NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 340

TOXICOLOGY AND CARCINOGENESIS STUDIES OF IODINATED GLYCEROL

(ORGANIDIN®)

(CAS NO. 5634-39-9)

IN F344/N RATS AND B6C3F$_1$ MICE

(GAVAGE STUDIES)

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

NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS STUDIES OF IODINATED GLYCEROL

(ORGANIDIN®)

(CAS NO. 5634-39-9)

IN F344/N RATS AND B6C3F$_1$ MICE

(GAVAGE STUDIES)

John Edgar French, Ph.D., Study Scientist

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

March 1990

NTP TR 340

NIH Publication No. 90-2596

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

CONTENTS

PAGE

ABSTRACT 3
EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY 7
CONTRIBUTORS 8
PEER REVIEW PANEL 10
SUMMARY OF PEER REVIEW COMMENTS 11
I. INTRODUCTION 13
II. MATERIALS AND METHODS 17
III. RESULTS 37
RATS 38
MICE 47
GENETIC TOXICOLOGY 56
IV. DISCUSSION AND CONCLUSIONS 63
V. REFERENCES 69

APPENDIXES

APPENDIX A SUMMARY OF LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF IODINATED GLYCEROL 73

APPENDIX B SUMMARY OF LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF IODINATED GLYCEROL 95

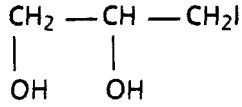
APPENDIX C SUMMARY OF LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF IODINATED GLYCEROL 115

APPENDIX D SUMMARY OF LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF IODINATED GLYCEROL 135

APPENDIX E SENTINEL ANIMAL PROGRAM 159

APPENDIX F INGREDIENTS, NUTRIENT COMPOSITION, AND CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION 163

APPENDIX G AUDIT SUMMARY 169



IODINATED GLYCEROL

3-Iodo-1,2-propanediol (major component as determined by the NTP, not the compounds indicated in the patent)

CAS No. 5634-39-9

$C_3H_7O_2I$ Molecular weight 202.0

Synonyms or Trade Names: Organidin®; iodopropylidene glycerol

ABSTRACT

Toxicology and carcinogenesis studies of iodinated glycerol (Organidin®, a complex mixture prepared by the reaction of iodine with glycerol and found to contain 33% 3-iodo-1,2-propanediol as the major component) were conducted because of human exposure to iodinated glycerol as an expectorant and its possible relationship to the formation of alkyl iodides, e.g., methyl iodide, a suspected animal carcinogen. These studies were conducted by giving iodinated glycerol in water by gavage (5 days per week) to groups of F344/N rats and B6C3F$_1$ mice for 16 days, 13 weeks, or 2 years. Genetic toxicology studies were conducted with iodinated glycerol in *Salmonella typhimurium*, mouse L5178Y lymphoma cells, Chinese hamster ovary (CHO) cells, and B6C3F$_1$ mice (in vivo bone marrow micronucleus test). Also, 3-iodo-1,2-propanediol was tested in *S. typhimurium* and B6C3F$_1$ mice (in vivo micronucleus assay).

Sixteen-Day and Thirteen-Week Studies: Sixteen-day studies were conducted by giving iodinated glycerol at doses up to 1,000 mg/kg to rats and up to 500 mg/kg to mice. All female rats and 4/5 male rats in the highest dose group died before the end of the studies; there were no dose-related effects on body weights of male or female rats or male mice at the end of the studies. The forestomach of 2/5 female mice that received 500 mg/kg was thickened and granular.

Thirteen-week studies were conducted by administering iodinated glycerol at doses up to 500 mg/kg to rats and mice. During these studies, 3/10 female rats and 1/10 female mice that received 500 mg/kg died. Final mean body weights of rats and mice that received 500 mg/kg were 4% lower than those of vehicle controls for males and 6%-7% lower for females.

Kidney tubular cell lesions, including cortical necrosis, regeneration, and calcification, were observed at increased incidences in the highest dose group of female rats. Lymphoid hyperplasia of the stomach was observed in dosed male and female rats. Kidney tubular cell regeneration was also observed in dosed female mice. Inflammation or abscesses of mild-to-moderate severity and hyperplasia, acanthosis, and/or hyperkeratosis of mild-to-moderate severity were observed in the forestomach of the highest dosed group of female mice.

Body Weight and Survival in the Two-Year Studies: Two-year studies were conducted by administering 0, 125, or 250 mg/kg iodinated glycerol in deionized water by gavage, 5 days per week for 103 weeks, to groups of 50 male F344/N rats and 50 male B6C3F$_1$ mice. Groups of 50 female F344/N rats and 50 female B6C3F$_1$ mice were administered iodinated glycerol on the same schedule at lower doses of 0, 62, or 125 mg/kg because of the increased severity of kidney and stomach lesions in the 13-week studies. Mean body weights of high dose male rats were 5%-10% lower than those of vehicle controls

from week 43 to week 68 and 10%-13% lower from week 72 to the end of the studies. Mean body weights of low dose male rats and high dose female rats were 4%-9% lower than those of vehicle controls from week 88 to the end of the studies. The survival of the high dose group of male rats was considerably lower than that of the vehicle controls after week 86. No other significant differences in survival were observed between any groups of rats of either sex (male: vehicle control, 28/50; low dose, 20/50; high dose, 2/50; female: 31/50; 30/50; 27/50). Mean body weights of dosed and vehicle control male mice were similar. Mean body weights of high dose female mice were 6%-8% lower than those of vehicle controls from week 40 to week 64 and were 9%-13% lower thereafter. No significant differences in survival were observed between any groups of mice of either sex (male: 36/50; 40/50; 32/50; female: 40/50; 33/50; 38/50).

Nonneoplastic and Neoplastic Effects in the Two-Year Studies: The incidences of mononuclear cell leukemia were increased in dosed male rats (vehicle control, 14/50; low dose, 29/50; high dose, 24/50).

Follicular cell carcinomas of the thyroid gland in male rats occurred at an increased incidence in low dose male rats (0/49; 5/49; 1/49). Reduced survival of high dose male rats may have been responsible for the decreased tumor incidence in this group relative to that in the low dose group. Follicular cell carcinomas were observed in one low dose and one high dose female rat. Follicular cell carcinomas of the thyroid gland have been observed in 3/293 water gavage vehicle control male F344/N rats and in 10/1,904 untreated control male F344/N rats.

Adenomas of the nasal cavity were observed in two high dose male rats. Adenomas of the nasal cavity have not been observed in 300 water gavage vehicle control male F344/N rats or in 1,936 untreated control male F344/N rats.

Squamous metaplasia and focal atrophy of the salivary glands were observed at increased incidences in dosed rats (squamous metaplasia--male: 0/48; 47/50; 48/49; female: 1/49; 48/50; 49/50; focal atrophy--male: 1/48; 10/50; 30/49; female: 0/49; 4/50; 11/50).

In dosed female mice, adenomas of the anterior pituitary gland were increased (10/47; 15/45; 24/46). The incidences of adenomas of the harderian gland in dosed female mice were increased (6/50; 8/40; 13/50). A carcinoma of the harderian gland was observed in another high dose female mouse.

Dilatation of the thyroid gland follicle and follicular cell hyperplasia were observed at increased incidences in dosed mice (dilatation--male: 0/48; 28/50; 32/50; female: 4/48; 11/48; 10/48; hyperplasia--male: 3/48; 46/50; 34/50; female: 2/48; 25/48; 35/48). The incidences of follicular cell adenomas were 3/48, 6/50, and 0/50 for males and 2/48, 3/48, and 4/48 for females.

Hyperkeratosis and acanthosis of the forestomach were observed at increased incidences in high dose male mice (hyperkeratosis: 0/49; 0/49; 5/50; acanthosis: 0/49; 1/49; 5/50). Squamous cell papillomas were observed in female mice (1/49; 2/50; 5/49). The historical incidence of forestomach squamous cell neoplasms is 4/339 (1.2%) in water gavage vehicle control female $B6C3F_1$ mice and is 18/1,994 (0.9%) in untreated control female $B6C3F_1$ mice. Squamous cell neoplasms were not observed in male mice.

Genetic Toxicology: Treatment of the base-substitution mutant *S. typhimurium* strains TA100 and TA1535 with iodinated glycerol in a preincubation protocol with and without S9 resulted in a dose-related increase in the number of revertant colonies; no increase in revertants was observed with the frame-shift mutant strains TA98 or TA1537. 3-Iodo-1,2-propanediol was also mutagenic in TA100 with or without S9; it was not mutagenic in TA98. Iodinated glycerol increased the number of trifluorothymidine-resistant cells in the mouse lymphoma L5178Y/$TK^{+/-}$ assay in the absence of exogenous metabolic activation; it was not tested with activation. Iodinated glycerol induced sister chromatid exchanges (SCEs) and chromosomal aberrations in CHO cells without S9; with S9, the

frequency of SCEs was increased more than without S9 but no chromosomal aberrations were induced. No increase in micronucleated polychromatic erythrocytes was observed in the bone marrow of $B6C3F_1$ mice after injection with either iodinated glycerol or 3-iodo-1,2-propanediol.

Conclusions: Under the conditions of these 2-year gavage studies, there was *some evidence of carcinogenic activity** for male F344/N rats administered iodinated glycerol, as indicated by increased incidences of mononuclear cell leukemia and follicular cell carcinomas of the thyroid gland. Adenomas of the nasal cavity in two high dose male rats may have been related to the administration of iodinated glycerol. There was *no evidence of carcinogenic activity* for female F344/N rats administered 62 or 125 mg/kg iodinated glycerol by gavage for 103 weeks. There was *no evidence of carcinogenic activity* for male $B6C3F_1$ mice administered 125 or 250 mg/kg iodinated glycerol by gavage for 103 weeks. There was *some evidence of carcinogenic activity* for female $B6C3F_1$ mice administered iodinated glycerol, as indicated by increased incidences of adenomas of the anterior pituitary gland and neoplasms of the harderian gland. Squamous cell papillomas of the forestomach may have been related to the administration of iodinated glycerol.

Significant nonneoplastic lesions considered related to exposure of iodinated glycerol were squamous metaplasia and focal atrophy of the salivary gland in male and female rats. Dilatation of the thyroid gland follicle and follicular cell hyperplasia were observed in male and female mice.

*Explanation of Levels of Evidence of Carcinogenic Activity is on page 7.
A summary of the Peer Review comments and the public discussion on this Technical Report appears on pages 11-12.

SUMMARY OF THE TWO-YEAR GAVAGE AND GENETIC TOXICOLOGY STUDIES OF IODINATED GLYCEROL

Male F344/N Rats	Female F344/N Rats	Male B6C3F$_1$ Mice	Female B6C3F$_1$ Mice
Doses			
0, 125, or 250 mg/kg iodinated glycerol in water, 5 d/wk	0, 62, or 125 mg/kg iodinated glycerol in water, 5 d/wk	0, 125, or 250 mg/kg iodinated glycerol in water, 5 d/wk	0, 62, or 125 mg/kg iodinated glycerol in water, 5 d/wk
Body weights in the 2-year study			
Dosed lower than vehicle controls	High dose lower than vehicle controls	Dosed and vehicle controls similar	High dose lower than vehicle controls
Survival rates in the 2-year study			
28/50; 20/50; 2/50	31/50; 30/50; 27/50	36/50; 40/50; 32/50	40/50; 33/50; 38/50
Nonneoplastic lesions			
Squamous metaplasia and focal atrophy of the salivary glands	Squamous metaplasia and focal atrophy of the salivary glands	Hyperkeratosis and acanthosis of the forestomach; dilatation of the thyroid gland follicle and follicular cell hyperplasia	Dilatation of the thyroid gland follicle and follicular cell hyperplasia
Neoplasms			
Mononuclear cell leukemia (14/50; 29/50; 24/50); follicular cell carcinomas of the thyroid gland (0/49; 5/49; 1/49)	None	None	Adenomas of the anterior pituitary gland (10/47; 15/45; 24/46); adenomas or carcinomas (combined) of the harderian gland (6/50; 8/40; 14/50)
Adenomas of the nasal cavity (0/48; 0/47; 2/49)			Squamous cell papillomas of the forestomach (1/49; 2/50; 5/49)
Level of evidence of carcinogenic activity			
Some evidence	No evidence	No evidence	Some evidence
Genetic toxicology			

Salmonella	Mouse L5178Y/TK	CHO Cells in Vitro	
Gene Mutation	Tft Resistance	SCE	Aberration
Positive with and without S9	Positive without S9; no test with S9	Positive with and without S9	Positive without S9; negative with S9

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 Iodinated Glycerol is based on the 13-week studies that began in April 1980 and ended in July 1980 and on the 2-year studies that began in April 1981 and ended in May 1983 at EG&G Mason Research Institute (Worcester, Massachusetts).

National Toxicology Program
(Evaluated Experiment, Interpreted Results, and Reported Findings)

John Edgar French, Ph.D., Study Scientist

John Bucher, Ph.D.
Scot L. Eustis, D.V.M., Ph.D.
Joseph K. Haseman, Ph.D.
James Huff, Ph.D.

(Discipline Leaders and Principal Contributors)

Jack Bishop, Ph.D.
Douglas W. Bristol, Ph.D.
R. Chhabra, Ph.D.
R. Griesemer, D.V.M., Ph.D.
C.W. Jameson, Ph.D.
E.E. McConnell, D.V.M.
G.N. Rao, D.V.M., Ph.D.
B.A. Schwetz, D.V.M., Ph.D.
Douglas Walters, Ph.D.

NTP Pathology Working Group
(Evaluated Slides and Prepared Pathology Report for Rats on 10/28/86)

Steven Stefanski, D.V.M. (Chair) (NTP)
J.C. Bhandari, D.V.M., Ph.D. (Dynamac Corp.)
Michael Elwell, D.V.M., Ph.D. (NTP)
Scot L. Eustis, D.V.M., Ph.D. (NTP)
Micheal Jokinen, D.V.M. (Experimental Pathology Laboratories, Inc.)
Nabeel Mehdi, Ph.D. (Toxicity Research Laboratories)
Linda Uraih, D.V.M. (NTP)

(Evaluated Slides and Prepared Pathology Report for Rats on 5/5/88)

Micheal Jokinen, D.V.M. (Chair) (NTP)
William Butler, M.B.B.S. (British Industrial Biological Research Association/Carter Wallace)
Michael Elwell, D.V.M., Ph.D. (NTP)
Scot L. Eustis, D.V.M., Ph.D. (NTP)
Jerry Hardisty, D.V.M. (Experimental Pathology Laboratories, Inc.)
Robert Squire, D.V.M., Ph.D. (Johns Hopkins University Hospital)
Jerry Ward, D.V.M., Ph.D. (National Cancer Institute)

(Evaluated Slides and Prepared Pathology Report for Mice on 9/30/86)

Frank Voelker, D.V.M. (Chair) (Pathology Associates, Inc.)
Roger Alison, M.R.C.V.S. (NTP)
Gary Boorman, D.V.M., Ph.D. (NTP)
Charles Capen, D.V.M., Ph.D. (Ohio State University)
Michael Elwell, D.V.M., Ph.D. (NTP)
Jerry Hardisty, D.V.M. (Experimental Pathology Laboratories, Inc.)
Agnes Russfield, M.D. (EG&G Mason Research Institute)

(Evaluated Slides and Prepared Pathology Report for Mice on 7/12/88)

Micheal Jokinen, D.V.M. (Chair) (NTP)
William Butler, M.B.B.S. (British Industrial Biological Research Association/Carter Wallace)
William Carlton, D.V.M., Ph.D. (Purdue University)
Michael Elwell, D.V.M., Ph.D. (NTP)
Scot L. Eustis, D.V.M., Ph.D. (NTP)
Robert Garman, D.V.M. (Carnegie-Mellon Institute of Research)
Jerry Hardisty, D.V.M. (Experimental Pathology Laboratories, Inc.)

CONTRIBUTORS (Continued)

Principal Contributors at EG&G Mason Research Institute (Conducted Studies and Evaluated Tissues)

H. Lilja, Ph.D.
S. Wyand, D.V.M.
M. Hagopian, Ph.D.
A. Russfield, M.D.

Principal Contributors at Experimental Pathology Laboratories, Inc. (Provided Pathology Quality Assurance)

J. Gauchat
J. Hardisty, D.V.M.

Principal Contributors at Carltech Associates, Inc. (Contractor for Technical Report Preparation)

William D. Theriault, Ph.D.
Abigail C. Jacobs, Ph.D.
John Warner, M.S.
Naomi Levy, B.A.

PEER REVIEW PANEL

The members of the Peer Review Panel who evaluated the draft Technical Report on iodinated glycerol on October 3, 1988, 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.

National Toxicology Program Board of Scientific Counselors Technical Reports Review Subcommittee

Robert A. Scala, Ph.D.* (Chair)
Senior Scientific Advisor, Medicine and Environmental Health Department
Research and Environmental Health Division, Exxon Corporation
East Millstone, New Jersey

Michael A. Gallo, Ph.D. (Principal Reviewer)
Associate Professor, Director of Toxicology
Department of Environmental and Community Medicine, UMDNJ - Rutgers Medical School
Piscataway, New Jersey

Frederica Perera, Dr. P.H.
Division of Environmental Sciences
School of Public Health
Columbia University
New York, New York

Ad Hoc Subcommittee Panel of Experts

John Ashby, Ph.D.
Imperial Chemical Industries, PLC
Central Toxicology Laboratory
Alderley Park, England

Robert H. Garman, D.V.M. (Principal Reviewer)
Carnegie-Mellon Institute of Research
Bushy Run Laboratories
Export, Pennsylvania

Lois Swirsky Gold, Ph.D. (Principal Reviewer)
University of California
Lawrence Berkeley Laboratory
Berkeley, California

Curtis D. Klaassen, Ph.D.
Professor, Department of Pharmacology and Toxicology, University of Kansas Medical Center, Kansas City, Kansas

William Lijinsky, Ph.D.*
Director, Chemical Carcinogenesis
Frederick Cancer Research Facility
Frederick, Maryland

Barbara McKnight, Ph.D.
Assistant Professor, Department of Biostatistics, University of Washington
Seattle, Washington

Franklin E. Mirer, Ph.D.
Director, Health and Safety Department
International Union, United Auto Workers, Detroit, Michigan

Paul M. Newberne, D.V.M., Ph.D.
Professor, Mallory Institute of Pathology
Boston, Massachusetts

James A. Popp, D.V.M., Ph.D.
Head, Department of Experimental Pathology and Toxicology
Chemical Industry Institute of Toxicology
Research Triangle Park, North Carolina

*Unable to attend

SUMMARY OF PEER REVIEW COMMENTS ON THE TOXICOLOGY AND CARCINOGENESIS STUDIES OF IODINATED GLYCEROL

On October 3, 1988, the draft Technical Report on the toxicology and carcinogenesis studies of iodinated glycerol 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, North Carolina.

Dr. J.E. French, NIEHS, began the discussion by reviewing the experimental design, results, and proposed conclusions (some evidence of carcinogenic activity for male rats; no evidence of carcinogenic activity for female rats; no evidence of carcinogenic activity for male mice; some evidence of carcinogenic activity for female mice). Significant nonneoplastic lesions considered related to exposure to iodinated glycerol were squamous metaplasia and focal atrophy of the salivary glands in male and female rats. Dilatation of the thyroid gland follicle and follicular cell hyperplasia were observed in male and female mice.

Dr. Gallo, a principal reviewer, agreed with the conclusions for female rats and male mice. He thought that the conclusion for male rats should be reduced to equivocal evidence of carcinogenic activity because the occurrence of mononuclear cell leukemia is variable and may have been affected by faulty environmental controls at the laboratory. For the thyroid gland, he stated that without knowledge of the functional status of the thyroid gland, association of follicular cell tumors with chemical exposure cannot be fully assessed. Dr. French responded that, because of the variability, the concurrent controls were more appropriate for comparison of the leukemia incidences. With regard to the thyroid gland, all of the tumors were carcinomas, an uncommon event. Dr. Gallo said that the conclusion for female mice should be reduced to equivocal evidence of carcinogenic activity because association of pituitary gland tumors with chemical exposure cannot be assessed due to lack of knowledge of the thyroid gland's functional status. Dr. Gallo said that the discussion should include more description of the role of free iodide on thyroid gland function and on how it may affect the thyroid gland in these studies. He suggested that short-term studies might be appropriate to evaluate the effect of iodinated glycerol on thyroid gland function. Dr. French said that additional 13-week studies were already in progress, including thyroid gland function tests.

Dr. Gold, the second principal reviewer, agreed with the conclusions. She noted that the target sites in female mice, the pituitary and harderian glands, have only infrequently been considered as target sites in NTP studies. She commented that it might be desirable to state the category of evidence separately for each target site instead of the current practice of adding a sentence without the evaluative category (in this case, adenomas of the nasal cavity in male rats).

Dr. Garman, the third principal reviewer, agreed with the conclusions. He agreed with Dr. Gallo's concern about the need for more information on the level of thyroid gland activity and for a more detailed description of thyroid gland morphology, including representative photomicrographs of thyroid glands from vehicle control and high dose animals. Dr. S. Eustis, NIEHS, commented that the lesions in the thyroid gland were not typical of a goitrogenic effect. He said that a more detailed description would be provided (pages 44 and 66).

Dr. J. Haseman, NIEHS, observed that the low dose group should be the focus for evaluation in male rats because of the high mortality occurring late in the study in the high dose animals. Dr. Perera cautioned that judgments concerning the levels of evidence should be based on actual results and not

on proposed mechanisms. Dr. Gallo agreed but said that consideration of mechanism was important to an understanding of how a chemical alters tissue physiology.

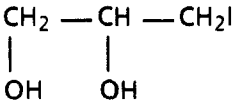
Dr. William H. Butler, British Industrial Biological Research Association, representing Carter-Wallace, Inc., discussed certain aspects of the pathologic evaluation, noting that he had reviewed the microslides at the NTP Archives and had participated in two NTP Pathology Working Groups. He began by describing what he considered to be deficiencies in the conduct of the studies. He noted that the incidences of leukemia in male rats were within the historical vehicle control range with no shortening of latency, whereas incidences of thyroid gland tumors were increased only in the low dose group and there was no evidence of goitrogenic effects; thus, the conclusion should be no evidence of carcinogenic activity. In female mice, pituitary gland tumors are common and highly variable and there was no decrease in latency, whereas the increase in harderian gland tumors was marginal; thus, the conclusion should be, at best, equivocal evidence of carcinogenic activity.

Dr. Gallo moved that the conclusion for male rats be accepted as written, some evidence of carcinogenic activity. Dr. Garman seconded the motion. Dr. Gallo noted that he based his motion primarily on the follicular cell carcinomas in the thyroid gland. The motion was approved by six affirmative votes to one negative vote (Dr. Gold). Dr. Gallo moved that the conclusions for female rats and male mice be accepted as written, no evidence of carcinogenic activity. Dr. Gold seconded the motion, which was approved unanimously. Dr. Gallo moved that the conclusion for female mice be accepted as written, some evidence of carcinogenic activity, but with squamous cell papillomas of the forestomach considered to be related rather than "may have been related." Thus, the tumors supporting the level of evidence would be in order of importance: adenomas of the anterior pituitary gland, neoplasms of the harderian gland, and papillomas of the forestomach. Dr. Mirer seconded the motion. In discussion, Dr. Gold disagreed and thought that each organ should be evaluated separately and noted that the increased incidences of squamous cell papillomas of the forestomach were not statistically significant, so the evaluation should not change. The motion received six negative votes and one affirmative vote (Dr. Gallo) and was not accepted. Dr. Gallo then moved to accept the conclusion as written, some evidence of carcinogenic activity. Dr. Garman seconded the motion, which was approved unanimously.

