

**NATIONAL TOXICOLOGY PROGRAM**  
**Technical Report Series**  
**No. 374**



**TOXICOLOGY AND CARCINOGENESIS**

**STUDIES OF**

**GLYCIDOL**

**(CAS NO. 556-52-5)**

**IN F344/N RATS AND B6C3F<sub>1</sub> 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<sub>1</sub> MICE**  
**(GAVAGE STUDIES)**

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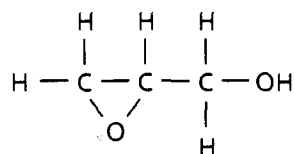
**U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES**  
**Public Health Service**  
**National Institutes of Health**

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**GLYCIDOL**

CAS No. 556-52-5

$\text{C}_3\text{H}_6\text{O}_2$

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<sub>1</sub> 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<sub>1</sub> 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<sub>1</sub> 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<sub>1</sub> 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<sub>1</sub> 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.

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\*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		
	Veh. Control	37.5 mg/kg	75 mg/kg	Veh. Control	37.5 mg/kg	75 mg/kg
<b>RATS</b>						
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
<b>MICE</b>						
	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  $\alpha$ -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

## **SUMMARY OF PEER REVIEW COMMENTS**

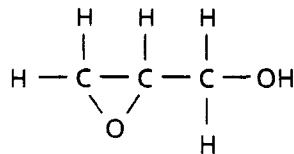
studies that they had conducted at all customer sites. He said that the studies indicated that about 70 persons were exposed annually at concentrations not exceeding 2 ppm.

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

# I. INTRODUCTION

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**GLYCIDOL**

CAS No. 556-52-5

$\text{C}_3\text{H}_6\text{O}_2$

Molecular weight 74.1

Synonyms: 2,3-epoxy-1-propanol

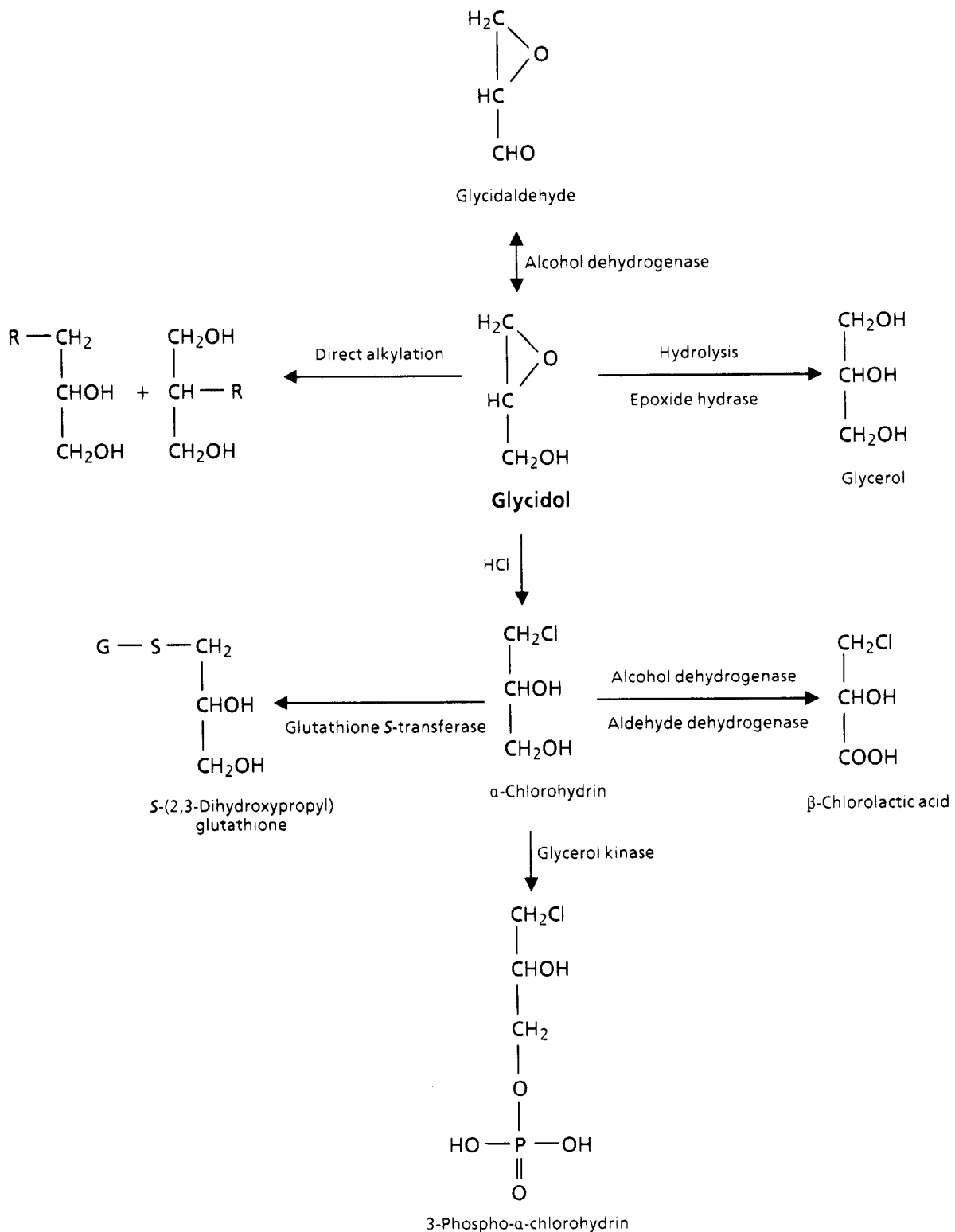
Glycidol is a colorless, viscous liquid soluble in both water and organic solvents. The threshold limit value time-weighted average for glycidol is 25 ppm (ACGIH, 1988). At 25° C, the vapor pressure of glycidol is 0.9 mm mercury. The carbon atom in the 2 position is chiral; thus, glycidol exists as two 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  $\alpha$  or  $\beta$  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  $\alpha$ -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  $\beta$ -chlorolactic acid. The latter compound was identified as the only radioactive urinary metabolite of glycidol isolated from rats administered [ $^{36}\text{Cl}$ ]saline for 3 days before glycidol administration (Jones and O'Brien, 1980). The same urinary metabolites are found after  $\alpha$ -chlorohydrin administration, suggesting that glycidol is converted to  $\alpha$ -chlorohydrin by direct reaction with hydrochloric acid in the stomach.  $\alpha$ -Chlorohydrin may then be converted to the glutathione metabolite by the action of glutathione transferase or oxidized to  $\beta$ -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**

# I. INTRODUCTION

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$\alpha$ -Chlorohydrin reduces sperm motility and causes infertility in male rats, perhaps as a result of the uptake of and phosphorylation of  $\alpha$ -chlorohydrin by sperm (Mohri et al., 1975; Chulavatnatol et al., 1977; Jones, 1978). Phosphorylated  $\alpha$ -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  $\alpha$ -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 embryoletality 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<sup>0</sup>-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 mam-

malian 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**

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## II. MATERIALS AND METHODS

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### 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 ( $\alpha$ -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  $\pm 10\%$  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<sub>1</sub> 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
<b>EXPERIMENTAL DESIGN</b>		
<b>Size of Study Groups</b> 5 males and 5 females of each species	10 males and 10 females of each species	50 males and 50 females of each species
<b>Doses</b> 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
<b>Date of First Dose</b> 11/19/79	3/3/80	Rats--7/20/81; mice--8/3/81
<b>Date of Last Dose</b> 12/4/79	5/30/80	Rats--7/8/83; mice--7/22/83
<b>Duration of Dosing</b> 5 d/wk on 14 d over 16 d	5 d/wk for 13 wk	5 d/wk for 103 wk
<b>Type and Frequency of Observation</b> 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
<b>Necropsy, Histologic Examinations, and Supplemental Studies</b>		
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, sternbrae, stomach, thymus, thyroid gland, trachea, and urinary bladder
<b>Strain and Species</b> F344/N rats; B6C3F <sub>1</sub> mice	F344/N rats; B6C3F <sub>1</sub> mice	F344/N rats; B6C3F <sub>1</sub> mice
<b>Animal Source</b> 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)**

<b>Sixteen-Day Studies</b>	<b>Thirteen-Week Studies</b>	<b>Two-Year Studies</b>
<b>ANIMALS AND ANIMAL MAINTENANCE</b>		
<b>Study Laboratory</b> Papanicolaou Cancer Research Institute	Papanicolaou Cancer Research Institute	Papanicolaou Cancer Research Institute
<b>Method of Animal Identification</b> Ear notch, toe clip	Ink mark, ear clip, toe clip	Ear notch, toe clip
<b>Time Held Before Study</b> Rats--19 d; mice--20 d	18 d	Rats--19 d; mice--25 d
<b>Age When Placed on Study</b> Rats--7 wk; mice--8 wk	Rats--7 wk; mice--8 wk	Rats--8 wk; mice--9 wk
<b>Age When Killed</b> 10 wk	Rats--21 wk; mice--22 wk	Rats--112 wk; mice--113-114 wk
<b>Necropsy Dates</b> 12/5/79	6/2/80-6/9/80	Rats--7/18/83; mice--8/1/83-8/3/83
<b>Method of Animal Distribution</b> 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
<b>Feed</b> 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
<b>Bedding</b> Sani Chips, hardwood pine (Pinewood Products Company)	Same as 16-d studies	Beta Chips (Northeastern Products, Inc., Warrensburg, NY)
<b>Water</b> Automatic watering system (Edstrom Industries, Waterford, WI); available ad libitum	Same as 16-d studies	Same as 16-d studies
<b>Cages</b> Polycarbonate (Lab Products, Inc., Garfield, NJ)	Same as 16-d studies	Same as 16-d studies
<b>Cage Filters</b> Cerex® spun-bonded nylon (Monsanto Co., St. Louis, MO)	Same as 16-d studies	Same as 16-d studies
<b>Animals per Cage</b> 5	5	5
<b>Other Chemicals on Study in the Same Room</b> None	None	None
<b>Animal Room Environment</b> 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

## II. MATERIALS AND METHODS

Four-week-old male and female F344/N rats and 5-week-old male and female B6C3F<sub>1</sub> 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<sub>1</sub> (C57BL/6N, female × C3H/HeN MTV<sup>-</sup>, 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<sub>1</sub> 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

## II. MATERIALS AND METHODS

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for the hybrid B6C3F<sub>1</sub> mice used in these studies. The influence of the potential genetic non-uniformity 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 histotechnology 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).

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### 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 non-neoplastic 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

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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 non-neoplastic 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)			Final Weight Relative to Vehicle Controls (percent)
		Initial (b)	Final	Change (c)	
<b>MALE</b>					
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)
<b>FEMALE</b>					
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)			Final Weight Relative to Vehicle Controls (percent)
		Initial (b)	Final	Change (c)	
<b>MALE</b>					
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)
<b>FEMALE</b>					
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
<b>MALE</b>					
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)
<b>FEMALE</b>					
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
<b>MALE</b>								
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	408	89	47
52	457	49	419	92	50	405	89	44
56	474	47	431	91	50	418	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	408	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	
<b>FEMALE</b>								
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	212	88	50
41	242	50	227	94	48	227	94	49
44	245	50	228	93	48	234	97	49
48	250	50	233	93	48	231	94	49
52	255	50	239	93	48	234	94	48
56	263	50	247	94	48	235	92	48
60	274	49	257	94	48	244	93	46
64	283	49	267	94	46	259	95	44
68	287	49	270	94	44	268	95	41
72	291	49	270	93	41	277	97	37
76	301	47	280	93	38	278	96	36
80	309	43	282	93	38	283	94	30
84	305	43	276	91	36	290	94	24
88	304	41	265	94	31	294	96	18
92	312	37	288	92	23	303	100	13
96	317	36	285	90	19	303	97	6
100	319	29	302	95	15	..	..	..
104	318	26	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	

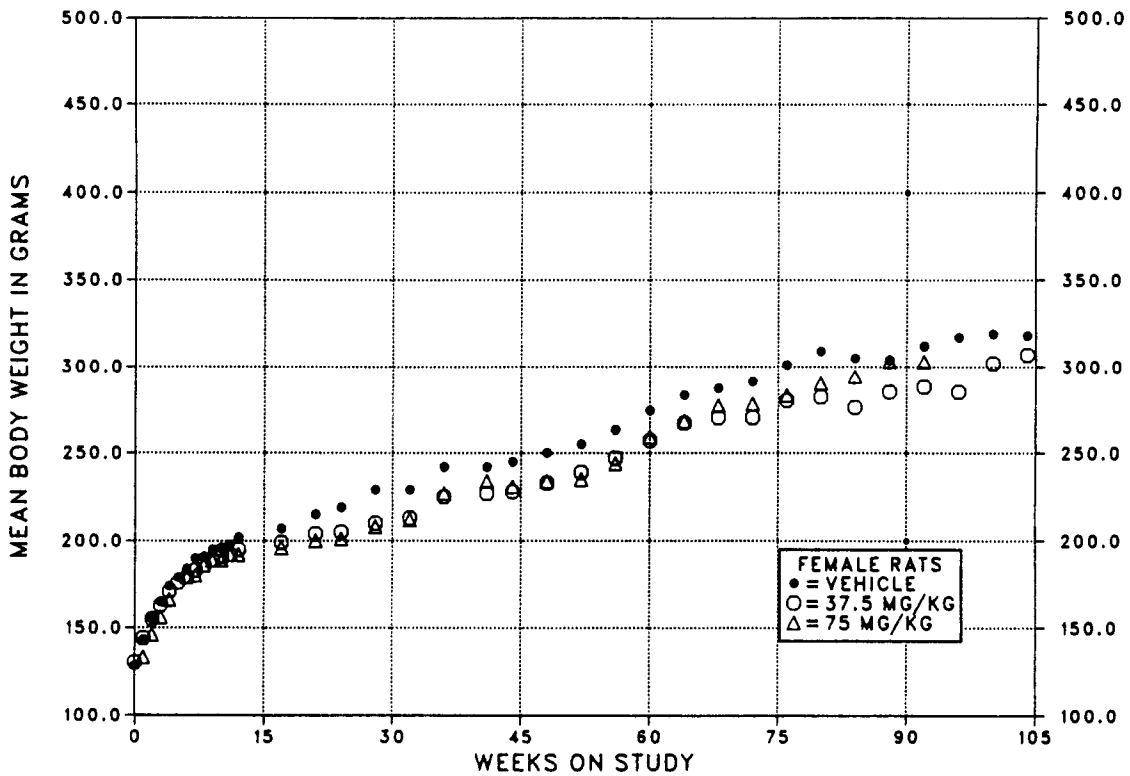
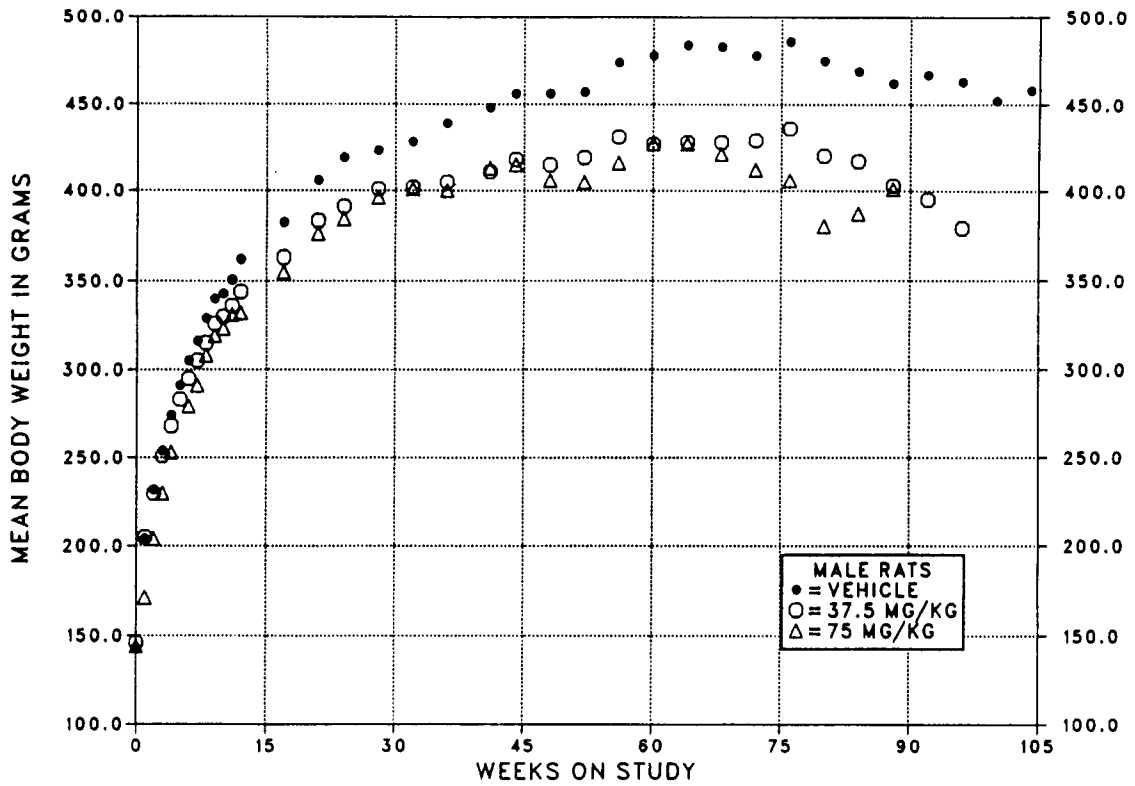


