than that of vehicle controls after week 101 (final survival--male: 33/50; 25/50; 27/50; female: 29/50; 27/50; 17/50).

Nonneoplastic and Neoplastic Effects in the Two-Year Studies: Chemical-related nonneoplastic lesions in both rats and mice included hyperkeratosis and epithelial dysplasia of the forestomach. Fibrosis of the spleen was also present in rats of each sex, and cysts of the preputial gland and kidney were present in male mice.

Exposure to glycidol induced dose-related increases in the incidences of neoplasms in numerous tissues in both rats and mice (see facing table). In male rats, mesotheliomas arising in the tunica vaginalis and frequently metastasizing to the peritoneum were considered the major cause of early death. Early deaths in female rats were associated with the presence of mammary gland neoplasms.

Genetic Toxicology: Glycidol was mutagenic in a variety of in vitro and in vivo short-term tests. Mutagenic activity was observed in *S. typhimurium* strains TA97, TA98, TA100, TA1535, and TA1537 exposed to glycidol with and without exogenous metabolic activation. Glycidol was positive in the absence of exogenous metabolic activation in the mouse lymphoma assay for induction of trifluorothymidine resistance in L5178Y/TK cells; it was not tested with activation. In cytogenetic tests with CHO cells, glycidol induced both sister chromatid exchanges and chromosomal aberrations in the presence and absence of exogenous metabolic activation. Glycidol induced sex-linked recessive lethal mutations and reciprocal translocations in the germ cells of male *D. melanogaster* exposed by feeding. The incidence of micronucleated polychromatic erythrocytes was increased in the bone marrow of male $B6C3F_1$ mice administered glycidol by intraperitoneal injection.

Conclusions: Under the conditions of these 2-year gavage studies, there was *clear evidence of carcinogenic activity** of glycidol for male F344/N rats, based on increased incidences of mesotheliomas of the tunica vaginalis; fibroadenomas of the mammary gland; gliomas of the brain; and neoplasms of the forestomach, intestine, skin, Zymbal gland, and thyroid gland. There was *clear evidence of carcinogenic activity* for female F344/N rats, based on increased incidences of fibroadenomas and adenocarcinomas of the mammary gland; gliomas of the brain; neoplasms of the oral mucosa, forestomach, clitoral gland, and thyroid gland; and leukemia. There was *clear evidence of carcinogenic activity* for male $B6C3F_1$ mice, based on increased incidences of neoplasms of the harderian gland, forestomach, skin, liver, and lung. There was *clear evidence of carcinogenic activity* for female $B6C3F_1$ mice, based on increased incidences of neoplasms of the harderian gland, mammary gland, uterus, subcutaneous tissue, and skin. Other neoplasms that may have been related to the administration of glycidol were fibrosarcomas of the glandular stomach in female rats and carcinomas of the urinary bladder and sarcomas of the epididymis in male mice.

*Explanation of Levels of Evidence of Carcinogenic Activity is on page 6.
A summary of the Peer Review comments and the public discussion on this Technical Report appears on pages 9-10.

NEOPLASMS ASSOCIATED WITH THE TWO-YEAR GAVAGE ADMINISTRATION OF GLYCIDOL (a)

Site/Neoplasm	Male			Female		
RATS	**Veh. Control**	**37.5 mg/kg**	**75 mg/kg**	**Veh. Control**	**37.5 mg/kg**	**75 mg/kg**
Tunica vaginalis/peritoneum						
Mesothelioma	3/49	34/50	39/47			
Mammary gland						
Fibroadenoma	3/45	8/39	7/17	14/49	32/46	29/44
Adenocarcinoma				1/50	11/48	16/48
Brain						
Glioma	0/46	5/50	6/30	0/49	4/46	4/46
Oral mucosa						
Papilloma or carcinoma				1/46	3/37	7/26
Forestomach						
Papilloma or carcinoma	1/46	2/50	6/32	0/47	4/38	11/30
Intestine						
Adenomatous polyp or adenocarcinoma	0/47	1/50	4/37			
Skin						
Sebaceous gland adenoma, basal cell tumor, or sebaceous gland adenocarcinoma	0/45	5/41	4/18			
Zymbal gland						
Carcinoma	1/49	3/50	6/48			
Clitoral gland						
Adenoma, adenocarcinoma, or carcinoma				5/49	9/47	12/45
Thyroid gland						
Follicular cell adenoma or carcinoma	1/46	4/42	6/19	0/49	1/38	3/35
Hematopoietic system						
Leukemia				13/49	14/44	20/41
MICE	**Veh. Control**	**25 mg/kg**	**50 mg/kg**	**Veh. Control**	**25 mg/kg**	**50 mg/kg**
Harderian gland (b)						
Adenoma or adenocarcinoma	8/46	12/41	22/44	4/46	11/43	17/43
Mammary gland						
Adenoma, fibroadenoma, or adenocarcinoma				2/50	6/50	15/50
Forestomach						
Squamous cell papilloma or carcinoma	1/50	2/50	10/50			
Uterus						
Carcinoma or adenocarcinoma				0/50	3/50	3/50
Subcutaneous tissue						
Sarcoma or fibrosarcoma				0/50	3/50	9/50
Skin						
Squamous cell papilloma or carcinoma	0/50	0/50	4/50	0/50	0/50	2/50
Liver						
Adenoma or carcinoma	24/50	31/50	35/50			
Lung						
Alveolar/bronchiolar adenoma or carcinoma	13/50	11/50	21/50			

(a) A blank space indicates that the tumor incidence at that site and in that sex was not increased by chemical exposure. Tumor incidence is expressed as the number of tumor-bearing animals divided by the number of animals alive in each group at the time the first tumor was observed in any of the three groups.
(b) The denominators for the incidence of harderian gland tumors are the actual number of harderian glands available for microscopic examination.

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

The National Toxicology Program describes the results of individual experiments on a chemical agent and notes the strength of the evidence for conclusions regarding each study. Negative results, in which the study animals do not have a greater incidence of neoplasia than control animals, do not necessarily mean that a chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of conditions. Positive results demonstrate that a chemical is carcinogenic for laboratory animals under the conditions of the study and indicate that exposure to the chemical has the potential for hazard to humans. Other organizations, such as the International Agency for Research on Cancer, assign a strength of evidence for conclusions based on an examination of all available evidence including: animal studies such as those conducted by the NTP, epidemiologic studies, and estimates of exposure. Thus, the actual determination of risk to humans from chemicals found to be carcinogenic in laboratory animals requires a wider analysis that extends beyond the purview of these studies.

Five categories of evidence of carcinogenic activity are used in the Technical Report series to summarize the strength of the evidence observed in each experiment: two categories for positive results ("Clear Evidence" and "Some Evidence"); one category for uncertain findings ("Equivocal Evidence"); one category for no observable effects ("No Evidence"); and one category for experiments that because of major flaws cannot be evaluated ("Inadequate Study"). These categories of interpretative conclusions were first adopted in June 1983 and then revised in March 1986 for use in the Technical Reports series to incorporate more specifically the concept of actual weight of evidence of carcinogenic activity. For each separate experiment (male rats, female rats, male mice, female mice), one of the following quintet is selected to describe the findings. These categories refer to the strength of the experimental evidence and not to either potency or mechanism.

- **Clear Evidence of Carcinogenic Activity** is demonstrated by studies that are interpreted as showing a dose-related (i) increase of malignant neoplasms, (ii) increase of a combination of malignant and benign neoplasms, or (iii) marked increase of benign neoplasms if there is an indication from this or other studies of the ability of such tumors to progress to malignancy.

- **Some Evidence of Carcinogenic Activity** is demonstrated by studies that are interpreted as showing a chemically related increased incidence of neoplasms (malignant, benign, or combined) in which the strength of the response is less than that required for clear evidence.

- **Equivocal Evidence of Carcinogenic Activity** is demonstrated by studies that are interpreted as showing a marginal increase of neoplasms that may be chemically related.

- **No Evidence of Carcinogenic Activity** is demonstrated by studies that are interpreted as showing no chemically related increases in malignant or benign neoplasms.

- **Inadequate Study of Carcinogenic Activity** is demonstrated by studies that because of major qualitative or quantitative limitations cannot be interpreted as valid for showing either the presence or absence of carcinogenic activity.

When a conclusion statement for a particular experiment is selected, consideration must be given to key factors that would extend the actual boundary of an individual category of evidence. This should allow for incorporation of scientific experience and current understanding of long-term carcinogenesis studies in laboratory animals, especially for those evaluations that may be on the borderline between two adjacent levels. These considerations should include:

- The adequacy of the experimental design and conduct;
- Occurrence of common versus uncommon neoplasia;
- Progression (or lack thereof) from benign to malignant neoplasia as well as from preneoplastic to neoplastic lesions;
- Some benign neoplasms have the capacity to regress but others (of the same morphologic type) progress. At present, it is impossible to identify the difference. Therefore, where progression is known to be a possibility, the most prudent course is to assume that benign neoplasms of those types have the potential to become malignant;
- Combining benign and malignant tumor incidences known or thought to represent stages of progression in the same organ or tissue;
- Latency in tumor induction;
- Multiplicity in site-specific neoplasia;
- Metastases;
- Supporting information from proliferative lesions (hyperplasia) in the same site of neoplasia or in other experiments (same lesion in another sex or species);
- The presence or absence of dose relationships;
- The statistical significance of the observed tumor increase;
- The concurrent control tumor incidence as well as the historical control rate and variability for a specific neoplasm;
- Survival-adjusted analyses and false positive or false negative concerns;
- Structure-activity correlations; and
- In some cases, genetic toxicology.

CONTRIBUTORS

The NTP Technical Report on the Toxicology and Carcinogenesis Studies of Glycidol is based on 13-week studies that began in March 1980 and ended in May 1980 and on 2-year studies that began in July 1981 and ended in July 1983 at Papanicolaou Cancer Research Institute (Miami, FL)

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PEER REVIEW PANEL

The members of the Peer Review Panel who evaluated the draft Technical Report on glycidol on June 27, 1989, are listed below. Panel members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, Panel members have five major responsibilities: (a) to ascertain that all relevant literature data have been adequately cited and interpreted, (b) to determine if the design and conditions of the NTP studies were appropriate, (c) to ensure that the Technical Report presents the experimental results and conclusions fully and clearly, (d) to judge the significance of the experimental results by scientific criteria, and (e) to assess the evaluation of the evidence of carcinogenicity and other observed toxic responses.

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SUMMARY OF PEER REVIEW COMMENTS ON THE TOXICOLOGY AND CARCINOGENESIS STUDIES OF GLYCIDOL

On June 27, 1989, the draft Technical Report on the toxicology and carcinogenesis studies of glycidol received public review by the National Toxicology Program Board of Scientific Counselors' Technical Reports Review Subcommittee and associated Panel of Experts. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Dr. R.D. Irwin, NIEHS, introduced the toxicology and carcinogenesis studies of glycidol by reviewing the experimental design, results, and proposed conclusions (clear evidence of carcinogenic activity for male and female rats and mice).

Dr. Irwin noted that because survival of chemically exposed rats was reduced by the early and widespread onset of neoplasia, the usual convention of expressing tumor incidence might underestimate the true incidence that would have occurred in the absence of such reduced survival. Therefore, tumor analyses for rats were based on the effective number of rats in each group, i.e., the number of rats alive at the time that the first rat died or was killed in a moribund condition with the tumor at a particular site.

Dr. Popp, a principal reviewer, agreed with the conclusions. He also agreed with the approach described by Dr. Irwin based on the effective number of animals and suggested that the rationale could be highlighted better in the Materials and Methods section. He asked for an explanation of the poor survival in vehicle control rats. Dr. Irwin indicated that there was no ready explanation and this would be noted in the Report.

Dr. McKnight, the second principal reviewer, agreed with the conclusions. She thought the tumor sites supporting the level of evidence should be listed in the conclusions. She said that the statement that exposure to the chemical accelerated the development of advanced stages of mononuclear cell leukemia should either be given more support or omitted. Dr. Irwin agreed and said that the effect on leukemia would be given less emphasis.

Dr. Garman, the third principal reviewer, agreed with the conclusions. He expressed concern about the brevity of the histopathology portion of the Report in that the sections dealing with microscopic lesions were restricted primarily to statements of lesion frequencies. Dr. S. Eustis, NIEHS, responded that extensive histologic descriptions had not been prepared because the studies were overwhelmingly positive and a large percentage of the neoplasms were malignant. He said that brief histologic descriptions would be added.

Dr. Gold suggested adding more details as to which target sites support the evaluation of clear evidence of carcinogenic activity and which do not. Dr. J. Huff, NIEHS, explained that the NTP philosophy was to arrive at an overall conclusion for each study. Dr. Ashby suggested that assignment of a level of evidence to each tumor site might be helpful in examining carcinogenic mechanisms. Dr. Gold asked that estimates of worker exposure from the National Occupational Exposure Survey be added to the Report.

In comments from the audience, Dr. Donald McFee, representing Occusafe, a private consulting firm, suggested that there be some discussion on the possible effects of the 6% impurities, especially α-chlorohydrin and diglycidyl ether. Mr. Ralph Johnson, Vice President of Environmental Affairs, Dixie Chemical Company, the sole domestic manufacturer of glycidol, commented on human exposure

studies that they had conducted at all customer sites. He said that the studies indicated that about 70 persons were exposed annually at concentrations not exceeding 2 ppm.

Dr. Popp moved that the Technical Report on glycidol be accepted with the conclusions as written for male and female rats and mice, clear evidence of carcinogenic activity. Dr. Garman seconded the motion, which was accepted unanimously by the Panel.

I. INTRODUCTION

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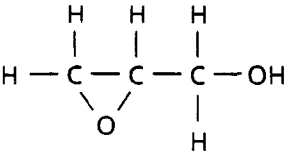

GLYCIDOL

CAS No. 556-52-5

$C_3H_6O_2$ Molecular weight 74.1

Synonyms: 2,3-epoxy-1-propanol

Glycidol is a colorless, viscous liquid soluble in both water and organic solvents. The threshold limit value time-weighted average for glycidol is 25 ppm (ACGIH, 1988). At 25° C, the vapor pressure of glycidol is 0.9 mm mercury. The carbon atom in the 2 position is chiral; thus, glycidol exists as two enantiomers, differing with respect to the projection of the hydroxymethyl group above or below the plane of the epoxide ring (March, 1978).

The primary use for glycidol is as a stabilizer in the manufacture of vinyl polymers; however, it is also used as an intermediate in the production of pharmaceuticals, as an additive for oil and synthetic hydraulic fluids, and as a diluent in some epoxy resins. The glycidol structure is present in two commercially important groups of derivatives, glycidyl ethers and glycidyl esters, neither of which is prepared directly from glycidol. Glycidyl ethers are prepared on a commercial scale in a closed system by addition of the appropriate alcohol to epichlorohydrin in the presence of a catalyst. The end product is a mixed ether, one component of which is the glycidyl group. Glycidyl esters are prepared by reacting the sodium salt of the appropriate carboxylic acid with epichlorohydrin. Both types of derivatives are used almost exclusively as diluents in epoxy resins. Over 10 million pounds of glycidyl compounds, the majority of which are glycidyl ethers and glycidyl esters, are produced or imported into the United States annually (Fed. Regist., 1983).

The scheme illustrated in Figure 1 shows the known and proposed metabolic reactions of glycidol. Because of the reactivity of epoxides, in solution glycidol can undergo several spontaneous reactions involving nucleophilic attack at the α or β carbon (March, 1978); at neutral pH and 37° C, glycidol slowly hydrolyzes to glycerol; in 0.1 M hydrochloric acid, the hydrolysis to glycerol (97.2%) and α-chlorohydrin (3-chloro-1,2-propanediol) (2.8%) occurs rapidly, with a half-life of 10 minutes. At pH 6, glycidol does not readily react with glutathione; however, at pH 7 or 8, the reaction to form *S*-(2,3-dihydroxypropyl)glutathione occurs readily. Glycidol may also directly alkylate various cellular components (Jones, 1975).

The major urinary metabolites isolated from rats administered glycidol by intraperitoneal injection are *S*-(2,3-dihydroxypropyl)glutathione, *S*-(2,3-dihydroxypropyl)cysteine, and β-chlorolactic acid. The latter compound was identified as the only radioactive urinary metabolite of glycidol isolated from rats administered [^{36}Cl]saline for 3 days before glycidol administration (Jones and O'Brien, 1980). The same urinary metabolites are found after α-chlorohydrin administration, suggesting that glycidol is converted to α-chlorohydrin by direct reaction with hydrochloric acid in the stomach. α-Chlorohydrin may then be converted to the glutathione metabolite by the action of glutathione transferase or oxidized to β-chlorolactate by the successive action of alcohol dehydrogenase and aldehyde dehydrogenase. The conversion of glycidol to glycerol by epoxide hydrase has been observed with rat liver microsomal preparations (Patel et al., 1980). The oxidation of glycidol to glycidaldehyde has not been observed, but glycidaldehyde is a potential metabolite formed by the action of alcohol dehydrogenase.

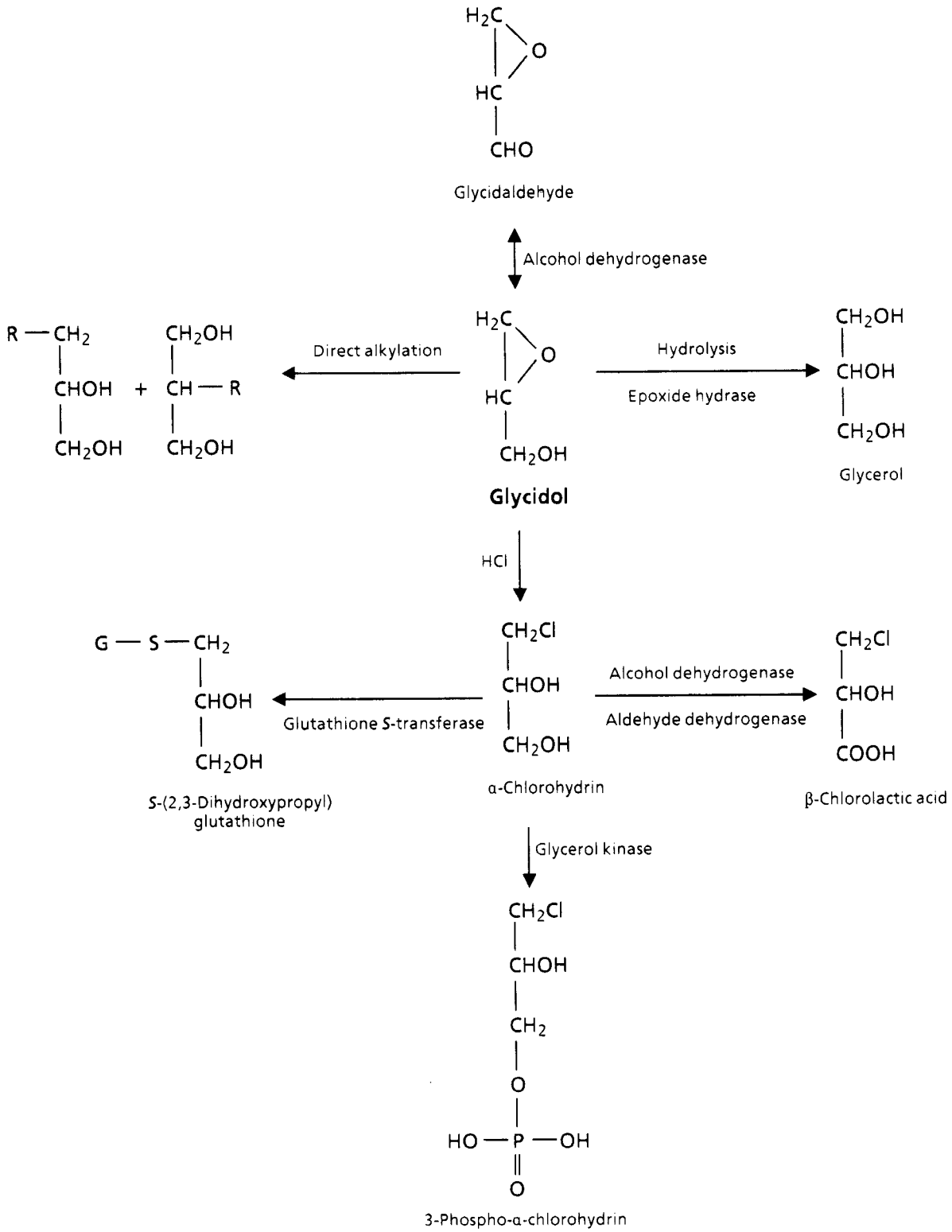

FIGURE 1. METABOLIC PATHWAYS FOR GLYCIDOL

α-Chlorohydrin reduces sperm motility and causes infertility in male rats, perhaps as a result of the uptake of and phosphorylation of α-chlorohydrin by sperm (Mohri et al., 1975; Chulavatnatol et al., 1977; Jones, 1978). Phosphorylated α-chlorohydrin is an inhibitor of triose phosphate isomerase and glyceraldehyde phosphate dehydrogenase, and as a result of its accumulation, glycolysis is inhibited, reducing the ATP concentration and hence motility of affected sperm. Glycidol causes similar antifertility when administered to male rats (Jackson et al., 1970); this has been attributed to conversion to α-chlorohydrin, as suggested by metabolic studies.

Glycidol has been evaluated for teratogenicity in both rats and mice. Intra-amniotic injection of glycidol into pregnant Sprague Dawley rats on day 13 of gestation caused embryolethality and induced malformation in a significant number of fetuses (Slott and Hales, 1985). No evidence of teratogenicity was observed in a study in which pregnant CD®-1 mice received 100, 150, or 200 mg/kg glycidol by gavage during days 6-15 of gestation (Marks et al., 1982).

Glycidol has produced positive results in several tests of genotoxicity. A number of reports have documented the induction of gene mutations in *Salmonella typhimurium* base substitution strains TA100 and TA1535 with or without S9 activation (McCann et al., 1975; Wade et al., 1979; Simmon et al., 1979; Thompson et al., 1981; Kaplan et al., 1982; Mamber et al., 1984). Glycidol induced gene mutations in *Saccharomyces cerevisiae* (Izard, 1973), *S. pombe* (Heslot, 1962; Migliore et al., 1982), and *Neurospora crassa* (Kolmark and Giles, 1955) in the absence of exogenous activation. In tests with mammalian cells, glycidol induced unscheduled DNA synthesis in human W138 cells and mouse L5178Y/TK cells in the absence of S9 (Thompson et al., 1981) and induced chromosomal aberrations and sister chromatid exchanges in human lymphocytes in the absence of S9 (Norppa et al., 1981). Glycidol administered to Wistar rats by intraperitoneal injection induced chromosomal aberrations in bone marrow cells of both males and females (Thompson and Gibson, 1984).

The dermal carcinogenicity of glycidol has been evaluated in a study in which a 5% solution in acetone was applied to the backs of female ICR/Ha Swiss mice, three times per week for 2 years (Van Duuren et al., 1967). Glycidol application produced no visible reaction on the skin; however, similar application of a 10% solution of glycidaldehyde to 41 mice induced the formation of papillomas in 6 and carcinomas in 3. In studies conducted by the National Toxicology Program (NTP) in rats and mice, diglycidyl resorcinol ether, a glycidol derivative, administered by gavage in corn oil for 2 years induced hyperkeratosis, hyperplasia, and neoplasms of the forestomach in both species (NTP, 1986); in 2-year inhalation studies, 1,2-epoxybutane induced papillary adenomas of the nasal cavity in male and female rats and alveolar/bronchiolar neoplasms in male rats (NTP, 1988). In inhalation studies, ethylene oxide induced neoplasms of the lung and harderian gland in both male and female mice (NTP, 1987).

Glycidol and certain representative glycidyl ethers and esters were selected for carcinogenicity evaluation by NTP because of the potential for widespread human exposure to glycidol and the glycidyl group associated with the presence of these compounds in epoxy resins.

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF GLYCIDOL

CHARACTERIZATION OF DOSE MIXTURES

SIXTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

- Study Design
- Source and Specifications of Animals
- Animal Maintenance
- Clinical Examinations and Pathology
- Statistical Methods

PROCUREMENT AND CHARACTERIZATION OF GLYCIDOL

Glycidol was obtained in one lot (lot no. 1536A) from the Dixie Chemical Company (Houston, TX). Purity and identity analyses were conducted at Midwest Research Institute (Kansas City, MO) (Appendix G). Chemical identity was confirmed by infrared and nuclear magnetic resonance spectroscopy.

Glycidol was found to be 94% pure, as determined by elemental analysis, Karl Fischer water analysis, titration of the epoxide function, and gas chromatography.

Impurities in the glycidol study material were identified and quantitated by gas chromatography and combined gas chromatography/mass spectrometry. Impurities with peak areas greater than or equal to 0.1% relative to the major peak area were as follows: methanol, approximately 0.1%; 3-methoxy-1,2-propanediol, 1.2%; 3-chloro-1,2-propanediol (α-chlorohydrin), 0.4%; diglycidyl ether, 2.8%; and 2,6-dimethanol-1,4-dioxane, 1.1%.

The identity of the chemical at the study laboratory was confirmed by infrared spectroscopy. The stability of the study material was monitored by epoxide titration and gas chromatographic analysis. No notable degradation occurred over the course of the studies.

CHARACTERIZATION OF DOSE MIXTURES

The 2-week stability of glycidol at 20 mg/ml in water stored at room temperature and 5° C was determined by the analytical laboratory. The water solutions were diluted with acetonitrile and analyzed by gas chromatography with a 10% Carbowax 20M column and a flame ionization detector. The water solutions were found to be unstable when stored at room temperature. Storage at 5° C resulted in minimal loss (2%) after 7 days, but a significant loss (5%) was observed after 14 days.

Studies conducted by the study laboratory indicated that dose mixtures (2.54 and 15.4 mg/ml) lost 0.2%-0.3% glycidol per day during storage at 3°-6° C. Additional losses occurred while the solutions were held for about 3 hours at room temperature during the dosing period. Losses averaged 2.7% after 7 days of storage and animal-room exposure. During the 13-week studies, glycidol/distilled water mixtures were stored at 2°-5° C for no longer than 9 days. During the 2-year studies, the dose mixtures were stored at 3°-6° C for no longer than 11 days.

During the 2-year studies, the dose mixtures were analyzed every 1 or 2 months, and concentrations varied from 89% to 113% of the target concentration (Table G2). For glycidol, it is estimated that the mixtures were formulated within ±10% of the target concentrations approximately 97% (61/63) of the time throughout the studies. Results of periodic referee analysis of dose mixtures by an independent laboratory were generally lower than those observed by the study laboratory, probably due in part to the instability of the chemical in water under the conditions of shipment and storage (Table G3).

SIXTEEN-DAY STUDIES

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories and observed for 19 (rats) or 20 (mice) days before the studies began. The rats were 7 weeks old when placed on study, and the mice were 8 weeks old.

Groups of five rats and five mice of each sex were administered 0, 37.5, 75, 150, 300, or 600 mg/kg glycidol in distilled water by gavage on 14 days over a 16-day period. Animals were housed five per cage. Water and feed were available ad libitum. Further experimental details are summarized in Table 1.

The rats and mice were observed twice per day and weighed once per week. A necropsy was performed on most animals. Tissues and groups examined are listed in Table 1.

THIRTEEN-WEEK STUDIES

Thirteen-week studies were conducted to evaluate the cumulative toxic effects of repeated administration of glycidol and to determine the doses to be used in the 2-year studies.

TABLE 1. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF GLYCIDOL

Sixteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
EXPERIMENTAL DESIGN		
Size of Study Groups		
5 males and 5 females of each species	10 males and 10 females of each species	50 males and 50 females of each species
Doses		
0, 37.5, 75, 150, 300, or 600 mg/kg glycidol in distilled water by gavage; dose vol--rats: 5 ml/kg; mice: 10 ml/kg	Rats--0, 25, 50, 100, 200, or 400 mg/kg glycidol in distilled water by gavage; mice--0, 19, 38, 75, 150, or 300 mg/kg (mice received 125% of the nominal doses during wk 2); dose vol--rats: 5 ml/kg; mice: 10 ml/kg	Rats--0, 37.5, or 75 mg/kg glycidol in distilled water by gavage; mice--0, 25, or 50 mg/kg; dose vol--rats: 5 ml/kg; mice: 10 ml/kg
Date of First Dose		
11/19/79	3/3/80	Rats--7/20/81; mice--8/3/81
Date of Last Dose		
12/4/79	5/30/80	Rats--7/8/83; mice--7/22/83
Duration of Dosing		
5 d/wk on 14 d over 16 d	5 d/wk for 13 wk	5 d/wk for 103 wk
Type and Frequency of Observation		
Observed 2 × d; weighed 1 wk before dosing and on d 8 and 16	Observed 2 × d; rats weighed at start of study and 1 × wk thereafter; mice weighed on d 3 and 1 × wk thereafter	Observed 2 × d; weighed initially, 1 × wk for 12 wk, and 1 × mo thereafter
Necropsy, Histologic Examinations, and Supplemental Studies		
Necropsy performed on all vehicle controls, all rats, and the following mice that lived to the end of the studies: 2 males and 3 females in the 300 mg/kg groups and 4 males and 3 females in the 150 mg/kg groups. Histologic exams performed on all rats in the 300 mg/kg groups and on all mice on which necropsies were performed. Tissues examined include: adrenal glands, bone marrow, brain, colon, duodenum, esophagus, eyes, external and middle ear, gallbladder (mice), harderian gland, heart, ileum, jejunum, kidneys, liver, lungs, mammary gland, mandibular and mesenteric lymph nodes, nasal cavity, pancreas, parathyroids, pituitary gland, rectum, salivary glands, sciatic nerve, seminal vesicles/prostate/testes or ovaries/uterus, skin, spinal cord, spleen, stomach, thigh muscle, thymus, thyroid gland, and trachea	Necropsy performed on all animals. Histologic exams performed on all vehicle controls, all mice dying before the end of the studies, all rats in the 200 and 400 mg/kg groups, and all mice in the 150 and 300 mg/kg groups. Histologic exams performed on brain from rats in the 100 mg/kg groups and mice in the 75 mg/kg groups and on testes from rats in the 25, 50, and 100 mg/kg groups and from mice in the 19, 38, and 75 mg/kg groups. Sperm count and motility analysis performed for male vehicle controls and rats in the 25, 100, and 200 mg/kg groups and mice in the 19, 75, and 150 mg/kg groups (on 5 animals per group)	Necropsy and histologic exams performed on all animals; tissues examined include: adrenal glands, brain, cecum, colon, costochondral junction, duodenum, esophagus, eyes, gallbladder (mice), gross lesions, harderian gland, heart and aorta, ileum, jejunum, kidneys, liver, lungs and bronchi, mammary gland, nasal cavity and turbinates, pancreas, parathyroids, pituitary gland, prostate/seminal vesicles/testes/epididymis/tunica vaginalis/scrotal sac or ovaries/uterus, rectum, salivary glands, skin, spleen, sternebrae, stomach, thymus, thyroid gland, trachea, and urinary bladder
Strain and Species		
F344/N rats; $B6C3F_1$ mice	F344/N rats; $B6C3F_1$ mice	F344/N rats; $B6C3F_1$ mice
Animal Source		
Charles River Breeding Laboratories (Portage, MI)	Charles River Breeding Laboratories (Portage, MI)	Charles River Breeding Laboratories (Kingston, NY)

TABLE 1. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF GLYCIDOL (Continued)

Sixteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
ANIMALS AND ANIMAL MAINTENANCE		
Study Laboratory		
Papanicolaou Cancer Research Institute	Papanicolaou Cancer Research Institute	Papanicolaou Cancer Research Institute
Method of Animal Identification		
Ear notch, toe clip	Ink mark, ear clip, toe clip	Ear notch, toe clip
Time Held Before Study		
Rats--19 d; mice--20 d	18 d	Rats--19 d; mice--25 d
Age When Placed on Study		
Rats--7 wk; mice--8 wk	Rats--7 wk; mice--8 wk	Rats--8 wk; mice--9 wk
Age When Killed		
10 wk	Rats--21 wk; mice--22 wk	Rats--112 wk; mice--113-114 wk
Necropsy Dates		
12/5/79	6/2/80-6/9/80	Rats--7/18/83; mice--8/1/83-8/3/83
Method of Animal Distribution		
Animals distributed to weight classes and then assigned to cages by one table of random numbers and to groups by another table of random numbers	Same as 16-d studies	Same as 16-d studies
Feed		
Purina Lab Chow® (Ralston Purina Co., St. Louis, MO); available ad libitum	NIH 07 Rat and Mouse Ration (Zeigler Bros., Inc., Gardners, PA); available ad libitum	Same as 13-wk studies
Bedding		
Sani Chips, hardwood pine (Pinewood Products Company)	Same as 16-d studies	Beta Chips (Northeastern Products, Inc., Warrensburg, NY)
Water		
Automatic watering system (Edstrom Industries, Waterford, WI); available ad libitum	Same as 16-d studies	Same as 16-d studies
Cages		
Polycarbonate (Lab Products, Inc., Garfield, NJ)	Same as 16-d studies	Same as 16-d studies
Cage Filters		
Cerex® spun-bonded nylon (Monsanto Co., St. Louis, MO)	Same as 16-d studies	Same as 16-d studies
Animals per Cage		
5	5	5
Other Chemicals on Study in the Same Room		
None	None	None
Animal Room Environment		
Temp--74°-76° F; hum--50%; fluorescent light 12 h/d; 15-18 room air changes/h	Temp--72°-76° F; hum--40%-60%; fluorescent light 12 h/d; 10-15 room air changes/h	Temp--68°-80° F; hum--30%-75%; fluorescent light 12 h/d; 10-15 room air changes/h

Four-week-old male and female F344/N rats and 5-week-old male and female B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories, observed for 18 days, distributed to weight classes, and then assigned to cages according to a table of random numbers. Cages were assigned to dosed and vehicle control groups according to another table of random numbers.

Groups of 10 rats of each sex were administered 0, 25, 50, 100, 200, or 400 mg/kg glycidol in distilled water by gavage, 5 days per week for 13 weeks. Groups of 10 mice of each sex were administered 0, 19, 38, 75, 150, or 300 mg/kg according to the same schedule. Because of a dose-mixing error, mice received 125% of the nominal doses during week 2. Rats and mice were housed five per cage in polycarbonate cages. Feed and water were available ad libitum. Further experimental details are summarized in Table 1.

Animals were observed two times per day; moribund animals were humanely killed. Individual animal weights were recorded once per week. At the end of the 13-week studies, survivors were killed. A necropsy was performed on all animals. Tissues and groups examined are listed in Table 1.

The general morphology of sperm, percentage of motile sperm, and number of sperm per sample were determined according to the method of Wyrobek and Bruce (1975) at the time of the scheduled kill for five male rats in the 0, 25, 100, and 200 mg/kg groups and for five male mice in the 0, 19, 75, and 150 mg/kg groups.

TWO-YEAR STUDIES

Study Design

Groups of 50 rats of each sex were administered 0, 37.5, or 75 mg/kg glycidol in distilled water by gavage, 5 days per week for 103 weeks. Groups of 50 mice of each sex were administered 0, 25, or 50 mg/kg according to the same schedule.

Source and Specifications of Animals

The male and female F344/N rats and B6C3F$_1$ (C57BL/6N, female × C3H/HeN MTV$^-$, male) mice used in these studies were produced under strict barrier conditions at Charles River Breeding Laboratories. Breeding stock for the foundation colonies at the production facility originated at the National Institutes of Health Repository. Animals shipped for study were progeny of defined microflora-associated parents that were transferred from isolators to barrier-maintained rooms. Rats were shipped to the study laboratory at 4-5 weeks of age and mice at 5-6 weeks. Rats were quarantined at the study facility for 19 days and mice for 25 days. Thereafter, a complete necropsy was performed on five animals of each sex and species to assess their health status. The rats were placed on study at 8 weeks of age and the mice at 9 weeks. The health of the animals was monitored during the course of the studies according to the protocols of the NTP Sentinel Animal Program (Appendix E).

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$_1$ study animal. In mid-1981, data were obtained that showed incompatibility between the NIH C3H reference colony and the C3H colony from a Program supplier. In August 1981, inbred parental lines of mice were further tested for genetic integrity via isozyme and protein electrophoresis profiles that demonstrate phenotype expressions of known genetic loci.

The C57BL/6N 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 from this supplier. Nevertheless, the genome of this line is more homogeneous than that of randomly bred stocks.

Male mice from the C3H colony and female mice from the C57BL/6N 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 these results is not known, but results of the studies are not affected because concurrent controls were included in each study.

Animal Maintenance

Animals were housed five per cage. Feed (Appendix F) and water were available ad libitum. Cages were not rotated during the studies. Further details of animal maintenance are given in Table 1.

Clinical Examinations and Pathology

All animals were observed two times per day. Body weights were recorded once per week for the first 12 weeks of the studies and once per month thereafter. Mean body weights were calculated for each group. Animals found moribund and those surviving to the end of the studies were humanely killed. A necropsy was performed on all animals; however, 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.

During necropsy, all organs and tissues were examined for grossly visible lesions. Tissues were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Tissues examined are listed in Table 1.

When the pathology evaluation was completed by the laboratory pathologist and the pathology data entered into the Carcinogenesis Bioassay Data System, the slides, paraffin blocks, and residual formalin-fixed tissues were sent to the NTP Archives. The slides, blocks, and residual wet tissues were audited for accuracy of labeling and animal identification and for thoroughness of tissue trimming. The slides, individual animal necropsy records, and pathology tables were sent to an independent pathology quality assessment laboratory. The individual animal records and pathology tables were compared for accuracy, slides and tissue counts were verified, and histotechnique was evaluated. All tissues with a tumor diagnosis, all potential target tissues, and all tissues from a randomly selected 10% of the animals were re-evaluated microscopically by a quality assessment pathologist. Potential target organs and tissues were the forestomach, brain, and spleen for male and female rats; tunica vaginalis and Zymbal gland for male rats; mammary gland and clitoral gland for female rats; liver, lung, and harderian gland for male and female mice; lung and teeth for male mice; and mammary gland for female mice. Nonneoplastic lesions were evaluated for accuracy and consistency of diagnosis in the potential target organs, in the randomly selected 10% of animals, and in tissues with unusual incidence patterns or trends. Tissues are generally not evaluated in a "blind" fashion (i.e., without knowledge of dose group) unless the lesions in question are subtle.

The quality assessment report and slides were submitted to a Pathology Working Group (PWG) Chairperson, who reviewed microscopically all potential target tissues and any other tissues for which there was a disagreement in diagnosis between the laboratory and quality assessment pathologists. Representative examples of potential chemical-related nonneoplastic lesions and neoplasms and examples of disagreements in diagnosis between the laboratory and quality assessment pathologists were shown to the PWG. The PWG, which included the laboratory pathologist, the quality assessment pathologist, and other pathologists experienced in rodent toxicology, examined the tissues without knowledge of dose group or previously rendered diagnoses. When the consensus diagnosis of the PWG differed from that of the laboratory pathologist, the diagnosis was changed to reflect the opinion of the PWG. This procedure has been described, in part, by Maronpot and Boorman (1982) and Boorman et al. (1985). The final pathology data represent a consensus of contractor pathologists and the NTP Pathology Working Group. For subsequent analysis of pathology data, the diagnosed lesions for each tissue type are combined according to the guidelines of McConnell et al. (1986).

Statistical Methods

Survival Analyses: The probability of survival was estimated by the product-limit procedure of Kaplan and Meier (1958) and is presented in the form of graphs. Animals were censored from the survival analyses at the time they were found to be missing or dead from other than natural causes; animals dying from natural causes were not 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) life table test for a dose-related trend. When significant survival differences were detected, additional analyses using these procedures were carried out to determine the time point at which significant differences in the survival curves were first detected. All reported P values for the survival analysis are two-sided.

Calculation of Incidence--Mice: The incidence of neoplastic or nonneoplastic lesions is 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 include only those animals for which the 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 a necropsy was performed.

Analysis of Tumor Incidence--Mice: The majority of tumors in this study were considered to be incidental to the cause of death or not rapidly lethal. Thus, the primary statistical method used was an incidental tumor analysis, which assumed that the diagnosed tumors were discovered as the result of death from an unrelated cause and thus did not affect the risk of death. In this approach, the proportions of tumor-bearing animals in dosed and vehicle control groups were compared in each of five time intervals: weeks 0-52, weeks 53-78, weeks 79-92, week 93 to the week before the terminal-kill period, and the terminal-kill period. The denominators of these proportions were the number of animals actually examined for tumors during the time interval. The individual time interval comparisons were then combined to obtain a single overall result.

In addition to incidental tumor analysis, alternative methods of statistical analysis were used, and the results of these tests are summarized in Appendixes C and D. These include the life table test (Cox, 1972; Tarone, 1975), appropriate for rapidly lethal tumors, and the Fisher exact test and the Cochran-Armitage trend test (Armitage, 1971; Gart et al., 1979), procedures based on the overall proportion of tumor-bearing animals. Tests of significance include pairwise comparisons of each dosed group with vehicle controls and a test for an overall dose-response trend. Continuity-corrected tests were used in the analysis of tumor incidence, and reported P values are one-sided. The procedures described above also were used to evaluate selected nonneoplastic lesions. (For further discussion of these statistical methods, see Haseman, 1984.)

Calculation of Incidence--Rats: Because early deaths from mesotheliomas or mammary gland neoplasms reduced the number of male or female rats at risk for development of neoplasms at other sites, the usual convention of expressing tumor incidence (the number of animals with tumors at a site divided by the total number of animals in which this site was examined) may underestimate the tumor incidence that would have been observed in the absence of early deaths. This would be especially true for tumors that were not rapidly lethal and/or developed later in the study. In an effort to express tumor incidence in terms of the "effective" number of animals actually at risk, all tumor incidences for rats were expressed as the number of tumor-bearing animals at a particular site divided by the number of animals alive in each group at the time the first tumor was observed at that site in any of the three (vehicle control, low dose, or high dose) groups.

Analysis of Tumor Incidence--Rats: Because of poor survival (196/200 dosed rats died before the end of the studies), the statistical approach outlined above for mice was not used for rats. For example, the incidental tumor test lacked power because, in each time interval, there were too few animals at risk in some groups for meaningful comparisons (e.g., the 93- to 104-week time interval included 29 male rat vehicle controls

but only 2 low dose males and no high dose males). The life table test was also misleading in some instances, since many tumors were not rapidly lethal; thus, life table analysis could exaggerate the significance of certain neoplastic effects. Consequently, the primary tumor analyses for rats were the Cochran-Armitage trend and Fisher exact tests based on the "effective" number of animals, as described above, a procedure recommended by Gart et al. (1979). For those few tumors considered to be rapidly lethal (e.g., mesotheliomas in male rats), the results of life table analyses are also given. The results of these tests are summarized in Appendixes A and B. Tests of significance include pairwise comparisons of each dosed group with vehicle controls and a test for an overall dose-response trend. Continuity-corrected tests were used in the analysis of tumor incidence, and reported P values are one-sided. The procedures described above also were used to evaluate selected nonneoplastic lesions. (For further discussion of these statistical methods, see Haseman, 1984.)

Historical Control Data: Although the concurrent control group is always the first and most appropriate control group used for evaluation, there are certain instances in which historical control data can be helpful in the overall assessment of tumor incidence. Consequently, control tumor incidences from the NTP historical control data base (Haseman et al., 1984, 1985) are included for those tumors appearing to show compound-related effects.

III. RESULTS

RATS

SIXTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs
Survival
Pathology and Statistical Analyses of Results

MICE

SIXTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs
Survival
Pathology and Statistical Analyses of Results

GENETIC TOXICOLOGY

III. RESULTS: RATS

SIXTEEN-DAY STUDIES

All rats that received 600 mg/kg died before the end of the studies (Table 2). Final mean body weights of male rats that received 150 or 300 mg/kg were 10% or 21% lower than that of the vehicle controls. The final mean body weights of dosed and vehicle control female rats were similar. Edema and degeneration of the epididymal stroma was observed in 4/5 males in the 300 mg/kg group; atrophy of the testis and granulomatous inflammation of the epididymis were seen in the fifth animal.

THIRTEEN-WEEK STUDIES

All rats that received 400 mg/kg died by week 2; 3/10 males and 1/10 females that received 200 mg/kg also died before the end of the studies (Table 3). Final mean body weights of rats that received 50, 100, or 200 mg/kg were 9%, 4%, or 15% lower than that of the vehicle controls for males and 6%, 7%, or 11% lower for females. Based on a qualitative grading scale of 0-4, sperm motility of chemically exposed male rats was reduced relative to that of vehicle controls (Table 4). The number of sperm in semen from the cauda epididymis was 4% that of the vehicle controls at 200 mg/kg, 30% at 100 mg/kg, and 64% at 25 mg/kg. Compound-related histologic lesions in the 400 mg/kg groups included necrosis of the granular cell layer of the cerebellum, demyelination in the medulla of the brain, tubular cell degeneration and/or necrosis of the kidney, lymphoid necrosis of the thymus, and testicular atrophy and/or degeneration (Table 5).

Dose Selection Rationale: Because of reduced body weights and survival at 200 and 400 mg/kg, histologic lesions of the brain, kidney, and thymus at 400 mg/kg, and brain lesions at 200 mg/kg, doses selected for rats for the 2-year studies were 37.5 and 75 mg/kg glycidol, administered in water by gavage 5 days per week.

TABLE 2. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE SIXTEEN-DAY GAVAGE STUDIES OF GLYCIDOL

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	5/5	120 ± 9	226 ± 6	+106 ± 7	
37.5	5/5	123 ± 7	216 ± 9	+93 ± 5	96
75	5/5	124 ± 5	215 ± 5	+91 ± 3	95
150	5/5	119 ± 6	204 ± 11	+85 ± 6	90
300	5/5	122 ± 6	178 ± 8	+56 ± 3	79
600	(d) 0/5	122 ± 5	(e)	(e)	(e)
FEMALE					
0	5/5	93 ± 3	139 ± 3	+46 ± 3	
37.5	5/5	95 ± 4	134 ± 5	+39 ± 5	96
75	5/5	94 ± 2	143 ± 4	+49 ± 4	103
150	5/5	96 ± 5	140 ± 5	+44 ± 3	101
300	5/5	94 ± 3	134 ± 3	+40 ± 3	96
600	(f) 0/5	94 ± 3	(e)	(e)	(e)

(a) Number surviving/number initially in the group
(b) Initial group mean body weight ± standard error of the mean
(c) Mean body weight change of the survivors ± standard error of the mean
(d) Day of death: 3,10,10,11,11
(e) No data are reported due to 100% mortality in this group.
(f) Day of death: 6,8,9,12,13

TABLE 3. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF GLYCIDOL

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	10/10	141 ± 6	361 ± 5	+220 ± 8	
25	10/10	142 ± 7	344 ± 8	+202 ± 5	95
50	10/10	141 ± 6	330 ± 9	+189 ± 6	91
100	10/10	139 ± 5	345 ± 6	+206 ± 6	96
200	(d) 7/10	143 ± 7	306 ± 10	+163 ± 11	85
400	(e) 0/10	140 ± 5	(f)	(f)	(f)
FEMALE					
0	10/10	127 ± 6	213 ± 5	+86 ± 6	
25	10/10	129 ± 6	208 ± 4	+79 ± 4	98
50	10/10	130 ± 5	200 ± 4	+70 ± 6	94
100	10/10	130 ± 4	198 ± 4	+68 ± 4	93
200	(g) 9/10	129 ± 6	189 ± 6	+62 ± 7	89
400	(h) 0/10	130 ± 4	(f)	(f)	(f)

(a) Number surviving/number initially in the group
(b) Initial group mean body weight ± standard error of the mean. Subsequent calculations are based on animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean
(d) Week of death: 11,12,12
(e) Week of death: 1,1,1,1,1,2,2,2,2,2
(f) No data are reported due to 100% mortality in this group.
(g) Week of death: 11
(h) Week of death: all 1

TABLE 4. SPERM COUNT AND MOTILITY FOR MALE RATS IN THE THIRTEEN-WEEK GAVAGE STUDY OF GLYCIDOL (a)

Dose (mg/kg)	Sperm Count (b) ($\times 10^{-7}$)	Motility (c)
0	13.6 ± 4.00	3.4
25	*8.7 ± 1.80	3.0
100	**4.1 ± 2.02	2.0
200	**0.6 ± 0.49	0.2

(a) For groups of five animals; P values vs. vehicle controls by Dunnett's test (Dunnett, 1955).
(b) Mean sperm count per cauda epididymis ± standard deviation
(c) Motility based on a 0-4 rating scale
*$P < 0.05$
**$P < 0.01$

TABLE 5. INCIDENCE AND SEVERITY OF SELECTED NONNEOPLASTIC LESIONS IN RATS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF GLYCIDOL (a)

Dose (mg/kg)	Cerebellar Necrosis	Brain Demyelination	Renal Tubular Cell Degeneration/ Necrosis	Thymic Lymphoid Necrosis	Testicular Atrophy
MALE					
0	0/10	0/10	0/6	0/6	2/10 (1.5)
100	0/10	0/10	--	--	3/9 (2.3)
200	2/10 (3.0)	5/10 (1.0)	0/8	0/8	**10/10 (3.7)
400	**10/10 (3.1)	6/10 (1.0)	*6/10 (1.8)	2/9 (2.5)	**9/10 (3.1)
FEMALE					
0	0/10	0/10	0/6	0/6	
100	0/10	--	--	--	
200	*4/10 (2.3)	0/10	0/6	1/7 (3.0)	
400	**9/10 (3.9)	6/10 (1.0)	**10/10 (3.9)	**9/10 (3.8)	

(a) Number observed/number examined; number in parentheses is the mean severity in animals with the lesion (1 = minimal; 2 = mild; 3 = moderate; 4 = marked).
*P<0.05 for the incidence in dosed groups vs. that in vehicle controls by Fisher exact test
**P<0.01 for the incidence in dosed groups vs. that in vehicle controls by Fisher exact test

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of high dose male rats were 6%-16% lower than those of vehicle controls between weeks 1 and 44 and 11%-20% lower thereafter (Table 6 and Figure 2). Mean body weights of low dose male rats were 5%-9% lower than those of vehicle controls between weeks 12 and 56 and 10%-18% lower thereafter. Mean body weights of high dose female rats were 3%-9% lower than those of vehicle controls throughout most of the studies, and mean body weights of low dose female rats were generally 6%-10% lower after week 24. No compound-related clinical signs were observed.

TABLE 6. MEAN BODY WEIGHTS AND SURVIVAL OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF GLYCIDOL

Weeks on Study	Vehicle Control		37.5 mg/kg			75 mg/kg		
	Av. Wt. (grams)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of vehicle controls)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of vehicle controls)	No. of Survivors
MALE								
0	143	50	146	102	50	144	101	50
1	204	50	205	100	50	171	84	50
2	232	50	230	99	50	204	88	50
3	254	50	251	99	50	230	91	50
4	274	50	268	98	50	253	92	50
5	291	50	283	97	50	..	..	..
6	305	50	295	97	50	279	91	50
7	316	50	305	97	50	291	92	50
8	329	50	315	96	50	308	94	50
9	340	50	326	96	50	319	94	50
10	343	50	330	96	50	323	94	50
11	351	50	336	96	50	331	94	50
12	362	50	344	95	50	332	92	50
17	382	50	363	95	50	355	93	49
21	406	49	383	94	50	376	93	49
24	419	49	391	93	50	384	92	49
28	423	49	401	95	50	396	94	49
32	428	49	402	94	50	401	94	49
36	439	49	405	92	50	400	91	49
41	448	49	411	92	50	413	92	49
44	456	49	418	92	50	415	91	48
48	456	49	415	91	50	406	89	47
52	457	49	419	92	50	405	89	44
56	474	47	431	91	50	416	88	42
60	478	47	427	89	50	427	89	37
64	484	46	428	88	50	427	88	30
68	483	46	428	89	48	421	87	20
72	478	45	429	90	39	412	86	17
76	486	44	436	90	33	406	84	7
80	476	43	420	88	30	380	80	3
84	469	40	417	89	25	387	83	3
88	462	36	403	87	16	401	87	1
92	467	29	395	85	2	..	..	..
96	463	23	379	82	2	..	..	..
100	452	20	..	..	..	..	..	..
104	458	16	..	..	..	..	..	..
Mean for weeks								
1-12	300.1		290.7	97		276.3	92	
17-52	431.4		400.8	93		395.1	92	
56-104	471.5		417.5	89		408.6	87	
FEMALE								
0	128	50	130	102	50	..	..	..
1	143	50	144	101	50	133	93	50
2	155	50	155	100	50	146	94	50
3	165	50	163	99	50	156	95	50
4	174	50	171	98	50	166	95	50
5	179	50	176	98	50	..	..	..
6	184	50	179	97	50	179	97	50
7	190	50	183	96	50	180	95	50
8	191	50	186	97	50	186	97	50
9	195	50	189	97	50	189	97	50
10	196	50	191	97	50	189	96	50
11	198	50	192	97	50	192	97	50
12	202	50	195	97	50	192	95	50
17	207	50	199	96	50	196	95	50
21	215	50	204	95	50	200	93	50
24	219	50	205	94	50	201	92	50
28	229	50	210	92	50	208	91	50
32	229	50	213	93	49	212	93	50
36	242	50	225	93	48	227	94	49
41	242	50	227	94	48	234	97	49
44	245	50	228	93	48	231	94	49
48	250	50	233	93	48	234	94	48
52	255	50	239	94	48	235	92	48
56	263	50	247	94	48	244	93	46
60	274	49	257	94	46	259	95	44
64	283	49	267	94	44	268	95	41
68	287	49	270	94	41	277	97	37
72	291	49	270	93	38	278	96	36
76	301	47	280	93	38	283	94	30
80	309	43	282	91	36	290	94	24
84	305	43	276	90	31	294	96	18
88	304	41	285	94	23	303	100	13
92	312	37	288	92	19	303	97	6
96	317	36	285	90	15	..	..	..
100	319	29	302	95	7	..	..	..
104	318	28	307	97	4	..	..	..
Mean for weeks								
1-12	181.0		177.0	98		173.5	96	
17-52	233.3		218.3	94		217.8	93	
56-104	298.7		278.2	93		279.9	94	

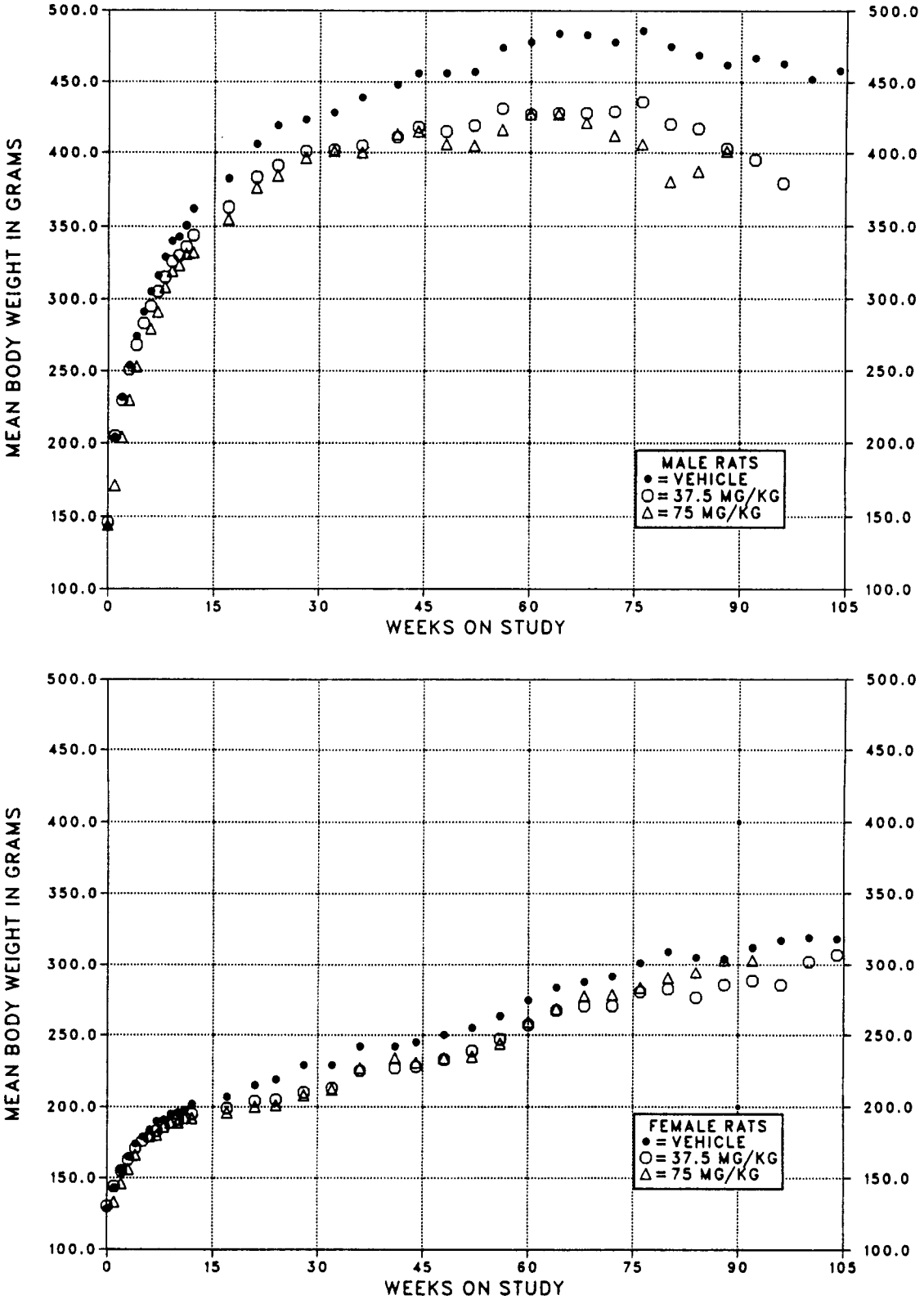

FIGURE 2. GROWTH CURVES FOR RATS ADMINISTERED GLYCIDOL IN WATER BY GAVAGE FOR TWO YEARS

Survival

Estimates of the probabilities of survival for male and female rats administered glycidol at the doses used in these studies and for vehicle controls are shown in Table 7 and in the Kaplan and Meier curves in Figure 3. Survival of male rats (low dose after week 75, high dose after week 60) and female rats (low dose after week 84, high dose after week 64) was significantly lower than that of the vehicle controls.