I. INTRODUCTION

Use, Production, and Exposure
Absorption, Metabolism, and Excretion
Reproductive and Developmental Toxicity
Toxicity and Carcinogenicity
Genetic Toxicology
Study Rationale

I. INTRODUCTION



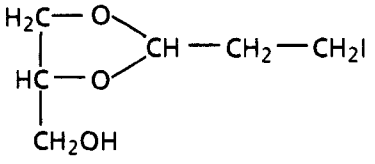
IODINATED GLYCEROL

3-Iodo-1,2-propanediol (major component as determined by the NTP, not the compounds indicated in the patent)

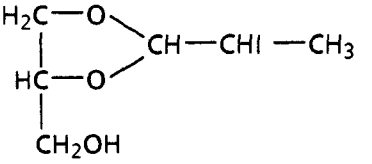
CAS No. 5634-39-9

$C_3H_7O_2I$ Molecular weight 202.0

Synonyms or Trade Names: Organidin®; iodopropylidene glycerol



Structure A



Structure B

STRUCTURES FOR IODINATED GLYCEROL AS GIVEN IN THE PATENT LITERATURE (PATENT NO. 2,872,378) (Merck, 1976). Isomeric mixture of 2-(1-iodoethyl)-1,3-dioxolane-4-methanol (67%-75%) and 2-(2-iodoethyl)-1,3-dioxolane-4-methanol (33%-25%)

Use, Production, and Exposure

Iodinated glycerol is a pale yellow liquid with a pungent, bitter aftertaste (Merck, 1983). Iodinated glycerol (Organidin®) is used in humans as a mucolytic expectorant to clear bronchiolar secretions (Seltzer, 1961). This compound is manufactured by reacting iodine and glycerol and is reported in the patent literature (Manchey et al., Denver Chem. Manuf., U.S. Patent No. 2,872,378, 1959) to be an isomeric mixture of the iodinated 1,3-dioxolane derivatives shown in the figure above.

Production of iodinated glycerol is probably greater than 1,000 lb (SRI, 1978). Exposure occurs through its use as a mucolytic expectorant in respiratory tract therapy in humans. A maximum exposure of 2.4 mg/kg per day is expected for individuals given the recommended dose (two 30-mg tablets each containing 15 mg of iodinated glycerol, administered four times per day for a total of 120 mg) (Seltzer, 1961; AMA, 1977). No information was available on exposure of the general population to iodinated glycerol.

Absorption, Metabolism, and Excretion

Hoffnagle and Osol (1958) administered iodinated glycerol (containing 100 µCi of ^{131}I, 2 mg iodinated glycerol per animal) orally or intravenously to male Wistar rats (250-300 g). Within 2 hours, 77% of the radiolabel was absorbed intact, with little or no decomposition of iodinated glycerol in the gastrointestinal tract. Within 24 hours after oral administration, approximately 30%-60% of the ^{131}I was found in the thyroid gland (approximately 3%-6% in the form of thyroxin); the remainder was excreted in the urine and feces. The blood, small intestine, liver,

kidney, and stomach were the principal compartments of distribution within 30 minutes of intravenous administration.

Barrigon et al. (1986) administered [^{125}I]iodinated glycerol (284 mg) orally to volunteers (age, sex, and weight unknown) who exhibited mean plasma concentration curves compatible with a two-compartment open model. Iodinated glycerol was excreted primarily in urine (94.8% in 48 hours) and followed a biphasic elimination curve. Initially, 41% of the dose was rapidly excreted ($t_{\frac{1}{2}}$ = 0.72 hours); the remaining portion was eliminated at a slower rate ($t_{\frac{1}{2}}$ = 4.85 hours).

3-Iodo-1,2-propanediol, a principal component of iodinated glycerol, was metabolized after intraperitoneal administration of 100 mg/kg to male Wistar rats (250-300 g) or 200 mg/kg to male ICI Swiss mice (30-50 g); two metabolites were found in the urine: *S*-(2,3-dihydroxypropyl)cysteine and *N*-acetyl-*S*-(2,3-dihydroxypropyl) cysteine (Jones, 1975). Metabolism of 3-iodo-1,2-propanediol, according to Jones (1975), is proposed to occur through the release of iodide and the formation of the epoxide intermediate, glycidol (2,3-epoxypropanol), and conjugation with glutathione. Release of radiolabeled carbon dioxide (approximately 22% in rats and 15% in mice) through glycerol formation, presumably from formation of glycidol, and subsequent metabolism support this hypothesis.

Reproductive and Developmental Toxicity

Iodide readily crosses the placenta and may cause fetal goiter (McLaren and Alexander, 1979). Holbreich (1982) indicated that administration of iodinated glycerol to pregnant women carries a high risk for induction of fetal goiter.

Toxicity and Carcinogenicity

No information was found in the scientific literature on the acute, cellular, subcellular, or systemic toxicity of 3-iodo-1,2-propanediol or iodinated glycerol, nor was information found on the long-term toxicity and carcinogenicity or on epidemiologic studies of 3-iodo-1,2-propanediol or iodinated glycerol.

Genetic Toxicology

In NTP Salmonella studies, treatment of the base-substitution mutant strains TA100 and TA1535 with iodinated glycerol in a preincubation protocol with and without Aroclor 1254-induced male Sprague Dawley rat or Syrian hamster liver S9 resulted in a strong dose-related increase in the number of revertant colonies recovered; no increase in revertants was observed in the frame-shift mutant strains TA98 and TA1537, with doses up to 10 mg/plate (Zeiger et al., 1987; see Table 23). There is no additional information in the literature on iodinated glycerol, but there are data from a dominant lethal study conducted with 3-iodo-1,2-propanediol, the major component of iodinated glycerol. Epstein et al. (1972) reported that 3-iodo-1,2-propanediol, injected intraperitoneally into 10 male mice at 80 mg/kg (inferred from the authors' discussion to be an LD_{25} dose), did not induce dominant lethal mutations, as measured by early fetal deaths and preimplantation losses in females mated to these dosed males.

3-Iodo-1,2-propanediol is proposed to react in vivo through the epoxide intermediate, glycidol (Jones, 1975). Mutagenicity studies conducted by the NTP on glycidol show it to be positive for induction of gene mutations in Salmonella (Canter et al., 1986), positive for induction of trifluorothymidine resistance in mouse L5178Y/TK cells (NTP, 1990), and positive for induction of sister chromatid exchanges and chromosomal aberrations in cultured Chinese hamster ovary cells (NTP, 1990). In addition, both sex-linked recessive lethal mutations and reciprocal translocations were induced in the germ cells of male *Drosophila melanogaster* flies fed a water solution containing 1,230 ppm glycidol. Results from an in vivo bone marrow micronucleus test with glycidol were weakly positive; dose-related increases in micronuclei were observed at the two highest dose levels (75 and 150 mg/kg) (NTP, 1990).

I. INTRODUCTION

Study Rationale

Iodinated glycerol was nominated and selected for study because of human exposure to iodinated glycerol as an expectorant and because of the compound's structural relationship to methyl iodide, a suspected animal carcinogen (IARC, 1986). Administration of iodinated glycerol by gavage was chosen to obtain oral exposure with a bolus dose regimen, which is the primary route for administration of the drug in humans.

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF IODINATED GLYCEROL

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES

FIRST SIXTEEN-DAY STUDIES

SECOND SIXTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

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

GENETIC TOXICOLOGY

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF IODINATED GLYCEROL

Iodinated glycerol (Azeo 35%) was obtained in one lot (lot no. 276-YY-30) from Wallace Laboratories (Cranbury, New Jersey) and was used for all studies. Purity and identity determinations were conducted at Midwest Research Institute (MRI) (Kansas City, Missouri). MRI reports on analyses performed in support of the iodinated glycerol studies are on file at the National Institute of Environmental Health Sciences.

Elemental analysis values for carbon and hydrogen were high, whereas that for oxygen agreed with theoretical values. The value for iodine was low when compared with values for structures in the patent literature. The iodine content was found to be 46.1% (w/w), which included 0.4% ionic iodine and 35.3% organically bound iodine, as defined by the manufacturer. The infrared (Figure 1), ultraviolet/visible, and nuclear magnetic resonance (Figures 2 to 4) spectra were not consistent with those expected for either of the structures given in the patent literature (Merck, 1976) for iodinated glycerol (Figure 5). The structure of the major component as determined by the NTP is given in Figure 6. The infrared spectrum differed only slightly from that of glycerol. The ultraviolet spectrum showed a single peak (λ_{max}, 254 nm; ε, 319.1 $\pm$ 15.6), which was consistent with the spectrum of alkyl iodides. The nuclear magnetic resonance spectra, taken in both methanol-d_4 and acetone-d_6, did not have peaks attributable to the methine proton on the carbon in the 2 position or significant peaks for the methyl group in structure B or for the methylene group in the 2 position of structure A.

A fluffy orange precipitate was formed when 2,4-dinitrophenylhydrazine in acidified ethanol was added to iodinated glycerol that had been refluxed for 1 hour with 2% hydrochloric acid, suggesting the presence of a ketone or aldehyde in the hydrolyzed mixture. The results of this test and the lack of a methine absorbance in the nuclear magnetic resonance spectrum do not support the proposed structure reported in the patent literature. The study material contained a relatively large amount of material (estimated at 10%-20%) tentatively identified as glycerol (determined by thin-layer chromatography with 0.25 mm silica gel 60, F-254 plates and an *n*-butanol:acetone:water [1:8:1] solvent system).

A second lot of iodinated glycerol was obtained from the supplier to confirm that the lot used in the studies was representative of the commercially available material. Lot no. 34220, received on 8/27/79, was analyzed by nuclear magnetic resonance spectroscopy and found to be nearly identical to lot no. 276-YY-30 (received by MRI on 4/17/79).

Water content as determined by Karl Fischer analysis was 1%. A minor component, four trace components, and one slight trace impurity were detected by thin-layer chromatography on silica gel plates with an ethyl acetate:methanol (9:1) solvent system. Six impurities with areas equal to 0.23%, 0.67%, 2.36%, 1.58%, 2.87%, and 1.99% that of the major peak were detected on a high-performance liquid chromatograph equipped with a fixed wavelength detector (254 nm) and a µPorasil column with a chloroform: tetrahydrofuran (60:40) solvent system. Because of the uncertainty of the mixture's composition, a purity estimate cannot be assigned.

Because of the inconsistencies observed in the analyses of the original study material, a third sample of iodinated glycerol (lot no. WM1454) was obtained from Carter-Wallace, Inc., for comparison analysis. Lot nos. 276-YY-30 and WM1454 were analyzed by carbon-13 nuclear magnetic resonance spectroscopy (carbon-13 NMR), gas chromatography/mass spectrometry (GC/MS) with electron impact (70 eV) ionization, gas chromatography/flame ionization detection (GC/FID), and high-performance liquid chromatography (HPLC). The carbon-13 NMR analysis was performed on acetone-d_6 solutions of the study material with a Varian VXR-300 Fourier transform spectrometer at ambient temperature. The chemical shifts were referenced to the 29.2-ppm acetone heptet. The GC/MS analysis was conducted with a 60-m DB-5 capillary column. The linear centroid data were handled by an Incos 2400 data system. The scan range was 35-450 amu. GC/FID quantitation of several components in the study material was performed with a 30-mm DB-5 megabore capillary column.

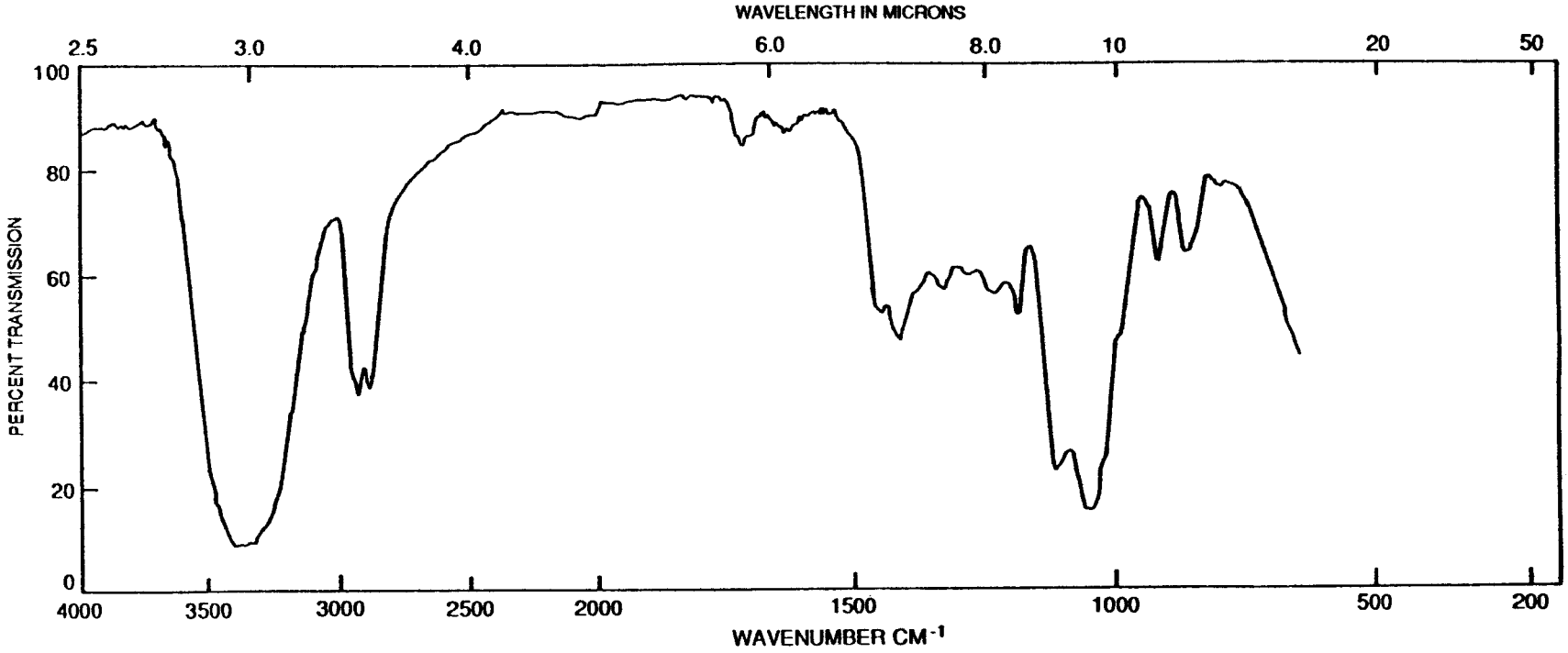


FIGURE 1. INFRARED ABSORPTION SPECTRUM OF IODINATED GLYCEROL (LOT NO. 276-YY-30)

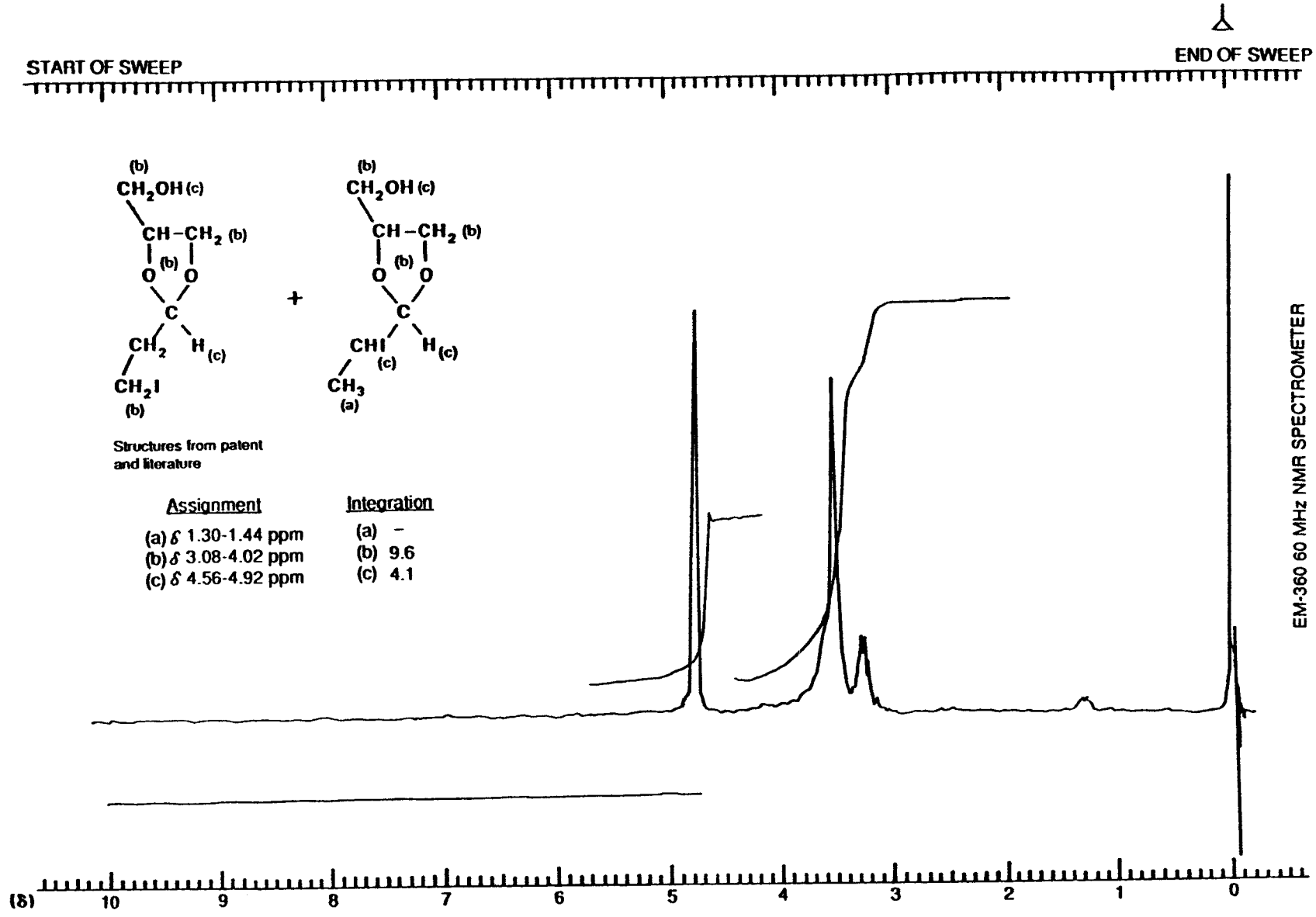


FIGURE 2. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF IODINATED GLYCEROL (LOT NO. 276-YY-30) IN METHANOL-d_4

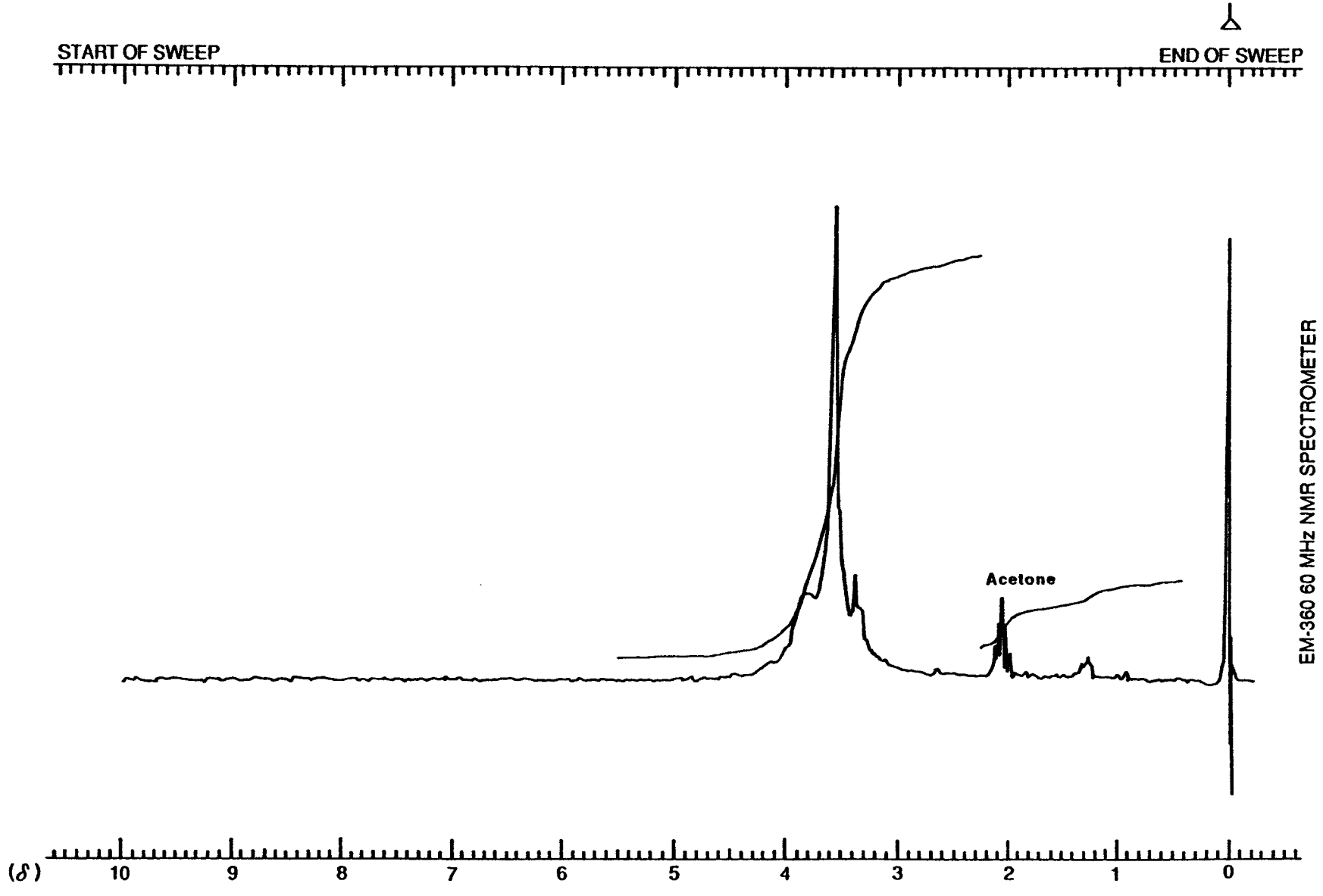


FIGURE 3. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF IODINATED GLYCEROL (LOT NO. 276-YY-30) IN ACETONE-d_6

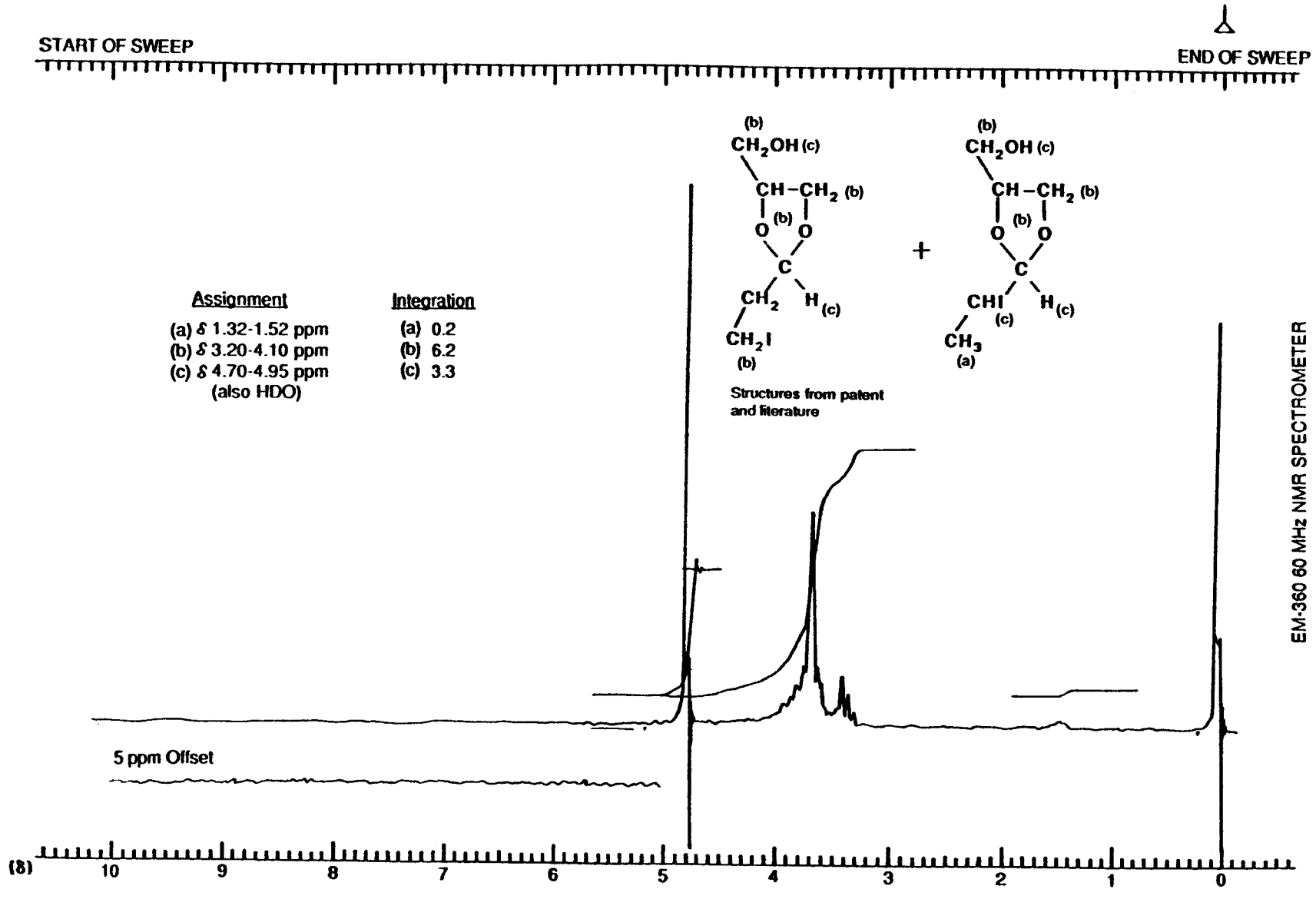
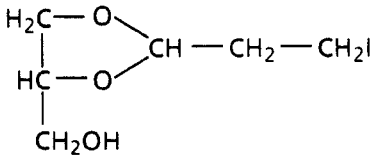
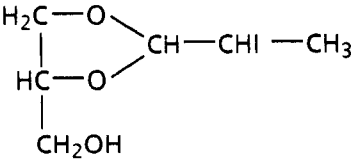