FIGURE 2. GROWTH CURVES FOR RATS ADMINISTERED GLYCIDOL IN WATER BY GAVAGE FOR TWO YEARS

#### 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.

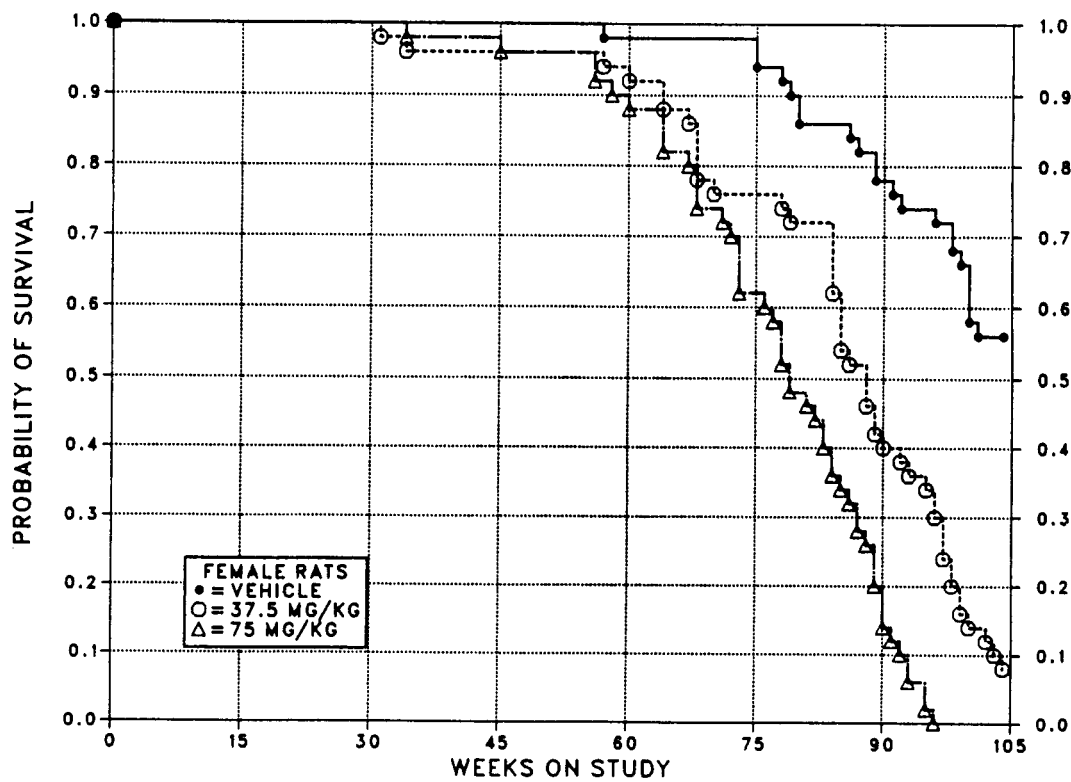
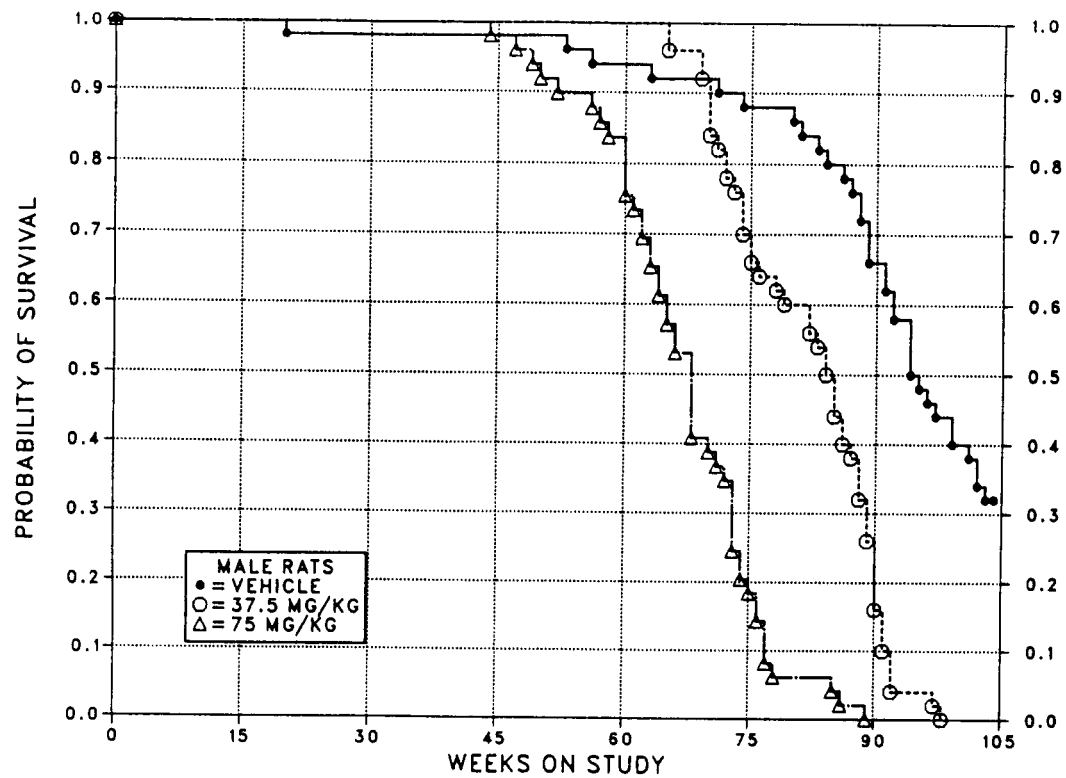
Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, statistical analyses of primary tumors that occurred with an incidence of at least 5% in at least one animal group, and historical control incidences for the neoplasms mentioned in this section are 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
<b>MALE (a)</b>			
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
<b>FEMALE (a)</b>			
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**



### III. RESULTS: RATS

*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
<b>Mesothelioma, NOS</b>			
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
<b>Malignant Mesothelioma</b>			
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
<b>All Mesothelioma (c)</b>			
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  $\pm$  SD): 4/300 (1%  $\pm$  2%); historical incidence for untreated controls: 47/1,596 (3%  $\pm$  3%)

### III. RESULTS: RATS

**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
<b>MALE</b>			
<b>Fibroadenoma (b)</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
<b>FEMALE</b>			
<b>Fibroadenoma (d)</b>			
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
<b>Adenocarcinoma (e)</b>			
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
<b>Fibroadenoma or Adenocarcinoma (f)</b>			
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  $\pm$  SD): 13/300 (4%  $\pm$  2%); historical incidence for untreated controls: 49/1,596 (3%  $\pm$  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  $\pm$  SD): 80/299 (27%  $\pm$  10%); historical incidence for untreated controls: 520/1,643 (32%  $\pm$  12%)

(e) Historical incidence for water gavage vehicle controls (mean  $\pm$  SD): 5/299 (2%  $\pm$  2%); historical incidence for untreated controls: 49/1,643 (3%  $\pm$  2%)

(f) Historical incidence for water gavage vehicle controls (mean  $\pm$  SD): 84/299 (28%  $\pm$  10%); historical incidence for untreated controls: 552/1,643 (34%  $\pm$  12%)

### III. RESULTS: RATS

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*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).

Glioma 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
<b>MALE</b>			
<b>Papilloma</b>			
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
<b>Carcinoma</b>			
Overall Rates	1/50 (2%)	1/50 (2%)	2/50 (4%)
<b>Papilloma or Carcinoma (c)</b>			
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
<b>FEMALE</b>			
<b>Papilloma</b>			
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
<b>Carcinoma</b>			
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
<b>Papilloma or Carcinoma (e)</b>			
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
<b>MALE</b>			
<b>Glioma (b)</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
<b>FEMALE</b>			
<b>Glioma (d)</b>			
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
<b>Focal Hyperplasia</b>			
Overall Rates	1/50 (2%)	0/50 (0%)	0/50 (0%)
<b>Squamous Cell Papilloma</b>			
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
<b>Squamous Cell Carcinoma</b>			
Overall Rates	0/50 (0%)	0/50 (0%)	1/50 (2%)
<b>Squamous Cell Papilloma or Carcinoma (c)</b>			
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%)

### III. RESULTS: RATS

*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
<b>Carcinoma (b)</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  $\pm$  SD): 3/300 (1%  $\pm$  1%); historical incidence for untreated controls: 19/1,596 (1%  $\pm$  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
<b>MALE</b>			
<b>Hyperplasia</b>			
Overall Rates	0/50 (0%)	4/50 (8%)	1/50 (2%)
<b>Adenoma</b>			
Overall Rates	0/50 (0%)	2/50 (4%)	2/50 (4%)
<b>Carcinoma</b>			
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
<b>Adenoma or Carcinoma (c)</b>			
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
<b>FEMALE</b>			
<b>Hyperplasia</b>			
Overall Rates	1/50 (2%)	1/50 (2%)	2/49 (4%)
<b>Adenoma</b>			
Overall Rates	0/50 (0%)	1/50 (2%)	0/49 (0%)
<b>Carcinoma</b>			
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
<b>Adenoma or Carcinoma (e)</b>			
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  $\pm$  SD): 6/293 (2%  $\pm$  3%); historical incidence for untreated controls: 20/1,576 (1%  $\pm$  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  $\pm$  SD): 10/292 (3%  $\pm$  3%); historical incidence for untreated controls: 16/1,612 (1%  $\pm$  1%)

### III. RESULTS: RATS

*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
<b>Mononuclear Cell Leukemia (b)</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  $\pm$  SD): 75/299 (25%  $\pm$  15%); historical incidence for untreated controls: 324/1,643 (20%  $\pm$  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
<b>Squamous Cell Papilloma (b)</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
<b>Basal Cell Tumor</b>			
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
<b>Sebaceous Gland Adenoma</b>			
Overall Rates	0/50 (0%)	1/50 (2%)	1/50 (2%)
<b>Sebaceous Gland Adenocarcinoma</b>			
Overall Rates	0/50 (0%)	0/50 (0%)	1/50 (2%)
<b>Sebaceous Gland Adenoma, Basal Cell Tumor, or Sebaceous Gland Adenocarcinoma (d)</b>			
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  $\pm$  SD): 13/300 (4%  $\pm$  2%); historical incidence for untreated controls: 31/1,596 (2%  $\pm$  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  $\pm$  SD): 5/300 (2%  $\pm$  1%); historical incidence for untreated controls: 31/1,596 (2%  $\pm$  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
<b>Hyperplasia</b>			
Overall Rates	1/50 (2%)	1/50 (2%)	1/50 (2%)
<b>Adenoma</b>			
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	P=0.085	P=0.036
Fisher Exact Test			
<b>Carcinoma</b>			
Overall Rates	2/50 (4%)	1/50 (2%)	5/50 (10%)
<b>Adenocarcinoma</b>			
Overall Rates	0/50 (0%)	1/50 (2%)	0/50 (0%)
<b>Adenoma, Carcinoma, or Adenocarcinoma (c)</b>			
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	P=0.171	P=0.035
Fisher Exact Test			

(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  $\pm$  SD): 22/299 (7%  $\pm$  5%); historical incidence for untreated controls: 115/1,643 (7%  $\pm$  5%)

### III. RESULTS: MICE

#### 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)			Final Weight Relative to Vehicle Controls (percent)
		Initial (b)	Final	Change (c)	
<b>MALE</b>					
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)
<b>FEMALE</b>					
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)			Final Weight Relative to Vehicle Controls (percent)
		Initial (b)	Final	Change (c)	
<b>MALE</b>					
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)
<b>FEMALE</b>					
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: 1,1,1,1,1,1,1,1,2  
 (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: 1,1,1,1,1,1,1,2,2  
 (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
<b>MALE</b>			
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
<b>FEMALE</b>			
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		25 mg/kg			50 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
<b>MALE</b>								
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	
<b>FEMALE</b>								
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	