Pathology and Statistical Analyses of Results

This section describes the statistically significant or biologically noteworthy changes in the incidences of rats with neoplastic or nonneoplastic lesions of the tunica vaginalis, mammary gland, forestomach, glandular stomach, brain, oral mucosa, Zymbal gland, small intestine, large intestine, thyroid gland, hematopoietic system, skin, clitoral gland, nasal cavity, spleen, and liver.

Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, statistical analyses of primary tumors that occurred with an incidence of at least 5% in at least one animal group, and historical control incidences for the neoplasms mentioned in this section are presented in Appendixes A and B for male and female rats, respectively.

TABLE 7. SURVIVAL OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF GLYCIDOL

	Vehicle Control	37.5 mg/kg	75 mg/kg
MALE (a)			
Animals initially in study	50	50	50
Natural deaths	1	5	3
Moribund kills	33	45	46
Animals surviving until study termination	16	0	0
Killed accidentally	0	0	1
Mean survival (weeks)	92	82	66
Survival P values (b)	<0.001	<0.001	<0.001
FEMALE (a)			
Animals initially in study	50	50	50
Natural deaths	8	14	11
Moribund kills	14	32	39
Animals surviving until study termination	28	4	0
Mean survival (weeks)	97	85	78
Survival P values (b)	<0.001	<0.001	<0.001

(a) Termination period: week 104
(b) The result of the life table trend test is in the vehicle control column, and the results of the life table pairwise comparisons with the vehicle controls are in the dosed columns.

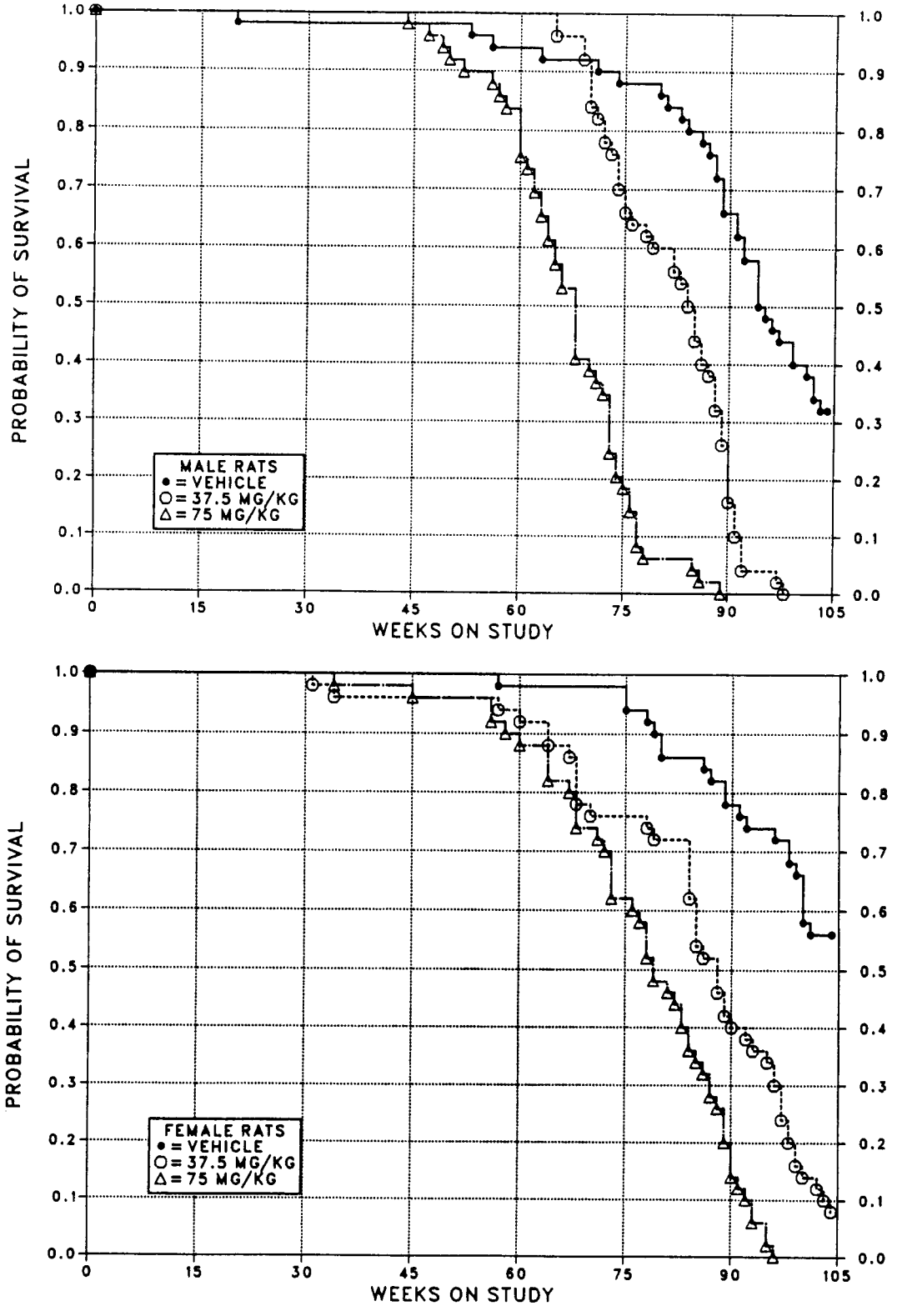

FIGURE 3. KAPLAN-MEIER SURVIVAL CURVES FOR RATS ADMINISTERED GLYCIDOL IN WATER BY GAVAGE FOR TWO YEARS

Tunica Vaginalis: Mesotheliomas and malignant mesotheliomas in male rats occurred with significant positive trends; the incidences in dosed male rats were significantly greater than those in vehicle controls (Table 8). All mesotheliomas were observed in the tunica vaginalis, the serosal membrane covering the testis and epididymis, which is an extension of the visceral peritoneum into the scrotum. Most of the malignant mesotheliomas extended into the peritoneal cavity to involve the serosal membranes of abdominal organs. The mesotheliomas consisted of single or multiple layers of pleomorphic mesothelial cells arranged in complex papillary and/or glandlike formations with variable amounts of hyalinized collagenous stroma. The malignant tumors exhibited greater pleomorphism and atypia, invasion of the subjacent organs, and implantation metastases on the serosal surfaces of abdominal organs. Mesotheliomas were not observed in female rats.

TABLE 8. MESOTHELIOMAS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF GLYCIDOL (a)

	Vehicle Control	37.5 mg/kg	75 mg/kg
Mesothelioma, NOS			
Overall Rates	0/50 (0%)	10/50 (20%)	8/50 (16%)
Effective Rates (b)	0/47 (0%)	10/50 (20%)	8/41 (20%)
Terminal Rates	0/16 (0%)	0/0	0/0
Week of First Observation		65	60
Life Table Tests	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test	P=0.004		
Fisher Exact Test		P<0.001	P=0.001
Malignant Mesothelioma			
Overall Rates	3/50 (6%)	24/50 (48%)	31/50 (62%)
Effective Rates (b)	3/49 (6%)	24/50 (48%)	31/47 (66%)
Terminal Rates	0/16 (0%)	0/0	0/0
Week of First Observation	86	65	49
Life Table Tests	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
All Mesothelioma (c)			
Overall Rates	3/50 (6%)	34/50 (68%)	39/50 (78%)
Effective Rates (b)	3/49 (6%)	34/50 (68%)	39/47 (83%)
Terminal Rates	0/16 (0%)	0/0	0/0
Week of First Observation	86	65	49
Life Table Tests	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) For a complete explanation of the entries in this table, see Table A3 (footnotes); the statistical analyses used are discussed in Section II (Statistical Methods).
(b) Number of tumor-bearing animals/effective number of animals, i.e., number of animals alive at the first occurrence of tumors in any of the three groups
(c) Historical incidence for water gavage vehicle controls (mean ± SD): 4/300 (1% ± 2%); historical incidence for untreated controls: 47/1,596 (3% ± 3%)

Mammary Gland: Fibroadenomas and adenocarcinomas in female rats occurred with significant positive trends; the incidences in chemically exposed female rats were significantly greater than those in vehicle controls (Table 9). Fibroadenomas in male rats occurred with a significant positive trend; the incidence in the high dose group was significantly greater than that in the vehicle controls. The fibroadenomas were lobulated masses consisting of tubular or gland-like formations of epithelium separated by varying but generally abundant amounts of collagenous stroma. The adenocarcinomas were composed of pleomorphic and/or epithelial cells with heterogenous growth patterns. Some of the adenocarcinomas occurred within or adjacent to fibroadenomas.

TABLE 9. MAMMARY GLAND TUMORS IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF GLYCIDOL (a)

	Vehicle Control	37.5 mg/kg	75 mg/kg
MALE			
Fibroadenoma (b)			
Overall Rates	3/50 (6%)	8/50 (16%)	7/50 (14%)
Effective Rates (c)	3/45 (7%)	8/39 (21%)	7/17 (41%)
Terminal Rates	1/16 (6%)	0/0	0/0
Week of First Observation	92	78	73
Cochran-Armitage Trend Test	P=0.001		
Fisher Exact Test		P=0.060	P=0.003
FEMALE			
Fibroadenoma (d)			
Overall Rates	14/50 (28%)	32/50 (64%)	29/50 (58%)
Effective Rates (c)	14/49 (29%)	32/46 (70%)	29/44 (66%)
Terminal Rates	10/28 (36%)	4/4 (100%)	0/0
Week of First Observation	87	68	64
Cochran-Armitage Trend Test	P<0.001		
Fisher Exact Test		P<0.001	P<0.001
Adenocarcinoma (e)			
Overall Rates	1/50 (2%)	11/50 (22%)	16/50 (32%)
Effective Rates (c)	1/50 (2%)	11/48 (23%)	16/48 (33%)
Terminal Rates	0/28 (0%)	0/4 (0%)	0/0
Week of First Observation	91	79	56
Life Table Tests	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P=0.001	P<0.001
Fibroadenoma or Adenocarcinoma (f)			
Overall Rates	14/50 (28%)	34/50 (68%)	37/50 (74%)
Effective Rates (c)	14/50 (28%)	34/48 (71%)	37/48 (77%)
Terminal Rates	10/28 (36%)	4/4 (100%)	0/0
Week of First Observation	87	68	56
Life Table Tests	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) For a complete explanation of the entries in this table, see Table A3 (footnotes); the statistical analyses used are discussed in Section II (Statistical Methods).
(b) Historical incidence of fibroadenomas or adenocarcinomas (combined) for water gavage vehicle controls (mean ± SD): 13/300 (4% ± 2%); historical incidence for untreated controls: 49/1,596 (3% ± 3%)
(c) Number of tumor-bearing animals/effective number of animals, i.e., number of animals alive at the first occurrence of tumors in any of the three groups
(d) Historical incidence for water gavage vehicle controls (mean ± SD): 80/299 (27% ± 10%); historical incidence for untreated controls: 520/1,643 (32% ± 12%)
(e) Historical incidence for water gavage vehicle controls (mean ± SD): 5/299 (2% ± 2%); historical incidence for untreated controls: 49/1,643 (3% ± 2%)
(f) Historical incidence for water gavage vehicle controls (mean ± SD): 84/299 (28% ± 10%); historical incidence for untreated controls: 552/1,643 (34% ± 12%)

Forestomach: Hyperkeratosis and epithelial dysplasia were observed at increased incidences in dosed rats (hyperkeratosis--male: vehicle control, 3/50; low dose, 13/50; high dose, 15/50; female: 1/50; 16/50; 13/50; dysplasia--male: 0/50; 10/50; 8/50; female: 0/50; 12/50; 10/50). Ulcers were observed at an increased incidence in high dose male rats (1/50; 1/50; 7/50). Squamous cell papillomas in males and females, squamous cell carcinomas in females, and squamous cell papillomas or carcinomas (combined) in males and females occurred with significant positive trends; the incidences of squamous cell papillomas and squamous cell papillomas or carcinomas (combined) in high dose males and females and of squamous cell carcinomas in high dose females were significantly greater than those in vehicle controls (Table 10).

Glandular Stomach: Fibrosarcomas were seen in 2/41 high dose female rats. The historical incidence of glandular stomach sarcomas in female F344/N rats is 0/295 for water gavage vehicle controls and 1/1,623 (<0.1%) for untreated controls.

Brain: Gliomas occurred in dosed male and female rats but not in vehicle controls (Table 11). Glial tumors are uncommon in F344 rats and have occurred with incidences of approximately 1% in untreated historical controls. The gliomas occurred with a significant positive trend in males, and the incidences in both high and low dose groups were significantly greater than that in vehicle controls. Although the incidences in dosed females were not statistically significant, they exceeded the highest incidence previously observed in a historical control group.

The gliomas generally were located in the cerebral cortex, corpus striatum, or thalamus. One was located in the medulla oblongata and another in the cerebellum. Most consisted of astrocytes, but several consisted of oligodendroglia.

Oral Mucosa: The incidences of squamous cell papillomas of the mouth or tongue in female rats occurred with a significant positive trend; the incidence in high dose female rats was significantly greater than that in vehicle controls, and one other high dose female had a squamous cell carcinoma (Table 12). Squamous cell papillomas or carcinomas (combined) of the mouth or tongue were seen in 3/50 vehicle control, 2/50 low dose, and 5/50 high dose male rats.

TABLE 10. FORESTOMACH SQUAMOUS CELL TUMORS IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF GLYCIDOL (a)

	Vehicle Control	37.5 mg/kg	75 mg/kg
MALE			
Papilloma			
Overall Rates	0/50 (0%)	1/50 (2%)	5/50 (10%)
Effective Rates (b)	0/46 (0%)	1/50 (2%)	5/32 (16%)
Terminal Rates	0/16 (0%)	0/0	0/0
Week of First Observation		85	64
Cochran-Armitage Trend Test	P=0.003		
Fisher Exact Test		P=0.521	P=0.010
Carcinoma			
Overall Rates	1/50 (2%)	1/50 (2%)	2/50 (4%)
Papilloma or Carcinoma (c)			
Overall Rates	1/50 (2%)	2/50 (4%)	6/50 (12%)
Effective Rates (b)	1/46 (2%)	2/50 (4%)	6/32 (19%)
Terminal Rates	1/16 (6%)	0/0	0/0
Week of First Observation	104	85	64
Cochran-Armitage Trend Test	P=0.007		
Fisher Exact Test		P=0.532	P=0.017
FEMALE			
Papilloma			
Overall Rates	0/50 (0%)	4/50 (8%)	8/50 (16%)
Effective Rates (b)	0/47 (0%)	4/38 (11%)	8/30 (27%)
Terminal Rates	0/28 (0%)	1/4 (25%)	0/0
Week of First Observation		84	77
Cochran-Armitage Trend Test	P<0.001		
Fisher Exact Test		P=0.036	P<0.001
Carcinoma			
Overall Rates	0/50 (0%)	0/50 (0%)	3/50 (6%)
Effective Rates (b)	0/43 (0%)	0/31 (0%)	3/18 (17%)
Terminal Rates	0/28 (0%)	0/4 (0%)	0/0
Week of First Observation			85
Cochran-Armitage Trend Test	P=0.006		
Fisher Exact Test		(d)	P=0.023
Papilloma or Carcinoma (e)			
Overall Rates	0/50 (0%)	4/50 (8%)	11/50 (22%)
Effective Rates (b)	0/47 (0%)	4/38 (11%)	11/30 (37%)
Terminal Rates	0/28 (0%)	1/4 (25%)	0/0
Week of First Observation		84	77
Cochran-Armitage Trend Test	P<0.001		
Fisher Exact Test		P=0.036	P<0.001

(a) For a complete explanation of the entries in this table, see Table A3 (footnotes); the statistical analyses used are discussed in Section II (Statistical Methods).
(b) Number of tumor-bearing animals/effective number of animals, i.e., number of animals alive at the first occurrence of tumors in any of the three groups
(c) Historical incidence for water gavage vehicle controls: 0/293; historical incidence for untreated controls (mean ± SD): 5/1,581 (0.3% ± 0.9%)
(d) No P value is presented because no tumors were observed in the 37.5 mg/kg and vehicle control groups.
(e) Historical incidence for water gavage vehicle controls (mean ± SD): 1/295 (0.3% ± 0.8%); historical incidence for untreated controls: 3/1,623 (0.2% ± 0.6%)

TABLE 11. BRAIN TUMORS IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF GLYCIDOL (a)

	Vehicle Control	37.5 mg/kg	75 mg/kg
MALE			
Glioma (b)			
Overall Rates	0/50 (0%)	5/50 (10%)	6/50 (12%)
Effective Rates (c)	0/46 (0%)	5/50 (10%)	6/30 (20%)
Terminal Rates	0/16 (0%)	0/0	0/0
Week of First Observation		70	65
Cochran-Armitage Trend Test	P=0.002		
Fisher Exact Test		P=0.035	P=0.003
FEMALE			
Glioma (d)			
Overall Rates	0/50 (0%)	4/50 (8%)	4/50 (8%)
Effective Rates (c)	0/49 (0%)	4/46 (9%)	4/46 (9%)
Terminal Rates	0/28 (0%)	1/4 (25%)	0/0
Week of First Observation		79	64
Cochran-Armitage Trend Test	P=0.052		
Fisher Exact Test		P=0.051	P=0.051

(a) For a complete explanation of the entries in this table, see Table A3 (footnotes); the statistical analyses used are discussed in Section II (Statistical Methods).
(b) Historical incidence of glial cell tumors for water gavage vehicle controls (mean ± SD): 2/300 (0.7% ± 1%); historical incidence for untreated controls: 14/1,590 (0.9% ± 1%)
(c) Number of tumor-bearing animals/effective number of animals, i.e., number of animals alive at the first occurrence of tumors in any of the three groups
(d) Historical incidence of glial cell tumors for water gavage vehicle controls (mean ± SD): 1/298 (0.3% ± 0.8%); historical incidence for untreated controls: 19/1,628 (1% ± 2%)

TABLE 12. MOUTH/TONGUE LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF GLYCIDOL (a)

	Vehicle Control	37.5 mg/kg	75 mg/kg
Focal Hyperplasia			
Overall Rates	1/50 (2%)	0/50 (0%)	0/50 (0%)
Squamous Cell Papilloma			
Overall Rates	1/50 (2%)	3/50 (6%)	6/50 (12%)
Effective Rates (b)	1/46 (2%)	3/37 (8%)	6/26 (23%)
Terminal Rates	1/28 (4%)	0/4 (0%)	0/0
Week of First Observation	104	79	79
Cochran-Armitage Trend Test	P=0.004		
Fisher Exact Test		P=0.230	P=0.008
Squamous Cell Carcinoma			
Overall Rates	0/50 (0%)	0/50 (0%)	1/50 (2%)
Squamous Cell Papilloma or Carcinoma (c)			
Overall Rates	1/50 (2%)	3/50 (6%)	7/50 (14%)
Effective Rates (b)	1/46 (2%)	3/37 (8%)	7/26 (27%)
Terminal Rates	1/28 (4%)	0/4 (0%)	0/0
Week of First Observation	104	79	79
Cochran-Armitage Trend Test	P=0.001		
Fisher Exact Test		P=0.230	P=0.003

(a) For a complete explanation of the entries in this table, see Table B3 (footnotes); the statistical analyses used are discussed in Section II (Statistical Methods).
(b) Number of tumor-bearing animals/effective number of animals, i.e., number of animals alive at the first occurrence of tumors in any of the three groups
(c) Historical incidence for water gavage vehicle controls (mean ± SD): 2/299 (0.7% ± 1%); historical incidence for untreated controls: 4/1,643 (0.2% ± 0.7%)

Zymbal Gland: Cysts were observed at an increased incidence in high dose male rats (vehicle control, 0/50; low dose, 1/50; high dose, 8/50). Carcinomas in male rats occurred with a significant positive trend (Table 13). Zymbal gland carcinomas were seen in 1/50 vehicle control, 1/50 low dose, and 2/50 high dose female rats.

Intestine--Small Intestine: Mucinous adenocarcinomas of the small intestine were seen in one low dose and two high dose male rats. The historical incidence of adenocarcinomas of the small intestine in male F344/N rats is 0/283 for water gavage vehicle controls and 5/1,557 (0.3%) for untreated controls.

Intestine--Large Intestine: Adenomatous polyps of the large intestine were seen in one high dose male rat and one high dose female rat; an adenocarcinoma was seen in a second high dose male rat. The historical incidence of adenocarcinomas of the large intestine in male F344/N rats is 0/300 for water gavage vehicle controls and 2/1,541 (0.1%) for untreated controls. Adenomatous polyps were not seen in any of the historical controls. No neoplasms of the large intestine were seen in 299 female water gavage vehicle control F344/N rats or in 1,601 female untreated controls.

Thyroid Gland: Follicular cell carcinomas and follicular cell adenomas or carcinomas (combined) in male and female rats occurred with significant positive trends; the incidences of follicular cell carcinomas and follicular cell adenomas or carcinomas (combined) in high dose male rats were significantly greater than those in vehicle controls (Table 14).

TABLE 13. ZYMBAL GLAND TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF GLYCIDOL (a)

	Vehicle Control	37.5 mg/kg	75 mg/kg
Carcinoma (b)			
Overall Rates	1/50 (2%)	3/50 (6%)	6/50 (12%)
Effective Rates (c)	1/49 (2%)	3/50 (6%)	6/48 (13%)
Terminal Rates	0/16 (0%)	0/0	0/0
Week of First Observation	92	83	47
Cochran-Armitage Trend Test	P=0.033		
Fisher Exact Test		P=0.316	P=0.053

(a) For a complete explanation of the entries in this table, see Table A3 (footnotes); the statistical analyses used are discussed in Section II (Statistical Methods).
(b) Historical incidence of adenomas or carcinomas (combined) for water gavage vehicle controls (mean ± SD): 3/300 (1% ± 1%); historical incidence for untreated controls: 19/1,596 (1% ± 2%)
(c) Number of tumor-bearing animals/effective number of animals, i.e., number of animals alive at the first occurrence of tumors in any of the three groups

TABLE 14. THYROID GLAND FOLLICULAR CELL LESIONS IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF GLYCIDOL (a)

	Vehicle Control	37.5 mg/kg	75 mg/kg
MALE			
Hyperplasia			
Overall Rates	0/50 (0%)	4/50 (8%)	1/50 (2%)
Adenoma			
Overall Rates	0/50 (0%)	2/50 (4%)	2/50 (4%)
Carcinoma			
Overall Rates	1/50 (2%)	2/50 (4%)	5/50 (10%)
Effective Rates (b)	1/46 (2%)	2/42 (5%)	5/19 (26%)
Terminal Rates	0/16 (0%)	0/0	0/0
Week of First Observation	101	85	71
Cochran-Armitage Trend Test	P=0.003		
Fisher Exact Test		P=0.466	P=0.007
Adenoma or Carcinoma (c)			
Overall Rates	1/50 (2%)	4/50 (8%)	6/50 (12%)
Effective Rates (b)	1/46 (2%)	4/42 (10%)	6/19 (32%)
Terminal Rates	0/16 (0%)	0/0	0/0
Week of First Observation	101	85	71
Cochran-Armitage Trend Test	P<0.001		
Fisher Exact Test		P=0.153	P=0.002
FEMALE			
Hyperplasia			
Overall Rates	1/50 (2%)	1/50 (2%)	2/49 (4%)
Adenoma			
Overall Rates	0/50 (0%)	1/50 (2%)	0/49 (0%)
Carcinoma			
Overall Rates	0/50 (0%)	0/50 (0%)	3/49 (6%)
Effective Rates (b)	0/49 (0%)	0/38 (0%)	3/35 (9%)
Terminal Rates	0/28 (0%)	0/4 (0%)	0/0
Week of First Observation			73
Cochran-Armitage Trend Test	P=0.022		
Fisher Exact Test		(d)	P=0.069
Adenoma or Carcinoma (e)			
Overall Rates	0/50 (0%)	1/50 (2%)	3/49 (6%)
Effective Rates (b)	0/49 (0%)	1/38 (3%)	3/35 (9%)
Terminal Rates	0/28 (0%)	1/4 (25%)	0/0
Week of First Observation		104	73
Cochran-Armitage Trend Test	P=0.034		
Fisher Exact Test		P=0.437	P=0.069

(a) For a complete explanation of the entries in this table, see Table A3 (footnotes); the statistical analyses used are discussed in Section II (Statistical Methods).
(b) Number of tumor-bearing animals/effective number of animals, i.e., number of animals alive at the first occurrence of tumors in any of the three groups
(c) Historical incidence for water gavage vehicle controls (mean ± SD): 6/293 (2% ± 3%); historical incidence for untreated controls: 20/1,576 (1% ± 2%)
(d) *No* P value is presented because *no* tumors were observed in the 37.5 mg/kg and vehicle control groups.
(e) Historical incidence for water gavage vehicle controls (mean ± SD): 10/292 (3% ± 3%); historical incidence for untreated controls: 16/1,612 (1% ± 1%)

Hematopoietic System: Mononuclear cell leukemia in female rats occurred with a significant positive trend; the incidence in the high dose group was significantly greater than that in the vehicle controls (Table 15). Mononuclear cell leukemia was seen in 25/50 vehicle control, 33/50 low dose, and 21/50 high dose male rats.

Skin: Squamous cell papillomas and sebaceous gland adenomas, basal cell tumors, or sebaceous gland adenocarcinomas (combined) in male rats occurred with significant positive trends; the incidences of squamous cell papillomas in high dose males, basal cell tumors in low dose males, and sebaceous gland adenomas, basal cell tumors, or sebaceous gland adenocarcinomas (combined) in dosed male rats were significantly greater than those in vehicle controls (Table 16). A squamous cell papilloma, a squamous cell carcinoma, and a basal cell tumor were seen in three different high dose female rats. None was observed in vehicle controls.

Clitoral Gland: Adenomas and adenomas, adenocarcinomas, or carcinomas (combined) in female rats occurred with significant positive trends; the incidences in the high dose group were significantly greater than those in the vehicle controls (Table 17).

Nasal Cavity: Squamous cell carcinomas were seen in one low dose and one high dose male rat and in one high dose female rat; an adenocarcinoma was seen in a second high dose male rat. The historical incidence of squamous cell neoplasms of the nasal cavity for male F344/N rats is 0/300 for water gavage vehicle controls and 1/1,596 (<0.1%) for untreated controls. The historical incidence of squamous cell neoplasms of the nasal cavity for female F344/N rats is 0/299 for water gavage vehicle controls and 0/1,643 for untreated controls.

Spleen: Fibrosis was observed at increased incidences in dosed rats (male: vehicle control, 13/50; low dose, 34/50; high dose, 28/50; female: 3/50; 14/49; 20/50).

Liver: Coagulative necrosis was observed at increased incidences in dosed male rats (male: vehicle control, 1/50; low dose, 7/50; high dose, 8/50; female: 3/50; 2/50; 6/50).

TABLE 15. HEMATOPOIETIC SYSTEM TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF GLYCIDOL (a)

	Vehicle Control	37.5 mg/kg	75 mg/kg
Mononuclear Cell Leukemia (b)			
Overall Rates	13/50 (26%)	14/50 (28%)	20/50 (40%)
Effective Rates (c)	13/49 (27%)	14/44 (32%)	20/41 (49%)
Terminal Rates	6/28 (21%)	0/4 (0%)	0/0
Week of First Observation	75	68	67
Life Table Tests	P<0.001	P=0.006	P<0.001
Cochran-Armitage Trend Test	P=0.020		
Fisher Exact Test		P=0.370	P=0.025

(a) For a complete explanation of the entries in this table, see Table B3 (footnotes); the statistical analyses used are discussed in Section II (Statistical Methods).
(b) Historical incidence of leukemia for water gavage vehicle controls (mean ± SD): 75/299 (25% ± 15%); historical incidence for untreated controls: 324/1,643 (20% ± 8%)
(c) Number of tumor-bearing animals/effective number of animals, i.e., number of animals alive at the first occurrence of tumors in any of the three groups

TABLE 16. SKIN TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF GLYCIDOL (a)

	Vehicle Control	37.5 mg/kg	75 mg/kg
Squamous Cell Papilloma (b)			
Overall Rates	0/50 (0%)	3/50 (6%)	3/50 (6%)
Effective Rates (c)	0/46 (0%)	3/48 (6%)	3/26 (12%)
Terminal Rates	0/16 (0%)	0/0	0/0
Week of First Observation		86	68
Cochran-Armitage Trend Test	P=0.026		
Fisher Exact Test		P=0.129	P=0.044
Basal Cell Tumor			
Overall Rates	0/50 (0%)	4/50 (8%)	2/50 (4%)
Effective Rates (c)	0/45 (0%)	4/41 (10%)	2/18 (11%)
Terminal Rates	0/16 (0%)	0/0	0/0
Week of First Observation		88	72
Cochran-Armitage Trend Test	P=0.040		
Fisher Exact Test		P=0.048	P=0.078
Sebaceous Gland Adenoma			
Overall Rates	0/50 (0%)	1/50 (2%)	1/50 (2%)
Sebaceous Gland Adenocarcinoma			
Overall Rates	0/50 (0%)	0/50 (0%)	1/50 (2%)
Sebaceous Gland Adenoma, Basal Cell Tumor, or Sebaceous Gland Adenocarcinoma (d)			
Overall Rates	0/50 (0%)	5/50 (10%)	4/50 (8%)
Effective Rates (c)	0/45 (0%)	5/41 (12%)	4/18 (22%)
Terminal Rates	0/16 (0%)	0/0	0/0
Week of First Observation		88	72
Cochran-Armitage Trend Test	P=0.003		
Fisher Exact Test		P=0.022	P=0.005

(a) For a complete explanation of the entries in this table, see Table A3 (footnotes); the statistical analyses used are discussed in Section II (Statistical Methods).
(b) Historical incidence of papillomas or carcinomas (combined) for water gavage vehicle controls (mean ± SD): 13/300 (4% ± 2%); historical incidence for untreated controls: 31/1,596 (2% ± 2%)
(c) Number of tumor-bearing animals/effective number of animals, i.e., number of animals alive at the first occurrence of tumors in any of the three groups
(d) Historical incidence of benign or malignant tumors (combined) for water gavage vehicle controls (mean ± SD): 5/300 (2% ± 1%); historical incidence for untreated controls: 31/1,596 (2% ± 2%)

TABLE 17. CLITORAL GLAND LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF GLYCIDOL (a)

	Vehicle Control	37.5 mg/kg	75 mg/kg
Hyperplasia			
Overall Rates	1/50 (2%)	1/50 (2%)	1/50 (2%)
Adenoma			
Overall Rates	3/50 (6%)	7/50 (14%)	7/50 (14%)
Effective Rates (b)	3/47 (6%)	7/38 (18%)	7/30 (23%)
Terminal Rates	3/28 (11%)	2/4 (50%)	0/0
Week of First Observation	104	88	77
Cochran-Armitage Trend Test	P=0.025		
Fisher Exact Test		P=0.085	P=0.036
Carcinoma			
Overall Rates	2/50 (4%)	1/50 (2%)	5/50 (10%)
Adenocarcinoma			
Overall Rates	0/50 (0%)	1/50 (2%)	0/50 (0%)
Adenoma, Carcinoma, or Adenocarcinoma (c)			
Overall Rates	5/50 (10%)	9/50 (18%)	12/50 (24%)
Effective Rates (b)	5/49 (10%)	9/47 (19%)	12/45 (27%)
Terminal Rates	4/28 (14%)	3/4 (75%)	0/0
Week of First Observation	100	60	68
Cochran-Armitage Trend Test	P=0.027		
Fisher Exact Test		P=0.171	P=0.035

(a) For a complete explanation of the entries in this table, see Table B3 (footnotes); the statistical analyses used are discussed in Section II (Statistical Methods).
(b) Number of tumor-bearing animals/effective number of animals, i.e., number of animals alive at the first occurrence of tumors in any of the three groups
(c) Historical incidence for water gavage vehicle controls (mean ± SD): 22/299 (7% ± 5%); historical incidence for untreated controls: 115/1,643 (7% ± 5%)

SIXTEEN-DAY STUDIES

All mice that received 600 mg/kg died within 4 days; 3/5 males and 2/5 females that received 300 mg/kg also died before the end of the studies (Table 18). Other deaths were gavage related. Final mean body weights of male mice were similar to that of vehicle controls. Final mean body weights of female mice that received 150 or 300 mg/kg were 7% or 8% lower than that of vehicle controls. Females that received 600 mg/kg and males and females that received 150 mg/kg had diarrhea. Inactivity and ruffled hair coats were observed for 2/5 males and 2/5 females that received 600 mg/kg and 3/5 males and 2/5 females that received 300 mg/kg. Focal demyelination in the medulla and thalamus of the brain was present in all female mice that received 300 mg/kg.

THIRTEEN-WEEK STUDIES

All mice that received 300 mg/kg died by the second week; 4/10 males and 3/10 females that received 150 mg/kg also died before the end of the studies (Table 19). Final mean body weights of chemically exposed mice were 6%-10% lower than those of vehicle controls except for males that received 38 mg/kg. Male and female mice that received 300 mg/kg were lethargic. The sperm count for chemically exposed males was 50% that for the vehicle controls at 150 mg/kg, 57% at 75 mg/kg, and 70% at 19 mg/kg (Table 20). Based on a qualitative grading scale of 0-4, sperm motility of chemically exposed male mice was reduced relative to that of vehicle controls. Compound-related lesions were observed in the medulla and thalamus (demyelination), testis (atrophy and/or degeneration), and kidney (tubular cell degeneration) (Table 21).

Dose Selection Rationale: Because of reduced survival and brain lesions, doses selected for mice for the 2-year studies were 25 and 50 mg/kg glycidol, administered in water by gavage 5 days per week.

TABLE 18. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE SIXTEEN-DAY GAVAGE STUDIES OF GLYCIDOL

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	5/5	25.9 ± 1.0	30.0 ± 0.8	+4.1 ± 0.5	
37.5	4/5	25.1 ± 1.3	28.9 ± 1.3	+3.7 ± 0.4	96.3
75	4/5	25.2 ± 0.9	29.9 ± 0.7	+4.0 ± 0.4	99.7
150	4/5	25.3 ± 0.8	28.9 ± 1.0	+3.7 ± 0.5	96.3
300	(d) 2/5	26.0 ± 1.0	29.6 ± 1.1	+2.2 ± 2.5	98.7
600	(e) 0/5	25.5 ± 0.8	(f)	(f)	(f)
FEMALE					
0	5/5	18.8 ± 0.3	22.2 ± 0.4	+3.4 ± 0.4	
37.5	5/5	18.6 ± 0.3	21.1 ± 0.2	+2.5 ± 0.3	95.0
75	2/5	19.0 ± 0.6	21.9 ± 0.3	+3.5 ± 0.2	98.6
150	3/5	18.7 ± 0.4	20.7 ± 0.3	+2.3 ± 0.3	93.2
300	(g) 3/5	18.7 ± 0.4	20.5 ± 1.5	+1.8 ± 0.8	92.3
600	(h) 0/5	18.8 ± 0.5	(f)	(f)	(f)

(a) Number surviving/number initially in the group; all deaths at 150 mg/kg or below were gavage related.
(b) Initial group mean body weight ± standard error of the mean. Subsequent calculations are based on animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean
(d) Day of death: 4,4,11
(e) Day of death: 1,1,1,2,4
(f) No data are reported due to 100% mortality in this group.
(g) Day of death: 3,4
(h) Day of death: 1,2,3,3,3

TABLE 19. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE THIRTEEN-WEEK GAVAGE STUDIES OF GLYCIDOL

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	10/10	29.4 ± 0.7	39.4 ± 1.1	+10.0 ± 0.6	
19	(d) 8/10	28.8 ± 0.5	36.5 ± 0.6	+8.2 ± 0.5	92.6
38	10/10	29.6 ± 0.9	41.4 ± 1.6	+11.8 ± 0.9	105.1
75	10/10	28.6 ± 0.7	37.1 ± 0.8	+8.5 ± 0.7	94.2
150	(e) 6/10	28.1 ± 0.7	36.6 ± 0.8	+7.7 ± 0.6	92.9
300	(f) 0/10	(g) 25.3 ± 0.4	(h)	(h)	(h)
FEMALE					
0	10/10	21.7 ± 0.3	29.7 ± 0.6	+8.0 ± 0.6	
19	10/10	21.9 ± 0.5	27.9 ± 0.8	+6.0 ± 0.5	93.9
38	10/10	21.3 ± 0.3	27.0 ± 0.5	+5.7 ± 0.3	90.9
75	10/10	22.1 ± 0.6	27.5 ± 0.9	+5.4 ± 0.4	92.6
150	(i) 7/10	(j) 22.2 ± 0.4	27.0 ± 1.2	+4.8 ± 0.7	90.9
300	(k) 0/10	(l) 19.9 ± 0.8	(h)	(h)	(h)

(a) Number surviving/number initially in the group
(b) Predosing body weights lost by laboratory; data presented are group mean body weight after 2 days of dosing ± standard error of the mean. Subsequent calculations are based on those animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean
(d) Week of death: 4,4
(e) Week of death: 4,5,6,8
(f) Week of death: 1,1,1,1,1,1,1,1,1,2
(g) Mean of five animals surviving at the time of weighing
(h) No data are reported due to 100% mortality in this group.
(i) Week of death: 1,1,5
(j) Mean of nine animals surviving at the time of weighing
(k) Week of death: 1,1,1,1,1,1,1,1,2,2
(l) Mean of seven animals surviving at the time of weighing

TABLE 20. SPERM COUNT AND MOTILITY FOR MALE MICE IN THE THIRTEEN-WEEK GAVAGE STUDY OF GLYCIDOL (a)

Dose (mg/kg)	Sperm Count (b) ($\times 10^{-7}$)	Motility (c)
0	3.0 ± 1.02	3.6
19	2.1 ± 0.45	3.2
75	*1.7 ± 0.37	2.8
150	**1.5 ± 0.50	1.6

(a) For groups of five animals; P values vs. vehicle controls by Dunnett's test (Dunnett, 1955).
(b) Mean sperm count per cauda epididymis ± standard deviation
(c) Motility based on a 0-4 rating scale
*$P<0.05$
**$P<0.01$

TABLE 21. INCIDENCE AND SEVERITY OF SELECTED NONNEOPLASTIC LESIONS IN MICE IN THE THIRTEEN-WEEK GAVAGE STUDIES OF GLYCIDOL (a)

Dose (mg/kg)	Brain Demyelination	Testicular Atrophy/ Degeneration	Renal Tubular Cell Degeneration
MALE			
0	0/10	2/10 (1.0)	0/10
75	0/10	3/9 (1.3)	--
150	*5/10 (1.8)	5/10 (1.6)	0/10
300	1/10 (1.0)	1/10 (2.0)	*4/10
FEMALE			
0	0/10		0/10
75	0/10		--
150	3/10 (1.0)		0/10
300	**6/10 (1.7)		0/10

(a) Number observed/number examined; number in parentheses is the mean severity in animals with the lesion (1 = minimal; 2 = mild; 3 = moderate; 4 = marked).
*P<0.05 for the incidence in dosed groups vs. that in vehicle controls by Fisher exact test
**P<0.01 for the incidence in dosed groups vs. that in vehicle controls by Fisher exact test

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of chemically exposed male mice were generally similar to or higher than those of vehicle controls (Table 22 and Figure 4). Mean body weights of high dose female mice were 9%-13% lower than those of vehicle controls from weeks 56 to 88 and 12%-21% lower thereafter, and mean body weights of low dose female mice were 5%-14% lower after week 28. No compound-related clinical signs were observed.

TABLE 22. MEAN BODY WEIGHTS AND SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF GLYCIDOL

Weeks on Study	Vehicle Control Av. Wt. (grams)	Vehicle Control No. of Survivors	25 mg/kg Av. Wt. (grams)	25 mg/kg Wt. (percent of vehicle controls)	25 mg/kg No. of Survivors	50 mg/kg Av. Wt. (grams)	50 mg/kg Wt. (percent of vehicle controls)	50 mg/kg No. of Survivors
MALE								
0	27.6	50	27.8	101	50	27.6	100	50
1	28.4	50	29.5	104	50	29.5	104	50
2	29.6	50	30.4	103	50	29.8	101	50
3	30.6	50	31.5	103	50	30.3	99	50
4	31.4	50	32.3	103	50	32.1	102	49
5	31.7	50	33.0	104	50	32.5	103	49
6	33.0	50	33.5	102	50	32.5	98	49
7	34.0	50	34.9	103	50	33.9	100	49
8	34.8	50	35.9	103	50	34.9	100	49
9-10	35.1	50	36.7	105	50	35.8	102	49
11	35.9	50	37.5	104	50	35.9	100	49
12	36.6	50	37.9	104	50	37.4	102	49
16	38.9	50	39.8	102	50	39.8	102	49
20	40.0	50	41.9	105	50	41.6	104	49
24	40.9	50	43.4	106	50	44.0	108	49
28	42.9	50	44.5	104	50	45.4	106	49
32	43.1	50	44.2	103	50	45.7	106	49
36	44.9	50	46.5	104	50	46.6	104	49
40	45.3	50	46.6	103	50	46.7	103	49
44	44.9	49	46.4	103	50	47.6	106	49
49	45.8	48	46.4	101	50	46.9	102	49
52	46.1	48	47.9	104	50	48.4	105	48
56	46.5	48	47.7	103	49	48.4	104	47
60	46.7	48	48.5	104	48	49.3	106	47
64	46.9	47	48.3	103	48	49.9	106	47
68	46.8	47	47.9	102	48	49.5	106	47
72	46.4	46	47.7	103	46	49.0	106	44
76	46.1	45	47.5	103	46	48.8	106	42
81	46.5	44	47.7	103	41	48.6	105	40
85	45.6	43	46.3	102	39	48.0	105	40
88	45.0	42	46.9	104	37	47.0	104	39
92	45.4	40	46.3	102	37	46.6	103	36
97	44.7	39	46.1	103	30	46.8	105	32
100	43.9	35	44.5	101	27	44.8	102	28
104	43.6	33	43.0	99	25	43.8	100	27
Mean for weeks								
1-12	32.8		33.9	103		33.1	101	
16-52	43.3		44.8	103		45.3	105	
56-104	45.7		46.8	102		47.7	104	
FEMALE								
0	21.1	50	20.8	99	50	20.9	99	50
1	21.7	50	21.1	97	50	21.6	100	50
2	22.6	50	22.4	99	50	22.7	100	50
3	23.5	50	23.3	99	50	23.6	100	49
4	24.4	50	23.9	98	50	24.2	99	49
5	24.3	50	24.3	100	50	24.2	100	49
6	25.2	50	24.7	98	50	24.8	98	49
7	25.6	50	24.9	97	50	25.4	99	49
8	26.2	50	25.5	97	50	25.7	98	49
9-10	26.4	50	25.7	97	50	26.0	98	49
11	26.4	50	26.1	99	50	26.5	100	49
12	27.0	50	26.8	99	50	26.7	99	49
16	28.5	50	27.9	98	50	28.3	99	49
20	31.2	50	30.1	96	50	29.8	96	49
24	32.3	50	31.0	96	50	31.1	96	49
28	33.9	49	32.2	95	50	32.1	95	49
32	35.3	49	32.6	92	50	32.6	92	49
36	37.0	49	34.4	93	50	34.4	93	49
40	37.1	49	34.8	94	50	41.1	111	49
44	40.4	49	37.1	92	50	37.3	92	49
49	42.1	49	38.2	91	50	38.4	91	49
52	41.6	49	39.5	95	50	39.9	96	49
56	44.5	48	41.4	93	50	40.5	91	48
60	47.0	48	43.4	92	50	42.8	91	48
64	48.8	48	44.5	91	49	43.6	89	46
68	50.7	48	45.9	91	48	45.6	90	45
72	51.1	47	46.5	91	47	46.0	90	44
76	52.8	45	47.1	89	46	46.3	88	44
81	53.8	44	48.8	91	45	47.1	88	40
85	53.7	44	49.3	92	41	46.7	87	38
88	53.5	42	50.4	94	36	48.1	90	33
92	54.7	38	51.2	94	32	48.4	88	29
97	55.5	36	47.6	86	30	46.6	84	28
100	54.6	29	48.9	90	28	45.1	83	19
104	53.5	29	49.0	92	27	42.4	79	17
Mean for weeks								
1-12	24.8		24.4	98		24.7	100	
16-52	35.9		33.8	94		34.5	96	
56-104	51.9		47.2	91		45.3	87	

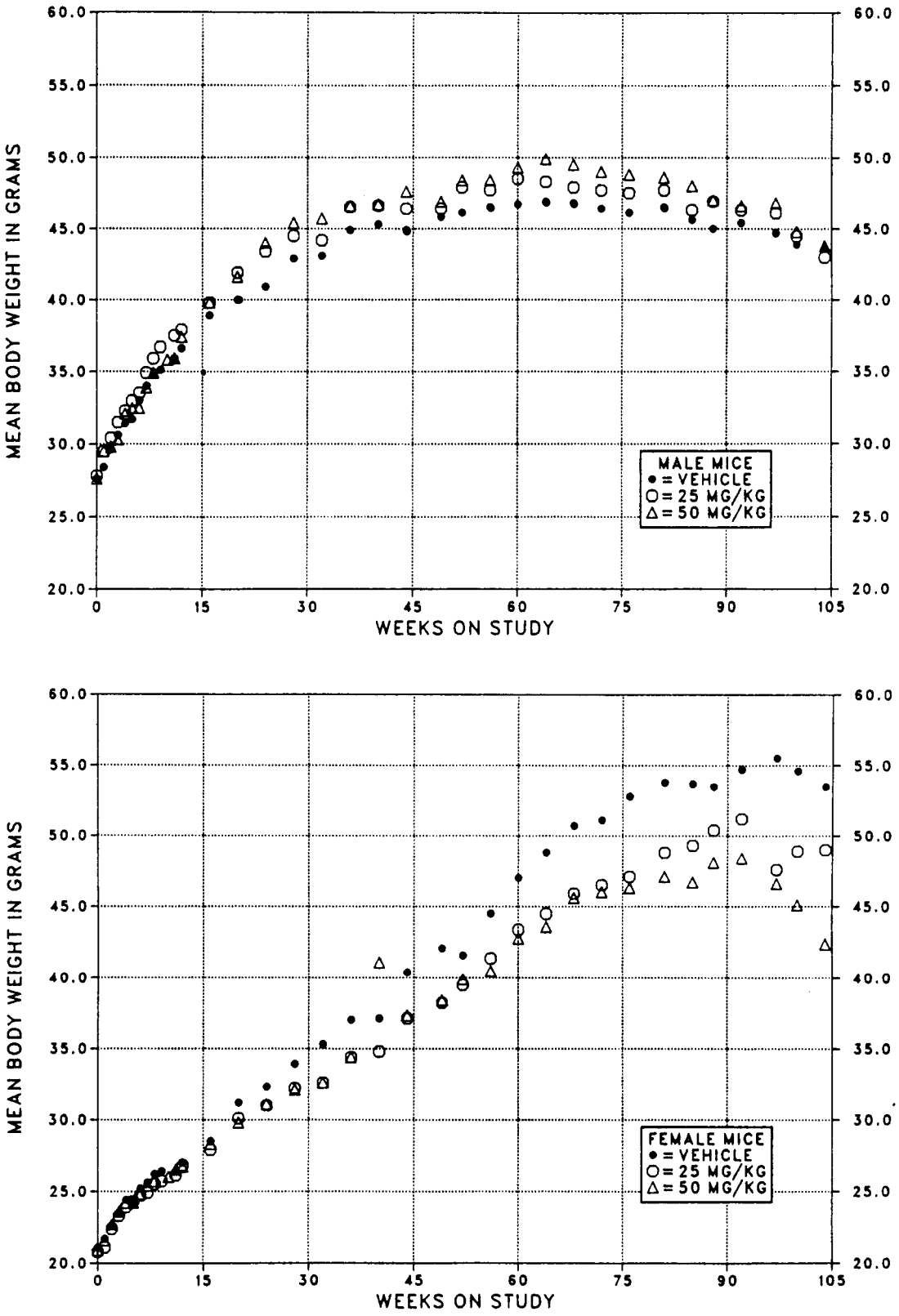

FIGURE 4. GROWTH CURVES FOR MICE ADMINISTERED GLYCIDOL IN WATER BY GAVAGE FOR TWO YEARS

Survival

Estimates of the probabilities of survival for male and female mice administered glycidol at the doses used in these studies and for vehicle controls are shown in Table 23 and in the Kaplan and Meier curves in Figure 5. The survival of the high dose group of female mice was significantly lower than that of the vehicle controls after week 101. No other significant differences were observed between any groups of either sex.

Pathology and Statistical Analyses of Results

This section describes the statistically significant or biologically noteworthy changes in the incidences of mice with neoplastic or nonneoplastic lesions of the harderian gland, mammary gland, subcutaneous tissue, skin, forestomach, liver, lung, circulatory system, hematopoietic system, uterus, urinary bladder, small intestine, epididymis, preputial gland, kidney, spleen, and adrenal gland.

Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, statistical analyses of primary tumors that occurred with an incidence of at least 5% in at least one animal group, and historical control incidences for the neoplasms mentioned in this section are presented in Appendixes C and D for male and female mice, respectively.

TABLE 23. SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF GLYCIDOL

	Vehicle Control	25 mg/kg	50 mg/kg
MALE (a)			
Animals initially in study	50	50	50
Natural deaths	1	0	4
Moribund kills	16	25	19
Animals surviving until study termination	33	25	27
Mean survival (weeks)	97	95	93
Survival P values (b)	0.226	0.144	0.254
FEMALE (a)			
Animals initially in study	50	50	50
Natural deaths	3	5	5
Moribund kills	18	18	27
Animals surviving until study termination	29	27	17
Killed accidentally	0	0	1
Mean survival (weeks)	97	96	91
Survival P values (b)	0.022	0.659	0.024

(a) Termination period: week 104
(b) The result of the life table trend test is in the vehicle control column, and the results of the life table pairwise comparisons with the vehicle controls are in the dosed columns.

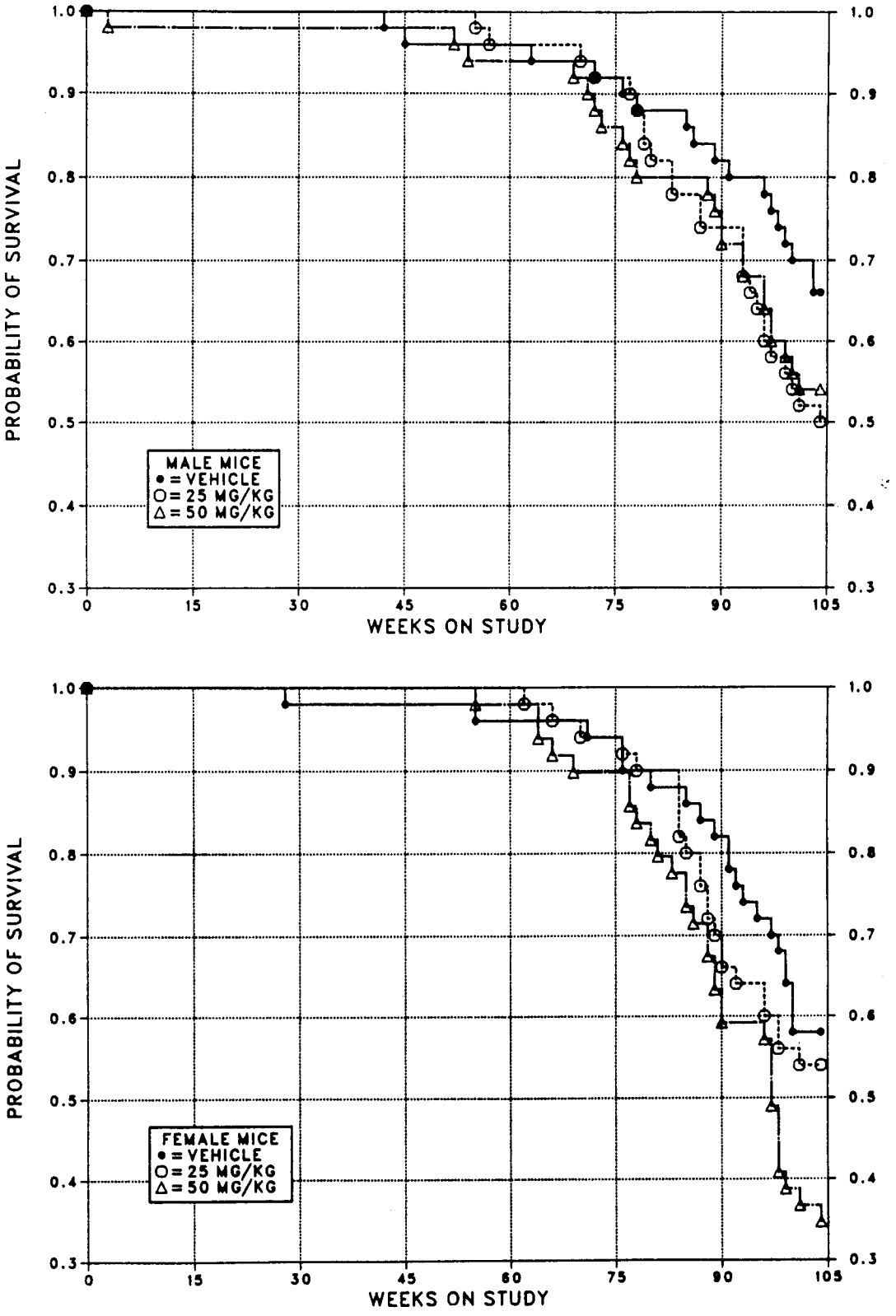

FIGURE 5. KAPLAN-MEIER SURVIVAL CURVES FOR MICE ADMINISTERED GLYCIDOL IN WATER BY GAVAGE FOR TWO YEARS

Harderian Gland: Adenomas in males and females and adenocarcinomas in males occurred with significant positive trends; the incidences in the high dose groups of males and females were significantly greater than those in vehicle controls (Table 24).

Adenomas of the harderian gland were circumscribed masses composed of columnar epithelium arranged in complex papillary formations with a delicate fibrovascular stroma. The adenocarcinomas were generally larger than the adenomas and exhibited some invasion of the adjacent soft tissues. They exhibited pleomorphism and atypia of the epithelium, often with areas of solid growth.