FIGURE 4. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF IODINATED GLYCEROL (LOT NO. 276-YY-30) IN D_2O



Structure A



Structure B

FIGURE 5. STRUCTURES FOR IODINATED GLYCEROL AS GIVEN IN THE PATENT LITERATURE (PATENT NO. 2,872,378)

(Merck, 1976)

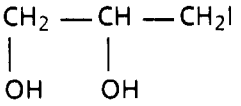


FIGURE 6. STRUCTURE OF THE MAJOR COMPONENT OF IODINATED GLYCEROL AS DETERMINED BY THE NTP

Quantitation of glycerol was performed by reverse-phase HPLC with a 5-μ Beckman Ultrasphere ODS C_{18} column. The mobile phase was 5% acetonitrile in water, and detection was by refractive index with a Shodex RI SE-51 detector.

The major component of both lots was identified as 3-iodo-1,2-propanediol (IPD). The identification was based on results from GC/MS and carbon-13 NMR with concurrent analyses of an IPD standard. The concentration was determined to be approximately 33% in lot no. 276-YY-30 and 34% in lot no. WM1454. Glycerol was also identified as a component in each lot based on results from GC/MS and carbon-13 NMR (Figure 7). The concentration of glycerol in lot no. 276-YY-30 was determined to be 17% by HPLC. Glycerol was not quantitated in lot no. WM1454; however, based on the results from GC/FID impurity analysis, the concentration was comparable with that of lot no. 276-YY-30.

Numerous impurities were evident in the GC/FID, HPLC, and GC/MS profiles as well as in the carbon-13 NMR spectrum. Although four of these components had a molecular weight of 258 g/mol, consistent with that described in the patent, it was concluded that these were isomers of (hydroxymethyl)-(iodomethyl)-*p*-dioxane instead of the iodopropylideneglycerol structures purported by the patent. The concentration of these four impurities was estimated at approximately 10% in lot no. 276-YY-30 and 6% in lot no. WM1454 from results of the GC/FID impurity profile.

The analytical data on the remaining components indicated that they were polymers of glycerol- and iodine-containing analogs. Specifically, isomers of diglyceryl ether, glyceryl iodoglyceryl ether, and trioxobicyclononane were identified from the GC/MS data. These components were estimated to account for approximately 40% of lot no. 276-YY-30.

The results from comparative analyses of lot nos. 276-YY-30 and WM1454 indicated that no significant differences existed in the composition of the two samples (Table 1).

Based on these results, it is concluded that the principal components of the iodinated glycerol study material and an iodinated glycerol reference material are IPD (~33%) and glycerol (~17%). The two iodopropylideneglycerol isomers described in the patent literature were not detected in these samples.

The iodinated glycerol study material was shown to be stable on storage for 2 weeks at 25° C. However, some deterioration was observed when samples were stored for 2 weeks at 60° C.

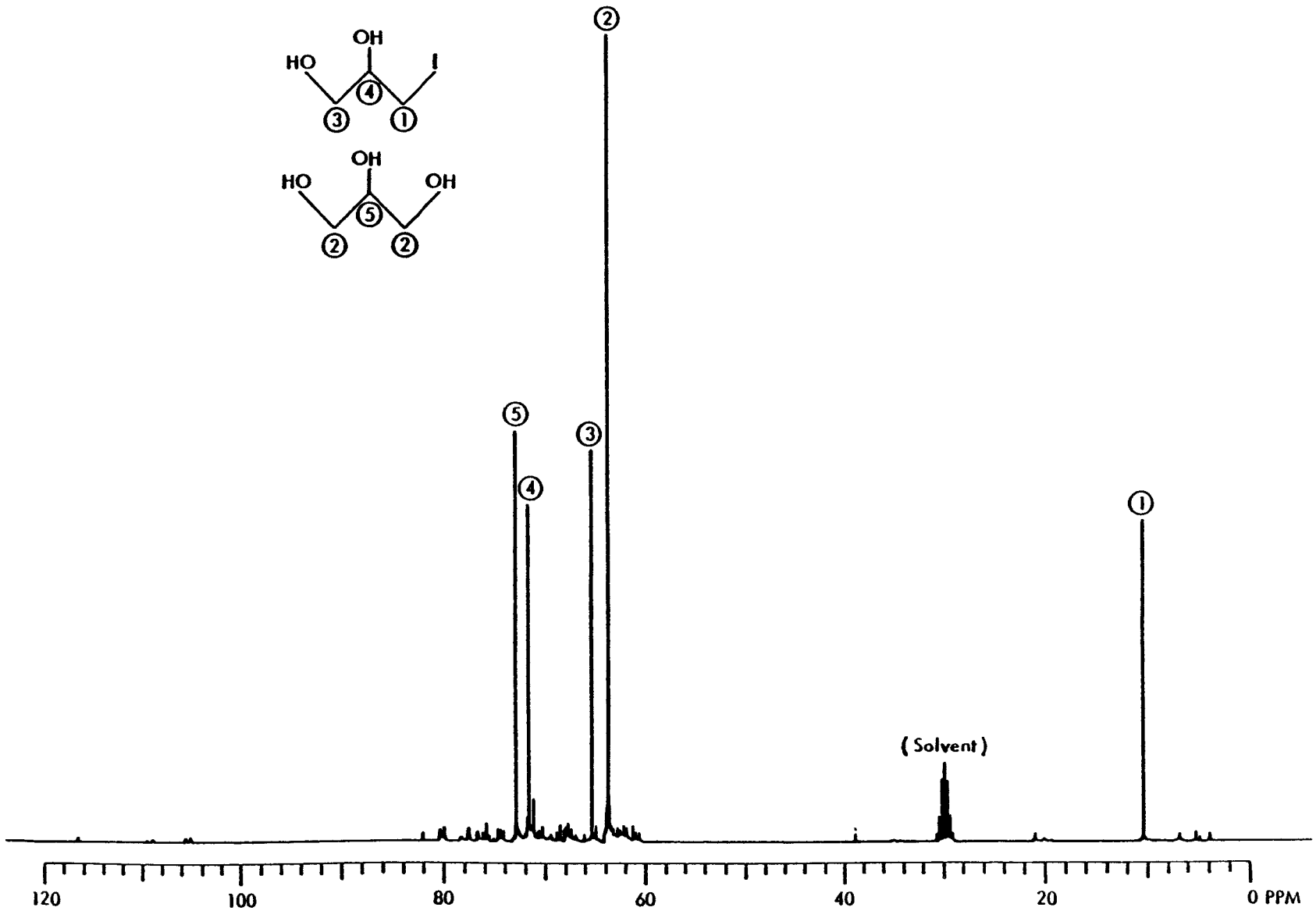


FIGURE 7. CARBON-13 NUCLEAR MAGNETIC RESONANCE SPECTRUM OF IODINATED GLYCEROL (LOT NO. 276-YY-30) IN ACETONE-d_6

TABLE 1. LOT COMPARISON RESULTS (a)

Component/Analysis	Lot No. 276-YY-30	Lot No. WM1454
IPD (GC/FID)	33%	34%
Glycerol (HPLC)	17%	(b) ~ 17%
HMIMD (GC/FID)	10%	6%
Water (Karl Fischer)	1%	2.4%

(a) IPD = 3-iodo-1,2-propanediol; GC/FID = gas chromatography/flame ionization detection; HPLC = high-performance liquid chromatography; HMIMD = (hydroxymethyl)-(iodomethyl)-*p*-dioxane
(b) Not quantitated by HPLC; amount estimated based on GC/FID impurity analysis.

The study material was stored at 0° C. Periodic characterization of the study material by high-performance liquid chromatography indicated no deterioration of major components over the course of the studies.

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES

Dose mixtures were prepared by adding iodinated glycerol to deionized water (Table 2). Iodinated glycerol in water at a concentration of 5% was shown to be stable for 7 days at room temperature. Dose mixtures were stored for no longer than 7 days.

Periodic analysis for iodinated glycerol in dose mixtures was performed to confirm that correct concentrations were administered to the animals. Results of the laboratory's periodic analyses indicated that samples were within 10% of the target concentration 98% (44/45) of the time (Table 3). Referee analysis was performed periodically by the analytical chemistry laboratory during the 2-year studies. Good agreement was found between the laboratories (Table 4).

TABLE 2. PREPARATION AND STORAGE OF DOSE MIXTURES IN THE GAVAGE STUDIES OF IODINATED GLYCEROL

First Sixteen-Day Studies	Second Sixteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
Preparation			
Formulations of iodinated glycerol and water prepared by hand shaking in a ground glass-stoppered graduated cylinder and then sealed in serum vials for administration	Same as first 16-d studies	Same as first 16-d studies	Same as first 16-d studies except solution stirred for 5 min after hand shaking
Maximum Storage Time			
1 wk	1 wk	2 wk	1 wk
Storage Conditions			
1° ± 4° C in the dark	0° ± 5° C	0° ± 5° C in the dark	Same as 13-wk studies

TABLE 3. RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR GAVAGE STUDIES OF IODINATED GLYCEROL

Date Mixed	Concentration of Iodinated Glycerol in Water for Target Concentration (mg/ml) (a)		
	12.4	25	50
04/21/81	12.9	24.8	50.0
05/12/81	(b) 16.7	25.4	50.5
05/14/81	(c) 12.9	--	--
06/23/81	13.0	26.1	49.9
09/01/81	12.7	25.7	51.0
10/13/81	13.1	25.7	50.6
12/15/81	11.4	24.6	49.6
02/02/82	12.2	24.8	49.9
03/23/82	12.6	24.8	50.0
06/22/82	12.5	25.5	50.6
07/13/82	13.1	25.4	49.5
09/21/82	12.9	24.5	49.8
11/09/82	12.3	25.2	50.2
01/25/83	12.5	24.2	46.5
04/12/83	13.0	24.7	49.3
04/26/83	12.6	24.4	49.2
Mean (mg/ml)	12.9	25.0	49.8
Standard deviation	1.14	0.54	1.04
Coefficient of variation (percent)	8.8	2.2	2.09
Range (mg/ml)	11.4-16.7	24.2-26.1	46.5-51.0
Number of samples	15	15	15

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

TABLE 4. RESULTS OF REFEREE ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR GAVAGE STUDIES OF IODINATED GLYCEROL

Date Mixed	Target Concentration (mg/ml)	Determined Concentration (mg/ml) Study Laboratory (a)	Referee Laboratory (b)
04/21/81	12.4	12.9	12.5
10/13/81	50.0	50.6	52.9
06/22/82	25.0	25.5	24.4
11/09/82	12.4	12.3	12.3
04/12/83	25.0	24.7	24.7

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

FIRST SIXTEEN-DAY STUDIES

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories and held for approximately 4 weeks before the studies began. Animals were 8 weeks old when placed on study. Groups of five rats of each sex were administered 0, 62, 125, 250, 500, or 1,000 mg/kg iodinated glycerol in deionized water by gavage, 5 days per week (12 doses over 16 days). Groups of five mice of each sex were administered 0, 31, 62, 125, 250, or 500 mg/kg on the same schedule. Rats and mice were observed twice per day and were weighed once per week. A necropsy was performed on all animals. Details of animal maintenance are presented in Table 5.

SECOND SIXTEEN-DAY STUDIES

Because of dehydration in all groups of mice, the 16-day studies in mice were repeated. Male and female B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories and held for 19 days before the studies began. Animals were 6-8 weeks old when placed on study. Groups of five mice of each sex were administered 0, 31, 62, 125, 250, or 500 mg/kg iodinated glycerol in deionized water by gavage, 5 days per week (12 doses over 16 days). Mice were observed twice per day and were weighed once per week. A necropsy was performed on all animals. Details of animal maintenance are presented in Table 5.

THIRTEEN-WEEK STUDIES

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

Three- to five-week-old male and female F344/N rats and 4- to 5-week-old male and female B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories, observed for 15 days, and assigned to cages such that average cage weights were approximately equal. Groups of 10 rats and 10 mice of each sex were administered 0, 31, 62, 125, 250, or 500 mg/kg iodinated glycerol in deionized water by gavage, 5 days per week for 13 weeks.

Animals were housed five per cage. Feed and water were available ad libitum. Further experimental details are summarized in Table 5. Animals were checked two times per day; moribund animals were 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 except those excessively autolyzed or cannibalized. Tissues and groups examined are listed in Table 5.

TABLE 5. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF IODINATED GLYCEROL

First Sixteen-Day Studies	Second Sixteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
EXPERIMENTAL DESIGN			
Size of Study Groups			
5 males and 5 females of each species	5 male and 5 female mice	10 males and 10 females of each species	50 males and 50 females of each species
Doses			
Rats--0, 62, 125, 250, 500, or 1,000 mg/kg iodinated glycerol in deionized water by gavage; mice--0, 31, 62, 125, 250, or 500 mg/kg; dose vol--5 ml/kg	0, 31, 62, 125, 250, or 500 mg/kg iodinated glycerol in deionized water by gavage; dose vol--5 ml/kg	0, 31, 62, 125, 250, or 500 mg/kg iodinated glycerol in deionized water by gavage; dose vol--5 ml/kg	Male--0, 125, or 250 mg/kg iodinated glycerol in deionized water by gavage; female--0, 62, or 125 mg/kg; dose vol--5 ml/kg
Date of First Dose			
10/29/79	2/4/80	4/25/80	Rats--5/18/81; mice--4/24/81
Date of Last Dose			
11/13/79	2/19/80	7/24/80	Rats--5/6/83; mice--4/15/83
Duration of Dosing			
5 d/wk (12 doses over 16 d)	5 d/wk (12 doses over 16 d)	5 d/wk for 13 wk	5 d/wk for 103 wk
Type and Frequency of Observation			
Observed 2 × d; weighed initially and 1 × wk thereafter	Observed 2 × d; weighed initially and 1 × wk thereafter	Observed 2 × d; weighed initially and 1 × wk thereafter	Observed 2 × d; weighed initially, 1 × wk for 12 wk, and then 1 × mo
Necropsy and Histologic Examinations			
Necropsy performed on all animals; histologic exams not performed	Same as first 16-d studies	Necropsy performed on all animals; the following tissues examined histologically for vehicle control and high dose groups: adrenal glands, brain, colon, esophagus, eyes (if grossly abnormal), gallbladder (mice), gross lesions, heart, kidneys, liver, lungs and bronchi, mammary gland, mandibular lymph nodes, pancreas, parathyroids, pituitary gland, prostate/testes or ovaries/uterus, regional lymph nodes, salivary glands, skin, small intestine, spinal cord (if neurologic signs present), spleen, sternebrae, stomach, thymus, thyroid gland, tissue masses, trachea, and urinary bladder; additional tissues examined for all rats and mice in the 62, 125, and 250 mg/kg groups: kidneys and stomach	Necropsy performed on all animals; histologic exams performed on the following tissues from vehicle control and high dose animals and from low dose male rats: adrenal glands, bone marrow, brain, colon, costochondral junction, duodenum, esophagus, gallbladder (mice), heart, ileum, jejunum, kidneys, larynx, liver, lungs and bronchi, mammary gland, mandibular and mesenteric lymph nodes, nasal cavity, pancreas, parathyroids, pituitary gland, prostate/testes/seminal vesicles or ovaries/uterus, regional lymph nodes (if abnormal), salivary glands, skin, spleen, stomach, thymus, thyroid gland, tissue masses, trachea, and urinary bladder; in addition, gross lesions and the following tissues from the low dose groups examined: female rats--adrenal glands, heart, liver, pituitary gland, salivary glands; mice--esophagus, forestomach (female), harderian gland, heart (female), liver (female), lung (female), pituitary gland, stomach, thyroid gland, and trachea

TABLE 5. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF IODINATED GLYCEROL (Continued)

First Sixteen-Day Studies	Second Sixteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
ANIMALS AND ANIMAL MAINTENANCE			
Strain and Species			
F344/N rats; $B6C3F_1$ mice	$B6C3F_1$ mice	F344/N rats; $B6C3F_1$ mice	F344/N rats; $B6C3F_1$ mice
Animal Source			
Charles River Breeding Laboratories (Portage, MI)	Charles River Breeding Laboratories (Portage, MI)	Rats--Charles River Breeding Laboratories (Kingston, NY); mice--Charles River Breeding Laboratories (Portage, MI)	Charles River Breeding Laboratories (Kingston, NY)
Study Laboratory			
EG&G Mason Research Institute	EG&G Mason Research Institute	EG&G Mason Research Institute	EG&G Mason Research Institute
Method of Animal Identification			
Ear punch	Ear punch	Ear punch	Ear punch
Time Held Before Study			
26 d	19 d	15 d	Rats--19 d; mice--16 d
Age When Placed on Study			
8 wk	6-8 wk	Rats--5-7 wk; mice--6-7 wk	Rats--7 wk; mice--8 wk
Age When Killed			
11 wk	8-10 wk	18-20 wk	Rats--111-112 wk; mice--112-114 wk
Necropsy Dates			
11/14/79-11/15/79	2/20/80-2/21/80	7/28/80-8/1/80	Rats--5/16/83-5/24/83; mice--4/25/83-5/3/83
Method of Animal Distribution			
Animals assigned to groups such that for each sex and species, all cage weights approximately equal	Same as first 16-d studies	Same as first 16-d studies	According to a table of random numbers
Feed			
Wayne Lab Blox® pellets (Allied Mills, Chicago, IL); available ad libitum	Same as first 16-d studies	NIH 07 Rat and Mouse Ration (Zeigler Bros., Gardners, PA); available ad libitum	Same as 13-wk studies
Bedding			
Aspen Bed (American Excelsior, Baltimore, MD)	Same as first 16-d studies	Same as first 16-d studies; Beta Chips (Agway, Inc., Syracuse, NY) used when Aspen Bed was unavailable	Same as first 16-d studies
Water			
Automatic watering system (Edstrom Industries, Waterford, WI); available ad libitum	Same as first 16-d studies	Same as first 16-d studies	Same as first 16-d studies
Cages			
Polycarbonate (Lab Products, Inc., Rochelle Park, NJ)	Same as first 16-d studies	Same as first 16-d studies	Same as first 16-d studies

TABLE 5. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF IODINATED GLYCEROL (Continued)

First Sixteen-Day Studies	Second Sixteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
ANIMALS AND ANIMAL MAINTENANCE (Continued)			
Cage Filters			
See Thru II (Lab Products, Inc., Rochelle Park, NJ)	Same as first 16-d studies	Reemay spun-bonded polyester filters (Snow Filtration, Cincinnati, OH)	Same as 13-wk studies
Animals per Cage			
5	5	5	5
Other Chemicals on Study in the Same Room			
None	None	None	None
Animal Room Environment			
Temp--20°-27° C; hum--29%-70%; fluorescent light 12 h/d; 10-12 room air changes/h	Temp--14°-28° C; hum--35%-50%; fluorescent light 12 h/d; 10-12 room air changes/h	Temp--17°-29° C; hum--43%-78%; fluorescent light 12 h/d; 12 room air changes/h	Temp--22.8° C (mean); range--18.3°-27.2° C; hum--50.3% (mean); fluorescent light 12 h/d; 15 room air changes/h

TWO-YEAR STUDIES

Study Design

Groups of 50 male rats and 50 male mice were administered 0, 125, or 250 mg/kg iodinated glycerol in deionized water by gavage, 5 days per week for 103 weeks. Groups of 50 female rats and 50 female mice were administered 0, 62, or 125 mg/kg on the same schedule.

Source and Specifications of Animals

The male and female F344/N rats and B6C3F$_1$ (C57BL/6N, female × C3H/HeN MTV$^-$, male) mice used in these studies were produced under strict barrier conditions at Charles River Breeding Laboratories. Breeding stock for the foundation colonies at the production facility originated at the National Institutes of Health Repository. Animals shipped for study were progeny of defined microflora-associated parents that were transferred from isolators to barrier-maintained rooms. Rats were shipped to the study laboratory at 4 weeks of age and mice, at 6 weeks. The rats were quarantined at the study laboratory for 19 days and the mice, for 16 days. Thereafter, a complete necropsy was performed on five animals of each sex and species to assess their health status. The rats were 52 days old when placed on study and the mice, 56 days old. The health of the animals was monitored during the course of the studies according to the protocols of the NTP Sentinel Animal Program (Appendix E).

A quality control skin grafting program has been in effect since early 1978 to monitor the genetic integrity of the inbred mice used to produce the hybrid B6C3F$_1$ study animal. In mid-1981, data were obtained that showed incompatibility between the NIH C3H reference colony and the C3H colony from a Program supplier. In August 1981, inbred parental lines of mice were further tested for genetic integrity via isozyme and protein electrophoresis profiles that demonstrate phenotype expressions of known genetic loci.

The C57BL/6N mice were homogeneous at all loci tested. Eighty-five percent of the C3H mice monitored were variant at one to three loci, indicating some heterogeneity in the C3H line from this supplier. Nevertheless, the genome of this line is more homogeneous than that of randomly bred stocks.