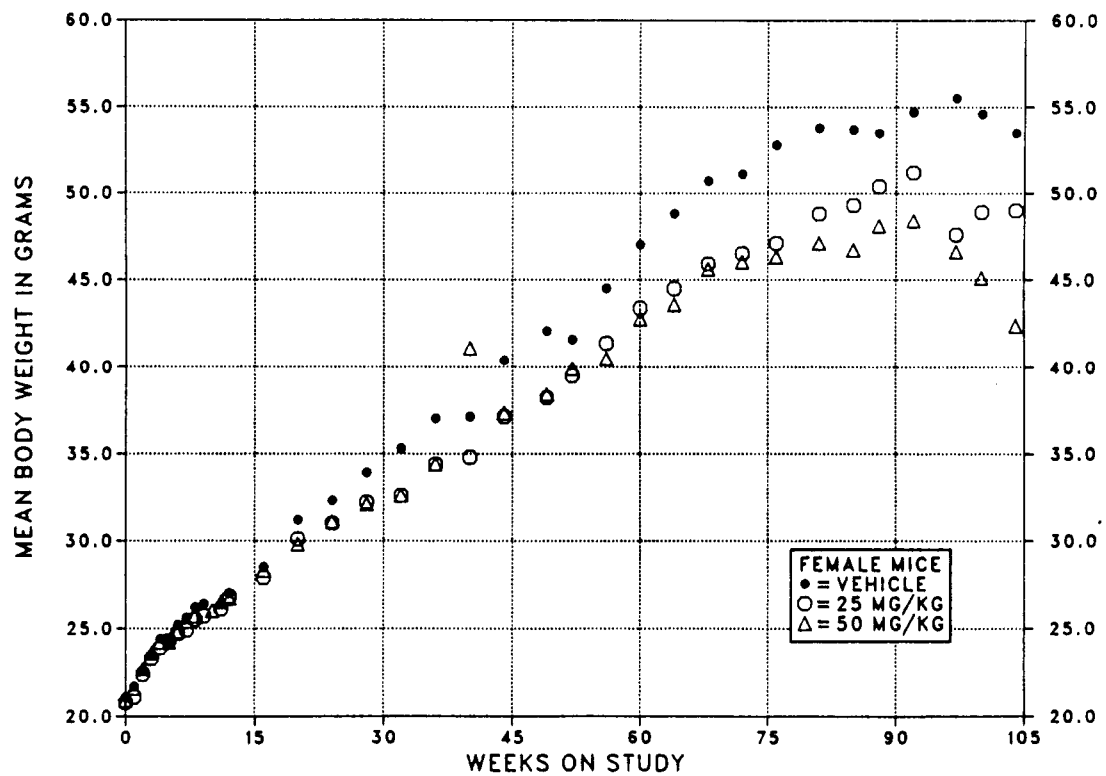
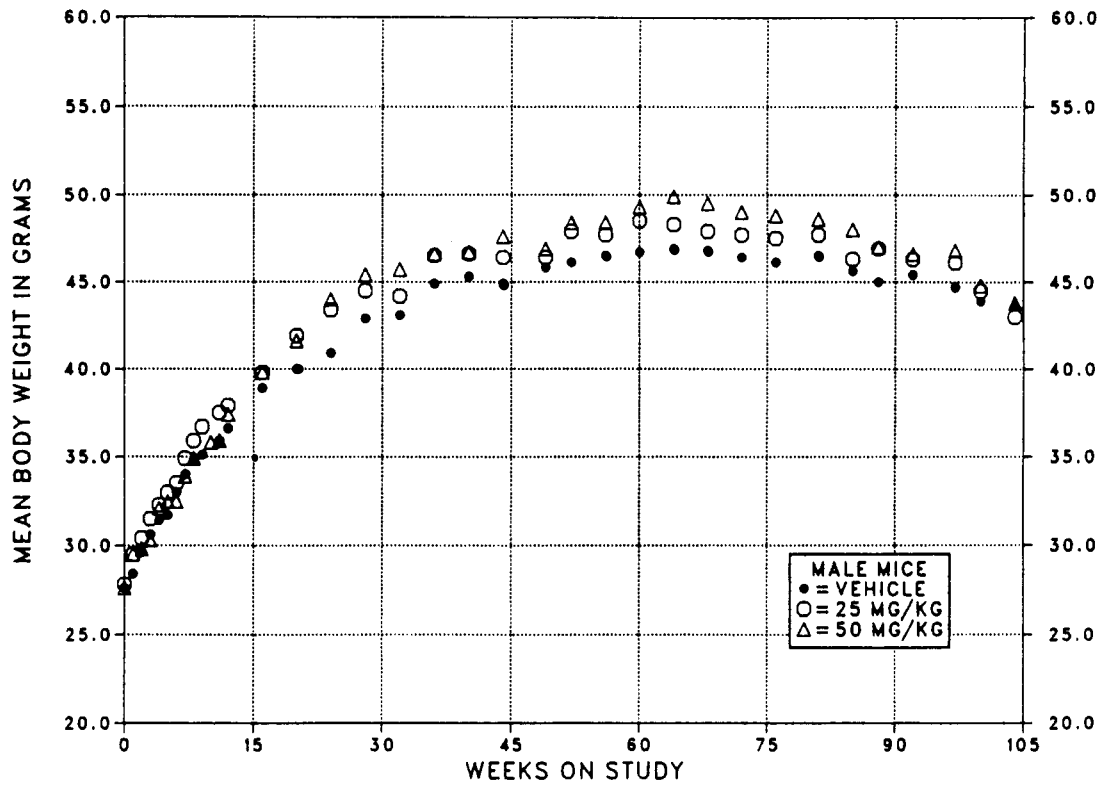


FIGURE 4. GROWTH CURVES FOR MICE ADMINISTERED GLYCIDOL IN WATER BY GAVAGE FOR TWO YEARS

### III. RESULTS: MICE

#### 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.

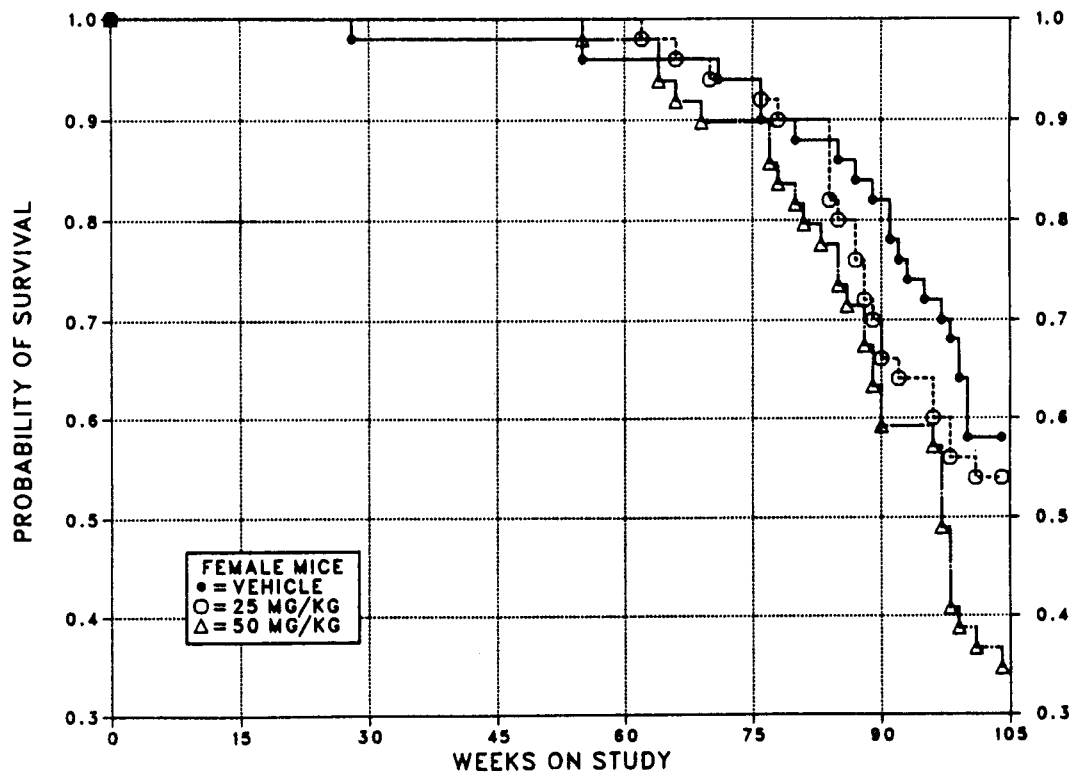
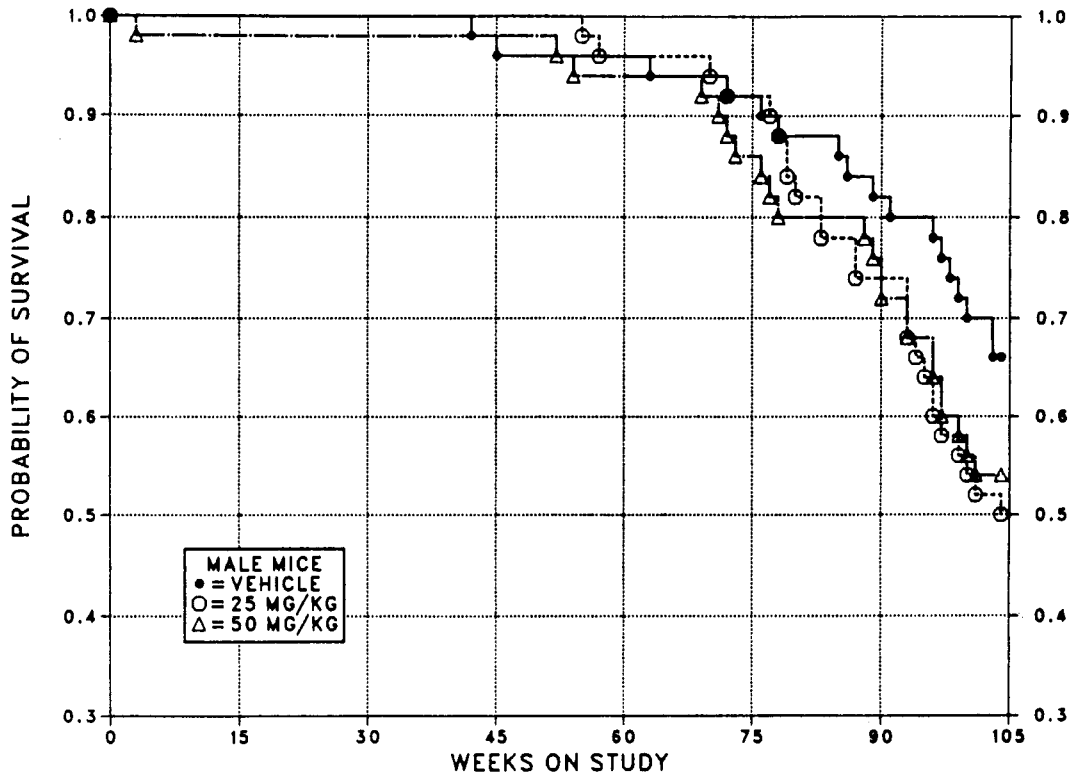
TABLE 23. SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF GLYCIDOL

	Vehicle Control	25 mg/kg	50 mg/kg
<b>MALE (a)</b>			
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
<b>FEMALE (a)</b>			
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**

### III. RESULTS: MICE

*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
<b>MALE</b>			
<b>Hyperplasia</b>			
Overall Rates	0/46 (0%)	0/41 (0%)	3/44 (7%)
<b>Adenoma</b>			
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
<b>Adenocarcinoma</b>			
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
<b>Adenoma or Adenocarcinoma (b)</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
<b>FEMALE</b>			
<b>Hyperplasia</b>			
Overall Rates	1/46 (2%)	2/43 (5%)	3/43 (7%)
<b>Adenoma</b>			
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
<b>Adenocarcinoma</b>			
Overall Rates	0/46 (0%)	1/43 (2%)	1/43 (2%)
<b>Adenoma or Adenocarcinoma (c)</b>			
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  $\pm$  SD): 22/350 (6%  $\pm$  4%); historical incidence for untreated controls: 67/1,692 (4%  $\pm$  3%)

(c) Historical incidence for water gavage vehicle controls (mean  $\pm$  SD): 12/350 (3%  $\pm$  4%); historical incidence for untreated controls: 51/1,689 (3%  $\pm$  3%)

### III. RESULTS: MICE

**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
<b>Hyperplasia</b>			
Overall Rates	1/50 (2%)	0/50 (0%)	0/50 (0%)
<b>Adenoma</b>			
Overall Rates	0/50 (0%)	1/50 (2%)	0/50 (0%)
<b>Fibroadenoma</b>			
Overall Rates	1/50 (2%)	0/50 (0%)	0/50 (0%)
<b>Adenocarcinoma (b)</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
<b>Adenoma, Fibroadenoma, or Adenocarcinoma (c)</b>			
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  $\pm$  SD): 2/350 (0.6%  $\pm$  1%); historical incidence for untreated controls: 33/1,689 (2%  $\pm$  2%)

(c) Historical incidence for water gavage vehicle controls (mean  $\pm$  SD): 4/350 (1%  $\pm$  2%); historical incidence for untreated controls: 35/1,689 (2%  $\pm$  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
<b>Sarcoma</b>			
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
<b>Fibrosarcoma</b>			
Overall Rates	0/50 (0%)	2/50 (4%)	3/50 (6%)
<b>Sarcoma or Fibrosarcoma (b)</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  $\pm$  SD): 6/350 (2%  $\pm$  2%); historical incidence for untreated controls: 40/1,689 (2%  $\pm$  3%)

### III. RESULTS: MICE

**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
<b>Hyperplasia</b>			
Overall Rates	0/50 (0%)	0/50 (0%)	1/50 (2%)
<b>Squamous Cell Papilloma (b)</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  $\pm$  SD): 2/350 (0.6%  $\pm$  2%); historical incidence for untreated controls: 9/1,692 (0.5%  $\pm$  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
<b>Epithelial Hyperplasia</b>			
Overall Rates	2/50 (4%)	4/50 (8%)	*8/50 (16%)
<b>Squamous Cell Papilloma</b>			
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
<b>Squamous Cell Carcinoma</b>			
Overall Rates	1/50 (2%)	0/50 (0%)	1/50 (2%)
<b>Squamous Cell Papilloma or Carcinoma (b)</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  $\pm$  SD): 8/331 (2%  $\pm$  2%); historical incidence for untreated controls: 10/1,645 (0.6%  $\pm$  1%)

\*P<0.05 vs. vehicle controls

### III. RESULTS: MICE

*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
<b>MALE</b>			
<b>Adenoma</b>			
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
<b>Carcinoma</b>			
Overall Rates	10/50 (20%)	17/50 (34%)	8/50 (16%)
<b>Adenoma or Carcinoma (b)</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
<b>FEMALE</b>			
<b>Adenoma</b>			
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
<b>Carcinoma</b>			
Overall Rates	3/50 (6%)	5/50 (10%)	4/50 (8%)
<b>Adenoma or Carcinoma (c)</b>			
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  $\pm$  SD): 106/347 (31%  $\pm$  6%); historical incidence for untreated controls: 494/1,678 (29%  $\pm$  8%)

(c) Historical incidence for water gavage vehicle controls (mean  $\pm$  SD): 29/348 (8%  $\pm$  5%); historical incidence for untreated controls: 163/1,683 (10%  $\pm$  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
<b>Alveolar Epithelium Hyperplasia</b>			
Overall Rates	5/50 (10%)	4/50 (8%)	3/50 (6%)
<b>Alveolar/Bronchiolar Adenoma</b>			
Overall Rates	6/50 (12%)	6/50 (12%)	8/50 (16%)
<b>Alveolar/Bronchiolar Carcinoma</b>			
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
<b>Alveolar/Bronchiolar Adenoma or Carcinoma (b)</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  $\pm$  SD): 65/347 (19%  $\pm$  8%); historical incidence for untreated controls: 277/1,684 (16%  $\pm$  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
<b>Hemangioma</b>			
Overall Rates	0/50 (0%)	1/50 (2%)	2/50 (4%)
<b>Hemangiosarcoma</b>			
Overall Rates	1/50 (2%)	2/50 (4%)	3/50 (6%)
<b>Hemangioma or Hemangiosarcoma (b)</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  $\pm$  SD): 8/350 (2%  $\pm$  1%); historical incidence for untreated controls: 48/1,689 (3%  $\pm$  3%)

### III. RESULTS: MICE

*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 (com-

bined) occurred with a significant positive trend (Table 33); these are uncommon neoplasms in female B6C3F<sub>1</sub> 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
<b>Lymphoma, All Malignant (b)</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  $\pm$  SD): 42/350 (12%  $\pm$  6%); historical incidence for untreated controls: 196/1,692 (12%  $\pm$  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
<b>Carcinoma</b>			
Overall Rates	0/50 (0%)	0/50 (0%)	1/50 (2%)
<b>Adenocarcinoma</b>			
Overall Rates	0/50 (0%)	3/50 (6%)	2/50 (4%)
<b>Carcinoma or Adenocarcinoma (b)</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  $\pm$  SD): 1/347 (0.3%  $\pm$  0.8%); historical incidence for untreated controls: 4/1,675 (0.2%  $\pm$  0.7%)

### III. RESULTS: MICE

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*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<sub>1</sub> 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<sub>1</sub> 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<sub>1</sub> 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).



### III. RESULTS: GENETIC TOXICOLOGY

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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<sub>1</sub> 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). The experimental procedures and results are presented in Appendix H.



## IV. DISCUSSION AND CONCLUSIONS

## 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

## IV. DISCUSSION AND CONCLUSIONS

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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<sub>1</sub> 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 alkylating 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*<sup>6</sup> 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*<sup>6</sup> of guanine, either in solution or in intact DNA.  $\alpha$ -Chlorohydrin, a metabolite formed in the stomach by the reaction of chloride with

## IV. DISCUSSION AND CONCLUSIONS

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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<sub>1</sub> 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<sub>1</sub> 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.