TABLE 24. HARDERIAN GLAND LESIONS IN MICE IN THE TWO-YEAR GAVAGE STUDIES OF GLYCIDOL (a)

	Vehicle Control	25 mg/kg	50 mg/kg
MALE			
Hyperplasia			
Overall Rates	0/46 (0%)	0/41 (0%)	3/44 (7%)
Adenoma			
Overall Rates	7/46 (15%)	10/41 (24%)	16/44 (36%)
Terminal Rates	6/33 (18%)	8/25 (32%)	11/27 (41%)
Week of First Observation	96	93	73
Incidental Tumor Tests	P=0.010	P=0.184	P=0.018
Adenocarcinoma			
Overall Rates	1/46 (2%)	2/41 (5%)	7/44 (16%)
Terminal Rates	1/33 (3%)	0/25 (0%)	4/27 (15%)
Week of First Observation	104	83	72
Incidental Tumor Tests	P=0.013	P=0.397	P=0.037
Adenoma or Adenocarcinoma (b)			
Overall Rates	8/46 (17%)	12/41 (29%)	22/44 (50%)
Terminal Rates	7/33 (21%)	8/25 (32%)	14/27 (52%)
Week of First Observation	96	83	72
Incidental Tumor Tests	P<0.001	P=0.115	P=0.001
FEMALE			
Hyperplasia			
Overall Rates	1/46 (2%)	2/43 (5%)	3/43 (7%)
Adenoma			
Overall Rates	4/46 (9%)	10/43 (23%)	16/43 (37%)
Terminal Rates	3/29 (10%)	5/27 (19%)	11/17 (65%)
Week of First Observation	95	88	88
Incidental Tumor Tests	P<0.001	P=0.078	P<0.001
Adenocarcinoma			
Overall Rates	0/46 (0%)	1/43 (2%)	1/43 (2%)
Adenoma or Adenocarcinoma (c)			
Overall Rates	4/46 (9%)	11/43 (26%)	17/43 (40%)
Terminal Rates	3/29 (10%)	6/27 (22%)	11/17 (65%)
Week of First Observation	95	88	88
Incidental Tumor Tests	P<0.001	P=0.047	P<0.001

(a) For a complete explanation of the entries in this table, see Table C3 (footnotes); the statistical analyses used are discussed in Section II (Statistical Methods).
(b) Historical incidence of adenomas or carcinomas (combined) for water gavage vehicle controls (mean ± SD): 22/350 (6% ± 4%); historical incidence for untreated controls: 67/1,692 (4% ± 3%)
(c) Historical incidence for water gavage vehicle controls (mean ± SD): 12/350 (3% ± 4%); historical incidence for untreated controls: 51/1,689 (3% ± 3%)

Mammary Gland: Adenocarcinomas in female mice occurred with a significant positive trend; the incidence in the high dose group was significantly greater than that in the vehicle controls (Table 25).

Subcutaneous Tissue: Sarcomas and sarcomas or fibrosarcomas (combined) in female mice occurred with significant positive trends; the incidences in the high dose group were significantly greater than those in the vehicle controls (Table 26). Subcutaneous tissue fibromas, sarcomas, or fibrosarcomas (combined) were seen in 11/50 vehicle control, 4/50 low dose, and 4/50 high dose male mice.

TABLE 25. MAMMARY GLAND LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF GLYCIDOL (a)

	Vehicle Control	25 mg/kg	50 mg/kg
Hyperplasia			
Overall Rates	1/50 (2%)	0/50 (0%)	0/50 (0%)
Adenoma			
Overall Rates	0/50 (0%)	1/50 (2%)	0/50 (0%)
Fibroadenoma			
Overall Rates	1/50 (2%)	0/50 (0%)	0/50 (0%)
Adenocarcinoma (b)			
Overall Rates	1/50 (2%)	5/50 (10%)	15/50 (30%)
Terminal Rates	0/29 (0%)	1/27 (4%)	3/17 (18%)
Week of First Observation	95	85	55
Incidental Tumor Tests	P<0.001	P=0.072	P=0.001
Adenoma, Fibroadenoma, or Adenocarcinoma (c)			
Overall Rates	2/50 (4%)	6/50 (12%)	15/50 (30%)
Terminal Rates	1/29 (3%)	1/27 (4%)	3/17 (18%)
Week of First Observation	95	85	55
Incidental Tumor Tests	P=0.001	P=0.078	P=0.003

(a) For a complete explanation of the entries in this table, see Table D3 (footnotes); the statistical analyses used are discussed in Section II (Statistical Methods).
(b) Historical incidence for water gavage vehicle controls (mean ± SD): 2/350 (0.6% ± 1%); historical incidence for untreated controls: 33/1,689 (2% ± 2%)
(c) Historical incidence for water gavage vehicle controls (mean ± SD): 4/350 (1% ± 2%); historical incidence for untreated controls: 35/1,689 (2% ± 2%)

TABLE 26. SUBCUTANEOUS TISSUE TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF GLYCIDOL (a)

	Vehicle Control	25 mg/kg	50 mg/kg
Sarcoma			
Overall Rates	0/50 (0%)	1/50 (2%)	6/50 (12%)
Terminal Rates	0/29 (0%)	0/27 (0%)	2/17 (12%)
Week of First Observation		96	80
Incidental Tumor Tests	P=0.007	P=0.383	P=0.023
Fibrosarcoma			
Overall Rates	0/50 (0%)	2/50 (4%)	3/50 (6%)
Sarcoma or Fibrosarcoma (b)			
Overall Rates	0/50 (0%)	3/50 (6%)	9/50 (18%)
Terminal Rates	0/29 (0%)	0/27 (0%)	2/17 (12%)
Week of First Observation		70	80
Incidental Tumor Tests	P=0.003	P=0.132	P=0.005

(a) For a complete explanation of the entries in this table, see Table D3 (footnotes); the statistical analyses used are discussed in Section II (Statistical Methods).
(b) Historical incidence for water gavage vehicle controls (mean ± SD): 6/350 (2% ± 2%); historical incidence for untreated controls: 40/1,689 (2% ± 3%)

Skin: Four squamous cell papillomas occurred in high dose male mice; this incidence was significant relative to that in the vehicle controls (Table 27). A squamous cell papilloma was seen in one high dose female mouse, and a squamous cell carcinoma was seen in a second high dose female mouse.

Forestomach: Epithelial hyperplasia was observed at increased incidences in high dose mice (male: vehicle control, 2/50; low dose, 4/50; high dose, 8/50; female: 3/50; 1/50; 10/50) (Table 28). Squamous cell papillomas and squamous cell papillomas or carcinomas (combined) in male mice occurred with significant positive trends; the incidences in the high dose group were significantly greater than those in the vehicle controls. Squamous cell papillomas were seen in the forestomach of 3/50 vehicle control, 1/50 low dose, and 4/50 high dose female mice.

TABLE 27. SKIN LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF GLYCIDOL (a)

	Vehicle Control	25 mg/kg	50 mg/kg
Hyperplasia			
Overall Rates	0/50 (0%)	0/50 (0%)	1/50 (2%)
Squamous Cell Papilloma (b)			
Overall Rates	0/50 (0%)	0/50 (0%)	4/50 (8%)
Terminal Rates	0/33 (0%)	0/25 (0%)	3/27 (11%)
Week of First Observation			90
Incidental Tumor Tests	P=0.010	(c)	P=0.047

(a) For a complete explanation of the entries in this table, see Table C3 (footnotes); the statistical analyses used are discussed in Section II (Statistical Methods).
(b) Historical incidence of papillomas or carcinomas (combined) for water gavage vehicle controls (mean ± SD): 2/350 (0.6% ± 2%); historical incidence for untreated controls: 9/1,692 (0.5% ± 1%)
(c) No P value is reported because no tumors were observed in the 25 mg/kg and vehicle control groups.

TABLE 28. FORESTOMACH LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF GLYCIDOL (a)

	Vehicle Control	25 mg/kg	50 mg/kg
Epithelial Hyperplasia			
Overall Rates	2/50 (4%)	4/50 (8%)	*8/50 (16%)
Squamous Cell Papilloma			
Overall Rates	0/50 (0%)	2/50 (4%)	9/50 (18%)
Terminal Rates	0/33 (0%)	0/25 (0%)	5/27 (19%)
Week of First Observation		83	71
Incidental Tumor Tests	P<0.001	P=0.367	P=0.003
Squamous Cell Carcinoma			
Overall Rates	1/50 (2%)	0/50 (0%)	1/50 (2%)
Squamous Cell Papilloma or Carcinoma (b)			
Overall Rates	1/50 (2%)	2/50 (4%)	10/50 (20%)
Terminal Rates	1/33 (3%)	0/25 (0%)	5/27 (19%)
Week of First Observation	104	83	71
Incidental Tumor Tests	P<0.001	P=0.593	P=0.005

(a) For a complete explanation of the entries in this table, see Table C3 (footnotes); the statistical analyses used are discussed in Section II (Statistical Methods).
(b) Historical incidence for water gavage vehicle controls (mean ± SD): 8/331 (2% ± 2%); historical incidence for untreated controls: 10/1,645 (0.6% ± 1%)
*P<0.05 vs. vehicle controls

Liver: Hepatocellular adenomas and hepatocellular adenomas or carcinomas (combined) occurred with significant positive trends in males; the incidences in the high dose group were significantly greater than those in the vehicle controls (Table 29). The incidence of hepatocellular adenomas or carcinomas (combined) was marginally increased in high dose female mice.

Lung: Incidences of alveolar/bronchiolar carcinomas and alveolar/bronchiolar adenomas or carcinomas (combined) were increased in chemically exposed male mice (Table 30). Alveolar/bronchiolar adenomas or carcinomas (combined) were seen in 6/50 vehicle control, 10/50 low dose, and 8/50 high dose female mice.

Circulatory System: Hemangiomas or hemangiosarcomas (combined) in female mice occurred with a significant positive trend by the life table test; however, the incidence in the high dose group was not significantly greater than that in the vehicle controls (Table 31).

TABLE 29. HEPATOCELLULAR TUMORS IN MICE IN THE TWO-YEAR GAVAGE STUDIES OF GLYCIDOL (a)

	Vehicle Control	25 mg/kg	50 mg/kg
MALE			
Adenoma			
Overall Rates	18/50 (36%)	16/50 (32%)	30/50 (60%)
Terminal Rates	11/33 (33%)	10/25 (40%)	21/27 (78%)
Week of First Observation	72	83	73
Incidental Tumor Tests	P=0.004	P=0.380N	P=0.008
Carcinoma			
Overall Rates	10/50 (20%)	17/50 (34%)	8/50 (16%)
Adenoma or Carcinoma (b)			
Overall Rates	24/50 (48%)	31/50 (62%)	35/50 (70%)
Terminal Rates	15/33 (45%)	15/25 (60%)	21/27 (78%)
Week of First Observation	72	55	52
Incidental Tumor Tests	P=0.018	P=0.204	P=0.017
FEMALE			
Adenoma			
Overall Rates	6/50 (12%)	3/50 (6%)	10/50 (20%)
Terminal Rates	6/29 (21%)	3/27 (11%)	5/17 (29%)
Week of First Observation	104	104	83
Incidental Tumor Tests	P=0.054	P=0.272N	P=0.081
Carcinoma			
Overall Rates	3/50 (6%)	5/50 (10%)	4/50 (8%)
Adenoma or Carcinoma (c)			
Overall Rates	9/50 (18%)	7/50 (14%)	14/50 (28%)
Terminal Rates	9/29 (31%)	5/27 (19%)	6/17 (35%)
Week of First Observation	104	84	78
Incidental Tumor Tests	P=0.051	P=0.377N	P=0.062

(a) For a complete explanation of the entries in this table, see Table C3 (footnotes); the statistical analyses used are discussed in Section II (Statistical Methods).
(b) Historical incidence for water gavage vehicle controls (mean ± SD): 106/347 (31% ± 6%); historical incidence for untreated controls: 494/1,678 (29% ± 8%)
(c) Historical incidence for water gavage vehicle controls (mean ± SD): 29/348 (8% ± 5%); historical incidence for untreated controls: 163/1,683 (10% ± 4%)

TABLE 30. LUNG LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF GLYCIDOL (a)

	Vehicle Control	25 mg/kg	50 mg/kg
Alveolar Epithelium Hyperplasia			
Overall Rates	5/50 (10%)	4/50 (8%)	3/50 (6%)
Alveolar/Bronchiolar Adenoma			
Overall Rates	6/50 (12%)	6/50 (12%)	8/50 (16%)
Alveolar/Bronchiolar Carcinoma			
Overall Rates	7/50 (14%)	5/50 (10%)	14/50 (28%)
Terminal Rates	5/33 (15%)	4/25 (16%)	11/27 (41%)
Week of First Observation	98	79	76
Incidental Tumor Tests	P=0.023	P=0.431N	P=0.044
Alveolar/Bronchiolar Adenoma or Carcinoma (b)			
Overall Rates	13/50 (26%)	11/50 (22%)	21/50 (42%)
Terminal Rates	10/33 (30%)	7/25 (28%)	15/27 (56%)
Week of First Observation	76	79	73
Incidental Tumor Tests	P=0.027	P=0.456N	P=0.045

(a) For a complete explanation of the entries in this table, see Table C3 (footnotes); the statistical analyses used are discussed in Section II (Statistical Methods).
(b) Historical incidence for water gavage vehicle controls (mean ± SD): 65/347 (19% ± 8%); historical incidence for untreated controls: 277/1,684 (16% ± 7%)

TABLE 31. CIRCULATORY SYSTEM TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF GLYCIDOL (a)

	Vehicle Control	25 mg/kg	50 mg/kg
Hemangioma			
Overall Rates	0/50 (0%)	1/50 (2%)	2/50 (4%)
Hemangiosarcoma			
Overall Rates	1/50 (2%)	2/50 (4%)	3/50 (6%)
Hemangioma or Hemangiosarcoma (b)			
Overall Rates	1/50 (2%)	3/50 (6%)	5/50 (10%)
Terminal Rates	0/29 (0%)	0/27 (0%)	3/17 (18%)
Week of First Observation	100	66	85
Life Table Tests	P=0.028	P=0.285	P=0.037
Incidental Tumor Tests	P=0.096	P=0.169	P=0.083

(a) For a complete explanation of the entries in this table, see Table D3 (footnotes); the statistical analyses used are discussed in Section II (Statistical Methods).
(b) Historical incidence for water gavage vehicle controls (mean ± SD): 8/350 (2% ± 1%); historical incidence for untreated controls: 48/1,689 (3% ± 3%)

Hematopoietic System: The incidence of lymphomas in low dose male mice was significantly greater than that in vehicle controls (Table 32).

Uterus: Carcinomas or adenocarcinomas (combined) occurred with a significant positive trend (Table 33); these are uncommon neoplasms in female $B6C3F_1$ mice, and their presence at increased incidences in dosed females is considered to be associated with chemical exposure.

TABLE 32. HEMATOPOIETIC SYSTEM TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF GLYCIDOL (a)

	Vehicle Control	25 mg/kg	50 mg/kg
Lymphoma, All Malignant (b)			
Overall Rates	5/50 (10%)	12/50 (24%)	7/50 (14%)
Terminal Rates	3/33 (9%)	6/25 (24%)	2/27 (7%)
Week of First Observation	89	93	54
Life Table Tests	P=0.229	P=0.021	P=0.294
Incidental Tumor Tests	P=0.392	P=0.076	P=0.485

(a) For a complete explanation of the entries in this table, see Table C3 (footnotes); the statistical analyses used are discussed in Section II (Statistical Methods).
(b) Historical incidence of lymphoma or leukemia (combined) for water gavage vehicle controls (mean ± SD): 42/350 (12% ± 6%); historical incidence for untreated controls: 196/1,692 (12% ± 6%)

TABLE 33. UTERINE GLANDULAR TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF GLYCIDOL (a)

	Vehicle Control	25 mg/kg	50 mg/kg
Carcinoma			
Overall Rates	0/50 (0%)	0/50 (0%)	1/50 (2%)
Adenocarcinoma			
Overall Rates	0/50 (0%)	3/50 (6%)	2/50 (4%)
Carcinoma or Adenocarcinoma (b)			
Overall Rates	0/50 (0%)	3/50 (6%)	3/50 (6%)
Terminal Rates	0/29 (0%)	3/27 (11%)	2/17 (12%)
Week of First Observation		104	97
Incidental Tumor Tests	P=0.046	P=0.107	P=0.078

(a) For a complete explanation of the entries in this table, see Table D3 (footnotes); the statistical analyses used are discussed in Section II (Statistical Methods).
(b) Historical incidence for water gavage vehicle controls (mean ± SD): 1/347 (0.3% ± 0.8%); historical incidence for untreated controls: 4/1,675 (0.2% ± 0.7%)

Urinary Bladder: Transitional cell carcinomas were seen in one low dose and one high dose male mouse; no urinary bladder neoplasms have been seen in 350 male water gavage vehicle control $B6C3F_1$ mice or in 1,647 untreated controls.

Small Intestine: Adenomatous polyps were seen in two low dose female mice, and an adenocarcinoma was seen in one high dose female mouse. The historical incidence of small intestine adenomatous polyps or adenocarcinomas (combined) in female $B6C3F_1$ mice is 1/330 (0.3%) for water gavage vehicle controls and 6/1,608 (0.4%) for untreated controls.

Epididymis: Sarcomas were seen in 2/50 high dose male mice; the historical incidence of epididymal sarcomas in $B6C3F_1$ mice is 0/350 in water gavage vehicle controls and 1/1,692 (<0.1%) in untreated controls.

Preputial Gland: The incidence of cysts in high dose male mice was greater than that in vehicle controls (vehicle control, 1/50; low dose, 0/50; high dose, 7/50).

Kidney: Cysts were observed at increased incidences in dosed male mice (male: vehicle control, 4/50; low dose, 11/50; high dose, 9/50; female: 2/50; 4/50; 2/50).

Spleen: Hyperplasia of the red pulp was observed at increased incidences in dosed female mice (male: vehicle control, 10/50; low dose, 4/50; high dose, 7/50; female: 2/50; 9/50; 16/50).

Adrenal Gland: Focal hyperplasia of the adrenal cortex was observed at increased incidences in dosed male mice (male: vehicle control, 0/50; low dose, 4/50; high dose, 6/50; female: 0/50; 2/50; 1/50).

Glycidol was mutagenic in *Salmonella typhimurium* strains TA97, TA98, TA100, TA1535, and TA1537 when tested in a preincubation protocol with doses of 1-10,000 µg/plate both in the presence and absence of Aroclor 1254-induced male Sprague Dawley or Syrian hamster liver S9 (Canter et al., 1986; Table H1). When tested for induction of trifluorothymidine resistance in mouse lymphoma cells, glycidol gave positive responses at doses as low as 1.25 nl/ml in the absence of S9; it was not tested with S9 (Table H2). Sister chromatid exchanges were induced in Chinese hamster ovary (CHO) cells treated with glycidol at concentrations of 1.1-150 µg/ml both in the presence and absence of Aroclor 1254-induced male Sprague Dawley rat liver S9; no cell cycle delay was observed, and strongly positive responses were recorded at all doses (Table H3). Glycidol (12.5-400 µg/ml) was a strong inducer of chromosomal aberrations in CHO cells both with and without S9 metabolic activation at all doses tested; due to glycidol-induced cell cycle delay, the incubation time before cell harvest was extended (Table H4). Glycidol induced both sex-linked recessive lethal mutations and reciprocal translocations in the germ cells of male *Drosophila melanogaster* fed a solution containing 1,230 ppm glycidol (Tables H5 and H6). The incidence of micronucleated polychromatic erythrocytes (PCEs) in the bone marrow of male $B6C3F_1$ mice administered two intraperitoneal injections of glycidol at 24-hour intervals was significantly increased over that in vehicle controls; in both trials, the incidence of micronucleated PCEs in the high dose animals (150 mg/kg $\times$ 2) was approximately three times the incidence in the vehicle controls (Table H7). The experimental procedures and results are presented in Appendix H.

IV. DISCUSSION AND CONCLUSIONS

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Glycidol (2,3-epoxypropanol) is a viscous, water-soluble liquid used as a stabilizer in the manufacture of vinyl polymers, as an additive for oil and synthetic hydraulic fluids, and as a diluent in some epoxy resins. The glycidol moiety is present in glycidyl esters and glycidyl ethers, a large class of commercially important derivatives that are widely used in epoxy resins. Because of the potential for human exposure to these compounds suggested by their pattern of use, glycidol and representative glycidyl esters and glycidyl ethers were evaluated in short-term toxicology studies and in 2-year toxicology and carcinogenicity studies.

During short-term studies, exposure to the top doses of glycidol reduced survival in both rats and mice. Focal demyelination of the brain occurred in mice but not in rats in the 16-day studies; consequently, doses selected for the 13-week studies in mice were lower than those selected for rats. Exposure to glycidol for 13 weeks caused cerebellar necrosis and demyelination of the medulla, renal tubular cell degeneration, and thymic lymphoid necrosis in rats and caused demyelination of the medulla and thalamus and renal tubular cell degeneration in mice. A dose-related reduction in sperm count and sperm motility and an increase in the incidence and severity of testicular atrophy occurred in chemically exposed male rats and mice at the higher doses. Based on these results, doses selected for the 2-year studies of mice were lower than those selected for rats.

Exposure to glycidol for 2 years induced dose-related increases in the incidences of neoplasms in numerous tissues in both rats and mice. Many animals with neoplasms were killed in a moribund condition, and virtually all (196/200) exposed rats died before the end of the 2-year studies. The most prominent lesion in male rats was mesothelioma, arising in the tunica vaginalis and frequently metastasizing into the peritoneal cavity, with the formation of large inguinal masses. Mesotheliomas occurred in 6% of vehicle control, 68% of low dose, and 83% of high dose male rats and were responsible for the deaths of chemically exposed males in which the tumor developed. The first male rat to die from mesothelioma was a high dose male, killed in a moribund condition at week 49, in which the neoplasm had metastasized into the peritoneal cavity. The first vehicle control male rat to die with mesothelioma was killed in a moribund condition at week 86. Thus, exposure to glycidol caused a marked, dose-related increase in the incidence of this neoplasm.

Survival of female rats was reduced by the killing of moribund animals, primarily because of neoplasms of the mammary gland. The combined incidences of fibroadenomas and adenocarcinomas were 28% in vehicle control, 71% in low dose, and 77% in high dose female rats. The first female rat to die with a mammary gland neoplasm was a high dose female that was killed in a moribund condition at week 56 with an adenocarcinoma. The first vehicle control female to die with a mammary gland neoplasm was killed in a moribund condition at week 87 with a fibroadenoma; however, this animal also had mononuclear cell leukemia, which may have been the cause of the moribund condition. The only vehicle control female with a mammary gland adenocarcinoma died at week 91. Therefore, chemical exposure caused marked dose-related increases in the incidences of mammary gland fibroadenomas and adenocarcinomas in female rats. Mononuclear cell leukemia may have also contributed to the early deaths of female rats, since many of the females dying after week 67 had advanced disease. The incidence of leukemia was dose related and significantly increased in high dose females and was therefore considered to be chemically related.

The dose-related increases in the incidences of neoplasms of the mammary gland, brain, thyroid gland, and forestomach in males and females; of the tunica vaginalis/peritoneum, skin, intestine, and Zymbal gland in males; and of the oral mucosa, clitoral gland, and hematopoietic system (mononuclear cell leukemia) in females are considered clear evidence of the carcinogenic activity of glycidol in F344/N rats. In addition, fibrosarcomas were found in the glandular stomach of two high dose females. These are uncommon neoplasms at this site in female F344/N rats, having never been observed in 295 water gavage vehicle control animals and having been found in only 1/1,623 untreated control animals in other NTP studies. Because of their low incidence and the absence of any indication of a

chemical effect in the glandular stomach of low dose animals in the current study, however, it was not possible to conclude that these neoplasms were associated with chemical exposure.

Incidences of harderian gland neoplasms were increased in chemically exposed mice of each sex. The incidences of adenomas or adenocarcinomas (combined) were 17% in vehicle control, 29% in low dose, and 50% in high dose male mice and 9% in vehicle control, 26% in low dose, and 40% in high dose female mice. The incidences of adenomas, fibroadenomas, or adenocarcinomas (combined) of the mammary gland in female mice were markedly increased, occurring in 4% of vehicle control, 12% of low dose, and 30% of high dose animals. In addition, neoplasms of the forestomach, liver, and lung were increased in male mice, and neoplasms of the uterus and subcutaneous tissue were increased in female mice. The dose-related increase in the incidence of neoplasms in each of these tissues is considered clear evidence of the carcinogenicity of glycidol in mice of each sex.

Transitional cell carcinomas were present in the urinary bladder of one low dose and one high dose male mouse, and epididymal sarcomas were present in two high dose male mice. These are uncommon neoplasms in male $B6C3F_1$ mice, and although they were present only in chemically exposed males, their low incidences and the absence of nonneoplastic lesions indicative of chemical-related effects on the urinary bladder or epididymis make it difficult to judge their association with exposure to glycidol.

At the doses used in the current studies, there were few indications of chemically related toxicity. Weight gain by some groups of exposed animals was moderately lower than that by vehicle controls; however, this was more likely attributable to the presence of neoplastic disease in these animals than to chemical toxicity. Moreover, with the exception of the forestomach, there was a notable absence of nonneoplastic histologic lesions attributable to chemical exposure in tissues in which chemically induced neoplasms occurred. In particular, regenerative and/or hyperplastic responses indicative of repair of toxic insult were not present and therefore did not influence neoplasm development in these tissues.

The results of the current studies are comparable to those of other long-term studies with alkylating agents. In long-term inhalation studies conducted with F344 rats, exposure to ethylene oxide at doses ranging from 33 to 300 ppm caused increased incidences of brain gliomas and mononuclear cell leukemia in male and female rats and mesotheliomas of the peritoneum, often involving the tunica vaginalis, in males (Lynch et al., 1984; Garman et al., 1985). In another study, male F344 rats were administered *N*-nitroso-*N*-ethylhydroxyethylurea (HENU-II), *N*-nitroso-*N*-hydroxyethyl-ethylurea (HENU-I), nitrosoethylurea (NEU), or nitrosohydroxyethylurea (NHU) by gavage in corn oil/ethyl acetate for 31 weeks and then were maintained, without being dosed, until all chemically exposed animals were dead (total duration, 80 weeks) (Lijinsky et al., 1985). All four compounds caused increased incidences of neoplasms at multiple sites, including papillomas or carcinomas of the forestomach; carcinomas of the lung, colon, thyroid gland, and Zymbal gland; and mesotheliomas of the peritoneum. In addition, HENU-I and HENU-II induced gliomas in the brain and neoplastic nodules or hepatocellular carcinomas.

Glycidol is structurally similar to ethylene oxide but quite different from the alkyl nitrosoureas. When viewed as alylating agents, however, the epoxides and nitrosoureas produce similar alkylated products with an appropriate nucleophile; these products would include ethylated (NEU, HENU-I), hydroxyethylated (ethylene oxide, NHU, HENU-II), and 1,2-dihydroxypropylated or 1,3-dihydroxyisopropylated (glycidol) adducts. In solution, glycidol readily alkylates deoxyadenosine at the 1 or N^6 position, deoxyguanosine at the 1 and 7 position, deoxycytosine at the 3 position, and thymidine at the 3 position to form 1,2-dihydroxypropyl adducts (Hemminki et al., 1980; Djuric and Sinsheimer, 1984; Hemminki and Lax, 1986; Djuric et al., 1986). In highly polymerized calf thymus DNA, glycidol reacts preferentially with guanine residues, although the products of this reaction have not been identified (Djuric et al., 1986). There has been no report of simple epoxides alkylating the O^6 of guanine, either in solution or in intact DNA. α-Chlorohydrin, a metabolite formed in the stomach by the reaction of chloride with

glycidol, was unreactive toward deoxyguanosine in solution (Hemminki and Lax, 1986); its reactivity with other bases and DNA has not been reported.

The experimental and tabulated data for the NTP Technical Report on glycidol were examined for accuracy, consistency, completeness, and compliance with Good Laboratory Practice regulations. As summarized in Appendix I, the audit revealed no major problems with the conduct of the studies or with collection and documentation of the experimental data. No discrepancies were found that influenced the final interpretation of the results of these studies.

Under the conditions of these 2-year gavage studies, there was *clear evidence of carcinogenic activity** of glycidol for male F344/N rats, based on increased incidences of mesotheliomas of the tunica vaginalis; fibroadenomas of the mammary gland; gliomas of the brain; and neoplasms of the forestomach, intestine, skin, Zymbal gland, and thyroid gland. There was *clear evidence of carcinogenic activity* for female F344/N rats, based on increased incidences of fibroadenomas and adenocarcinomas of the mammary gland; gliomas of the brain; neoplasms of the oral mucosa, forestomach, clitoral gland, and thyroid gland; and leukemia. There was *clear evidence of carcinogenic activity* for male B6C3F$_1$ mice, based on increased incidences of neoplasms of the harderian gland, forestomach, skin, liver, and lung. There was *clear evidence of carcinogenic activity* for female B6C3F$_1$ mice, based on increased incidences of neoplasms of the harderian gland, mammary gland, uterus, subcutaneous tissue, and skin. Other neoplasms that may have been related to the administration of glycidol were fibrosarcomas of the glandular stomach in female rats and carcinomas of the urinary bladder and sarcomas of the epididymis in male mice.

*Explanation of Levels of Evidence of Carcinogenic Activity is on page 6.
A summary of the Peer Review comments and the public discussion on this Technical Report appears on pages 9-10.

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APPENDIX A

SUMMARY OF LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF GLYCIDOL

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF GLYCIDOL

	Vehicle Control	37.5 mg/kg	75 mg/kg
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		3 (6%)	3 (6%)
Basal cell tumor		4 (8%)	2 (4%)
Sebaceous adenoma		1 (2%)	1 (2%)
Sebaceous adenocarcinoma			1 (2%)
Keratoacanthoma	1 (2%)	4 (8%)	1 (2%)
*Subcutaneous tissue	(50)	(50)	(50)
Fibroma	2 (4%)	2 (4%)	4 (8%)
Fibrosarcoma	3 (6%)	2 (4%)	1 (2%)
Lipoma	1 (2%)		
Neurofibroma		1 (2%)	
RESPIRATORY SYSTEM			
#Nasal cavity	(50)	(50)	(50)
Squamous cell carcinoma		1 (2%)	1 (2%)
Adenocarcinoma, NOS			1 (2%)
#Lung/bronchiole	(50)	(50)	(50)
Papilloma, NOS			1 (2%)
#Lung	(50)	(50)	(50)
Carcinoma, NOS, metastatic		1 (2%)	
Squamous cell carcinoma, metastatic		1 (2%)	
Alveolar/bronchiolar adenoma	1 (2%)	3 (6%)	2 (4%)
Alveolar/bronchiolar carcinoma	1 (2%)	2 (4%)	2 (4%)
Fibrosarcoma, metastatic		1 (2%)	
Neurilemoma, malignant		1 (2%)	
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Malignant lymphoma, histiocytic type			1 (2%)
Leukemia, mononuclear cell	25 (50%)	33 (66%)	21 (42%)
#Spleen	(50)	(50)	(50)
Sarcoma, NOS	2 (4%)		
Fibroma			1 (2%)
Fibrosarcoma			1 (2%)
#Lymph node	(50)	(49)	(50)
Mesothelioma, metastatic		1 (2%)	
Osteosarcoma, metastatic		1 (2%)	
#Glandular stomach	(50)	(50)	(50)
Mast cell sarcoma		1 (2%)	
#Thymus	(46)	(47)	(43)
Mesothelioma, metastatic	1 (2%)		
CIRCULATORY SYSTEM			
#Spleen	(50)	(50)	(50)
Hemangiosarcoma		1 (2%)	
*Skeletal muscle	(50)	(50)	(50)
Hemangiosarcoma	1 (2%)		
DIGESTIVE SYSTEM			
*Mouth	(50)	(50)	(50)
Squamous cell papilloma	1 (2%)	1 (2%)	1 (2%)
Squamous cell carcinoma	1 (2%)		

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF GLYCIDOL (Continued)

	Vehicle Control	37.5 mg/kg	75 mg/kg
DIGESTIVE SYSTEM (Continued)			
*Tongue	(50)	(50)	(50)
Squamous cell papilloma	1 (2%)		2 (4%)
Squamous cell carcinoma		1 (2%)	2 (4%)
#Liver	(50)	(50)	(50)
Neoplastic nodule	1 (2%)		1 (2%)
Hepatocellular carcinoma		1 (2%)	
Fibrosarcoma, metastatic			1 (2%)
#Pancreas	(50)	(48)	(50)
Fibrosarcoma		1 (2%)	
#Forestomach	(50)	(50)	(50)
Squamous cell papilloma		1 (2%)	5 (10%)
Squamous cell carcinoma	1 (2%)	1 (2%)	2 (4%)
#Small intestine	(50)	(50)	(50)
Mucinous adenocarcinoma		1 (2%)	2 (4%)
Mesothelioma, invasive			1 (2%)
#Jejunum	(50)	(50)	(50)
Mucinous adenocarcinoma			1 (2%)
#Colon	(50)	(50)	(50)
Adenocarcinoma, NOS			1 (2%)
Adenomatous polyp, NOS			1 (2%)
#Cecum	(50)	(50)	(50)
Sarcoma, NOS		1 (2%)	
URINARY SYSTEM			
#Kidney	(50)	(50)	(50)
Tubular cell adenoma		1 (2%)	2 (4%)
Sarcoma, NOS	1 (2%)		
#Urinary bladder	(50)	(50)	(49)
Transitional cell papilloma		1 (2%)	
ENDOCRINE SYSTEM			
#Anterior pituitary	(50)	(50)	(50)
Carcinoma, NOS		1 (2%)	
Adenoma, NOS	8 (16%)	7 (14%)	2 (4%)
#Adrenal cortex	(50)	(50)	(50)
Adenoma, NOS	1 (2%)		
#Adrenal medulla	(50)	(50)	(50)
Pheochromocytoma	13 (26%)	4 (8%)	1 (2%)
Pheochromocytoma, malignant	1 (2%)	1 (2%)	
#Thyroid	(50)	(50)	(50)
Follicular cell adenoma		2 (4%)	2 (4%)
Follicular cell carcinoma	1 (2%)	2 (4%)	5 (10%)
C-cell adenoma	2 (4%)	3 (6%)	3 (6%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Fibroadenoma	3 (6%)	8 (16%)	7 (14%)
*Preputial gland	(50)	(50)	(50)
Adenoma, NOS	5 (10%)	7 (14%)	1 (2%)
Adenocarcinoma, NOS	5 (10%)		4 (8%)
#Testis	(50)	(50)	(50)
Interstitial cell tumor	46 (92%)	50 (100%)	49 (98%)
NERVOUS SYSTEM			
#Brain/meninges	(50)	(50)	(50)
Granular cell tumor, NOS	2 (4%)		1 (2%)

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF GLYCIDOL (Continued)

	Vehicle Control	37.5 mg/kg	75 mg/kg
NERVOUS SYSTEM (Continued)			
#Brain	(50)	(50)	(50)
Glioma, NOS		5 (10%)	6 (12%)
SPECIAL SENSE ORGANS			
*Ear	(50)	(50)	(50)
Fibrosarcoma	1 (2%)		
*Zymbal gland	(50)	(50)	(50)
Carcinoma, NOS	1 (2%)	3 (6%)	6 (12%)
MUSCULOSKELETAL SYSTEM			
*Bone	(50)	(50)	(50)
Osteosarcoma		1 (2%)	
*Skeletal muscle	(50)	(50)	(50)
Neurilemoma, invasive		1 (2%)	
BODY CAVITIES			
*Peritoneal mesothelium	(50)	(50)	(50)
Mesothelioma, metastatic	2 (4%)	19 (38%)	28 (56%)
*Pleura	(50)	(50)	(50)
Mesothelioma, metastatic	1 (2%)		
*Pericardium	(50)	(50)	(50)
Mesothelioma, metastatic	1 (2%)		
*Tunica vaginalis	(50)	(50)	(50)
Mesothelioma, NOS		10 (20%)	8 (16%)
Mesothelioma, malignant	3 (6%)	24 (48%)	31 (62%)
ALL OTHER SYSTEMS			
Adipose tissue			
Sarcoma, NOS	1		
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	1	5	3
Moribund sacrifice	33	45	46
Terminal sacrifice	16		
Dosing accident			1
TUMOR SUMMARY			
Total animals with primary tumors**	48	50	49
Total primary tumors	136	197	190
Total animals with benign tumors	46	50	49
Total benign tumors	85	103	91
Total animals with malignant tumors	36	48	48
Total malignant tumors	48	84	89
Total animals with secondary tumors##	3	23	28
Total secondary tumors	5	25	30
Total animals with tumors-- uncertain benign or malignant	2	10	10
Total uncertain tumors	3	10	10

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
** Primary tumors: all tumors except secondary tumors
# Number of animals examined microscopically at this site
Secondary tumors: metastatic tumors or tumors invasive into an adjacent organ

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF GLYCIDOL: VEHICLE CONTROL

ANIMAL NUMBER	006	015	027	023	032	008	041	048	002	001	005	037	026	021	016	046	033	035	011	039	045	004	040	017	019
WEEKS ON STUDY	020	053	056	063	071	074	080	081	083	084	086	087	088	088	089	089	089	091	091	092	092	094	094	094	094
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma									X													X			
Fibrosarcoma																			X			X			
Lipoma					X																				
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																									
Trachea	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+
Nasal cavity	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	−	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	−	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	−	+
Sarcoma, NOS																									
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	−	+	+	+	+
Thymus	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	+	+	+	+
Mesothelioma, metastatic																							X		
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell papilloma						X																			
Squamous cell carcinoma			X																						
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+
Neoplastic nodule																				X					
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+
Squamous cell carcinoma																									
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS									X						X										
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Pheochromocytoma																		X			X	X	X		X
Pheochromocytoma, malignant																X									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+
Follicular cell carcinoma																									
C cell adenoma									X							X									
Parathyroid	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

\+ Tissue examined microscopically
− Required tissue not examined microscopically
X Tumor incidence
N Necropsy, no autolysis, no microscopic examination
S Animal missexed
  No tissue information submitted
C Necropsy, no histology due to protocol
A Autolysis
M Animal missing
B No necropsy performed

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: VEHICLE CONTROL (Continued)

ANIMAL NUMBER	0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
	5 3 4 0 2 0 1 4 2 0 1 1 1 1 2 2 2 2 3 3 3 3 4 4 4
	0 0 3 3 9 7 2 7 2 9 0 3 4 8 0 4 5 8 1 4 6 8 2 4 9
WEEKS ON STUDY	0 0 0 0 0 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
	9 9 9 9 9 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
	5 6 7 9 9 1 2 2 3 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4
INTEGUMENTARY SYSTEM	
Skin	+ +
Keratoacanthoma	X
Subcutaneous tissue	+ +
Fibroma	
Fibrosarcoma	X
Lipoma	
RESPIRATORY SYSTEM	
Lungs and bronchi	+ +
Alveolar/bronchiolar adenoma	X
Alveolar bronchiolar carcinoma	X
Trachea	+ +
Nasal cavity	+ +
HEMATOPOIETIC SYSTEM	
Bone marrow	+ − +
Spleen	+ + + + + + + + + + + + − + + + + + + + + + + +
Sarcoma, NOS	X X
Lymph nodes	+ +
Thymus	+ + − +
Mesothelioma, metastatic	
CIRCULATORY SYSTEM	
Heart	+ +
DIGESTIVE SYSTEM	
Oral cavity	N N N N N N N N N N N N N N N N N N N N N N N N N
Squamous cell papilloma	X
Squamous cell carcinoma	
Salivary gland	+ − + +
Liver	+ +
Neoplastic nodule	
Bile duct	+ +
Pancreas	+ +
Esophagus	+ +
Stomach	+ +
Squamous cell carcinoma	X
Small intestine	+ +
Large intestine	+ +
URINARY SYSTEM	
Kidney	+ +
Sarcoma, NOS	X
Urinary bladder	+ +
ENDOCRINE SYSTEM	
Pituitary	+ +
Adenoma, NOS	X X X X X
Adrenal	+ +
Adenoma, NOS	X
Pheochromocytoma	X X X X X X X X
Pheochromocytoma, malignant	
Thyroid	+ +
Follicular cell carcinoma	X
C cell adenoma	
Parathyroid	− + − +

TOTAL TISSUES TUMORS
*50
1
*50
2
3
1
50
1
1
50
50
49
50
2
50
46
1
50
*50
2
1
49
50
1
50
50
50
50
1
50
50
50
1
50
8
50
1
13
1
50
1
2
47

* Animals necropsied

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: VEHICLE CONTROL (Continued)

ANIMAL NUMBER	0006	0015	0027	0023	0032	0008	0041	0048	0002	0001	0005	0037	0026	0021	0016	0046	0033	0035	0011	0039	0045	0004	0040	0017	0019
WEEKS ON STUDY	020	053	056	063	071	074	080	081	083	084	086	087	088	088	089	089	089	091	091	092	092	094	094	094	094
REPRODUCTIVE SYSTEM																									
Mammary gland	+	N	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma																					X				
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																		X							
Adenocarcinoma, NOS										X							X					X		
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granular cell tumor, NOS														X						X					
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
Fibrosarcoma																									
Zymbal 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				
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
Hemangiosarcoma															X										
BODY CAVITIES																									
Pleura	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Mesothelioma, metastatic																									
Pericardium	N	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, metastatic																									
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
Mesothelioma, metastatic											X												X		
Tunica vaginalis	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma, malignant											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
Leukemia, mononuclear cell				X					X			X	X	X	X			X	X	X	X	X	X	X	X
Adipose tissue																									
Sarcoma, NOS																									

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: VEHICLE CONTROL (Continued)

ANIMAL NUMBER	05 00	03 00	04 03	00 03	02 09	00 07	01 02	04 07	02 02	00 09	01 00	01 03	01 04	01 18	02 00	02 04	02 05	02 08	03 01	03 34	03 36	03 38	04 02	04 04	04 09	TOTAL TISSUES TUMORS
WEEKS ON STUDY	09 95	09 96	09 97	09 99	09 99	10 01	10 02	10 02	10 03	10 04	10 04	10 04	10 04	10 04	10 04	10 04	10 04	10 04	10 04	10 04	10 04	10 04	10 04	10 04	10 04	
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroadenoma							X													X						3
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell tumor	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	46
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS			X						X													X			X	5
Adenocarcinoma, NOS		X										X														5
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granular cell tumor, NOS																										2
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
Fibrosarcoma									X																	1
Zymbal 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
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	*50
Hemangiosarcoma																										1
BODY CAVITIES																										
Pleura	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Mesothelioma, metastatic			X																							1
Pericardium	N	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, metastatic			X																							1
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, metastatic																										2
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Mesothelioma, malignant			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
Leukemia, mononuclear cell		X				X	X	X					X	X		X		X		X			X		X	25
Adipose tissue																										
Sarcoma, NOS																				X						1

* Animals necropsied

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF GLYCIDOL: 37.5 mg/kg

ANIMAL NUMBER	01 14	02 29	01 15	00 01	02 25	00 05	04 43	00 07	02 26	03 37	03 33	03 35	02 21	02 22	04 44	02 20	04 48	03 32	00 06	02 24	00 09	04 46	01 18	00 88	04 49
WEEKS ON STUDY	06 65	06 55	06 99	06 99	07 00	07 00	07 00	07 07	07 11	07 72	07 72	07 73	07 74	07 74	07 74	07 75	07 75	07 76	07 78	07 79	08 02	08 82	08 83	08 84	08 84
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	N	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Basal cell tumor																									
Sebaceous adenoma																									
Keratoacanthoma																		X				X			
Subcutaneous tissue	+	+	+	N	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																									
Fibrosarcoma																					X				
Neurofibroma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, metastatic																									
Squamous cell carcinoma, metastatic																									
Alveolar/bronchiolar adenoma															X										
Alveolar/bronchiolar carcinoma																									
Fibrosarcoma, metastatic																									
Neurilemoma, malignant																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																									
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Lymph nodes	+	+	+	+	+	+	+	+	—	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma, metastatic																									
Osteosarcoma, metastatic																		X							
Thymus	+	—	+	+	—	—	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell papilloma																									
Squamous cell carcinoma																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	—	+	+	+	+	—	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Squamous cell carcinoma																									
Mast cell sarcoma				X																					
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mucinous adenocarcinoma													X												
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS										X															
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional cell papilloma																									

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: 37.5 mg/kg (Continued)

ANIMAL NUMBER	0050	0036	0042	0031	0045	0028	0002	0030	0039	0041	0011	0119	0112	0013	0038	0016	0040	0004	0034	0223	0171	0311	0447	0107	0207	TOTAL TISSUES TUMORS
WEEKS ON STUDY	085	085	085	086	086	087	088	088	088	089	089	089	090	090	090	090	090	091	091	091	092	092	092	097	098	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell papilloma					X																		X		X	3
Basal cell tumor								X			X	X										X				4
Sebaceous adenoma													X													1
Keratoacanthoma															X								X			4
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma	X														X											2
Fibrosarcoma				X																						2
Neurofibroma													X													1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS, metastatic				X																						1
Squamous cell carcinoma, metastatic					X																					1
Alveolar/bronchiolar adenoma										X														X		3
Alveolar/bronchiolar carcinoma													X	X												2
Fibrosarcoma, metastatic				X																						1
Neurilemoma, malignant																				X						1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma					X																					1
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma														X												1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Mesothelioma, metastatic									X																	1
Osteosarcoma, metastatic																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell papilloma																				X						1
Squamous cell carcinoma												X														1
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma																			X							1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Fibrosarcoma																								X		1
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma			X																							1
Squamous cell carcinoma		X																								1
Mast cell sarcoma																										1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mucinous adenocarcinoma																										1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, NOS																										1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tubular cell adenoma																									X	1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Transitional cell papilloma										X																1

* Animals necropsied

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: 37.5 mg/kg (Continued)

ANIMAL NUMBER	0014	0029	0015	0001	0025	0005	0043	0007	0026	0037	0033	0035	0021	0022	0044	0020	0048	0032	0006	0024	0009	0046	0018	0008	0049
WEEKS ON STUDY	065	065	069	069	070	070	070	070	071	072	072	073	074	074	074	075	075	076	078	079	082	082	083	084	084
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																									
Adenoma, NOS					X														X			X			
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma				X					X															X	
Pheochromocytoma, malignant																									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																									
Follicular cell carcinoma																									
C-cell adenoma																									
Parathyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	N	+	+	+	+	+	N	+	+	+	N	+	+	+	+	+	+	+	N	+	+	+	+
Fibroadenoma																			X						
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	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
Adenoma, NOS																								X	X
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Glioma, NOS					X																				
SPECIAL SENSE ORGANS																									
Zymbal 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		
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma																		X							
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
Neurilemoma, invasive																									
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
Mesothelioma, metastatic	X				X	X			X		X						X		X			X	X		X
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma, NOS		X		X				X					X												
Mesothelioma, malignant	X				X	X			X		X	X			X	X	X		X			X	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
Leukemia, mononuclear cell		X	X		X		X	X		X	X		X	X	X	X		X		X	X			X	

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: 37.5 mg/kg (Continued)

ANIMAL NUMBER	05 50	03 36	04 42	00 03	04 45	02 88	00 02	03 30	03 39	04 41	01 11	01 19	01 12	01 13	03 38	01 16	04 40	00 04	03 34	02 23	01 17	03 31	04 47	01 10	02 07	TOTAL. TISSUES TUMORS
WEEKS ON STUDY	08 55	08 55	08 55	08 66	08 66	08 77	08 88	08 88	08 88	08 89	08 89	08 99	09 00	09 00	09 00	09 00	09 00	09 01	09 11	09 11	09 92	09 92	09 92	09 97	09 98	
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS				X																						1
Adenoma, NOS			X				X																X	X		7
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma													X													4
Pheochromocytoma, malignant																				X						1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell adenoma			X					X																		2
Follicular cell carcinoma		X																				X				2
C cell adenoma						X								X										X		3
Parathyroid	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	48
REPRODUCTIVE SYSTEM																										
Mammary gland	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroadenoma					X	X							X			X	X					X		X		8
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell tumor	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS						X						X	X						X					X		7
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Glioma, NOS		X	X							X															X	5
SPECIAL SENSE ORGANS																										
Zymbal 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																3
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Osteosarcoma																										1
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	*50
Neurilemoma, invasive																			X							1
BODY CAVITIES																										
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Mesothelioma, metastatic								X	X	X			X	X	X		X					X			X	19
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Mesothelioma, NOS			X			X					X					X			X	X						10
Mesothelioma, malignant	X			X				X	X	X			X	X	X		X					X			X	24
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
Leukemia, mononuclear cell	X				X	X	X	X	X	X		X	X		X	X	X	X	X	X	X	X	X		X	33

* Animals necropsied

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF GLYCIDOL: 75 mg/kg

ANIMAL NUMBER	00051	00133	00177	00199	00339	00229	00189	00445	00115	00125	00302	00262	00333	00220	00550	00011	00336	00335	00046	00464	00161	00404	00477	00030	00110
WEEKS ON STUDY	01 4	04 4	04 7	04 9	05 0	05 2	05 6	05 7	05 8	06 0	06 0	06 0	06 0	06 1	06 2	06 2	06 3	06 3	06 4	06 4	06 5	06 5	06 6	06 6	06 8
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Basal cell tumor																									
Sebaceous adenoma																									
Sebaceous adenocarcinoma																									
Keratoacanthoma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																									
Fibrosarcoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma, NOS																									
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																									
Adenocarcinoma, NOS											X														
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																									
Fibrosarcoma																									
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	−	−	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell papilloma																									X
Squamous cell carcinoma																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																									X
Fibrosarcoma, metastatic																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																			X						
Squamous cell carcinoma																				X					
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mucinous adenocarcinoma														@X											X
Mesothelioma, invasive						X																			
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																									
Adenomatous polyp, NOS																									
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																X								X	
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma																	X								
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																									
Follicular cell carcinoma																									
C cell adenoma																									
Parathyroid	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

@ Multiple occurrence of morphology

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: 75 mg/kg (Continued)

ANIMAL NUMBER	0 2 8	0 3 8	0 3 4	0 4 2	0 0 7	0 0 2	0 0 8	0 4 1	0 4 3	0 2 3	0 4 9	0 1 1	0 3 1	0 0 6	0 3 7	0 2 7	0 3 2	0 4 8	0 4 4	0 2 5	0 2 1	0 0 9	0 2 2	0 1 4	0 2 4	TOTAL TISSUES TUMORS
WEEKS ON STUDY	0 6 8	0 6 8	0 6 8	0 6 8	0 6 8	0 7 0	0 7 1	0 7 2	0 7 3	0 7 3	0 7 3	0 7 3	0 7 3	0 7 4	0 7 4	0 7 5	0 7 6	0 7 6	0 7 7	0 7 7	0 7 7	0 7 8	0 8 5	0 8 6	0 8 9	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell papilloma			X							X														X		3
Basal cell tumor								X								X										2
Sebaceous adenoma																							X			1
Sebaceous adenocarcinoma																	X									1
Keratoacanthoma																					X					1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma							X						X						X					X		4
Fibrosarcoma						X																				1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Papilloma, NOS																	X									1
Alveolar/bronchiolar adenoma					X							X														2
Alveolar/bronchiolar carcinoma									X													X				2
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma							X																			1
Adenocarcinoma, NOS																										1
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroma											X															1
Fibrosarcoma																							X			1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	–	+	–	+	+	+	+	+	+	+	–	+	+	–	+	+	+	+	43
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell papilloma			X									X														3
Squamous cell carcinoma	X			X																						2
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule																										1
Fibrosarcoma, metastatic																							X			1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma														X		X						X			X	5
Squamous cell carcinoma																									X	2
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mucinous adenocarcinoma																										2
Mesothelioma, invasive																										1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS										X																1
Adenomatous polyp, NOS																X										1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tubular cell adenoma															X									X		2
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS																										2
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma																										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell adenoma																				X		X				2
Follicular cell carcinoma							X				X								X			X			X	5
C cell adenoma								X														X		X		3
Parathyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	47

* Animals necropsied

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: 75 mg/kg (Continued)

ANIMAL NUMBER	005	013	017	019	039	029	018	045	015	012	030	026	033	020	050	001	036	035	004	046	016	040	047	003	010
WEEKS ON STUDY	014	044	047	049	050	052	056	057	058	060	060	060	060	061	062	062	063	063	064	064	065	065	066	066	068
REPRODUCTIVE SYSTEM																									
Mammary gland	N	+	+	+	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma																									
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	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
Adenoma, NOS																									
Adenocarcinoma, NOS					X							X													
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granular cell tumor, NOS																									
Glioma, NOS																					X				
SPECIAL SENSE ORGANS																									
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS			X			X																	X		
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
Mesothelioma, metastatic				X		X			X	X		X	X		X	X	X	X	X			X		X	
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma, NOS											X			X						X			X		
Mesothelioma, malignant				X		X	X	X	X	X		X	X		X	X	X	X	X			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
Malignant lymphoma, histiocytic type																									
Leukemia, mononuclear cell							X								X		X	X		X				X	X

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: 75 mg/kg (Continued)

ANIMAL NUMBER	028	038	034	042	007	002	008	041	043	023	049	011	031	006	037	027	032	048	044	025	021	009	022	014	024	TOTAL TISSUES TUMORS
WEEKS ON STUDY	068	068	068	068	068	070	071	072	073	073	073	073	073	074	074	075	076	076	077	077	077	078	085	086	089	
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroadenoma											X					X		X	X	X			X		X	7
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell tumor	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	49
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS																X										1
Adenocarcinoma, NOS																			X						X	4
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granular cell tumor, NOS						X																				1
Glioma, NOS					X	X				X									X			X				6
SPECIAL SENSE ORGANS																										
Zymbal 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		6
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, metastatic			X	X	X		X					X	X	X	X			X		X	X	X	X	X	X	28
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Mesothelioma, NOS	X	X						X		X																8
Mesothelioma, malignant			X	X	X	X	X					X	X	X	X			X		X	X	X	X	X	X	31
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, histiocytic type		X																								1
Leukemia, mononuclear cell		X		X				X	X	X			X		X	X		X		X	X		X	X	X	21

* Animals necropsied

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF GLYCIDOL

	Vehicle Control	37.5 mg/kg	75 mg/kg
Skin: Squamous Cell Papilloma			
Overall Rates (a)	0/50 (0%)	3/50 (6%)	3/50 (6%)
Effective Rates (b)	0/46 (0%)	3/48 (6%)	3/26 (12%)
Terminal Rates (c)	0/16 (0%)	0/0	0/0
Week of First Observation		86	68
Life Table Tests (d)	P<0.001	P<0.001	P=0.004
Incidental Tumor Tests (d)	P=0.012	P=0.080	P=0.168
Cochran-Armitage Trend Test (d)	P=0.026		
Fisher Exact Test (d)		P=0.129	P=0.044
Skin: Basal Cell Tumor			
Overall Rates (a)	0/50 (0%)	4/50 (8%)	2/50 (4%)
Effective Rates (b)	0/45 (0%)	4/41 (10%)	2/18 (11%)
Terminal Rates (c)	0/16 (0%)	0/0	0/0
Week of First Observation		88	72
Life Table Tests (d)	P<0.001	P=0.003	P=0.042
Incidental Tumor Tests (d)	P=0.157	P=0.172	P=0.742
Cochran-Armitage Trend Test (d)	P=0.040		
Fisher Exact Test (d)		P=0.048	P=0.078
Skin: Sebaceous Gland Adenoma or Basal Cell Tumor			
Overall Rates (a)	0/50 (0%)	5/50 (10%)	3/50 (6%)
Effective Rates (b)	0/45 (0%)	5/41 (12%)	3/18 (17%)
Terminal Rates (c)	0/16 (0%)	0/0	0/0
Week of First Observation		88	72
Life Table Tests (d)	P<0.001	P<0.001	P=0.001
Incidental Tumor Tests (d)	P=0.032	P=0.116	P=0.168
Cochran-Armitage Trend Test (d)	P=0.011		
Fisher Exact Test (d)		P=0.022	P=0.021
Skin: Sebaceous Gland Adenoma, Basal Cell Tumor, or Sebaceous Gland Adenocarcinoma			
Overall Rates (a)	0/50 (0%)	5/50 (10%)	4/50 (8%)
Effective Rates (b)	0/45 (0%)	5/41 (12%)	4/18 (22%)
Terminal Rates (c)	0/16 (0%)	0/0	0/0
Week of First Observation		88	72
Life Table Tests (d)	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests (d)	P=0.023	P=0.116	P=0.153
Cochran-Armitage Trend Test (d)	P=0.003		
Fisher Exact Test (d)		P=0.022	P=0.005
Skin: Keratoacanthoma			
Overall Rates (a)	1/50 (2%)	4/50 (8%)	1/50 (2%)
Effective Rates (b)	1/44 (2%)	4/33 (12%)	1/9 (11%)
Terminal Rates (c)	0/16 (0%)	0/0	0/0
Week of First Observation	99	76	77
Life Table Tests (d)	P=0.003	P=0.007	P=0.146
Incidental Tumor Tests (d)	P=0.493	P=0.267	P=0.896
Cochran-Armitage Trend Test (d)	P=0.110		
Fisher Exact Test (d)		P=0.103	P=0.313
Subcutaneous Tissue: Fibroma			
Overall Rates (a)	2/50 (4%)	2/50 (4%)	4/50 (8%)
Effective Rates (b)	2/46 (4%)	2/42 (5%)	4/19 (21%)
Terminal Rates (c)	0/16 (0%)	0/0	0/0
Week of First Observation	83	85	71
Life Table Tests (d)	P<0.001	P=0.334	P<0.001
Incidental Tumor Tests (d)	P=0.136	P=0.673N	P=0.251
Cochran-Armitage Trend Test (d)	P=0.040		
Fisher Exact Test (d)		P=0.657	P=0.055

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF GLYCIDOL (Continued)