Male mice from the C3H colony and female mice from the C57BL/6N colony were used as parents for the hybrid B6C3F$_1$ mice used in these studies. The influence of the potential genetic nonuniformity in the hybrid mice on these results is not known, but results of the studies are not affected because concurrent controls were included in each study.

Animal Maintenance

Animals were housed five per cage. Feed and water were available ad libitum. Further details of animal maintenance are given in Table 5. Cages were not rotated during the studies.

Clinical Examinations and Pathology

All animals were observed two times per day, and clinical signs were recorded at least once per month. Body weights by cage were recorded once per week for the first 12 weeks of the study 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 including those found dead, except for tissues that were excessively autolyzed or missing. Thus, the number of animals from which particular organs or tissues were examined microscopically varies and is not necessarily equal to the number of animals that were placed on study.

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. Histopathologic examination of tissues was performed according to an "inverse pyramid" design (McConnell, 1983a,b). That is, complete histopathologic examinations (Table 5) were performed on all high dose and vehicle control animals and on low dose animals dying before the end of the study. In addition, histopathologic examinations were performed on all grossly visible lesions in all dose groups. Potential target organs for chemically related neoplastic and nonneoplastic effects were identified from the short-term studies or the literature and were determined by examination of the pathology data; these target organs/tissues in the lower dose group were examined histopathologically. If mortality in the highest dose group exceeded that in the vehicle control group by 15%, complete histopathologic examinations were performed on all animals in the second highest dose group in addition to those in the high dose group.

When the pathology evaluation was completed, the slides, paraffin blocks, and residual wet tissues were sent to the NTP Archives for inventory, slide/block match, and wet tissue audit. The slides, individual animal data records, and pathology tables were sent to an independent quality assessment laboratory. The individual animal records and tables were compared for accuracy, slides and tissue counts were verified, and histotechnique was evaluated. All tumor diagnoses, all target tissues, and all tissues from a randomly selected 10% of the animals were evaluated by a quality assessment pathologist. The quality assessment report and slides were submitted to the Pathology Working Group (PWG) Chairperson, who reviewed all target tissues and those about which there was a disagreement between the laboratory and quality assessment pathologists.

Representative slides selected by the Chairperson were reviewed by the PWG without knowledge of previously rendered diagnoses. When the consensus diagnosis of the PWG differed from that of the laboratory pathologist, the laboratory pathologist was asked to reconsider the original diagnosis. This procedure has been described, in part, by Maronpot and Boorman (1982) and Boorman et al. (1985). The final diagnoses represent a consensus of contractor pathologists and the NTP Pathology Working Group. Special PWG sessions were conducted on all vehicle control and dosed male rats and female mice to further evaluate hematopoietic neoplasms and anterior pituitary neoplasms, respectively. The materials for these evaluations were coded, randomized, and evaluated in a blind fashion. For subsequent analysis of pathology data, the diagnosed lesions for each tissue type are combined according to the guidelines of McConnell et al. (1986).

Slides/tissues are generally not evaluated in a blind fashion (i.e., without knowledge of dose group) unless lesions in question are subtle or unless there is an inconsistent diagnosis of

lesions by the laboratory pathologist. Nonneoplastic lesions are not examined routinely by the quality assessment pathologist or PWG unless they are considered part of the toxic effect of the chemical.

Statistical Methods

Data Recording: Data on this experiment were recorded in the Carcinogenesis Bioassay Data System (Linhart et al., 1974). The data elements include descriptive information on the chemicals, animals, experimental design, survival, body weight, and individual pathology results, as recommended by the International Union Against Cancer (Berenblum, 1969).

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: 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: Three statistical methods are used to analyze tumor incidence data: life table tests, incidental tumor analysis, and Fisher exact/Cochran-Armitage trend analyses. Tests of significance include pairwise comparisons of each dosed group with vehicle controls and tests for overall dose-response trends. For studies in which administration of the study compound has little effect on survival, the results of the three alternative analyses will generally be similar. When differing results are obtained by the three methods, the final interpretation of the data will depend on the extent to which the tumor under consideration is regarded as being the cause of death. Continuity-corrected tests are used in the analysis of tumor incidence, and reported P values are one-sided. The procedures described below also were used to evaluate selected nonneoplastic lesions.

Life Table Analyses--The first method of analysis assumed that all tumors of a given type observed in animals dying before the end of the study were "fatal"; i.e., they either directly or indirectly caused the death of the animal. According to this approach, the proportions of tumor-bearing animals in the dosed and vehicle control groups were compared at each point in time at which an animal died with a tumor of interest. The denominators of these proportions were the total number of animals at risk in each group. These results, including the data from animals killed at the end of the study, were then combined by the Mantel-Haenszel method (1959) to obtain an overall P value. This method of adjusting for intercurrent mortality is the life table method of Cox (1972) and of Tarone (1975). The underlying variable considered by this analysis is time to death due to tumor. If the tumor is rapidly lethal, then time to death due to tumor closely approximates time to tumor onset. In this case, the life table test also provides a comparison of the time-specific tumor incidences.

Incidental Tumor Analyses--The second method of analysis assumed that all tumors of a given type observed in animals that died before the end of the study were "incidental"; i.e., they were merely observed at necropsy in animals dying of an unrelated cause. According to this

approach, the proportions of 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 by the previously described method to obtain a single overall result. (See Haseman, 1984, for the computational details of both methods.)

Fisher Exact/Cochran-Armitage Trend Analyses--In addition to survival-adjusted methods, the results of the Fisher exact test for pairwise comparisons and the Cochran-Armitage linear trend test (Armitage, 1971; Gart et al., 1979) are given in the appendixes containing the analyses of tumor incidence. These two tests are based on the overall proportion of tumor-bearing animals and do not adjust for survival differences.

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.

GENETIC TOXICOLOGY

Salmonella Protocol: Testing was performed as reported by Ames et al. (1975) with modifications listed below and described in greater detail by Zeiger et al. (1987). Chemicals were sent to the laboratories as coded aliquots from Radian Corporation (Austin, Texas). The study chemical was incubated with the *Salmonella typhimurium* tester strains (TA98, TA100, TA1535, and TA1537) either in buffer 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.

Iodinated glycerol was tested in all four strains; based on these test results, 3-iodo-1,2-propanediol was tested only in strains TA98 and TA100. All trials were repeated.

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.

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

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

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

Chinese Hamster Ovary Cytogenetics Assays: Testing was performed as reported by Galloway et al. (1985, 1987) and is described briefly below. Chemicals were sent to the laboratories as coded aliquots from Radian Corporation (Austin, Texas). Chemicals were tested in cultured Chinese hamster ovary (CHO) cells for induction of sister chromatid exchanges (SCEs) and chromosomal aberrations both in the presence and absence of Aroclor 1254-induced male Sprague Dawley rat liver S9 and cofactor mix. Cultures were handled under gold lights to prevent photolysis of bromodeoxyuridine (BrdU)-substituted DNA. Each test consisted of concurrent solvent and positive controls and of at least three doses of the study chemical; the high dose was limited by toxicity or solubility but did not exceed 5 mg/ml.

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

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

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

Cells were selected for scoring on the basis of good morphology and completeness of karyotype (21 ± 2 chromosomes). All slides were scored blind, and those from a single test were read by the same person. For the SCE test, 50 second-division metaphase cells were usually scored for frequency of SCEs per cell from each dose; 100 or 200 first-division metaphase cells were scored at each dose for the chromosomal aberration test. Classes of aberrations included simple (breaks and terminal deletions), complex (rearrangements and translocations), and other (pulverized cells, despiralized chromosomes, and cells containing 10 or more aberrations).

Statistical analyses were conducted on both the slopes of the dose-response curves and the individual dose points. An SCE frequency 20% above the concurrent solvent control value was chosen as a statistically conservative positive response. The probability of this level of difference occurring by chance at one dose point is less than 0.01; the probability for such a chance occurrence at two dose points is less than 0.001. Chromosomal aberration data are presented as percentage of cells with aberrations. As with SCEs, both the dose-response curve and individual dose points were statistically analyzed. A statistically significant ($P < 0.003$) effect on the slope of the curve or on a dose point ($P < 0.05$) was sufficient for a conclusion of positive for a test.

Preliminary range-finding studies were performed to determine appropriate doses for the in vivo micronucleus test. Factors affecting dose selection included solubility of the chemical and animal lethality and/or cell cycle delay induced by chemical exposure. Male mice were injected intraperitoneally twice, at 24-hour intervals, with the study chemical dissolved in phosphate-buffered saline; the total dosing 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 polychromatic erythrocytes were scored for frequency 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 an exposure group, plus or minus the standard error of the mean.

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

FIRST SIXTEEN-DAY STUDIES

SECOND SIXTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

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

GENETIC TOXICOLOGY

SIXTEEN-DAY STUDIES

Nine of 10 rats that received 1,000 mg/kg iodinated glycerol and 1/5 females that received 500 mg/kg died before the end of the studies (Table 6). Mean body weights of surviving rats did not appear to be related to chemical administration. No clinical signs or gross lesions observed at necropsy could be clearly related to the chemical.

THIRTEEN-WEEK STUDIES

Three of 10 female rats that received 500 mg/kg and 1/10 females that received 62 mg/kg died before the end of the studies (Table 7). Final mean body weights of rats that received 500 mg/kg were 4% lower than that of vehicle controls for males and 7% lower for females. Kidney tubular cell regeneration was observed in both vehicle control and dosed male rats (Table 8). The degree of severity of the lesion was greater in the 500 mg/kg group than in the vehicle control group. Kidney tubular cell regeneration and calcification were observed at increased incidences in the survivors of the highest dose group of female rats. The average severity increased from minimal to mild to moderate as the dose increased. Severe renal cortical necrosis was observed in three high dose females that died early. Lymphoid hyperplasia of the stomach was observed in dosed male and female rats.

Dose Selection Rationale: Because of the incidence of deaths and the incidence and severity of kidney tubular cell regeneration and calcification in rats receiving 500 mg/kg, doses selected for rats for the 2-year studies of iodinated glycerol were 125 and 250 mg/kg for males and 62 and 125 mg/kg for females, administered in water by gavage 5 days per week.

TABLE 6. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE SIXTEEN-DAY GAVAGE STUDIES OF IODINATED GLYCEROL

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	5/5	181 ± 4	231 ± 6	+50 ± 3	
62	5/5	181 ± 4	220 ± 9	+39 ± 8	95
125	5/5	179 ± 3	227 ± 4	+48 ± 2	98
250	5/5	180 ± 4	232 ± 7	+52 ± 4	100
500	5/5	179 ± 4	226 ± 5	+47 ± 4	98
1,000	(d) 1/5	180 ± 3	224	+46	97
FEMALE					
0	5/5	137 ± 2	151 ± 3	+14 ± 3	
62	5/5	137 ± 3	151 ± 3	+14 ± 1	100
125	5/5	137 ± 2	156 ± 4	+19 ± 2	103
250	5/5	137 ± 2	154 ± 4	+17 ± 2	102
500	(e) 4/5	137 ± 2	152 ± 3	+14 ± 2	101
1,000	(f) 0/5	137 ± 2	(g)	(g)	(g)

(a) Number surviving/number initially in the group
(b) Initial mean group 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: all 9
(e) Day of death: 5
(f) Day of death: 2,2,3,3,4
(g) No data are reported due to the 100% mortality in this group.

TABLE 7. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF IODINATED GLYCEROL

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final (c)	Change (d)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	10/10	121 ± 3	330 ± 8	+209 ± 7	
31	10/10	123 ± 3	321 ± 9	+198 ± 8	97
62	10/10	121 ± 3	320 ± 9	+199 ± 10	97
125	10/10	122 ± 3	331 ± 13	+209 ± 11	100
250	10/10	122 ± 3	328 ± 9	+206 ± 8	99
500	10/10	122 ± 3	318 ± 7	+196 ± 6	96
FEMALE					
0	10/10	104 ± 2	200 ± 3	+96 ± 2	
31	10/10	104 ± 2	204 ± 4	+100 ± 3	102
62	(e) 9/10	104 ± 2	205 ± 3	+100 ± 2	103
125	10/10	104 ± 2	207 ± 2	+103 ± 2	104
250	10/10	104 ± 2	202 ± 4	+98 ± 3	101
500	(f) 7/10	103 ± 2	186 ± 3	+82 ± 4	93

(a) Number surviving/number initially in the group
(b) Initial mean group body weight ± standard error of the mean. Subsequent calculations are based on animals surviving to the end of the study.
(c) Final body weights were taken after 12 weeks on study.
(d) Mean body weight change of the survivors ± standard error of the mean
(e) Week of death: 12
(f) Week of death: 11,12,13; (the rat dying during week 13 is included in the final mean body weight and weight change calculations).

TABLE 8. NUMBERS OF RATS WITH RENAL LESIONS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF IODINATED GLYCEROL (a,b)

Lesion	Male		Female		
	Vehicle Control	500 mg/kg	Vehicle Control	250 mg/kg	500 mg/kg
Tubular cell regeneration	7	10	0	0	8
Calcification	0	0	2	2	7

(a) Ten animals examined in each group
(b) Results of quality assurance pathology review

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of high dose male rats were 5%-10% lower than those of vehicle controls from week 43 to week 68 and 10%-13% lower thereafter (Table 9 and Figure 8). Mean body weights of low dose male rats and high dose female rats were 4%-9% lower than those of vehicle controls from week 88 to the end of the studies. Sneezing in male and female high dose rats may have been compound related.

TABLE 9. MEAN BODY WEIGHTS AND SURVIVAL OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF IODINATED GLYCEROL

Weeks on Study	Vehicle Control Av. Wt. (grams)	Vehicle Control No. of Survivors	Low Dose Av. Wt. (grams)	Low Dose Wt. (percent of veh. controls)	Low Dose No. of Survivors	High Dose Av. Wt. (grams)	High Dose Wt. (percent of veh. controls)	High Dose No. of Survivors
MALE				**125 mg/kg**			**250 mg/kg**	
0	112	50	102	91	50	109	97	50
1	157	50	149	95	50	155	99	50
2	191	50	182	95	50	182	95	50
3	214	50	210	98	50	215	100	50
4	239	50	236	99	50	240	100	50
5	253	50	250	99	50	254	100	50
6	262	50	262	100	50	268	102	50
8	287	50	289	101	50	293	102	50
9	296	50	298	101	50	300	101	50
11	310	50	311	100	50	311	100	50
12	310	50	319	103	50	314	101	50
16	342	50	339	99	50	340	99	49
20	365	50	359	98	50	356	98	49
24	379	50	379	100	50	374	99	49
27	390	50	389	100	50	373	96	49
31	409	50	405	99	50	397	97	49
36	423	50	421	100	50	411	97	49
40	438	50	434	99	50	424	97	49
43	443	50	428	97	50	420	95	49
48	452	50	442	98	49	424	94	49
52	451	50	444	98	48	424	94	49
56	454	50	444	98	47	419	92	49
60	457	50	448	98	47	422	92	49
63	467	49	452	97	47	426	91	49
68	464	49	449	97	47	418	90	48
72	461	48	436	95	47	411	89	47
76	466	47	446	96	46	416	89	45
80	455	46	436	96	45	411	90	44
83	458	44	443	97	42	398	87	40
88	450	42	429	95	40	396	88	30
92	444	39	417	94	38	393	89	27
96	445	37	409	92	32	385	87	21
100	437	35	404	92	24	385	88	9
104	432	28	408	94	20	376	87	4
FEMALE				**62 mg/kg**			**125 mg/kg**	
0	93	50	92	99	50	90	97	50
1	121	50	120	99	50	117	97	50
2	136	50	137	101	50	132	97	50
3	146	50	145	99	50	142	97	50
4	160	50	161	101	50	152	95	50
5	169	50	168	99	50	164	97	50
6	164	50	165	101	50	168	102	50
8	199	50	184	92	50	179	90	50
9	191	50	189	99	50	187	98	50
11	209	50	195	93	50	193	92	50
12	199	50	197	99	50	203	102	50
16	206	50	207	100	50	204	99	50
20	212	50	213	100	50	205	97	50
24	221	50	219	99	50	219	99	50
27	219	50	223	102	50	223	102	50
31	235	50	246	105	50	233	99	50
36	240	50	238	99	50	238	99	50
40	248	50	246	99	50	245	99	50
43	256	50	252	98	49	252	98	50
48	264	50	260	98	49	258	98	50
52	266	50	264	99	49	262	98	50
56	274	50	275	100	49	268	98	50
60	286	50	283	99	49	280	98	50
63	300	49	296	99	49	294	98	50
68	315	49	311	99	48	298	95	50
72	321	47	313	98	48	300	93	49
76	331	45	322	97	48	312	94	49
80	327	44	314	96	46	311	95	48
83	335	43	326	97	44	312	93	47
88	343	41	333	97	41	321	94	45
92	340	40	328	96	41	317	93	39
96	342	36	331	97	36	328	96	37
100	347	32	330	95	33	315	91	33
104	345	31	334	97	30	320	93	27

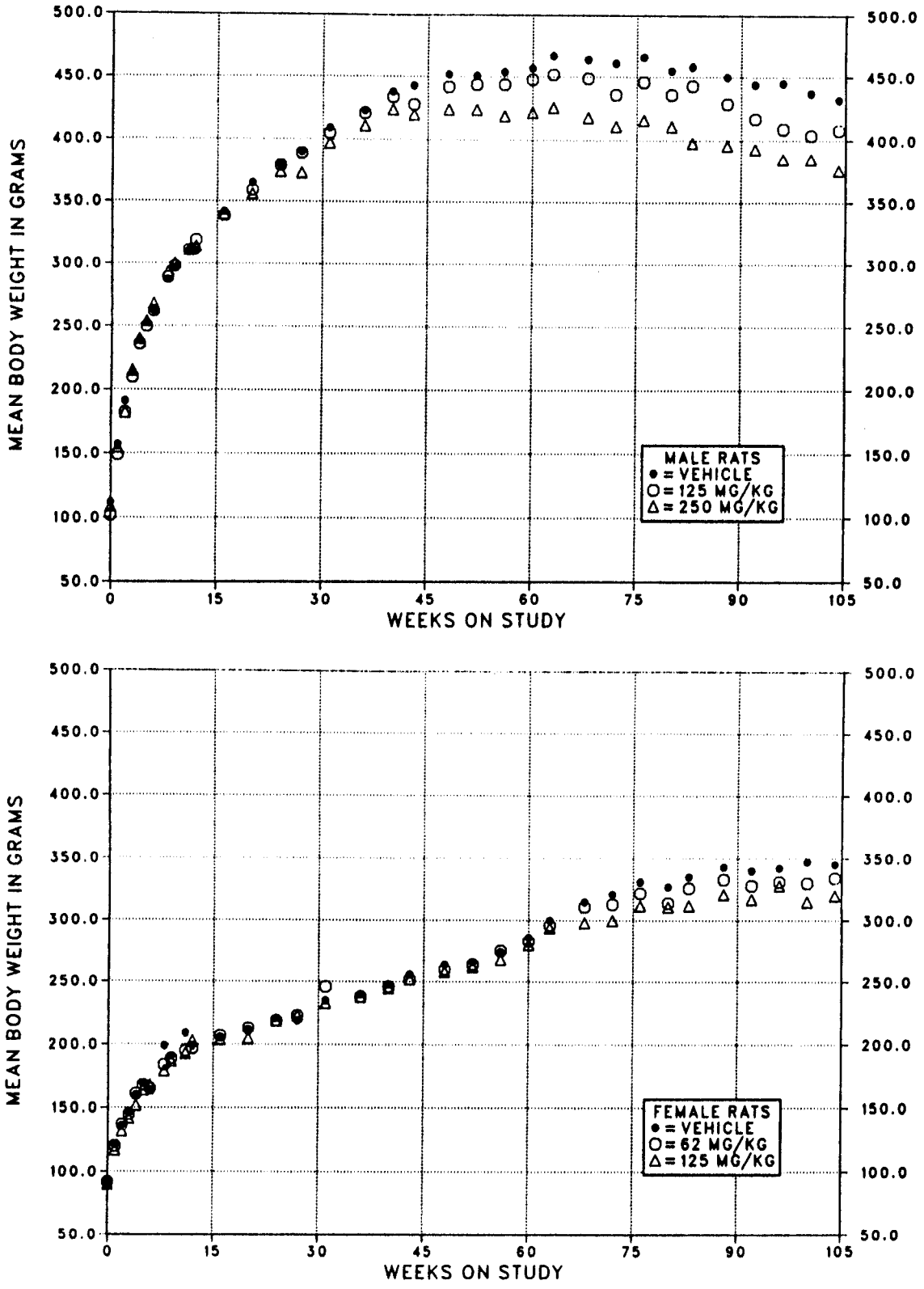


FIGURE 8. GROWTH CURVES FOR RATS ADMINISTERED IODINATED GLYCEROL IN WATER BY GAVAGE FOR TWO YEARS

Survival

Estimates of the probabilities of survival for male and female rats administered iodinated glycerol at the doses used in these studies and for vehicle controls are shown in Table 10 and in the Kaplan and Meier curves in Figure 9. The survival of the high dose group of male rats was significantly lower than that of the vehicle controls after week 86. No other significant differences in survival 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 rats with neoplastic or nonneoplastic lesions of the hematopoietic system, thyroid gland, nasal cavity, salivary glands, testis, anterior pituitary gland, and liver.

Lesions in male rats are summarized in Appendix A. Histopathologic findings on neoplasms are summarized in Table A1. Table A2 gives the survival and tumor status for individual male rats. Table A3 contains the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups. The statistical analyses used are discussed in Section II (Statistical Methods) and Table A3 (footnotes). Because of the markedly reduced survival of high dose male rats, the incidental tumor test has reduced sensitivity for detecting carcinogenic effects. Consequently, the results of the Cochran-Armitage and Fisher exact tests are also given in Tables 11 and 12. Historical incidences of tumors in control male rats are listed in Table A4. Findings on nonneoplastic lesions are summarized in Table A5.

TABLE 10. SURVIVAL OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF IODINATED GLYCEROL

	Vehicle Control	62 mg/kg	125 mg/kg	250 mg/kg
MALE (a)				
Animals initially in study	50		50	50
Natural deaths	6		14	10
Moribund kills	17		16	38
Animals surviving until study termination	(b) 27		20	(c) 2
Survival P values (d)	<0.001		0.136	<0.001
FEMALE (a)				
Animals initially in study	50	50	50	
Natural deaths	4	11	5	
Moribund deaths	14	9	18	
Animals surviving until study termination	31	30	27	
Accidentally killed	1	0	0	
Survival P values (d)	0.538	0.884	0.603	

(a) Termination period: weeks 104-105
(b) One animal died or was killed in a moribund condition during the termination period and was combined, for statistical purposes, with those killed at termination.
(c) Two animals died or were killed in a moribund condition during the observation period before the beginning of the terminal kill and were combined, for statistical purposes, with those killed at termination.
(d) 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.