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\*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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## V. REFERENCES

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## APPENDIX A

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

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**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
<b>INTEGUMENTARY SYSTEM</b>			
*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%)	
<b>RESPIRATORY SYSTEM</b>			
#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%)	
<b>HEMATOPOIETIC SYSTEM</b>			
*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%)		
<b>CIRCULATORY SYSTEM</b>			
#Spleen	(50)	(50)	(50)
Hemangiosarcoma		1 (2%)	
*Skeletal muscle	(50)	(50)	(50)
Hemangiosarcoma	1 (2%)		
<b>DIGESTIVE SYSTEM</b>			
*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
<b>DIGESTIVE SYSTEM (Continued)</b>			
*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%)	
<b>URINARY SYSTEM</b>			
#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%)	
<b>ENDOCRINE SYSTEM</b>			
#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%)
<b>REPRODUCTIVE SYSTEM</b>			
*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%)
<b>NERVOUS SYSTEM</b>			
#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
<b>NERVOUS SYSTEM (Continued)</b>			
#Brain	(50)	(50)	(50)
Glioma, NOS		5 (10%)	6 (12%)
<b>SPECIAL SENSE ORGANS</b>			
*Ear	(50)	(50)	(50)
Fibrosarcoma	1 (2%)		
*Zymbal gland	(50)	(50)	(50)
Carcinoma, NOS	1 (2%)	3 (6%)	6 (12%)
<b>MUSCULOSKELETAL SYSTEM</b>			
*Bone	(50)	(50)	(50)
Osteosarcoma		1 (2%)	
*Skeletal muscle	(50)	(50)	(50)
Neurilemoma, invasive		1 (2%)	
<b>BODY CAVITIES</b>			
*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%)
<b>ALL OTHER SYSTEMS</b>			
Adipose tissue			
Sarcoma, NOS	1		
<b>ANIMAL DISPOSITION SUMMARY</b>			
Animals initially in study	50	50	50
Natural death	1	5	3
Moribund sacrifice	33	45	46
Terminal sacrifice	16		
Dosing accident			1
<b>TUMOR SUMMARY</b>			
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	06	01	02	03	04	05	06	07	08	09	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30					
WEEKS ON STUDY	20	25	31	36	41	47	52	58	63	69	74	79	85	90	96	101	107	112	118	123	129	134	140	145	151	156	162	167	173	178	184					
<b>INTEGUMENTARY SYSTEM</b>																																				
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
Keratoacanthoma																																				
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Fibroma																																				
Fibrosarcoma																																				
Lipoma																																				
<b>RESPIRATORY SYSTEM</b>																																				
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Alveolar/bronchiolar adenoma																																				
Alveolar/bronchiolar carcinoma																																				
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
<b>HEMATOPOIETIC SYSTEM</b>																																				
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Sarcoma, NOS																																				
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Thymus	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Mesothelioma, metastatic																																				
<b>CIRCULATORY SYSTEM</b>																																				
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
<b>DIGESTIVE SYSTEM</b>																																				
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	N	N	N	N	N	N	N	N			
Squamous cell papilloma																																				
Squamous cell carcinoma																																				
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Neoplastic nodules																																				
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																																				
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
<b>URINARY SYSTEM</b>																																				
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Sarcoma, NOS																																				
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
<b>ENDOCRINE SYSTEM</b>																																				
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Adenoma, NOS																																				
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																																				
Pheochromocytoma																																				
Pheochromocytoma, malignant																																				
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell carcinoma																																				
C cell adenoma																																				
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	06	01	02	03	04	05	06	07	08	09	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	
WEEKS ON STUDY	20	25	30	35	40	45	50	55	60	65	70	75	80	85	90	95	100	105	110	115	120	125	130	135	140	145	150	155	160	165	170	
<b>REPRODUCTIVE SYSTEM</b>																																
Mammary gland	+	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	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	N	N	N	N	N	N	
Adenoma, NOS																																
Adenocarcinoma, NOS											X													X							X	
<b>NERVOUS SYSTEM</b>																																
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Granular cell tumor, NOS																																
<b>SPECIAL SENSE ORGANS</b>																																
Ear	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	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	N	N	N	N	N	N	
Carcinoma, NOS																																
<b>MUSCULOSKELETAL SYSTEM</b>																																
Muscle	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
Hemangiosarcoma																																
<b>BODY CAVITIES</b>																																
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	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	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	N	N	N	N	N	N	
Mesothelioma, metastatic																																
Tunica vaginalis	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Mesothelioma, malignant																																
<b>ALL OTHER SYSTEMS</b>																																
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
Leukemia, mononuclear cell																																
Adipose tissue					X						X																					
Sarcoma, NOS																																



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

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																																							
	1	2	1	0	2	0	4	0	2	3	3	3	2	2	4	2	4	3	0	2	0	4	1	0	4																																					
WEEKS ON STUDY	4	9	5	1	5	5	3	7	6	7	3	5	1	2	4	0	8	2	6	4	9	6	8	8	9																																					
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	0																																					
6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	8	8	8	8	8																																					
5	5	9	9	0	0	0	0	0	1	2	2	3	4	4	4	5	5	6	8	9	2	2	3	4	4																																					
<b>INTEGUMENTARY SYSTEM</b>																																																														
Skin																																																														
Squamous cell papilloma																																																														
Basal cell tumor																																																														
Sebaceous adenoma																																																														
Keratoacanthoma																																																														
Subcutaneous tissue																																																														
Fibroma																																																														
Fibrosarcoma																																																														
Neurofibroma																																																														
+																												+	+	N	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
<b>RESPIRATORY SYSTEM</b>																																																														
Lungs and bronchi																																																														
Carcinoma, NOS, metastatic																																																														
Squamous cell carcinoma, metastatic																																																														
Alveolar/bronchiolar adenoma																																																														
Alveolar/bronchiolar carcinoma																																																														
Fibrosarcoma, metastatic																																																														
Neurilemoma, malignant																																																														
Trachea																																																														
Nasal cavity																																																														
Squamous cell carcinoma																																																														
+																												+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
<b>HEMATOPOIETIC SYSTEM</b>																																																														
Bone marrow																																																														
Spleen																																																														
Hemangiosarcoma																																																														
Lymph nodes																																																														
Mesothelioma, metastatic																																																														
Osteosarcoma, metastatic																																																														
Thymus																																																														
+																												+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
<b>CIRCULATORY SYSTEM</b>																																																														
Heart																																																														
+																												+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
<b>DIGESTIVE SYSTEM</b>																																																														
Oral cavity																																																														
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																																																														
Small intestine																																																														
Mucinous adenocarcinoma																																																														
Large intestine																																																														
Sarcoma, NOS																																																														
N																												N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N		
+																												+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
+																												+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
+																												+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
+																												+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
+																												+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
+																												+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
+																												+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
<b>URINARY SYSTEM</b>																																																														
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	0 1 4	0 2 9	0 1 5	0 1 5	0 2 5	0 4 5	0 3 7	0 0 7	0 2 6	0 3 7	0 3 3	0 2 5	0 2 1	0 2 2	0 4 4	0 2 0	0 4 3	0 2 6	0 4 4	0 0 9	0 4 6	0 1 8	0 0 8	0 4 9
WEEKS ON STUDY	6 5	6 5	6 9	6 9	7 0	7 0	7 0	7 0	7 1	7 2	7 2	7 3	7 4	7 4	7 4	7 5	7 5	7 6	7 8	7 9	8 2	8 2	8 3	8 4
<b>ENDOCRINE SYSTEM</b>																								
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																								
Adenoma, NOS					X													X				X		
Adrenal	+	+	+	+	+	+	+	+																
Pheochromocytoma				X					X															
Pheochromocytoma, malignant																								
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																								
Follicular cell carcinoma																								
C-cell adenoma																								
Parathyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
<b>REPRODUCTIVE SYSTEM</b>																								
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
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																								X
<b>NERVOUS SYSTEM</b>																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Glioma, NOS				X																				
<b>SPECIAL SENSE ORGANS</b>																								
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
Carcinoma, NOS																								X
<b>MUSCULOSKELETAL SYSTEM</b>																								
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
Neurilemoma, invasive																								
<b>BODY CAVITIES</b>																								
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Mesothelioma, metastatic	X				X	X			X	X						X	X				X	X		X
Mesothelioma, NOS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma, malignant	X	X		X	X			X		X	X				X	X	X				X	X		X
<b>ALL OTHER SYSTEMS</b>																								
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
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 IN THE TWO-YEAR GAVAGE STUDY OF GLYCIDOL: 75 mg/kg**

ANIMAL NUMBER	05	03	07	09	09	09	08	05	05	02	00	06	03	00	00	01	06	05	04	06	06	00	07	03	00			
WEEKS ON STUDY	14	4	7	9	0	2	6	7	8	0	0	0	0	0	0	1	2	2	3	3	4	4	5	5	6	6	8	
<b>INTEGUMENTARY SYSTEM</b>																												
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Squamous cell papilloma																												
Basal cell tumor																												
Sebaceous adenoma																												
Sebaceous adenocarcinoma																												
Keratoacanthoma																												
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Fibroma																												
Fibrosarcoma																												
<b>RESPIRATORY SYSTEM</b>																												
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Papilloma, NOS																												
Alveolar/bronchiolar adenoma																												
Alveolar/bronchiolar carcinoma																												
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Squamous cell carcinoma																												
Adenocarcinoma, NOS																												
<b>HEMATOPOIETIC SYSTEM</b>																												
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Fibroma																												
Fibrosarcoma																												
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	+	+	+	
<b>CIRCULATORY SYSTEM</b>																												
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
<b>DIGESTIVE SYSTEM</b>																												
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	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																												
Squamous cell carcinoma																												
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Mucinous adenocarcinoma																											+	
Mesothelioma, invasive																											X	
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Adenocarcinoma, NOS																												
Adenomatous polyp, NOS																												
<b>URINARY SYSTEM</b>																												
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Tubular cell adenoma																												
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
<b>ENDOCRINE SYSTEM</b>																												
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Adenoma, NOS																												
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Pheochromocytoma																												
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	05	06	07	08	09	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
WEEKS ON STUDY	4	4	7	9	0	2	6	7	8	0	0	0	0	1	2	2	3	3	4	4	5	5	6	6	6	6
<b>REPRODUCTIVE SYSTEM</b>																										
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	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																
<b>NERVOUS SYSTEM</b>																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Granular cell tumor, NOS																										
Glioma, NOS																										X
<b>SPECIAL SENSE ORGANS</b>																										
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	N
Carcinoma, NOS			X			X																				X
<b>BODY CAVITIES</b>																										
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Mesothelioma, metastatic			X		X			X	X		X	X		X	X	X	X	X	X		X		X		X	
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Mesothelioma, NOS											X		X								X					
Mesothelioma, malignant			X		X	X	X	X	X		X	X		X	X	X	X	X	X		X		X		X	
<b>ALL OTHER SYSTEMS</b>																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
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	042	047	052	057	062	067	072	077	082	087	092	097	102	107	112	117	122	127	132	137	142	147	152	157	162	167	172	177	182	187	192	197	TOTAL TISSUES TUMORS	
WEEKS ON STUDY	68	68	68	68	68	70	71	71	71	71	71	71	71	71	71	71	71	71	71	71	71	71	71	71	71	71	71	71	71	71	71	71	71	71		
<b>REPRODUCTIVE SYSTEM</b>																																				
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50	
Fibroadenoma																																			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	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	N	N	N	N	N	N	N	N	N	*50	
Adenoma, NOS																																			1	
Adenocarcinoma, NOS																																			4	
<b>NERVOUS SYSTEM</b>																																				
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Granular cell tumor, NOS																																			1	
Ghoma, NOS				X	X					X																									6	
<b>SPECIAL SENSE ORGANS</b>																																				
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	N	N	N	N	N	N	N	N	N	*50	
Carcinoma, NOS																																			6	
<b>BODY CAVITIES</b>																																				
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50	
Mesothelioma, metastatic				X	X	X		X																												28
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50	
Mesothelioma, NOS	X	X																																	8	
Mesothelioma, malignant			X	X	X	X	X																												31	
<b>ALL OTHER SYSTEMS</b>																																				
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50	
Malignant lymphoma, histiocytic type				X																															1	
Leukemia, mononuclear cell			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
<b>Skin: Squamous Cell Papilloma</b>			
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
<b>Skin: Basal Cell Tumor</b>			
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
<b>Skin: Sebaceous Gland Adenoma or Basal Cell Tumor</b>			
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
<b>Skin: Sebaceous Gland Adenoma, Basal Cell Tumor, or Sebaceous Gland Adenocarcinoma</b>			
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
<b>Skin: Keratoacanthoma</b>			
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		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
<b>Subcutaneous Tissue: Fibroma</b>			
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	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
<b>Subcutaneous Tissue: Fibroma or Neurofibroma</b>			
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
<b>Subcutaneous Tissue: Fibrosarcoma</b>			
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
<b>Subcutaneous Tissue: Fibroma or Fibrosarcoma</b>			
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
<b>Subcutaneous Tissue: Fibroma, Neurofibroma, or Fibrosarcoma</b>			
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
<b>Lung: Alveolar/Bronchiolar Adenoma</b>			
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
<b>Lung: Alveolar/Bronchiolar Adenoma or Carcinoma</b>			
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
<b>Hematopoietic System: Mononuclear Cell Leukemia</b>			
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
<b>Tongue: Squamous Cell Papilloma or Carcinoma</b>			
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
<b>Oral Cavity (Mouth or Tongue): Squamous Cell Papilloma</b>			
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
<b>Oral Cavity (Mouth or Tongue): Squamous Cell Papilloma or Carcinoma</b>			
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
<b>Forestomach: Squamous Cell Papilloma</b>			
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
<b>Forestomach: Squamous Cell Papilloma or Carcinoma</b>			
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
<b>Anterior Pituitary Gland: Adenoma</b>			
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
<b>Anterior Pituitary Gland: Adenoma or Carcinoma</b>			
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
<b>Adrenal Medulla: Pheochromocytoma</b>			
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
<b>Adrenal Medulla: Pheochromocytoma or Malignant Pheochromocytoma</b>			
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
<b>Thyroid Gland: C-Cell Adenoma</b>			
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
<b>Thyroid Gland: Follicular Cell Carcinoma</b>			
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
<b>Thyroid Gland: Follicular Cell Adenoma or Carcinoma</b>			
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
<b>Mammary Gland: Fibroadenoma</b>			
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
<b>Preputial Gland: Adenoma</b>			
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
<b>Preputial Gland: Adenocarcinoma</b>			
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	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
<b>Preputial Gland: Adenoma, Adenocarcinoma, or Carcinoma</b>			
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
<b>Testis: Interstitial Cell Tumor</b>			
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
<b>Brain: Glioma</b>			
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
<b>Zymbal Gland: Carcinoma</b>			
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
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
<b>Tunica Vaginalis: Mesothelioma, NOS</b>			
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
<b>Tunica Vaginalis: Malignant Mesothelioma</b>			
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
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
<b>Tunica Vaginalis: All Mesothelioma (f)</b>			
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	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
<b>All Sites: Benign Tumors</b>			
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
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
<b>All Sites: Malignant Tumors</b>			
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
<b>All Sites: All Tumors</b>			
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
<b>Historical Incidence for All Water Gavage Vehicle Controls</b>	
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
<b>TOTAL</b>	<b>4/300 (1.3%)</b>
<b>SD (f)</b>	<b>1.63%</b>
<b>Range (g)</b>	
High	2/50
Low	0/50
<b>Overall Historical Incidence for Untreated Controls</b>	
<b>TOTAL</b>	<b>(h) 47/1,596 (2.9%)</b>
<b>SD (f)</b>	<b>2.65%</b>
<b>Range (g)</b>	
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
<b>Historical Incidence for All Water Gavage Vehicle Controls</b>	
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
<b>Overall Historical Incidence for Untreated Controls</b>	
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
<b>Historical Incidence for All Water Gavage Vehicle Controls</b>	
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
<b>TOTAL</b>	<b>2/300 (0.7%)</b>
SD (g)	1.03%
<b>Range (h)</b>	
High	1/50
Low	0/50
<b>Overall Historical Incidence for Untreated Controls</b>	
<b>TOTAL</b>	<b>(i) 14/1,590 (0.9%)</b>
SD (g)	1.43%
<b>Range (h)</b>	
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
<b>Historical Incidence for All Water Gavage Vehicle Controls</b>		
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
<b>Overall Historical Incidence for Untreated Controls</b>		
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
<b>Historical Incidence for All Water Gavage Vehicle Controls</b>	
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
<b>Overall Historical Incidence for Untreated Controls</b>	
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
<b>Historical Incidence for All Water Gavage Vehicle Controls</b>	
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
<b>Overall Historical Incidence for Untreated Controls</b>	
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
<b>Historical Incidence for All Water Gavage Vehicle Controls</b>	
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
<b>TOTAL</b>	<b>0/300</b>
<b>SD (e)</b>	<b>0.00%</b>
<b>Range (f)</b>	
High	0/50
Low	0/50
<b>Overall Historical Incidence for Untreated Controls</b>	
<b>TOTAL</b>	<b>(g) 2/1,541 (0.1%)</b>
<b>SD (e)</b>	<b>0.50%</b>
<b>Range (f)</b>	
High	<b>1/49</b>
Low	<b>0/50</b>