	Vehicle Control	37.5 mg/kg	75 mg/kg
Subcutaneous Tissue: Fibroma or Neurofibroma			
Overall Rates (a)	2/50 (4%)	3/50 (6%)	4/50 (8%)
Effective Rates (b)	2/46 (4%)	3/42 (7(%)	4/19 (21%)
Terminal Rates (c)	0/16 (0%)	0/0	0/0
Week of First Observation	83	85	71
Life Table Tests (d)	P<0.001	P=0.131	P<0.001
Incidental Tumor Tests (d)	P=0.115	P=0.609	P=0.251
Cochran-Armitage Trend Test (d)	P=0.037		
Fisher Exact Test (d)		P=0.456	P=0.055
Subcutaneous Tissue: Fibrosarcoma			
Overall Rates (a)	3/50 (6%)	2/50 (4%)	1/50 (2%)
Effective Rates (b)	3/46 (7%)	2/46 (4%)	1/20 (5%)
Terminal Rates (c)	1/16 (6%)	0/0	0/0
Week of First Observation	91	82	70
Life Table Tests (d)	P=0.089	P=0.286	P=0.334
Incidental Tumor Tests (d)	P=0.638	P=0.673N	P=0.819N
Cochran-Armitage Trend Test (d)	P=0.476N		
Fisher Exact Test (d)		P=0.500N	P=0.648N
Subcutaneous Tissue: Fibroma or Fibrosarcoma			
Overall Rates (a)	4/50 (8%)	4/50 (8%)	5/50 (10%)
Effective Rates (b)	4/46 (9%)	4/46 (9%)	5/20 (25%)
Terminal Rates (c)	1/16 (6%)	0/0	0/0
Week of First Observation	83	82	70
Life Table Tests (d)	P<0.001	P=0.115	P<0.001
Incidental Tumor Tests (d)	P=0.153	P=0.641N	P=0.305
Cochran-Armitage Trend Test (d)	P=0.078		
Fisher Exact Test (d)		P=0.643	P=0.087
Subcutaneous Tissue: Fibroma, Neurofibroma, or Fibrosarcoma			
Overall Rates (a)	4/50 (8%)	5/50 (10%)	5/50 (10%)
Effective Rates (b)	4/46 (9%)	5/46 (11%)	5/20 (25%)
Terminal Rates (c)	1/16 (6%)	0/0	0/0
Week of First Observation	83	82	70
Life Table Tests (d)	P<0.001	P=0.045	P<0.001
Incidental Tumor Tests (d)	P=0.130	P=0.581	P=0.305
Cochran-Armitage Trend Test (d)	P=0.072		
Fisher Exact Test (d)		P=0.500	P=0.087
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (e)	1/50 (2%)	3/50 (6%)	2/50 (4%)
Effective Rates (b)	1/46 (2%)	3/48 (6%)	2/26 (8%)
Terminal Rates (c)	0/16 (0%)	0/0	0/0
Week of First Observation	103	74	68
Life Table Tests (d)	P=0.003	P=0.012	P=0.094
Incidental Tumor Tests (d)	P=0.263	P=0.157	P=0.742
Cochran-Armitage Trend Test (d)	P=0.203		
Fisher Exact Test (d)		P=0.325	P=0.294
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	2/50 (4%)	5/50 (10%)	4/50 (8%)
Effective Rates (b)	2/46 (4%)	5/48 (10%)	4/26 (15%)
Terminal Rates (c)	1/16 (6%)	0/0	0/0
Week of First Observation	103	74	68
Life Table Tests (d)	P<0.001	P<0.001	P=0.001
Incidental Tumor Tests (d)	P=0.099	P=0.074	P=0.543
Cochran-Armitage Trend Test (d)	P=0.082		
Fisher Exact Test (d)		P=0.235	P=0.120

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF GLYCIDOL (Continued)

	Vehicle Control	37.5 mg/kg	75 mg/kg
Hematopoietic System: Mononuclear Cell Leukemia			
Overall Rates (a)	25/50 (50%)	33/50 (66%)	21/50 (42%)
Effective Rates (b)	25/48 (52%)	33/50 (66%)	21/44 (48%)
Terminal Rates (c)	7/16 (44%)	0/0	0/0
Week of First Observation	63	65	56
Life Table Tests (d)	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests (d)	P=0.343	P=0.164	P=0.114
Cochran-Armitage Trend Test (d)	P=0.394N		
Fisher Exact Test (d)		P=0.116	P=0.417N
Tongue: Squamous Cell Papilloma or Carcinoma			
Overall Rates (a)	1/50 (2%)	1/50 (2%)	4/50 (8%)
Effective Rates (b)	1/46 (2%)	1/48 (2%)	4/26 (15%)
Terminal Rates (c)	0/16 (0%)	0/0	0/0
Week of First Observation	102	91	68
Life Table Tests (d)	P<0.001	P=0.338	P=0.011
Incidental Tumor Tests (d)	P=0.158	P=0.692	P=0.543
Cochran-Armitage Trend Test (d)	P=0.026		
Fisher Exact Test (d)		P=0.742N	P=0.054
Oral Cavity (Mouth or Tongue): Squamous Cell Papilloma			
Overall Rates (a)	2/50 (4%)	1/50 (2%)	3/50 (6%)
Effective Rates (b)	2/46 (4%)	1/48 (2%)	3/26 (12%)
Terminal Rates (c)	0/16 (0%)	0/0	0/0
Week of First Observation	74	91	68
Life Table Tests (d)	P=0.016	P=0.595	P=0.077
Incidental Tumor Tests (d)	P=0.614N	P=0.453N	P=0.457N
Cochran-Armitage Trend Test (d)	P=0.203		
Fisher Exact Test (d)		P=0.484N	P=0.246
Oral Cavity (Mouth or Tongue): Squamous Cell Papilloma or Carcinoma			
Overall Rates (a)	3/50 (6%)	2/50 (4%)	5/50 (10%)
Effective Rates (b)	3/48 (6%)	2/50 (4%)	5/44 (11%)
Terminal Rates (c)	0/16 (0%)	0/0	0/0
Week of First Observation	56	89	68
Life Table Tests (d)	P=0.005	P=0.488	P=0.044
Incidental Tumor Tests (d)	P=0.500N	P=0.283N	P=0.167N
Cochran-Armitage Trend Test (d)	P=0.234		
Fisher Exact Test (d)		P=0.480N	P=0.309
Forestomach: Squamous Cell Papilloma			
Overall Rates (a)	0/50 (0%)	1/50 (2%)	5/50 (10%)
Effective Rates (b)	0/46 (0%)	1/50 (2%)	5/32 (16%)
Terminal Rates (c)	0/16 (0%)	0/0	0/0
Week of First Observation		85	64
Life Table Tests (d)	P<0.001	P=0.406	P<0.001
Incidental Tumor Tests (d)	P=0.028	P=0.631	P=0.139
Cochran-Armitage Trend Test (d)	P=0.003		
Fisher Exact Test (d)		P=0.521	P=0.010
Forestomach: Squamous Cell Papilloma or Carcinoma			
Overall Rates (a)	1/50 (2%)	2/50 (4%)	6/50 (12%)
Effective Rates (b)	1/46 (2%)	2/50 (4%)	6/32 (19%)
Terminal Rates (c)	1/16 (6%)	0/0	0/0
Week of First Observation	104	85	64
Life Table Tests (d)	P<0.001	P=0.142	P<0.001
Incidental Tumor Tests (d)	P=0.018	P=0.392	P=0.125
Cochran-Armitage Trend Test (d)	P=0.007		
Fisher Exact Test (d)		P=0.532	P=0.017

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF GLYCIDOL (Continued)

	Vehicle Control	37.5 mg/kg	75 mg/kg
Anterior Pituitary Gland: Adenoma			
Overall Rates (e)	8/50 (16%)	7/50 (14%)	2/50 (4%)
Effective Rates (b)	8/47 (17%)	7/50 (14%)	2/36 (6%)
Terminal Rates (c)	5/16 (31%)	0/0	0/0
Week of First Observation	83	70	62
Life Table Tests (d)	P=0.004	P=0.005	P=0.215
Incidental Tumor Tests (d)	P=0.596	P=0.298	P=0.716N
Cochran-Armitage Trend Test (d)	P=0.088N		
Fisher Exact Test (d)		P=0.448N	P=0.104N
Anterior Pituitary Gland: Adenoma or Carcinoma			
Overall Rates (e)	8/50 (16%)	8/50 (16%)	2/50 (4%)
Effective Rates (b)	8/47 (17%)	8/50 (16%)	2/36 (6%)
Terminal Rates (c)	5/16 (31%)	0/0	0/0
Week of First Observation	83	70	62
Life Table Tests (d)	P=0.002	P=0.002	P=0.215
Incidental Tumor Tests (d)	P=0.540	P=0.225	P=0.716N
Cochran-Armitage Trend Test (d)	P=0.098N		
Fisher Exact Test (d)		P=0.554N	P=0.104N
Adrenal Medulla: Pheochromocytoma			
Overall Rates (e)	13/50 (26%)	4/50 (8%)	1/50 (2%)
Effective Rates (b)	13/47 (28%)	4/50 (8%)	1/34 (3%)
Terminal Rates (c)	6/16 (38%)	0/0	0/0
Week of First Observation	91	69	63
Life Table Tests (d)	P=0.134	P=0.134	P=0.435
Incidental Tumor Tests (d)	P=0.139N	P=0.379N	P=0.677N
Cochran-Armitage Trend Test (d)	P=0.001N		
Fisher Exact Test (d)		P=0.011N	P=0.003N
Adrenal Medulla: Pheochromocytoma or Malignant Pheochromocytoma			
Overall Rates (e)	14/50 (28%)	5/50 (10%)	1/50 (2%)
Effective Rates (b)	14/47 (30%)	5/50 (10%)	1/34 (3%)
Terminal Rates (c)	6/16 (38%)	0/0	0/0
Week of First Observation	89	69	63
Life Table Tests (d)	P=0.098	P=0.087	P=0.459
Incidental Tumor Tests (d)	P=0.102N	P=0.306N	P=0.563N
Cochran-Armitage Trend Test (d)	P<0.001N		
Fisher Exact Test (d)		P=0.013N	P=0.002N
Thyroid Gland: C-Cell Adenoma			
Overall Rates (e)	2/50 (4%)	3/50 (6%)	3/50 (6%)
Effective Rates (b)	2/45 (4%)	3/41 (7%)	3/18 (17%)
Terminal Rates (c)	0/16 (0%)	0/0	0/0
Week of First Observation	83	87	72
Life Table Tests (d)	P<0.001	P=0.132	P<0.001
Incidental Tumor Tests (d)	P=0.159	P=0.609	P=0.385
Cochran-Armitage Trend Test (d)	P=0.098		
Fisher Exact Test (d)		P=0.455	P=0.136
Thyroid Gland: Follicular Cell Carcinoma			
Overall Rates (e)	1/50 (2%)	2/50 (4%)	5/50 (10%)
Effective Rates (b)	1/46 (2%)	2/42 (5%)	5/19 (26%)
Terminal Rates (c)	0/16 (0%)	0/0	0/0
Week of First Observation	101	85	71
Life Table Tests (d)	P<0.001	P=0.051	P<0.001
Incidental Tumor Tests (d)	P=0.034	P=0.474	P=0.139
Cochran-Armitage Trend Test (d)	P=0.003		
Fisher Exact Test (d)		P=0.466	P=0.007

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF GLYCIDOL (Continued)

	Vehicle Control	37.5 mg/kg	75 mg/kg
Thyroid Gland: Follicular Cell Adenoma or Carcinoma			
Overall Rates (e)	1/50 (2%)	4/50 (8%)	6/50 (12%)
Effective Rates (b)	1/46 (2%)	4/42 (10%)	6/19 (32%)
Terminal Rates (c)	0/16 (0%)	0/0	0/0
Week of First Observation	101	85	71
Life Table Tests (d)	P<0.001	P=0.006	P<0.001
Incidental Tumor Tests (d)	P=0.018	P=0.227	P=0.125
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P=0.153	P=0.002
Mammary Gland: Fibroadenoma			
Overall Rates (a)	3/50 (6%)	8/50 (16%)	7/50 (14%)
Effective Rates (b)	3/45 (7%)	8/39 (21%)	7/17 (41%)
Terminal Rates (c)	1/16 (6%)	0/0	0/0
Week of First Observation	92	78	73
Life Table Tests (d)	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests (d)	P=0.009	P=0.082	P=0.043
Cochran-Armitage Trend Test (d)	P=0.001		
Fisher Exact Test (d)		P=0.060	P=0.003
Preputial Gland: Adenoma			
Overall Rates (e)	5/50 (10%)	7/50 (14%)	1/50 (2%)
Effective Rates (b)	5/44 (11%)	7/35 (20%)	1/10 (10%)
Terminal Rates (c)	2/16 (13%)	0/0	0/0
Week of First Observation	91	84	75
Life Table Tests (d)	P<0.001	P<0.001	P=0.209
Incidental Tumor Tests (d)	P=0.206	P=0.124	P=0.819N
Cochran-Armitage Trend Test (d)	P=0.419		
Fisher Exact Test (d)		P=0.227	P=0.694N
Preputial Gland: Adenocarcinoma			
Overall Rates (e)	5/50 (10%)	0/50 (0%)	4/50 (8%)
Effective Rates (b)	5/49 (10%)	0/50 (0%)	4/46 (9%)
Terminal Rates (c)	1/16 (6%)	0/0	0/0
Week of First Observation	84		50
Life Table Tests (d)	P=0.012	P=0.325N	P=0.004
Incidental Tumor Tests (d)	P=0.454	P=0.090N	P=0.331
Cochran-Armitage Trend Test (d)	P=0.447N		
Fisher Exact Test (d)		P=0.027N	P=0.541N
Preputial Gland: Adenoma, Adenocarcinoma, or Carcinoma			
Overall Rates (e)	10/50 (20%)	7/50 (14%)	5/50 (10%)
Effective Rates (b)	10/49 (20%)	7/50 (14%)	5/46 (11%)
Terminal Rates (c)	3/16 (19%)	0/0	0/0
Week of First Observation	84	84	50
Life Table Tests (d)	P<0.001	P=0.010	P<0.001
Incidental Tumor Tests (d)	P=0.175	P=0.527	P=0.372
Cochran-Armitage Trend Test (d)	P=0.124N		
Fisher Exact Test (d)		P=0.282N	P=0.161N
Testis: Interstitial Cell Tumor			
Overall Rates (e)	46/50 (92%)	50/50 (100%)	49/50 (98%)
Effective Rates (b)	46/49 (94%)	50/50 (100%)	49/49 (100%)
Terminal Rates (c)	16/16 (100%)	0/0	0/0
Week of First Observation	71	65	44
Life Table Tests (d)	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests (d)	P<0.001	P=0.003	P<0.001
Cochran-Armitage Trend Test (d)	P=0.037		
Fisher Exact Test (d)		P=0.117	P=0.121

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF GLYCIDOL (Continued)

	Vehicle Control	37.5 mg/kg	75 mg/kg
Brain: Glioma			
Overall Rates (e)	0/50 (0%)	5/50 (10%)	6/50 (12%)
Effective Rates (b)	0/46 (0%)	5/50 (10%)	6/30 (20%)
Terminal Rates (c)	0/16 (0%)	0/0	0/0
Week of First Observation		70	65
Life Table Tests (d)	P<0.001	P=0.002	P<0.001
Incidental Tumor Tests (d)	P=0.042	P=0.048	P=0.416
Cochran-Armitage Trend Test (d)	P=0.002		
Fisher Exact Test (d)		P=0.035	P=0.003
Zymbal Gland: Carcinoma			
Overall Rates (e)	1/50 (2%)	3/50 (6%)	6/50 (12%)
Effective Rates (b)	1/49 (2%)	3/50 (6%)	6/48 (13%)
Terminal Rates (c)	0/16 (0%)	0/0	0/0
Week of First Observation	92	83	47
Life Table Tests (d)	P<0.001	P=0.069	P<0.001
Incidental Tumor Tests (d)	P=0.074	P=0.559	P=0.183
Cochran-Armitage Trend Test (d)	P=0.033		
Fisher Exact Test (d)		P=0.316	P=0.053
Tunica Vaginalis: Mesothelioma, NOS			
Overall Rates (a)	0/50 (0%)	10/50 (20%)	8/50 (16%)
Effective Rates (b)	0/47 (0%)	10/50 (20%)	8/41 (20%)
Terminal Rates (c)	0/16 (0%)	0/0	0/0
Week of First Observation		65	60
Life Table Tests (d)	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests (d)	P=0.158	P=0.037	P=0.324
Cochran-Armitage Trend Test (d)	P=0.004		
Fisher Exact Test (d)		P<0.001	P=0.001
Tunica Vaginalis: Malignant Mesothelioma			
Overall Rates (a)	3/50 (6%)	24/50 (48%)	31/50 (62%)
Effective Rates (b)	3/49 (6%)	24/50 (48%)	31/47 (66%)
Terminal Rates (c)	0/16 (0%)	0/0	0/0
Week of First Observation	86	65	49
Life Table Tests (d)	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests (d)	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P<0.001	P<0.001
Tunica Vaginalis: All Mesothelioma (f)			
Overall Rates (a)	3/50 (6%)	34/50 (68%)	39/50 (78%)
Effective Rates (b)	3/49 (6%)	34/50 (68%)	39/47 (83%)
Terminal Rates (c)	0/16 (0%)	0/0	0/0
Week of First Observation	86	65	49
Life Table Tests (d)	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests (d)	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P<0.001	P<0.001
All Sites: Benign Tumors			
Overall Rates (a)	46/50 (92%)	50/50 (100%)	49/50 (98%)
Effective Rates (b)	46/49 (94%)	50/50 (100%)	49/49 (100%)
Terminal Rates (c)	16/16 (100%)	0/0	0/0
Week of First Observation	71	65	44
Life Table Tests (d)	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests (d)	P<0.001	P=0.003	P<0.001
Cochran-Armitage Trend Test (d)	P=0.037		
Fisher Exact Test (d)		P=0.117	P=0.121

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF GLYCIDOL (Continued)

	Vehicle Control	37.5 mg/kg	75 mg/kg
All Sites: Malignant Tumors			
Overall Rates (a)	36/50 (72%)	48/50 (96%)	48/50 (96%)
Effective Rates (b)	36/49 (73%)	48/50 (96%)	48/48 (100%)
Terminal Rates (c)	10/16 (63%)	0/0	0/0
Week of First Observation	56	65	47
Life Table Tests (d)	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests (d)	P<0.001	P=0.012	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P=0.002	P<0.001
All Sites: All Tumors			
Overall Rates (a)	48/50 (96%)	50/50 (100%)	49/50 (98%)
Effective Rates (b)	48/49 (98%)	50/50 (100%)	49/49 (100%)
Terminal Rates (c)	16/16 (100%)	0/0	0/0
Week of First Observation	56	65	44
Life Table Tests (d)	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests (d)	P=0.012	P=0.236	P=0.022
Cochran-Armitage Trend Test (d)	P=0.269		
Fisher Exact Test (d)		P=0.495	P=0.500

(a) Number of tumor-bearing animals/number of animals examined grossly at the site
(b) Number of tumor-bearing animals/effective number of animals, i.e., number of animals alive at the first occurrence of tumors in any of the three groups
(c) Observed tumor incidence in animals killed at the end of the study
(d) Beneath the vehicle 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 vehicle 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 nonfatal. The Cochran-Armitage trend and Fisher exact tests were based on animals surviving to the first occurrence of the tumor in any of the three groups. A negative trend or lower incidence in a dosed group than in vehicle controls is indicated by (N).
(e) Number of tumor-bearing animals/number of animals examined microscopically at the site
(f) All mesotheliomas were observed in the tunica vaginalis; most of those diagnosed as malignant also appeared in other organs, especially the peritoneal mesothelium.

TABLE A4a. HISTORICAL INCIDENCE OF MESOTHELIAL TUMORS IN MALE F344/N RATS (a)

Study	Incidence of Mesotheliomas in Controls
Historical Incidence for All Water Gavage Vehicle Controls	
Iodinated glycerol (b)	1/50
Malonaldehyde, sodium salt (c)	2/50
Chlorpheniramine maleate (c)	0/50
Tetrakis(hydroxymethyl)phosphonium chloride (c)	(d) 1/50
Tetrakis(hydroxymethyl)phosphonium sulfate (c)	0/50
Methyl carbamate (e)	0/50
TOTAL	4/300 (1.3%)
SD (f)	1.63%
Range (g)	
High	2/50
Low	0/50
Overall Historical Incidence for Untreated Controls	
TOTAL	(h) 47/1,596 (2.9%)
SD (f)	2.65%
Range (g)	
High	5/50
Low	0/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Study conducted at EG&G Mason Research Institute
(c) Study conducted at Battelle Columbus Laboratories
(d) Malignant mesothelioma
(e) Study conducted at Microbiological Associates, Inc.
(f) Standard deviation
(g) Range and SD are presented for groups of 35 or more animals.
(h) Includes 11 malignant mesotheliomas

TABLE A4b. HISTORICAL INCIDENCE OF FORESTOMACH SQUAMOUS CELL TUMORS IN MALE F344/N RATS (a)

Study	Incidence of Papillomas or Carcinomas in Controls
Historical Incidence for All Water Gavage Vehicle Controls	
Iodinated glycerol (b)	0/49
Malonaldehyde, sodium salt (c)	0/50
Chlorpheniramine maleate (c)	0/50
Tetrakis(hydroxymethyl)phosphonium chloride (c)	0/48
Tetrakis(hydroxymethyl)phosphonium sulfate (c)	0/46
Methyl carbamate (d)	0/50
TOTAL	0/293
SD (e)	0.00%
Range (f)	
High	0/50
Low	0/50
Overall Historical Incidence for Untreated Controls	
TOTAL	(g) 5/1,581 (0.3%)
SD (e)	0.92%
Range (f)	
High	2/49
Low	0/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Study conducted at EG&G Mason Research Institute
(c) Study conducted at Battelle Columbus Laboratories
(d) Study conducted at Microbiological Associates, Inc.
(e) Standard deviation
(f) Range and SD are presented for groups of 35 or more animals.
(g) Includes three squamous cell papillomas and two squamous cell carcinomas

TABLE A4c. HISTORICAL INCIDENCE OF BRAIN GLIAL CELL TUMORS IN MALE F344/N RATS (a)

Study	Incidence in Controls
Historical Incidence for All Water Gavage Vehicle Controls	
Iodinated glycerol (b)	(c) 1/50
Malonaldehyde, sodium salt (d)	0/50
Chlorpheniramine maleate (d)	0/50
Tetrakis(hydroxymethyl)phosphonium chloride (d)	(e) 1/50
Tetrakis(hydroxymethyl)phosphonium sulfate (d)	0/50
Methyl carbamate (f)	0/50
TOTAL	2/300 (0.7%)
SD (g)	1.03%
Range (h)	
High	1/50
Low	0/50
Overall Historical Incidence for Untreated Controls	
TOTAL	(i) 14/1,590 (0.9%)
SD (g)	1.43%
Range (h)	
High	2/50
Low	0/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Study conducted at EG&G Mason Research Institute
(c) Glioma, NOS
(d) Study conducted at Battelle Columbus Laboratories
(e) Astrocytoma
(f) Study conducted at Microbiological Associates, Inc.
(g) Standard deviation
(h) Range and SD are presented for groups of 35 or more animals.
(i) Includes 3 gliomas, NOS, 10 astrocytomas, and 1 oligodendroglioma

TABLE A4d. HISTORICAL INCIDENCE OF MAMMARY GLAND TUMORS IN MALE F344/N RATS (a)

Study	Incidence in Controls	
	Fibroadenoma	Fibroadenoma or Adenocarcinoma
Historical Incidence for All Water Gavage Vehicle Controls		
Iodinated glycerol (b)	3/50	3/50
Malonaldehyde, sodium salt (c)	2/50	2/50
Chlorpheniramine maleate (c)	3/50	3/50
Tetrakis(hydroxymethyl)phosphonium chloride (c)	2/50	2/50
Tetrakis(hydroxymethyl)phosphonium sulfate (c)	2/50	2/50
Methyl carbamate (d)	1/50	1/50
TOTAL	13/300 (4.3%)	13/300 (4.3%)
SD (e)	1.51%	1.51%
Range (f)		
High	3/50	3/50
Low	1/50	1/50
Overall Historical Incidence for Untreated Controls		
TOTAL	(g) 47/1,596 (2.9%)	(g,h) 49/1,596 (3.1%)
SD (e)	3.07%	3.03%
Range (f)		
High	6/49	6/49
Low	0/50	0/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Study conducted at EG&G Mason Research Institute
(c) Study conducted at Battelle Columbus Laboratories
(d) Study conducted at Microbiological Associates, Inc.
(e) Standard deviation
(f) Range and SD are presented for groups of 35 or more animals.
(g) Includes two adenomas, NOS
(h) Includes one carcinoma, NOS, and one adenocarcinoma, NOS

TABLE A4e. HISTORICAL INCIDENCE OF ZYMBAL GLAND TUMORS IN MALE F344/N RATS (a)

Study	Incidence of Adenomas or Carcinomas in Controls
Historical Incidence for All Water Gavage Vehicle Controls	
Iodinated glycerol (b)	(c) 1/50
Malonaldehyde, sodium salt (d)	0/50
Chlorpheniramine maleate (d)	0/50
Tetrakis(hydroxymethyl)phosphonium chloride (d)	(c) 1/50
Tetrakis(hydroxymethyl)phosphonium sulfate (d)	0/50
Methyl carbamate (e)	(f) 1/50
TOTAL	3/300 (1.0%)
SD (g)	1.10%
Range (h)	
High	1/50
Low	0/50
Overall Historical Incidence for Untreated Controls	
TOTAL	(i) 19/1,596 (1.2%)
SD (g)	1.82%
Range (h)	
High	4/50
Low	0/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Study conducted at EG&G Mason Research Institute
(c) Carcinoma
(d) Study conducted at Battelle Columbus Laboratories
(e) Study conducted at Microbiological Associates, Inc.
(f) Adenoma
(g) Standard deviation
(h) Range and SD are presented for groups of 35 or more animals.
(i) Includes 1 papillary adenoma, 11 carcinomas, NOS, and 7 squamous cell carcinomas

TABLE A4f. HISTORICAL INCIDENCE OF TUMORS OF THE SMALL INTESTINE IN MALE F344/N RATS (a)

Study	Incidence of Adenocarcinomas in Controls
Historical Incidence for All Water Gavage Vehicle Controls	
Iodinated glycerol (b)	0/50
Malonaldehyde, sodium salt (c)	0/49
Chlorpheniramine maleate (c)	0/49
Tetrakis(hydroxymethyl)phosphonium chloride (c)	0/48
Tetrakis(hydroxymethyl)phosphonium sulfate (c)	0/45
Methyl carbamate (d)	0/42
TOTAL	0/283
SD (e)	0.00%
Range (f)	
High	0/50
Low	0/50
Overall Historical Incidence for Untreated Controls	
TOTAL	(g) 5/1,557 (0.3%)
SD (e)	0.77%
Range (f)	
High	1/44
Low	0/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Study conducted at EG&G Mason Research Institute
(c) Study conducted at Battelle Columbus Laboratories
(d) Study conducted at Microbiological Associates, Inc.
(e) Standard deviation
(f) Range and SD are presented for groups of 35 or more animals.
(g) Includes one carcinoma, NOS, and one mucinous adenocarcinoma; no benign tumors have been observed.

TABLE A4g. HISTORICAL INCIDENCE OF TUMORS OF THE LARGE INTESTINE IN MALE F344/N RATS (a)

Study	Incidence of Adenocarcinomas in Controls
Historical Incidence for All Water Gavage Vehicle Controls	
Iodinated glycerol (b)	0/50
Malonaldehyde, sodium salt (c)	0/50
Chlorpheniramine maleate (c)	0/50
Tetrakis(hydroxymethyl)phosphonium chloride (c)	0/50
Tetrakis(hydroxymethyl)phosphonium sulfate (c)	0/50
Methyl carbamate (d)	0/50
TOTAL	0/300
SD (e)	0.00%
Range (f)	
High	0/50
Low	0/50
Overall Historical Incidence for Untreated Controls	
TOTAL	(g) 2/1,541 (0.1%)
SD (e)	0.50%
Range (f)	
High	1/49
Low	0/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Study conducted at EG&G Mason Research Institute
(c) Study conducted at Battelle Columbus Laboratories
(d) Study conducted at Microbiological Associates, Inc.
(e) Standard deviation
(f) Range and SD are presented for groups of 35 or more animals.
(g) Mucinous adenocarcinomas; no benign tumors have been observed.

TABLE A4h. HISTORICAL INCIDENCE OF THYROID GLAND FOLLICULAR CELL TUMORS IN MALE F344/N RATS (a)

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence for All Water Gavage Vehicle Controls			
Iodinated glycerol (b)	0/49	0/49	0/49
Malonaldehyde, sodium salt (c)	3/50	1/50	4/50
Chlorpheniramine maleate (c)	0/50	1/50	1/50
Tetrakis(hydroxymethyl)phosphonium chloride (c)	0/47	0/47	0/47
Tetrakis(hydroxymethyl)phosphonium sulfate (c)	0/47	1/47	1/47
Methyl carbamate (d)	0/50	0/50	0/50
TOTAL	3/293 (1.0%)	3/293 (1.0%)	6/293 (2.0%)
SD (e)	2.45%	1.12%	3.10%
Range (f)			
High	3/50	1/47	4/50
Low	0/50	0/50	0/50
Overall Historical Incidence for Untreated Controls			
TOTAL	(g) 11/1,576 (0.7%)	9/1,576 (0.6%)	(g) 20/1,576 (1.3%)
SD (e)	1.36%	0.92%	1.63%
Range (f)			
High	2/44	1/49	3/50
Low	0/50	0/50	0/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Study conducted at EG&G Mason Research Institute
(c) Study conducted at Battelle Columbus Laboratories
(d) Study conducted at Microbiological Associates, Inc.
(e) Standard deviation
(f) Range and SD are presented for groups of 35 or more animals.
(g) Includes one cystadenoma, NOS, and one papillary cystadenoma, NOS

TABLE A4i. HISTORICAL INCIDENCE OF INTEGUMENTARY SYSTEM SQUAMOUS CELL TUMORS IN MALE F344/N RATS (a)

Study	Incidence in Controls		
	Papilloma	Carcinoma	Papilloma or Carcinoma
Historical Incidence for All Water Gavage Vehicle Controls			
Iodinated glycerol (b)	2/50	0/50	2/50
Malonaldehyde, sodium salt (c)	(d) 2/50	0/50	(d) 2/50
Chlorpheniramine maleate (c)	3/50	1/50	4/50
Tetrakis(hydroxymethyl)phosphonium chloride (c)	(d) 1/50	0/50	1/50
Tetrakis(hydroxymethyl)phosphonium sulfate (c)	3/50	0/50	3/50
Methyl carbamate (e)	1/50	0/50	1/50
TOTAL	12/300 (4.0%)	1/300 (0.3%)	13/300 (4.3%)
SD (f)	1.79%	0.82%	2.34%
Range (g)			
High	3/50	1/50	4/50
Low	1/50	0/50	1/50
Overall Historical Incidence for Untreated Controls			
TOTAL	(d) 21/1,596 (1.3%)	10/1,596 (0.6%)	(d) 31/1,596 (1.9%)
SD (f)	1.50%	1.08%	1.81%
Range (g)			
High	2/49	2/49	3/49
Low	0/50	0/50	0/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Study conducted at EG&G Mason Research Institute
(c) Study conducted at Battelle Columbus Laboratories
(d) Includes one papilloma, NOS
(e) Study conducted at Microbiological Associates, Inc.
(f) Standard deviation
(g) Range and SD are presented for groups of 35 or more animals.

TABLE A4j. HISTORICAL INCIDENCE OF INTEGUMENTARY SYSTEM BASAL CELL TUMORS IN MALE F344/N RATS (a)

Study	Incidence in Controls		
	Benign	Malignant	Benign or Malignant
Historical Incidence for All Water Gavage Vehicle Controls			
Iodinated glycerol (b)	(c) 1/50	0/50	(c) 1/50
Malonaldehyde, sodium salt (d)	0/50	(e) 1/50	(e) 1/50
Chlorpheniramine maleate (d)	(f) 1/50	0/50	(f) 1/50
Tetrakis(hydroxymethyl)phosphonium chloride (d)	0/50	0/50	0/50
Tetrakis(hydroxymethyl)phosphonium sulfate (d)	(c) 1/50	0/50	(c) 1/50
Methyl carbamate (g)	(f) 1/50	0/50	(f) 1/50
TOTAL	4/300 (1.3%)	1/300 (0.3%)	5/300 (1.7%)
SD (h)	1.03%	0.82%	0.82%
Range (i)			
High	1/50	1/50	1/50
Low	0/50	0/50	0/50
Overall Historical Incidence for Untreated Controls			
TOTAL	(j) 21/1,596 (1.3%)	(k) 10/1,596 (0.6%)	(j,k) 31/1,596 (1.9%)
SD (h)	1.95%	1.07%	2.31%
Range (i)			
High	3/50	2/50	4/50
Low	0/50	0/50	0/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Study conducted at EG&G Mason Research Institute
(c) Basal cell tumor
(d) Study conducted at Battelle Columbus Laboratories
(e) Sebaceous adenocarcinoma
(f) Trichoepithelioma
(g) Study conducted at Microbiological Associates, Inc.
(h) Standard deviation
(i) Range and SD are presented for groups of 35 or more animals.
(j) Includes 11 basal cell tumors, 5 trichoepitheliomas, 1 adnexal adenoma, and 4 sebaceous adenomas
(k) All malignant tumors observed were basal cell carcinomas.

TABLE A4k. HISTORICAL INCIDENCE OF NASAL CAVITY TUMORS IN MALE F344/N RATS (a)

	Number Examined	Number of Tumors	Diagnosis
Historical Incidence for All Water Gavage Vehicle Controls			
	300	0	
Overall Historical Incidence for Untreated Controls			
	1,596	1 (<0.1%)	Squamous cell carcinoma

(a) Data as of May 12, 1988, for studies of at least 104 weeks; no adenomas or adenocarcinomas have been observed.

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF GLYCIDOL

	Vehicle Control	37.5 mg/kg	75 mg/kg
Animals initially in study	50	50	50
Animals necropsied	50	50	50
Animals examined histopathologically	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Epidermal inclusion cyst	1 (2%)	4 (8%)	3 (6%)
Inflammation, acute		1 (2%)	
Inflammation, chronic		2 (4%)	2 (4%)
Hyperplastic nodule	1 (2%)		
Hyperkeratosis		1 (2%)	
*Subcutaneous tissue	(50)	(50)	(50)
Hematoma, NOS	1 (2%)		
Inflammation, chronic		1 (2%)	1 (2%)
RESPIRATORY SYSTEM			
#Nasal cavity	(50)	(50)	(50)
Inflammation, acute	5 (10%)	1 (2%)	4 (8%)
Inflammation, acute suppurative			1 (2%)
Inflammation, acute/chronic	9 (18%)	1 (2%)	3 (6%)
Inflammation, chronic	3 (6%)	1 (2%)	9 (18%)
#Trachea	(50)	(50)	(50)
Inflammation, suppurative		1 (2%)	
Inflammation, chronic		1 (2%)	
Inflammation, chronic diffuse	4 (8%)		3 (6%)
#Lung/bronchus	(50)	(50)	(50)
Bronchiectasis	5 (10%)	1 (2%)	
Inflammation, suppurative	6 (12%)	1 (2%)	1 (2%)
#Lung	(50)	(50)	(50)
Atelectasis	4 (8%)	1 (2%)	
Edema, NOS			1 (2%)
Hemorrhage	2 (4%)	5 (10%)	1 (2%)
Hemorrhage, chronic			1 (2%)
Pneumonia, aspiration			1 (2%)
Inflammation, acute	1 (2%)	2 (4%)	1 (2%)
Inflammation, chronic		1 (2%)	
Pneumonia, interstitial chronic	3 (6%)	5 (10%)	6 (12%)
Inflammation, chronic focal	6 (12%)	6 (12%)	9 (18%)
Hyperplasia, adenomatous		1 (2%)	
Hyperplasia, alveolar epithelium	1 (2%)		2 (4%)
Metaplasia, osseous			1 (2%)
HEMATOPOIETIC SYSTEM			
#Spleen	(50)	(50)	(50)
Fibrosis	13 (26%)	34 (68%)	28 (56%)
Hemosiderosis	1 (2%)		4 (8%)
Angiectasis			1 (2%)
Metaplasia, NOS			4 (8%)
Hematopoiesis	1 (2%)	2 (4%)	
#Splenic red pulp	(50)	(50)	(50)
Atrophy, focal			2 (4%)
#Lymph node	(50)	(49)	(50)
Hemorrhage		1 (2%)	2 (4%)
Inflammation, acute			1 (2%)
Hyperplasia, NOS			1 (2%)
Angiectasis	2 (4%)		2 (4%)
Hyperplasia, lymphoid			1 (2%)
#Lung	(50)	(50)	(50)
Hyperplasia, lymphoid	30 (60%)	17 (34%)	14 (28%)

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF GLYCIDOL (Continued)

	Vehicle Control	37.5 mg/kg	75 mg/kg
HEMATOPOIETIC SYSTEM (Continued)			
#Thymus	(46)	(47)	(43)
Cyst, NOS	1 (2%)		
Multiple cysts	1 (2%)		
Angiectasis	1 (2%)		
CIRCULATORY SYSTEM			
#Heart	(50)	(50)	(50)
Inflammation, acute			1 (2%)
#Heart/atrium	(50)	(50)	(50)
Thrombosis, NOS		3 (6%)	1 (2%)
#Myocardium	(50)	(50)	(50)
Degeneration, NOS	48 (96%)	48 (96%)	47 (94%)
#Myocardium/left ventricle	(50)	(50)	(50)
Hypertrophy, NOS			1 (2%)
#Mitral valve	(50)	(50)	(50)
Endocardiosis		1 (2%)	
*Artery	(50)	(50)	(50)
Periarteritis	4 (8%)		1 (2%)
#Liver	(50)	(50)	(50)
Thrombosis, NOS		1 (2%)	
#Adrenal cortex	(50)	(50)	(50)
Thrombosis, NOS	1 (2%)		
DIGESTIVE SYSTEM			
*Mouth	(50)	(50)	(50)
Inflammation, acute			1 (2%)
*Tongue	(50)	(50)	(50)
Inflammation, chronic focal	1 (2%)		1 (2%)
Hyperplasia, epithelial			1 (2%)
#Salivary gland	(49)	(50)	(50)
Inflammation, acute	1 (2%)		
Inflammation, chronic		1 (2%)	2 (4%)
Atrophy, NOS	1 (2%)		
#Liver	(50)	(50)	(50)
Inflammation, acute focal	1 (2%)	2 (4%)	1 (2%)
Inflammation, chronic focal	4 (8%)	1 (2%)	3 (6%)
Degeneration, cystic		1 (2%)	
Degeneration, lipoid		2 (4%)	3 (6%)
Necrosis, NOS	1 (2%)		
Necrosis, coagulative	1 (2%)	7 (14%)	8 (16%)
Amyloidosis	1 (2%)		
Basophilic cyto change	13 (26%)	3 (6%)	3 (6%)
Eosinophilic cyto change	1 (2%)		
Clear cell change	14 (28%)		15 (30%)
Pleomorphism			1 (2%)
Hyperplasia, focal	6 (12%)	8 (16%)	9 (18%)
Angiectasis	7 (14%)	21 (42%)	15 (30%)
Nodular regeneration		1 (2%)	
#Periportal bile duct	(50)	(50)	(50)
Hyperplasia, NOS	7 (14%)	14 (28%)	5 (10%)
#Liver/centrilobular	(50)	(50)	(50)
Inflammation, acute			1 (2%)
Degeneration, NOS	1 (2%)	1 (2%)	1 (2%)
#Liver/periportal	(50)	(50)	(50)
Inflammation, chronic			1 (2%)
#Liver/Kupffer cell	(50)	(50)	(50)
Pigmentation, NOS	1 (2%)		

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF GLYCIDOL (Continued)

	Vehicle Control	37.5 mg/kg	75 mg/kg
DIGESTIVE SYSTEM (Continued)			
#Pancreas	(50)	(48)	(50)
Hemorrhage		1 (2%)	
Inflammation, chronic	2 (4%)		1 (2%)
Atrophy, NOS	1 (2%)		
Hyperplasia, focal		1 (2%)	2 (4%)
*Pharynx	(50)	(50)	(50)
Inflammation, chronic			1 (2%)
#Glandular stomach	(50)	(50)	(50)
Mineralization	1 (2%)		
Hemorrhage		1 (2%)	
Inflammation, acute diffuse			1 (2%)
Inflammation, chronic focal	2 (4%)		
Erosion	1 (2%)	1 (2%)	
Amyloidosis	1 (2%)		
Hyperplasia, focal	1 (2%)		
#Forestomach	(50)	(50)	(50)
Cyst, NOS			1 (2%)
Ulcer, acute			2 (4%)
Inflammation, acute diffuse			2 (4%)
Ulcer, chronic	1 (2%)	1 (2%)	5 (10%)
Inflammation, chronic focal	1 (2%)	1 (2%)	1 (2%)
Hyperkeratosis	3 (6%)	13 (26%)	15 (30%)
Dysplasia, epithelial		10 (20%)	8 (16%)
#Small intestine	(50)	(50)	(50)
Diverticulum			1 (2%)
Hyperplasia, epithelial			1 (2%)
Metaplasia, osseous			1 (2%)
#Colon	(50)	(50)	(50)
Hemorrhage		1 (2%)	
URINARY SYSTEM			
#Kidney	(50)	(50)	(50)
Persistent embryonic structure	1 (2%)		
Cyst, NOS	2 (4%)	2 (4%)	
Inflammation, acute focal		1 (2%)	
Nephropathy	37 (74%)	27 (54%)	25 (50%)
#Kidney/tubule	(50)	(50)	(50)
Necrosis, NOS	1 (2%)	1 (2%)	
Pigmentation, NOS	2 (4%)		
Hemoglobin pigment	1 (2%)		
#Kidney/pelvis	(50)	(50)	(50)
Inflammation, chronic			1 (2%)
Hyperplasia, epithelial	1 (2%)		
#Urinary bladder	(50)	(50)	(49)
Edema, NOS			1 (2%)
Hemorrhage	1 (2%)	1 (2%)	
Inflammation, focal		1 (2%)	
Erosion		1 (2%)	
ENDOCRINE SYSTEM			
#Pituitary intermedia	(50)	(50)	(50)
Colloid cyst		1 (2%)	
Pigmentation, NOS		1 (2%)	
#Anterior pituitary	(50)	(50)	(50)
Colloid cyst	2 (4%)	1 (2%)	3 (6%)
Pigmentation, NOS	1 (2%)		
Hyperplasia, focal	8 (16%)	4 (8%)	3 (6%)
Angiectasis		2 (4%)	2 (4%)

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF GLYCIDOL (Continued)

	Vehicle Control	37.5 mg/kg	75 mg/kg
ENDOCRINE SYSTEM (Continued)			
#Adrenal cortex	(50)	(50)	(50)
Colloid cyst	1 (2%)		
Degeneration, lipoid	3 (6%)		1 (2%)
Hypertrophy, focal		1 (2%)	2 (4%)
Hyperplasia, focal	3 (6%)	9 (18%)	2 (4%)
Angiectasis		2 (4%)	
#Adrenal medulla	(50)	(50)	(50)
Hyperplasia, focal	11 (22%)	12 (24%)	9 (18%)
#Thyroid	(50)	(50)	(50)
Ultimobranchial cyst		1 (2%)	
Follicular cyst, NOS		1 (2%)	1 (2%)
Hyperplasia, C-cell	11 (22%)	5 (10%)	2 (4%)
Hyperplasia, follicular cell		4 (8%)	1 (2%)
#Parathyroid	(47)	(48)	(47)
Hyperplasia, NOS	3 (6%)		
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Cyst, NOS	1 (2%)		
Hematoma, NOS	1 (2%)		
Inflammation, chronic	1 (2%)		
Hyperplasia, NOS	1 (2%)		
*Preputial gland	(50)	(50)	(50)
Inflammation, NOS	4 (8%)	3 (6%)	4 (8%)
Inflammation, chronic			1 (2%)
Hyperplasia, NOS			1 (2%)
Hyperplasia, focal		2 (4%)	1 (2%)
Hyperkeratosis			1 (2%)
#Prostate	(50)	(50)	(50)
Cyst, NOS	1 (2%)		1 (2%)
Inflammation, NOS	5 (10%)	6 (12%)	3 (6%)
Inflammation, chronic			1 (2%)
*Seminal vesicle	(50)	(50)	(50)
Inflammation, NOS	2 (4%)		1 (2%)
#Testis	(50)	(50)	(50)
Necrosis, coagulative			2 (4%)
*Epididymis	(50)	(50)	(50)
Mineralization	1 (2%)		
Degeneration, hydropic		1 (2%)	
NERVOUS SYSTEM			
#Brain/ependyma	(50)	(50)	(50)
Edema, NOS			1 (2%)
*Choroid plexus	(50)	(50)	(50)
Inflammation, chronic			1 (2%)
#Brain	(50)	(50)	(50)
Mineralization			3 (6%)
Hemorrhage	3 (6%)	1 (2%)	
Malacia			1 (2%)
Pigmentation, NOS			1 (2%)
*Spinal cord	(50)	(50)	(50)
Hemorrhage		1 (2%)	
SPECIAL SENSE ORGANS			
*Eye	(50)	(50)	(50)
Hemorrhage, chronic			1 (2%)
Inflammation, chronic	1 (2%)	1 (2%)	

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF GLYCIDOL (Continued)

	Vehicle Control	37.5 mg/kg	75 mg/kg
SPECIAL SENSE ORGANS (Continued)			
*Eye/retina	(50)	(50)	(50)
Degeneration, NOS		1 (2%)	
*Eye/crystalline lens	(50)	(50)	(50)
Cataract		1 (2%)	
*Harderian gland	(50)	(50)	(50)
Inflammation, chronic	1 (2%)		
*Zymbal gland	(50)	(50)	(50)
Dilatation/ducts	1 (2%)		
Cyst, NOS		1 (2%)	8 (16%)
*Eustachian tube	(50)	(50)	(50)
Inflammation, chronic			1 (2%)
MUSCULOSKELETAL SYSTEM			
*Bone	(50)	(50)	(50)
Exostosis		1 (2%)	
BODY CAVITIES			
*Tunica vaginalis	(50)	(50)	(50)
Hyperplasia, NOS		2 (4%)	
ALL OTHER SYSTEMS			
Adipose tissue			
Hemorrhage	3		1
Necrosis, fat	3	2	2
SPECIAL MORPHOLOGY SUMMARY			
None			

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
# Number of animals examined microscopically at this site

APPENDIX B

SUMMARY OF LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF GLYCIDOL

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF GLYCIDOL

	Vehicle Control	37.5 mg/kg	75 mg/kg
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%)
Squamous cell carcinoma			1 (2%)
Basal cell tumor			1 (2%)
Sebaceous adenoma		1 (2%)	
Keratoacanthoma	1 (2%)		
*Subcutaneous tissue	(50)	(50)	(50)
Fibroma	1 (2%)	3 (6%)	
Fibrosarcoma		1 (2%)	2 (4%)
Rhabdomyosarcoma			1 (2%)
RESPIRATORY SYSTEM			
#Nasal cavity	(50)	(50)	(50)
Squamous cell carcinoma			1 (2%)
#Trachea	(50)	(50)	(49)
Fibrosarcoma, invasive			1 (2%)
#Lung	(50)	(50)	(50)
Adenocarcinoma, NOS, metastatic		1 (2%)	2 (4%)
Alveolar/bronchiolar adenoma	1 (2%)		
Alveolar/bronchiolar carcinoma			1 (2%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Leukemia, mononuclear cell	13 (26%)	14 (28%)	20 (40%)
#Lymph node	(50)	(50)	(50)
Fibrosarcoma, invasive		1 (2%)	
CIRCULATORY SYSTEM			
None			
DIGESTIVE SYSTEM			
*Mouth	(50)	(50)	(50)
Squamous cell papilloma			1 (2%)
Squamous cell carcinoma			1 (2%)
*Tongue	(50)	(50)	(50)
Squamous cell papilloma	1 (2%)	3 (6%)	5 (10%)
#Salivary gland	(48)	(50)	(49)
Sarcoma, NOS		1 (2%)	
Fibrosarcoma, invasive		1 (2%)	
#Liver	(50)	(50)	(50)
Squamous cell carcinoma, invasive			1 (2%)
#Glandular stomach	(50)	(50)	(50)
Fibrosarcoma			2 (4%)
#Forestomach	(50)	(50)	(50)
Squamous cell papilloma		4 (8%)	8 (16%)
Squamous cell carcinoma			3 (6%)
#Colon	(50)	(50)	(50)
Adenomatous polyp, NOS			1 (2%)

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF GLYCIDOL (Continued)

	Vehicle Control	37.5 mg/kg	75 mg/kg
URINARY SYSTEM			
#Kidney	(50)	(50)	(50)
Tubular cell adenocarcinoma			1 (2%)
#Urinary bladder	(48)	(50)	(50)
Neurilemoma		1 (2%)	
ENDOCRINE SYSTEM			
#Anterior pituitary	(50)	(50)	(49)
Adenoma, NOS	18 (36%)	14 (28%)	6 (12%)
#Adrenal cortex	(50)	(50)	(50)
Adenoma, NOS	1 (2%)		2 (4%)
Adenocarcinoma, NOS	1 (2%)		1 (2%)
#Adrenal medulla	(50)	(50)	(50)
Pheochromocytoma	1 (2%)	1 (2%)	2 (4%)
#Thyroid	(50)	(50)	(49)
Follicular cell adenoma		1 (2%)	
Follicular cell carcinoma			3 (6%)
C-cell adenoma	5 (10%)	2 (4%)	1 (2%)
Fibrosarcoma, invasive		1 (2%)	
#Parathyroid	(47)	(48)	(45)
Adenoma, NOS	1 (2%)		
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Adenocarcinoma, NOS	1 (2%)	11 (22%)	16 (32%)
Fibroadenoma	14 (28%)	32 (64%)	29 (58%)
*Clitoral gland	(50)	(50)	(50)
Carcinoma, NOS	2 (4%)	1 (2%)	5 (10%)
Adenoma, NOS	3 (6%)	7 (14%)	7 (14%)
Adenocarcinoma, NOS		1 (2%)	
#Uterus	(50)	(50)	(50)
Adenoma, NOS			1 (2%)
Adenocarcinoma, NOS	1 (2%)		2 (4%)
Adenocarcinoma, NOS, invasive			1 (2%)
Fibroma		1 (2%)	
Fibrosarcoma		1 (2%)	
Leiomyosarcoma			2 (4%)
Endometrial stromal polyp	19 (38%)	21 (42%)	14 (28%)
Endometrial stromal sarcoma			1 (2%)
Granular cell tumor, NOS		1 (2%)	
Deciduoma			1 (2%)
#Ovary	(50)	(50)	(50)
Adenocarcinoma, NOS			1 (2%)
Granulosa cell tumor		2 (4%)	
NERVOUS SYSTEM			
#Brain	(50)	(50)	(50)
Glioma, NOS		4 (8%)	4 (8%)
SPECIAL SENSE ORGANS			
*Harderian gland	(50)	(50)	(50)
Adenoma, NOS	1 (2%)		
*Ear	(50)	(50)	(50)
Fibrosarcoma, invasive		1 (2%)	
*Zymbal gland	(50)	(50)	(50)
Carcinoma, NOS	1 (2%)	1 (2%)	2 (4%)

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF GLYCIDOL (Continued)

	Vehicle Control	37.5 mg/kg	75 mg/kg
MUSCULOSKELETAL SYSTEM			
*Bone	(50)	(50)	(50)
Fibrosarcoma, invasive		1 (2%)	
*Vertebral column	(50)	(50)	(50)
Neurilemoma, malignant	1 (2%)		
*Skeletal muscle	(50)	(50)	(50)
Neurilemoma, invasive	1 (2%)		
BODY CAVITIES			
*Thoracic cavity	(50)	(50)	(50)
Fibrosarcoma			1 (2%)
*Mediastinum	(50)	(50)	(50)
Neurilemoma			1 (2%)
*Mesentery	(50)	(50)	(50)
Squamous cell carcinoma, invasive			1 (2%)
ALL OTHER SYSTEMS			
None			
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	8	14	11
Moribund sacrifice	14	32	39
Terminal sacrifice	28	4	
TUMOR SUMMARY			
Total animals with primary tumors**	43	43	47
Total primary tumors	87	129	152
Total animals with benign tumors	38	41	36
Total benign tumors	67	91	81
Total animals with malignant tumors	19	25	40
Total malignant tumors	20	35	71
Total animals with secondary tumors##	1	2	5
Total secondary tumors	1	6	6
Total animals with tumors-- uncertain benign or malignant		3	
Total uncertain tumors		3	

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
** Primary tumors: all tumors except secondary tumors
# Number of animals examined microscopically at this site
Secondary tumors: metastatic tumors or tumors invasive into an adjacent organ

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF GLYCIDOL: VEHICLE CONTROL

ANIMAL NUMBER	0116	0110	0220	0077	0335	0465	0003	0001	0111	0550	0066	0115	0227	0118	0231	0112	0243	0443	0441	0144	0448	0363	0002	0044	0055
WEEKS ON STUDY	057	075	075	078	079	080	080	086	087	089	089	091	092	096	098	098	099	100	100	100	100	101	104	104	104
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	N	+	+	+	+	N	+	+	N	N	+	N	+	+	+	+	+
Keratoacanthoma						X																			
Subcutaneous tissue	+	+	+	+	+	+	+	+	N	+	+	+	+	N	+	+	N	N	+	N	+	+	+	+	+
Fibroma																			X						
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	–	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell papilloma																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS		X			X					X	X	X						X			X			X	
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Adenocarcinoma, NOS																									
Pheochromocytoma																									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C cell adenoma																						X			X
Parathyroid	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS										X															
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS												X													
Fibroadenoma									X	X		X									X			X	X
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																		X							
Adenoma, NOS																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																									
Endometrial stromal polyp								X	X	X	X			X		X		X	X			X			X
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																									
Zymbal 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					
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neurilemoma, malignant	X																								
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
Neurilemoma, invasive	X																								
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell			X	X					X					X		X			X		X		X		

+ Tissue examined microscopically
– Required tissue not examined microscopically
X Tumor incidence
N Necropsy, no autolysis, no microscopic examination
S Animal missexed
. No tissue information submitted
C: Necropsy, no histology due to protocol
A: Autolysis
M. Animal missing
B: No necropsy performed

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: VEHICLE CONTROL (Continued)

ANIMAL NUMBER	008	009	013	017	019	021	022	023	025	026	028	029	030	032	033	034	037	038	039	040	041	042	045	047	049	TOTAL TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Keratoacanthoma																										1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma				X																						1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	—	+	+	+	+	+	+	+	+	—	+	+	46
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell papilloma																									X	1
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	—	—	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	—	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	—	48
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS								X		X		X	X	X	X	X			X		X				X	18
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS							X																			1
Adenocarcinoma, NOS													X													1
Pheochromocytoma																									X	1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C cell adenoma								X								X	X								5
Parathyroid	+	+	+	—	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	—	+	+	47
Adenoma, NOS																										1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenocarcinoma, NOS																										1
Fibroadenoma		X	X		X				X	X				X				X						X		14
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
Adenoma, NOS					X							X												X		3
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS																	X									1
Endometrial stromal polyp			X			X			X		X			X	X	X						X		X		19
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS																			X							1
Zymbal 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
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Neurilemoma, malignant																										1
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	*50
Neurilemoma, invasive																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leukemia, mononuclear cell					X		X		X								X							X		13

* Animals necropsied

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF GLYCIDOL: 37.5 mg/kg

ANIMAL NUMBER	0 1 7	0 2 0	0 1 2	0 0 1	0 1 1	0 0 8	0 1 3	0 4 9	0 2 7	0 0 4	0 5 0	0 3 4	0 2 6	0 3 5	0 2 3	0 2 4	0 4 1	0 4 0	0 4 7	0 1 8	0 0 7	0 3 7	0 2 1	0 4 6	0 4 3
WEEKS ON STUDY	0 3 1	0 3 4	0 5 7	0 6 0	0 6 4	0 6 4	0 6 7	0 6 8	0 6 8	0 6 8	0 6 8	0 7 0	0 7 8	0 7 9	0 8 4	0 8 4	0 8 4	0 8 4	0 8 4	0 8 5	0 8 5	0 8 5	0 8 5	0 8 6	0 8 8
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+
Sebaceous adenoma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+
Fibroma							X			X															
Fibrosarcoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS, metastatic																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, invasive																									
Thymus	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell papilloma														X											
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																									
Fibrosarcoma, invasive																									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																			X						
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neurilemoma																									
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS				X				X						X				X			X			X	
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma																									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																									
C cell adenoma																									
Fibrosarcoma, invasive																									
Parathyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	+	+	+	+	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS														X						X					X
Fibroadenoma								X		X		X		X			X	X		X	X			X	X
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																									
Adenoma, NOS																									
Adenocarcinoma, NOS				X																					
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																			X						
Fibrosarcoma																									
Endometrial stromal polyp		X								X	X	X		X			X	X	X				X	X	
Granular cell tumor, NOS																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor											X														X
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Glioma, NOS														X											
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
Fibrosarcoma, invasive																									
Zymbal 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																
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, 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
Leukemia, mononuclear cell											X								X			X	X	X	X