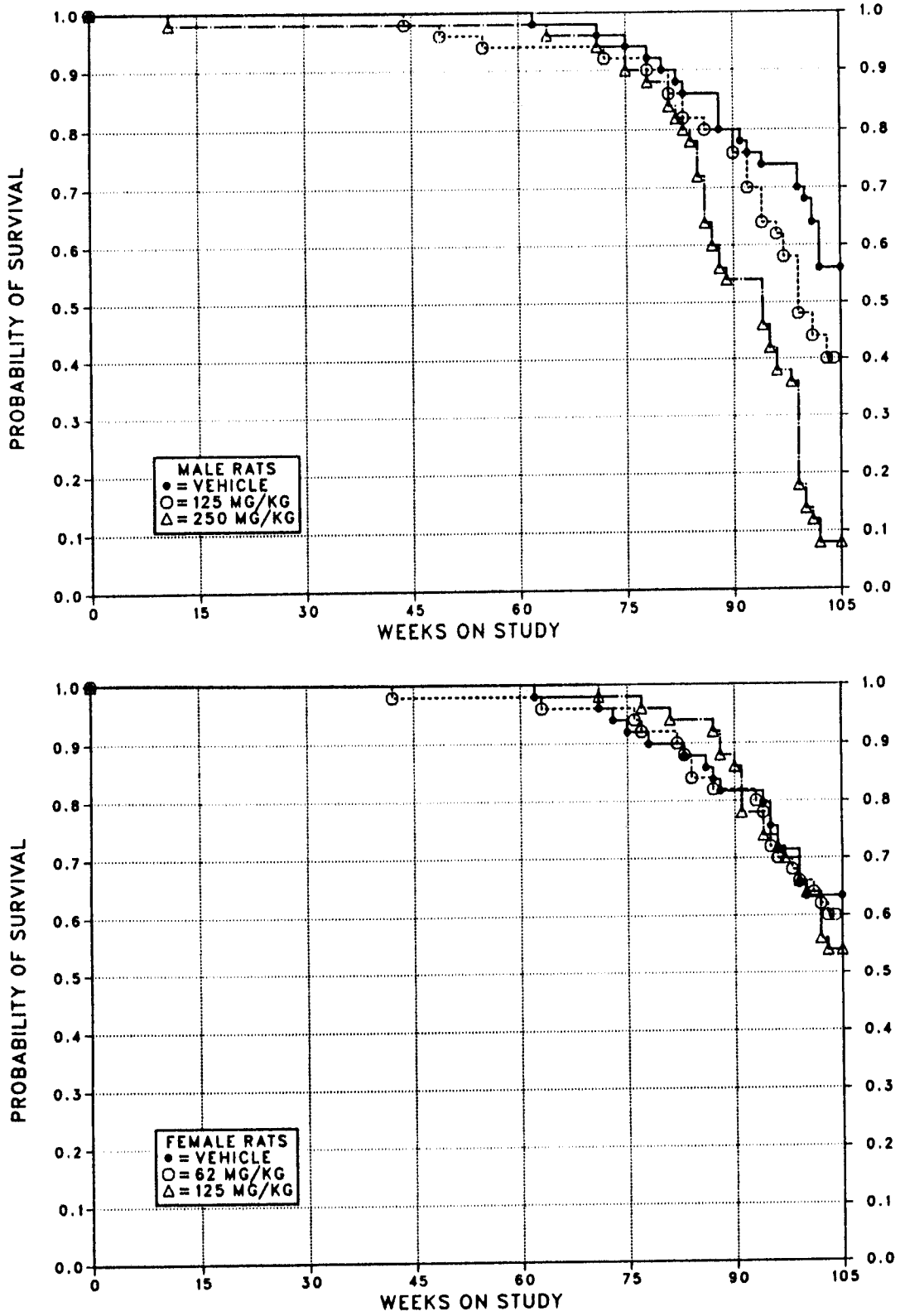


FIGURE 9. KAPLAN-MEIER SURVIVAL CURVES FOR RATS ADMINISTERED IODINATED GLYCEROL IN WATER BY GAVAGE FOR TWO YEARS

Lesions in female rats are summarized in Appendix B. Histopathologic findings on neoplasms are summarized in Table B1. Table B2 gives the survival and tumor status for individual female rats. Table B3 contains the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups. The statistical analyses used are discussed in Section II (Statistical Methods) and Table B3 (footnotes). Historical incidences of tumors in control female rats are listed in Table B4. Findings on nonneoplastic lesions are summarized in Table B5.

Hematopoietic System: Mononuclear cell leukemia in male rats occurred with a positive trend; the incidences in the dosed groups were greater than that in the vehicle controls (Table 11).

Thyroid Gland: Follicular cell carcinomas occurred with a significantly greater incidence in low dose male rats than in vehicle controls (Table 12). Follicular cell carcinomas were observed in one low dose and one high dose female rat. Follicular cell adenomas were not observed in male or female rats. The follicular cell carcinomas were circumscribed, expansile masses that compressed the adjacent thyroid parenchyma. The masses consisted of disorganized follicular epithelium arranged in irregular follicle-like structures and solid clusters. Variable cellular pleomorphism and atypia and a scirrhous reaction, characterized by the proliferation of immature collagenous connective tissue, were sometimes present. Foci of cystic hyperplasia consisted of dilated follicles with short papillary projections of follicular epithelium extending into the lumen. The affected follicles were usually filled with colloid. Lesions classified as follicular cell hyperplasia were small foci of irregular follicles with complex in-folding of the follicular epithelium. There were no other chemical-related nonneoplastic lesions of the thyroid gland in male or female rats. The size of the follicles, height of the follicular epithelium, and staining qualities of the colloid in rats given iodinated glycerol were not different from those in vehicle controls. Thus, the spectrum of lesions characteristic of a "goitrogenic" effect were not present in the thyroid of exposed rats.

Nasal Cavity: Adenomas were observed in 2/49 high dose male rats. Adenomas were not diagnosed in 1,936 untreated historical control male F344/N rats. A squamous cell papilloma and a squamous cell carcinoma have been observed in 1,936 untreated historical control male F344/N rats.

TABLE 11. MONONUCLEAR CELL LEUKEMIA IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF IODINATED GLYCEROL (a,b)

	Vehicle Control	125 mg/kg	250 mg/kg
Overall Rates	14/50 (28%)	29/50 (58%)	24/50 (48%)
Adjusted Rates	35.9%	69.5%	65.2%
Terminal Rates	6/28 (21%)	9/20 (45%)	0/4 (0%)
Week of First Observation	62	55	64
Life Table Tests	P<0.001	P=0.001	P<0.001
Incidental Tumor Tests	P=0.174	P=0.003	P=0.226
Cochran-Armitage Trend Test	P=0.028		
Fisher Exact Test		P=0.002	P=0.032

(a) The statistical analyses used are discussed in Section II (Statistical Methods) and Table A3 (footnotes).
(b) Historical incidence of leukemia in water gavage vehicle controls (mean ± SD): 118/300 (39% ± 16%); historical incidence in untreated controls: 636/1,936 (33% ± 15%

TABLE 12. THYROID GLAND LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF IODINATED GLYCEROL

	Vehicle Control	125 mg/kg	250 mg/kg
Cystic Hyperplasia			
Overall Rates	0/49 (0%)	6/49 (12%)	3/49 (6%)
Follicular Cell Hyperplasia			
Overall Rates	0/49 (0%)	1/49 (2%)	2/49 (4%)
Follicular Cell Carcinoma (a)			
Overall Rates	0/49 (0%)	5/49 (10%)	1/49 (2%)
Adjusted Rates	0.0%	22.8%	25.0%
Terminal Rates	0/27 (0%)	4/20 (20%)	1/4 (25%)
Week of First Observation		99	104
Life Table Tests	P=0.029	P=0.014	P=0.134
Incidental Tumor Tests	P=0.056	P=0.020	P=0.134
Cochran-Armitage Trend Test	P=0.399		
Fisher Exact Test		P=0.028	P=0.500

(a) Historical incidence of adenomas or carcinomas (combined) in water gavage vehicle controls (mean ± SD): 6/293 (2% ± 3%) and of carcinomas (alone): 3/293 (1% ± 1.1%); historical incidence of adenomas or carcinomas (combined) in untreated controls: 23/1,904 (1% ± 2%) and of carcinomas (alone): 10/1,904 (0.5% ± 0.9%)

Salivary Glands: Squamous metaplasia of the ducts of the mandibular salivary gland and focal atrophy of the glandular parenchyma occurred at increased incidences in dosed rats (squamous metaplasia--male: vehicle control, 0/48; low dose, 47/50; high dose, 48/49; female: 1/49; 48/50; 49/50; focal atrophy--male: 1/48; 10/50; 30/49; female: 0/49; 4/50; 11/50). Squamous metaplasia was characterized by the replacement of the normal cuboidal or columnar epithelium of ducts with a stratified squamous epithelium. Foci of atrophy were characterized by reduced size of the acini and atrophy of the acinar cells. There was no inflammatory reaction accompanying these changes.

Testis: The incidences of interstitial cell tumors in male rats were similar among dosed and vehicle control groups (vehicle control, 46/50; low dose, 49/50; high dose, 48/50). However, the incidental tumor test, which is most appropriate for nonfatal tumors such as these, showed a significant trend and the incidences in the dosed groups were significantly increased relative to that in the vehicle controls. The statistical significance was largely attributed to the pattern of mortality and reduced survival in the dosed groups, and the interstitial cell tumors were not considered chemically related.

Anterior Pituitary Gland: Adenomas or carcinomas (combined) in female rats occurred with a significant positive trend by the life table test; the incidence in the high dose group was significantly greater than that in the vehicle controls by the life table test (Table 13). The following incidences of adenomas or carcinomas (combined) were seen in male rats: vehicle control, 26/48; low dose, 12/47; high dose, 7/46.

Liver: Angiectasis was observed at increased incidences in dosed male rats (male: vehicle control, 2/50; low dose, 8/50; high dose, 11/50; female: 1/49; 0/50; 1/50).

TABLE 13. ANTERIOR PITUITARY GLAND LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF IODINATED GLYCEROL

	Vehicle Control	62 mg/kg	125 mg/kg
Focal Hyperplasia			
Overall Rates	2/48 (4%)	1/50 (2%)	1/50 (2%)
Adenoma			
Overall Rates	26/48 (54%)	24/50 (48%)	33/50 (66%)
Adjusted Rates	70.0%	58.5%	81.9%
Terminal Rates	20/31 (65%)	14/30 (47%)	20/27 (74%)
Week of First Observation	83	42	87
Life Table Tests	P=0.064	P=0.466N	P=0.064
Incidental Tumor Tests	P=0.158	P=0.266N	P=0.141
Carcinoma			
Overall Rates	0/48 (0%)	3/50 (6%)	1/50 (2%)
Adjusted Rates	0.0%	9.7%	3.7%
Terminal Rates	0/31 (0%)	2/30 (7%)	1/27 (4%)
Week of First Observation		103	104
Life Table Tests	P=0.342	P=0.119	P=0.472
Incidental Tumor Tests	P=0.372	P=0.130	P=0.472
Adenoma or Carcinoma (a)			
Overall Rates	26/48 (54%)	27/50 (54%)	34/50 (68%)
Adjusted Rates	70.0%	64.9%	84.5%
Terminal Rates	20/31 (65%)	16/30 (53%)	21/27 (78%)
Week of First Observation	83	42	87
Life Table Tests	P=0.043	P=0.461	P=0.042
Incidental Tumor Tests	P=0.108	P=0.495N	P=0.092

(a) Historical incidence in water gavage vehicle controls (mean ± SD): 140/290 (48% ± 6%); historical incidence in untreated controls: 939/1,922 (49% ± 11%)

FIRST SIXTEEN-DAY STUDIES

Deaths occurred in vehicle control mice and in the dosed groups because of dehydration due to a malfunction in the automatic watering system. These studies were repeated.

SECOND SIXTEEN-DAY STUDIES

One female mouse that received 500 mg/kg and one female vehicle control died before the end of the studies (Table 14). The forestomach of 2/5 females that received 500 mg/kg was thickened and granular.

THIRTEEN-WEEK STUDIES

One of 10 female mice that received 500 mg/kg died before the end of the studies and had severe necrosis of the kidney (Table 15). Compound-related effects in female mice included kidney tubular cell regeneration randomly scattered throughout the renal cortex and inflammation or abscess of the forestomach (Table 16). The inflammation and abscesses were characterized microscopically by focal aggregates of polymorphonuclear leukocytes within the stratified squamous epithelium of the forestomach.

Dose Selection Rationale: Iodinated glycerol doses selected for mice for the 2-year studies were 125 and 250 mg/kg for males (based on mild gastric lesions) and 62 and 125 mg/kg for females (based on kidney and stomach lesions) administered in water by gavage 5 days per week.

TABLE 14. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE SECOND SIXTEEN-DAY GAVAGE STUDIES OF IODINATED GLYCEROL

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	5/5	28.3 ± 1.0	30.6 ± 1.0	+2.3 ± 0.3	
31	5/5	28.0 ± 1.1	29.9 ± 1.0	+1.9 ± 0.6	97.7
62	5/5	28.3 ± 1.4	29.6 ± 1.4	+1.3 ± 0.4	96.7
125	5/5	28.4 ± 1.7	30.4 ± 1.6	+2.0 ± 0.5	99.3
250	5/5	28.1 ± 1.7	29.2 ± 1.5	+1.1 ± 1.1	95.4
500	5/5	28.3 ± 0.9	29.4 ± 0.7	+1.1 ± 0.5	96.1
FEMALE					
0	(d) 4/5	22.3 ± 1.2	23.8 ± 1.4	+0.9 ± 0.4	
31	5/5	22.5 ± 0.7	23.3 ± 0.5	+0.8 ± 0.4	97.9
62	5/5	22.2 ± 0.7	22.9 ± 0.8	+0.7 ± 0.4	96.2
125	5/5	21.5 ± 0.6	22.2 ± 0.5	+0.7 ± 0.4	93.3
250	5/5	22.2 ± 0.5	22.8 ± 0.4	+0.6 ± 0.5	95.8
500	(e) 4/5	21.8 ± 0.5	22.3 ± 0.5	+0.5 ± 0.4	93.7

(a) Number surviving/number initially in group
(b) Initial mean group 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) Death occurred on the day of necropsy.
(e) Day of death: 2

TABLE 15. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE THIRTEEN-WEEK GAVAGE STUDIES OF IODINATED GLYCEROL

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	10/10	25.5 ± 0.5	34.5 ± 1.3	+9.0 ± 0.9	
31	10/10	25.8 ± 0.5	36.4 ± 0.9	+10.6 ± 0.5	105.5
62	10/10	25.6 ± 0.5	36.7 ± 1.1	+11.1 ± 0.8	106.4
125	10/10	25.4 ± 0.5	34.0 ± 0.6	+8.6 ± 0.3	98.6
250	10/10	25.9 ± 0.5	35.1 ± 0.4	+9.2 ± 0.4	101.7
500	10/10	25.4 ± 0.5	34.5 ± 0.9	+9.1 ± 0.5	100.0
FEMALE					
0	10/10	19.6 ± 0.3	27.4 ± 0.7	+7.8 ± 0.5	
31	10/10	20.0 ± 0.3	28.7 ± 0.6	+8.7 ± 0.4	104.7
62	10/10	19.4 ± 0.3	27.1 ± 0.5	+7.7 ± 0.5	98.9
125	10/10	19.8 ± 0.3	27.0 ± 0.5	+7.2 ± 0.3	98.5
250	10/10	19.6 ± 0.2	27.4 ± 0.3	+7.8 ± 0.3	100.0
500	(d) 9/10	19.6 ± 0.3	27.7 ± 0.4	+8.2 ± 0.5	101.1

(a) Number surviving/number initially in group
(b) Initial mean group 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: 1

TABLE 16. NUMBERS OF FEMALE MICE WITH SELECTED LESIONS IN THE THIRTEEN-WEEK GAVAGE STUDY OF IODINATED GLYCEROL (a)

Site/Lesion	Vehicle Control	125 mg/kg	250 mg/kg	500 mg/kg
Kidney				
Tubular cell regeneration	0	0	2	5
Forestomach				
Inflammation or abscess	0	(b)	0	5
Hyperplasia, acanthosis, and/or hyperkeratosis	0	(b)	0	7

(a) Ten animals were examined in each group.
(b) Not examined

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of dosed and vehicle control male mice were similar (Table 17 and Figure 10). Mean body weights of high dose female mice were 6%-8% lower than those of vehicle controls from week 40 to week 64 and were 9%-13% lower thereafter. No compound-related clinical signs were observed.

TABLE 17. MEAN BODY WEIGHTS AND SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF IODINATED GLYCEROL

Weeks on Study	Vehicle Control Av. Wt. (grams)	Vehicle Control No. of Survivors	Low Dose Av. Wt. (grams)	Low Dose Wt. (percent of veh. controls)	Low Dose No. of Survivors	High Dose Av. Wt. (grams)	High Dose Wt. (percent of veh. controls)	High Dose No. of Survivors
MALE				**125 mg/kg**			**250 mg/kg**	
0	23.7	50	23.3	98	50	23.0	97	50
1	25.2	50	25.2	100	50	25.2	100	50
2	26.1	50	26.8	103	50	27.5	105	49
3	27.0	50	26.8	99	50	27.0	100	49
4	28.0	50	27.0	96	50	27.3	98	49
5	28.5	50	28.6	100	50	29.3	103	49
6	30.0	50	29.6	99	50	28.9	96	49
7	29.9	50	30.7	103	50	30.4	102	49
8	30.0	50	31.1	104	50	30.4	101	49
9	32.1	50	31.4	98	50	31.6	98	49
10	32.5	50	31.8	98	50	30.9	95	49
11	32.0	50	32.6	102	50	31.8	99	49
12	33.4	50	32.6	98	50	32.7	98	49
16	34.1	50	34.0	100	50	33.9	99	47
20	34.9	50	34.9	100	50	34.9	100	47
24	36.0	50	35.8	99	50	35.8	99	47
28	36.0	50	36.0	100	50	36.4	101	47
32	35.6	50	34.6	97	50	34.4	97	47
36	36.1	50	37.2	103	50	36.5	101	47
40	37.3	50	37.2	100	50	37.2	100	45
44	37.7	50	38.3	102	50	38.0	101	45
48	39.8	49	39.5	99	50	39.0	98	45
52	37.3	48	37.8	101	50	38.0	102	44
56	38.8	48	38.0	98	50	38.5	99	44
60	38.0	48	38.3	101	50	38.2	101	44
64	39.1	48	38.6	99	50	39.3	101	44
68	39.1	48	38.2	98	50	38.8	99	43
72	39.5	48	38.7	98	50	38.6	98	43
76	39.8	47	38.7	97	50	38.8	97	42
80	39.3	47	39.4	100	50	39.0	99	41
84	39.3	46	38.8	99	50	38.6	98	41
88	39.8	46	38.4	96	48	38.9	98	39
92	39.5	44	38.8	98	46	38.9	98	37
96	39.3	41	38.9	99	45	40.3	103	35
100	38.9	38	38.4	99	42	37.7	97	35
104	39.4	36	38.5	98	40	38.2	97	32
FEMALE				**62 mg/kg**			**125 mg/kg**	
0	18.8	50	18.9	101	50	18.4	98	50
1	19.5	50	19.7	101	49	19.8	102	50
2	20.0	50	20.5	103	49	20.7	104	50
3	20.6	50	20.9	101	49	21.4	104	50
4	21.7	50	21.1	97	49	21.6	100	50
5	22.8	50	23.1	101	49	23.0	101	50
6	24.5	50	23.1	94	49	23.1	94	50
7	23.8	50	23.7	100	49	23.8	100	50
8	24.9	50	24.5	98	49	24.5	98	50
9	25.5	50	25.1	98	49	24.1	95	50
10	25.1	50	25.0	100	49	24.4	97	50
11	25.0	50	24.6	98	49	24.1	96	50
12	26.0	50	26.2	101	49	25.2	97	50
16	27.7	50	27.0	97	49	26.0	94	50
20	29.0	50	28.1	97	49	28.1	97	50
24	30.3	50	29.9	99	49	29.0	96	50
28	31.2	50	30.7	98	49	29.5	95	50
32	31.1	50	30.4	98	49	29.6	95	50
36	32.3	50	31.7	98	49	30.9	96	50
40	33.5	50	32.8	98	48	31.3	93	50
44	35.3	50	34.6	98	48	32.9	93	50
48	36.8	50	35.4	96	47	34.2	93	50
52	37.0	50	36.1	98	47	34.9	94	50
56	38.7	50	37.4	97	46	35.5	92	49
60	39.3	50	38.7	98	46	36.2	92	49
64	40.3	50	39.1	97	46	36.9	92	49
68	41.7	50	39.5	95	46	36.1	87	49
72	41.8	50	40.1	96	46	36.7	88	48
76	41.6	50	40.4	97	45	36.5	88	48
80	44.1	50	42.5	96	44	39.0	88	48
84	43.2	50	42.8	99	43	38.1	88	48
88	43.4	48	43.9	101	42	39.6	91	47
92	45.0	47	45.4	101	39	40.1	89	47
96	45.4	46	46.3	102	37	41.2	91	46
100	45.3	44	47.3	104	35	40.8	90	43
104	44.7	42	45.5	102	34	40.9	91	38

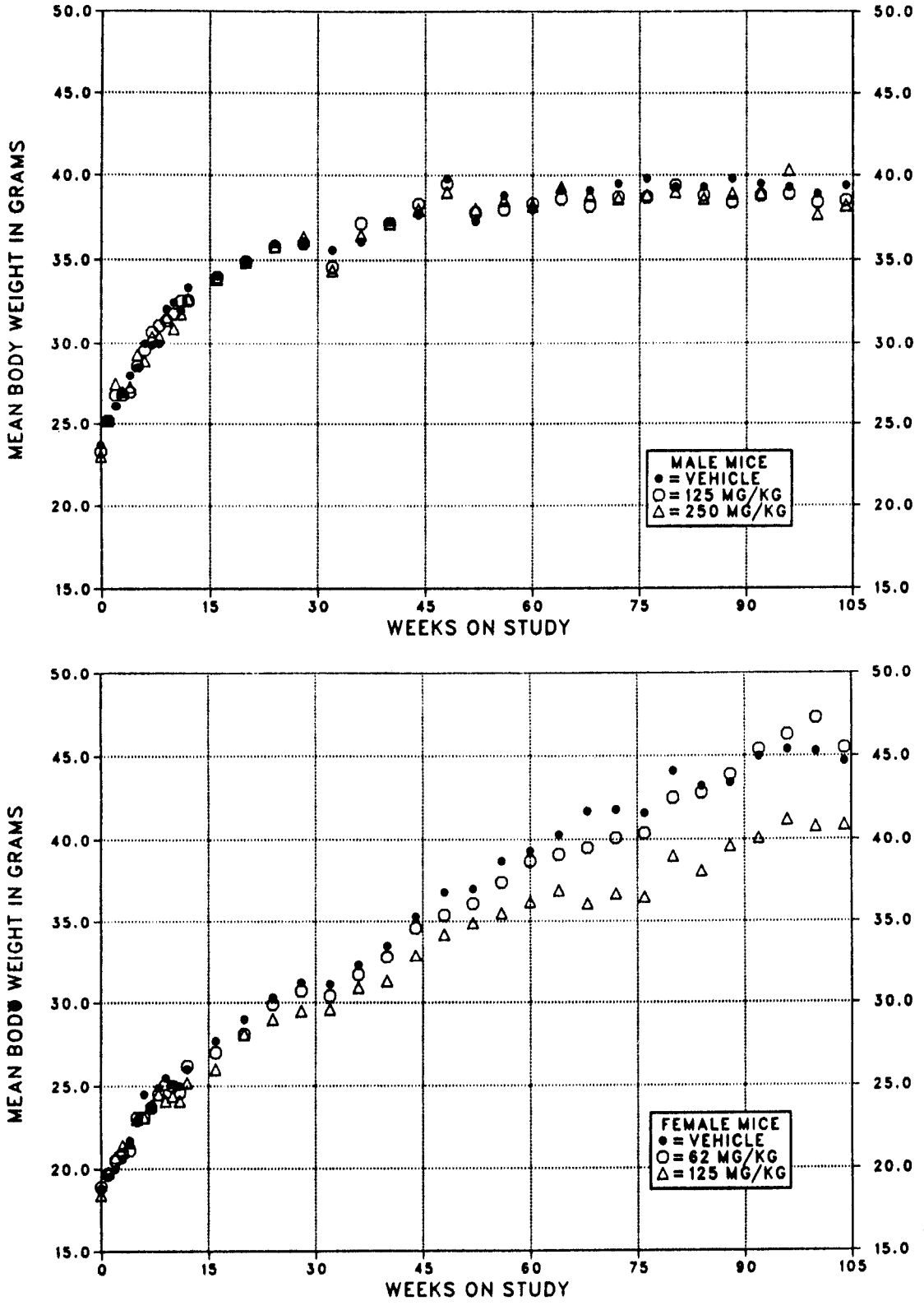


FIGURE 10. GROWTH CURVES FOR MICE ADMINISTERED IODINATED GLYCEROL IN WATER BY GAVAGE FOR TWO YEARS

Survival

Estimates of the probabilities of survival for male and female mice administered iodinated glycerol at the doses used in these studies and for vehicle controls are shown in Table 18 and in the Kaplan and Meier curves in Figure 11. No significant differences in survival 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 anterior pituitary gland, harderian gland, liver, thyroid gland, and forestomach.