- (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
<b>Historical Incidence for All Water Gavage Vehicle Controls</b>			
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
<b>Overall Historical Incidence for Untreated Controls</b>			
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
<b>Historical Incidence for All Water Gavage Vehicle Controls</b>			
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
<b>TOTAL</b>	<b>12/300 (4.0%)</b>	<b>1/300 (0.3%)</b>	<b>13/300 (4.3%)</b>
<b>SD (f)</b>	<b>1.79%</b>	<b>0.82%</b>	<b>2.34%</b>
<b>Range (g)</b>			
High	3/50	1/50	4/50
Low	1/50	0/50	1/50
<b>Overall Historical Incidence for Untreated Controls</b>			
<b>TOTAL</b>	<b>(d) 21/1,596 (1.3%)</b>	<b>10/1,596 (0.6%)</b>	<b>(d) 31/1,596 (1.9%)</b>
<b>SD (f)</b>	<b>1.50%</b>	<b>1.08%</b>	<b>1.81%</b>
<b>Range (g)</b>			
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
<b>Historical Incidence for All Water Gavage Vehicle Controls</b>			
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
<b>Overall Historical Incidence for Untreated Controls</b>			
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
<b>Historical Incidence for All Water Gavage Vehicle Controls</b>			
	300	0	
<b>Overall Historical Incidence for Untreated Controls</b>			
	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
<b>INTEGUMENTARY SYSTEM</b>			
*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%)
<b>RESPIRATORY SYSTEM</b>			
#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%)
<b>HEMATOPOIETIC SYSTEM</b>			
#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
<b>HEMATOPOIETIC SYSTEM (Continued)</b>			
#Thymus	(46)	(47)	(43)
Cyst, NOS	1 (2%)		
Multiple cysts	1 (2%)		
Angiectasis	1 (2%)		
<b>CIRCULATORY SYSTEM</b>			
#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%)		
<b>DIGESTIVE SYSTEM</b>			
*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
<b>DIGESTIVE SYSTEM (Continued)</b>			
#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%)	
<b>URINARY SYSTEM</b>			
#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%)	
<b>ENDOCRINE SYSTEM</b>			
#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
<b>ENDOCRINE SYSTEM (Continued)</b>			
#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%)		
<b>REPRODUCTIVE SYSTEM</b>			
*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%)	
<b>NERVOUS SYSTEM</b>			
#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%)	
<b>SPECIAL SENSE ORGANS</b>			
*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
<b>SPECIAL SENSE ORGANS (Continued)</b>			
*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%)
<b>MUSCULOSKELETAL SYSTEM</b>			
*Bone	(50)	(50)	(50)
Exostosis		1 (2%)	
<b>BODY CAVITIES</b>			
*Tunica vaginalis	(50)	(50)	(50)
Hyperplasia, NOS		2 (4%)	
<b>ALL OTHER SYSTEMS</b>			
Adipose tissue			
Hemorrhage	3		1
Necrosis, fat	3	2	2
<b>SPECIAL MORPHOLOGY SUMMARY</b>			
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

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**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
<b>INTEGUMENTARY SYSTEM</b>			
*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%)
<b>RESPIRATORY SYSTEM</b>			
#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%)
<b>HEMATOPOIETIC SYSTEM</b>			
*Multiple organs	(50)	(50)	(50)
Leukemia, mononuclear cell	13 (26%)	14 (28%)	20 (40%)
#Lymph node	(50)	(50)	(50)
Fibrosarcoma, invasive		1 (2%)	
<b>CIRCULATORY SYSTEM</b>			
None			
<b>DIGESTIVE SYSTEM</b>			
*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
<b>URINARY SYSTEM</b>			
#Kidney	(50)	(50)	(50)
Tubular cell adenocarcinoma			1 (2%)
#Urinary bladder	(48)	(50)	(50)
Neurilemoma		1 (2%)	
<b>ENDOCRINE SYSTEM</b>			
#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%)		
<b>REPRODUCTIVE SYSTEM</b>			
*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%)	
<b>NERVOUS SYSTEM</b>			
#Brain	(50)	(50)	(50)
Glioma, NOS		4 (8%)	4 (8%)
<b>SPECIAL SENSE ORGANS</b>			
*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
<b>MUSCULOSKELETAL SYSTEM</b>			
*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%)		
<b>BODY CAVITIES</b>			
*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%)
<b>ALL OTHER SYSTEMS</b>			
None			
<b>ANIMAL DISPOSITION SUMMARY</b>			
Animals initially in study	50	50	50
Natural death	8	14	11
Moribund sacrifice	14	32	39
Terminal sacrifice	28	4	
<b>TUMOR SUMMARY</b>			
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 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
<b>Subcutaneous Tissue: Fibroma</b>			
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
<b>Subcutaneous Tissue: Fibroma or Fibrosarcoma</b>			
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
<b>Hematopoietic System: Mononuclear Cell Leukemia</b>			
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
<b>Tongue: Squamous Cell Papilloma</b>			
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
<b>Oral Cavity (Mouth or Tongue): Squamous Cell Papilloma</b>			
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
<b>Oral Cavity (Mouth or Tongue): Squamous Cell Papilloma or Carcinoma</b>			
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
<b>Forestomach: Squamous Cell Papilloma</b>			
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
<b>Forestomach: Squamous Cell Carcinoma</b>			
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
<b>Forestomach: Squamous Cell Papilloma or Carcinoma</b>			
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
<b>Anterior Pituitary Gland: Adenoma</b>			
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
<b>Adrenal Cortex: Adenoma or Adenocarcinoma</b>			
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
<b>Thyroid Gland: C-Cell Adenoma</b>			
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
<b>Thyroid Gland: Follicular Cell Carcinoma</b>			
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
<b>Thyroid Gland: Follicular Cell Adenoma or Carcinoma</b>			
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
<b>Mammary Gland: Fibroadenoma</b>			
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
<b>Mammary Gland: Adenocarcinoma</b>			
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
<b>Mammary Gland: Fibroadenoma or Adenocarcinoma</b>			
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
<b>Clitoral Gland: Adenoma</b>			
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
<b>Clitoral Gland: Carcinoma</b>			
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
<b>Clitoral Gland: Carcinoma or Adenocarcinoma</b>			
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
<b>Clitoral Gland: Adenoma, Carcinoma, or Adenocarcinoma</b>			
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
<b>Uterus: Adenoma or Adenocarcinoma</b>			
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
<b>Uterus: Endometrial Stromal Polyp</b>			
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
<b>Brain: Glioma</b>			
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
<b>All Sites: Benign Tumors</b>			
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
<b>All Sites: Malignant Tumors</b>			
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
<b>All Sites: All Tumors</b>			
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
<b>Historical Incidence for All Water Gavage Vehicle Controls</b>	
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
<b>Overall Historical Incidence for Untreated Controls</b>	
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
<b>Historical Incidence for All Water Gavage Controls</b>			
	295	0	
<b>Overall Historical Incidence for Untreated Controls</b>			
	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
<b>Historical Incidence for All Water Gavage Vehicle Controls</b>	
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
<b>Overall Historical Incidence for Untreated Controls</b>	
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
<b>Historical Incidence for All Water Gavage Vehicle Controls</b>	
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
<b>TOTAL</b>	<b>2/299 (0.7%)</b>
<b>SD (g)</b>	<b>1.03%</b>
<b>Range (h)</b>	
High	1/50
Low	0/50
<b>Overall Historical Incidence for Untreated Controls</b>	
<b>TOTAL</b>	<b>(i) 4/1,643 (0.2%)</b>
<b>SD (g)</b>	<b>0.66%</b>
<b>Range (h)</b>	
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
<b>Historical Incidence for All Water Gavage Vehicle Controls</b>			
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
<b>Overall Historical Incidence for Untreated Controls</b>			
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
<b>Historical Incidence for All Water Gavage Vehicle Controls</b>		
	299	0
<b>Overall Historical Incidence for Untreated Controls</b>		
	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
<b>Historical Incidence for All Water Gavage Vehicle Controls</b>			
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
<b>Overall Historical Incidence for Untreated Controls</b>			
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
<b>Historical Incidence for All Water Gavage Vehicle Controls</b>	
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
<b>TOTAL</b>	<b>75/299 (25.1%)</b>
SD (e)	14.90%
<b>Range (f)</b>	
High	23/49
Low	4/50
<b>Overall Historical Incidence for Untreated Controls</b>	
<b>TOTAL</b>	<b>324/1,643 (19.7%)</b>
SD (e)	8.10%
<b>Range (f)</b>	
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
<b>Historical Incidence for All Water Gavage Vehicle Controls</b>			
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
<b>Overall Historical Incidence for Untreated Controls</b>			
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
<b>Historical Incidence for All Water Gavage Vehicle Controls</b>		
	299	0
<b>Overall Historical Incidence for Untreated Controls</b>		
	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
<b>INTEGUMENTARY SYSTEM</b>			
*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%)		
<b>RESPIRATORY SYSTEM</b>			
#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%)		
<b>HEMATOPOIETIC SYSTEM</b>			
#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%)
<b>CIRCULATORY SYSTEM</b>			
#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
<b>CIRCULATORY SYSTEM (Continued)</b>			
#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%)	
<b>DIGESTIVE SYSTEM</b>			
*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
<b>DIGESTIVE SYSTEM (Continued)</b>			
#Ileum	(50)	(50)	(50)
Inflammation, chronic		1 (2%)	
#Colon	(50)	(50)	(50)
Fibrosis, focal		1 (2%)	
<b>URINARY SYSTEM</b>			
#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%)	
<b>ENDOCRINE SYSTEM</b>			
#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%)
<b>REPRODUCTIVE SYSTEM</b>			
*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
<b>REPRODUCTIVE SYSTEM (Continued)</b>			
*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 follicle cyst			2 (4%)
<b>NERVOUS SYSTEM</b>			
#Brain	(50)	(50)	(50)
Hemorrhage	1 (2%)	2 (4%)	
*Spinal cord	(50)	(50)	(50)
Hemorrhage	1 (2%)		
<b>SPECIAL SENSE ORGANS</b>			
*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%)
<b>MUSCULOSKELETAL SYSTEM</b>			
*Skeletal muscle	(50)	(50)	(50)
Inflammation, chronic		1 (2%)	
<b>BODY CAVITIES</b>			
*Peritoneum	(50)	(50)	(50)
Inflammation, chronic			1 (2%)
<b>ALL OTHER SYSTEMS</b>			
Adipose tissue			
Hemorrhage			2
Inflammation, chronic		2	
Necrosis, fat	5	1	2
<b>SPECIAL MORPHOLOGY SUMMARY</b>			
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

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**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 initially in study	50	50	50
Animals necropsied	50	50	50
Animals examined histopathologically	50	50	50
<b>INTEGUMENTARY SYSTEM</b>			
*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%)
<b>RESPIRATORY SYSTEM</b>			
#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%)
<b>HEMATOPOIETIC SYSTEM</b>			
*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%)		
<b>CIRCULATORY SYSTEM</b>			
#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%)
<b>DIGESTIVE SYSTEM</b>			
*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
<b>DIGESTIVE SYSTEM (Continued)</b>			
#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%)	
<b>URINARY SYSTEM</b>			
#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%)
<b>ENDOCRINE SYSTEM</b>			
#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%)	
<b>REPRODUCTIVE SYSTEM</b>			
*Seminal vesicle	(50)	(50)	(50)
Adenocarcinoma, NOS			1 (2%)
*Epididymis	(50)	(50)	(50)
Sarcoma, NOS			2 (4%)
Mesothelioma, NOS			1 (2%)
<b>NERVOUS SYSTEM</b>			
None			
<b>SPECIAL SENSE ORGANS</b>			
*Harderian gland	(50)	(50)	(50)
Adenoma, NOS	7 (14%)	10 (20%)	16 (32%)
Adenocarcinoma, NOS	1 (2%)	2 (4%)	7 (14%)
<b>MUSCULOSKELETAL SYSTEM</b>			
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
<b>BODY CAVITIES</b>			
*Pleural cavity	(50)	(50)	(50)
Alveolar/bronchiolar carcinoma, invasive			1 (2%)
<b>ALL OTHER SYSTEMS</b>			
Omentum			
Hepatocellular carcinoma, invasive	1		
<b>ANIMAL DISPOSITION SUMMARY</b>			
Animals initially in study	50	50	50
Natural death	1		4
Moribund sacrifice	16	25	19
Terminal sacrifice	33	25	27
<b>TUMOR SUMMARY</b>			
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: 50 mg/kg**  
(Continued)