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: 37.5 mg/kg (Continued)

ANIMAL NUMBER	0042	0009	0289	0366	0444	0338	0455	0330	0222	0331	0255	0110	0033	0115	0332	0333	0288	0114	0448	0005	0006	0002	0166	0199	0339	TOTAL TISSUES TUMORS
WEEKS ON STUDY	0888	0888	0889	0889	0990	0992	0993	0995	0996	0996	0997	0997	0997	0998	0998	0999	0999	0999	1000	1002	1003	1004	1004	1004	1004	1004	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sebaceous adenoma																				X						1
Subcutaneous tissue	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma																						X				3
Fibrosarcoma			X																							1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS, metastatic												X														1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, invasive			X																							1
Thymus	+	+	+	+	+	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	−	+	+	+	46
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell papilloma				X														X								3
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, NOS											X															1
Fibrosarcoma, invasive			X																							1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma				X								X												X		4
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neurilemoma										X																1
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS		X				X	X		X	X	X		X												X	14
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma																X										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell adenoma																						X				1
C cell adenoma										X			X													2
Fibrosarcoma, invasive			X																							1
Parathyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenocarcinoma, NOS			X		X	X					X	X		X		X	X									11
Fibroadenoma	X	X	X	X		X	X	X		X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	32
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS																						X				1
Adenoma, NOS		X	X			X					X									X		X			X	7
Adenocarcinoma, NOS																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroma																										1
Fibrosarcoma		X																								1
Endometrial stromal polyp					X	X		X		X	X			X		X	X	X	X	X						21
Granular cell tumor, NOS								X																		1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa cell tumor																										2
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Glioma, NOS							X					X									X					4
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
Fibrosarcoma, invasive			X																							1
Zymbal 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
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibrosarcoma, 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
Leukemia, mononuclear cell						X				X	X		X	X		X	X			X						14

* Animals necropsied

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF GLYCIDOL: 75 mg/kg

ANIMAL NUMBER	0 3 6	0 4 7	0 3 1	0 2 1	0 2 9	0 4 9	0 1 1	0 1 9	0 3 8	0 4 4	0 3 7	0 2 6	0 4 5	0 0 1	0 3 5	0 3 0	0 3 4	0 0 5	0 0 8	0 2 7	0 4 8	0 0 7	0 2 3	0 0 6	0 4 1
WEEKS ON STUDY	0 3 4	0 4 5	0 5 6	0 5 6	0 5 8	0 6 0	0 6 4	0 6 4	0 6 4	0 6 7	0 6 8	0 6 8	0 6 8	0 7 1	0 7 2	0 7 3	0 7 3	0 7 3	0 7 3	0 7 6	0 7 7	0 7 8	0 7 8	0 7 8	0 7 9
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									X
Squamous cell carcinoma																									
Basal cell tumor																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																									
Rhabdomyosarcoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS, metastatic																			X						
Alveolar/bronchiolar carcinoma																						X			
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+
Fibrosarcoma, invasive															X										
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																X									
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	–	+	+	+	+	–	+	+	–	+	–	–	+	–	+	–
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell papilloma																									
Squamous cell carcinoma																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, invasive																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																					X				
Squamous cell carcinoma																									
Fibrosarcoma	X																								
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenomatous polyp, NOS																						X			
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenocarcinoma																						X			
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																				X					
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Adenocarcinoma, NOS																									
Pheochromocytoma																									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+
Follicular cell carcinoma																X				X					
C cell adenoma																									
Parathyroid	+	+	+	+	+	+	–	+	–	+	–	+	+	+	+	+	+	–	+	+	+	+	+	+	+

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: 75 mg/kg (Continued)

ANIMAL NUMBER	0042	0033	0115	0140	0228	0220	0025	0050	0043	0046	0032	0090	0093	0141	0116	0117	0222	0225	0118	0339	0110	0212	0134	0244	TOTAL TISSUES TUMORS
WEEKS ON STUDY	0797	0881	0882	0883	0883	0884	0885	0886	0887	0887	0888	0889	0889	0889	0900	0900	0900	0911	0922	0933	0933	0955	0955	0966	
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell papilloma																									1
Squamous cell carcinoma	X																								1
Basal cell tumor																			X						1
Subcutaneous tissue	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibrosarcoma						X									X										2
Rhabdomyosarcoma																					X				1
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS, metastatic																						X			2
Alveolar/bronchiolar carcinoma																									1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibrosarcoma, invasive																									1
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma																									1
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	42
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																									
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell papilloma	X							X		X							X	X					X		6
Squamous cell carcinoma						X																			1
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma, invasive														X											1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma															X	X	X			X	X	X	X		8
Squamous cell carcinoma								X				X		X											3
Fibrosarcoma										X															2
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenomatous polyp, NOS																									1
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tubular cell adenocarcinoma																									1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, NOS								X	X		X			X			X								6
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS																					X		X		2
Adenocarcinoma, NOS								X																	1
Pheochromocytoma					X														X						2
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell carcinoma															X										3
C cell adenoma																			X						1
Parathyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	45

* Animals necropsied

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: 75 mg/kg (Continued)

ANIMAL NUMBER	0 3 6	0 4 7	0 3 1	0 2 1	0 2 9	0 4 9	0 1 1	0 1 9	0 3 8	0 4 4	0 3 7	0 2 6	0 4 5	0 0 1	0 3 5	0 3 0	0 3 4	0 0 5	0 0 8	0 2 7	0 4 8	0 0 7	0 2 3	0 0 6	0 4 1
WEEKS ON STUDY	0 3 4	0 4 5	0 5 6	0 5 6	0 5 8	0 6 0	0 6 4	0 6 4	0 6 4	0 6 7	0 6 8	0 6 8	0 6 8	0 7 1	0 7 2	0 7 3	0 7 3	0 7 3	0 7 3	0 7 6	0 7 7	0 7 8	0 7 8	0 7 8	0 7 9
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS				X	X				X				X			X				X					
Fibroadenoma								X	X					X			X			X	X		X	X	
Preputial/cutoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS											X	X					X								
Adenoma, NOS																					X				
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Adenocarcinoma, NOS														X											
Adenocarcinoma, NOS, invasive		X																							
Leiomyosarcoma																									
Endometrial stromal polyp									X		X	X													
Endometrial stromal sarcoma				X																					
Deciduoma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS		X																							
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Glioma, NOS									X																
SPECIAL SENSE ORGANS																									
Zymbal 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				
BODY CAVITIES																									
Pleura	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Fibrosarcoma															X										
Mediastinum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Neurilemoma						X																			
Mesentery	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	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
Leukemia, mononuclear cell										X						X	X					X	X		

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: 75 mg/kg (Continued)

ANIMAL NUMBER	042	033	015	040	028	020	002	050	004	043	046	032	009	003	014	016	017	022	025	018	039	010	012	013	024	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	079	081	082	083	083	084	084	085	086	087	087	088	089	089	089	090	090	090	091	092	093	093	095	095	096	
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenocarcinoma, NOS		X		X		X						X		X	X		X			X			X			16
Fibroadenoma	X	X		X	X		X	X	X	X	X	X	X	X		X	X	X	X		X	X	X	X	X	29
Preputial/chtoral 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																		5
Adenoma, NOS					X								X	X			X						X	X		7
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS																X										1
Adenocarcinoma, NOS															X											2
Adenocarcinoma, NOS, invasive																										1
Leiomyosarcoma														X		X										2
Endometrial stromal polyp		X			X		X	X		X	X		X		X	X					X	X				14
Endometrial stromal sarcoma																										1
Deciduoma											X															1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Glioma, NOS							X							X								X				4
SPECIAL SENSE ORGANS																										
Zymbal 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
BODY CAVITIES																										
Pleura	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Fibrosarcoma																										1
Mediastinum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Neurilemoma																										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, 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
Leukemia, mononuclear cell			X			X	X	X	X		X	X		X	X	X	X	X	X			X	X	X		20

* Animals necropsied

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF GLYCIDOL

	Vehicle Control	37.5 mg/kg	75 mg/kg
Subcutaneous Tissue: Fibroma			
Overall Rates (a)	1/50 (2%)	3/50 (6%)	0/50 (0%)
Effective Rates (b)	1/49 (2%)	3/44 (7%)	0/41 (0%)
Terminal Rates (c)	0/28 (0%)	1/4 (25%)	0/0
Week of First Observation	100	67	
Life Table Tests (d)	P=0.413	P=0.085	(e)
Incidental Tumor Tests (d)	P=0.353N	P=0.368	P=0.617N
Cochran-Armitage Trend Test (d)	P=0.436N		
Fisher Exact Test (d)		P=0.269	P=0.544N
Subcutaneous Tissue: Fibroma or Fibrosarcoma			
Overall Rates (a)	1/50 (2%)	4/50 (8%)	2/50 (4%)
Effective Rates (b)	1/49 (2%)	4/44 (9%)	2/41 (5%)
Terminal Rates (c)	0/28 (0%)	1/4 (25%)	0/0
Week of First Observation	100	67	84
Life Table Tests (d)	P=0.035	P=0.033	P=0.056
Incidental Tumor Tests (d)	P=0.548	P=0.261	P=0.627
Cochran-Armitage Trend Test (d)	P=0.331		
Fisher Exact Test (d)		P=0.149	P=0.433
Hematopoietic System: Mononuclear Cell Leukemia			
Overall Rates (a)	13/50 (26%)	14/50 (28%)	20/50 (40%)
Effective Rates (b)	13/49 (27%)	14/44 (32%)	20/41 (49%)
Terminal Rates (c)	6/28 (21%)	0/4 (0%)	0/0
Week of First Observation	75	68	67
Life Table Tests (d)	P<0.001	P=0.006	P<0.001
Incidental Tumor Tests (d)	P=0.086	P=0.502N	P=0.133
Cochran-Armitage Trend Test (d)	P=0.020		
Fisher Exact Test (d)		P=0.370	P=0.025
Tongue: Squamous Cell Papilloma			
Overall Rates (a)	1/50 (2%)	3/50 (6%)	5/50 (10%)
Effective Rates (b)	1/46 (2%)	3/37 (8%)	5/26 (19%)
Terminal Rates (c)	1/28 (4%)	0/4 (0%)	0/0
Week of First Observation	104	79	79
Life Table Tests (d)	P<0.001	P=0.061	P<0.001
Incidental Tumor Tests (d)	P=0.084	P=0.318	P=0.147
Cochran-Armitage Trend Test (d)	P=0.012		
Fisher Exact Test (d)		P=0.230	P=0.021
Oral Cavity (Mouth or Tongue): Squamous Cell Papilloma			
Overall Rates (a)	1/50 (2%)	3/50 (6%)	6/50 (12%)
Effective Rates (b)	1/46 (2%)	3/37 (8%)	6/26 (23%)
Terminal Rates (c)	1/28 (4%)	0/4 (0%)	0/0
Week of First Observation	104	79	79
Life Table Tests (d)	P<0.001	P=0.061	P<0.001
Incidental Tumor Tests (d)	P=0.032	P=0.318	P=0.062
Cochran-Armitage Trend Test (d)	P=0.004		
Fisher Exact Test (d)		P=0.230	P=0.008
Oral Cavity (Mouth or Tongue): Squamous Cell Papilloma or Carcinoma			
Overall Rates (a)	1/50 (2%)	3/50 (6%)	7/50 (14%)
Effective Rates (b)	1/46 (2%)	3/37 (8%)	7/26 (27%)
Terminal Rates (c)	1/28 (4%)	0/4 (0%)	0/0
Week of First Observation	104	79	79
Life Table Tests (d)	P<0.001	P=0.061	P<0.001
Incidental Tumor Tests (d)	P=0.017	P=0.318	P=0.042
Cochran-Armitage Trend Test (d)	P=0.001		
Fisher Exact Test (d)		P=0.230	P=0.003

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF GLYCIDOL

	Vehicle Control	37.5 mg/kg	75 mg/kg
Forestomach: Squamous Cell Papilloma			
Overall Rates (a)	0/50 (0%)	4/50 (8%)	8/50 (16%)
Effective Rates (b)	0/47 (0%)	4/38 (11%)	8/30 (27%)
Terminal Rates (c)	0/28 (0%)	1/4 (25%)	0/0
Week of First Observation		84	77
Life Table Tests (d)	P<0.001	P=0.007	P<0.001
Incidental Tumor Tests (d)	P<0.001	P=0.053	P=0.004
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P=0.036	P<0.001
Forestomach: Squamous Cell Carcinoma			
Overall Rates (a)	0/50 (0%)	0/50 (0%)	3/50 (6%)
Effective Rates (b)	0/43 (0%)	0/31 (0%)	3/18 (17%)
Terminal Rates (c)	0/28 (0%)	0/4 (0%)	0/0
Week of First Observation			85
Life Table Tests (d)	P=0.004	(f)	P=0.011
Incidental Tumor Tests (d)	P=0.084	(f)	P=0.301
Cochran-Armitage Trend Test (d)	P=0.006		
Fisher Exact Test (d)		(f)	P=0.023
Forestomach: Squamous Cell Papilloma or Carcinoma			
Overall Rates (a)	0/50 (0%)	4/50 (8%)	11/50 (22%)
Effective Rates (b)	0/47 (0%)	4/38 (11%)	11/30 (37%)
Terminal Rates (c)	0/28 (0%)	1/4 (25%)	0/0
Week of First Observation		84	77
Life Table Tests (d)	P<0.001	P=0.007	P<0.001
Incidental Tumor Tests (d)	P<0.001	P=0.053	P=0.002
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P=0.036	P<0.001
Anterior Pituitary Gland: Adenoma			
Overall Rates (g)	18/50 (36%)	14/50 (28%)	6/50 (12%)
Effective Rates (b)	18/49 (37%)	14/47 (30%)	6/45 (13%)
Terminal Rates (c)	11/28 (39%)	1/4 (25%)	0/0
Week of First Observation	75	60	76
Life Table Tests (d)	P=0.018	P=0.030	P=0.049
Incidental Tumor Tests (d)	P=0.044N	P=0.452N	P=0.063N
Cochran-Armitage Trend Test (d)	P=0.008N		
Fisher Exact Test (d)		P=0.307N	P=0.008N
Adrenal Cortex: Adenoma or Adenocarcinoma			
Overall Rates (g)	2/50 (4%)	0/50 (0%)	3/50 (6%)
Effective Rates (b)	2/43 (5%)	0/31 (0%)	3/18 (17%)
Terminal Rates (c)	2/28 (7%)	0/4 (0%)	0/0
Week of First Observation	104		85
Life Table Tests (d)	P=0.002	P=0.653N	P<0.001
Incidental Tumor Tests (d)	P=0.039	P=0.707N	P=0.086
Cochran-Armitage Trend Test (d)	P=0.133		
Fisher Exact Test (d)		P=0.334N	P=0.147
Thyroid Gland: C-Cell Adenoma			
Overall Rates (g)	5/50 (10%)	2/50 (4%)	1/49 (2%)
Effective Rates (b)	5/38 (13%)	2/20 (10%)	1/6 (17%)
Terminal Rates (c)	4/28 (14%)	0/4 (0%)	0/0
Week of First Observation	101	96	92
Life Table Tests (d)	P=0.104	P=0.465	P=0.145
Incidental Tumor Tests (d)	P=0.543N	P=0.549N	P=0.748N
Cochran-Armitage Trend Test (d)	P=0.612		
Fisher Exact Test (d)		P=0.543N	P=0.609

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF GLYCIDOL (Continued)

	Vehicle Control	37.5 mg/kg	75 mg/kg
Thyroid Gland: Follicular Cell Carcinoma			
Overall Rates (g)	0/50 (0%)	0/50 (0%)	3/49 (6%)
Effective Rates (b)	0/49 (0%)	0/38 (0%)	3/35 (9%)
Terminal Rates (c)	0/28 (0%)	0/4 (0%)	0/0
Week of First Observation			73
Life Table Tests (d)	P=0.010	(f)	P=0.032
Incidental Tumor Tests (d)	P=0.141	(f)	P=0.430
Cochran-Armitage Trend Test (d)	P=0.022		
Fisher Exact Test (d)		(f)	P=0.069
Thyroid Gland: Follicular Cell Adenoma or Carcinoma			
Overall Rates (g)	0/50 (0%)	1/50 (2%)	3/49 (6%)
Effective Rates (b)	0/49 (0%)	1/38 (3%)	3/35 (9%)
Terminal Rates (c)	0/28 (0%)	1/4 (25%)	0/0
Week of First Observation		104	73
Life Table Tests (d)	P=0.002	P=0.166	P=0.032
Incidental Tumor Tests (d)	P=0.042	P=0.128	P=0.430
Cochran-Armitage Trend Test (d)	P=0.034		
Fisher Exact Test (d)		P=0.437	P=0.069
Mammary Gland: Fibroadenoma			
Overall Rates (a)	14/50 (28%)	32/50 (64%)	29/50 (58%)
Effective Rates (b)	14/49 (29%)	32/46 (70%)	29/44 (66%)
Terminal Rates (c)	10/28 (36%)	4/4 (100%)	0/0
Week of First Observation	87	68	64
Life Table Tests (d)	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests (d)	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P<0.001	P<0.001
Mammary Gland: Adenocarcinoma			
Overall Rates (a)	1/50 (2%)	11/50 (22%)	16/50 (32%)
Effective Rates (b)	1/50 (2%)	11/48 (23%)	16/48 (33%)
Terminal Rates (c)	0/28 (0%)	0/4 (0%)	0/0
Week of First Observation	91	79	56
Life Table Tests (d)	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests (d)	P=0.007	P=0.033	P=0.027
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P=0.001	P<0.001
Mammary Gland: Fibroadenoma or Adenocarcinoma			
Overall Rates (a)	14/50 (28%)	34/50 (68%)	37/50 (74%)
Effective Rates (b)	14/50 (28%)	34/48 (71%)	37/48 (77%)
Terminal Rates (c)	10/28 (36%)	4/4 (100%)	0/0
Week of First Observation	87	68	56
Life Table Tests (d)	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests (d)	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P<0.001	P<0.001
Clitoral Gland: Adenoma			
Overall Rates (g)	3/50 (6%)	7/50 (14%)	7/50 (14%)
Effective Rates (b)	3/47 (6%)	7/38 (18%)	7/30 (23%)
Terminal Rates (c)	3/28 (11%)	2/4 (50%)	0/0
Week of First Observation	104	88	77
Life Table Tests (d)	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests (d)	P=0.015	P=0.049	P=0.031
Cochran-Armitage Trend Test (d)	P=0.025		
Fisher Exact Test (d)		P=0.085	P=0.036

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF GLYCIDOL (Continued)

	Vehicle Control	37.5 mg/kg	75 mg/kg
Clitoral Gland: Carcinoma			
Overall Rates (g)	2/50 (4%)	1/50 (2%)	5/50 (10%)
Effective Rates (b)	2/49 (4%)	1/43 (2%)	5/40 (13%)
Terminal Rates (c)	1/28 (4%)	1/4 (25%)	0/0
Week of First Observation	100	104	68
Life Table Tests (d)	P=0.001	P=0.499	P=0.010
Incidental Tumor Tests (d)	P=0.084	P=0.713	P=0.419
Cochran-Armitage Trend Test (d)	P=0.087		
Fisher Exact Test (d)		P=0.549N	P=0.142
Clitoral Gland: Carcinoma or Adenocarcinoma			
Overall Rates (g)	2/50 (4%)	2/50 (4%)	5/50 (10%)
Effective Rates (b)	2/49 (4%)	2/47 (4%)	5/45 (11%)
Terminal Rates (c)	1/28 (4%)	1/4 (25%)	0/0
Week of First Observation	100	60	68
Life Table Tests (d)	P=0.003	P=0.264	P=0.010
Incidental Tumor Tests (d)	P=0.149	P=0.554	P=0.419
Cochran-Armitage Trend Test (d)	P=0.122		
Fisher Exact Test (d)		P=0.676	P=0.184
Clitoral Gland: Adenoma, Carcinoma, or Adenocarcinoma			
Overall Rates (g)	5/50 (10%)	9/50 (18%)	12/50 (24%)
Effective Rates (b)	5/49 (10%)	9/47 (19%)	12/45 (27%)
Terminal Rates (c)	4/28 (14%)	3/4 (75%)	0/0
Week of First Observation	100	60	68
Life Table Tests (d)	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests (d)	P=0.004	P=0.044	P=0.024
Cochran-Armitage Trend Test (d)	P=0.027		
Fisher Exact Test (d)		P=0.171	P=0.035
Uterus: Adenoma or Adenocarcinoma			
Overall Rates (a)	1/50 (2%)	0/50 (0%)	3/50 (6%)
Effective Rates (b)	1/49 (2%)	0/38 (0%)	3/37 (8%)
Terminal Rates (c)	1/28 (4%)	0/4 (0%)	0/0
Week of First Observation	104		71
Life Table Tests (d)	P=0.010	P=0.834N	P=0.017
Incidental Tumor Tests (d)	P=0.142	P=0.872N	P=0.364
Cochran-Armitage Trend Test (d)	P=0.123		
Fisher Exact Test (d)		P=0.563N	P=0.210
Uterus: Endometrial Stromal Polyp			
Overall Rates (a)	19/50 (38%)	21/50 (42%)	14/50 (28%)
Effective Rates (b)	19/50 (38%)	21/49 (43%)	14/50 (28%)
Terminal Rates (c)	10/28 (36%)	0/4 (0%)	0/0
Week of First Observation	86	34	64
Life Table Tests (d)	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests (d)	P=0.275N	P=0.558N	P=0.585N
Cochran-Armitage Trend Test (d)	P=0.175N		
Fisher Exact Test (d)		P=0.387	P=0.198N
Brain: Glioma			
Overall Rates (g)	0/50 (0%)	4/50 (8%)	4/50 (8%)
Effective Rates (b)	0/49 (0%)	4/46 (9%)	4/46 (9%)
Terminal Rates (c)	0/28 (0%)	1/4 (25%)	0/0
Week of First Observation		79	64
Life Table Tests (d)	P<0.001	P=0.006	P=0.003
Incidental Tumor Tests (d)	P=0.073	P=0.151	P=0.153
Cochran-Armitage Trend Test (d)	P=0.052		
Fisher Exact Test (d)		P=0.051	P=0.051

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF GLYCIDOL (Continued)

	Vehicle Control	37.5 mg/kg	75 mg/kg
All Sites: Benign Tumors			
Overall Rates (a)	38/50 (76%)	41/50 (82%)	36/50 (72%)
Effective Rates (b)	38/50 (76%)	41/49 (84%)	36/50 (72%)
Terminal Rates (c)	24/28 (86%)	4/4 (100%)	0/0
Week of First Observation	75	34	60
Life Table Tests (d)	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests (d)	P=0.037	P=0.032	P=0.056
Cochran-Armitage Trend Test (d)	P=0.360N		
Fisher Exact Test (d)		P=0.242	P=0.410N
All Sites: Malignant Tumors			
Overall Rates (a)	19/50 (38%)	25/50 (50%)	40/50 (80%)
Effective Rates (b)	19/50 (38%)	25/49 (51%)	40/50 (80%)
Terminal Rates (c)	8/28 (29%)	1/4 (25%)	0/0
Week of First Observation	57	60	34
Life Table Tests (d)	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests (d)	P=0.002	P=0.441	P=0.019
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P=0.135	P<0.001
All Sites: All Tumors			
Overall Rates (a)	43/50 (86%)	43/50 (86%)	47/50 (94%)
Effective Rates (b)	43/50 (86%)	43/49 (88%)	47/50 (94%)
Terminal Rates (c)	25/28 (89%)	4/4 (100%)	0/0
Week of First Observation	57	34	34
Life Table Tests (d)	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests (d)	P=0.014	P=0.311	P=0.145
Cochran-Armitage Trend Test (d)	P=0.129		
Fisher Exact Test (d)		P=0.516	P=0.159

(a) Number of tumor-bearing animals/number of animals examined grossly at the site
(b) Number of tumor-bearing animals/effective number of animals, i.e., number of animals alive at the first occurrence of tumors in any of the three groups
(c) Observed tumor incidence in animals killed at the end of the study
(d) Beneath the vehicle 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 vehicle 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 nonfatal. The Cochran-Armitage trend and Fisher exact tests were based on animals surviving to the first occurrence of the tumor in any of the three groups. A negative trend or lower incidence in a dosed group than in vehicle controls is indicated by (N).
(e) No P value is presented because all high dose animals died before the tumor was observed in the vehicle control group.
(f) No P value is presented because no tumors were observed in the 37.5 mg/kg and vehicle control groups.
(g) Number of tumor-bearing animals/number of animals examined microscopically at the site

TABLE B4a. HISTORICAL INCIDENCE OF FORESTOMACH SQUAMOUS CELL TUMORS IN FEMALE F344/N RATS (a)

Study	Incidence of Papillomas or Carcinomas in Controls
Historical Incidence for All Water Gavage Vehicle Controls	
Iodinated glycerol (b)	0/49
Malonaldehyde, sodium salt (c)	(d) 1/50
Chlorpheniramine maleate (c)	0/50
Tetrakis(hydroxymethyl)phosphonium chloride (c)	0/50
Tetrakis(hydroxymethyl)phosphonium sulfate (c)	0/46
Methyl carbamate (e)	0/50
TOTAL	1/295 (0.3%)
SD (f)	0.82%
Range (g)	
High	1/50
Low	0/50
Overall Historical Incidence for Untreated Controls	
TOTAL	(h) 3/1,623 (0.2%)
SD (f)	0.59%
Range (g)	
High	1/49
Low	0/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Study conducted at EG&G Mason Research Institute
(c) Study conducted at Battelle Columbus Laboratories
(d) Squamous cell papilloma
(e) Study conducted at Microbiological Associates, Inc.
(f) Standard deviation
(g) Range and SD are presented for groups of 35 or more animals.
(h) Includes two squamous cell papillomas and one squamous cell carcinoma

TABLE B4b. HISTORICAL INCIDENCE OF GLANDULAR STOMACH SARCOMAS IN FEMALE F344/N RATS (a)

	Number Examined	Number of Tumors	Diagnosis
Historical Incidence for All Water Gavage Controls			
	295	0	
Overall Historical Incidence for Untreated Controls			
	1,623	1 (<0.1%)	Sarcoma, NOS

(a) Data as of May 12, 1988, for studies of at least 104 weeks; no fibrosarcomas have been observed.

TABLE B4c. HISTORICAL INCIDENCE OF BRAIN GLIAL CELL TUMORS IN FEMALE F344/N RATS (a)

Study	Incidence in Controls
Historical Incidence for All Water Gavage Vehicle Controls	
Iodinated glycerol (b)	0/49
Malonaldehyde, sodium salt (c)	(d) 1/50
Chlorpheniramine maleate (c)	0/50
Tetrakis(hydroxymethyl)phosphonium chloride (c)	0/50
Tetrakis(hydroxymethyl)phosphonium sulfate (c)	0/49
Methyl carbamate (e)	0/50
TOTAL	1/298 (0.3%)
SD (f)	0.82%
Range (g)	
High	1/50
Low	0/50
Overall Historical Incidence for Untreated Controls	
TOTAL	(h) 19/1,628 (1.2%)
SD (f)	1.59%
Range (g)	
High	3/50
Low	0/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Study conducted at EG&G Mason Research Institute
(c) Study conducted at Battelle Columbus Laboratories
(d) Astrocytoma
(e) Study conducted at Microbiological Associates, Inc.
(f) Standard deviation
(g) Range and SD are presented for groups of 35 or more animals.
(h) Includes 15 astrocytomas and 4 oligodendrogliomas

TABLE B4d. HISTORICAL INCIDENCE OF ORAL CAVITY SQUAMOUS CELL TUMORS IN FEMALE F344/N RATS (a)

Study	Incidence of Papillomas or Carcinomas in Controls
Historical Incidence for All Water Gavage Vehicle Controls	
Iodinated glycerol (b)	0/50
Malonaldehyde, sodium salt (c)	(d) 1/50
Chlorpheniramine maleate (c)	0/50
Tetrakis(hydroxymethyl)phosphonium chloride (c)	(e) 1/50
Tetrakis(hydroxymethyl)phosphonium sulfate (c)	0/49
Methyl carbamate (f)	0/50
TOTAL	2/299 (0.7%)
SD (g)	1.03%
Range (h)	
High	1/50
Low	0/50
Overall Historical Incidence for Untreated Controls	
TOTAL	(i) 4/1,643 (0.2%)
SD (g)	0.66%
Range (h)	
High	1/50
Low	0/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks; all tumors were observed in the tongue.
(b) Study conducted at EG&G Mason Research Institute
(c) Study conducted at Battelle Columbus Laboratories
(d) Squamous cell carcinoma
(e) Squamous cell papilloma
(f) Study conducted at Microbiological Associates, Inc.
(g) Standard deviation
(h) Range and SD are presented for groups of 35 or more animals.
(i) Includes one squamous cell papilloma and three squamous cell carcinomas

TABLE B4e. HISTORICAL INCIDENCE OF MAMMARY GLAND TUMORS IN FEMALE F344/N RATS (a)

Study	Incidence in Controls		
	Fibroadenoma	Adenocarcinoma	Fibroadenoma or Adenocarcinoma
Historical Incidence for All Water Gavage Vehicle Controls			
Iodinated glycerol (b)	13/50	0/50	13/50
Malonaldehyde, sodium salt (c)	6/50	1/50	7/50
Chlorpheniramine maleate (c)	14/50	3/50	15/50
Tetrakis(hydroxymethyl)phosphonium chloride (c)	11/50	1/50	11/50
Tetrakis(hydroxymethyl)phosphonium sulfate (c)	21/49	0/49	21/49
Methyl carbamate (d)	15/50	0/50	17/50
TOTAL	(e) 80/299 (26.8%)	5/299 (1.7%)	84/299 (28.1%)
SD (f)	10.12%	2.34%	9.97%
Range (g)			
High	21/49	3/50	21/49
Low	6/50	0/50	7/50
Overall Historical Incidence for Untreated Controls			
TOTAL	(h) 520/1,643 (31.6%)	(i) 49/1,643 (3.0%)	(h,i) 552/1,643 (33.6%)
SD (f)	12.23%	2.07%	11.95%
Range (g)			
High	30/50	4/50	32/50
Low	5/50	0/50	6/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Study conducted at EG&G Mason Research Institute
(c) Study conducted at Battelle Columbus Laboratories
(d) Study conducted at Microbiological Associates, Inc.
(e) Eight adenomas, NOS, were observed, all in animals also bearing fibroadenomas.
(f) Standard deviation
(g) Range and SD are presented for groups of 35 or more animals.
(h) Includes 11 adenomas, NOS, 2 cystadenomas, NOS, and 1 papillary cystadenoma, NOS
(i) Includes two carcinomas, NOS, two papillary adenocarcinomas, NOS, and one papillary cystadenocarcinoma, NOS

TABLE B4f. HISTORICAL INCIDENCE OF TUMORS OF THE LARGE INTESTINE IN FEMALE F344/N RATS (a)

	Number Examined	Number of Tumors
Historical Incidence for All Water Gavage Vehicle Controls	299	0
Overall Historical Incidence for Untreated Controls	1,601	0

(a) Data as of May 12, 1988, for studies of at least 104 weeks

TABLE B4g. HISTORICAL INCIDENCE OF THYROID GLAND FOLLICULAR CELL TUMORS IN FEMALE F344/N RATS (a)

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence for All Water Gavage Vehicle Controls			
Iodinated glycerol (b)	0/46	0/46	0/46
Malonaldehyde, sodium salt (c)	2/50	0/50	2/50
Chlorpheniramine maleate (c)	0/47	0/47	0/47
Tetrakis(hydroxymethyl)phosphonium chloride (c)	3/50	0/50	3/50
Tetrakis(hydroxymethyl)phosphonium sulfate (c)	0/49	1/49	1/49
Methyl carbamate (d)	4/50	0/50	4/50
TOTAL	9/292 (3.1%)	1/292 (0.3%)	10/292 (3.4%)
SD (e)	3.52%	0.83%	3.26%
Range (f)			
High	4/50	1/49	4/50
Low	0/49	0/50	0/47
Overall Historical Incidence for Untreated Controls			
TOTAL	(g) 12/1,612 (0.7%)	4/1,612 (0.2%)	(g) 16/1,612 (1.0%)
SD (e)	0.99%	0.67%	1.15%
Range (f)			
High	1/48	1/49	2/49
Low	0/50	0/50	0/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Study conducted at EG&G Mason Research Institute
(c) Study conducted at Battelle Columbus Laboratories
(d) Study conducted at Microbiological Associates, Inc.
(e) Standard deviation
(f) Range and SD are presented for groups of 35 or more animals.
(g) Includes one papillary adenoma

TABLE B4h. HISTORICAL INCIDENCE OF HEMATOPOIETIC SYSTEM TUMORS IN FEMALE F344/N RATS (a)

Study	Incidence of Leukemia in Controls
Historical Incidence for All Water Gavage Vehicle Controls	
Iodinated glycerol (b)	15/50
Malonaldehyde, sodium salt (c)	5/50
Chlorpheniramine maleate (c)	11/50
Tetrakis(hydroxymethyl)phosphonium chloride (c)	4/50
Tetrakis(hydroxymethyl)phosphonium sulfate (c)	23/49
Methyl carbamate (d)	17/50
TOTAL	75/299 (25.1%)
SD (e)	14.90%
Range (f)	
High	23/49
Low	4/50
Overall Historical Incidence for Untreated Controls	
TOTAL	324/1,643 (19.7%)
SD (e)	8.10%
Range (f)	
High	20/50
Low	3/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Study conducted at EG&G Mason Research Institute
(c) Study conducted at Battelle Columbus Laboratories
(d) Study conducted at Microbiological Associates, Inc.
(e) Standard deviation
(f) Range and SD are presented for groups of 35 or more animals.

TABLE B4i. HISTORICAL INCIDENCE OF CLITORAL GLAND TUMORS IN FEMALE F344/N RATS (a)

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence for All Water Gavage Vehicle Controls			
Iodinated glycerol (b)	0/50	2/50	2/50
Malonaldehyde, sodium salt (c)	1/50	0/50	1/50
Chlorpheniramine maleate (c)	5/50	0/50	5/50
Tetrakis(hydroxymethyl)phosphonium chloride (c)	0/50	(d) 3/50	3/50
Tetrakis(hydroxymethyl)phosphonium sulfate (c)	4/49	4/49	8/49
Methyl carbamate (e)	3/50	0/50	3/50
TOTAL	13/299 (4.3%)	9/299 (3.0%)	22/299 (7.4%)
SD (f)	4.30%	3.57%	5.12%
Range (g)			
High	5/50	4/49	8/49
Low	0/50	0/50	1/50
Overall Historical Incidence for Untreated Controls			
TOTAL	(h) 62/1,643 (3.8%)	(i) 53/1,643 (3.2%)	(h,i) 115/1,643 (7.0%)
SD (f)	4.36%	3.49%	4.86%
Range (g)			
High	10/50	6/49	10/50
Low	0/50	0/50	0/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Study conducted at EG&G Mason Research Institute
(c) Study conducted at Battelle Columbus Laboratories
(d) Adenocarcinomas
(e) Study conducted at Microbiological Associates, Inc.
(f) Standard deviation
(g) Range and SD are presented for groups of 35 or more animals.
(h) Includes one papilloma, NOS
(i) Includes three squamous cell carcinomas and four adenocarcinomas, NOS

TABLE B4j. HISTORICAL INCIDENCE OF NASAL CAVITY TUMORS IN FEMALE F344/N RATS (a)

	Number Examined	Number of Tumors
Historical Incidence for All Water Gavage Vehicle Controls		
	299	0
Overall Historical Incidence for Untreated Controls		
	1,643	0

(a) Data as of May 12, 1988, for studies of at least 104 weeks

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF GLYCIDOL

	Vehicle Control	37.5 mg/kg	75 mg/kg
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, chronic		1 (2%)	
Amyloidosis	1 (2%)		
Hyperkeratosis			1 (2%)
*Subcutaneous tissue	(50)	(50)	(50)
Hemorrhage	1 (2%)		
Granuloma, foreign body	1 (2%)		
RESPIRATORY SYSTEM			
#Nasal cavity	(50)	(50)	(50)
Congenital malformation, NOS	1 (2%)		1 (2%)
Inflammation, acute	2 (4%)		4 (8%)
Inflammation, acute/chronic	4 (8%)	5 (10%)	1 (2%)
Inflammation, chronic	10 (20%)	3 (6%)	1 (2%)
Hyperkeratosis	1 (2%)		
Metaplasia, squamous		1 (2%)	
#Trachea	(50)	(50)	(49)
Inflammation, chronic diffuse	7 (14%)		3 (6%)
#Lung/bronchus	(50)	(50)	(50)
Bronchiectasis	3 (6%)		
Inflammation, suppurative	1 (2%)		
Inflammation, chronic			1 (2%)
#Lung	(50)	(50)	(50)
Atelectasis	2 (4%)		1 (2%)
Congestion, NOS		4 (8%)	
Edema, NOS		5 (10%)	4 (8%)
Hemorrhage		1 (2%)	1 (2%)
Hemorrhage, chronic	1 (2%)		1 (2%)
Inflammation, acute		1 (2%)	1 (2%)
Inflammation, acute focal			1 (2%)
Pneumonia, interstitial chronic	6 (12%)	4 (8%)	9 (18%)
Inflammation, chronic focal	14 (28%)	5 (10%)	3 (6%)
Hyperplasia, alveolar epithelium	1 (2%)		
HEMATOPOIETIC SYSTEM			
#Spleen	(50)	(49)	(50)
Hemorrhage	1 (2%)		
Fibrosis	3 (6%)	14 (29%)	20 (40%)
Infarct, NOS	1 (2%)		
Hemosiderosis	12 (24%)	7 (14%)	11 (22%)
Hematopoiesis	1 (2%)	2 (4%)	
#Lymph node	(50)	(50)	(50)
Hemorrhage		1 (2%)	
Hyperplasia, NOS	1 (2%)	1 (2%)	
Angiectasis	2 (4%)	1 (2%)	
Plasmacytosis		1 (2%)	
#Lung	(50)	(50)	(50)
Hyperplasia, lymphoid	18 (36%)	1 (2%)	11 (22%)
CIRCULATORY SYSTEM			
#Lung	(50)	(50)	(50)
Thrombosis, NOS			2 (4%)

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF GLYCIDOL (Continued)

	Vehicle Control	37.5 mg/kg	75 mg/kg
CIRCULATORY SYSTEM (Continued)			
#Heart	(50)	(50)	(50)
Inflammation, acute			1 (2%)
Inflammation, chronic	2 (4%)		2 (4%)
#Heart/atrium	(50)	(50)	(50)
Thrombosis, NOS			1 (2%)
Endocardiosis			1 (2%)
#Myocardium	(50)	(50)	(50)
Degeneration, NOS	49 (98%)	48 (96%)	46 (92%)
#Mitral valve	(50)	(50)	(50)
Endocardiosis			1 (2%)
*Artery	(50)	(50)	(50)
Arteriosclerosis, NOS	1 (2%)	1 (2%)	
*Vein	(50)	(50)	(50)
Thrombosis, NOS		1 (2%)	
DIGESTIVE SYSTEM			
*Mouth	(50)	(50)	(50)
Inflammation, chronic		1 (2%)	
*Tongue	(50)	(50)	(50)
Inflammation, chronic focal	1 (2%)		
Hyperplasia, focal	1 (2%)		
#Salivary gland	(48)	(50)	(49)
Inflammation, chronic	1 (2%)		
Atrophy, NOS	1 (2%)	1 (2%)	
#Liver	(50)	(50)	(50)
Hemorrhage			1 (2%)
Inflammation, chronic focal	22 (44%)	11 (22%)	5 (10%)
Inflammation, granulomatous focal	1 (2%)		
Scar		1 (2%)	
Degeneration, lipoid	3 (6%)	1 (2%)	2 (4%)
Necrosis, focal		1 (2%)	1 (2%)
Necrosis, coagulative	3 (6%)	2 (4%)	6 (12%)
Nuclear alteration			1 (2%)
Basophilic cyto change	36 (72%)	22 (44%)	24 (48%)
Clear cell change	2 (4%)	2 (4%)	1 (2%)
Hyperplasia, focal	1 (2%)	5 (10%)	5 (10%)
Angiectasis			6 (12%)
#Periportal bile duct	(50)	(50)	(50)
Hyperplasia, NOS	1 (2%)	2 (4%)	2 (4%)
#Liver/centrilobular	(50)	(50)	(50)
Degeneration, NOS			1 (2%)
#Pancreas	(50)	(50)	(49)
Inflammation, chronic	2 (4%)	2 (4%)	
Necrosis, NOS		1 (2%)	
Atrophy, NOS	1 (2%)		
#Esophagus	(50)	(50)	(50)
Dysplasia, epithelial			1 (2%)
#Glandular stomach	(50)	(50)	(50)
Diverticulosis			1 (2%)
Cyst, NOS	1 (2%)		
Erosion		1 (2%)	
Fibrosis			2 (4%)
#Forestomach	(50)	(50)	(50)
Ulcer, acute		1 (2%)	
Inflammation, acute focal		1 (2%)	1 (2%)
Ulcer, chronic	1 (2%)	3 (6%)	
Erosion			1 (2%)
Hyperkeratosis	1 (2%)	16 (32%)	13 (26%)
Dysplasia, epithelial		12 (24%)	10 (20%)

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF GLYCIDOL (Continued)

	Vehicle Control	37.5 mg/kg	75 mg/kg
DIGESTIVE SYSTEM (Continued)			
#Ileum	(50)	(50)	(50)
Inflammation, chronic		1 (2%)	
#Colon	(50)	(50)	(50)
Fibrosis, focal		1 (2%)	
URINARY SYSTEM			
#Kidney	(50)	(50)	(50)
Hamartoma		1 (2%)	
Cyst, NOS	2 (4%)		1 (2%)
Inflammation, acute focal			2 (4%)
Nephropathy	13 (26%)	5 (10%)	
Hemoglobin pigment	1 (2%)		
#Kidney/glomerulus	(50)	(50)	(50)
Atypia, NOS		1 (2%)	
#Kidney/tubule	(50)	(50)	(50)
Degeneration, hyaline			1 (2%)
#Urinary bladder	(48)	(50)	(50)
Edema, NOS			1 (2%)
Hemorrhage		1 (2%)	
Inflammation, chronic diffuse		1 (2%)	
Hyperplasia, papillary		1 (2%)	
ENDOCRINE SYSTEM			
#Pituitary intermedia	(50)	(50)	(49)
Colloid cyst	1 (2%)	1 (2%)	7 (14%)
Hemorrhage		1 (2%)	
Angiectasis		1 (2%)	
#Anterior pituitary	(50)	(50)	(49)
Mineralization			1 (2%)
Colloid cyst	19 (38%)	17 (34%)	24 (49%)
Fibrosis		1 (2%)	
Cytoplasmic vacuolization	1 (2%)		
Hyperplasia, focal	12 (24%)	9 (18%)	4 (8%)
Angiectasis	6 (12%)	10 (20%)	6 (12%)
#Adrenal cortex	(50)	(50)	(50)
Accessory structure		1 (2%)	
Degeneration, lipoid	2 (4%)	2 (4%)	2 (4%)
Necrosis, coagulative			1 (2%)
Hypertrophy, focal	2 (4%)		
Hyperplasia, focal	17 (34%)	17 (34%)	12 (24%)
Angiectasis		2 (4%)	2 (4%)
#Adrenal medulla	(50)	(50)	(50)
Inflammation, chronic			1 (2%)
Hyperplasia, NOS	1 (2%)		
Hyperplasia, focal	5 (10%)	7 (14%)	2 (4%)
#Thyroid	(50)	(50)	(49)
Hyperplasia, C-cell	10 (20%)	5 (10%)	2 (4%)
Hyperplasia, follicular cell	1 (2%)	1 (2%)	2 (4%)
#Pancreatic islets	(50)	(50)	(49)
Cell size alteration			1 (2%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Cyst, NOS	2 (4%)		
Multiple cysts	1 (2%)		

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF GLYCIDOL (Continued)

	Vehicle Control	37.5 mg/kg	75 mg/kg
REPRODUCTIVE SYSTEM (Continued)			
*Clitoral gland	(50)	(50)	(50)
Cyst, NOS		1 (2%)	
Inflammation, NOS	1 (2%)		
Inflammation, acute	2 (4%)	1 (2%)	1 (2%)
Hyperplasia, NOS	1 (2%)		
Hyperplasia, focal		1 (2%)	1 (2%)
*Vagina	(50)	(50)	(50)
Epidermal inclusion cyst	1 (2%)		
Inflammation, chronic		1 (2%)	
#Uterus	(50)	(50)	(50)
Hemorrhage		3 (6%)	3 (6%)
Inflammation, suppurative	15 (30%)	1 (2%)	14 (28%)
#Uterus/endometrium	(50)	(50)	(50)
Cyst, NOS			2 (4%)
Hyperplasia, cystic	11 (22%)	6 (12%)	12 (24%)
#Ovary	(50)	(50)	(50)
Cyst, NOS	3 (6%)	1 (2%)	6 (12%)
Luteinized follic cyst			2 (4%)
NERVOUS SYSTEM			
#Brain	(50)	(50)	(50)
Hemorrhage	1 (2%)	2 (4%)	
*Spinal cord	(50)	(50)	(50)
Hemorrhage	1 (2%)		
SPECIAL SENSE ORGANS			
*Eye	(50)	(50)	(50)
Hemorrhage	1 (2%)	2 (4%)	5 (10%)
Inflammation, chronic		1 (2%)	1 (2%)
*Eye/retina	(50)	(50)	(50)
Degeneration, NOS	22 (44%)	16 (32%)	19 (38%)
*Eye/crystalline lens	(50)	(50)	(50)
Cataract	23 (46%)	16 (32%)	20 (40%)
*Harderian gland	(50)	(50)	(50)
Inflammation, chronic	10 (20%)	10 (20%)	6 (12%)
MUSCULOSKELETAL SYSTEM			
*Skeletal muscle	(50)	(50)	(50)
Inflammation, chronic		1 (2%)	
BODY CAVITIES			
*Peritoneum	(50)	(50)	(50)
Inflammation, chronic			1 (2%)
ALL OTHER SYSTEMS			
Adipose tissue			
Hemorrhage			2
Inflammation, chronic		2	
Necrosis, fat	5	1	2
SPECIAL MORPHOLOGY SUMMARY			
None			

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
# Number of animals examined microscopically at this site

APPENDIX C

SUMMARY OF LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF GLYCIDOL

TABLE C1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF GLYCIDOL

	Vehicle Control	25 mg/kg	50 mg/kg
Animals intially 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			4 (8%)
Basal cell tumor			2 (4%)
Sebaceous adenoma		1 (2%)	
Keratoacanthoma		1 (2%)	
*Subcutaneous tissue	(50)	(50)	(50)
Sarcoma, NOS	2 (4%)	3 (6%)	1 (2%)
Fibroma		1 (2%)	
Fibrosarcoma	9 (18%)		3 (6%)
RESPIRATORY SYSTEM			
#Nose	(49)	(50)	(50)
Papilloma, NOS	1 (2%)		
#Lung	(50)	(50)	(50)
Adenocarcinoma, NOS, metastatic		2 (4%)	1 (2%)
Hepatocellular carcinoma, metastatic	2 (4%)	7 (14%)	2 (4%)
Alveolar/bronchiolar adenoma	6 (12%)	6 (12%)	8 (16%)
Alveolar/bronchiolar carcinoma	7 (14%)	5 (10%)	14 (28%)
Fibrosarcoma, metastatic			1 (2%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Malignant lymphoma, lymphocytic type			1 (2%)
Malignant lymphoma, histiocytic type		1 (2%)	3 (6%)
Malignant lymphoma, mixed type	4 (8%)	11 (22%)	3 (6%)
#Lymph node	(49)	(50)	(50)
Sarcoma, NOS, metastatic		1 (2%)	
#Thymus	(40)	(37)	(42)
Malignant lymphoma, mixed type	1 (3%)		
CIRCULATORY SYSTEM			
#Spleen	(50)	(50)	(50)
Hemangioma			1 (2%)
Hemangiosarcoma		1 (2%)	
#Heart	(50)	(50)	(50)
Alveolar/bronchiolar carcinoma, metastatic			1 (2%)
#Liver	(50)	(50)	(50)
Hemangioma			1 (2%)
Hemangiosarcoma	1 (2%)	3 (6%)	1 (2%)
#Jejunum	(50)	(50)	(50)
Hemangiosarcoma			1 (2%)
DIGESTIVE SYSTEM			
*Tongue	(50)	(50)	(50)
Squamous cell papilloma			1 (2%)
*Tooth	(50)	(50)	(50)
Odontoma, NOS	1 (2%)		
#Liver	(50)	(50)	(50)
Hepatocellular adenoma	18 (36%)	16 (32%)	30 (60%)
Hepatocellular carcinoma	10 (20%)	17 (34%)	8 (16%)
Fibrosarcoma, metastatic			1 (2%)

TABLE C1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF GLYCIDOL (Continued)

	Vehicle Control	25 mg/kg	50 mg/kg
DIGESTIVE SYSTEM (Continued)			
#Pancreas	(50)	(50)	(50)
Alveolar/bronchiolar carcinoma, metastatic			1 (2%)
#Forestomach	(50)	(50)	(50)
Squamous cell papilloma		2 (4%)	9 (18%)
Squamous cell carcinoma	1 (2%)		1 (2%)
#Duodenum	(50)	(50)	(50)
Adenocarcinoma, NOS		1 (2%)	
#Jejunum	(50)	(50)	(50)
Adenocarcinoma, NOS	1 (2%)	1 (2%)	
Adenomatous polyp, NOS	1 (2%)	1 (2%)	
#Ileum	(50)	(50)	(50)
Adenocarcinoma, NOS	1 (2%)	1 (2%)	
URINARY SYSTEM			
#Kidney	(50)	(50)	(50)
Alveolar/bronchiolar carcinoma, metastatic			1 (2%)
Tubular cell adenoma	1 (2%)		
#Urinary bladder	(50)	(50)	(50)
Transitional cell carcinoma		1 (2%)	1 (2%)
ENDOCRINE SYSTEM			
#Anterior pituitary	(49)	(50)	(50)
Adenoma, NOS		1 (2%)	
#Adrenal	(50)	(50)	(50)
Cortical adenoma	1 (2%)	1 (2%)	1 (2%)
#Adrenal/capsule	(50)	(50)	(50)
Adenoma, NOS	2 (4%)	1 (2%)	5 (10%)
#Adrenal medulla	(50)	(50)	(50)
Pheochromocytoma	3 (6%)		1 (2%)
#Thyroid	(49)	(49)	(50)
Adenoma, NOS			1 (2%)
Follicular cell adenoma	1 (2%)	2 (4%)	
REPRODUCTIVE SYSTEM			
*Seminal vesicle	(50)	(50)	(50)
Adenocarcinoma, NOS			1 (2%)
*Epididymis	(50)	(50)	(50)
Sarcoma, NOS			2 (4%)
Mesothelioma, NOS			1 (2%)
NERVOUS SYSTEM			
None			
SPECIAL SENSE ORGANS			
*Harderian gland	(50)	(50)	(50)
Adenoma, NOS	7 (14%)	10 (20%)	16 (32%)
Adenocarcinoma, NOS	1 (2%)	2 (4%)	7 (14%)
MUSCULOSKELETAL SYSTEM			
None			

TABLE C1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF GLYCIDOL (Continued)

	Vehicle Control	25 mg/kg	50 mg/kg
BODY CAVITIES			
*Pleural cavity	(50)	(50)	(50)
Alveolar/bronchiolar carcinoma, invasive			1 (2%)
ALL OTHER SYSTEMS			
Omentum			
Hepatocellular carcinoma, invasive	1		
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	1		4
Moribund sacrifice	16	25	19
Terminal sacrifice	33	25	27
TUMOR SUMMARY			
Total animals with primary tumors**	42	47	49
Total primary tumors	80	90	128
Total animals with benign tumors	28	35	38
Total benign tumors	41	43	80
Total animals with malignant tumors	28	38	38
Total malignant tumors	38	47	47
Total animals with secondary tumors##	3	10	6
Total secondary tumors	3	10	9
Total animals with tumors-- uncertain benign or malignant	1		1
Total uncertain tumors	1		1

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
** Primary tumors: all tumors except secondary tumors
# Number of animals examined microscopically at this site
Secondary tumors: metastatic tumors or tumors invasive into an adjacent organ

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF GLYCIDOL: VEHICLE CONTROL

ANIMAL NUMBER	0003	0011	0049	0117	0112	0004	0027	0288	0222	0226	0055	0013	0199	0311	0188	0333	0455	0001	0002	0006	0007	0008	0009	0110	0114
WEEKS ON STUDY	0422	0445	0633	0772	0766	0778	0855	0866	0889	0891	0966	0977	0988	0999	1000	1003	1033	1044	1044	1044	1044	1044	1044	1044	1044
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS				X																					
Fibrosarcoma								X			X		X	X	X		X								
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic										X															
Alveolar/bronchiolar adenoma					X													X	X						
Alveolar/bronchiolar carcinoma													X	X											X
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nasal cavity	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma, NOS																						X			
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	–	–	+	+	+	–	–	–	+	+	+	–	+	–	–	+	–	+	+	+	+	+	+	+	+
Malignant lymphoma, mixed type																									
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Odontoma, NOS																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma				X		X	X						X		X	X	X					X	X		X	
Hepatocellular carcinoma							X	X		X												X				
Hemangiosarcoma			X																						
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																									
Hepatocellular carcinoma, invasive																									
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS		@X																							
Adenomatous polyp, NOS																									
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																						X			
Cortical adenoma																								X	
Pheochromocytoma																				X		X		X	
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
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS											X								X					X	
Adenocarcinoma, 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, mixed type									X						X									X	

+ Tissue examined microscopically
– Required tissue not examined microscopically
X Tumor incidence
N Necropsy, no autolysis, no microscopic examination
S Animal missexed
@ Multiple occurrence of morphology
No tissue information submitted
C. Necropsy, no histology due to protocol
A: Autolysis
M. Animal missing
B. No necropsy performed

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: VEHICLE CONTROL (Continued)

ANIMAL NUMBER	0 1 5	0 1 6	0 2 0	0 2 1	0 2 3	0 2 4	0 2 5	0 2 9	0 3 0	0 3 2	0 3 4	0 3 5	0 3 6	0 3 7	0 3 8	0 3 9	0 4 0	0 4 1	0 4 2	0 4 3	0 4 4	0 4 6	0 4 7	0 4 8	0 5 0	TOTAL TISSUES TUMORS
WEEKS ON STUDY	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS									X																	2
Fibrosarcoma					X		X				X															9
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic									X																	2
Alveolar/bronchiolar adenoma				X							X											X				6
Alveolar/bronchiolar carcinoma	X								X								X	X								7
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nasal cavity	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Papilloma, NOS																										1
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	40
Malignant lymphoma, mixed type		X																								1
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Odontoma, NOS												X														1
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma				X			X		X			X				X		X	X	X						18
Hepatocellular carcinoma		X				X			X		X									X			X			10
Hemangiosarcoma																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma																					X					1
Hepatocellular carcinoma, invasive																				X						1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS																										1
Adenomatous polyp, NOS																							X			1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tubular cell adenoma																X										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS																X										2
Cortical adenoma																										1
Pheochromocytoma																										3
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell adenoma							X																			1
Parathyroid	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS	X									X			X						X							7
Adenocarcinoma, 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, mixed type													X													4

* Animals necropsied

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF GLYCIDOL: 25 mg/kg

ANIMAL NUMBER	04121	04223	02311	01118	01801	01912	04545	02909	04400	04009	02808	04807	03909	01313	02202	01616	04404	04403	00202	00907	04646	04949	02505	00504
WEEKS ON STUDY	05515	05717	07010	07712	07717	07818	07919	07909	08800	08833	08837	08807	09933	09913	09903	09944	09955	09936	09926	09997	09909	10100	10101	10104
INTEGUMENTARY SYSTEM																								
Skin	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+
Sebaceous adenoma																			X					
Keratoacanthoma																	X							
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS								X		X			X											
Fibroma																							X	
RESPIRATORY SYSTEM																								
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS, metastatic									X		X													
Hepatocellular carcinoma, metastatic	X		X			X		X							X									
Alveolar/bronchiolar adenoma							X		X				X											
Alveolar/bronchiolar carcinoma								X																
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																								
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS, metastatic										X														
Thymus	+	+	−	+	−	+	+	−	+	+	+	+	−	+	+	−	−	+	+	−	+	−	−	+
CIRCULATORY SYSTEM																								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																								
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma										X		X				X		X			X			X
Hepatocellular carcinoma	X	X	X	X	X	X		X	X		X				X				X					
Hemangiosarcoma												X												
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma									X										X					
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS												X						X						
Adenomatous polyp, NOS																								
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional cell carcinoma				X																				
ENDOCRINE SYSTEM																								
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS										X														
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																						X		
Cortical adenoma																								
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+
Follicular cell adenoma																								
Parathyroid	−	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+
REPRODUCTIVE SYSTEM																								
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																								
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS															X		X							
Adenocarcinoma, 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
Malignant lymphoma, histiocytic type																							X	
Malignant lymphoma, mixed type															X					X	X	X		X