Lesions in male mice are summarized in Appendix C. Histopathologic findings on neoplasms are summarized in Table C1. Table C2 gives the survival and tumor status for individual male mice. Table C3 contains the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups. The statistical analyses used are discussed in Section II (Statistical Methods) and Table C3 (footnotes). Findings on nonneoplastic lesions are summarized in Table C4.

Lesions in female mice are summarized in Appendix D. Histopathologic findings on neoplasms are summarized in Table D1. Table D2 gives the survival and tumor status for individual female mice. Table D3 contains the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups. The statistical analyses used are discussed in Section II (Statistical Methods) and Table D3 (footnotes). Historical incidences of tumors in control female mice are listed in Table D4. Findings on nonneoplastic lesions are summarized in Table D5.

TABLE 18. SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF IODINATED GLYCEROL

	Vehicle Control	62 mg/kg	125 mg/kg	250 mg/kg
MALE (a)				
Animals initially in study	50		50	50
Natural deaths	7		5	9
Moribund kills	7		5	10
Animals surviving until study termination	36		40	(b) 31
Survival P values (c)	0.320		0.431	0.388
FEMALE (a)				
Animals initially in study	50	50	50	
Natural deaths	6	9	4	
Moribund kills	6	8	8	
Animals surviving until study termination	(d) 38	33	38	
Survival P values (c)	0.724	0.111	0.768	

(a) Termination period: male--weeks 104-106; female--weeks 105-106
(b) One animal died or was killed in a moribund condition during the termination period and was combined, for statistical purposes, with those killed at termination.
(c) 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.
(d) Two animals died or were killed in a moribund condition during the termination period and were combined, for statistical purposes, with those killed at termination.

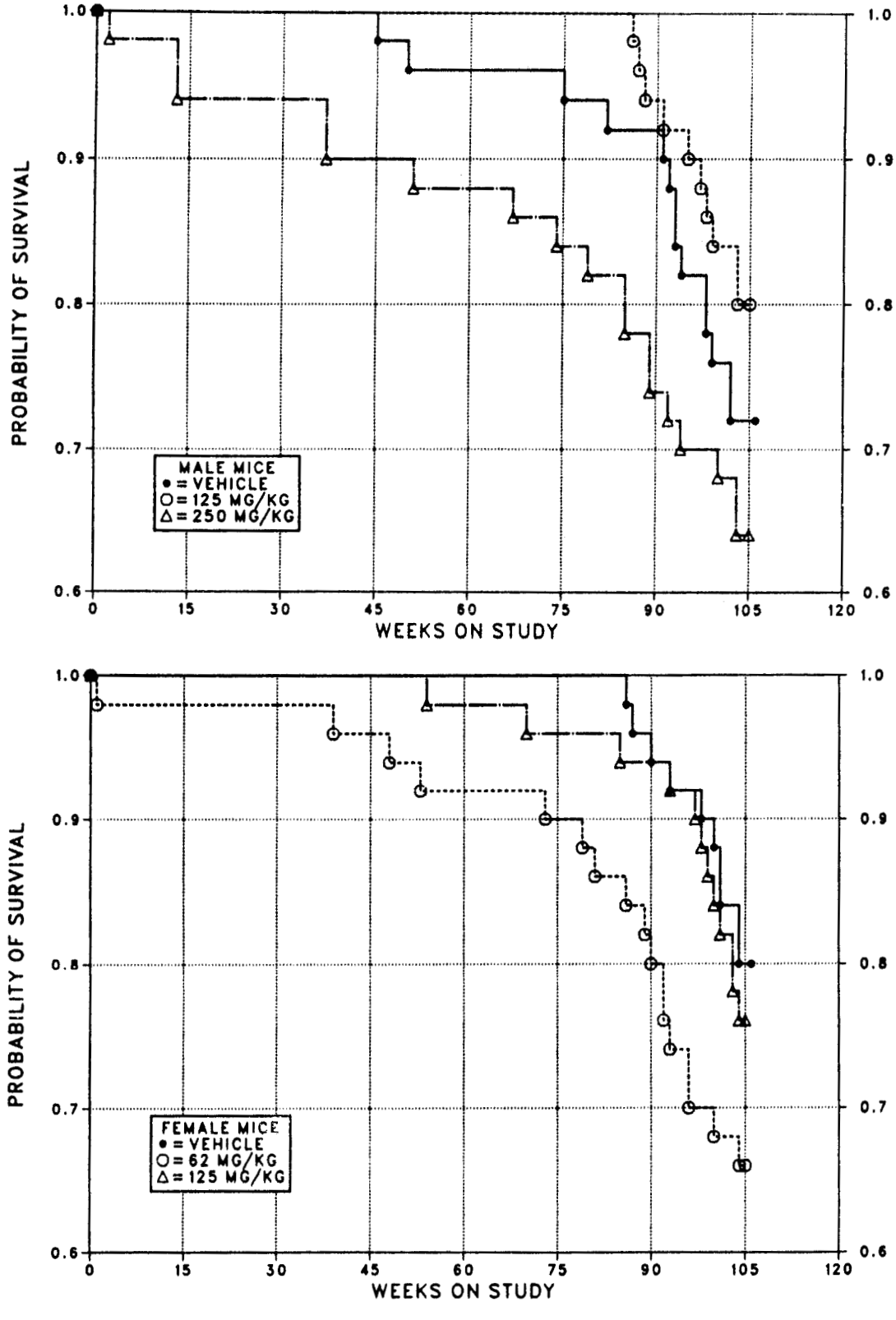


FIGURE 11. KAPLAN-MEIER SURVIVAL CURVES FOR MICE ADMINISTERED IODINATED GLYCEROL IN WATER BY GAVAGE FOR TWO YEARS

Anterior Pituitary Gland: Adenomas in females occurred with a significant positive trend; the incidence in the high dose group was significantly greater than that in the vehicle controls (Table 19). No carcinomas were observed. Hyperplasia of the anterior pituitary gland was not increased in dosed female mice in relation to the vehicle controls. Cysts and hyperplasia were observed at increased incidences in high dose male mice (cysts: vehicle control, 1/44; low dose, 2/42; high dose, 5/45; focal hyperplasia: 0/44; 1/42; 5/45). Anterior pituitary gland neoplasms were seen in 0/44 vehicle control, 1/42 low dose, and 1/45 high dose male mice.

Harderian Gland: Adenomas in female mice occurred with a significant positive trend, and the incidence of adenomas or carcinomas (combined) in high dose female mice was significantly greater than that in vehicle controls (Table 20).

TABLE 19. ANTERIOR PITUITARY GLAND LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF IODINATED GLYCEROL (a)

	Vehicle Control	62 mg/kg	125 mg/kg
Hyperplasia			
Overall Rates	21/47 (45%)	18/45 (40%)	19/46 (41%)
Adenoma (b)			
Overall Rates	10/47 (21%)	15/45 (33%)	24/46 (52%)
Adjusted Rates	25.0%	44.4%	58.0%
Terminal Rates	8/37 (22%)	11/29 (38%)	18/35 (51%)
Week of First Observation	87	89	93
Life Table Tests	P=0.002	P=0.059	P=0.003
Incidental Tumor Tests	P=0.001	P=0.068	P=0.002

(a) The statistical analyses used are discussed in Section II (Statistical Methods) and Table D3 (footnotes).
(b) Historical incidence of adenomas or carcinomas (combined) in water gavage vehicle controls (mean ± SD): 48/322 (15% ± 6%); historical incidence in untreated controls: 244/1,782 (14% ± 11%)

TABLE 20. HARDERIAN GLAND LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF IODINATED GLYCEROL

	Vehicle Control	62 mg/kg	125 mg/kg
Hyperplasia			
Overall Rates	1/50 (2%)	1/40 (3%)	1/50 (2%)
Adenoma			
Overall Rates	6/50 (12%)	8/40 (20%)	13/50 (26%)
Adjusted Rates	14.6%	22.4%	32.3%
Terminal Rates	5/40 (13%)	6/33 (18%)	11/38 (29%)
Week of First Observation	104	92	97
Life Table Tests	P=0.041	P=0.251	P=0.052
Incidental Tumor Tests	P=0.041	P=0.201	P=0.062
Carcinoma			
Overall Rates	0/50 (0%)	0/40 (0%)	1/50 (2%)
Adenoma or Carcinoma (a)			
Overall Rates	6/50 (12%)	8/40 (20%)	14/50 (28%)
Adjusted Rates	14.6%	22.4%	34.8%
Terminal Rates	5/40 (13%)	6/33 (18%)	12/38 (32%)
Week of First Observation	104	92	97
Life Table Tests	P=0.025	P=0.251	P=0.032
Incidental Tumor Tests	P=0.024	P=0.201	P=0.039

(a) Historical incidence in water gavage vehicle controls (mean ± SD): 12/350 (3% ± 4%); historical incidence in untreated controls: 48/2,040 (2% ± 2%)

Liver: The incidences of hepatocellular adenomas and hepatocellular adenomas or carcinomas (combined) in low dose female mice were significantly greater than those in the vehicle controls (Table 21). Because the incidence of hepatocellular neoplasms observed in dosed female mice falls within the historical control range and the incidence observed in the concurrent control group was unusually low, the observation of hepatocellular neoplasms in female mice is not believed to be related to chemical administration.

Thyroid Gland: Dilated follicles and follicular cell hyperplasia were observed at increased incidences in dosed mice (dilatation--male: vehicle control, 0/48; low dose, 28/50; high dose, 32/50; female: 4/48; 11/48; 10/48; hyperplasia--male: 3/48; 46/50; 34/50; female: 2/48; 25/48; 35/48). The abnormally dilated follicles were often located in the periphery of the glands; usually only one or several were affected. Follicular cell hyperplasia was focal or multifocal in distribution and characterized by variation in the size and shape of affected follicles, papillary infoldings into the lumens, and hypertrophy of the follicular epithelium. The colloid in the affected follicles was often more basophilic than that in the surrounding parenchyma. In areas unaffected by the follicular dilatation or hyperplasia, the follicles and colloid were normal for aging male and female mice.

TABLE 21. HEPATOCELLULAR TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF IODINATED GLYCEROL

	Vehicle Control	62 mg/kg	125 mg/kg
Adenoma			
Overall Rates	0/50 (0%)	4/50 (8%)	3/50 (6%)
Adjusted Rates	0.0%	12.1%	7.3%
Terminal Rates	0/40 (0%)	4/33 (12%)	2/38 (5%)
Week of First Observation		105	93
Life Table Tests	P=0.117	P=0.041	P=0.117
Incidental Tumor Tests	P=0.127	P=0.041	P=0.131
Carcinoma			
Overall Rates	0/50 (0%)	1/50 (2%)	1/50 (2%)
Adenoma or Carcinoma (a)			
Overall Rates	0/50 (0%)	5/50 (10%)	4/50 (8%)
Adjusted Rates	0.0%	14.0%	9.9%
Terminal Rates	0/40 (0%)	4/33 (12%)	3/38 (8%)
Week of First Observation		53	93
Life Table Tests	P=0.071	P=0.022	P=0.060
Incidental Tumor Tests	P=0.103	P=0.041	P=0.068

(a) Historical incidence in water gavage vehicle controls (mean ± SD): 29/348 (8% ± 5%); historical incidence in untreated controls: 184/2,032 (9% ± 5%)

Forestomach: Hyperkeratosis and acanthosis were observed at increased incidences in high dose male mice (hyperkeratosis--male: vehicle control, 0/49; low dose, 0/49; high dose, 5/50; female: 6/49; 2/50; 3/49; acanthosis--male: 0/49; 1/49; 5/50; female: 5/49; 4/50; 2/49). The incidences of squamous cell papillomas found in dosed female mice were not significantly different from that in the vehicle controls (Table 22) but exceeded the greatest incidence observed in an untreated historical control group (4/50). Squamous cell neoplasms were not diagnosed in any of the male mice.

TABLE 22. FORESTOMACH SQUAMOUS CELL PAPILLOMAS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF IODINATED GLYCEROL (a)

	Vehicle Control	62 mg/kg	125 mg/kg
Overall Rates	1/49 (2%)	2/50 (4%)	5/49 (10%)
Adjusted Rates	2.5%	6.1%	12.4%
Terminal Rates	1/40 (3%)	2/33 (6%)	3/38 (8%)
Week of First Observation	105	105	103
Life Table Tests	P=0.060	P=0.433	P=0.097
Incidental Tumor Tests	P=0.077	P=0.433	P=0.127

(a) Historical incidence of stomach papillomas in water gavage vehicle controls (mean): 4/339 (1%); historical incidence of stomach neoplasms in untreated controls: 18/1,994 (0.9%)

GENETIC TOXICOLOGY

In NTP Salmonella studies, treatment of the base-substitution mutant strains TA100 and TA1535 with iodinated glycerol in a preincubation protocol with and without Aroclor 1254-induced male Sprague Dawley rat or Syrian hamster liver S9 resulted in a strong dose-related increase in the number of revertant colonies recovered; no increase in revertants was observed in the frame-shift mutant strains TA98 and TA1537, with doses up to 10 mg/plate (Table 23). 3-Iodo-1,2-propanediol was also mutagenic in the Salmonella test (Table 24). A strong dose-related increase in revertant colonies was observed in strain TA100 with and without S9; no increase was observed in strain TA98. The magnitude of the response was greater with 3-iodo-1,2-propanediol than with iodinated glycerol at identical doses. Iodinated glycerol induced trifluorothymidine resistance in mouse lymphoma L5178Y/TK cells in the absence of S9 within a dose range of 0.25-3.0 µl/ml (Table 25); it was not tested with S9. When tested for cytogenetic effects in cultured Chinese hamster ovary (CHO) cells, iodinated glycerol induced both sister chromatid exchanges (SCEs) and chromosomal aberrations in trials conducted without S9; in the presence of Aroclor 1254-induced male Sprague Dawley rat liver S9, iodinated glycerol significantly increased the frequency of SCEs (Table 26), but no chromosomal aberrations were induced (Table 27). Iodinated glycerol did not induce cell cycle delay in treated CHO cells. Results from the in vivo bone marrow micronucleus tests with iodinated glycerol (Table 28) and with 3-iodo-1,2-propanediol (Table 29) were negative; intraperitoneal doses up to 500 mg/kg iodinated glycerol or intraperitoneal doses up to 250 mg/kg 3-iodo-1,2-propanediol (two times in a 24-hour interval) did not cause an increase in micronucleated polychromatic erythrocytes.

TABLE 23. MUTAGENICITY OF IODINATED GLYCEROL 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
TA100	0	138 ± 7.4	97 ± 3.2	134 ± 4.3	112 ± 2.3	160 ± 3.8	92 ± 6.6
	100	--	117 ± 3.8	--	127 ± 13.1	--	141 ± 0.3
	333	185 ± 5.0	150 ± 8.3	178 ± 9.7	178 ± 19.0	187 ± 7.7	169 ± 16.2
	1,000	288 ± 13.0	220 ± 20.7	254 ± 5.8	282 ± 11.5	320 ± 8.4	239 ± 16.5
	3,333	546 ± 16.5	394 ± 20.7	455 ± 11.5	484 ± 22.9	565 ± 11.1	466 ± 42.2
	6,666	708 ± 27.5	--	631 ± 17.1	--	771 ± 12.8	--
	10,000	833 ± 40.3	678 ± 52.8	695 ± 15.4	823 ± 32.5	893 ± 54.7	858 ± 48.0
	Trial summary	Positive	Positive	Positive	Positive	Positive	Positive
	Positive control (c)	348 ± 9.5	408 ± 10.8	1,422 ± 62.9	1,203 ± 145.6	943 ± 29.1	654 ± 48.4
TA1535	0	19 ± 2.4	22 ± 3.1	8 ± 2.2	6 ± 0.6	7 ± 0.9	5 ± 0.3
	10	--	29 ± 5.8	--	9 ± 3.2	--	7 ± 0.7
	33	--	36 ± 2.3	--	10 ± 2.2	--	14 ± 0.9
	100	--	35 ± 2.8	--	27 ± 1.9	--	21 ± 4.9
	333	99 ± 3.9	52 ± 5.2	69 ± 5.7	65 ± 11.2	96 ± 5.8	57 ± 4.0
	1,000	230 ± 11.8	135 ± 8.3	176 ± 18.4	183 ± 15.3	254 ± 20.0	155 ± 17.9
	3,333	601 ± 0.9	--	450 ± 23.6	--	585 ± 17.8	--
	6,666	789 ± 9.6	--	607 ± 27.8	--	809 ± 18.0	--
	10,000	908 ± 22.2	--	711 ± 12.0	--	902 ± 21.2	--
	Trial summary	Positive	Positive	Positive	Positive	Positive	Positive
	Positive control (c)	407 ± 5.8	440 ± 14.2	443 ± 9.5	513 ± 19.6	156 ± 15.8	218 ± 6.2
TA1537	0	4 ± 0.0	--	8 ± 3.2	--	8 ± 3.4	--
	333	5 ± 2.0	--	6 ± 0.6	--	5 ± 0.6	--
	1,000	4 ± 0.6	--	6 ± 2.1	--	4 ± 0.6	--
	3,333	8 ± 2.1	--	7 ± 1.0	--	6 ± 1.2	--
	6,666	5 ± 1.5	--	5 ± 1.2	--	4 ± 0.9	--
	10,000	6 ± 0.3	--	5 ± 0.6	--	4 ± 0.6	--
	Trial summary	Negative	--	Negative	--	Negative	--
	Positive control (c)	174 ± 16.3	--	399 ± 21.3	--	203 ± 10.0	--
TA98	0	14 ± 0.3	--	29 ± 1.7	--	20 ± 0.6	--
	333	16 ± 3.7	--	25 ± 0.7	--	21 ± 2.9	--
	1,000	16 ± 3.8	--	23 ± 3.4	--	26 ± 1.3	--
	3,333	15 ± 2.2	--	18 ± 3.5	--	17 ± 1.2	--
	6,666	18 ± 1.5	--	21 ± 3.1	--	17 ± 2.1	--
	10,000	16 ± 1.7	--	23 ± 1.7	--	16 ± 2.6	--
	Trial summary	Negative	--	Negative	--	Negative	--
	Positive control (c)	948 ± 37.5	--	1,266 ± 27.6	--	797 ± 67.0	--

(a) Study performed at SRI International. Data are presented in Zeiger et al. (1987). Cells and study compound or solvent (distilled water) were incubated in the absence of exogenous metabolic activation (−S9) or with Aroclor 1254-induced S9 from male Syrian hamster liver or male Sprague Dawley rat liver. High dose was limited by toxicity or solubility but did not exceed 10 mg/plate; 0 µg/plate dose is the solvent control.

(b) Revertants are presented as mean ± standard error from three plates.

(c) Positive control; 2-aminoanthracene was used on all strains in the presence of S9. In the absence of metabolic activation, 4-nitro-*o*-phenylenediamine was used with TA98, sodium azide was used with TA100 and TA1535, and 9-aminoacridine was used with TA1537.

TABLE 24. MUTAGENICITY OF 3-IODO-1,2-PROPANEDIOL IN *SALMONELLA TYPHIMURIUM* (a)

Strain	Dose (µg/plate)	Revertants/plate (b) −S9	+S9 (hamster)	+S9 (rat)
TA98	0	19 ± 1.9	30 ± 1.8	14 ± 0.9
	100	19 ± 1.0	30 ± 2.7	11 ± 2.7
	333	22 ± 3.3	33 ± 4.1	16 ± 0.6
	1,000	18 ± 2.0	32 ± 5.9	17 ± 0.6
	3,333	19 ± 2.8	34 ± 3.4	15 ± 0.9
	10,000	17 ± 1.7	23 ± 1.5	15 ± 2.6
Trial summary		Negative	Negative	Negative
Positive control (c)		575 ± 13.0	543 ± 17.1	186 ± 14.0

Strain	Dose (µg/plate)	−S9 Trial 1	−S9 Trial 2	+S9 (hamster) Trial 1	+S9 (hamster) Trial 2	+S9 (hamster) Trial 3	+S9 (rat) Trial 1	+S9 (rat) Trial 2	+S9 (rat) Trial 3
TA100	0	142 ± 9.5	157 ± 9.3	174 ± 3.4	117 ± 18.7	178 ± 5.8	165 ± 0.3	154 ± 4.8	173 ± 13.2
	10	--	--	187 ± 8.2	129 ± 4.1	200 ± 7.2	173 ± 10.7	133 ± 6.5	196 ± 3.5
	33	151 ± 4.2	148 ± 6.7	195 ± 7.4	152 ± 4.9	207 ± 3.7	203 ± 15.7	200 ± 19.5	179 ± 9.5
	100	182 ± 3.5	179 ± 7.4	222 ± 6.7	189 ± 2.0	209 ± 4.6	230 ± 33.8	205 ± 2.4	214 ± 15.2
	333	236 ± 4.9	229 ± 3.5	379 ± 21.7	227 ± 4.6	289 ± 10.9	376 ± 18.0	242 ± 4.6	239 ± 3.7
	1,000	450 ± 33.2	362 ± 11.7	728 ± 34.9	310 ± 9.5	456 ± 3.6	760 ± 20.0	372 ± 44.3	379 ± 2.5
	3,333	1,251 ± 192.8	673 ± 4.9						
Trial summary		Positive	Positive	Positive	Positive	Positive	Positive	Positive	Positive
Positive control (c)		1,010 ± 21.7	454 ± 66.6	868 ± 26.4	665 ± 27.9	1,146 ± 19.9	489 ± 13.1	544 ± 19.5	699 ± 5.5

(a) Study performed at SRI International. Data are presented in Zeiger et al. (1987). Cells and study compound or solvent (distilled water) were incubated in the absence of exogenous metabolic activation (−S9) or with 30% Aroclor 1254-induced S9 from male Syrian hamster liver or male Sprague Dawley rat liver. High dose was limited by toxicity or solubility but did not exceed 10 mg/plate; 0 µg/plate dose is the solvent control.
(b) Revertants are presented as mean ± standard error from three plates.
(c) Positive control; 2-aminoanthracene was used on all strains in the presence of S9. In the absence of metabolic activation, 4-nitro-*o*-phenylenediamine was used with TA98 and sodium azide was used with TA100.