ANIMAL NUMBER	WEEKS ON STUDY																				TOTAL: TISSUES TUMORS			
	0 7	0 8	0 9	0 0	0 1	0 2	0 3	0 4	0 5	0 6	0 7	0 8	0 9	0 0	0 1	0 2	0 3	0 4	0 5	0 6		0 7	0 8	0 9
<b>INTEGUMENTARY SYSTEM</b>																								
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
<b>RESPIRATORY SYSTEM</b>																								
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	14
Fibrosarcoma, metastatic																							X	1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
<b>HEMATOPOIETIC SYSTEM</b>																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma							X																	1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
<b>CIRCULATORY SYSTEM</b>																								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma, meta																								1
<b>DIGESTIVE SYSTEM</b>																								
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	*50
Squamous cell papilloma																								1
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	30
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	8
Fibrosarcoma, metastatic																								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			9
Squamous cell carcinoma																								1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma							X																	1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
<b>URINARY SYSTEM</b>																								
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	0 7	0 8	0 9	0 0	0 1	0 1	0 2	0 5	0 7	0 9	0 0	0 3	0 7	0 9	0 0	0 1	0 2	0 6	0 7	0 9	0 0	0 3	0 5	0 6	0 7	0 8	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	1 0 4		
<b>ENDOCRINE SYSTEM</b>																												
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Adenoma, NOS			X																X								5	
Cortical adenoma																											1	
Pheochromocytoma																							X				1	
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Adenoma, NOS	X																										1	
Parathyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47	
<b>REPRODUCTIVE SYSTEM</b>																												
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	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	N	*50	
Sarcoma, NOS																											2	
Mesothelioma, NOS																											1	
<b>NERVOUS SYSTEM</b>																												
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
<b>SPECIAL SENSE ORGANS</b>																												
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	N	*50	
Adenoma, NOS				X					X					X								X	X	X	X	X	X	16
Adenocarcinoma, NOS					X					X																	X	7
<b>BODY CAVITIES</b>																												
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	N	*50	
Alveolar/bronchiolar carcinoma, invas																											1	
<b>ALL OTHER SYSTEMS</b>																												
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50	
Malignant lymphoma, lymphocytic type																											1	
Malignant lymphoma, histiocytic type																											3	
Malignant lymphoma, mixed type																											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
<b>Skin: Squamous Cell Papilloma</b>			
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
<b>Subcutaneous Tissue: Fibrosarcoma</b>			
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
<b>Subcutaneous Tissue: Fibroma or Fibrosarcoma</b>			
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
<b>Subcutaneous Tissue: Sarcoma or Fibrosarcoma</b>			
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
<b>Subcutaneous Tissue: Fibroma, Sarcoma, or Fibrosarcoma</b>			
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
<b>Lung: Alveolar/Bronchiolar Adenoma</b>			
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
<b>Lung: Alveolar/Bronchiolar Carcinoma</b>			
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
<b>Lung: Alveolar/Bronchiolar Adenoma or Carcinoma</b>			
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
<b>Hematopoietic System: Malignant Lymphoma, Histiocytic Type</b>			
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
<b>Hematopoietic System: Malignant Lymphoma, Mixed Type</b>			
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
<b>Hematopoietic System: Lymphoma, All Malignant</b>			
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
<b>Circulatory System: Hemangiosarcoma</b>			
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
<b>Circulatory System: Hemangioma or Hemangiosarcoma</b>			
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
<b>Liver: Hepatocellular Adenoma</b>			
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
<b>Liver: Hepatocellular Carcinoma</b>			
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
<b>Liver: Hepatocellular Adenoma or Carcinoma</b>			
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
<b>Forestomach: Squamous Cell Papilloma</b>			
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
<b>Forestomach: Squamous Cell Papilloma or Carcinoma</b>			
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
<b>Small Intestine: Adenomatous Polyp or Adenocarcinoma</b>			
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
<b>Adrenal Capsule: Adenoma</b>			
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
<b>Adrenal Medulla: Pheochromocytoma</b>			
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
<b>Harderian Gland: Adenoma</b>			
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
<b>Harderian Gland: Adenocarcinoma</b>			
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
<b>Harderian Gland: Adenoma or Adenocarcinoma</b>			
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
<b>All Sites: Benign Tumors</b>			
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
<b>All Sites: Malignant Tumors</b>			
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
<b>All Sites: All Tumors</b>			
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<sub>1</sub> MICE (a)**

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
<b>Historical Incidence for All Water Gavage Vehicle Controls</b>			
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
<b>Overall Historical Incidence for Untreated Controls</b>			
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<sub>1</sub> MICE (a)**

Study	Incidence in Controls		
	Papilloma	Carcinoma	Papilloma or Carcinoma
<b>Historical Incidence for All Water Gavage Vehicle Controls</b>			
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
<b>Overall Historical Incidence for Untreated Controls</b>			
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  
 (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 C4c. HISTORICAL INCIDENCE OF FORESTOMACH SQUAMOUS CELL TUMORS IN MALE B6C3F<sub>1</sub> MICE (a)**

Study	Incidence in Controls		
	Papilloma	Carcinoma	Papilloma or Carcinoma
<b>Historical Incidence for All Water Gavage Vehicle Controls</b>			
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
<b>TOTAL</b>	<b>6/331 (1.8%)</b>	<b>2/331 (0.6%)</b>	<b>8/331 (2.4%)</b>
SD (e)	2.43%	1.01%	2.43%
Range (f)			
High	3/50	1/47	3/50
Low	0/49	0/50	0/49
<b>Overall Historical Incidence for Untreated Controls</b>			
<b>TOTAL</b>	<b>(g) 9/1,645 (0.5%)</b>	<b>1/1,645 (0.1%)</b>	<b>(g) 10/1,645 (0.6%)</b>
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<sub>1</sub> MICE (a)**

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
<b>Historical Incidence for All Water Gavage Vehicle Controls</b>			
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
<b>Overall Historical Incidence for Untreated Controls</b>			
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<sub>1</sub> MICE (a)**

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
<b>Historical Incidence for All Water Gavage Vehicle Controls</b>			
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
<b>Overall Historical Incidence for Untreated Controls</b>			
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<sub>1</sub> MICE (a)**

Study	Incidence in Controls	
	Lymphoma	Lymphoma or Leukemia
<b>Historical Incidence for All Water Gavage Vehicle Controls</b>		
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
<b>Overall Historical Incidence for Untreated Controls</b>		
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<sub>1</sub> MICE (a)**

	Number Examined	Number of Tumors
<b>Historical Incidence for All Water Gavage Vehicle Controls</b>		
	350	0
<b>Overall Historical Incidence for Untreated Controls</b>		
	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<sub>1</sub> MICE (a)**

	Number Examined	Number of Tumors	Diagnosis
<b>Historical Incidence for All Water Gavage Vehicle Controls</b>			
	350	0	
<b>Overall Historical Incidence for Untreated Controls</b>			
	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
<b>INTEGUMENTARY SYSTEM</b>			
*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%)	
<b>RESPIRATORY SYSTEM</b>			
#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%)
<b>HEMATOPOIETIC SYSTEM</b>			
#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%)	
<b>CIRCULATORY SYSTEM</b>			
#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
<b>CIRCULATORY SYSTEM (Continued)</b>			
#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%)	
<b>DIGESTIVE SYSTEM</b>			
*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%)
<b>URINARY SYSTEM</b>			
#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
<b>ENDOCRINE SYSTEM</b>			
#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%)	
<b>REPRODUCTIVE SYSTEM</b>			
*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%)
<b>NERVOUS SYSTEM</b>			
#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%)
<b>SPECIAL SENSE ORGANS</b>			
*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
<b>SPECIAL SENSE ORGANS (Continued)</b>			
*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%)
<b>MUSCULOSKELETAL SYSTEM</b>			
*Bone	(50)	(50)	(50)
Fracture, NOS	1 (2%)		
Hyperplasia, focal	1 (2%)		2 (4%)
<b>BODY CAVITIES</b>			
None			
<b>ALL OTHER SYSTEMS</b>			
Adipose tissue			
Necrosis, fat	2		2
<b>SPECIAL MORPHOLOGY SUMMARY</b>			
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

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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
<b>INTEGUMENTARY SYSTEM</b>			
*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%)
<b>RESPIRATORY SYSTEM</b>			
#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%)
<b>HEMATOPOIETIC SYSTEM</b>			
*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%)
<b>CIRCULATORY SYSTEM</b>			
*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%)
<b>DIGESTIVE SYSTEM</b>			
#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
<b>DIGESTIVE SYSTEM (Continued)</b>			
#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%)
<b>URINARY SYSTEM</b>			
#Kidney	(50)	(50)	(50)
Tubular cell adenocarcinoma		1 (2%)	
<b>ENDOCRINE SYSTEM</b>			
#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%)	
<b>REPRODUCTIVE SYSTEM</b>			
*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%)	
<b>NERVOUS SYSTEM</b>			
#Brain	(50)	(49)	(50)
Adenocarcinoma, NOS, invasive			1 (2%)
<b>SPECIAL SENSE ORGANS</b>			
*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
<b>MUSCULOSKELETAL SYSTEM</b>			
*Skeletal muscle	(50)	(50)	(50)
Sarcoma, NOS	1 (2%)	1 (2%)	1 (2%)
Sarcoma, NOS, invasive			1 (2%)
<b>BODY CAVITIES</b>			
*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%)		
<b>ALL OTHER SYSTEMS</b>			
*Multiple organs	(50)	(50)	(50)
Mesothelioma, malignant			1 (2%)
<b>ANIMAL DISPOSITION SUMMARY</b>			
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
<b>TUMOR SUMMARY</b>			
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: VEHICLE CONTROL  
(Continued)**

ANIMAL NUMBER	0																				TOTAL TISSUES TUMORS						
	1	2	3	4	6	8	9	5	6	2	3	4	5	6	8	9	0	1	4	5		6	7	8	9	0	
WEEKS ON STUDY	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1		
<b>RESPIRATORY SYSTEM</b>																											
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Adenocarcinoma, NOS, metastatic																											
Alveolar/bronchiolar adenoma										X			X							X							
Alveolar/bronchiolar carcinoma																											
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
<b>HEMATOPOIETIC SYSTEM</b>																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
<b>CIRCULATORY SYSTEM</b>																											
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
<b>DIGESTIVE SYSTEM</b>																											
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Hepatocellular adenoma																											
Hepatocellular carcinoma																											
Malg. lymphoma, undifferentiated type																											
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Squamous cell papilloma																											
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
<b>URINARY SYSTEM</b>																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
<b>ENDOCRINE SYSTEM</b>																											
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Adenoma, NOS																											
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Adenoma, NOS																											
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Adenoma, NOS																											
Follicular cell adenoma																											
Parathyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
<b>REPRODUCTIVE SYSTEM</b>																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Adenocarcinoma, NOS																											
Fibroadenoma																											
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Leiomyosarcoma																											
Endometrial stromal polyp																											
Hemangiosarcoma																											
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Papillary cystadenoma, NOS																											
<b>NERVOUS SYSTEM</b>																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
<b>SPECIAL SENSE ORGANS</b>																											
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																											
<b>MUSCULOSKELETAL SYSTEM</b>																											
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																											
<b>BODY CAVITIES</b>																											
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																											
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																											
<b>ALL OTHER SYSTEMS</b>																											
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		
Malg. lymphoma, undifferentiated type																											
Malg. lymphoma, lymphocytic type																											
Malg. lymphoma, histiocytic type																											
Malignant lymphoma, mixed type																											

\* Animals necropsied

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

ANIMAL NUMBER	01	02	03	04	05	06	07	08	09	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	
WEEKS ON STUDY	6	6	7	7	7	8	8	8	8	8	8	8	8	8	8	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9
<b>INTEGUMENTARY SYSTEM</b>																															
Skin	+																														
Sebaceous adenoma	+																														
Subcutaneous tissue	+																														
Sarcoma, NOS	+																														
Fibrosarcoma	+																														
Hemangiosarcoma	+																														
	X	X																													
<b>RESPIRATORY SYSTEM</b>																															
Lungs and bronchi	+																														
Adenocarcinoma, NOS, metastatic	+																														
Hepatocellular carcinoma, metastatic	+																														
Alveolar/bronchiolar adenoma	+																														
Alveolar/bronchiolar carcinoma	+																														
Trachea	+																														
Nasal cavity	+																														
<b>HEMATOPOIETIC SYSTEM</b>																															
Bone marrow	+																														
Spleen	+																														
Lymph nodes	+																														
Thymus	+																														
	-	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
<b>CIRCULATORY SYSTEM</b>																															
Heart	+																														
	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
<b>DIGESTIVE SYSTEM</b>																															
Salivary gland	+																														
Liver	+																														
Hepatocellular adenoma	+																														
Hepatocellular carcinoma	+																														
Bile duct	+																														
Gallbladder & common bile duct	+																														
Pancreas	+																														
Esophagus	+																														
Stomach	+																														
Squamous cell papilloma	+																														
Small intestine	+																														
Adenomatous polyp, NOS	+																														
Large intestine	+																														
<b>URINARY SYSTEM</b>																															
Kidney	+																														
Tubular cell adenocarcinoma	+																														
Urinary bladder	+																														
	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

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

ANIMAL NUMBER	WEEKS ON STUDY																				TOTAL: TISSUES TUMORS
	1 4	1 4	1 4	1 4	1 4	1 4	1 4	1 4	1 4	1 4	1 4	1 4	1 4	1 4	1 4	1 4	1 4	1 4	1 4	1 4	
<b>INTEGUMENTARY SYSTEM</b>																					
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sebacous adenoma																	X				1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS																					1
Fibrosarcoma																					2
Hemangiosarcoma																					1
<b>RESPIRATORY SYSTEM</b>																					
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS, metastatic																					1
Hepatocellular carcinoma, metastatic																					4
Alveolar/bronchiolar adenoma																					6
Alveolar/bronchiolar carcinoma																				X	X
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
<b>HEMATOPOIETIC SYSTEM</b>																					
Bone marrow	+	+	-	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	42
<b>CIRCULATORY SYSTEM</b>																					
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
<b>DIGESTIVE SYSTEM</b>																					
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma																					3
Hepatocellular carcinoma																					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
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
<b>URINARY SYSTEM</b>																					
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	01	02	03	04	05	06	07	08	09	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	
WEEKS ON STUDY	06	06	07	07	07	08	08	08	08	08	08	08	08	08	09	09	09	09	09	09	09	10	10	11	11	11
<b>ENDOCRINE SYSTEM</b>																										
Pituitary	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Adenoma, NOS																								X	X	
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Adenoma, NOS																										
Cortical adenoma																		X								
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Follicular cell adenoma													X													
C-cell adenoma																										
Parathyroid	+	-	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
<b>REPRODUCTIVE SYSTEM</b>																										
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																										
<b>NERVOUS SYSTEM</b>																										
Brain	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
<b>SPECIAL SENSE ORGANS</b>																										
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											
Adenocarcinoma, NOS																										
<b>MUSCULOSKELETAL SYSTEM</b>																										
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																										
<b>BODY CAVITIES</b>																										
Pertoneum	N	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	
<b>ALL OTHER SYSTEMS</b>																										
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																										
Malignant lymphoma, mixed type	X			X	X		X	X			X	X		X								X				



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

ANIMAL NUMBER	0 0																				TOTAL TISSUES TUMORS	
	3 6 8 1 2 3 4 8 0 2 7 8 9 0 1 3 4 6 7 9 1 5 6 8 0																					
WEEKS ON STUDY	1 1																					
	0 0																					
4 4																						
<b>ENDOCRINE SYSTEM</b>																						
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																						1
Parathyroid	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
<b>REPRODUCTIVE SYSTEM</b>																						
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenoma, NOS																						1
Adenocarcinoma, NOS	X																					5
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS																						3
Sarcoma, NOS																					X	1
Endometrial stromal polyp																						3
Hemangioma					X																	1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS																						1
Luteoma																					X	1
<b>NERVOUS SYSTEM</b>																						
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
<b>SPECIAL SENSE ORGANS</b>																						
Harderian gland	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												10
Adenocarcinoma, NOS											X											1
<b>MUSCULOSKELETAL SYSTEM</b>																						
Muscle	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
<b>BODY CAVITIES</b>																						
Peritoneum	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
<b>ALL OTHER SYSTEMS</b>																						
Multiple organs, NOS	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																				X		2
Malignant lymphoma, histiocytic type																						1
Malignant lymphoma, mixed type	X			X		X	X	X	X									X	X		X	19

\* Animals necropsied



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

ANIMAL NUMBER	0397	0427	0428	0429	0430	0431	0432	0433	0434	0435	0436	0437	0438	0439	0440	0441	0442	0443	0444	0445	0446	0447	0448	0449	0450	TOTAL TISSUES TUMORS	
WEEKS ON STUDY	7	8	8	8	8	9	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11		
<b>INTEGUMENTARY SYSTEM</b>																											
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50	
Squamous cell papilloma																										1	
Squamous cell carcinoma				X																						1	
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50	
Sarcoma, NOS			X																							6	
Fibrosarcoma							X	X																		3	
<b>RESPIRATORY SYSTEM</b>																											
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Adenocarcinoma, NOS, metastatic																										4	
Hepatocellular carcinoma, metastatic																										1	
Alveolar/bronchiolar adenoma		X					X																			5	
Alveolar/bronchiolar carcinoma	X																									3	
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
<b>HEMATOPOIETIC SYSTEM</b>																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Malignant lymphoma, mixed type																										2	
Thymus	+	-	-	+	+	+	-	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	39	
<b>CIRCULATORY SYSTEM</b>																											
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
<b>DIGESTIVE SYSTEM</b>																											
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Hepatocellular adenoma																										10	
Hepatocellular carcinoma			X					X	X																	4	
Hemangioma																										1	
Hemangiosarcoma																										1	
Malignant lymphoma, histiocytic type																										1	
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	N	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50	
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Sarcoma, NOS, invasive																										1	
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Squamous cell papilloma																										4	
Mast cell tumor																										1	
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Adenocarcinoma, NOS																										1	
Leiomyosarcoma																										1	
Malignant lymphoma, mixed type																										1	
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
<b>URINARY SYSTEM</b>																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
<b>ENDOCRINE SYSTEM</b>																											
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Adenoma, NOS	X		X	X			X	X		X							X	X	X	X	X	X	X	X	X	14	
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Cortical adenoma																										1	
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Parathyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43	