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: 25 mg/kg (Continued)

ANIMAL NUMBER	0003	0004	0006	0008	0010	0014	0015	0017	0019	0020	0021	0024	0026	0027	0030	0031	0032	0033	0034	0035	0036	0037	0038	0047	0050	TOTAL TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sebaceous adenoma																										1
Keratoacanthoma																										1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS																										3
Fibroma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS, metastatic																										2
Hepatocellular carcinoma, metastatic												X							X							7
Alveolar/bronchiolar adenoma									X				X								X					6
Alveolar/bronchiolar carcinoma	X		X			X														X						5
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																								X		1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, NOS, metastatic																										1
Thymus	+	+	+	+	–	–	+	+	+	+	+	+	+	+	–	+	+	+	+	–	+	+	+	+	+	37
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma	X	X	X			X					X	X				X		X			X			X		16
Hepatocellular carcinoma												X			X				X	X		X		X		17
Hemangiosarcoma																X	X									3
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																										2
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS																				X						3
Adenomatous polyp, NOS			X																							1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Transitional cell carcinoma																										1
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS																										1
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS																										1
Cortical adenoma																X										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell adenoma					X															X						2
Parathyroid	–	–	+	+	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	41
REPRODUCTIVE SYSTEM																										
Mammary gland	+	N	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS		X		X		X		X	X	X					X				X							10
Adenocarcinoma, NOS																										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	*50
Malignant lymphoma, histiocytic type																										1
Malignant lymphoma, mixed type	X									X	X		X		X										X	11

* Animals necropsied

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF GLYCIDOL: 50 mg/kg

ANIMAL NUMBER	04211	02414	03414	05040	04414	01144	02255	04499	01166	00044	02211	03333	04422	03388	02828	03355	02222	02266	00033	00055	01133	01188	00066	00011	00002
WEEKS ON STUDY	00313	05252	05444	06699	07111	07722	07733	07766	07777	07788	08088	08099	09000	09900	09933	09933	09966	09966	09977	09977	09999	10000	10011	10044	10444
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma													X												
Basal cell tumor																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																				X					
Fibrosarcoma															X										
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS, metastatic													X												
Hepatocellular carcinoma, metastatic						X			X																
Alveolar/bronchiolar adenoma							X				X					X	X								X
Alveolar/bronchiolar carcinoma								X			X													X	X	
Fibrosarcoma, metastatic															X										
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	−	−	−	+	+	+	−	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar bronchiolar carcinoma, metastatic								X																	
DIGESTIVE SYSTEM																									
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell papilloma																			X						
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma							X			X	X		X	X	X	X					X		X	X	X
Hepatocellular carcinoma		X				X			X				X				X			X					
Fibrosarcoma, metastatic																									
Hemangioma																									
Hemangiosarcoma						X																			
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic								X																	
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma					X						X										X		X		
Squamous cell carcinoma												X													
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic								X																	
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional cell carcinoma											X														

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: 50 mg/kg (Continued)

ANIMAL NUMBER	0007	0008	0009	0010	0011	0012	0015	0017	0019	0020	0023	0027	0029	0030	0031	0032	0036	0037	0039	0040	0043	0045	0046	0047	0048	TOTAL:
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell papilloma						X												X			X					4
Basal cell tumor	X																							X		2
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS																										1
Fibrosarcoma										X		X														3
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS, metastatic																										1
Hepatocellular carcinoma, metastatic																										2
Alveolar/bronchiolar adenoma													X										X	X		8
Alveolar/bronchiolar carcinoma						X			X			X		X	X		X	X	X			X			X	14
Fibrosarcoma, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma					X																					1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	–	+	+	+	+	+	+	+	+	42
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma, meta																										1
DIGESTIVE SYSTEM																										
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell papilloma																										1
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma	X	X	X	X	X			X		X	X	X	X	X		X	X	X	X	X	X	X	X			30
Hepatocellular carcinoma			X																				X			8
Fibrosarcoma, metastatic										X																1
Hemangioma	X																									1
Hemangiosarcoma																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma, meta																										1
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma						X	X				X				X					X						9
Squamous cell carcinoma																										1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma					X																					1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma, meta																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Transitional cell carcinoma																										1

* Animals necropsied

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: 50 mg/kg (Continued)

ANIMAL NUMBER	04 21	02 41	03 44	05 50	04 44	01 44	02 25	04 49	01 66	00 44	02 11	03 33	04 22	03 38	02 28	03 35	02 22	02 26	00 03	00 55	01 33	01 18	00 66	00 11	00 02
WEEKS ON STUDY	00 33	05 22	05 44	06 99	07 11	07 22	07 33	07 66	07 77	07 88	08 88	08 99	09 00	09 00	09 33	09 33	09 66	09 66	09 77	09 77	09 99	10 00	10 11	10 44	10 44
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS															X	X									
Cortical adenoma																									
Pheochromocytoma																									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Parathyroid	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																			X						
Epididymis	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Sarcoma, NOS																									
Mesothelioma, 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	N
Adenoma, NOS							X				X		X					X	X					X	X
Adenocarcinoma, NOS						X						X		X											
BODY CAVITIES																									
Pleura	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Alveolar/bronchiolar 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	N
Malignant lymphoma, lymphocytic type				X																					
Malignant lymphoma, histiocytic type			X															X				X			
Malignant lymphoma, mixed type					X																				X

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: 50 mg/kg (Continued)

ANIMAL NUMBER	00 07	00 08	00 09	01 10	01 11	01 12	01 15	01 17	01 19	02 20	02 23	02 27	02 29	03 30	03 31	03 32	03 36	03 37	03 39	04 00	04 03	04 05	04 06	04 07	04 08	TOTAL TISSUES TUMORS
WEEKS ON STUDY	10 04	10 04	10 04	10 04	10 04	10 04	10 04	10 04	10 04	10 04	10 04	10 04	10 04	10 04	10 04	10 04	10 04	10 04	10 04	10 04	10 04	10 04	10 04	10 04	10 04	
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS		X														X						X				5
Cortical adenoma																				X						1
Pheochromocytoma													X													1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS	X																									1
Parathyroid	+	+	+	+	+	+	+	+	-	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	47
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenocarcinoma, NOS																										1
Epididymis	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Sarcoma, NOS											X							X								2
Mesothelioma, 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	*50
Adenoma, NOS				X				X			X		X							X	X	X	X		X	16
Adenocarcinoma, NOS				X					X							X									X	7
BODY CAVITIES																										
Pleura	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Alveolar/bronchiolar carcinoma, invas																										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, lymphocytic type																										1
Malignant lymphoma, histiocytic type																										3
Malignant lymphoma, mixed type													X													3

* Animals necropsied

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF GLYCIDOL

	Vehicle Control	25 mg/kg	50 mg/kg
Skin: Squamous Cell Papilloma			
Overall Rates (a)	0/50 (0%)	0/50 (0%)	4/50 (8%)
Adjusted Rates (b)	0.0%	0.0%	13.5%
Terminal Rates (c)	0/33 (0%)	0/25 (0%)	3/27 (11%)
Week of First Observation			90
Life Table Tests (d)	P=0.012	(e)	P=0.045
Incidental Tumor Tests (d)	P=0.010	(e)	P=0.047
Cochran-Armitage Trend Test (d)	P=0.015		
Fisher Exact Test (d)		(e)	P=0.059
Subcutaneous Tissue: Fibrosarcoma			
Overall Rates (a)	9/50 (18%)	0/50 (0%)	3/50 (6%)
Adjusted Rates (b)	22.5%	0.0%	10.0%
Terminal Rates (c)	3/33 (9%)	0/25 (0%)	2/27 (7%)
Week of First Observation	86		93
Life Table Tests (d)	P=0.049N	P=0.009N	P=0.127N
Incidental Tumor Tests (d)	P=0.015N	P<0.001N	P=0.045N
Cochran-Armitage Trend Test (d)	P=0.021N		
Fisher Exact Test (d)		P=0.001N	P=0.061N
Subcutaneous Tissue: Fibroma or Fibrosarcoma			
Overall Rates (a)	9/50 (18%)	1/50 (2%)	3/50 (6%)
Adjusted Rates (b)	22.5%	3.7%	10.0%
Terminal Rates (c)	3/33 (9%)	0/25 (0%)	2/27 (7%)
Week of First Observation	86	101	93
Life Table Tests (d)	P=0.059N	P=0.031N	P=0.127N
Incidental Tumor Tests (d)	P=0.016N	P=0.001N	P=0.045N
Cochran-Armitage Trend Test (d)	P=0.025N		
Fisher Exact Test (d)		P=0.008N	P=0.061N
Subcutaneous Tissue: Sarcoma or Fibrosarcoma			
Overall Rates (a)	11/50 (22%)	3/50 (6%)	4/50 (8%)
Adjusted Rates (b)	26.7%	7.3%	12.8%
Terminal Rates (c)	4/33 (12%)	0/25 (0%)	2/27 (7%)
Week of First Observation	72	80	93
Life Table Tests (d)	P=0.058N	P=0.060N	P=0.110N
Incidental Tumor Tests (d)	P=0.012N	P=0.003N	P=0.025N
Cochran-Armitage Trend Test (d)	P=0.023N		
Fisher Exact Test (d)		P=0.020N	P=0.045N
Subcutaneous Tissue: Fibroma, Sarcoma, or Fibrosarcoma			
Overall Rates (a)	11/50 (22%)	4/50 (8%)	4/50 (8%)
Adjusted Rates (b)	26.7%	10.8%	12.8%
Terminal Rates (c)	4/33 (12%)	0/25 (0%)	2/27 (7%)
Week of First Observation	72	80	93
Life Table Tests (d)	P=0.066N	P=0.114N	P=0.110N
Incidental Tumor Tests (d)	P=0.012N	P=0.007N	P=0.025N
Cochran-Armitage Trend Test (d)	P=0.025N		
Fisher Exact Test (d)		P=0.045N	P=0.045N
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (f)	6/50 (12%)	6/50 (12%)	8/50 (16%)
Adjusted Rates (b)	17.0%	17.9%	23.4%
Terminal Rates (c)	5/33 (15%)	3/25 (12%)	4/27 (15%)
Week of First Observation	76	79	73
Life Table Tests (d)	P=0.233	P=0.499	P=0.276
Incidental Tumor Tests (d)	P=0.309	P=0.610	P=0.389
Cochran-Armitage Trend Test (d)	P=0.330		
Fisher Exact Test (d)		P=0.620	P=0.387

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF GLYCIDOL (Continued)

	Vehicle Control	25 mg/kg	50 mg/kg
Lung: Alveolar/Bronchiolar Carcinoma			
Overall Rates (f)	7/50 (14%)	5/50 (10%)	14/50 (28%)
Adjusted Rates (b)	19.6%	17.3%	45.6%
Terminal Rates (c)	5/33 (15%)	4/25 (16%)	11/27 (41%)
Week of First Observation	98	79	76
Life Table Tests (d)	P=0.017	P=0.540N	P=0.026
Incidental Tumor Tests (d)	P=0.023	P=0.431N	P=0.044
Cochran-Armitage Trend Test (d)	P=0.043		
Fisher Exact Test (d)		P=0.380N	P=0.070
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (f)	13/50 (26%)	11/50 (22%)	21/50 (42%)
Adjusted Rates (b)	35.4%	33.7%	62.4%
Terminal Rates (c)	10/33 (30%)	7/25 (28%)	15/27 (56%)
Week of First Observation	76	79	73
Life Table Tests (d)	P=0.016	P=0.561	P=0.019
Incidental Tumor Tests (d)	P=0.027	P=0.456N	P=0.045
Cochran-Armitage Trend Test (d)	P=0.051		
Fisher Exact Test (d)		P=0.408N	P=0.069
Hematopoietic System: Malignant Lymphoma, Histiocytic Type			
Overall Rates (a)	0/50 (0%)	1/50 (2%)	3/50 (6%)
Adjusted Rates (b)	0.0%	3.7%	8.2%
Terminal Rates (c)	0/33 (0%)	0/25 (0%)	0/27 (0%)
Week of First Observation		101	54
Life Table Tests (d)	P=0.051	P=0.448	P=0.102
Incidental Tumor Tests (d)	P=0.082	P=0.607	P=0.195
Cochran-Armitage Trend Test (d)	P=0.060		
Fisher Exact Test (d)		P=0.500	P=0.121
Hematopoietic System: Malignant Lymphoma, Mixed Type			
Overall Rates (a)	5/50 (10%)	11/50 (22%)	3/50 (6%)
Adjusted Rates (b)	13.7%	36.0%	9.4%
Terminal Rates (c)	3/33 (9%)	6/25 (24%)	2/27 (7%)
Week of First Observation	89	93	71
Life Table Tests (d)	P=0.465N	P=0.036	P=0.450N
Incidental Tumor Tests (d)	P=0.337N	P=0.108	P=0.363N
Cochran-Armitage Trend Test (d)	P=0.326N		
Fisher Exact Test (d)		P=0.086	P=0.357N
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	5/50 (10%)	12/50 (24%)	7/50 (14%)
Adjusted Rates (b)	13.7%	38.4%	18.7%
Terminal Rates (c)	3/33 (9%)	6/25 (24%)	2/27 (7%)
Week of First Observation	89	93	54
Life Table Tests (d)	P=0.229	P=0.021	P=0.294
Incidental Tumor Tests (d)	P=0.392	P=0.076	P=0.485
Cochran-Armitage Trend Test (d)	P=0.341		
Fisher Exact Test (d)		P=0.054	P=0.380
Circulatory System: Hemangiosarcoma			
Overall Rates (a)	1/50 (2%)	4/50 (8%)	2/50 (4%)
Adjusted Rates (b)	2.1%	13.8%	5.8%
Terminal Rates (c)	0/33 (0%)	3/25 (12%)	1/27 (4%)
Week of First Observation	63	87	72
Life Table Tests (d)	P=0.353	P=0.139	P=0.470
Incidental Tumor Tests (d)	P=0.436	P=0.186	P=0.637
Cochran-Armitage Trend Test (d)	P=0.406		
Fisher Exact Test (d)		P=0.181	P=0.500

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF GLYCIDOL (Continued)

	Vehicle Control	25 mg/kg	50 mg/kg
Circulatory System: Hemangioma or Hemangiosarcoma			
Overall Rates (a)	1/50 (2%)	4/50 (8%)	3/50 (6%)
Adjusted Rates (b)	2.1%	13.8%	9.5%
Terminal Rates (c)	0/33 (0%)	3/25 (12%)	2/27 (7%)
Week of First Observation	63	87	72
Life Table Tests (d)	P=0.206	P=0.139	P=0.268
Incidental Tumor Tests (d)	P=0.265	P=0.186	P=0.389
Cochran-Armitage Trend Test (d)	P=0.252		
Fisher Exact Test (d)		P=0.181	P=0.309
Liver: Hepatocellular Adenoma			
Overall Rates (f)	18/50 (36%)	16/50 (32%)	30/50 (60%)
Adjusted Rates (b)	44.4%	50.2%	82.8%
Terminal Rates (c)	11/33 (33%)	10/25 (40%)	21/27 (78%)
Week of First Observation	72	83	73
Life Table Tests (d)	P=0.002	P=0.452	P=0.003
Incidental Tumor Tests (d)	P=0.004	P=0.380N	P=0.008
Cochran-Armitage Trend Test (d)	P=0.010		
Fisher Exact Test (d)		P=0.417N	P=0.014
Liver: Hepatocellular Carcinoma			
Overall Rates (f)	10/50 (20%)	17/50 (34%)	8/50 (16%)
Adjusted Rates (b)	26.6%	40.6%	20.7%
Terminal Rates (c)	7/33 (21%)	6/25 (24%)	2/27 (7%)
Week of First Observation	85	55	52
Life Table Tests (d)	P=0.509N	P=0.055	P=0.530N
Incidental Tumor Tests (d)	P=0.271N	P=0.142	P=0.395N
Cochran-Armitage Trend Test (d)	P=0.361N		
Fisher Exact Test (d)		P=0.088	P=0.398N
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (f)	24/50 (48%)	31/50 (62%)	35/50 (70%)
Adjusted Rates (b)	56.6%	73.8%	84.9%
Terminal Rates (c)	15/33 (45%)	15/25 (60%)	21/27 (78%)
Week of First Observation	72	55	52
Life Table Tests (d)	P=0.007	P=0.040	P=0.007
Incidental Tumor Tests (d)	P=0.018	P=0.204	P=0.017
Cochran-Armitage Trend Test (d)	P=0.016		
Fisher Exact Test (d)		P=0.114	P=0.021
Forestomach: Squamous Cell Papilloma			
Overall Rates (a)	0/50 (0%)	2/50 (4%)	9/50 (18%)
Adjusted Rates (b)	0.0%	5.5%	27.6%
Terminal Rates (c)	0/33 (0%)	0/25 (0%)	5/27 (19%)
Week of First Observation		83	71
Life Table Tests (d)	P<0.001	P=0.208	P=0.001
Incidental Tumor Tests (d)	P<0.001	P=0.367	P=0.003
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P=0.247	P=0.001
Forestomach: Squamous Cell Papilloma or Carcinoma			
Overall Rates (a)	1/50 (2%)	2/50 (4%)	10/50 (20%)
Adjusted Rates (b)	3.0%	5.5%	29.4%
Terminal Rates (c)	1/33 (3%)	0/25 (0%)	5/27 (19%)
Week of First Observation	104	83	71
Life Table Tests (d)	P<0.001	P=0.439	P=0.003
Incidental Tumor Tests (d)	P<0.001	P=0.593	P=0.005
Cochran-Armitage Trend Test (d)	P=0.001		
Fisher Exact Test (d)		P=0.500	P=0.004

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF GLYCIDOL (Continued)

	Vehicle Control	25 mg/kg	50 mg/kg
Small Intestine: Adenomatous Polyp or Adenocarcinoma			
Overall Rates (a)	2/50 (4%)	4/50 (8%)	0/50 (0%)
Adjusted Rates (b)	5.0%	12.9%	0.0%
Terminal Rates (c)	1/33 (3%)	2/25 (8%)	0/27 (0%)
Week of First Observation	45	87	
Life Table Tests (d)	P=0.273N	P=0.268	P=0.262N
Incidental Tumor Tests (d)	P=0.252N	P=0.193	P=0.262N
Cochran-Armitage Trend Test (d)	P=0.222N		
Fisher Exact Test (d)		P=0.339	P=0.247N
Adrenal Capsule: Adenoma			
Overall Rates (f)	2/50 (4%)	1/50 (2%)	5/50 (10%)
Adjusted Rates (b)	6.1%	3.6%	16.0%
Terminal Rates (c)	2/33 (6%)	0/25 (0%)	3/27 (11%)
Week of First Observation	104	100	93
Life Table Tests (d)	P=0.097	P=0.584N	P=0.155
Incidental Tumor Tests (d)	P=0.117	P=0.503N	P=0.188
Cochran-Armitage Trend Test (d)	P=0.133		
Fisher Exact Test (d)		P=0.500N	P=0.218
Adrenal Medulla: Pheochromocytoma			
Overall Rates (f)	3/50 (6%)	0/50 (0%)	1/50 (2%)
Adjusted Rates (b)	9.1%	0.0%	3.7%
Terminal Rates (c)	3/33 (9%)	0/25 (0%)	1/27 (4%)
Week of First Observation	104		104
Life Table Tests (d)	P=0.228N	P=0.165N	P=0.378N
Incidental Tumor Tests (d)	P=0.229N	P=0.173N	P=0.378N
Cochran-Armitage Trend Test (d)	P=0.176N		
Fisher Exact Test (d)		P=0.121N	P=0.309N
Harderian Gland: Adenoma			
Overall Rates (f)	7/46 (15%)	10/41 (24%)	16/44 (36%)
Adjusted Rates (b)	20.2%	34.6%	48.4%
Terminal Rates (c)	6/33 (18%)	8/25 (32%)	11/27 (41%)
Week of First Observation	96	93	73
Life Table Tests (d)	P=0.006	P=0.146	P=0.009
Incidental Tumor Tests (d)	P=0.010	P=0.184	P=0.018
Cochran-Armitage Trend Test (d)	P=0.014		
Fisher Exact Test (d)		P=0.210	P=0.019
Harderian Gland: Adenocarcinoma			
Overall Rates (f)	1/46 (2%)	2/41 (5%)	7/44 (16%)
Adjusted Rates (b)	3.0%	5.0%	21.0%
Terminal Rates (c)	1/33 (3%)	0/25 (0%)	4/27 (15%)
Week of First Observation	104	83	72
Life Table Tests (d)	P=0.011	P=0.453	P=0.021
Incidental Tumor Tests (d)	P=0.013	P=0.397	P=0.037
Cochran-Armitage Trend Test (d)	P=0.012		
Fisher Exact Test (d)		P=0.456	P=0.025
Harderian Gland: Adenoma or Adenocarcinoma			
Overall Rates (f)	8/46 (17%)	12/41 (29%)	22/44 (50%)
Adjusted Rates (b)	23.2%	37.9%	61.1%
Terminal Rates (c)	7/33 (21%)	8/25 (32%)	14/27 (52%)
Week of First Observation	96	83	72
Life Table Tests (d)	P<0.001	P=0.103	P<0.001
Incidental Tumor Tests (d)	P<0.001	P=0.115	P=0.001
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P=0.145	P=0.001

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF GLYCIDOL (Continued)

	Vehicle Control	25 mg/kg	50 mg/kg
All Sites: Benign Tumors			
Overall Rates (a)	28/50 (56%)	35/50 (70%)	38/50 (76%)
Adjusted Rates (b)	66.2%	87.3%	94.9%
Terminal Rates (c)	19/33 (58%)	20/25 (80%)	25/27 (93%)
Week of First Observation	72	79	71
Life Table Tests (d)	P=0.004	P=0.018	P=0.005
Incidental Tumor Tests (d)	P=0.005	P=0.128	P=0.014
Cochran-Armitage Trend Test (d)	P=0.021		
Fisher Exact Test (d)		P=0.107	P=0.028
All Sites: Malignant Tumors			
Overall Rates (a)	28/50 (56%)	38/50 (76%)	38/50 (76%)
Adjusted Rates (b)	61.6%	80.4%	84.0%
Terminal Rates (c)	16/33 (48%)	16/25 (64%)	20/27 (74%)
Week of First Observation	45	55	52
Life Table Tests (d)	P=0.015	P=0.016	P=0.016
Incidental Tumor Tests (d)	P=0.032	P=0.085	P=0.035
Cochran-Armitage Trend Test (d)	P=0.020		
Fisher Exact Test (d)		P=0.028	P=0.028
All Sites: All Tumors			
Overall Rates (a)	42/50 (84%)	47/50 (94%)	49/50 (98%)
Adjusted Rates (b)	87.4%	94.0%	100.0%
Terminal Rates (c)	27/33 (82%)	22/25 (88%)	27/27 (100%)
Week of First Observation	45	55	52
Life Table Tests (d)	P=0.019	P=0.038	P=0.019
Incidental Tumor Tests (d)	P=0.016	P=0.244	P=0.024
Cochran-Armitage Trend Test (d)	P=0.008		
Fisher Exact Test (d)		P=0.100	P=0.015

(a) Number of tumor-bearing animals/number of animals examined grossly at the site
(b) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence in animals killed at the end of the study
(d) Beneath the vehicle 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 vehicle 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 nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group than in vehicle controls is indicated by (N).
(e) No P value is reported because no tumors were observed in the dosed and vehicle control groups
(f) Number of tumor-bearing animals/number of animals examined microscopically at the site

TABLE C4a. HISTORICAL INCIDENCE OF HARDERIAN GLAND TUMORS IN MALE B6C3F$_1$ MICE (a)

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence for All Water Gavage Vehicle Controls			
Iodinated glycerol (b)	4/50	0/50	4/50
Chlorpheniramine maleate (c)	6/50	(d) 1/50	7/50
Tetrakis(hydroxymethyl)phosphonium chloride (c)	1/50	0/50	1/50
Malonaldehyde, sodium salt (c)	3/50	0/50	3/50
Tetrakis(hydroxymethyl)phosphonium sulfate (c)	1/50	(e) 1/50	2/50
Methyl carbamate (f)	2/50	0/50	2/50
Chlorinated trisodium phosphate (b)	3/50	0/50	3/50
TOTAL	20/350 (5.7%)	2/350 (0.6%)	22/350 (6.3%)
SD (g)	3.55%	0.98%	3.90%
Range (h)			
High	6/50	1/50	7/50
Low	1/50	0/50	1/50
Overall Historical Incidence for Untreated Controls			
TOTAL	(i) 61/1,692 (3.6%)	(j) 6/1,692 (0.4%)	(i,j) 67/1,692 (4.0%)
SD (g)	3.23%	0.78%	3.14%
Range (h)			
High	6/50	1/49	6/50
Low	0/50	0/50	0/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Study conducted at EG&G Mason Research Institute
(c) Study conducted at Battelle Columbus Laboratories
(d) Adenocarcinoma, NOS
(e) Papillary adenocarcinoma
(f) Study conducted at Microbiological Associates, Inc.
(g) Standard deviation
(h) Range and SD are presented for groups of 35 or more animals.
(i) Includes five papillary adenomas, five cystadenomas, NOS, and six papillary cystadenomas, NOS
(j) Includes two adenocarcinomas, NOS

TABLE C4b. HISTORICAL INCIDENCE OF INTEGUMENTARY SYSTEM SQUAMOUS CELL TUMORS IN MALE B6C3F$_1$ MICE (a)

Study	Incidence in Controls		
	Papilloma	Carcinoma	Papilloma or Carcinoma
Historical Incidence for All Water Gavage Vehicle Controls			
Iodinated glycerol (b)	0/50	0/50	0/50
Chlorpheniramine maleate (c)	0/50	0/50	0/50
Tetrakis(hydroxymethyl)phosphonium chloride (c)	0/50	0/50	0/50
Malonaldehyde, sodium salt (c)	0/50	0/50	0/50
Tetrakis(hydroxymethyl)phosphonium sulfate (c)	2/50	0/50	2/50
Methyl carbamate (d)	0/50	0/50	0/50
Chlorinated trisodium phosphate (b)	0/50	0/50	0/50
TOTAL	2/350 (0.6%)	0/350	2/350 (0.6%)
SD (e)	1.51%	0.00%	1.51%
Range (f)			
High	2/50	0/50	2/50
Low	0/50	0/50	0/50
Overall Historical Incidence for Untreated Controls			
TOTAL	(g) 4/1,692 (0.2%)	5/1,692 (0.3%)	(g) 9/1,692 (0.5%)
SD (e)	0.82%	0.72%	1.02%
Range (f)			
High	2/50	1/49	2/50
Low	0/50	0/50	0/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Study conducted at EG&G Mason Research Institute
(c) Study conducted at Battelle Columbus Laboratories
(f) Study conducted at Microbiological Associates, Inc.
(e) Standard deviation
(f) Range and SD are presented for groups of 35 or more animals.
(g) Includes one papilloma, NOS

TABLE C4c. HISTORICAL INCIDENCE OF FORESTOMACH SQUAMOUS CELL TUMORS IN MALE $B6C3F_1$ MICE (a)

Study	Incidence in Controls		
	Papilloma	Carcinoma	Papilloma or Carcinoma
Historical Incidence for All Water Gavage Vehicle Controls			
Iodinated glycerol (b)	0/49	0/49	0/49
Chlorpheniramine maleate (c)	1/50	1/50	2/50
Tetrakis(hydroxymethyl)phosphonium chloride (c)	0/47	1/47	1/47
Malonaldehyde, sodium salt (c)	0/44	0/44	0/44
Tetrakis(hydroxymethyl)phosphonium sulfate (c)	0/41	0/41	0/41
Methyl carbamate (d)	2/50	0/50	2/50
Chlorinated trisodium phosphate (b)	3/50	0/50	3/50
TOTAL	6/331 (1.8%)	2/331 (0.6%)	8/331 (2.4%)
SD (e)	2.43%	1.01%	2.43%
Range (f)			
High	3/50	1/47	3/50
Low	0/49	0/50	0/49
Overall Historical Incidence for Untreated Controls			
TOTAL	(g) 9/1,645 (0.5%)	1/1,645 (0.1%)	(g) 10/1,645 (0.6%)
SD (e)	1.16%	0.34%	1.19%
Range (f)			
High	2/49	1/50	2/49
Low	0/50	0/50	0/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Study conducted at EG&G Mason Research Institute
(c) Study conducted at Battelle Columbus Laboratories
(d) Study conducted at Microbiological Associates, Inc.
(e) Standard deviation
(f) Range and SD are presented for groups of 35 or more animals.
(g) Includes one papilloma, NOS

TABLE C4d. HISTORICAL INCIDENCE OF HEPATOCELLULAR TUMORS IN MALE B6C3F$_1$ MICE (a)

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence for All Water Gavage Vehicle Controls			
Iodinated glycerol (b)	8/50	2/50	10/50
Chlorpheniramine maleate (c)	10/50	6/50	16/50
Tetrakis(hydroxymethyl)phosphonium chloride (c)	8/49	10/49	17/49
Malonaldehyde, sodium salt (c)	4/50	14/50	17/50
Tetrakis(hydroxymethyl)phosphonium sulfate (c)	9/48	10/48	18/48
Methyl carbamate (d)	9/50	5/50	14/50
Chlorinated trisodium phosphate (b)	6/50	9/50	14/50
TOTAL	54/347 (15.6%)	56/347 (16.1%)	106/347 (30.5%)
SD (e)	4.21%	8.03%	5.83%
Range (f)			
High	10/50	14/50	18/48
Low	4/50	2/50	10/50
Overall Historical Incidence for Untreated Controls			
TOTAL	233/1,678 (13.9%)	285/1,678 (17.0%)	494/1,678 (29.4%)
SD (e)	7.50%	6.31%	8.04%
Range (f)			
High	22/50	15/50	29/50
Low	2/45	4/50	7/48

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Study conducted at EG&G Mason Research Institute
(c) Study conducted at Battelle Columbus Laboratories
(d) Study conducted at Microbiological Associates, Inc.
(e) Standard deviation
(f) Range and SD are presented for groups of 35 or more animals.

TABLE C4e. HISTORICAL INCIDENCE OF ALVEOLAR/BRONCHIOLAR TUMORS IN MALE B6C3F$_1$ MICE (a)

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence for All Water Gavage Vehicle Controls			
Iodinated glycerol (b)	8/50	1/50	9/50
Chlorpheniramine maleate (c)	12/50	5/50	16/50
Tetrakis(hydroxymethyl)phosphonium chloride (c)	1/50	3/50	4/50
Malonaldehyde, sodium salt (c)	7/47	5/47	10/47
Tetrakis(hydroxymethyl)phosphonium sulfate (c)	5/50	2/50	7/50
Methyl carbamate (d)	11/50	0/50	11/50
Chlorinated trisodium phosphate (b)	2/50	6/50	8/50
TOTAL	46/347 (13.3%)	22/347 (6.3%)	65/347 (18.7%)
SD (e)	8.42%	4.63%	7.51%
Range (f)			
High	12/50	6/50	16/50
Low	1/50	0/50	4/50
Overall Historical Incidence for Untreated Controls			
TOTAL	204/1,684 (12.1%)	80/1,684 (4.8%)	277/1,684 (16.4%)
SD (e)	6.18%	2.70%	6.91%
Range (f)			
High	14/50	5/49	17/50
Low	1/50	0/49	4/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Study conducted at EG&G Mason Research Institute
(c) Study conducted at Battelle Columbus Laboratories
(d) Study conducted at Microbiological Associates, Inc.
(e) Standard deviation
(f) Range and SD are presented for groups of 35 or more animals.

TABLE C4f. HISTORICAL INCIDENCE OF HEMATOPOIETIC SYSTEM TUMORS IN MALE B6C3F$_1$ MICE (a)

Study	Incidence in Controls	
	Lymphoma	Lymphoma or Leukemia
Historical Incidence for All Water Gavage Vehicle Controls		
Iodinated glycerol (b)	10/50	10/50
Chlorpheniramine maleate (c)	9/50	9/50
Tetrakis(hydroxymethyl)phosphonium chloride (c)	9/50	9/50
Malonaldehyde, sodium salt (c)	4/50	4/50
Tetrakis(hydroxymethyl)phosphonium sulfate (c)	2/50	2/50
Methyl carbamate (d)	4/50	4/50
Chlorinated trisodium phosphate (b)	4/50	4/50
TOTAL	42/350 (12.0%)	42/350 (12.0%)
SD (e)	6.43%	6.43%
Range (f)		
High	10/50	10/50
Low	2/50	2/50
Overall Historical Incidence for Untreated Controls		
TOTAL	193/1,692 (11.4%)	196/1,692 (11.6%)
SD (e)	6.07%	6.31%
Range (f)		
High	13/50	14/50
Low	1/50	1/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Study conducted at EG&G Mason Research Institute
(c) Study conducted at Battelle Columbus Laboratories
(d) Study conducted at Microbiological Associates, Inc.
(e) Standard deviation
(f) Range and SD are presented for groups of 35 or more animals.

TABLE C4g. HISTORICAL INCIDENCE OF URINARY BLADDER TUMORS IN MALE B6C3F$_1$ MICE (a)

	Number Examined	Number of Tumors
Historical Incidence for All Water Gavage Vehicle Controls		
	350	0
Overall Historical Incidence for Untreated Controls		
	1,647	0

(a) Data as of May 12, 1988, for studies of at least 104 weeks

TABLE C4h. HISTORICAL INCIDENCE OF EPIDIDYMAL SARCOMAS IN MALE B6C3F$_1$ MICE (a)

	Number Examined	Number of Tumors	Diagnosis
Historical Incidence for All Water Gavage Vehicle Controls			
	350	0	
Overall Historical Incidence for Untreated Controls			
	1,692	1	Sarcoma, NOS

(a) Data as of May 12, 1988, for studies of at least 104 weeks

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF GLYCIDOL

	Vehicle Control	25 mg/kg	50 mg/kg
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, chronic		1 (2%)	1 (2%)
Scar	2 (4%)		
Hyperplasia, NOS			1 (2%)
Acanthosis	1 (2%)		
*Subcutaneous tissue	(50)	(50)	(50)
Scar		2 (4%)	
RESPIRATORY SYSTEM			
#Nasal cavity	(49)	(50)	(50)
Inflammation, NOS	2 (4%)	5 (10%)	1 (2%)
Metaplasia, squamous	1 (2%)		
#Nose	(49)	(50)	(50)
Polyp, inflammatory			1 (2%)
#Lung/bronchus	(50)	(50)	(50)
Inflammation, suppurative			1 (2%)
#Lung	(50)	(50)	(50)
Hemorrhage		1 (2%)	1 (2%)
Inflammation, chronic focal			1 (2%)
Inflammation, granulomatous		2 (4%)	
Hyperplasia, alveolar epithelium	5 (10%)	4 (8%)	3 (6%)
Histiocytosis			1 (2%)
HEMATOPOIETIC SYSTEM			
#Bone marrow	(50)	(50)	(50)
Hyperplasia, hematopoietic	2 (4%)		
#Spleen	(50)	(50)	(50)
Fibrosis, focal		1 (2%)	
Hyperplasia, lymphoid		1 (2%)	
#Splenic red pulp	(50)	(50)	(50)
Hyperplasia, NOS	10 (20%)	4 (8%)	7 (14%)
#Lymph node	(49)	(50)	(50)
Hemorrhage			2 (4%)
Hyperplasia, NOS	2 (4%)		2 (4%)
Hyperplasia, megakaryocytic	1 (2%)		
Myelopoiesis			1 (2%)
#Mesenteric lymph node	(49)	(50)	(50)
Hyperplasia, lymphoid		2 (4%)	
#Lung	(50)	(50)	(50)
Leukocytosis, NOS			1 (2%)
#Liver	(50)	(50)	(50)
Myelopoiesis	1 (2%)	1 (2%)	
#Peyer's patch	(50)	(50)	(50)
Hyperplasia, lymphoid			1 (2%)
#Kidney	(50)	(50)	(50)
Hyperplasia, lymphoid		5 (10%)	
#Adrenal cortex	(50)	(50)	(50)
Myelopoiesis		1 (2%)	
CIRCULATORY SYSTEM			
#Lymph node	(49)	(50)	(50)
Thrombosis, NOS		3 (6%)	

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF GLYCIDOL (Continued)

	Vehicle Control	25 mg/kg	50 mg/kg
CIRCULATORY SYSTEM (Continued)			
#Heart	(50)	(50)	(50)
Inflammation, NOS	3 (6%)		2 (4%)
#Myocardium	(50)	(50)	(50)
Degeneration, NOS		3 (6%)	
*Artery	(50)	(50)	(50)
Periarteritis	3 (6%)	1 (2%)	
*Vein	(50)	(50)	(50)
Thrombosis, NOS		1 (2%)	
DIGESTIVE SYSTEM			
*Tooth	(50)	(50)	(50)
Inflammation, NOS	6 (12%)	2 (4%)	2 (4%)
Dysplasia, NOS	15 (30%)	17 (34%)	22 (44%)
#Liver	(50)	(50)	(50)
Inflammation, chronic focal	1 (2%)	1 (2%)	1 (2%)
Scar	1 (2%)		
Degeneration, lipoid			1 (2%)
Necrosis, coagulative	5 (10%)	5 (10%)	5 (10%)
Nuclear alteration	1 (2%)		2 (4%)
Basophilic cyto change	1 (2%)	1 (2%)	2 (4%)
Eosinophilic cyto change	1 (2%)	1 (2%)	1 (2%)
Clear cell change	2 (4%)		4 (8%)
Hyperplasia, focal		1 (2%)	
*Gallbladder	(50)	(50)	(50)
Distention		1 (2%)	
#Pancreas	(50)	(50)	(50)
Edema, NOS	1 (2%)		
Inflammation, acute			1 (2%)
Atrophy, NOS	1 (2%)	2 (4%)	1 (2%)
#Glandular stomach	(50)	(50)	(50)
Inflammation, NOS	3 (6%)	1 (2%)	1 (2%)
Atrophy, NOS			1 (2%)
Hyperplasia, focal			2 (4%)
#Forestomach	(50)	(50)	(50)
Inflammation, acute		1 (2%)	
Inflammation, acute focal	1 (2%)		1 (2%)
Ulcer, chronic			3 (6%)
Inflammation, chronic focal	1 (2%)		1 (2%)
Hyperplasia, epithelial	2 (4%)	4 (8%)	8 (16%)
Hyperkeratosis	3 (6%)	8 (16%)	7 (14%)
URINARY SYSTEM			
#Kidney	(50)	(50)	(50)
Cyst, NOS	4 (8%)	11 (22%)	9 (18%)
Inflammation, acute	2 (4%)		
Inflammation, acute focal		1 (2%)	
Nephropathy	1 (2%)	1 (2%)	1 (2%)
Metaplasia, osseous	1 (2%)		
#Kidney/tubule	(50)	(50)	(50)
Degeneration, NOS	1 (2%)		
#Kidney/pelvis	(50)	(50)	(50)
Inflammation, acute		1 (2%)	
#Urinary bladder	(50)	(50)	(50)
Hyperplasia, epithelial	1 (2%)	1 (2%)	1 (2%)
*Urethra	(50)	(50)	(50)
Inflammation, acute			1 (2%)

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF GLYCIDOL (Continued)

	Vehicle Control	25 mg/kg	50 mg/kg
ENDOCRINE SYSTEM			
#Anterior pituitary	(49)	(50)	(50)
Cyst, NOS		1 (2%)	2 (4%)
Hyperplasia, focal	1 (2%)		
Angiectasis			1 (2%)
#Adrenal/capsule	(50)	(50)	(50)
Hyperplasia, focal	2 (4%)	3 (6%)	2 (4%)
#Adrenal cortex	(50)	(50)	(50)
Cyst, NOS		1 (2%)	
Hypertrophy, NOS	1 (2%)		
Hypertrophy, focal	2 (4%)	1 (2%)	4 (8%)
Hyperplasia, focal		4 (8%)	6 (12%)
#Adrenal medulla	(50)	(50)	(50)
Hyperplasia, focal	2 (4%)	3 (6%)	
#Thyroid	(49)	(49)	(50)
Follicular cyst, NOS		1 (2%)	
Hyperplasia, follicular cell	2 (4%)	1 (2%)	2 (4%)
#Parathyroid	(47)	(41)	(47)
Cyst, NOS		1 (2%)	
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Inflammation, chronic		1 (2%)	
*Bulbourethral gland	(50)	(50)	(50)
Hemorrhage	1 (2%)		
*Preputial gland	(50)	(50)	(50)
Cyst, NOS	1 (2%)		7 (14%)
Inflammation, NOS	8 (16%)	15 (30%)	11 (22%)
Hyperplasia, NOS		4 (8%)	
Hyperkeratosis		1 (2%)	
#Prostate	(50)	(50)	(50)
Inflammation, suppurative	1 (2%)		
Inflammation, chronic			1 (2%)
*Seminal vesicle	(50)	(50)	(50)
Dilatation, NOS	1 (2%)		
Hemorrhage			1 (2%)
Inflammation, chronic	2 (4%)		
#Testis/tubule	(50)	(50)	(50)
Mineralization	1 (2%)		
Dilatation, NOS			1 (2%)
*Epididymis	(50)	(50)	(50)
Inflammation, chronic			2 (4%)
Inflammation, granulomatous		1 (2%)	1 (2%)
NERVOUS SYSTEM			
#Brain/meninges	(50)	(50)	(50)
Inflammation, chronic	2 (4%)		1 (2%)
#Brain	(50)	(50)	(50)
Mineralization	4 (8%)		3 (6%)
Hemorrhage		1 (2%)	1 (2%)
SPECIAL SENSE ORGANS			
*Eye	(50)	(50)	(50)
Degeneration, NOS		1 (2%)	
*Eye/cornea	(50)	(50)	(50)
Congenital malformation, NOS		1 (2%)	
Inflammation, chronic	4 (8%)		2 (4%)

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF GLYCIDOL (Continued)

	Vehicle Control	25 mg/kg	50 mg/kg
SPECIAL SENSE ORGANS (Continued)			
*Eye/retina	(50)	(50)	(50)
Degeneration, NOS	1 (2%)		
*Eye/crystalline lens	(50)	(50)	(50)
Cataract			1 (2%)
*Harderian gland	(50)	(50)	(50)
Inflammation, NOS	1 (2%)		
Hyperplasia, NOS			3 (6%)
MUSCULOSKELETAL SYSTEM			
*Bone	(50)	(50)	(50)
Fracture, NOS	1 (2%)		
Hyperplasia, focal	1 (2%)		2 (4%)
BODY CAVITIES			
None			
ALL OTHER SYSTEMS			
Adipose tissue			
Necrosis, fat	2		2
SPECIAL MORPHOLOGY SUMMARY			
No lesion reported	1		

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
# Number of animals examined microscopically at this site

APPENDIX D

SUMMARY OF LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF GLYCIDOL

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF GLYCIDOL

	Vehicle Control	25 mg/kg	50 mg/kg
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%)
Squamous cell carcinoma			1 (2%)
Sebaceous adenoma		1 (2%)	
*Subcutaneous tissue	(50)	(50)	(50)
Sarcoma, NOS		1 (2%)	6 (12%)
Fibrosarcoma		2 (4%)	3 (6%)
RESPIRATORY SYSTEM			
#Lung	(50)	(50)	(50)
Adenocarcinoma, NOS, metastatic	1 (2%)	1 (2%)	4 (8%)
Hepatocellular carcinoma, metastatic		1 (2%)	1 (2%)
Alveolar/bronchiolar adenoma	3 (6%)	4 (8%)	5 (10%)
Alveolar/bronchiolar carcinoma	3 (6%)	6 (12%)	3 (6%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Malignant lymphoma, undifferentiated type	2 (4%)		1 (2%)
Malignant lymphoma, lymphocytic type	3 (6%)	2 (4%)	1 (2%)
Malignant lymphoma, histiocytic type	1 (2%)	1 (2%)	2 (4%)
Malignant lymphoma, mixed type	11 (22%)	19 (38%)	11 (22%)
#Mesenteric lymph node	(50)	(50)	(50)
Malignant lymphoma, mixed type			2 (4%)
#Liver	(50)	(50)	(50)
Malignant lymphoma, undifferentiated type	1 (2%)		
Malignant lymphoma, histiocytic type			1 (2%)
#Forestomach	(50)	(50)	(50)
Mast cell tumor			1 (2%)
#Jejunum	(50)	(50)	(50)
Malignant lymphoma, mixed type			1 (2%)
CIRCULATORY SYSTEM			
*Peritoneal cavity	(50)	(50)	(50)
Hemangiosarcoma		1 (2%)	
*Subcutaneous tissue	(50)	(50)	(50)
Hemangiosarcoma		1 (2%)	
#Liver	(50)	(50)	(50)
Hemangioma			1 (2%)
Hemangiosarcoma			1 (2%)
#Uterus	(50)	(50)	(50)
Hemangioma		1 (2%)	
Hemangiosarcoma	1 (2%)		2 (4%)
#Ovary	(50)	(50)	(50)
Hemangioma			1 (2%)
DIGESTIVE SYSTEM			
#Liver	(50)	(50)	(50)
Hepatocellular adenoma	6 (12%)	3 (6%)	10 (20%)
Hepatocellular carcinoma	3 (6%)	5 (10%)	4 (8%)
#Pancreas	(50)	(50)	(50)
Sarcoma, NOS, invasive			1 (2%)

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF GLYCIDOL (Continued)

	Vehicle Control	25 mg/kg	50 mg/kg
DIGESTIVE SYSTEM (Continued)			
#Forestomach	(50)	(50)	(50)
Squamous cell papilloma	3 (6%)	1 (2%)	4 (8%)
#Duodenum	(50)	(50)	(50)
Adenomatous polyp, NOS		2 (4%)	
#Jejunum	(50)	(50)	(50)
Leiomyosarcoma			1 (2%)
#Ileum	(50)	(50)	(50)
Adenocarcinoma, NOS			1 (2%)
URINARY SYSTEM			
#Kidney	(50)	(50)	(50)
Tubular cell adenocarcinoma		1 (2%)	
ENDOCRINE SYSTEM			
#Pituitary pars intermedia	(49)	(49)	(49)
Adenoma, NOS	1 (2%)		
#Anterior pituitary	(49)	(49)	(49)
Adenoma, NOS	18 (37%)	5 (10%)	14 (29%)
#Adrenal	(50)	(50)	(50)
Cortical adenoma		1 (2%)	1 (2%)
#Adrenal/capsule	(50)	(50)	(50)
Adenoma, NOS	3 (6%)	1 (2%)	
#Thyroid	(50)	(50)	(50)
Adenoma, NOS	1 (2%)		
Follicular cell adenoma	1 (2%)	2 (4%)	
C-cell adenoma		1 (2%)	
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Adenoma, NOS		1 (2%)	
Adenocarcinoma, NOS	1 (2%)	5 (10%)	15 (30%)
Fibroadenoma	1 (2%)		
#Uterus	(50)	(50)	(50)
Carcinoma, NOS			1 (2%)
Adenocarcinoma, NOS		3 (6%)	2 (4%)
Sarcoma, NOS		1 (2%)	
Leiomyosarcoma	1 (2%)		1 (2%)
Endometrial stromal polyp	2 (4%)	3 (6%)	5 (10%)
#Ovary	(50)	(50)	(50)
Papillary cystadenoma, NOS	1 (2%)		
Luteoma		1 (2%)	
#Ovary/granulosa cell	(50)	(50)	(50)
Adenoma, NOS		1 (2%)	
NERVOUS SYSTEM			
#Brain	(50)	(49)	(50)
Adenocarcinoma, NOS, invasive			1 (2%)
SPECIAL SENSE ORGANS			
*Harderian gland	(50)	(50)	(50)
Adenoma, NOS	4 (8%)	10 (20%)	16 (32%)
Adenocarcinoma, NOS		1 (2%)	1 (2%)

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF GLYCIDOL (Continued)

	Vehicle Control	25 mg/kg	50 mg/kg
MUSCULOSKELETAL SYSTEM			
*Skeletal muscle	(50)	(50)	(50)
Sarcoma, NOS	1 (2%)	1 (2%)	1 (2%)
Sarcoma, NOS, invasive			1 (2%)
BODY CAVITIES			
*Peritoneum	(50)	(50)	(50)
Sarcoma, NOS		1 (2%)	
*Peritoneal mesothelium	(50)	(50)	(50)
Mesothelioma, metastatic	1 (2%)		
*Pleural cavity	(50)	(50)	(50)
Mesothelioma, malignant			1 (2%)
*Pleura	(50)	(50)	(50)
Mesothelioma, malignant	1 (2%)		
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Mesothelioma, malignant			1 (2%)
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	3	5	5
Moribund sacrifice	18	18	27
Terminal sacrifice	29	27	17
Accidentally killed, NDA			1
TUMOR SUMMARY			
Total animals with primary tumors**	45	46	47
Total primary tumors	73	89	123
Total animals with benign tumors	28	25	32
Total benign tumors	44	38	58
Total animals with malignant tumors	28	35	40
Total malignant tumors	29	51	64
Total animals with secondary tumors##	2	2	8
Total secondary tumors	2	2	8
Total animals with tumors-- uncertain benign or malignant			1
Total uncertain tumors			1

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
** Primary tumors: all tumors except secondary tumors
# Number of animals examined microscopically at this site
Secondary tumors: metastatic tumors or tumors invasive into an adjacent organ

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF GLYCIDOL: VEHICLE CONTROL

ANIMAL NUMBER	0024	0022	0015	0027	0008	0037	0028	0005	0029	0020	0017	0031	0043	0001	0004	0023	0021	0030	0010	0042	0002	0003	0006	0007	0009
WEEKS ON STUDY	028	055	071	076	076	080	085	087	089	091	091	092	093	095	097	098	099	099	099	100	100	100	104	104	104
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS, metastatic														X											
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																					X	X		X	
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+
Nasal cavity	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																							X		
Hepatocellular carcinoma																									X
Malignant lymphoma, undifferentiated type																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS						X				X	X						X	X		X			X	X	X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																		X							
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Follicular cell adenoma																									
Parathyroid	–	–	+	–	+	+	+	+	+	+	–	–	+	+	+	–	–	+	+	+	+	+	+	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS														X											
Fibroadenoma																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma																									
Endometrial stromal polyp								X																	
Hemangiosarcoma																			X						
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papillary cystadenoma, 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	N
Adenoma, NOS														X											
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
Sarcoma, NOS																X									
BODY CAVITIES																									
Pleura	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Mesothelioma, malignant																	X								
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
Mesothelioma, metastatic																	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, undifferentiated type				X	X																				
Malignant lymphoma, lymphocytic type	X	X																			X				
Malignant lymphoma, histiocytic typee												X													
Malignant lymphoma, mixed type			X			X	X	X			X		X		X					X					

+: Tissue examined microscopically
–: Required tissue not examined microscopically
X: Tumor incidence
N: Necropsy, no autolysis, no microscopic examination
S: Animal missexed
.: No tissue information submitted
C: Necropsy, no histology due to protocol
A: Autolysis
M: Animal missing
B: No necropsy performed

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: VEHICLE CONTROL (Continued)

ANIMAL NUMBER	0111	0112	0113	0114	0116	0118	0119	0025	0026	0032	0033	0034	0035	0036	0038	0039	0040	0041	0044	0045	0046	0047	0048	0049	0050	TOTAL:
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	TISSUES TUMORS
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS, metastatic																										1
Alveolar/bronchiolar adenoma											X			X					X							3
Alveolar/bronchiolar carcinoma																										3
Trachea	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma			X				X					X				X					X					6
Hepatocellular carcinoma	X																								X	3
Malig. lymphoma, undifferentiated type				X																						1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma			X																X					X		3
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, NOS		X	X		X		X	X		X				X		X					X			X		19
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS													X					X								3
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS																			X							1
Follicular cell adenoma							X																			1
Parathyroid	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	42
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenocarcinoma, NOS																										1
Fibroadenoma			X																							1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma																			X							1
Endometrial stromal polyp									X																	2
Hemangiosarcoma																										1
Ovary	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Papillary cystadenoma, 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	*50
Adenoma, NOS												X									X			X		4
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	*50
Sarcoma, NOS																										1
BODY CAVITIES																										
Pleura	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Mesothelioma, malignant																										1
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, metastatic																										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
Malig. lymphoma, undifferentiated type																										2
Malig. lymphoma, lymphocytic type																										3
Malig. lymphoma, histiocytic type																										1
Malignant lymphoma, mixed type						X								X								X				11

* Animals necropsied

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF GLYCIDOL: 25 mg/kg

ANIMAL NUMBER	0 1 0	0 2 1	0 1 5	0 1 9	0 3 2	0 1 6	0 4 3	0 0 7	0 4 9	0 0 9	0 2 5	0 4 7	0 2 4	0 3 5	0 4 0	0 3 8	0 2 6	0 0 5	0 2 3	0 4 4	0 4 2	0 1 7	0 0 4	0 0 1	0 0 2
WEEKS ON STUDY	0 6 2	0 6 6	0 7 0	0 7 6	0 7 8	0 8 4	0 8 4	0 8 4	0 8 4	0 8 5	0 8 7	0 8 7	0 8 8	0 8 8	0 8 9	0 9 0	0 9 0	0 9 2	0 9 6	0 9 6	0 9 8	0 9 8	1 0 1	1 0 4	1 0 4
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sebaceous adenoma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																				X					
Fibrosarcoma			X					X																	
Hemangiosarcoma		X																							
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS, metastatic																X									
Hepatocellular carcinoma, metastatic						X																			
Alveolar/bronchiolar adenoma																									X
Alveolar/bronchiolar carcinoma																				X			X		
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Hepatocellular carcinoma						X											X								
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenomatous polyp, NOS											X														
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenocarcinoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: 25 mg/kg (Continued)

ANIMAL NUMBER	00303	00306	00308	01101	01102	01103	01104	01108	02000	02202	02207	02208	02209	03001	03301	03303	03304	03306	03307	03309	04101	04505	04606	04808	05000	TOTAL:
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sebaceous adenoma															X											1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS																										1
Fibrosarcoma																										2
Hemangiosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	50
Adenocarcinoma, NOS, metastatic																										1
Hepatocellular carcinoma, metastatic																										1
Alveolar/bronchiolar adenoma					X						X											X				4
Alveolar/bronchiolar carcinoma		X						X					X								X					6
Trachea	+	+	+	+	+	–	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	49
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	–	+	+	+	+	+	–	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	50
Spleen	+	+	–	+	+	+	+	+	–	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	–	+	+	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma												X					X			X						3
Hepatocellular carcinoma												X												X	X	5
Bile duct	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	–	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	–	+	+	50
Squamous cell papilloma																			X							1
Small intestine	+	–	+	+	+	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenomatous polyp, NOS																									X	2
Large intestine	+	+	+	+	+	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tubular cell adenocarcinoma	X																									1
Urinary bladder	+	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

* Animals necropsied

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: 25 mg/kg (Continued)

ANIMAL NUMBER	0010	0021	0159	0193	0326	0164	0433	0007	0499	0099	0255	0477	0244	0355	0400	0388	0266	0055	0233	0444	0422	0177	0044	0101	0002
WEEKS ON STUDY	062	066	070	076	078	084	084	084	084	085	087	087	088	088	089	090	090	092	096	096	098	098	101	104	104
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																						X		X	
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Cortical adenoma														X											
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma													X												
C-cell adenoma																									
Parathyroid	+	–	+	–	–	+	+	+	+	+	–	+	+	+	+	+	+	+	+	–	+	+	+	–	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																			X						
Adenocarcinoma, NOS										X						X				X		X			
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																									
Sarcoma, NOS																									
Endometrial stromal polyp								X																	X
Hemangioma																			X						
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																			X						
Luteoma																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS													X	X			X	X			X				
Adenocarcinoma, NOS																									
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
Sarcoma, 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
Sarcoma, NOS																									
Hemangiosarcoma																							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, lymphocytic type																					X				
Malignant lymphoma, histiocytic type	X																								
Malignant lymphoma, mixed type				X	X		X		X			X	X			X						X			

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: 25 mg/kg (Continued)