TABLE 25. INDUCTION OF TRIFLUOROTHYMIDINE RESISTANCE BY IODINATED GLYCEROL IN MOUSE L5178Y LYMPHOMA CELLS (a,b)

Compound	Concentration (µl/ml)	Cloning Efficiency (percent)	Relative Total Growth (percent)	Tft-Resistant Cells	Mutant Fraction (c)
Trial 1					
Distilled water (d)		89.0 ± 5.3	99.8 ± 12.8	130.0 ± 6.9	49.0 ± 1.9
Iodinated glycerol	0.125	84.0 ± 9.7	84.3 ± 10.2	133.7 ± 8.1	54.3 ± 7.1
	0.25	55.0 ± 11.7	61.7 ± 13.1	128.0 ± 6.4	(e) 82.7 ± 13.3
	0.375	77.3 ± 0.9	71.7 ± 5.3	197.7 ± 7.5	(e) 85.0 ± 3.8
	0.5	83.7 ± 4.4	64.0 ± 4.0	269.7 ± 13.5	(e) 109.0 ± 10.8
	0.75	59.7 ± 4.3	55.0 ± 3.5	367.0 ± 27.2	(e) 210.3 ± 30.9
	1	71.7 ± 3.5	49.7 ± 1.9	542.7 ± 34.0	(e) 252.3 ± 15.6
Methyl methanesulfonate	5 µg/ml	66.0 ± 4.9	47.3 ± 1.5	680.0 ± 32.9	(e) 349.0 ± 41.1
Trial 2					
Distilled water (f)		103.5 ± 0.5	100.0 ± 7.0	92.0 ± 5.0	29.5 ± 1.5
Iodinated glycerol	0.5	79.7 ± 3.8	72.0 ± 3.2	148.7 ± 8.8	(e) 62.3 ± 0.9
	0.75	88.0 ± 5.9	64.0 ± 0.6	244.3 ± 25.2	(e) 92.3 ± 3.5
	1	78.7 ± 1.2	53.3 ± 2.9	313.3 ± 29.0	(e) 134.0 ± 13.3
	1.5	74.7 ± 6.2	44.7 ± 2.0	519.7 ± 46.8	(e) 232.3 ± 9.8
	2	90.0 ± 4.0	38.0 ± 1.7	732.3 ± 34.5	(e) 272.0 ± 17.4
	3	78.7 ± 8.1	15.7 ± 1.9	789.0 ± 4.5	(e) 343.7 ± 39.2
Methyl methanesulfonate	5 µg/ml	71.3 ± 3.3	50.0 ± 4.6	610.0 ± 32.1	(e) 284.7 ± 2.4

(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 indicated; the average for the three tests is presented in the table. Cells (6×10^5/ml) were treated for 4 hours at 37° C in medium, washed, resuspended in medium, and incubated for 48 hours at 37° C. After expression, 3×10^6 cells were plated in medium and soft agar supplemented with trifluorothymidine (Tft) for selection of Tft-resistant cells, and 600 cells were plated in nonselective medium and soft agar to determine the cloning efficiency.

(b) Mean ± standard error of replicate trials for approximately 3×10^6 cells each. All data are evaluated statistically for both trend and peak response ($P < 0.05$ for at least one of the three highest dose sets). Both responses must be significantly ($P < 0.05$) positive for a chemical to be considered capable of inducing Tft resistance. If only one of these responses is significant, the call is "equivocal"; the absence of both trend and peak response results in a "negative" call.

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

(d) Data presented are the results 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 results of two tests.

TABLE 26. INDUCTION OF SISTER CHROMATID EXCHANGES IN CHINESE HAMSTER OVARY CELLS BY *IODINATED GLYCEROL* (a)

Compound	Dose (µg/ml)	Total Cells	No. of Chromosomes	No. of SCEs	SCEs/ Chromosome	SCEs/ Cell	Hours in BrdU	Relative SCEs/Cell (percent) (b)
−S9 (c)--Summary: Positive								
Medium		50	1,048	370	0.35	7.4	25.8	
Iodinated glycerol	50	50	1,047	701	0.67	14.0	25.8	189.2
	167	10	210	282	1.34	28.2	25.8	381.1
	500	5	105	220	2.10	44.0	25.8	594.6
	1,670	0	--	--	--	--	25.8	--
Mitomycin C	0.001	50	1,044	627	0.60	12.5	25.8	168.9
	0.01	5	104	211	2.03	42.2	25.8	570.3
+S9 (d)								
Trial 1--Summary: Positive								
Medium		50	1,047	485	0.46	9.7	25.8	
Iodinated glycerol	500	50	1,049	497	0.47	9.9	25.8	102.1
	1,670	50	1,050	701	0.67	14.0	25.8	144.3
	5,000	50	1,047	902	0.86	18.0	25.8	185.6
Cyclophosphamide	0.4	50	1,046	657	0.63	13.1	25.8	135.1
	2	5	105	200	1.90	40.0	25.8	412.4
Trial 2--Summary: Positive								
Medium		25	525	184	0.35	7.4	25.5	
Iodinated glycerol	2,500	25	525	310	0.59	12.4	25.5	167.6
	3,750	25	525	462	0.88	18.5	25.5	250.0
	5,000	25	524	488	0.93	19.5	25.5	263.5
Cyclophosphamide	0.4	25	525	357	0.68	14.3	25.5	193.2
	2	5	105	232	2.21	46.4	25.5	627.0

(a) Study performed by Litton Bionetics, Inc. SCE = sister chromatid exchange; BrdU = bromodeoxyuridine. A detailed description of the SCE protocol is presented by Galloway et al. (1985, 1987). Briefly, Chinese hamster ovary cells were incubated with study compound or medium 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 medium
(c) In the absence of S9, Chinese hamster ovary cells were incubated with study compound or medium 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 27. INDUCTION OF CHROMOSOMAL ABERRATIONS IN CHINESE HAMSTER OVARY CELLS BY IODINATED GLYCEROL (a)

Trial 1					Trial 2				
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
−S9 (b)--Harvest time: 10 hours					−S9 (b)--Harvest time: 10.3 hours				
Medium					Medium				
	200	5	0.03	2.0		100	3	0.03	3.0
Iodinated glycerol					Iodinated glycerol				
1,250	200	14	0.07	7.0	1,250	100	5	0.05	5.0
1,875	46	0	0.00	0.0	1,875	100	12	0.12	9.0
2,500	200	1	0.01	0.5	2,500	100	24	0.24	19.0
Summary: Equivocal					Summary: Weakly positive				
Mitomycin C					Mitomycin C				
0.25	200	29	0.15	11.5	0.25	50	20	0.40	32.0
0.75	25	17	0.68	44.0	0.75	25	15	0.60	32.0
+S9 (c)--Harvest time: 11.8 hours									
Medium									
	200	1	0.01	0.5					
Iodinated glycerol									
2,500	200	0	0.00	0.0					
2,750	200	0	0.00	0.0					
5,000	200	2	0.01	1.0					
Summary: Negative									
Cyclophosphamide									
7.5	200	27	0.14	10.5					
37.5	25	17	0.68	48.0					

(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, 1987). Briefly, Chinese hamster ovary cells were incubated with study compound or medium 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 medium 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 medium 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.

TABLE 28. FREQUENCY OF MICRONUCLEI IN BONE MARROW POLYCHROMATIC ERYTHROCYTES IN MICE TREATED WITH IODINATED GLYCEROL (a)

Treatment (mg/kg)	Micronucleated Cells/1,000 Cells (b)	Number of Mice
Control (c)		
0	1.5 ± 0.4	5
Iodinated glycerol		
125	0.3 ± 0.2	5
250	1.1 ± 0.4	5
500	0.6 ± 0.3	5
Mitomycin C (d)		
1.0	37.7 ± 4.6	5

(a) Study performed at Environmental Health Research and Testing, Inc. Male mice were injected intraperitoneally twice, at 24-hour intervals, with iodinated glycerol dissolved in phosphate-buffered saline (PBS); bone marrow smears were prepared 24 hours after the second injection. In each of five animals per dose group, 2,000 polychromatic erythrocytes were scored for frequency of micronuclei.
(b) Values are mean ± standard error of the mean.
(c) Control animals received 0.4 ml PBS per injection.
(d) Positive control

TABLE 29. FREQUENCY OF MICRONUCLEI IN BONE MARROW POLYCHROMATIC ERYTHROCYTES IN MICE TREATED WITH 3-IODO-1,2-PROPANEDIOL (a)

Treatment (mg/kg)	Micronucleated Cells/1,000 Cells (b)	Number of Mice
Control (c)		
0	0.6 ± 0.2	5
3-Iodo-1,2-propanediol		
62.5	0.4 ± 0.2	5
125	0.8 ± 0.5	5
250	0.8 ± 0.6	5
Mitomycin C (d)		
1.0	30.2 ± 2.7	5

(a) Study performed at Environmental Health Research and Testing, Inc. Male mice were injected intraperitoneally twice, at 24-hour intervals, with 3-iodo-1,2-propanediol dissolved in phosphate-buffered saline (PBS); bone marrow smears were prepared 24 hours after the second injection. In each of five animals per dose group, 2,000 polychromatic erythrocytes were scored for frequency of micronuclei.
(b) Values are mean ± standard error of the mean.
(c) Control animals received 0.4 ml PBS per injection.
(d) Positive control

IV. DISCUSSION AND CONCLUSIONS

IV. DISCUSSION AND CONCLUSIONS

These studies were conducted because of human exposure to iodinated glycerol as a mucolytic expectorant in respiratory therapy and because of the compound's possible relationship to other alkyl iodides (e.g., methyl iodide, an alkylating agent).

As indicated in the chemistry section of this Report, the iodopropylideneglycerol isomers described in the patent for iodinated glycerol were not observed when the study material used in these studies was analyzed. Analysis of the iodinated glycerol study material indicated that the principal components are 3-iodo-1,2-propanediol (33%) and glycerol (17%). Numerous other components were present in the study material. Four of these components were tentatively identified as isomeric (hydroxymethyl)-(iodomethyl)-*p*-dioxane species and were cumulatively estimated to be present at a concentration of approximately 10%. The balance of the study material (~40%) is thought to contain polymers of glycerol and iodoglycerol.

3-Iodo-1,2-propanediol, the major component of iodinated glycerol, is presumed to be the most active component and may contribute to its mutagenicity. Glycidol was proposed as the reactive intermediate of 3-iodo-1,2-propanediol in vivo (Jones, 1975). In vitro studies with rat liver supernatants indicate that 3-iodo-1,2-propanediol is conjugated with glutathione via an epoxide intermediate, proposed to be glycidol, to form the primary metabolite, *S*-(2,3-dihydroxypropyl)glutathione. The similarity of the results obtained in NTP-sponsored in vitro genotoxicity studies with iodinated glycerol and separately with glycidol is consistent and suggests that 3-iodo-1,2-propanediol, possibly through a glycidol intermediate, is a genetically active component of iodinated glycerol; 3-iodo-1,2-propanediol was mutagenic in Salmonella strain TA100..

This compound was completely metabolized (no parent compound was found) and excreted in the urine after intraperitoneal administration of 100 mg/kg to male Wistar rats (250-300 g) or male ICI Swiss mice (30-50 g) (Jones, 1975). The hydrolysis of 3-iodo-1,2-propanediol and other iodo-containing compounds would result in the release of iodide.

In the 16-day and 13-week studies, deaths of rats and mice were observed at doses of 500 mg/kg. The principal findings from the 13-week gavage studies (doses up to 500 mg/kg) included: tubular cell regeneration and calcification of the kidney in dosed female rats; lymphoid hyperplasia in the stomach of dosed male and female rats; and kidney tubular cell regeneration, inflammation, or abscesses of the forestomach and hyperplasia, acanthosis, and/or hyperkeratosis of the forestomach in dosed female mice. Doses for the 2-year studies were based on the incidences of deaths and toxicity to the kidney in rats and incidences of deaths and toxicity to the kidney and forestomach in mice in the 13-week studies.

In the 2-year study, survival of high dose male rats was reduced. The cause of death of high dose male rats dying late in the study was not clear; i.e., there was no apparent dose-related increase in kidney toxicity or lethal malignancies observed in animals dying between weeks 89 and 103 of exposure. This decrease in survival may be related to the cumulative toxicity of iodinated glycerol and/or its metabolites, including iodide.

The incidences of mononuclear cell leukemia were increased in dosed male rats (see Table 11). There was a significant positive trend by both life table and Cochran-Armitage trend tests, and the incidences in both dosed groups were significantly greater than that in the vehicle controls by the life table test and Fisher exact test. Analysis of the incidence of leukemia at selected intervals during the 2-year studies (Table 30) indicates that leukemia was dose related and occurred at a greater incidence in the high dose group of male rats before week 89 of exposure. After week 89, fewer animals were diagnosed with leukemia in the high dose group than in the low dose group. The cause for this decreased incidence of leukemia in the high dose group after week 89 of exposure is not apparent but may be related to cumulative toxicity and the increased number of deaths due to iodinated glycerol exposure, as suggested above.

Davey and Moloney (1970) determined that approximately 80% of all deaths due to mononuclear cell leukemia in untreated F344 rats

TABLE 30. INCIDENCES OF MALE F344/N RATS WITH MONONUCLEAR CELL LEUKEMIA AT SELECTED INTERVALS IN THE TWO-YEAR GAVAGE STUDIES OF IODINATED GLYCEROL (a)

Dose (mg/kg)	Week					
	0-85	85-88	89-96	97-103	0-103	0-104
0	2/7	2/3	1/3	3/9	8/22	14/50
125	5/9	1/1	7/9	7/11	20/30	29/50
250	7/11	7/11	5/9	5/15	24/46	24/50

(a) No. of animals with leukemia/total no. dying during indicated interval

involved extensive bronchopulmonary infections and severe hemolytic anemia. The age at death due to spontaneous occurrence of leukemia in untreated animals varied from 14 to 30 months, with a mean age of 24.5 months. In the current studies, secondary infection was not a cause of death, probably because of the use of barrier-bred and barrier-maintained animals. Severe hemolytic anemia and immunosuppression are characteristic features of this disease (Stromberg et al., 1983, 1988).

In NTP untreated controls, the mean historical incidence of mononuclear cell leukemia in 25- to 26-month-old male F344/N rats (Table A4a) is approximately 33%. The term mononuclear cell leukemia as used in this report refers to a neoplastic disease of F344 rats which is characterized by infiltration of pleomorphic blastlike mononuclear cells in various organs, especially in the spleen, liver, and bone marrow. The leukemia appears to originate in the spleen, and this organ is often markedly enlarged; bone marrow infiltration occurs later and usually involves less than one-half the animals at risk (Stromberg and Vogtsberger, 1983). This disease has also been described as large granular lymphocyte leukemia (Losco and Ward, 1984; Stromberg, 1985).

Neoplasms of the anterior pituitary gland were increased in dosed female mice (see Table 19) and occurred at a marginally increased incidence in high dose female rats (see Table 13). In female mice, there was a significant positive trend, and the incidence in high dose female mice was significantly greater than that in vehicle controls. The incidence of adenomas of the anterior pituitary gland in vehicle control female mice was similar to the incidences in historical control female mice. There was no indication of compound-related hyperplasia of the pituitary gland in female rats or female mice. Conversely, the incidences of anterior pituitary gland neoplasms were decreased in dosed male rats (Table A3) and not notably changed in dosed male mice (Table C1). Hyperplasia of the pituitary gland was not compound related in male rats; however, the incidence of hyperplasia in the pituitary gland of high dose male mice was increased (vehicle control, 0/44; low dose, 1/42; high dose, 5/45).

According to Furth et al. (1976), pituitary gland tumors in rats can be induced by hormonal imbalance, ionizing radiation, or chemical carcinogens but are most effectively induced by a combination of hormonal imbalance and physical or chemical carcinogens. Liebelt (1979) indicated that pituitary gland tumors in mice may be induced by any exposure that produces thyroid deficiency because reduced circulating levels of triiodothyronine (T_3) and thyroxin (T_4) stimulate thyroid-stimulating hormone secreting cells, which may result in pituitary gland tissue becoming hyperplastic and ultimately neoplastic.

In the current studies, sections from the pituitary gland from three or four vehicle control and high dose female mice that exhibited either no remarkable lesions or hyperplasia or adenomas were selectively stained for thyroid-stimulating hormone (TSH) by an immunohistochemical procedure. The normal background of TSH-positive cells was seen in the normal tissue, but the foci of hyperplasia and the adenomas in general did not contain TSH-positive cells. Despite the absence of staining for TSH, it is unknown if the

pituitary cells in the foci of hyperplasia or adenoma were secreting TSH. Cells rapidly synthesizing and secreting the hormone may not store sufficient amounts to detect with the methods used. Also, in the absence of data on serum TSH levels, it is unknown if there was excessive secretion of TSH by the pituitary glands as a whole in dosed animals. Baker and Yu (1971) dosed female Sprague Dawley rats with propylthiouracil or exposed them to iodine-131 irradiation after thyroidectomy and observed an increase in proliferative lesions of the pituitary gland and an increase in TSH-positive thyrotropes in animals in a thyroid-deficient state.

In the current 2-year studies, follicular cell carcinomas of the thyroid gland occurred at a significantly increased incidence in low dose male rats by the incidental tumor test (see Table 12). The follicular cell carcinomas were late-appearing neoplasms; one was present in a low dose male dying at week 99, the others were present in animals killed at the end of the study. Thus, the reduced survival of high dose male rats may have been responsible for the lower incidence in this group relative to that in the low dose group. There was no evidence of a chemically related effect in the thyroid gland of female rats. Follicular cell carcinomas were observed in one low dose and one high dose female rat, well within the range of untreated historical controls. In mice, follicular cell hyperplasia of the thyroid gland was considerably increased (Tables C4 and D5) and occurred in 52%-92% of dosed animals. Follicular cell adenomas were observed in a few vehicle control and dosed mice (Tables C1 and D1).

There is abundant information associating the development of thyroid follicular cell neoplasms in experimental animals with perturbation of thyroid-pituitary homeostasis (Napalkov, 1976; Biancifiori, 1979; Hill et al., 1989). Chemicals that interfere with the synthesis of the thyroid hormones, T_4 or T_3, or increase the rate of their catabolism and removal from the circulation cause increases in the synthesis and secretion of TSH from the pituitary gland. In addition, excessive dietary iodide may result in proliferative lesions in the thyroid gland by inhibiting the proportional uptake of iodide by the follicular cells, thereby blocking iodide peroxidation to iodine and interfering with the release of T_4 and T_3 from the follicular cells (Nagataki, 1974; Capen, 1983; Stevens, 1985). A small group of thyroid carcinogens seem to produce their effect without altering the function of the pituitary gland and may be inducing follicular cell neoplasms through a genotoxic mechanism.

Whether any of these possible mechanisms were involved in the development of the thyroid neoplasms in male rats in the 2-year study of iodinated glycerol is unknown. Since 3-iodo-1,2-propanediol, the principal component of iodinated glycerol (33%), may undergo hydrolysis with the release of iodide, a role for iodide in the development of the thyroid lesions is possible. Measurements of circulating levels of T_3, T_4, or TSH were not performed. However, chemicals (goitrogens) which alter the circulating levels of these hormones typically cause diffuse follicular cell hyperplasia, which precedes the development of adenoma and carcinoma. The lack of follicular cell hyperplasia and adenoma in male rats does not support a role for TSH in the development of the follicular cell carcinomas. Further, the focal nature of the hyperplastic lesions in the thyroid gland of mice is not typical of the goitrogenic compounds. The limited data on the genetic toxicity of iodinated glycerol indicate that it is mutagenic in two strains of Salmonella and clastogenic in Chinese hamster ovary cells. Thus, a role for genotoxicity in the development of follicular cell carcinomas in male rats is possible.

The incidence of adenomas of the harderian gland was increased in high dose female mice. A carcinoma of the harderian gland was observed in one high dose female mouse. Harderian gland neoplasms may also be influenced by hormonal disturbances (Weisburger et al., 1984).

Several other lesions and clinical observations were seen in these 2-year studies. Squamous metaplasia and focal atrophy of the salivary glands were observed at increased incidences in dosed male and female rats. Similar lesions may be observed in rats with sialodacryoadenitis virus infections; however, serologic tests for this virus were negative in these studies. These lesions are probably due to iodide accumulation in the salivary gland, a site of increased concentration and excretion of iodide. Similarly, uncommon adenomas of the nasal cavity observed in

two high dose male rats may be due to a systemic effect. The sneezing or coughing observed in high dose male and female rats may have been due to a pharmacologic response or increased nasal secretions due to the excretion of metabolized iodide.

In the forestomach, hyperkeratosis and acanthosis were observed at an increased incidence in high dose male mice. No forestomach neoplasms were observed in male mice in the 2-year studies. Squamous cell papillomas were increased in female mice in a dose-related manner, whereas the nonneoplastic lesions, acanthosis and hyperkeratosis, were observed at incidences that decreased with dose. The marginal increase in these forestomach neoplasms may have resulted from long-term exposure to iodinated glycerol and/or its metabolites, including iodide. The spectrum of forestomach lesions observed in dosed male and female mice in 16-day, 13-week, and 2-year studies indicates that iodinated glycerol is cytotoxic and that there may be a difference between sexes in sensitivity to exposure. The biology of the forestomach neoplasms observed in female mice in this study is unknown.

In summary, other than mononuclear cell leukemia, the principal lesions in these 2-year studies of iodinated glycerol occurred in the pituitary gland, the thyroid gland, and possible sites of absorption, metabolism, and excretion of iodinated glycerol and/or its metabolites, including iodide. The homeostatic interrelationship between the hypothalamus (thyrotropic releasing factor) and the thyroid gland and associated regulatory control mechanisms for thyroid hormones, T_4 and T_3, the major regulators of metabolism, growth, and development, and homeostatic mechanisms, is complex. An insult to any part of this axis can result in a myriad of physiologic changes that may influence hyperplastic and neoplastic response. Comparison of hyperplastic and neoplastic responses of the pituitary and thyroid glands by organ site, species, and sex suggests a possible goitrogenic-like response in male and female mice after exposure to iodinated glycerol (Table 31). However, occurrence of carcinomas of the follicular cells of the thyroid gland in male rats in the absence of follicular cell hyperplasia suggests that this lesion is distinct from a proliferative response due to hormonal imbalance. The absence in both rats and mice of kidney lesions that were observed at the high doses in the 13-week studies suggests that the doses used in the 2-year studies were within the threshold for complete metabolism of active components, as suggested by the studies of Jones (1975), and below that causing nephrotoxicity. Nonneoplastic responses in iodide-accumulating and iodide-secreting tissues suggest that iodide toxicity may have occurred over the course of the studies.

TABLE 31. SUMMARY OF THE NUMBER OF F344/N RATS AND B6C3F$_1$ MICE WITH PITUITARY AND THYROID GLAND LESIONS IN THE TWO-YEAR GAVAGE STUDIES OF IODINATED GLYCEROL (a)

	Pituitary Gland		Thyroid Gland	
	Hyperplasia	Neoplasms	Follicular Cell Hyperplasia	Follicular Cell Neoplasms
Male rats (b)	6; 6; 5	26; 12; 7 (Ad or Ca)	0; 1; 2	0; 5; 1 (Ca)
Female rats (c)	2; 1; 1	26; 27; 34 (Ad or Ca)	0; 1; 1	0; 1; 1 (Ca)
Male mice (b)	0; 1; 5	0; 1; 1 (Ad)	3; 46; 34	3; 6; 0 (Ad)
Female mice (c)	21; 18; 19	10; 15; 24 (Ad)	2; 25; 35	2; 3; 4 (Ad)

(a) Ad = adenomas; Ca = carcinomas
(b) Doses: 0; 125 mg/kg; 250 mg/kg
(c) Doses: 0; 62 mg/kg; 125 mg/kg

IV. DISCUSSION AND CONCLUSIONS

The experimental and tabulated data for the NTP Technical Report on iodinated glycerol were examined for accuracy, consistency, completeness, and compliance with Good Laboratory Practice regulations. As summarized in Appendix G, 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 *some evidence of carcinogenic activity** for male F344/N rats administered iodinated glycerol, as indicated by increased incidences of mononuclear cell leukemia and follicular cell carcinomas of the thyroid gland. Adenomas of the nasal cavity in two high dose male rats may have been related to the administration of iodinated glycerol. There was *no evidence of carcinogenic activity* for female F344/N rats administered 62 or 125 mg/kg iodinated glycerol by gavage for 103 weeks. There was *no evidence of carcinogenic activity* for male B6C3F$_1$ mice administered 125 or 250 mg/kg iodinated glycerol by gavage for 103 weeks. There was *some evidence of carcinogenic activity* for female B6C3F$_1$ mice administered iodinated glycerol, as indicated by increased incidences of adenomas of the anterior pituitary gland and neoplasms of the harderian gland. Squamous cell papillomas of the forestomach may have been related to the administration of iodinated glycerol.