\* 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
<b>Subcutaneous Tissue: Sarcoma</b>			
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
<b>Subcutaneous Tissue: Fibrosarcoma</b>			
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
<b>Subcutaneous Tissue: Sarcoma or Fibrosarcoma</b>			
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
<b>Lung: Alveolar/Bronchiolar Adenoma</b>			
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
<b>Lung: Alveolar/Bronchiolar Carcinoma</b>			
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
<b>Lung: Alveolar/Bronchiolar Adenoma or Carcinoma</b>			
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
<b>Hematopoietic System: Malignant Lymphoma, Undifferentiated Type</b>			
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
<b>Hematopoietic System: Malignant Lymphoma, Lymphocytic Type</b>			
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
<b>Hematopoietic System: Malignant Lymphoma, Histiocytic Type</b>			
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
<b>Hematopoietic System: Malignant Lymphoma, Mixed Type</b>			
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
<b>Hematopoietic System: Lymphoma, All Malignant</b>			
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
<b>Circulatory System: Hemangiosarcoma</b>			
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
<b>Circulatory System: Hemangioma or Hemangiosarcoma</b>			
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
<b>Liver: Hepatocellular Adenoma</b>			
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
<b>Liver: Hepatocellular Carcinoma</b>			
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
<b>Liver: Hepatocellular Adenoma or Carcinoma</b>			
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
<b>Forestomach: Squamous Cell Papilloma</b>			
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
<b>Anterior Pituitary Gland: Adenoma</b>			
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
<b>Adrenal Capsule: Adenoma</b>			
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
<b>Mammary Gland: Adenocarcinoma</b>			
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
<b>Mammary Gland: Adenoma, Fibroadenoma, or Adenocarcinoma</b>			
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
<b>Uterus: Endometrial Stromal Polyp</b>			
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
<b>Uterus: Adenocarcinoma</b>			
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
<b>Uterus: Carcinoma or Adenocarcinoma</b>			
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
<b>Harderian Gland: Adenoma</b>			
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
<b>Harderian Gland: Adenoma or Adenocarcinoma</b>			
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
<b>All Sites: Benign Tumors</b>			
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
<b>All Sites: Malignant Tumors</b>			
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
<b>All Sites: All Tumors</b>			
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<sub>1</sub> MICE (a)

Study	Incidence in Controls		
	Adenoma	Adenocarcinoma	Adenoma or Adenocarcinoma
<b>Historical Incidence for All Water Gavage Vehicle Controls</b>			
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
<b>Overall Historical Incidence for Untreated Controls</b>			
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<sub>1</sub> MICE (a)

Study	Incidence in Controls		
	Fibroadenoma	Adenocarcinoma	Fibroadenoma or Adenocarcinoma
<b>Historical Incidence for All Water Gavage Vehicle Controls</b>			
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
<b>Overall Historical Incidence for Untreated Controls</b>			
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<sub>1</sub> MICE (a)**

Study	Incidence in Controls
<b>Historical Incidence for All Water Gavage Vehicle Controls</b>	
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
<b>Overall Historical Incidence for Untreated Controls</b>	
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<sub>1</sub> MICE (a)**

Study	Incidence of Papillomas or Carcinomas in Controls
<b>Historical Incidence for All Water Gavage Vehicle Controls</b>	
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
<b>Overall Historical Incidence for Untreated Controls</b>	
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<sub>1</sub> MICE (a)

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
<b>Historical Incidence for All Water Gavage Vehicle Controls</b>			
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
<b>Overall Historical Incidence for Untreated Controls</b>			
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<sub>1</sub> MICE (a)**

Study	Incidence in Controls		
	Hemangioma	Hemangiosarcoma	Hemangioma or Hemangiosarcoma
<b>Historical Incidence for All Water Gavage Vehicle Controls</b>			
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
<b>TOTAL</b>	<b>4/350 (1.1%)</b>	<b>4/350 (1.1%)</b>	<b>8/350 (2.3%)</b>
SD (e)	1.07%	1.07%	1.38%
<b>Range (f)</b>			
High	1/50	1/50	2/50
Low	0/50	0/50	0/50
<b>Overall Historical Incidence for Untreated Controls</b>			
<b>TOTAL</b>	<b>25/1,689 (1.5%)</b>	<b>23/1,689 (1.4%)</b>	<b>48/1,689 (2.8%)</b>
SD (e)	1.89%	1.89%	2.85%
<b>Range (f)</b>			
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<sub>1</sub> MICE (a)**

Study	Incidence of Adenomas or Adenocarcinomas in Controls
<b>Historical Incidence for All Water Gavage Vehicle Controls</b>	
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
<b>Overall Historical Incidence for Untreated Controls</b>	
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<sub>1</sub> MICE (a)**

Study	Incidence in Controls		
	Adenomatous Polyp	Adenocarcinoma	Adenomatous Polyp or Adenocarcinoma
<b>Historical Incidence for All Water Gavage Vehicle Controls</b>			
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
<b>Overall Historical Incidence for Untreated Controls</b>			
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
<b>INTEGUMENTARY SYSTEM</b>			
*Skin	(50)	(50)	(50)
Epidermal inclusion cyst	1 (2%)		
*Subcutaneous tissue	(50)	(50)	(50)
Hemorrhage			1 (2%)
<b>RESPIRATORY SYSTEM</b>			
#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%)
<b>HEMATOPOIETIC SYSTEM</b>			
#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%)		
<b>CIRCULATORY SYSTEM</b>			
#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
<b>DIGESTIVE SYSTEM</b>			
*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%)
<b>URINARY SYSTEM</b>			
#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%)	
<b>ENDOCRINE SYSTEM</b>			
#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
<b>ENDOCRINE SYSTEM (Continued)</b>			
#Thyroid	(50)	(50)	(50)
Follicular cyst, NOS		3 (6%)	
Inflammation, chronic			2 (4%)
Hyperplasia, follicular cell	8 (16%)	2 (4%)	6 (12%)
<b>REPRODUCTIVE SYSTEM</b>			
*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%)	
<b>NERVOUS SYSTEM</b>			
#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%)
<b>SPECIAL SENSE ORGANS</b>			
*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%)
<b>MUSCULOSKELETAL SYSTEM</b>			
*Bone	(50)	(50)	(50)
Fibrous osteodystrophy	3 (6%)		1 (2%)
<b>BODY CAVITIES</b>			
*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
<b>ALL OTHER SYSTEMS</b>			
Adipose tissue			
Hemorrhage			1
Necrosis, fat	2	1	4
<b>SPECIAL MORPHOLOGY SUMMARY</b>			
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

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# APPENDIX E. SENTINEL ANIMAL PROGRAM

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## 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<sub>1</sub> 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:

	<u>Hemagglutination Inhibition</u>	<u>Complement Fixation</u>	<u>ELISA</u>
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
<b>RATS</b>		
6	10/10	RCV
12	6/9	RCV
18	5/10 8/10	KRV RCV
24	10/10	RCV/SDA
<b>MICE</b>		
6	--	None positive
12	--	None positive
18	(b) 2/10	Reo 3
24	(b) 1/10 1/10	Reo 3 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)**

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TABLE F1	INGREDIENTS OF NIH 07 RAT AND MOUSE RATION 202
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TABLE F3	NUTRIENT COMPOSITION OF NIH 07 RAT AND MOUSE RATION 203
TABLE F4	CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION 204

**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
<b>Vitamins</b>		
A	5,500,000 IU	Stabilized vitamin A palmitate or acetate
D <sub>3</sub>	4,600,000 IU	D-activated animal sterol
K <sub>3</sub>	2.8 g	Menadione
<i>d</i> - $\alpha$ -Tocopheryl acetate	20,000 IU	
Choline	560.0 g	Choline chloride
Folic acid	2.2 g	
Niacin	30.0 g	
<i>d</i> -Pantothenic acid	18.0 g	<i>d</i> -Calcium pantothenate
Riboflavin	3.4 g	
Thiamine	10.0 g	Thiamine mononitrate
B <sub>12</sub>	4,000 $\mu$ g	
Pyridoxine	1.7 g	Pyridoxine hydrochloride
Biotin	140.0 mg	<i>d</i> -Biotin
<b>Minerals</b>		
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 $\pm$ Standard Deviation	Range	Number of Samples
Crude protein (percent by weight)	23.6 $\pm$ 0.87	22.2-25.3	25
Crude fat (percent by weight)	4.92 $\pm$ 0.54	3.3-5.7	25
Crude fiber (percent by weight)	3.30 $\pm$ 0.26	2.9-3.8	25
Ash (percent by weight)	6.43 $\pm$ 0.39	5.7-7.2	25
<b>Amino Acids (percent of total diet) (a)</b>			
Arginine	1.323 $\pm$ 0.830	1.21-1.39	4
Cystine	0.310 $\pm$ 0.099	0.218-0.400	4
Glycine	1.155 $\pm$ 0.069	1.06-1.21	4
Histidine	0.572 $\pm$ 0.030	0.530-0.603	4
Isoleucine	0.910 $\pm$ 0.033	0.881-0.944	4
Leucine	1.949 $\pm$ 0.065	1.85-1.99	4
Lysine	1.275 $\pm$ 0.076	1.20-1.37	4
Methionine	0.422 $\pm$ 0.187	0.306-0.699	4
Phenylalanine	0.909 $\pm$ 0.167	0.665-1.04	4
Threonine	0.844 $\pm$ 0.029	0.824-0.886	4
Tryptophan	0.187	0.171-0.211	3
Tyrosine	0.631 $\pm$ 0.094	0.566-0.769	4
Valine	1.11 $\pm$ 0.050	1.05-1.17	4
<b>Essential Fatty Acids (percent of total diet) (a)</b>			
Linoleic	2.44	2.37-2.52	3
Linolenic	0.274	0.256-0.308	3
Arachidonic	0.008		1
<b>Vitamins (a)</b>			
Vitamin A (IU/kg)	12,088 $\pm$ 4,119	7,500-24,000	25
Vitamin D (IU/kg)	4,650	3,000-6,300	2
$\alpha$ -Tocopherol (ppm)	41.53 $\pm$ 7.52	31.1-48.9	4
Thiamine (ppm) (b)	16.2 $\pm$ 2.30	12.0-21.0	24
Riboflavin (ppm)	7.5 $\pm$ 0.96	6.1-8.2	4
Niacin (ppm)	85.0 $\pm$ 14.2	65.0-97.0	4
Pantothenic acid (ppm)	29.3 $\pm$ 4.6	23.0-34.0	4
Pyridoxine (ppm)	7.6 $\pm$ 1.5	5.6-8.8	4
Folic acid (ppm)	2.8 $\pm$ 0.88	1.8-3.7	4
Biotin (ppm)	0.27 $\pm$ 0.05	0.21-0.32	4
Vitamin B <sub>12</sub> (ppb)	21.0 $\pm$ 11.9	11.0-38.0	4
Choline (ppm)	3,302.0 $\pm$ 120.0	3,200.0-3,430.0	4
<b>Minerals (a)</b>			
Calcium (percent)	1.23 $\pm$ 0.10	1.08-1.44	25
Phosphorus (percent)	0.98 $\pm$ 0.05	0.88-1.11	25
Potassium (percent)	0.862 $\pm$ 0.100	0.772-0.974	3
Chloride (percent)	0.546 $\pm$ 0.100	0.442-0.635	4
Sodium (percent)	0.311 $\pm$ 0.038	0.258-0.350	4
Magnesium (percent)	0.169 $\pm$ 0.133	0.151-0.181	4
Sulfur (percent)	0.316 $\pm$ 0.070	0.270-0.420	4
Iron (ppm)	447.0 $\pm$ 57.3	409.0-523.0	4
Manganese (ppm)	90.6 $\pm$ 8.20	81.7-95.5	4
Zinc (ppm)	53.6 $\pm$ 5.27	46.1-58.6	4
Copper (ppm)	10.77 $\pm$ 3.19	8.09-15.39	4
Iodine (ppm)	2.95 $\pm$ 1.05	1.52-3.82	4
Chromium (ppm)	1.81 $\pm$ 0.28	1.44-2.09	4
Cobalt (ppm)	0.68 $\pm$ 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
<i>E. coli</i> (MPN/g) (j)	<3		25
Total nitrosamines (ppb)	3.42 ± 2.72	0.8-9.3	25
<i>N</i> -Nitrosodimethylamine (ppb)	2.68 ± 2.37	0.8-8.3	25
<i>N</i> -Nitrosopyrrolidine (ppb)	1.14 ± 0.48	<0.5-2.9	25
<b>Pesticides (ppm)</b>			
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)**

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- (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

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## APPENDIX G. CHEMICAL CHARACTERIZATION

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### 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  $1.1087 \pm 0.0012(8)$ . Chemical identity was confirmed by spectroscopy. The infrared and nuclear magnetic resonance spectra (Figures G1 and G2) agreed with the literature spectra (Sadler 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

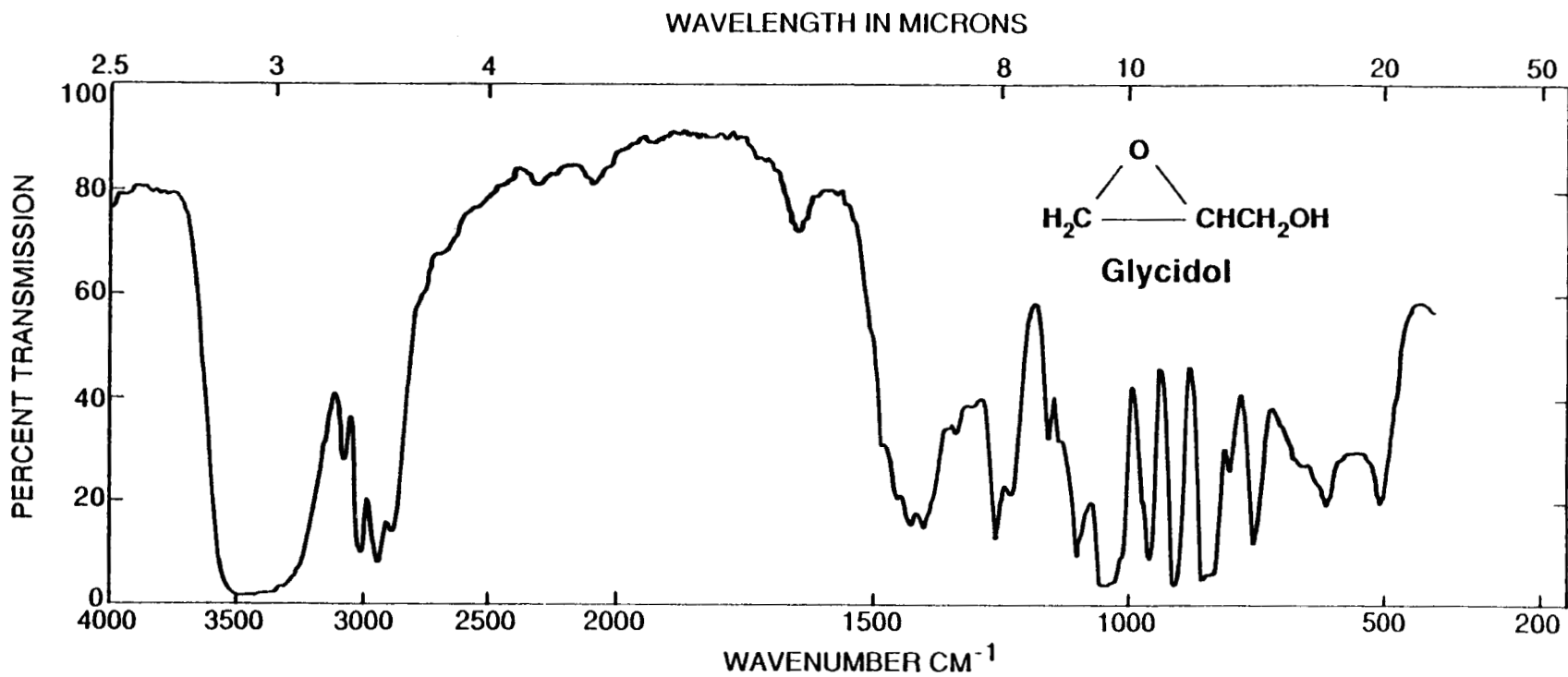


FIGURE G1. INFRARED ABSORPTION SPECTRUM OF GLYCIDOL (LOT NO. 1536A)