ANIMAL NUMBER	0003	0006	0008	0111	0112	0113	0114	0118	0120	0122	0127	0128	0129	0130	0131	0133	0134	0136	0137	0139	0141	0145	0146	0148	0150	TOTAL:
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	TISSUES TUMORS
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, NOS	X				X														X							5
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS															X											1
Cortical adenoma																										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell adenoma																						X				2
C-cell adenoma												X														1
Parathyroid	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	42
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenoma, NOS																										1
Adenocarcinoma, NOS		X																								5
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS											X								X						X	3
Sarcoma, NOS																				X						1
Endometrial stromal polyp					X																					3
Hemangioma																										1
Ovary	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS																										1
Luteoma																						X				1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS									X				X		X	X								X		10
Adenocarcinoma, NOS											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	*50
Sarcoma, NOS																								X		1
BODY CAVITIES																										
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Sarcoma, NOS																								X		1
Hemangiosarcoma																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	X	N	N	N	N	N	N	N	N	*50
Malignant lymphoma, lymphocytic type																	X									2
Malignant lymphoma, histiocytic type																										1
Malignant lymphoma, mixed type	X			X		X	X	X	X			X							X	X		X				19

* Animals necropsied

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF GLYCIDOL: 50 mg/kg

ANIMAL NUMBER	0014	0015	0022	0047	0111	0444	0006	0112	0009	0033	0030	0048	0044	0018	0028	0331	0333	0171	0221	0334	0449	0336	0054	0433	0133
WEEKS ON STUDY	0002	0555	0664	0664	0666	0699	0777	0777	0778	0800	0811	0833	0855	0855	0866	0888	0888	0889	0891	0901	0900	0996	0997	0997	0997
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Squamous cell carcinoma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS										X			X						X						
Fibrosarcoma														X											
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS, metastatic		X					X									X								X	
Hepatocellular carcinoma, metastatic									X																
Alveolar/bronchiolar adenoma																			X						X
Alveolar/bronchiolar carcinoma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, mixed type																									
Thymus	+	–	+	–	–	+	+	+	+	–	+	+	+	+	–	–	+	+	+	+	+	+	+	+	–
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma												X						X					X		
Hepatocellular carcinoma									X									X				X			
Hemangioma														X											
Hemangiosarcoma																									
Malignant lymphoma, histiocytic type																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS, invasive																	X								
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																X								X	
Mast cell tumor				X																					
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																			X						
Leiomyosarcoma																									
Malignant lymphoma, mixed type																		X							
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+
Adenoma, NOS																					X				X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid	–	–	+	+	+	+	+	–	–	–	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: 50 mg/kg (Continued)

ANIMAL NUMBER	039	042	027	002	020	023	007	032	001	008	010	016	019	024	025	026	029	035	037	038	040	041	045	046	050	TOTAL:
WEEKS ON STUDY	097	098	098	098	098	099	101	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell papilloma																			X							1
Squamous cell carcinoma				X																						1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS			X										X						X							6
Fibrosarcoma							X	X																		3
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS, metastatic																										4
Hepatocellular carcinoma, metastatic																										1
Alveolar/bronchiolar adenoma		X					X													X						5
Alveolar/bronchiolar carcinoma	X									X					X											3
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Malignant lymphoma, mixed type													X								X					2
Thymus	+	−	−	+	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	39
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma			X					X	X		X		X			X						X				10
Hepatocellular carcinoma															X											4
Hemangioma																										1
Hemangiosarcoma													X													1
Malignant lymphoma, histiocytic type																								X		1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	N	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, NOS, invasive																										1
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma									X										X							4
Mast cell tumor																										1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS																										1
Leiomyosarcoma													X													1
Malignant lymphoma, mixed type																										1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, NOS	X		X	X			X	X		X						X	X	X	X	X	X					14
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma																					X					1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43

* Animals necropsied

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: 50 mg/kg (Continued)

ANIMAL NUMBER	0014	0015	0022	0047	0111	0044	0006	0112	0009	0033	0030	0048	0040	0018	0028	0031	0033	0017	0021	0034	0049	0036	0005	0043	0013
WEEKS ON STUDY	0002	0555	0664	0664	0666	0669	0777	0777	0778	0780	0881	0883	0885	0885	0886	0888	0888	0889	0889	0900	0900	0996	0997	0997	0997
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS		X					X	X				X		X	X	X				X				X	X
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*	+	+	+	+
Carcinoma, NOS																									
Adenocarcinoma, NOS																									
Leiomyosarcoma																									
Endometrial stromal polyp																		X							
Hemangiosarcoma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS, invasive																					X				
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																	X						X	X	
Adenocarcinoma, NOS																		X							
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
Sarcoma, NOS																	X								
Sarcoma, NOS, invasive																									
BODY CAVITIES																									
Pleura	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Mesothelioma, malignant																						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
Mesothelioma, malignant																						X			
Malignant lymphoma, undifferentiated type						X																			
Malignant lymphoma, lymphocytic type				X																					
Malignant lymphoma, histiocytic type											X												X		
Malignant lymphoma, mixed type								X						X											

* Animals necropsied

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: 50 mg/kg (Continued)

ANIMAL NUMBER	0 3 9	0 4 2	0 2 7	0 0 2	0 2 0	0 2 3	0 0 7	0 3 2	0 0 1	0 0 8	0 1 0	0 1 6	0 1 9	0 2 4	0 2 5	0 2 6	0 2 9	0 3 5	0 3 7	0 3 8	0 4 0	0 4 1	0 4 5	0 4 6	0 5 0	TOTAL.
WEEKS ON STUDY	0 9 7	0 9 8	0 9 8	0 9 8	0 9 8	0 9 9	1 0 1	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	TISSUES TUMORS
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenocarcinoma, NOS					X		X							X			X		X							15
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS	X																									1
Adenocarcinoma, NOS												X									X					2
Leiomyosarcoma													X													1
Endometrial stromal polyp							X				X						X						X			5
Hemangiosarcoma															X							X				2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma							X																			1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS, invasive																										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	*50
Adenoma, NOS						X	X		X		X			X	X	X	X	X	X			X	X		X	16
Adenocarcinoma, NOS																										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	*50
Sarcoma, NOS																										1
Sarcoma, NOS, invasive													X													1
BODY CAVITIES																										
Pleura	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Mesothelioma, malignant																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Mesothelioma, malignant																										1
Malig. lymphoma, undifferentiated type																										1
Malignant lymphoma, lymphocytic type																										1
Malignant lymphoma, histiocytic type																										2
Malignant lymphoma, mixed type	X	X		X	X	X									X		X			X		X				11

* Animals necropsied

TABLE D3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF GLYCIDOL

	Vehicle Control	25 mg/kg	50 mg/kg
Subcutaneous Tissue: Sarcoma			
Overall Rates (a)	0/50 (0%)	1/50 (2%)	6/50 (12%)
Adjusted Rates (b)	0.0%	3.1%	21.5%
Terminal Rates (c)	0/29 (0%)	0/27 (0%)	2/17 (12%)
Week of First Observation		96	80
Life Table Tests (d)	P=0.002	P=0.477	P=0.007
Incidental Tumor Tests (d)	P=0.007	P=0.383	P=0.023
Cochran-Armitage Trend Test (d)	P=0.005		
Fisher Exact Test (d)		P=0.500	P=0.013
Subcutaneous Tissue: Fibrosarcoma			
Overall Rates (a)	0/50 (0%)	2/50 (4%)	3/50 (6%)
Adjusted Rates (b)	0.0%	4.3%	12.9%
Terminal Rates (c)	0/29 (0%)	0/27 (0%)	0/17 (0%)
Week of First Observation		70	85
Life Table Tests (d)	P=0.052	P=0.242	P=0.070
Incidental Tumor Tests (d)	P=0.171	P=0.335	P=0.193
Cochran-Armitage Trend Test (d)	P=0.082		
Fisher Exact Test (d)		P=0.247	P=0.121
Subcutaneous Tissue: Sarcoma or Fibrosarcoma			
Overall Rates (a)	0/50 (0%)	3/50 (6%)	9/50 (18%)
Adjusted Rates (b)	0.0%	7.3%	32.2%
Terminal Rates (c)	0/29 (0%)	0/27 (0%)	2/17 (12%)
Week of First Observation		70	80
Life Table Tests (d)	P<0.001	P=0.118	P<0.001
Incidental Tumor Tests (d)	P=0.003	P=0.132	P=0.005
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P=0.121	P=0.001
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (e)	3/50 (6%)	4/50 (8%)	5/50 (10%)
Adjusted Rates (b)	10.3%	14.8%	19.8%
Terminal Rates (c)	3/29 (10%)	4/27 (15%)	1/17 (6%)
Week of First Observation	104	104	89
Life Table Tests (d)	P=0.121	P=0.460	P=0.172
Incidental Tumor Tests (d)	P=0.193	P=0.460	P=0.305
Cochran-Armitage Trend Test (d)	P=0.290		
Fisher Exact Test (d)		P=0.500	P=0.357
Lung: Alveolar/Bronchiolar Carcinoma			
Overall Rates (e)	3/50 (6%)	6/50 (12%)	3/50 (6%)
Adjusted Rates (b)	9.8%	20.4%	14.3%
Terminal Rates (c)	2/29 (7%)	4/27 (15%)	2/17 (12%)
Week of First Observation	100	96	97
Life Table Tests (d)	P=0.333	P=0.209	P=0.446
Incidental Tumor Tests (d)	P=0.447	P=0.135	P=0.542
Cochran-Armitage Trend Test (d)	P=0.573		
Fisher Exact Test (d)		P=0.243	P=0.661
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (e)	6/50 (12%)	10/50 (20%)	8/50 (16%)
Adjusted Rates (b)	19.8%	34.3%	31.9%
Terminal Rates (c)	5/29 (17%)	8/27 (30%)	3/17 (18%)
Week of First Observation	100	96	89
Life Table Tests (d)	P=0.093	P=0.160	P=0.132
Incidental Tumor Tests (d)	P=0.185	P=0.111	P=0.264
Cochran-Armitage Trend Test (d)	P=0.341		
Fisher Exact Test (d)		P=0.207	P=0.387

TABLE D3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF GLYCIDOL (Continued)

	Vehicle Control	25 mg/kg	50 mg/kg
Hematopoietic System: Malignant Lymphoma, Undifferentiated Type			
Overall Rates (a)	3/50 (6%)	0/50 (0%)	1/50 (2%)
Adjusted Rates (b)	7.6%	0.0%	2.2%
Terminal Rates (c)	1/29 (3%)	0/27 (0%)	0/17 (0%)
Week of First Observation	76		69
Life Table Tests (d)	P=0.212N	P=0.127N	P=0.368N
Incidental Tumor Tests (d)	P=0.090N	P=0.093N	P=0.162N
Cochran-Armitage Trend Test (d)	P=0.176N		
Fisher Exact Test (d)		P=0.121N	P=0.309N
Hematopoietic System: Malignant Lymphoma, Lymphocytic Type			
Overall Rates (a)	3/50 (6%)	2/50 (4%)	1/50 (2%)
Adjusted Rates (b)	7.0%	6.9%	2.1%
Terminal Rates (c)	0/29 (0%)	1/27 (4%)	0/17 (0%)
Week of First Observation	28	98	64
Life Table Tests (d)	P=0.296N	P=0.530N	P=0.355N
Incidental Tumor Tests (d)	P=0.164N	P=0.604	P=0.170N
Cochran-Armitage Trend Test (d)	P=0.222N		
Fisher Exact Test (d)		P=0.500N	P=0.309N
Hematopoietic System: Malignant Lymphoma, Histiocytic Type			
Overall Rates (a)	1/50 (2%)	1/50 (2%)	3/50 (6%)
Adjusted Rates (b)	2.6%	2.0%	11.2%
Terminal Rates (c)	0/29 (0%)	0/27 (0%)	1/17 (6%)
Week of First Observation	92	62	81
Life Table Tests (d)	P=0.151	P=0.747	P=0.216
Incidental Tumor Tests (d)	P=0.286	P=0.665N	P=0.379
Cochran-Armitage Trend Test (d)	P=0.202		
Fisher Exact Test (d)		P=0.753	P=0.309
Hematopoietic System: Malignant Lymphoma, Mixed Type			
Overall Rates (a)	11/50 (22%)	19/50 (38%)	14/50 (28%)
Adjusted Rates (b)	26.7%	51.7%	50.7%
Terminal Rates (c)	3/29 (10%)	11/27 (41%)	6/17 (35%)
Week of First Observation	71	76	77
Life Table Tests (d)	P=0.069	P=0.057	P=0.095
Incidental Tumor Tests (d)	P=0.321	P=0.107	P=0.410
Cochran-Armitage Trend Test (d)	P=0.291		
Fisher Exact Test (d)		P=0.063	P=0.322
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	18/50 (36%)	22/50 (44%)	19/50 (38%)
Adjusted Rates (b)	38.9%	57.1%	59.4%
Terminal Rates (c)	4/29 (14%)	12/27 (44%)	7/17 (41%)
Week of First Observation	28	62	64
Life Table Tests (d)	P=0.134	P=0.229	P=0.177
Incidental Tumor Tests (d)	P=0.460N	P=0.294	P=0.415N
Cochran-Armitage Trend Test (d)	P=0.459		
Fisher Exact Test (d)		P=0.270	P=0.500
Circulatory System: Hemangiosarcoma			
Overall Rates (a)	1/50 (2%)	2/50 (4%)	3/50 (6%)
Adjusted Rates (b)	3.1%	5.5%	16.7%
Terminal Rates (c)	0/29 (0%)	0/27 (0%)	3/17 (18%)
Week of First Observation	100	66	104
Life Table Tests (d)	P=0.120	P=0.483	P=0.153
Incidental Tumor Tests (d)	P=0.221	P=0.389	P=0.195
Cochran-Armitage Trend Test (d)	P=0.222		
Fisher Exact Test (d)		P=0.500	P=0.309

TABLE D3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF GLYCIDOL (Continued)

	Vehicle Control	25 mg/kg	50 mg/kg
Circulatory System: Hemangioma or Hemangiosarcoma			
Overall Rates (a)	1/50 (2%)	3/50 (6%)	5/50 (10%)
Adjusted Rates (b)	3.1%	8.5%	23.1%
Terminal Rates (c)	0/29 (0%)	0/27 (0%)	3/17 (18%)
Week of First Observation	100	66	85
Life Table Tests (d)	P=0.028	P=0.285	P=0.037
Incidental Tumor Tests (d)	P=0.096	P=0.169	P=0.083
Cochran-Armitage Trend Test (d)	P=0.070		
Fisher Exact Test (d)		P=0.309	P=0.102
Liver: Hepatocellular Adenoma			
Overall Rates (e)	6/50 (12%)	3/50 (6%)	10/50 (20%)
Adjusted Rates (b)	20.7%	11.1%	41.7%
Terminal Rates (c)	6/29 (21%)	3/27 (11%)	5/17 (29%)
Week of First Observation	104	104	83
Life Table Tests (d)	P=0.029	P=0.272N	P=0.038
Incidental Tumor Tests (d)	P=0.054	P=0.272N	P=0.081
Cochran-Armitage Trend Test (d)	P=0.146		
Fisher Exact Test (d)		P=0.243N	P=0.207
Liver: Hepatocellular Carcinoma			
Overall Rates (e)	3/50 (6%)	5/50 (10%)	4/50 (8%)
Adjusted Rates (b)	10.3%	15.6%	13.7%
Terminal Rates (c)	3/29 (10%)	3/27 (11%)	1/17 (6%)
Week of First Observation	104	84	78
Life Table Tests (d)	P=0.245	P=0.319	P=0.319
Incidental Tumor Tests (d)	P=0.376	P=0.409	P=0.452
Cochran-Armitage Trend Test (d)	P=0.427		
Fisher Exact Test (d)		P=0.357	P=0.500
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (e)	9/50 (18%)	7/50 (14%)	14/50 (28%)
Adjusted Rates (b)	31.0%	22.6%	51.1%
Terminal Rates (c)	9/29 (31%)	5/27 (19%)	6/17 (35%)
Week of First Observation	104	84	78
Life Table Tests (d)	P=0.017	P=0.452N	P=0.020
Incidental Tumor Tests (d)	P=0.051	P=0.377N	P=0.062
Cochran-Armitage Trend Test (d)	P=0.130		
Fisher Exact Test (d)		P=0.393N	P=0.171
Forestomach: Squamous Cell Papilloma			
Overall Rates (a)	3/50 (6%)	1/50 (2%)	4/50 (8%)
Adjusted Rates (b)	10.3%	3.7%	16.7%
Terminal Rates (c)	3/29 (10%)	1/27 (4%)	2/17 (12%)
Week of First Observation	104	104	88
Life Table Tests (d)	P=0.241	P=0.330N	P=0.290
Incidental Tumor Tests (d)	P=0.288	P=0.330N	P=0.359
Cochran-Armitage Trend Test (d)	P=0.412		
Fisher Exact Test (d)		P=0.309N	P=0.500
Anterior Pituitary Gland: Adenoma			
Overall Rates (e)	18/49 (37%)	5/49 (10%)	14/49 (29%)
Adjusted Rates (b)	51.7%	17.7%	56.6%
Terminal Rates (c)	13/29 (45%)	4/27 (15%)	7/17 (41%)
Week of First Observation	80	98	90
Life Table Tests (d)	P=0.445	P=0.005N	P=0.350
Incidental Tumor Tests (d)	P=0.411N	P=0.003N	P=0.533N
Cochran-Armitage Trend Test (d)	P=0.208N		
Fisher Exact Test (d)		P=0.002N	P=0.259N

TABLE D3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF GLYCIDOL (Continued)

	Vehicle Control	25 mg/kg	50 mg/kg
Adrenal Capsule: Adenoma			
Overall Rates (e)	3/50 (6%)	1/50 (2%)	0/50 (0%)
Adjusted Rates (b)	9.6%	3.7%	0.0%
Terminal Rates (c)	2/29 (7%)	1/27 (4%)	0/17 (0%)
Week of First Observation	99	104	
Life Table Tests (d)	P=0.113N	P=0.343N	P=0.223N
Incidental Tumor Tests (d)	P=0.092N	P=0.378N	P=0.166N
Cochran-Armitage Trend Test (d)	P=0.060N		
Fisher Exact Test (d)		P=0.309N	P=0.121N
Mammary Gland: Adenocarcinoma			
Overall Rates (a)	1/50 (2%)	5/50 (10%)	15/50 (30%)
Adjusted Rates (b)	2.7%	14.5%	43.0%
Terminal Rates (c)	0/29 (0%)	1/27 (4%)	3/17 (18%)
Week of First Observation	95	85	55
Life Table Tests (d)	P<0.001	P=0.085	P<0.001
Incidental Tumor Tests (d)	P<0.001	P=0.072	P=0.001
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P=0.102	P<0.001
Mammary Gland: Adenoma, Fibroadenoma, or Adenocarcinoma			
Overall Rates (a)	2/50 (4%)	6/50 (12%)	15/50 (30%)
Adjusted Rates (b)	6.1%	17.3%	43.0%
Terminal Rates (c)	1/29 (3%)	1/27 (4%)	3/17 (18%)
Week of First Observation	95	85	55
Life Table Tests (d)	P<0.001	P=0.110	P<0.001
Incidental Tumor Tests (d)	P=0.001	P=0.078	P=0.003
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P=0.134	P<0.001
Uterus: Endometrial Stromal Polyp			
Overall Rates (a)	2/50 (4%)	3/50 (6%)	5/50 (10%)
Adjusted Rates (b)	5.7%	9.5%	23.4%
Terminal Rates (c)	1/29 (3%)	2/27 (7%)	3/17 (18%)
Week of First Observation	87	84	89
Life Table Tests (d)	P=0.065	P=0.476	P=0.093
Incidental Tumor Tests (d)	P=0.113	P=0.591	P=0.170
Cochran-Armitage Trend Test (d)	P=0.158		
Fisher Exact Test (d)		P=0.500	P=0.218
Uterus: Adenocarcinoma			
Overall Rates (a)	0/50 (0%)	3/50 (6%)	2/50 (4%)
Adjusted Rates (b)	0.0%	11.1%	11.1%
Terminal Rates (c)	0/29 (0%)	3/27 (11%)	2/17 (12%)
Week of First Observation		104	104
Life Table Tests (d)	P=0.094	P=0.107	P=0.140
Incidental Tumor Tests (d)	P=0.084	P=0.107	P=0.130
Cochran-Armitage Trend Test (d)	P=0.202		
Fisher Exact Test (d)		P=0.121	P=0.247
Uterus: Carcinoma or Adenocarcinoma			
Overall Rates (a)	0/50 (0%)	3/50 (6%)	3/50 (6%)
Adjusted Rates (b)	0.0%	11.1%	14.3%
Terminal Rates (c)	0/29 (0%)	3/27 (11%)	2/17 (12%)
Week of First Observation		104	97
Life Table Tests (d)	P=0.039	P=0.107	P=0.062
Incidental Tumor Tests (d)	P=0.046	P=0.107	P=0.078
Cochran-Armitage Trend Test (d)	P=0.101		
Fisher Exact Test (d)		P=0.121	P=0.121

TABLE D3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF GLYCIDOL (Continued)

	Vehicle Control	25 mg/kg	50 mg/kg
Harderian Gland: Adenoma			
Overall Rates (e)	4/46 (9%)	10/43 (23%)	16/43 (37%)
Adjusted Rates (b)	12.8%	29.7%	68.4%
Terminal Rates (c)	3/29 (10%)	5/27 (19%)	11/17 (65%)
Week of First Observation	95	88	88
Life Table Tests (d)	P<0.001	P=0.056	P<0.001
Incidental Tumor Tests (d)	P<0.001	P=0.078	P<0.001
Cochran-Armitage Trend Test (d)	P=0.001		
Fisher Exact Test (d)		P=0.055	P=0.001
Harderian Gland: Adenoma or Adenocarcinoma			
Overall Rates (e)	4/46 (9%)	11/43 (26%)	17/43 (40%)
Adjusted Rates (b)	12.8%	32.9%	69.4%
Terminal Rates (c)	3/29 (10%)	6/27 (22%)	11/17 (65%)
Week of First Observation	95	88	88
Life Table Tests (d)	P<0.001	P=0.034	P<0.001
Incidental Tumor Tests (d)	P<0.001	P=0.047	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P=0.032	P<0.001
All Sites: Benign Tumors			
Overall Rates (a)	28/50 (56%)	25/50 (50%)	32/50 (64%)
Adjusted Rates (b)	75.0%	68.7%	93.9%
Terminal Rates (c)	20/29 (69%)	16/27 (59%)	15/17 (88%)
Week of First Observation	80	84	83
Life Table Tests (d)	P=0.005	P=0.527N	P=0.003
Incidental Tumor Tests (d)	P=0.048	P=0.355N	P=0.041
Cochran-Armitage Trend Test (d)	P=0.240		
Fisher Exact Test (d)		P=0.344N	P=0.270
All Sites: Malignant Tumors			
Overall Rates (a)	28/50 (56%)	35/50 (70%)	40/50 (80%)
Adjusted Rates (b)	58.8%	76.9%	86.8%
Terminal Rates (c)	10/29 (34%)	17/27 (63%)	11/17 (65%)
Week of First Observation	28	62	55
Life Table Tests (d)	P=0.001	P=0.120	P=0.002
Incidental Tumor Tests (d)	P=0.038	P=0.083	P=0.070
Cochran-Armitage Trend Test (d)	P=0.007		
Fisher Exact Test (d)		P=0.107	P=0.009
All Sites: All Tumors			
Overall Rates (a)	45/50 (90%)	46/50 (92%)	47/50 (94%)
Adjusted Rates (b)	91.8%	93.8%	100.0%
Terminal Rates (c)	25/29 (86%)	24/27 (89%)	17/17 (100%)
Week of First Observation	28	62	55
Life Table Tests (d)	P=0.009	P=0.306	P=0.009
Incidental Tumor Tests (d)	P=0.336	P=0.451	P=0.369
Cochran-Armitage Trend Test (d)	P=0.290		
Fisher Exact Test (d)		P=0.500	P=0.357

(a) Number of tumor-bearing animals/number of animals examined grossly at the site
(b) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence in animals killed at the end of the study
(d) Beneath the vehicle 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 vehicle 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 nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group than in vehicle controls is indicated by (N).
(e) Number of tumor-bearing animals/number of animals examined microscopically at the site

TABLE D4a. HISTORICAL INCIDENCE OF HARDERIAN GLAND TUMORS IN FEMALE B6C3F$_1$ MICE (a)

Study	Incidence in Controls		
	Adenoma	Adenocarcinoma	Adenoma or Adenocarcinoma
Historical Incidence for All Water Gavage Vehicle Controls			
Iodinated glycerol (b)	6/50	0/50	6/50
Chlorpheniramine maleate (c)	2/50	0/50	2/50
Tetrakis(hydroxymethyl)phosphonium chloride (c)	0/50	0/50	0/50
Malonaldehyde, sodium salt (c)	0/50	0/50	0/50
Tetrakis(hydroxymethyl)phosphonium sulfate (c)	0/50	(d) 2/50	2/50
Methyl carbamate (e)	1/50	0/50	1/50
Chlorinated trisodium phosphate (b)	0/50	(f) 1/50	1/50
TOTAL	9/350 (2.6%)	3/350 (0.9%)	12/350 (3.4%)
SD (g)	4.43%	1.57%	4.12%
Range (h)			
High	6/50	2/50	6/50
Low	0/50	0/50	0/50
Overall Historical Incidence for Untreated Controls			
TOTAL	(i) 43/1,689 (2.5%)	(j) 8/1,689 (0.5%)	(i,j) 51/1,689 (3.0%)
SD (g)	2.89%	0.99%	2.93%
Range (h)			
High	6/50	2/50	6/50
Low	0/50	0/50	0/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Study conducted at EG&G Mason Research Institute
(c) Study conducted at Battelle Columbus Laboratories
(d) Papillary adenocarcinomas
(e) Study conducted at Microbiological Associates, Inc.
(f) Carcinoma, NOS
(g) Standard deviation
(h) Range and SD are presented for groups of 35 or more animals.
(i) Includes three papillary adenomas and two papillary cystadenomas, NOS
(j) Includes three carcinomas, NOS, two papillary adenocarcinomas, and one papillary cystadenocarcinoma, NOS

TABLE D4b. HISTORICAL INCIDENCE OF MAMMARY GLAND TUMORS IN FEMALE B6C3F$_1$ MICE (a)

Study	Incidence in Controls		
	Fibroadenoma	Adenocarcinoma	Fibroadenoma or Adenocarcinoma
Historical Incidence for All Water Gavage Vehicle Controls			
Iodinated glycerol (b)	0/50	0/50	0/50
Chlorpheniramine maleate (c)	0/50	1/50	1/50
Tetrakis(hydroxymethyl)phosphonium chloride (c)	0/50	0/50	0/50
Malonaldehyde, sodium salt (c)	0/50	1/50	1/50
Tetrakis(hydroxymethyl)phosphonium sulfate (c)	0/50	0/50	0/50
Methyl carbamate (d)	0/50	0/50	0/50
Chlorinated trisodium phosphate (b)	2/50	0/50	2/50
TOTAL	2/350 (0.6%)	2/350 (0.6%)	4/350 (1.1%)
SD (e)	1.51%	0.98%	1.57%
Range (f)			
High	2/50	1/50	2/50
Low	0/50	0/50	0/50
Overall Historical Incidence for Untreated Controls			
TOTAL	(g) 2/1,689 (0.1%)	(h) 33/1,689 (2.0%)	(g,h) 35/1,689 (2.1%)
SD (e)	0.48%	2.15%	2.20%
Range (f)			
High	1/49	3/48	3/48
Low	0/50	0/50	0/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Study conducted at EG&G Mason Research Institute
(c) Study conducted at Battelle Columbus Laboratories
(d) Study conducted at Microbiological Associates, Inc.
(e) Standard deviation
(f) Range and SD are presented for groups of 35 or more animals.
(g) Includes one adenoma, NOS
(h) Includes one intraductal carcinoma, three acinar cell carcinomas, three adenosquamous carcinomas, and one adenocarcinoma/squamous metaplasia

TABLE D4c. HISTORICAL INCIDENCE OF INTEGUMENTARY SYSTEM FIBROSARCOMAS IN FEMALE $B6C3F_1$ MICE (a)

Study	Incidence in Controls
Historical Incidence for All Water Gavage Vehicle Controls	
Iodinated glycerol (b)	0/50
Chlorpheniramine maleate (c)	(d) 2/50
Tetrakis(hydroxymethyl)phosphonium chloride (c)	(d) 1/50
Malonaldehyde, sodium salt (c)	0/50
Tetrakis(hydroxymethyl)phosphonium sulfate (c)	(d) 2/50
Methyl carbamate (e)	0/50
Chlorinated trisodium phosphate (b)	1/50
TOTAL	6/350 (1.7%)
SD (f)	1.80%
Range (g)	
High	2/50
Low	0/50
Overall Historical Incidence for Untreated Controls	
TOTAL	(h) 40/1,689 (2.4%)
SD (f)	2.52%
Range (g)	
High	5/49
Low	0/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks, no fibromas or neurofibromas were observed.
(b) Study conducted at EG&G Mason Research Institute
(c) Study conducted at Battelle Columbus Laboratories
(d) Includes one sarcoma, NOS
(e) Study conducted at Microbiological Associates, Inc.
(f) Standard deviation
(g) Range and SD are presented for groups of 35 or more animals.
(h) Includes 18 sarcomas, NOS, and 1 neurofibrosarcoma

TABLE D4d. HISTORICAL INCIDENCE OF INTEGUMENTARY SYSTEM SQUAMOUS CELL TUMORS IN FEMALE B6C3F$_1$ MICE (a)

Study	Incidence of Papillomas or Carcinomas in Controls
Historical Incidence for All Water Gavage Vehicle Controls	
Iodinated glycerol (b)	0/50
Chlorpheniramine maleate (c)	0/50
Tetrakis(hydroxymethyl)phosphonium chloride (c)	0/50
Malonaldehyde, sodium salt (c)	0/50
Tetrakis(hydroxymethyl)phosphonium sulfate (c)	0/50
Methyl carbamate (d)	0/50
Chlorinated trisodium phosphate (b)	0/50
TOTAL	0/350
SD (e)	0.00%
Range (f)	
High	0/50
Low	0/50
Overall Historical Incidence for Untreated Controls	
TOTAL	(g) 4/1,689 (0.2%)
SD (e)	0.84%
Range (f)	
High	(h) 2/48
Low	0/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Study conducted at EG&G Mason Research Institute
(c) Study conducted at Battelle Columbus Laboratories
(d) Study conducted at Microbiological Associates, Inc.
(e) Standard deviation
(f) Range and SD are presented for groups of 35 or more animals.
(g) Includes two squamous cell papillomas and two squamous cell carcinomas
(h) Includes one squamous cell papilloma and one squamous cell carcinoma

TABLE D4e. HISTORICAL INCIDENCE OF HEPATOCELLULAR TUMORS IN FEMALE B6C3F$_1$ MICE (a)

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence for All Water Gavage Vehicle Controls			
Iodinated glycerol (b)	0/50	0/50	0/50
Chlorpheniramine maleate (c)	4/50	2/50	6/50
Tetrakis(hydroxymethyl)phosphonium chloride (c)	3/49	1/49	4/49
Malonaldehyde, sodium salt (c)	0/50	2/50	2/50
Tetrakis(hydroxymethyl)phosphonium sulfate (c)	5/50	3/50	7/50
Methyl carbamate (d)	4/49	1/49	4/49
Chlorinated trisodium phosphate (b)	6/50	0/50	6/50
TOTAL	22/348 (6.3%)	9/348 (2.6%)	29/348 (8.3%)
SD (e)	4.69%	2.22%	4.95%
Range (f)			
High	6/50	3/50	7/50
Low	0/50	0/50	0/50
Overall Historical Incidence for Untreated Controls			
TOTAL	100/1,683 (5.9%)	(g) 68/1,683 (4.0%)	(g) 163/1,683 (9.7%)
SD (e)	3.75%	2.30%	4.25%
Range (f)			
High	8/49	4/48	10/49
Low	0/50	0/49	2/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Study conducted at EG&G Mason Research Institute
(c) Study conducted at Battelle Columbus Laboratories
(d) Study conducted at Microbiological Associates, Inc.
(e) Standard deviation
(f) Range and SD are presented for groups of 35 or more animals.
(g) Includes one hepatoblastoma

TABLE D4f. HISTORICAL INCIDENCE OF CIRCULATORY SYSTEM TUMORS IN FEMALE B6C3F$_1$ MICE (a)

Study	Incidence in Controls		
	Hemangioma	Hemangiosarcoma	Hemangioma or Hemangiosarcoma
Historical Incidence for All Water Gavage Vehicle Controls			
Iodinated glycerol (b)	1/50	1/50	2/50
Chlorpheniramine maleate (c)	0/50	1/50	1/50
Tetrakis(hydroxymethyl)phosphonium chloride (c)	0/50	0/50	0/50
Malonaldehyde, sodium salt (c)	1/50	1/50	2/50
Tetrakis(hydroxymethyl)phosphonium sulfate (c)	1/50	0/50	1/50
Methyl carbamate (d)	1/50	0/50	1/50
Chlorinated trisodium phosphate (b)	0/50	1/50	1/50
TOTAL	4/350 (1.1%)	4/350 (1.1%)	8/350 (2.3%)
SD (e)	1.07%	1.07%	1.38%
Range (f)			
High	1/50	1/50	2/50
Low	0/50	0/50	0/50
Overall Historical Incidence for Untreated Controls			
TOTAL	25/1,689 (1.5%)	23/1,689 (1.4%)	48/1,689 (2.8%)
SD (e)	1.89%	1.89%	2.85%
Range (f)			
High	4/50	4/50	6/50
Low	0/50	0/50	0/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Study conducted at EG&G Mason Research Institute
(c) Study conducted at Battelle Columbus Laboratories
(d) Study conducted at Microbiological Associates, Inc.
(e) Standard deviation
(f) Range and SD are presented for groups of 35 or more animals.

TABLE D4g. HISTORICAL INCIDENCE OF UTERINE TUMORS IN FEMALE B6C3F$_1$ MICE (a)

Study	Incidence of Adenomas or Adenocarcinomas in Controls
Historical Incidence for All Water Gavage Vehicle Controls	
Iodinated glycerol (b)	0/50
Chlorpheniramine maleate (c)	0/50
Tetrakis(hydroxymethyl)phosphonium chloride (c)	(d) 1/50
Malonaldehyde, sodium salt (c)	0/49
Tetrakis(hydroxymethyl)phosphonium sulfate (c)	0/50
Methyl carbamate (e)	0/49
Chlorinated trisodium phosphate (b)	0/49
TOTAL	1/347 (0.3%)
SD (f)	0.76%
Range (g)	
High	1/50
Low	0/50
Overall Historical Incidence for Untreated Controls	
TOTAL	(h) 4/1,675 (0.2%)
SD (f)	0.66%
Range (g)	
High	1/48
Low	0/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Study conducted at EG&G Mason Research Institute
(c) Study conducted at Battelle Columbus Laboratories
(d) Carcinoma, NOS
(e) Study conducted at Microbiological Associates, Inc.
(f) Standard deviation
(g) Range and SD are presented for groups of 35 or more animals.
(h) Includes one adenoma, NOS, and three adenocarcinomas, NOS

TABLE D4h. HISTORICAL INCIDENCE OF TUMORS OF THE SMALL INTESTINE IN FEMALE B6C3F$_1$ MICE (a)

Study	Incidence in Controls		
	Adenomatous Polyp	Adenocarcinoma	Adenomatous Polyp or Adenocarcinoma
Historical Incidence for All Water Gavage Vehicle Controls			
Iodinated glycerol (b)	0/50	1/50	1/50
Chlorpheniramine maleate (c)	0/47	0/47	0/47
Tetrakis(hydroxymethyl)phosphonium chloride (c)	0/47	0/47	0/47
Malonaldehyde, sodium salt (c)	0/45	0/45	0/45
Tetrakis(hydroxymethyl)phosphonium sulfate (c)	0/49	0/49	0/49
Methyl carbamate (d)	0/46	0/46	0/46
Chlorinated trisodium phosphate (b)	0/46	0/46	0/46
TOTAL	0/330	1/330 (0.3%)	1/330 (0.3%)
SD (e)	0.00%	0.76%	0.76%
Range (f)			
High	0/50	1/50	1/50
Low	0/50	0/49	0/49
Overall Historical Incidence for Untreated Controls			
TOTAL	4/1,608 (0.2%)	(g) 2/1,608 (0.1%)	(g) 6/1,608 (0.4%)
SD (e)	0.67%	0.51%	0.80%
Range (f)			
High	1/48	1/46	1/46
Low	0/50	0/50	0/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Study conducted at EG&G Mason Research Institute
(c) Study conducted at Battelle Columbus Laboratories
(d) Study conducted at Microbiological Associates, Inc.
(e) Standard deviation
(f) Range and SD are presented for groups of 35 or more animals.
(g) Includes one mucinous adenocarcinoma

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF GLYCIDOL

	Vehicle Control	25 mg/kg	50 mg/kg
Animals initially in study	50	50	50
Animals necropsied	50	50	50
Animals examined histopathologically	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Epidermal inclusion cyst	1 (2%)		
*Subcutaneous tissue	(50)	(50)	(50)
Hemorrhage			1 (2%)
RESPIRATORY SYSTEM			
#Nasal cavity	(49)	(50)	(50)
Congenital malformation, NOS		1 (2%)	
Inflammation, NOS		1 (2%)	
#Lung	(50)	(50)	(50)
Hemorrhage	1 (2%)		
Inflammation, acute focal			1 (2%)
Pneumonia, interstitial chronic		1 (2%)	
Inflammation, chronic focal	3 (6%)		
Inflammation, granulomatous	1 (2%)		
Hyperplasia, alveolar epithelium	1 (2%)		2 (4%)
HEMATOPOIETIC SYSTEM			
#Bone marrow	(50)	(50)	(49)
Fibrosis		4 (8%)	
Necrosis, coagulative		1 (2%)	
#Spleen	(50)	(50)	(50)
Hemorrhage	1 (2%)		
Inflammation, granulomatous focal	1 (2%)		
Necrosis, NOS			1 (2%)
Hyperplasia, lymphoid	3 (6%)	1 (2%)	
#Splenic red pulp	(50)	(50)	(50)
Hyperplasia, NOS	2 (4%)	9 (18%)	16 (32%)
#Lymph node	(50)	(50)	(50)
Hemorrhage			1 (2%)
Hyperplasia, NOS	2 (4%)		
Myelopoiesis			2 (4%)
#Lumbar lymph node	(50)	(50)	(50)
Hyperplasia, lymphoid	1 (2%)		
#Lung	(50)	(50)	(50)
Hyperplasia, lymphoid		1 (2%)	
#Liver	(50)	(50)	(50)
Myelopoiesis		1 (2%)	2 (4%)
#Adrenal cortex	(50)	(50)	(50)
Myelopoiesis		1 (2%)	2 (4%)
#Thymus	(47)	(42)	(39)
Inflammation, chronic	1 (2%)		
Hyperplasia, NOS	1 (2%)		
CIRCULATORY SYSTEM			
#Heart	(50)	(50)	(50)
Inflammation, NOS			5 (10%)
*Artery	(50)	(50)	(50)
Periarteritis			1 (2%)
#Ovary	(50)	(50)	(50)
Thrombosis, NOS			1 (2%)

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF GLYCIDOL (Continued)

	Vehicle Control	25 mg/kg	50 mg/kg
DIGESTIVE SYSTEM			
*Tooth	(50)	(50)	(50)
Dysplasia, NOS	1 (2%)		
#Liver	(50)	(50)	(50)
Hemorrhage	1 (2%)		
Cirrhosis, NOS		1 (2%)	
Degeneration, lipoid	2 (4%)		
Necrosis, coagulative	5 (10%)	4 (8%)	6 (12%)
Eosinophilic cyto change	1 (2%)		3 (6%)
Clear cell change	1 (2%)	1 (2%)	
Angiectasis	1 (2%)	1 (2%)	1 (2%)
#Liver/periportal	(50)	(50)	(50)
Inflammation, chronic	1 (2%)		
#Liver/Kupffer cell	(50)	(50)	(50)
Pigmentation, NOS		1 (2%)	
#Pancreas	(50)	(50)	(50)
Inflammation, chronic			1 (2%)
Atrophy, NOS			1 (2%)
#Glandular stomach	(50)	(50)	(50)
Inflammation, NOS	1 (2%)		
Dysplasia, epithelial		1 (2%)	
#Forestomach	(50)	(50)	(50)
Inflammation, acute focal			1 (2%)
Ulcer, chronic	2 (4%)	1 (2%)	2 (4%)
Inflammation, chronic diffuse	1 (2%)		
Hyperplasia, epithelial	3 (6%)	1 (2%)	10 (20%)
Hyperkeratosis	5 (10%)	3 (6%)	11 (22%)
#Duodenum	(50)	(50)	(50)
Inflammation, NOS	1 (2%)		
Ulcer, chronic			1 (2%)
URINARY SYSTEM			
#Kidney	(50)	(50)	(50)
Cyst, NOS	2 (4%)	4 (8%)	2 (4%)
#Kidney/tubule	(50)	(50)	(50)
Degeneration, hyaline		1 (2%)	1 (2%)
#Urinary bladder	(50)	(50)	(50)
Edema, NOS	2 (4%)		
Dysplasia, NOS		1 (2%)	
Dysplasia, epithelial		1 (2%)	
ENDOCRINE SYSTEM			
#Pituitary intermedia	(49)	(49)	(49)
Hyperplasia, focal			2 (4%)
#Anterior pituitary	(49)	(49)	(49)
Hyperplasia, NOS	1 (2%)		
Hyperplasia, focal	6 (12%)	9 (18%)	9 (18%)
#Adrenal/capsule	(50)	(50)	(50)
Hyperplasia, focal	1 (2%)		
#Adrenal cortex	(50)	(50)	(50)
Cyst, NOS			1 (2%)
Hemorrhage	1 (2%)		2 (4%)
Degeneration, lipoid	3 (6%)		2 (4%)
Atrophy, focal		2 (4%)	
Hyperplasia, focal		2 (4%)	1 (2%)
#Zona reticularis	(50)	(50)	(50)
Degeneration, lipoid		1 (2%)	
#Adrenal medulla	(50)	(50)	(50)
Amyloidosis		1 (2%)	
Hyperplasia, focal	1 (2%)	1 (2%)	

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF GLYCIDOL (Continued)

	Vehicle Control	25 mg/kg	50 mg/kg
ENDOCRINE SYSTEM (Continued)			
#Thyroid	(50)	(50)	(50)
Follicular cyst, NOS		3 (6%)	
Inflammation, chronic			2 (4%)
Hyperplasia, follicular cell	8 (16%)	2 (4%)	6 (12%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Hyperplasia, NOS	1 (2%)		
#Uterus	(50)	(50)	(50)
Dilatation, NOS	1 (2%)		
Hemorrhage	2 (4%)	7 (14%)	15 (30%)
Angiectasis		1 (2%)	
#Uterus/endometrium	(50)	(50)	(50)
Hyperplasia, cystic	40 (80%)	44 (88%)	40 (80%)
#Ovary	(50)	(50)	(50)
Cyst, NOS	14 (28%)	13 (26%)	20 (40%)
Hemorrhage		2 (4%)	2 (4%)
Inflammation, chronic	1 (2%)		
Atrophy, NOS	2 (4%)	4 (8%)	2 (4%)
Hyperplasia, tubular cell	1 (2%)	1 (2%)	1 (2%)
Angiectasis	1 (2%)	1 (2%)	
#Ovary/granulosa cell	(50)	(50)	(50)
Hyperplasia, NOS		1 (2%)	
NERVOUS SYSTEM			
#Brain/meninges	(50)	(49)	(50)
Inflammation, acute		1 (2%)	
Inflammation, chronic	5 (10%)		
#Brain	(50)	(49)	(50)
Mineralization	3 (6%)		6 (12%)
Epidermal inclusion cyst		1 (2%)	
Hemorrhage	3 (6%)		
Degeneration, NOS			1 (2%)
SPECIAL SENSE ORGANS			
*Eye	(50)	(50)	(50)
Degeneration, NOS		1 (2%)	
*Eye/crystalline lens	(50)	(50)	(50)
Cataract			1 (2%)
*Harderian gland	(50)	(50)	(50)
Hyperplasia, NOS	1 (2%)	2 (4%)	3 (6%)
MUSCULOSKELETAL SYSTEM			
*Bone	(50)	(50)	(50)
Fibrous osteodystrophy	3 (6%)		1 (2%)
BODY CAVITIES			
*Peritoneal mesothelium	(50)	(50)	(50)
Inflammation, chronic			1 (2%)
*Pleura	(50)	(50)	(50)
Inflammation, chronic			1 (2%)
*Pericardium	(50)	(50)	(50)
Inflammation, chronic			1 (2%)

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF GLYCIDOL (Continued)

	Vehicle Control	25 mg/kg	50 mg/kg
ALL OTHER SYSTEMS			
Adipose tissue			
Hemorrhage			1
Necrosis, fat	2	1	4
SPECIAL MORPHOLOGY SUMMARY			
No lesion reported		1	

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
# Number of animals examined microscopically at this site

APPENDIX E

SENTINEL ANIMAL PROGRAM

APPENDIX E. SENTINEL ANIMAL PROGRAM

Methods

Rodents used in the Carcinogenesis Program of the National Toxicology Program are produced in optimally clean facilities to eliminate potential pathogens that may affect study 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 is monitored via viral serology on sera from extra (sentinel) animals in the study rooms. These animals are untreated, and these animals and the study animals are both subject to identical environmental conditions. The sentinel animals come from the same production source and weanling groups as the animals used for the studies of chemical compounds.

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

	Hemagglutination Inhibition	Complement Fixation	ELISA
Mice	PVM (pneumonia virus of mice) Reo 3 (reovirus type 3) (6,12,18,24 mo) GDVII (Theiler's encephalomyelitis virus) Poly (polyoma virus) MVM (minute virus of mice) Ectro (infectious ectromelia) Sendai (6,18,24 mo)	M. Ad. (mouse adenovirus) LCM (lymphocytic choriomeningitis virus) MHV (6,12,18 mo) Sendai (12 mo)	MHV (mouse hepatitis virus) (24 mo) Reo 3 (18,24 mo)
Rats	PVM KRV (Kilham rat virus) H-1 (Toolan's H-1 virus) Sendai (6,18,24 mo)	RCV (rat coronavirus) (6,12,18 mo) Sendai (12 mo)	RCV/SDA (sialodacryoadenitis virus) (24 mo)

Results

Results are presented in Table E1.

TABLE E1. MURINE VIRUS ANTIBODY DETERMINATIONS FOR RATS AND MICE IN THE TWO-YEAR GAVAGE STUDIES OF GLYCIDOL (a)

Interval (months)	Number of Animals	Positive Serologic Reaction for
RATS		
6	10/10	RCV
12	6/9	RCV
18	5/10	KRV
	8/10	RCV
24	10/10	RCV/SDA
MICE		
6	--	None positive
12	--	None positive
18	(b) 2/10	Reo 3
24	(b) 1/10	Reo 3
	1/10	MHV

(a) Blood samples were taken from sentinel animals at 6, 12, and 18 months after the start of dosing and from the vehicle control animals just before they were killed; samples were sent to Microbiological Associates, Inc. (Bethesda, MD) for determination of antibody titers.
(b) The positive results were obtained with the hemagglutination test; no positive results were obtained by ELISA.

APPENDIX F

INGREDIENTS, NUTRIENT COMPOSITION, AND CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION

Pellet Diet: July 1981 to July 1983

(Manufactured by Zeigler Bros., Inc., Gardners, PA)

TABLE F1. INGREDIENTS OF NIH 07 RAT AND MOUSE RATION (a)

Ingredients (b)	Percent by Weight
Ground #2 yellow shelled corn	24.50
Ground hard winter wheat	23.00
Soybean meal (49% protein)	12.00
Fish meal (60% protein)	10.00
Wheat middlings	10.00
Dried skim milk	5.00
Alfalfa meal (dehydrated, 17% protein)	4.00
Corn gluten meal (60% protein)	3.00
Soy oil	2.50
Dried brewer's yeast	2.00
Dry molasses	1.50
Dicalcium phosphate	1.25
Ground limestone	0.50
Salt	0.50
Premixes (vitamin and mineral)	0.25

(a) NCI, 1976; NIH, 1978
(b) Ingredients ground to pass through a U.S. Standard Screen No. 16 before being mixed

TABLE F2. VITAMINS AND MINERALS IN NIH 07 RAT AND MOUSE RATION (a)

	Amount	Source
Vitamins		
A	5,500,000 IU	Stabilized vitamin A palmitate or acetate
D_3	4,600,000 IU	D-activated animal sterol
K_3	2.8 g	Menadione
d-α-Tocopheryl acetate	20,000 IU	
Choline	560.0 g	Choline chloride
Folic acid	2.2 g	
Niacin	30.0 g	
d-Pantothenic acid	18.0 g	*d*-Calcium pantothenate
Riboflavin	3.4 g	
Thiamine	10.0 g	Thiamine mononitrate
B_{12}	4,000 µg	
Pyridoxine	1.7 g	*Pyridoxine hydrochloride*
Biotin	140.0 mg	*d*-Biotin
Minerals		
Iron	120.0 g	Iron sulfate
Manganese	60.0 g	Manganous oxide
Zinc	16.0 g	Zinc oxide
Copper	4.0 g	Copper sulfate
Iodine	1.4 g	Calcium iodate
Cobalt	0.4 g	Cobalt carbonate

(a) Per ton (2,000 lb) of finished product

TABLE F3. NUTRIENT COMPOSITION OF NIH 07 RAT AND MOUSE RATION

Nutrients	Mean ± Standard Deviation	Range	Number of Samples
Crude protein (percent by weight)	23.6 ± 0.87	22.2-25.3	25
Crude fat (percent by weight)	4.92 ± 0.54	3.3-5.7	25
Crude fiber (percent by weight)	3.30 ± 0.26	2.9-3.8	25
Ash (percent by weight)	6.43 ± 0.39	5.7-7.2	25
Amino Acids (percent of total diet) (a)			
Arginine	1.323 ± 0.830	1.21-1.39	4
Cystine	0.310 ± 0.099	0.218-0.400	4
Glycine	1.155 ± 0.069	1.06-1.21	4
Histidine	0.572 ± 0.030	0.530-0.603	4
Isoleucine	0.910 ± 0.033	0.881-0.944	4
Leucine	1.949 ± 0.065	1.85-1.99	4
Lysine	1.275 ± 0.076	1.20-1.37	4
Methionine	0.422 ± 0.187	0.306-0.699	4
Phenylalanine	0.909 ± 0.167	0.665-1.04	4
Threonine	0.844 ± 0.029	0.824-0.886	4
Tryptophan	0.187	0.171-0.211	3
Tyrosine	0.631 ± 0.094	0.566-0.769	4
Valine	1.11 ± 0.050	1.05-1.17	4
Essential Fatty Acids (percent of total diet) (a)			
Linoleic	2.44	2.37-2.52	3
Linolenic	0.274	0.256-0.308	3
Arachidonic	0.008		1
Vitamins (a)			
Vitamin A (IU/kg)	12,088 ± 4,119	7,500-24,000	25
Vitamin D (IU/kg)	4,650	3,000-6,300	2
α-Tocopherol (ppm)	41.53 ± 7.52	31.1-48.9	4
Thiamine (ppm) (b)	16.2 ± 2.30	12.0-21.0	24
Riboflavin (ppm)	7.5 ± 0.96	6.1-8.2	4
Niacin (ppm)	85.0 ± 14.2	65.0-97.0	4
Pantothenic acid (ppm)	29.3 ± 4.6	23.0-34.0	4
Pyridoxine (ppm)	7.6 ± 1.5	5.6-8.8	4
Folic acid (ppm)	2.8 ± 0.88	1.8-3.7	4
Biotin (ppm)	0.27 ± 0.05	0.21-0.32	4
Vitamin B_{12} (ppb)	21.0 ± 11.9	11.0-38.0	4
Choline (ppm)	3,302.0 ± 120.0	3,200.0-3,430.0	4
Minerals (a)			
Calcium (percent)	1.23 ± 0.10	1.08-1.44	25
Phosphorus (percent)	0.98 ± 0.05	0.88-1.11	25
Potassium (percent)	0.862 ± 0.100	0.772-0.974	3
Chloride (percent)	0.546 ± 0.100	0.442-0.635	4
Sodium (percent)	0.311 ± 0.038	0.258-0.350	4
Magnesium (percent)	0.169 ± 0.133	0.151-0.181	4
Sulfur (percent)	0.316 ± 0.070	0.270-0.420	4
Iron (ppm)	447.0 ± 57.3	409.0-523.0	4
Manganese (ppm)	90.6 ± 8.20	81.7-95.5	4
Zinc (ppm)	53.6 ± 5.27	46.1-58.6	4
Copper (ppm)	10.77 ± 3.19	8.09-15.39	4
Iodine (ppm)	2.95 ± 1.05	1.52-3.82	4
Chromium (ppm)	1.81 ± 0.28	1.44-2.09	4
Cobalt (ppm)	0.68 ± 0.14	0.49-0.80	4

(a) One to four lots of feed analyzed for nutrients reported in this table were done on lots of feed manufactured during 1983-85.
(b) One lot (7/22/821) was not analyzed for thiamine.

TABLE F4. CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION

Contaminants	Mean ± Standard Deviation	Range	Number of Samples
Arsenic (ppm)	0.50 ± 0.13	0.29-0.77	25
Cadmium (ppm) (a)	<0.10	<0.10	25
Lead (ppm) (b)	0.74 ± 0.42	0.33-1.97	23
Lead (ppm) (c)	0.92 ± 0.75	0.33-3.37	25
Mercury (ppm)	<0.05		25
Selenium (ppm)	0.29 ± 0.07	0.14-0.40	25
Aflatoxins (ppb)	<10	<5.0-<10.0	25
Nitrate nitrogen (ppm) (d)	9.22 ± 4.39	1.9-17.0	25
Nitrite nitrogen (ppm) (d)	2.19 ± 1.55	0.6-6.9	25
BHA (ppm) (e)	5.86 ± 4.87	2.0-17.0	25
BHT (ppm) (e)	3.00 ± 2.7	<1.0-12.0	25
Aerobic plate count (CFU/g) (f)	43,936 ± 31,267	4,900-110,000	25
Coliform (MPN/g) (g,h)	14.96 ± 22.36	<3-93	24
Coliform (MPN/g) (i)	32.76 ± 91.66	<3-460	25
E. coli (MPN/g) (j)	<3		25
Total nitrosamines (ppb)	3.42 ± 2.72	0.8-9.3	25
N-Nitrosodimethylamine (ppb)	2.68 ± 2.37	0.8-8.3	25
N-Nitrosopyrrolidine (ppb)	1.14 ± 0.48	<0.5-2.9	25
Pesticides (ppm)			
α-BHC (a,k)	<0.01		25
β-BHC (a)	<0.02		25
γ-BHC (a)	<0.01		25
δ-BHC (a)	<0.01		25
Heptachlor (a)	<0.01		25
Aldrin (a)	<0.01		25
Heptachlor epoxide (a)	<0.01		25
DDE (a)	<0.01		25
DDD (a)	<0.01		25
DDT (a)	<0.01		25
HCB (a)	<0.01		25
Mirex (a)	<0.01		25
Methoxychlor (l)	<0.05	0.09 (8/26/81); 0.06 (7/26/83)	25
Dieldrin (a)	<0.01		25
Endrin (a)	<0.01		25
Telodrin (a)	<0.01		25
Chlordane (a)	<0.05		25
Toxaphene (a)	<0.1		25
Estimated PCBs (a)	<0.2		25
Ronnel (a)	<0.01		25
Ethion (a)	<0.02		25
Trithion (a)	<0.05		25
Diazinon (a)	<0.1		25
Methyl parathion (a)	<0.02		25
Ethyl parathion (a)	<0.02		25
Malathion (m)	0.09 ± 0.06	<0.05-0.27	25
Endosulfan I (n)	<0.01		20
Endosulfan II (n)	<0.01		20
Endosulfan sulfate (n)	<0.03		20

TABLE F4. CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION (Continued)

(a) All values were less than the detection limit, given in the table as the mean.
(b) Mean, standard deviation, and range exclude two high values of 2.65 and 3.37 ppm obtained for lots produced on 8/26/81 and 7/21/82.
(c) Mean, standard deviation, and range include the high values given in footnote (b).
(d) Source of contamination: alfalfa, grains, and fish meal
(e) Source of contamination: soy oil and fish meal
(f) CFU = colony-forming unit
(g) MPN = most probable number
(h) Mean, standard deviation, and range exclude one high value of 460 MPN/g obtained for the lot produced on 9/23/82.
(i) Mean, standard deviation, and range include the high value given in footnote (h).
(j) All values were less than 3 MPN/g.
(k) BHC = hexachlorocyclohexane or benzene hexachloride
(l) Two observations were above the detection limit. The values and the dates they were obtained are given under the range.
(m) Eleven lots contained more than 0.05 ppm.
(n) Four lots (7/22/81-11/25/81) were not analyzed for endosulfan I, endosulfan II, or endosulfan sulfate.