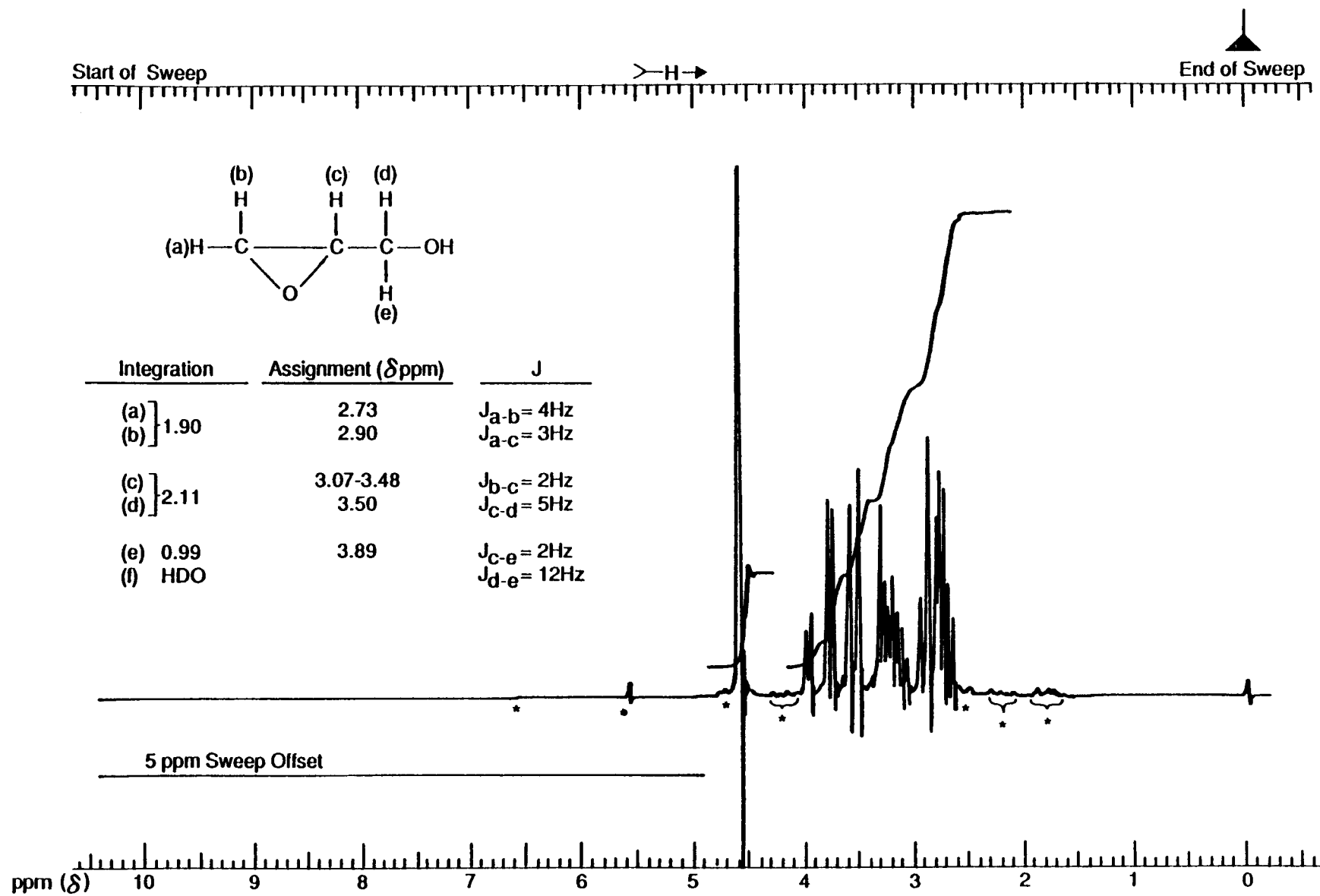


FIGURE G2. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF GLYCIDOL (LOT NO. 1536A)

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

<b>Sixteen-Day Studies</b>	<b>Thirteen-Week Studies</b>	<b>Two-Year Studies</b>
<b>Preparation</b> 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
<b>Maximum Storage Time</b> 11 d	9 d	11 d
<b>Storage Conditions</b> 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  $\pm 10\%$  of the target concentrations. For the glycidol studies, the mixtures were formulated within  $\pm 10\%$  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**

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## APPENDIX H. GENETIC TOXICOLOGY

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### 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  $6 \times 10^6$  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,  $3 \times 10^6$  cells were plated in medium and soft agar supplemented with Tft for selection of Tft-resistant cells (TK<sup>+/+</sup>), 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.



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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 ( $21 \pm 2$  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

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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  $\mu$ l) 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

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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<sub>1</sub> 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  $\pm$  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  $\mu\text{g}/\text{plate}$  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  $\mu\text{g}/\text{ml}$  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  $\mu\text{g}/\text{ml}$ ) 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<sub>1</sub> 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).

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
<b>Study performed at SRI International</b>							
<b>TA100</b>	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	--
<b>Trial summary</b>		Positive	Positive	Positive	Positive	Positive	Positive
<b>Positive control (c)</b>		487 ± 10.5	353 ± 10.3	1,380 ± 23.3	1,580 ± 96.6	530 ± 16.3	810 ± 26.8
<b>TA1535</b>	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	--
<b>Trial summary</b>		Positive	Positive	Positive	Positive	Positive	Positive
<b>Positive control (c)</b>		540 ± 15.3	402 ± 14.3	356 ± 17.7	518 ± 29.9	154 ± 9.3	195 ± 27.7
<b>TA1537</b>	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	--
<b>Trial summary</b>		Weakly positive	Weakly positive	Positive	Positive	Equivocal	Positive
<b>Positive control (c)</b>		237 ± 54.5	145 ± 3.2	434 ± 32.2	435 ± 11.9	189 ± 11.7	171 ± 5.2
<b>TA98</b>	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	--
<b>Trial summary</b>		Positive	Positive	Weakly positive	Positive	Positive	Positive
<b>Positive control (c)</b>		863 ± 17	718 ± 16.7	1,276 ± 38.5	1,334 ± 104.6	863 ± 31.6	488 ± 31.1

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

Strain	Dose ( $\mu\text{g}/\text{plate}$ )	Revertants/Plate (b)					
		-S9		+S9 (hamster)		+S9 (rat)	
		Trial 1	Trial 2	Trial 1	Trial 2	Trial 1	Trial 2
<b>Study performed at Microbiological Associates, Inc.</b>							
TA100	0	113 $\pm$ 3.9	92 $\pm$ 4.9	94 $\pm$ 4.9	88 $\pm$ 9.5	101 $\pm$ 6.4	101 $\pm$ 8.0
	1	--	84 $\pm$ 5.8	--	96 $\pm$ 4.8	--	95 $\pm$ 4.6
	10	--	146 $\pm$ 5.2	--	117 $\pm$ 8.5	--	140 $\pm$ 7.9
	100	482 $\pm$ 16.2	292 $\pm$ 7.3	463 $\pm$ 10.6	391 $\pm$ 14.0	472 $\pm$ 14.0	378 $\pm$ 9.0
	333	1,041 $\pm$ 19.7	--	1,015 $\pm$ 8.8	--	1,041 $\pm$ 11.5	--
	1,000	1,808 $\pm$ 32.7	1,018 $\pm$ 11.4	1,632 $\pm$ 10.2	(d) 1,302 $\pm$ 38.7	1,951 $\pm$ 9.0	1,269 $\pm$ 26.4
	3,333	3,075 $\pm$ 117.2	--	2,910 $\pm$ 135.4	--	2,973 $\pm$ 9.4	--
	10,000	3,332 $\pm$ 63.5	(d) 2,088 $\pm$ 2.2	3,422 $\pm$ 44.8	(d) 2,487 $\pm$ 59.8	3,435 $\pm$ 14.5	(d) 2,465 $\pm$ 41.0
Trial summary		Positive	Positive	Positive	Positive	Positive	Positive
Positive control (c)		1,353 $\pm$ 28.5	712 $\pm$ 7.0	1,303 $\pm$ 61.9	843 $\pm$ 32.8	1,779 $\pm$ 21.8	1,368 $\pm$ 25.4
TA1535	0	30 $\pm$ 2.9	21 $\pm$ 1.5	11 $\pm$ 2.2	8 $\pm$ 0.6	13 $\pm$ 2.7	7 $\pm$ 2.6
	1	--	20 $\pm$ 4.6	--	10 $\pm$ 0.7	--	15 $\pm$ 2.1
	10	--	72 $\pm$ 11.1	--	57 $\pm$ 5.2	--	70 $\pm$ 11.0
	100	473 $\pm$ 1.8	477 $\pm$ 15.8	522 $\pm$ 16.2	443 $\pm$ 3.4	533 $\pm$ 16.3	516 $\pm$ 14.4
	333	935 $\pm$ 21.5	--	1,194 $\pm$ 24.6	--	1,193 $\pm$ 13.8	--
	1,000	1,329 $\pm$ 26.3	1,338 $\pm$ 21.2	2,231 $\pm$ 62.4	1,422 $\pm$ 30.7	2,218 $\pm$ 61.2	1,360 $\pm$ 31.4
	3,333	2,303 $\pm$ 64.4	--	2,867 $\pm$ 46.9	--	2,929 $\pm$ 41.6	--
	10,000	1,831 $\pm$ 39.2	(d) 1,238 $\pm$ 23.4	1,697 $\pm$ 20.3	(d) 1,930 $\pm$ 41.0	981 $\pm$ 26.9	(d) 1,336 $\pm$ 84.0
Trial summary		Positive	Positive	Positive	Positive	Positive	Positive
Positive control (c)		847 $\pm$ 17.6	915 $\pm$ 21.2	101 $\pm$ 11.4	66 $\pm$ 2.1	141 $\pm$ 11.6	76 $\pm$ 1.3
TA97	0	111 $\pm$ 10.0	102 $\pm$ 6.4	112 $\pm$ 5.0	117 $\pm$ 4.1	124 $\pm$ 1.9	136 $\pm$ 1.5
	1	--	99 $\pm$ 3.8	--	120 $\pm$ 7.7	--	149 $\pm$ 3.7
	10	--	99 $\pm$ 3.8	--	115 $\pm$ 7.8	--	152 $\pm$ 11.6
	100	119 $\pm$ 3.5	109 $\pm$ 6.7	175 $\pm$ 15.6	172 $\pm$ 6.9	161 $\pm$ 12.7	179 $\pm$ 3.2
	333	230 $\pm$ 2.8	--	275 $\pm$ 13.3	--	265 $\pm$ 10.5	--
	1,000	383 $\pm$ 2.8	317 $\pm$ 8.8	519 $\pm$ 15.4	455 $\pm$ 4.7	457 $\pm$ 15.3	439 $\pm$ 11.4
	3,333	903 $\pm$ 45.6	--	1,131 $\pm$ 43.1	--	976 $\pm$ 53.2	--
	10,000	868 $\pm$ 16.6	(d) 452 $\pm$ 2.1	963 $\pm$ 74.4	(d) 1,215 $\pm$ 15.9	842 $\pm$ 85.8	(d) 998 $\pm$ 9.0
Trial summary		Positive	Positive	Positive	Positive	Positive	Positive
Positive control (c)		501 $\pm$ 14.5	617 $\pm$ 24.6	930 $\pm$ 45.0	549 $\pm$ 31.7	1,318 $\pm$ 35.7	910 $\pm$ 43.3
TA98	0	22 $\pm$ 0.3	17 $\pm$ 0.9	35 $\pm$ 1.3	23 $\pm$ 3.2	36 $\pm$ 1.2	26 $\pm$ 1.5
	1	--	16 $\pm$ 2.1	--	33 $\pm$ 2.9	--	29 $\pm$ 3.2
	10	--	21 $\pm$ 2.0	--	25 $\pm$ 6.5	--	28 $\pm$ 1.5
	100	21 $\pm$ 4.7	17 $\pm$ 3.5	32 $\pm$ 4.1	38 $\pm$ 3.8	31 $\pm$ 1.8	33 $\pm$ 5.3
	333	22 $\pm$ 2.5	--	48 $\pm$ 4.7	--	37 $\pm$ 3.5	--
	1,000	29 $\pm$ 2.3	20 $\pm$ 3.0	43 $\pm$ 2.7	48 $\pm$ 7.5	44 $\pm$ 2.3	42 $\pm$ 2.7
	3,333	40 $\pm$ 3.5	--	60 $\pm$ 5.7	--	59 $\pm$ 3.1	--
	10,000	44 $\pm$ 2.1	(d) 35 $\pm$ 0.9	58 $\pm$ 8.3	(d) 53 $\pm$ 8.0	49 $\pm$ 4.1	39 $\pm$ 4.5
Trial summary		Weakly positive	Equivocal	Weakly positive	Weakly positive	Equivocal	Equivocal
Positive control (c)		1,716 $\pm$ 40.7	1,279 $\pm$ 22.7	925 $\pm$ 13.2	818 $\pm$ 3.9	1,264 $\pm$ 34.8	1,376 $\pm$ 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  $\mu\text{g}/\text{plate}$  dose is the solvent control.

(b) Revertants are presented as mean  $\pm$  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 TRIFLUOROTHYMININE 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)
<b>Trial 1</b>					
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
<b>Trial 2</b>					
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 ( $6 \times 10^5$ /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,  $3 \times 10^6$  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  $1 \times 10^6$  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  $1 \times 10^6$  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)
<b>-S9 (c)</b>								
<b>Trial 1--Summary: Positive</b>								
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
<b>Trial 2--Summary: Positive</b>								
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
<b>+S9 (d)</b>								
<b>Trial 1--Summary: Positive</b>								
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
<b>Trial 2--Summary: Positive</b>								
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)**

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(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
<b>Trial 1--Harvest time: 20.5 hours (d)</b>					<b>Harvest time: 20.5 hours (d)</b>				
Medium	100	1	0.01	1.0	Medium	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
<b>Trial 2--Harvest time: 20.5 hours (d)</b>									
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			Overall Total (b)
				Mating 1	Mating 2	Mating 3	
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<sub>1</sub> heterozygous females were crossed to their siblings and placed in individual vials. F<sub>1</sub> 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 <sub>1</sub> Tested				Total No. of Tests	Total No. of Trans-locations	Total Trans-locations (percent)
		1	2	3	4			
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<sub>1</sub> males were backcrossed to *y;bw;st p* females, and the F<sub>2</sub> 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<sub>1</sub> 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

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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

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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.