APPENDIX G

CHEMICAL CHARACTERIZATION, ANALYSIS, AND DOSE PREPARATION OF GLYCIDOL FOR THE TOXICOLOGY STUDIES

APPENDIX G. CHEMICAL CHARACTERIZATION

Procurement and Characterization of Glycidol

Glycidol was obtained in one lot (lot no. 1536A) from the Dixie Chemical Company (Houston, TX). Purity and identity analyses were conducted at Midwest Research Institute (MRI) (Kansas City, MO). MRI reports on analyses performed in support of the glycidol studies are on file at the National Institute of Environmental Health Sciences.

Lot no. 1536A was obtained as a clear, colorless liquid with a boiling point of 160.8° C and a density of 1.1087 ± 0.0012(δ). Chemical identity was confirmed by spectroscopy. The infrared and nuclear magnetic resonance spectra (Figures G1 and G2) agreed with the literature spectra (Sadtler Standard Spectra). The ultraviolet/visible spectrum was consistent with that expected for the structure.

The purity of glycidol was determined by elemental analysis, Karl Fischer water analysis, titration in chloroform of the epoxide function with a 0.1 N perchloric acid titrant and a crystal violet indicator, after addition of excess tetrabutyl ammonium iodide to produce hydrogen iodide, and by gas chromatography with flame ionization detection, a nitrogen carrier at a flow rate of 70 ml/minute, and a 20% SP2100/0.1% Carbowax 1500 on a 100/200 Supelcoport column (system 1) or a 10% Carbowax 20M-TPA on a 80/100 Chromosorb W(AW) column (system 2).

Cumulative data indicated that the glycidol study material was approximately 94% pure. The results of the elemental analyses for hydrogen and oxygen were in agreement with the theoretical values; that for carbon was slightly low.

Water content was 0.71%. Titration of the epoxide group indicated a purity of 93.5%. Thirteen impurities were detected by each gas chromatographic system. In system 1, one impurity peak had an area of 2.7% relative to the major peak area, two unresolved peaks had a combined relative area of 1.6%, and the remaining peaks had a total relative area of 1.1%. In system 2, two peaks had relative areas of 2.5% and 1.3%, with the remaining peak areas totaling 0.47%.

Impurities in glycidol lot no. 1536A were identified and quantitated by gas chromatography (system 1) using helium as a carrier and flame ionization detection or by coupling to a Finnigan 4000 mass spectrometer operating at 70 eV with a scan range of 25-300 amu. Impurities with peak areas greater than 0.1% relative to that of the major peak were as follows: methanol, approximately 0.1%; 3-methoxy-1,2-propanediol, 1.2%; 3-chloro-1,2-propanediol, 0.4%; diglycidyl ether, 2.8%; and 2,6-dimethanol-1,4-dioxane, 1.1%.

Stability studies performed by gas chromatographic system 2 with 0.3% *n*-octanol as an internal standard indicated that glycidol was stable as a bulk chemical when kept at temperatures up to 25° C for at least 2 weeks. Decomposition was indicated at 60° C. Further confirmation of the stability of the bulk chemical during the 2-year studies (storage at −21° C) was obtained by epoxide titration as described above and gas chromatographic analysis with system 2 (carrier gas flow rate: 30 ml/minute). No notable degradation occurred over the course of the studies.

Preparation and Characterization of Dose Mixtures

The appropriate amounts of glycidol and distilled water were mixed to give the desired concentrations (Table G1). In studies conducted by the analytical chemistry laboratory by gas chromatography with a 10% Carbowax 20M column, solutions of glycidol in water (20 mg/ml) stored at room temperature in the dark showed losses of 3.9%, 21.7%, and 37.6% after 1, 7, and 14 days, respectively; solutions stored at 5° C in the dark showed losses of 1.8% and 4.6% after 7 and 14 days. Studies conducted by the study laboratory with the same analytical method indicated that dose mixtures (2.54 and 15.4 mg/ml) lost

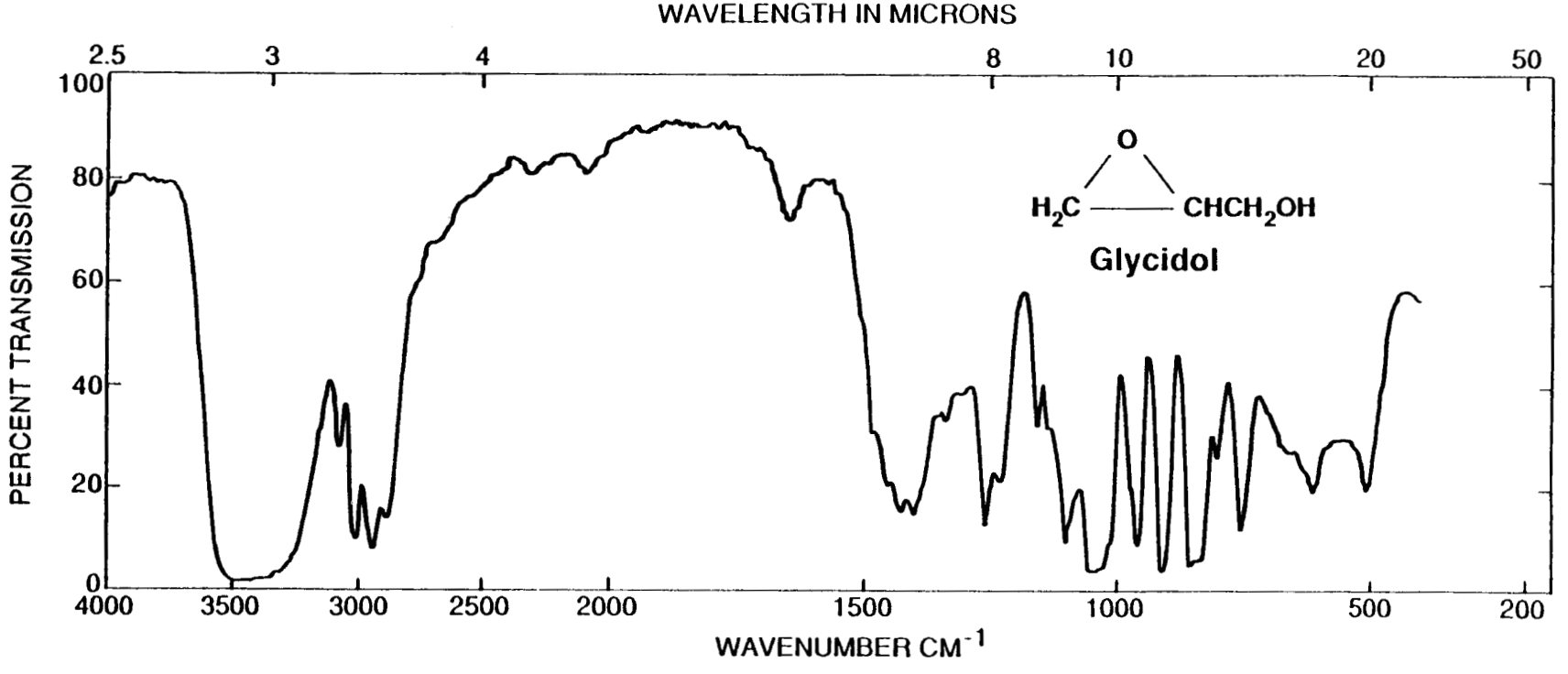

FIGURE G1. INFRARED ABSORPTION SPECTRUM OF GLYCIDOL (LOT NO. 1536A)

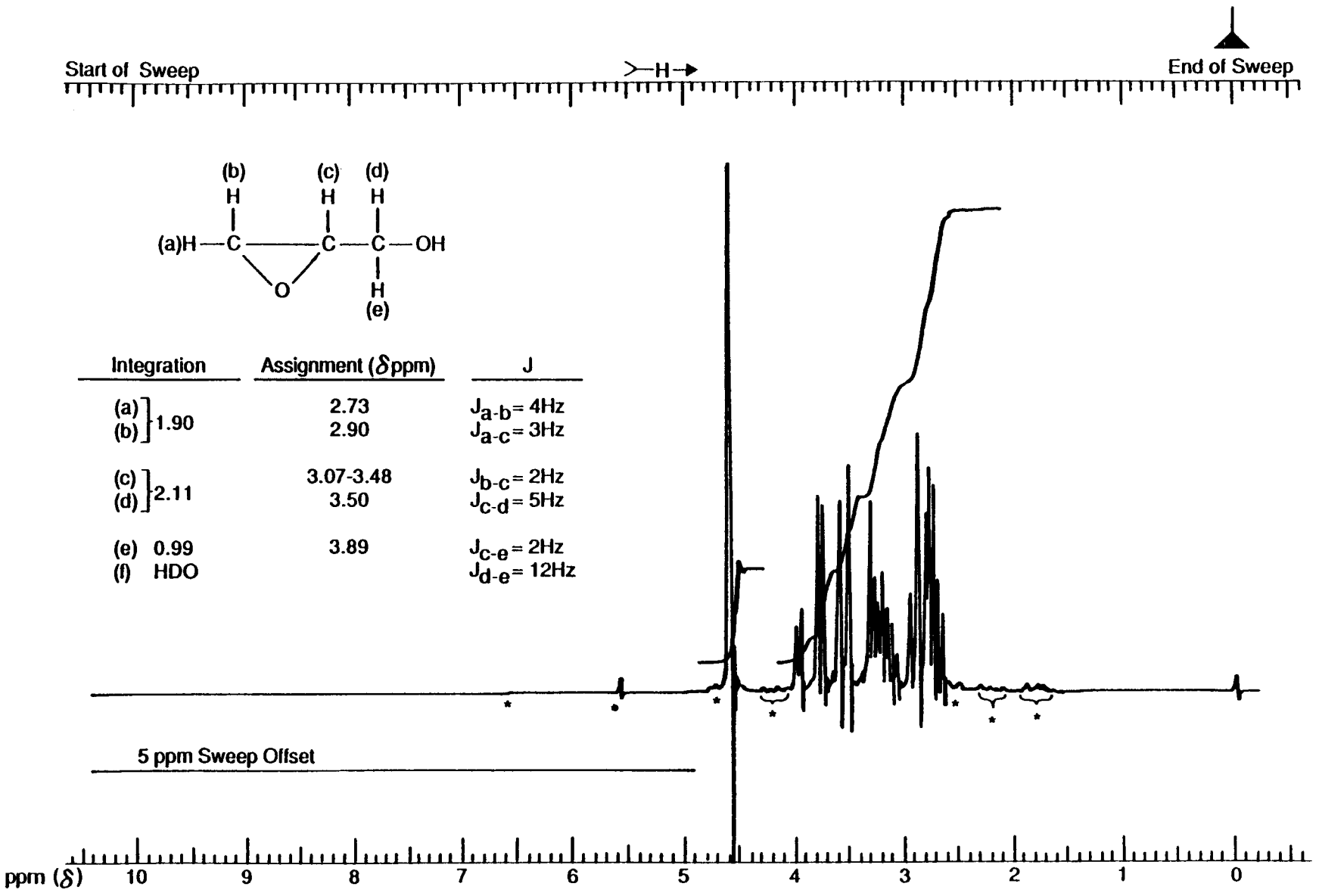

FIGURE G2. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF GLYCIDOL (LOT NO. 1536A)

TABLE G1. PREPARATION AND STORAGE OF DOSE MIXTURES IN THE GAVAGE STUDIES OF GLYCIDOL

Sixteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
Preparation		
A stock solution was made by dissolving the chemical in distilled water; all dose mixtures were made by dilution of the stock solution with distilled water	Same as 16-d studies	Same as 16-d studies
Maximum Storage Time		
11 d	9 d	11 d
Storage Conditions		
4° C	2°-5° C	3°-6° C

0.2%-0.3% glycidol per day during storage at 3°-6° C. Additional losses occurred while the solutions were held for about 3 hours at room temperature during the dosing period. Losses averaged 2.7% after 7 days of storage and animal-room exposure. During the 13-week studies, glycidol/distilled water solutions were stored at 2°-5° C for no longer than 9 days. During the 2-year studies, the dose mixtures were stored at 3°-6° C for no longer than 11 days.

Periodic analyses for glycidol in dose mixtures with the same gas chromatographic quantitation procedure were performed to determine if the dose mixtures contained the correct concentrations of glycidol. Dose mixtures were not analyzed during the 13-week studies. During the 2-year studies, the dose mixtures were analyzed every 1 or 2 months, and concentrations varied from 89% to 113% of the target concentration (Table G2). Data on the number of times that concentrations were within specifications can be extrapolated to indicate the frequency with which mixtures were formulated within the specified ± 10% of the target concentrations. For the glycidol studies, the mixtures were formulated within ± 10% of the target concentrations approximately 97% (61/63) of the time throughout the studies. Results of periodic referee analysis of dose mixtures by an independent laboratory were generally lower than those observed by the study laboratory, probably due in part to the instability of the chemical in water under the conditions of shipment and storage (Table G3).

TABLE G2. RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR GAVAGE STUDIES OF GLYCIDOL

Date Mixed	Concentration of Glycidol in Distilled Water for Target Concentration (mg/ml) (a)			
	2.5	5.0	7.5	15.0
07/16/81			7.45	14.7
07/30/81	2.40	4.80		
08/13/81		(b) 4.45		14.9
08/14/81		(c) 5.15		
09/11/81	2.45		7.15	
10/08/81		5.45		14.7
11/12/81	2.26		7.70	
12/03/81		5.05		15.5
12/17/81	2.50		7.30	
01/14/82		4.80		14.7
02/11/82	2.51		7.46	
03/11/82		(b) 5.65		15.2
03/15/82	2.43	(c) 4.95		
04/08/82	2.60		7.40	
05/06/82		5.05		15.0
06/03/82	2.46		7.56	
07/01/82		5.06		14.9
07/22/82	2.53		7.38	
08/26/82		4.95		14.8
09/23/82	2.54		7.57	
10/28/82		4.99		15.2
11/17/82	2.59		7.55	
12/16/82		4.95		15.0
01/13/83	2.50		7.62	
02/10/83	2.54	5.00		15.4
03/03/83	2.54		7.45	
04/07/83		4.81		14.6
05/05/83	2.54	4.98	7.46	15.0
06/09/83	2.40	5.06		
	2.37			
06/30/83	2.47		7.29	
07/14/83	2.46	5.04		
Mean (mg/ml)	2.48	5.01	7.45	15.0
Standard deviation	0.083	0.266	0.145	0.27
Coefficient of variation (percent)	3.3	5.3	1.9	1.8
Range (mg/ml)	2.26-2.60	4.45-5.65	7.15-7.70	14.6-15.5
Number of samples	19	16	14	14

(a) Results of duplicate analysis
(b) Out of specifications; not used in the studies.
(c) Remix; not included in the mean.

TABLE G3. RESULTS OF REFEREE ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR GAVAGE STUDIES OF GLYCIDOL

Date Mixed	Target Concentration (mg/ml)	Determined Concentration (mg/ml)	
		Study Laboratory (a)	Referee Laboratory (b)
07/16/81	7.5	7.45	7.23
03/15/82	5.0	4.95	4.86
09/23/82	2.5	2.54	2.40
03/03/83	7.5	7.45	7.29
07/14/83	2.5	2.46	2.47

(a) Results of duplicate analysis
(b) Results of triplicate analysis

APPENDIX H

GENETIC TOXICOLOGY

OF GLYCIDOL

METHODS

Salmonella Protocol: Testing was performed as reported by Canter et al. (1986) with modifications listed below. Chemicals were sent to the laboratories as coded aliquots from Radian Corporation (Austin, TX). The study chemical was incubated with the *Salmonella typhimurium* tester strains (TA97, TA98, TA100, TA1535, and TA1537) either in water or S9 mix (metabolic activation enzymes and cofactors from Aroclor 1254-induced male Sprague Dawley rat or Syrian hamster liver) for 20 minutes at 37° C before the addition of soft agar supplemented with L-histidine and D-biotin and subsequent plating on minimal glucose agar plates. Incubation was continued for an additional 48 hours.

Glycidol was tested in TA98, TA100, TA1535, and TA1537 at SRI International and in strains TA97, TA98, TA100, and TA1535 at Microbiological Associates, Inc. Each test consisted of triplicate plates of concurrent positive and negative controls and of at least five doses of the study chemical. The high dose was limited by toxicity or solubility but did not exceed 10 mg/plate. All negative assays were repeated, and all positive assays were repeated under the conditions that elicited the positive response. In the second trial, different doses within the same range (0-10,000 µg/plate) were sometimes tested to further clarify or define the response observed in the first trial.

A positive response was defined as a reproducible, dose-related increase in histidine-independent (revertant) colonies in any one strain/activation combination. An equivocal response was defined as an increase in revertants which was not dose related, not reproducible, or of insufficient magnitude to support a determination of mutagenicity. A response was considered negative when no increase in revertant colonies was observed after chemical treatment.

Mouse Lymphoma Protocol: The experimental protocol is presented in detail by Myhr et al. (1985) and follows the basic format of Clive et al. (1979). All study chemicals were supplied as coded aliquots from Radian Corporation (Austin, TX). The highest dose of the study compound was determined by solubility or toxicity and did not exceed 5 mg/ml. Mouse L5178Y/TK lymphoma cells were maintained at 37° C as suspension cultures in Fischer's medium supplemented with 2 mM L-glutamine, 110 µg/ml sodium pyruvate, 0.05% pluronic F68, antibiotics, and heat-inactivated horse serum; normal cycling time was about 10 hours. To reduce the number of spontaneously occurring trifluorothymidine (Tft)-resistant cells, subcultures were exposed once to medium containing thymidine, hypoxanthine, methotrexate, and glycine for 1 day; to thymidine, hypoxanthine, and glycine for 1 day; and to normal medium for 3-5 days. For cloning, horse serum content was increased and Noble agar was added. Freshly prepared S9 metabolic activation factors were obtained from the liver of either Aroclor 1254-induced or noninduced male F344 rats.

All doses within an experiment, including concurrent positive and solvent controls, were replicated. Treated cultures contained 6×10^6 cells in 10 ml of medium. This volume included the S9 fraction in those experiments performed with metabolic activation. Incubation with the study chemical continued for 4 hours, after which time the medium plus chemical was removed and the cells were resuspended in 20 ml of fresh medium and incubated for an additional 2 days to express the mutant phenotype. Cell density was monitored so that log phase growth was maintained. After the 48-hour expression period, 3×10^6 cells were plated in medium and soft agar supplemented with Tft for selection of Tft-resistant cells ($TK^{+/+}$), and 600 cells were plated in nonselective medium and soft agar to determine cloning efficiency. Plates were incubated at 37° C under 5% carbon dioxide for 10-12 days. All data were evaluated statistically for both trend and peak response. Both responses had to be significant ($P < 0.05$) for a chemical to be considered capable of inducing Tft resistance; a single significant response led to an "equivocal" conclusion, and the absence of both a trend and a peak response resulted in a "negative" call.

Minimum criteria for accepting an experiment as valid and a detailed description of the statistical analysis and data evaluation are presented in Myhr et al. (1985). This assay was initially performed without S9; if a clearly positive response was not obtained, the experiment was repeated with induced S9.

Chinese Hamster Ovary Cytogenetics Assays: Testing was performed as reported by Galloway et al. (1985) and is described briefly below. Chemicals were sent to the laboratory as coded aliquots from Radian Corporation (Austin, TX). Chemicals were tested in cultured Chinese hamster ovary (CHO) cells for induction of sister chromatid exchanges (SCEs) and chromosomal aberrations both in the presence and absence of Aroclor 1254-induced male Sprague Dawley rat liver S9 and cofactor mix. Cultures were handled under gold lights to prevent photolysis of bromodeoxyuridine (BrdU)-substituted DNA. Each test consisted of concurrent solvent and positive controls and of at least three doses of the study chemical; the high dose was limited by toxicity or solubility but did not exceed 5 mg/ml.

In the SCE test without S9, CHO cells were incubated for 26 hours with the study chemical in McCoy's 5A medium supplemented with 10% fetal bovine serum, L-glutamine (2 mM), and antibiotics. BrdU was added 2 hours after culture initiation. After 26 hours, the medium containing the study chemical was removed and replaced with fresh medium plus BrdU and colcemid, and incubation was continued for 2 more hours. Cells were then harvested by mitotic shake-off, fixed, and stained with Hoechst 33258 and Giemsa. In the SCE test with S9, cells were incubated with the chemical, serum-free medium, and S9 for 2 hours. The medium was then removed and replaced with medium containing BrdU and no study chemical; incubation proceeded for an additional 26 hours, with colcemid present for the final 2 hours. Harvesting and staining were the same as for cells treated without S9.

In the chromosomal aberration test without S9, cells were incubated in McCoy's 5A medium with the study chemical for 8 hours; colcemid was added, and incubation was continued for 2 hours. The cells were then harvested by mitotic shake-off, fixed, and stained with Giemsa. For the chromosomal aberration test with S9, cells were treated with the study chemical and S9 for 2 hours, after which the treatment medium was removed and the cells were incubated for 10 hours in fresh medium, with colcemid present for the final 2 hours. Cells were harvested in the same manner as for the treatment without S9.

For the SCE test, if significant chemical-induced cell cycle delay was seen, incubation time was lengthened to ensure a sufficient number of scorable cells. The harvest time for the chromosomal aberration test was based on the cell cycle information obtained in the SCE test; if cell cycle delay was anticipated, the incubation period was extended approximately 5 hours.

Cells were selected for scoring on the basis of good morphology and completeness of karyotype (21 ± 2 chromosomes). All slides were scored blind, and those from a single test were read by the same person. For the SCE test, 5, 10, 25, or 50 second-division metaphase cells were scored for frequency of SCEs per cell from each dose; 25 or 100 first-division metaphase cells were scored at each dose for the chromosomal aberration test. Classes of aberrations included simple (breaks and terminal deletions), complex (rearrangements and translocations), and other (pulverized cells, despiralized chromosomes, and cells containing 10 or more aberrations).

Statistical analyses were conducted on both the slopes of the dose-response curves and the individual dose points. An SCE frequency 20% above the concurrent solvent control value was chosen as a statistically conservative positive response. The probability of this level of difference occurring by chance at one dose point is less than 0.01; the probability for such a chance occurrence at two dose points is less than 0.001. Chromosomal aberration data are presented as percentage of cells with aberrations. As with SCEs, both the dose-response curve and individual dose points were statistically

analyzed. A statistically significant ($P<0.003$) trend test or a significantly increased dose point ($P<0.05$) was sufficient to indicate a chemical effect.

Drosophila Melanogaster Protocol: The assays for gene mutation and chromosomal translocation induction were performed as described by Zimmering et al. (1985). Study chemicals were supplied as coded aliquots from Radian Corporation (Austin, TX). Initially, study chemicals were assayed in the sex-linked recessive lethal (SLRL) test by feeding to adult Canton-S wild-type males that were no more than 24 hours old. If no response was obtained, the chemical was retested by injection into adult males. If either route of administration produced a positive result, the chemical was assayed for induction of reciprocal translocations (RTs) by using the same method of exposure. If, because of the physical nature of the chemical, feeding experiments were not possible, injection was selected as the method of study chemical administration, and a positive result was followed by an RT test.

To administer a chemical by injection, a glass Pasteur pipette is drawn out in a flame to a microfine filament and the tip is broken off to allow delivery of the test solution. Injection is either done manually by attaching a rubber bulb to the other end of the pipette and forcing through sufficient solution to slightly distend the abdomen of the fly (0.2-0.3 µl) or by attaching the pipette to a microinjector that automatically delivers a calibrated volume. Flies are anesthetized with ether and immobilized on a strip of double-stick tape; injection into the thorax under the wing is performed with the aid of a dissecting microscope.

Toxicity tests attempted to set concentrations of study chemical at a level that would produce 30% mortality after 72 hours of feeding or 24 hours after injection, while keeping induced sterility at an acceptable level. For the SLRL test, exposure by feeding was done by allowing Canton-S males (10-20 flies per vial) to feed for 72 hours on a solution of the study chemical in 5% sucrose. In the injection experiments, 24- to 72-hour-old Canton-S males were given a solution of the chemical dissolved in 0.7% saline or peanut oil and allowed 24 hours to recover. Exposed males were mated to three *Basc* females for 3 days and given fresh females at 2-day intervals to produce three matings of 3, 2, and 2 days; sample sperm from successive matings were treated as successively earlier postmeiotic stages. F_1 heterozygous females were allowed to mate with their siblings and then were placed in individual vials. F_1 daughters from the same parental male were kept together to identify clusters. (A cluster occurs when a number of mutants from a given male result from a single spontaneous premeiotic mutation event and is identified when the number of mutants from that male exceeds the number predicted by a Poisson distribution.) If a cluster was identified, all data from the male in question were discarded. After 17 days, presumptive lethal mutations were identified as vials containing no wild-type males; these were retested. At least two experiments were performed for each study chemical, resulting in the testing of some 740 treated and 3,000 control chromosomes. The only exceptions occurred when the results of the first experiment were clearly positive (induced frequency of recessive lethal mutations equal to or greater than 1%); then, the second trial was run.

Recessive lethal data were analyzed by the normal test (Margolin et al., 1983). A test result was considered to be positive if the P value was less than 0.01 and the mutation frequency in the tested group was greater than 0.10% or if the P value was less than 0.05 and the frequency in the treatment group was greater than 0.15%. A test was considered to be inconclusive if (a) the P value was between 0.05 and 0.01 but the frequency in the treatment group was between 0.10% and 0.15% or (b) the P value was between 0.10 and 0.05 but the frequency in the treatment group was greater than 0.10%. A result was considered to be negative if the P value was greater than 0.10 or if the frequency in the treatment group was less than 0.10%.

For the RT test, the exposure regimen was the same as that for the SLRL test except that small mass matings were used (10 males and 20 females). Exposed males were mated to y;bw;st p females for 3 days and discarded. The females were transferred to fresh medium every 3-4 days for a period of

about 3 weeks to produce a total of four broods. The results of the SLRL test were used to narrow the germ-cell stage most likely to be affected by the chemical; for example, if earlier germ-cell stages seemed to exhibit increased sensitivity, mating of the males was continued and translocation tests were carried out from the offspring derived from these earlier germ cell stages. F_1 males were mated individually to y;bw;st p females and the progeny were examined for missing classes, which indicate the occurrence of a translocation in the parental male. Suspected RTs were retested. The translocation data were analyzed according to the conditional binomial (Kastenbaum and Bowman, 1970).

Micronucleus Test: Preliminary range-finding studies were performed to determine appropriate doses for the in vivo micronucleus test. Dose selection in this study was based on animal lethality; no decrease in the percentage of polychromatic erythrocytes (PCEs) in the bone marrow was observed in any of the dose groups. Male mice were given two intraperitoneal injections, 24 hours apart, with the glycidol dissolved in phosphate-buffered saline; the total dose volume was 0.4 ml. Solvent control animals were injected with 0.4 ml phosphate-buffered saline only. The positive control mice received injections of mitomycin C. Twenty-four hours after the second injection, the mice were killed by cervical dislocation, and smears were prepared of the bone marrow cells obtained from the femurs. Air-dried smears were fixed and stained; 2,000 PCEs were scored for the number of micronucleated cells in each of five animals per dose group. The results were tabulated as the mean of the pooled results from all animals within a dose group ± the standard error of the mean.

RESULTS

Glycidol was mutagenic in *S. typhimurium* strains TA97, TA98, TA100, TA1535, and TA1537 when tested in a preincubation protocol with doses of 1-10,000 µg/plate both in the presence and absence of Aroclor 1254-induced male Sprague Dawley or Syrian hamster liver S9 (Canter et al., 1986; Table H1). When tested for induction of trifluorothymidine resistance in mouse lymphoma cells, glycidol gave positive responses at doses as low as 1.25 nl/ml in the absence of S9; it was not tested with S9 (Table H2). SCEs were induced in CHO cells treated with glycidol at concentrations of 1.1-150 µg/ml both in the presence and absence of Aroclor 1254-induced male Sprague Dawley rat liver S9; no cell cycle delay was observed, and strongly positive responses were recorded at all doses (Table H3). Glycidol (12.5-400 µg/ml) was a strong inducer of chromosomal aberrations in CHO cells both with and without S9 metabolic activation at all doses tested; due to glycidol-induced cell cycle delay, the incubation time before cell harvest was extended (Table H4). Glycidol induced both sex-linked recessive lethal mutations and reciprocal translocations in the germ cells of male *D. melanogaster* fed a solution containing 1,230 ppm glycidol (Tables H5 and H6). The incidence of micronucleated PCEs in the bone marrow of male B6C3F_1 mice administered two intraperitoneal injections of glycidol at 24-hour intervals was significantly increased over that in vehicle controls; in both trials, the incidence of micronucleated PCEs in the high dose animals (150 mg/kg × 2) was approximately three times the incidence in the vehicle controls (Table H7).

TABLE H1. MUTAGENICITY OF GLYCIDOL IN *SALMONELLA TYPHIMURIUM* (a)

Strain	Dose (µg/plate)	Revertants/Plate (b)					
		−S9		+S9 (hamster)		+S9 (rat)	
		Trial 1	Trial 2	Trial 1	Trial 2	Trial 1	Trial 2
Study performed at SRI International							
TA100	0	98 ± 7.7	127 ± 6.4	123 ± 7.9	136 ± 15.0	140 ± 4.5	151 ± 14.2
	1	--	132 ± 7.9	--	137 ± 6.7	--	126 ± 8.1
	3	--	138 ± 8.7	--	157 ± 18.3	--	139 ± 0.3
	10	--	180 ± 1.0	--	211 ± 11.2	--	222 ± 8.4
	33	--	253 ± 9.5	--	296 ± 6.7	--	303 ± 3.2
	100	409 ± 24.8	410 ± 11.3	498 ± 15.5	486 ± 18.3	465 ± 17.5	533 ± 3.5
	333	714 ± 59.4	--	792 ± 9.8	--	732 ± 9.6	--
	1,000	1,150 ± 7.2	--	1,179 ± 37.9	--	1,232 ± 8.2	--
	3,333	1,445 ± 44.6	--	1,594 ± 30.8	--	1,622 ± 35.2	--
	10,000	678 ± 45.5	--	1,316 ± 22.5	--	1,337 ± 36.9	--
Trial summary		Positive	Positive	Positive	Positive	Positive	Positive
Positive control (c)		487 ± 10.5	353 ± 10.3	1,380 ± 23.3	1,580 ± 96.6	530 ± 16.3	810 ± 26.8
TA1535	0	23 ± 6.8	20 ± 3.0	9 ± 2.0	10 ± 2.2	11 ± 3.3	7 ± 0.9
	1	--	33 ± 3.2	--	14 ± 2.7	--	19 ± 3.3
	3	--	53 ± 2.6	--	33 ± 5.7	--	33 ± 4.0
	10	--	98 ± 6.7	--	92 ± 9.8	--	90 ± 1.2
	33	--	194 ± 4.8	--	221 ± 14.7	--	218 ± 4.2
	100	495 ± 14.1	459 ± 17.7	531 ± 23.3	478 ± 11.0	541 ± 23.2	470 ± 8.1
	333	776 ± 27.1	--	873 ± 19.1	--	858 ± 6.7	--
	1,000	1,044 ± 36.8	--	1,148 ± 25.8	--	1,204 ± 59.3	--
	3,333	1,137 ± 11.4	--	1,366 ± 41.8	--	1,429 ± 18.4	--
	10,000	(d) 181 ± 101.7	--	1,304 ± 69.4	--	1,315 ± 34.7	--
Trial summary		Positive	Positive	Positive	Positive	Positive	Positive
Positive control (c)		540 ± 15.3	402 ± 14.3	356 ± 17.7	518 ± 29.9	154 ± 9.3	195 ± 27.7
TA1537	0	10 ± 2.2	5 ± 0.9	9 ± 1.9	6 ± 0.6	10 ± 1.2	4 ± 0.3
	100	9 ± 2.8	--	9 ± 2.6	--	15 ± 1.5	--
	333	8 ± 2.9	7 ± 1.2	18 ± 1.7	8 ± 1.9	7 ± 1.2	7 ± 0.7
	1,000	15 ± 0.3	12 ± 2.0	23 ± 2.8	7 ± 0.3	10 ± 2.2	15 ± 1.5
	1,666	--	13 ± 2.3	--	12 ± 3.3	--	19 ± 5.4
	3,333	21 ± 3.5	15 ± 1.9	28 ± 2.3	22 ± 3.8	22 ± 2.2	23 ± 1.8
	6,666	--	16 ± 3.4	--	22 ± 3.8	--	13 ± 3.0
	10,000	8 ± 1.3	--	8 ± 0.3	--	5 ± 0.9	--
Trial summary		Weakly positive	Weakly positive	Positive	Positive	Equivocal	Positive
Positive control (c)		237 ± 54.5	145 ± 3.2	434 ± 32.2	435 ± 11.9	189 ± 11.7	171 ± 5.2
TA98	0	16 ± 0.7	16 ± 1.2	25 ± 2.6	21 ± 1.5	21 ± 1.5	21 ± 2.7
	100	32 ± 3.5	--	20 ± 0.7	--	26 ± 3.2	--
	333	28 ± 4.4	22 ± 2.7	19 ± 3.8	32 ± 4.2	36 ± 6.5	30 ± 1.9
	1,000	34 ± 3.0	25 ± 3.7	32 ± 2.1	40 ± 6.4	36 ± 2.7	43 ± 7.8
	1,666	--	30 ± 3.5	--	44 ± 5.3	--	34 ± 3.1
	3,333	50 ± 3.4	34 ± 3.2	47 ± 5.5	58 ± 2.0	64 ± 1.5	42 ± 5.5
	6,666	--	42 ± 1.5	--	57 ± 2.6	--	47 ± 2.5
	10,000	43 ± 6.2	--	15 ± 1.2	--	50 ± 7.2	--
Trial summary		Positive	Positive	Weakly positive	Positive	Positive	Positive
Positive control (c)		863 ± 17	718 ± 16.7	1,276 ± 36.5	1,334 ± 104.6	863 ± 31.6	488 ± 31.1

TABLE H1. MUTAGENICITY OF GLYCIDOL IN *SALMONELLA TYPHIMURIUM* (Continued)

Strain	Dose (µg/plate)	Revertants/Plate (b) −S9 Trial 1	−S9 Trial 2	+S9 (hamster) Trial 1	+S9 (hamster) Trial 2	+S9 (rat) Trial 1	+S9 (rat) Trial 2
Study performed at Microbiological Associates, Inc.							
TA100	0	113 ± 3.9	92 ± 4.9	94 ± 4.9	88 ± 9.5	101 ± 6.4	101 ± 8.0
	1	--	84 ± 5.8	--	96 ± 4.8	--	95 ± 4.6
	10	--	146 ± 5.2	--	117 ± 8.5	--	140 ± 7.9
	100	482 ± 16.2	292 ± 7.3	463 ± 10.6	391 ± 14.0	472 ± 14.0	378 ± 9.0
	333	1,041 ± 19.7	--	1,015 ± 8.8	--	1,041 ± 11.5	--
	1,000	1,808 ± 32.7	1,018 ± 11.4	1,632 ± 10.2	(d) 1,302 ± 38.7	1,951 ± 9.0	1,269 ± 26.4
	3,333	3,075 ± 117.2	--	2,910 ± 135.4	--	2,973 ± 9.4	--
	10,000	3,332 ± 63.5	(d) 2,088 ± 2.2	3,422 ± 44.8	(d) 2,487 ± 59.8	3,435 ± 14.5	(d) 2,465 ± 41.0
Trial summary		Positive	Positive	Positive	Positive	Positive	Positive
Positive control (c)		1,353 ± 28.5	712 ± 7.0	1,303 ± 61.9	843 ± 32.8	1,779 ± 21.8	1,368 ± 25.4
TA1535	0	30 ± 2.9	21 ± 1.5	11 ± 2.2	8 ± 0.6	13 ± 2.7	7 ± 2.6
	1	--	20 ± 4.6	--	10 ± 0.7	--	15 ± 2.1
	10	--	72 ± 11.1	--	57 ± 5.2	--	70 ± 11.0
	100	473 ± 1.8	477 ± 15.8	522 ± 16.2	443 ± 3.4	533 ± 16.3	516 ± 14.4
	333	935 ± 21.5	--	1,194 ± 24.6	--	1,193 ± 13.8	--
	1,000	1,329 ± 26.3	1,338 ± 21.2	2,231 ± 62.4	1,422 ± 30.7	2,218 ± 61.2	1,360 ± 31.4
	3,333	2,303 ± 64.4	--	2,867 ± 46.9	--	2,929 ± 41.6	--
	10,000	1,831 ± 39.2	(d) 1,238 ± 23.4	1,697 ± 20.3	(d) 1,930 ± 41.0	981 ± 26.9	(d) 1,336 ± 84.0
Trial summary		Positive	Positive	Positive	Positive	Positive	Positive
Positive control (c)		847 ± 17.6	915 ± 21.2	101 ± 11.4	68 ± 2.1	141 ± 11.6	76 ± 1.3
TA97	0	111 ± 10.0	102 ± 6.4	112 ± 5.0	117 ± 4.1	124 ± 1.9	136 ± 1.5
	1	--	99 ± 3.8	--	120 ± 7.7	--	149 ± 3.7
	10	--	99 ± 3.8	--	115 ± 7.8	--	152 ± 11.6
	100	119 ± 3.5	109 ± 6.7	175 ± 15.6	172 ± 6.9	161 ± 12.7	179 ± 3.2
	333	230 ± 2.8	--	275 ± 13.3	--	265 ± 10.5	--
	1,000	383 ± 2.8	317 ± 8.8	519 ± 15.4	455 ± 4.7	457 ± 15.3	439 ± 11.4
	3,333	903 ± 45.6	--	1,131 ± 43.1	--	976 ± 53.2	--
	10,000	888 ± 16.6	(d) 452 ± 2.1	963 ± 74.4	(d) 1,215 ± 15.9	842 ± 85.8	(d) 998 ± 9.0
Trial summary		Positive	Positive	Positive	Positive	Positive	Positive
Positive control (c)		501 ± 14.5	617 ± 24.6	930 ± 45.0	549 ± 31.7	1,318 ± 35.7	910 ± 43.3
TA98	0	22 ± 0.3	17 ± 0.9	35 ± 1.3	23 ± 3.2	36 ± 1.2	26 ± 1.5
	1	--	16 ± 2.1	--	33 ± 2.9	--	29 ± 3.2
	10	--	21 ± 2.0	--	25 ± 6.5	--	28 ± 1.5
	100	21 ± 4.7	17 ± 3.5	32 ± 4.1	38 ± 3.8	31 ± 1.8	33 ± 5.3
	333	22 ± 2.5	--	48 ± 4.7	--	37 ± 3.5	--
	1,000	29 ± 2.3	20 ± 3.0	43 ± 2.7	48 ± 7.5	44 ± 2.3	42 ± 2.7
	3,333	40 ± 3.5	--	60 ± 5.7	--	59 ± 3.1	--
	10,000	44 ± 2.1	(d) 35 ± 0.9	58 ± 8.3	(d) 53 ± 8.0	49 ± 4.1	39 ± 4.5
Trial summary		Weakly positive	Equivocal	Weakly positive	Weakly positive	Equivocal	Equivocal
Positive control (c)		1,716 ± 40.7	1,279 ± 22.7	925 ± 13.2	818 ± 3.9	1,264 ± 34.8	1,376 ± 40.4

(a) The detailed protocol and data are presented in Canter et al. (1986). Cells and study compound or solvent (water) were incubated in the absence of exogenous metabolic activation (−S9) or with Aroclor 1254-induced S9 from male Syrian hamster liver or male Sprague Dawley rat liver. High dose was limited by toxicity or solubility but did not exceed 10 mg/plate; 0 µg/plate dose is the solvent control.
(b) Revertants are presented as mean ± standard error from three plates.
(c) Positive control; 2-aminoanthracene was used on all strains in the presence of S9. In the absence of metabolic activation, 4-nitro-*o*-phenylenediamine was used with TA98, sodium azide was used with TA100 and TA1535, and 9-aminoacridine was used with TA1537 and TA97.
(d) Slight toxicity

TABLE H2. INDUCTION OF TRIFLUOROTHYMIDINE RESISTANCE IN MOUSE L5178Y/TK LYMPHOMA CELLS BY GLYCIDOL (a,b)

Compound	Concentration (nl/ml)	Cloning Efficiency (percent)	Relative Total Growth (percent)	Tft-Resistant Cells	Mutant Fraction (c)
Trial 1					
Water (d)		97.0 ± 5.7	99.8 ± 19.4	110.0 ± 11.9	38.0 ± 3.0
Glycidol	5	69.7 ± 4.8	64.3 ± 5.5	449.3 ± 22.1	(e) 215.7 ± 4.8
	(f) 10	65.0 ± 2.0	27.5 ± 3.5	809.5 ± 35.5	(e) 416.5 ± 29.5
	(g) 20	31	11	689	745
	30	14.3 ± 1.3	1.7 ± 0.7	463.0 ± 40.9	(e) 1,112.7 ± 25.5
	40	Lethal	--	--	--
Methyl methanesulfonate	(h) 5	102.7 ± 4.7	94.0 ± 3.1	383.3 ± 50.3	(e) 125.3 ± 19.2
Trial 2					
Water		104.0 ± 8.5	100.0 ± 2.5	86.7 ± 6.7	28.3 ± 2.7
Glycidol	0.313	75.0 ± 6.0	63.7 ± 2.0	76.0 ± 9.8	34.0 ± 3.2
	0.625	103.7 ± 7.0	75.7 ± 4.7	100.7 ± 5.9	32.7 ± 2.0
	1.25	96.3 ± 6.9	72.7 ± 0.9	168.3 ± 3.0	(e) 58.7 ± 3.0
	2.5	97.3 ± 3.8	63.7 ± 4.7	293.0 ± 21.1	(e) 101.3 ± 8.0
	5	83.7 ± 6.5	49.0 ± 2.1	522.7 ± 45.1	(e) 208.7 ± 7.4
	10	67.7 ± 11.7	35.0 ± 6.4	748.7 ± 33.8	(e) 386.0 ± 55.1
Methyl methanesulfonate	(h) 5	83.3 ± 6.4	57.0 ± 8.7	441.7 ± 20.5	(e) 178.7 ± 12.3

(a) Study performed at Litton Bionetics, Inc. The experimental protocol is presented in detail by Myhr et al. (1985) and follows the basic format of Clive et al. (1979). The highest dose of study compound is determined by solubility or toxicity and may not exceed 5 mg/ml. All doses are tested in triplicate unless otherwise specified; the average for the tests is presented in the table. Cells (6×10^5/ml) were treated for 4 hours at 37° C in medium, washed, resuspended in medium, and incubated for 48 hours at 37° C. After expression, 3×10^6 cells were plated in medium and soft agar supplemented with trifluorothymidine (Tft) for selection of Tft-resistant cells, and 600 cells were plated in nonselective medium and soft agar to determine the cloning efficiency.

(b) Mean ± standard error from replicate trials of approximately 1×10^6 cells each. All data are evaluated statistically for both trend and peak response ($P<0.05$ for at least one of the three highest dose sets). Both responses must be significantly ($P<0.05$) positive for a chemical to be considered capable of inducing Tft resistance. If only one of these responses is significant, the call is "equivocal"; the absence of both trend and peak response results in a "negative" call.

(c) Mutant fraction (frequency) is a ratio of the Tft-resistant cells to the cloning efficiency, divided by 3 (to arrive at MF per 1×10^6 cells treated); MF = mutant fraction.

(d) Data presented are the average of four tests.

(e) Significant positive response; occurs when the relative mutant fraction (average MF of treated culture/average MF of solvent control) is greater than or equal to 1.6.

(f) Data presented are the average of two tests.

(g) Data presented are for one test.

(h) Concentration in micrograms per milliliter

TABLE H3. INDUCTION OF SISTER CHROMATID EXCHANGES IN CHINESE HAMSTER OVARY CELLS BY GLYCIDOL (a)

Compound	Dose (µg/ml)	Total Cells	No. of Chromosomes	No. of SCEs	SCEs/ Chromosome	SCEs/ Cell	Hours in BrdU	Relative SCEs/Cell (percent) (b)
−S9 (c)								
Trial 1--Summary: Positive								
Medium		50	1,015	432	0.43	8.6	25.8	
Glycidol	1.11	10	206	590	2.86	59.0	25.8	686.0
	3.69	10	205	856	4.18	85.6	25.8	995.3
	11.07	5	104	868	8.35	173.6	25.8	2,018.6
Mitomycin C	0.005	50	1,018	669	0.66	13.4	25.8	155.8
	0.01	5	102	192	1.88	38.4	25.8	446.5
Trial 2--Summary: Positive								
Medium		50	1,036	453	0.44	9.1	25.6	
Glycidol	10.1	10	207	883	4.27	88.3	25.6	970.3
	12.5	5	105	572	5.45	114.4	25.6	1,257.1
	15	5	102	683	6.70	136.6	25.6	1,501.1
Mitomycin C	0.0015	50	1,020	780	0.76	15.6	25.6	171.4
	0.01	5	105	220	2.10	44.0	25.6	483.5
+S9 (d)								
Trial 1--Summary: Positive								
Medium		50	1,038	538	0.52	10.8	25.8	
Glycidol	11.1	25	513	896	1.75	35.8	25.8	331.5
	36.9	25	510	1,754	3.44	70.2	25.8	650.0
	110.7	25	511	2,652	5.19	106.1	25.8	982.4
Cyclophosphamide	0.4	50	1,021	855	0.84	17.1	25.8	158.3
	2	5	108	273	2.53	54.6	25.8	505.6
Trial 2--Summary: Positive								
Medium		50	1,032	606	0.59	12.1	25.6	
Glycidol	100.5	10	206	860	4.17	86.0	25.6	710.7
	124.5	5	107	596	5.57	119.2	25.6	985.1
	150	5	106	599	5.65	119.8	25.6	990.1
Cyclophosphamide	0.4	50	1,024	739	0.72	14.8	25.6	122.3
	2	5	104	142	1.37	28.4	25.6	234.7

TABLE H3. INDUCTION OF SISTER CHROMATID EXCHANGES IN CHINESE HAMSTER OVARY CELLS BY GLYCIDOL (Continued)

(a) Study performed at Litton Bionetics, Inc. SCE = sister chromatid exchange; BrdU = bromodeoxyuridine. A detailed description of the SCE protocol is presented by Galloway et al. (1985). Briefly, Chinese hamster ovary cells were incubated with study compound or solvent as described in (c) and (d) below and cultured for sufficient time to reach second metaphase division. Cells were then collected by mitotic shake-off, fixed, air dried, and stained.
(b) SCEs/cell of culture exposed to study chemical relative to those of culture exposed to solvent
(c) In the absence of S9, Chinese hamster ovary cells were incubated with study compound or solvent for 2 hours at 37° C. Then BrdU was added, and incubation was continued for 24 hours. Cells were washed, fresh medium containing BrdU and colcemid was added, and incubation was continued for 2-3 hours.
(d) In the presence of S9, cells were incubated with study compound or solvent for 2 hours at 37° C. Cells were then washed, and medium containing BrdU was added. Cells were incubated for a further 26 hours, with colcemid present for the final 2-3 hours. S9 was from the liver of Aroclor 1254-induced male Sprague Dawley rats.

TABLE H4. INDUCTION OF CHROMOSOMAL ABERRATIONS IN CHINESE HAMSTER OVARY CELLS BY GLYCIDOL (a)

	−S9 (b)					+S9 (c)				
Dose (µg/ml)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells with Abs	Dose (µg/ml)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells with Abs
Trial 1--Harvest time: 20.5 hours (d)					Harvest time: 20.5 hours (d)				
Medium					Medium				
	100	1	0.01	1.0		100	7	0.07	5.0
Glycidol					Glycidol				
12.5	100	16	0.16	12.0	198.7	25	44	1.76	60.0
24.8	25	19	0.76	44.0	301.2	25	163	6.52	96.0
49.9	25	52	2.08	80.0	400.7	25	172	6.88	100.0
Summary: Positive					Summary: Positive				
Mitomycin C					Cyclophosphamide				
0.025	100	12	0.12	32.0	2.5	100	20	0.20	13.0
0.062	25	18	0.72	16.0	12.5	25	17	0.68	44.0
Trial 2--Harvest time: 20.5 hours (d)									
Medium									
	100	0	0.00	3.0					
Glycidol									
50.3	25	46	1.84	80.0					
75.0	25	88	3.52	84.0					
100.0	25	120	4.80	84.0					
Summary: Positive									
Mitomycin C									
0.025	100	10	0.10	24.0					
0.062	25	12	0.48	10.0					

(a) Study performed at Litton Bionetics, Inc. Abs = aberrations. A detailed presentation of the technique for detecting chromosomal aberrations is found in Galloway et al. (1985). Briefly, Chinese hamster ovary cells were incubated with study compound or solvent as indicated in (b) and (c). Cells were arrested in first metaphase by addition of colcemid and harvested by mitotic shake-off, fixed, and stained in 6% Giemsa.
(b) In the absence of S9, cells were incubated with study compound or solvent for 8-10 hours at 37° C. Cells were then washed, and fresh medium containing colcemid was added for an additional 2-3 hours followed by harvest.
(c) In the presence of S9, cells were incubated with study compound or solvent for 2 hours at 37° C. Cells were then washed, medium was added, and incubation was continued for 8-10 hours. Colcemid was added for the last 2-3 hours of incubation before harvest. S9 was from the liver of Aroclor 1254-induced male Sprague Dawley rats.
(d) Because of significant chemical-induced cell cycle delay, incubation time prior to addition of colcemid was lengthened to provide sufficient metaphases at harvest.

TABLE H5. INDUCTION OF SEX-LINKED RECESSIVE LETHAL MUTATIONS IN *DROSOPHILA MELANOGASTER* BY GLYCIDOL (a)

Route of Exposure	Dose (ppm)	Incidence of Deaths (percent)	Incidence of Sterility (percent)	No. of Lethals/No. of X Chromosomes Tested Mating 1	Mating 2	Mating 3	Overall Total (b)
Feeding	1,230	0	35	42/596	17/138	0/006	59/740 (7.97%)
	0			1/974	5/975	2/900	8/2,849 (0.28%)

(a) Study performed at University of Wisconsin--Madison. A detailed protocol of the sex-linked recessive lethal assay is presented by Zimmering et al. (1985). Exposure by feeding was done by allowing 24-hour-old Canton-S males to feed for 3 days on a solution of the study chemical dissolved in 5% sucrose. Exposed males were mated to three *Basc* females for 3 days and given fresh females at 2-day intervals to produce three broods of 3, 2, and 2 days; sample sperm from successive matings were treated as spermatozoa (mating 1), spermatids (mating 2), and spermatocytes (mating 3). F_1 heterozygous females were crossed to their siblings and placed in individual vials. F_1 daughters from the same parental male were kept together to identify clusters; no clusters were found. After 17 days, presumptive lethal mutations were identified as vials containing no wild-type males; these were retested. Results were significant at the 5% level (Margolin et al., 1983).
(b) Combined total of number of lethal mutations/number of X chromosomes tested for three mating trials

TABLE H6. INDUCTION OF RECIPROCAL TRANSLOCATIONS IN *DROSOPHILA MELANOGASTER* BY GLYCIDOL (a)

Route of Exposure	Dose (ppm)	Transfers Translocations/Total F_1 Tested 1	2	3	4	Total No. of Tests	Total No. of Trans-locations	Total Trans-locations (percent)
Feeding	1,230	1/515	14/608	6/29	0/1	1,153	21	1.82
Historical control	0					116,163	2	0.00

(a) Study performed at University of Wisconsin--Madison. A detailed protocol of the reciprocal translocation assay is presented by Zimmering et al. (1985). Exposed males were mated to three y;bw;st p females for 3 days and discarded. In this manner, sample sperm from successive cultures were stored for increasing lengths of time. Individual F_1 males were backcrossed to y;bw;st p females, and the F_2 were screened for pseudolinkage. This procedure allows the recovery of translocations involving the Y, second, or third chromosomes in any combination. Presumptive translocations were retested. Results were significant (Kastenbaum and Bowman, 1970).

TABLE H7. INCIDENCE OF MICRONUCLEI IN BONE MARROW POLYCHROMATIC ERYTHROCYTES OF MICE ADMINISTERED GLYCIDOL (a)

	Dose (mg/kg)	Micronucleated Cells/1,000 Cells (b) Trial 1	Trial 2
Vehicle controls (c)	0	1.5 ± 0.4	0.6 ± 0.2
Glycidol	37.5	1.5 ± 0.3	1.3 ± 0.3
	75	2.4 ± 0.4	0.7 ± 0.3
	150	4.4 ± 0.8	1.9 ± 0.6
		P<0.001	0.01<P<0.05
Mitomycin C (d)	1	37.7 ± 4.6	30.2 ± 2.7

(a) Study performed at Environmental Health Research and Testing, Inc. Glycidol, dissolved in phosphate-buffered saline, was administered by intraperitoneal injection to male $B6C3F_1$ mice two times, at 24-hour intervals; bone marrow smears were prepared 24 hours after the second injection. For each trial, 2,000 polychromatic erythrocytes were scored for the number of micronuclei in each of five animals per dose group.
(b) Mean ± standard error of the mean
(c) Vehicle control animals received injections of 0.4 ml phosphate-buffered saline.
(d) Positive control material was dissolved in phosphate-buffered saline and administered by intraperitoneal injection.

APPENDIX I

AUDIT SUMMARY

APPENDIX I. AUDIT SUMMARY

The pathology specimens, experimental data, study documents, and draft Technical Report No. 374 for the 2-year studies of glycidol in rats and mice were audited for the National Institute of Environmental Health Sciences (NIEHS) at the National Toxicology Program (NTP) Archives by quality assurance, resource-support contractors. The audits included review of:

(1) All records concerning animal receipt, quarantine, randomization, and disposition prior to study start.

(2) All inlife records including protocol, correspondence, animal husbandry, environmental conditions, dosing, external masses, mortality, animal identification, and serology.

(3) Body weight and clinical observation data; all data were scanned before individual data for a random 10% sample of animals in each study group were reviewed in detail.

(4) All study chemical records.

(5) All postmortem records for individual animals concerning date of death, disposition code, condition code, tissue accountability, correlation of masses or clinical signs recorded at the last inlife observation with gross observations and microscopic diagnoses, consistency of data entry on necropsy record forms, and correlation between gross observations and microscopic diagnoses.

(6) Inventory for wet tissue bags from all animals and residual wet tissues from a random 20% sample of animals in each study group, plus other relevant cases, to evaluate the integrity of individual animal identity and the thoroughness of necropsy and trimming procedure performance.

(7) Blocks and slides of tissues from a random 20% sample of animals from each study group, plus animals with less than complete or correct identification, to examine for proper inventory, labeling, matching of tissue sections, and preservation.

(8) All microscopic diagnoses for a random 10% sample of animals, plus 100% of the changes in diagnoses made to preliminary pathology tables, to verify their incorporation into the final pathology tables.

(9) The extent of correlation between the data, factual information, and procedures for the 2-year studies presented in the draft Technical Report and the study records available at the NTP Archives.

Review of the available records indicated that protocol-specified procedures for animal care were followed adequately. Records that documented the preparation, analysis, and administration of doses to animals were accurate. The review of body weight records showed that 108/110 recalculated mean values were correct and that the original records contained data for four groups of rats that were weighed twice during the same week; this duplication was not included in the Technical Report.

Data entries on necropsy forms were made appropriately for rats and mice. The observation of external masses recorded during the last few months of life was thorough, and their correlation with observations made at necropsy was excellent (184/185 in rats and 67/67 in mice correlated). The date of death and disposition code recorded at necropsy for each unscheduled-death animal (252 rats and 140 mice) had matching entries in the inlife records, except for one low dose female mouse that had been designated for moribund kill but apparently died naturally on its way to necropsy. The survival values presented in the Technical Report for the low dose male and high dose female groups of mice were actually 26 and 18, respectively; one animal in each group survived to the start of the terminal-kill period but was assigned a disposition code of moribund kill and counted as such. The condition code

assigned at necropsy was consistent with gross observations and disposition code for all mice and 297/300 rats.

Individual animal identifiers (ears and toes) were present and correct in the residual tissue bags for 54/64 mice examined; ears were present and correct for 55/69 rats examined; however, feet had not been retained (per protocol at that time) and study group could not be verified. Review of the entire data trail for the 69 rats and 10 mice with less than complete and correct identifiers indicated that the integrity of individual animal identity had been maintained throughout the studies. A total of 11 untrimmed potential lesions were found in the wet tissues of 69 rats examined, and 3 were found in those of 64 mice examined. Intestinal segments and cecum were opened incompletely in 43/62 mice. Each gross observation made at necropsy had a corresponding microscopic diagnosis for all but three in rats and four in mice. Blocks and slides were present and labeled correctly; corresponding tissue sections in blocks and on slides matched each other properly for all but eight pairings each in rats and mice. All post-Pathology Working group changes in diagnoses had been incorporated into the final pathology tables. The incidences of tumors given in the Technical Report were the same as those in the final pathology tables at the Archives.

This summary describes general audit findings and the extent to which the data and factual information presented in the Technical Report are supported by records at the NTP Archives. Full details are presented in audit reports that are on file at the NIEHS.

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