Significant nonneoplastic lesions considered related to exposure of iodinated glycerol were squamous metaplasia and focal atrophy of the salivary gland in male and female rats. Dilatation of the thyroid gland follicle and follicular cell hyperplasia were observed in male and female mice.

*Explanation of Levels of Evidence of Carcinogenic Activity is on page 7.
A summary of the Peer Review comments and the public discussion on this Technical Report appears on pages 11-12.

V. REFERENCES

V. REFERENCES

1. American Medical Association (AMA) (1977) AMA Department of Drugs, AMA Drug Evaluations, 3rd ed. Littleton, MA: PSG Publishing Co., p. 658.

2. Ames, B.N.; McCann, J.; Yamasaki, E. (1975) Methods for detecting carcinogens and mutagens with the Salmonella/mammalian-microsome mutagenicity test. Mutat. Res. 31:347-364.

3. Armitage, P. (1971) Statistical Methods in Medical Research. New York: John Wiley & Sons, Inc., pp. 362-365.

4. Baker, B.L.; Yu, Y.-Y. (1971) Hypophyseal changes induced by thyroid deficiency and thyroxine administration as revealed by immunochemical staining. Endocrinology 89:996-1004.

5. Barrigon, S.; Moreno, A.; Rebollo, D.; Garcia de Jalon, P.D. (1986) Parametros farmacocineticos del ^{125}I-yodopropilidenglicerol (IPG), en voluntarios sanos. Rev. Farmacol. Clin. Exp. 3:73-79.

6. Berenblum, I., Ed. (1969) Carcinogenicity Testing: A Report of the Panel on Carcinogenicity of the Cancer Research Commission of UICC, Vol. 2. Geneva: International Union Against Cancer.

7. Biancifiori, C. (1979) Tumours of the thyroid gland. Turosov, V.S., Ed.: Pathology of Tumours in Laboratory Animals. Vol. II. Tumours of the Mouse. IARC Scientific Publications No. 23, pp. 451-473.

8. Boorman, G.A.; Montgomery, C.A., Jr.; Eustis, S.L.; Wolfe, M.J.; McConnell, E.E.; Hardisty, J.F. (1985) Quality assurance in pathology for rodent carcinogenicity studies. Milman, H.; Weisburger, E., Eds.: Handbook of Carcinogen Testing. Park Ridge, NJ: Noyes Publications, pp. 345-357.

9. Canter, D.A.; Zeiger, E.; Haworth, S.; Lawlor, T.; Mortelmans, K.; Speck, W. (1986) Comparative mutagenicity of aliphatic epoxides in Salmonella. Mutat. Res. 172:105-138.

10. Capen, C.C. (1983) Chemical injury of thyroid: Pathologic and mechanistic considerations. Toxicology Forum: 1983 Annual Winter Meeting. Washington, DC: Bowers Reporting Co., pp. 260-273.

11. Clive, D.; Johnson, K.O.; Spector, J.F.S.; Batson, A.G.; Brown, M.M.M. (1979) Validation and characterization of the L5178Y/TK$^{+/-}$ mouse lymphoma mutagen assay system. Mutat. Res. 59:61-108.

12. Cox, D.R. (1972) Regression models and life tables. J. R. Stat. Soc. B34:187-220.

13. Davey, F.R.; Moloney, W.C. (1970) Postmortem observations on Fischer rats with leukemia and other disorders. Lab. Invest. 23:327-334.

14. Epstein, S.S.; Arnold, E.; Andrea, J.; Bass, W.; Bishop, Y. (1972) Detection of chemical mutagens by the dominant lethal assay in the mouse. Toxicol. Appl. Pharmacol. 23:288-325.

15. Furth, J.; Nakane, P.; Pasteels, J.L. (1976) Tumours of the pituitary gland. Turosov, V.S., Ed.: Pathology of Tumours in Laboratory Animals. Vol. I. Tumours of the Rat. IARC Scientific Publications No. 6, pp. 201-227.

16. Galloway, S.M.; Bloom, A.D.; Resnick, M.; Margolin, B.H.; Nakamura, F.; Archer, P.; Zeiger, E. (1985) Development of a standard protocol for in vitro cytogenetic testing with Chinese hamster ovary cells: Comparison of results for 22 compounds in two laboratories. Environ. Mutagen. 7:1-51.

17. Galloway, S.M.; Armstrong, M.J.; Reuben, C.; Colman, S.; Brown, B.; Cannon, C.; Bloom, A.D.; Nakamura, F.; Ahmed, M.; Duk, S.; Rimpo, J.; Margolin, B.H.; Resnick, M.A.; Anderson, B.; Zeiger, E. (1987) Chromosome aberrations and sister chromatid exchanges in Chinese hamster ovary cells: Evaluations of 108 chemicals. Environ. Molec. Mutagen. 10(Suppl. 10):1-175.

18. Gart, J.J.; Chu, K.C.; Tarone, R.E. (1979) Statistical issues in interpretation of chronic bioassay tests for carcinogenicity. J. Natl. Cancer Inst. 62:957-974.

19. Haseman, J.K. (1984) Statistical issues in the design, analysis and interpretation of animal carcinogenicity studies. Environ. Health Perspect. 58:385-392.

20. Haseman, J.K.; Huff, J.; Boorman, G.A. (1984) Use of historical control data in carcinogenicity studies in rodents. Toxicol. Pathol. 12: 126-135.

21. Haseman, J.K.; Huff, J.; Rao, G.N.; Arnold, J.; Boorman, G.A.; McConnell, E.E. (1985) Neoplasms observed in untreated and corn oil gavage control groups of F344/N rats and (C57BL/6N × C3H/HeN)F_1 (B6C3F_1) mice. J. Natl. Cancer Inst. 75:975-984.

22. Hill, R.N.; Erdreich, L.S.; Paynter, O.E.; Roberts, P.A.; Rosenthal, S.L.; Wilkinson, C.F. (1989) Thyroid follicular cell carcinogenesis. Fundam. Appl. Toxicol. 12:629-697.

23. Hoffnagle, G.P.; Osol, A. (1958) The distribution and fate of iodine in iodopropylidene-glycerol in the rat. J. Am. Pharm. Assoc. 47:149-153.

24. Holbreich, M. (1982) Asthma and other allergic disorders in pregnancy. Am. Fam. Physician 25:187-192.

25. International Agency for Research on Cancer (IARC) (1986) Methyl iodide. IARC Monographs on Evalution of the Carcinogenic Risk of Chemicals to Man: Some Halogenated Hydrocarbons and Pesticide Exposures, Vol. 41. Lyon: IARC, pp. 213-227.

26. Jones, A.R. (1975) The metabolism of 3-chloro-, 3-bromo- and 3-iodopropan-1,2-diol in rats and mice. Xenobiotica 5:155-165.

27. Kaplan, E.L.; Meier, P. (1958) Nonparametric estimation from incomplete observations. J. Am. Stat. Assoc. 53:457-481.

28. Liebelt, A.G. (1979) Tumours of the pituitary gland. Turosov, V.S., Ed.: Pathology of Tumours in Laboratory Animals. Vol. II. Tumours of the Mouse. IARC Scientific Publications No. 23, pp. 411-449.

29. Linhart, M.S.; Cooper, J.; Martin, R.L.; Page, N.; Peters, J. (1974) Carcinogenesis Bioassay Data System. Comput. Biomed. Res. 7:230-248.

30. Losco, P.E.; Ward, J.M. (1984) The early stages of large granular lymphocyte leukemia in the F344 rat. Vet. Pathol. 21:286-291.

31. Mantel, N.; Haenszel, W. (1959) Statistical aspects of the analysis of data from retrospective studies of disease. J. Natl. Cancer Inst. 22:719-748.

32. Maronpot, R.R.; Boorman, G.A. (1982) Interpretation of rodent hepatocellular proliferative alterations and hepatocellular tumors in chemical safety assessment. Toxicol. Pathol. 10:71-80.

33. McConnell, E.E. (1983a) Pathology requirements for rodent two-year studies. I. A review of current procedures. Toxicol. Pathol. 11:60-64.

34. McConnell, E.E. (1983b) Pathology requirements for rodent two-year studies. II. Alternative approaches. Toxicol. Pathol. 11:65-76.

35. McConnell, E.E.; Solleveld, H.A.; Swenberg, J.A.; Boorman, G.A. (1986) Guidelines for combining neoplasms for evaluation of rodent carcinogenesis studies. J. Natl. Cancer Inst. 76:283-289.

36. McLaren, E.H.; Alexander, W.D. (1979) Goitrogens. Clin. Endocrinol. Metab. 8:129-144.

37. The Merck Index (1976) 9th ed. Rahway, NJ: Merck & Co., Inc., p. 661.

38. The Merck Index (1983) 10th ed. Rahway, NJ: Merck & Co., Inc., p. 726.

39. Myhr, B.; Bowers, L.; Caspary, W.J. (1985) Assays for the induction of gene mutations at the thymidine kinase locus in L5178Y mouse lymphoma cells in culture. Prog. Mutat. Res. 5: 555-568.

40. Nagataki, S. (1974) Effects of excess quantities of iodide. Greep, R.O.; Astwood, E.B.; Greer, M.A.; Solomon, D.H.; Geiger, S.R., Eds.: Handbook of Physiology, Vol. 3. Washington, DC: American Physiological Society, pp. 329-344.

V. REFERENCES

41. Napalkov, N.P. (1976) Tumours of the thyroid gland. Turosov, V.S., Ed.: Pathology of Tumours in Laboratory Animals. Vol. I. Tumours of the Rat. IARC Scientific Publications No. 6, pp. 239-261.

42. National Cancer Institute (NCI) (1976) Guidelines for Carcinogen Bioassay in Small Rodents. NCI Technical Report No. 1. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, Bethesda, MD. 65 p.

43. National Institutes of Health (NIH) (1978) Open Formula Rat and Mouse Ration (NIH-07). Specification NIH-11-1335. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, Bethesda, MD.

44. National Toxicology Program (NTP) (1990) Toxicology and Carcinogenesis Studies of Glycidol in F344/N Rats and B6C3F_1 Mice. NTP Technical Report No. 374. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Bethesda, Md. 229 p.

45. Seltzer, A. (1961) Mucolytic expectorant therapy with an iodinated "glyceril" ether. Ann. Allergy 19:381-385.

46. Stanford Research Institute (SRI) (1978) Data Base on Category E Drug Exposure. NCI Contract No. NO1-CP-33285. Menlo Park, CA.

47. Stevens, J.T. (1985) Effect of chemicals on the thyroid gland. Thomas, J.A.; Korach, K.S.; McLachlan, J.A., Eds.: Endocrine Toxicology. New York: Raven Press, pp. 135-147.

48. Stromberg, P.C. (1985) Large granular lymphocyte leukemia in F344 rats: Model for human Tg lymphoma, malignant histiocytosis, and T-cell chronic lymphocytic leukemia. Am. J. Pathol. 119:517-519.

49. Stromberg, P.C.; Vogtsberger, L.M. (1983) Pathology of the mononuclear cell leukemia of Fischer rats. I. Morphologic studies. Vet. Pathol. 20:698-708.

50. Stromberg, P.C.; Vogtsberger, L.M.; Marsh, L.R.; Wilson, F.D. (1983) Pathology of the mononuclear cell leukemia of Fischer rats. II. Hematology. Vet. Pathol. 20:709-717.

51. Stromberg, P.C.; McMurray, D.N.; Brown, C.A. (1988) Inhibition of in vitro mitogen induced lymphoproliferative responses by sera from F344 rats with large granular lymphocyte leukemia. J. Clin. Lab. Immunol. 25:89-95.

52. Tarone, R.E. (1975) Tests for trend in life table analysis. Biometrika 62:679-682.

53. Weisburger, E.K.; Murthy, A.S.K.; Lilja, H.S.; Lamb, J.C., IV (1984) Neoplastic response of F344 rats and B6C3F_1 mice to the polymer and dyestuff intermediates 4,4'-methylenebis (*N*,*N*-dimethyl)benzenamine, 4,4'-oxydianiline, and 4,4'-methylenedianiline. J. Natl. Cancer Inst. 72:1457-1463.

54. Zeiger, E.; Anderson, B.; Haworth, S.; Lawlor, T.; Mortelmans, K.; Speck, W. (1987) *Salmonella* mutagenicity tests: III. Results from the testing of 255 chemicals. Environ. Mutagen. 9(Suppl. 9):1-110.

APPENDIX A

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

		PAGE
TABLE A1	SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF IODINATED GLYCEROL	75
TABLE A2	INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF IODINATED GLYCEROL	78
TABLE A3	ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF IODINATED GLYCEROL	84
TABLE A4a	HISTORICAL INCIDENCE OF LEUKEMIA IN CONTROL MALE F344/N RATS	88
TABLE A4b	HISTORICAL INCIDENCE OF THYROID GLAND FOLLICULAR CELL TUMORS IN CONTROL MALE F344/N RATS	89
TABLE A4c	HISTORICAL INCIDENCE OF NASAL CAVITY TUMORS IN CONTROL MALE F344/N RATS	89
TABLE A4d	HISTORICAL INCIDENCE OF TESTICULAR INTERSTITIAL CELL TUMORS IN CONTROL MALE F344/N RATS	90
TABLE A5	SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF IODINATED GLYCEROL	91

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

	Vehicle Control	Low Dose	High Dose
Animals initially in study	50	50	50
Animals necropsied	50	50	50
Animals examined histopathologically	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Squamous cell papilloma	2 (4%)		
Squamous cell carcinoma			1 (2%)
Basal cell tumor	1 (2%)	1 (2%)	
Basal cell carcinoma		1 (2%)	
Trichoepithelioma		1 (2%)	
Keratoacanthoma	3 (6%)	2 (4%)	2 (4%)
*Subcutaneous tissue	(50)	(50)	(50)
Fibroma	1 (2%)	2 (4%)	1 (2%)
Fibrosarcoma		1 (2%)	
Neurofibrosarcoma	1 (2%)		
RESPIRATORY SYSTEM			
#Nasal cavity	(48)	(47)	(49)
Adenoma, NOS			2 (4%)
#Lung	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	1 (2%)	2 (4%)	
Alveolar/bronchiolar carcinoma			1 (2%)
Pheochromocytoma, metastatic	1 (2%)		
Chordoma, metastatic	1 (2%)		
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Leukemia, mononuclear cell	14 (28%)	29 (58%)	24 (48%)
CIRCULATORY SYSTEM			
#Spleen	(50)	(50)	(50)
Hemangiosarcoma		2 (4%)	
DIGESTIVE SYSTEM			
#Liver	(50)	(50)	(50)
Neoplastic nodule		2 (4%)	2 (4%)
#Pancreas	(49)	(49)	(49)
Acinar cell adenoma			1 (2%)
Acinar cell carcinoma		1 (2%)	
URINARY SYSTEM			
#Kidney	(50)	(50)	(50)
Tubular cell adenoma			1 (2%)
Lipoma	1 (2%)		
#Urinary bladder	(49)	(49)	(48)
Mesothelioma, invasive			1 (2%)

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

	Vehicle Control	Low Dose	High Dose
ENDOCRINE SYSTEM			
#Anterior pituitary	(48)	(47)	(46)
Carcinoma, NOS	1 (2%)	2 (4%)	
Adenoma, NOS	25 (52%)	10 (21%)	7 (15%)
#Adrenal cortex	(50)	(50)	(49)
Adenoma, NOS			1 (2%)
#Adrenal medulla	(50)	(50)	(49)
Pheochromocytoma	23 (46%)	19 (38%)	10 (20%)
Pheochromocytoma, malignant	5 (10%)	1 (2%)	
#Thyroid	(49)	(49)	(49)
Follicular cell carcinoma		5 (10%)	1 (2%)
C-cell adenoma	3 (6%)	2 (4%)	2 (4%)
C-cell carcinoma	4 (8%)	1 (2%)	
#Pancreatic islets	(49)	(49)	(49)
Islet cell adenoma	3 (6%)		
Islet cell carcinoma	2 (4%)	1 (2%)	
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Fibroadenoma	3 (6%)	2 (4%)	3 (6%)
*Preputial gland	(50)	(50)	(50)
Carcinoma, NOS	3 (6%)	1 (2%)	3 (6%)
Adenoma, NOS	1 (2%)	1 (2%)	
#Testis	(50)	(50)	(50)
Interstitial cell tumor	46 (92%)	49 (98%)	48 (96%)
*Scrotum	(50)	(50)	(50)
Sarcoma, NOS		1 (2%)	
NERVOUS SYSTEM			
#Cerebrum	(50)	(50)	(50)
Oligodendroglioma			1 (2%)
#Brain	(50)	(50)	(50)
Glioma, NOS	1 (2%)		
SPECIAL SENSE ORGANS			
*External ear	(50)	(50)	(50)
Squamous cell papilloma		1 (2%)	
Fibroma		1 (2%)	
*Zymbal gland	(50)	(50)	(50)
Carcinoma, NOS	1 (2%)		2 (4%)
MUSCULOSKELETAL SYSTEM			
*Vertebral column	(50)	(50)	(50)
Chordoma	1 (2%)		
BODY CAVITIES			
None			
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
C-cell carcinoma, metastatic		1 (2%)	
Histiocytic sarcoma	1 (2%)		
Mesothelioma, NOS	1 (2%)	1 (2%)	1 (2%)
Mesothelioma, malignant		1 (2%)	1 (2%)

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

	Vehicle Control	Low Dose	High Dose
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	6	14	10
Moribund sacrifice	17	16	38
Terminal sacrifice	27	20	2
TUMOR SUMMARY			
Total animals with primary tumors**	50	49	49
Total primary tumors	148	143	115
Total animals with benign tumors	50	49	48
Total benign tumors	113	93	78
Total animals with malignant tumors	29	37	29
Total malignant tumors	34	47	34
Total animals with secondary tumors##	2	1	1
Total secondary tumors	2	1	1
Total animals with tumors-- uncertain benign or malignant	1	3	3
Total uncertain tumors	1	3	3

* Number of animals receiving complete necropsy examinations; 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 IODINATED GLYCEROL: VEHICLE CONTROL

ANIMAL NUMBER	022	032	010	050	024	030	014	025	033	041	016	017	029	007	043	001	013	031	036	038	039	042	002	003	005
WEEKS ON STUDY	062	071	075	078	080	082	083	088	088	088	091	092	094	099	099	100	101	101	102	102	102	102	104	104	104
INTEGUMENTARY SYSTEM																									
Skin	+	N	+	+	+	+	+	+	+	N	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma															X										
Basal cell tumor																									
Keratoacanthoma																									
Subcutaneous tissue	+	N	+	+	+	+	+	+	+	N	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																						X			
Neurofibrosarcoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Pheochromocytoma, metastatic																									
Chordoma, metastatic						X																			
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	−	+	−	+	+	+	−	−	+	+	+	−	−	−	+	−	+	+	−	−	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+
Esophagus	+	+	+	+	+	−	−	−	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lipoma						X																			
Urinary bladder	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	−	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+
Carcinoma, NOS																						X			
Adenoma, NOS			X		X	X		X	X	X							X	X					X		X	X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma			X	X	X								X				X		X	X	X	X	X	X	
Pheochromocytoma, malignant														X											
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell adenoma								X																	X
C-cell carcinoma																								X	
Parathyroid	−	−	+	−	+	−	−	−	+	−	+	+	+	+	−	−	−	−	−	+	−	+	−	+	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+
Islet cell adenoma												X											X		
Islet cell carcinoma								X								X									
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	+	+	N	N	N	N	+	+	N	+	N	N	+	N	N	+	N	N	N	N	+
Fibroadenoma					X												X								
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor	X	X	X	X	X	X	X		X	X	X	X	X	X	X		X	X	X	X			X	X	X
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS															X										
Adenoma, NOS																					X				
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Glioma, NOS											X														
SPECIAL SENSE ORGANS																									
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS												X													
MUSCULOSKELETAL SYSTEM																									
Bone	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Chordoma						X																			
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Histiocytic sarcoma				X																					
Mesothelioma, NOS							X																		
Leukemia, mononuclear cell	X		X					X	X			X		X			X		X						

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

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

ANIMAL NUMBER	00006	00008	00009	00012	00015	00018	00020	00023	00026	00027	00028	00034	00035	00037	00044	00045	00046	00047	00048	00049	00004	00011	00019	00021	00040	TOTAL:
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	105	105	105	105	105	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	N	+	+	N	+	+	+	+	+	+	+	+	N	+	+	+	+	*50
Squamous cell papilloma																						X				2
Basal cell tumor								X																		1
Keratoacanthoma			X							X															X	3
Subcutaneous tissue	+	+	+	+	+	+	+	+	N	+	+	N	+	+	+	+	+	+	+	+	N	+	+	+	+	*50
Fibroma																										1
Neurofibrosarcoma						X																				1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																								X		1
Pheochromocytoma, metastatic																				X						1
Chordoma, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	49
Nasal cavity	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	−	−	+	+	+	+	+	+	+	+	+	+	−	−	+	−	+	+	−	+	+	−	+	+	33
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	−	+	+	+	44
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	49
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lipoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	48
Carcinoma, NOS																										1
Adenoma, NOS	X			X		X	X	X		X				X	X	X			X		X	X	X	X		25
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma	X		X	X		X	X	X		X					X			X			X	X			X	23
Pheochromocytoma, malignant													X	X			X			X						5
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	49
C-cell adenoma																									X	3
C-cell carcinoma												X				X						X				4
Parathyroid	+	−	−	−	+	+	−	−	+	−	−	−	−	−	−	+	−	−	−	+	−	−	+	−	+	19
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islet cell adenoma	X																									3
Islet cell carcinoma																										2
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	N	+	+	+	N	+	N	N	N	+	+	N	N	+	N	N	N	N	N	N	N	+	N	*50
Fibroadenoma												X														3
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell tumor	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	46
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS																					X		X			3
Adenoma, NOS																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Glioma, NOS																										1
SPECIAL SENSE ORGANS																										
Zymbal gland	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS																										1
MUSCULOSKELETAL SYSTEM																										
Bone	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Chordoma																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Histiocytic sarcoma																										1
Mesothelioma, NOS																										1
Leukemia, mononuclear cell						X	X										X	X	X					X		14

* Animals necropsied

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF IODINATED GLYCEROL: LOW DOSE

ANIMAL NUMBER	0015	0037	0039	0006	0034	0020	0032	0003	0017	0030	0005	0013	0002	0019	0048	0038	0040	0050	0036	0008	0009	0021	0022	0025	0026
WEEKS ON STUDY	0444	0449	0555	0722	0778	0881	0881	0883	0863	0886	0900	0900	0902	0922	0922	0944	0944	0944	0966	0977	0977	0999	0999	0999	0999
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+
Basal cell tumor																									
Basal cell carcinoma																									
Trichoepithelioma																									
Keratoacanthoma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+
Fibroma																		X							
Fibrosarcoma		X																							
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																X									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nasal cavity	−	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									X
Lymph nodes	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	−	−	−	−	−	−	+	−	+	−	+	+	+	+	+	+	+	+	+	−	−	+	−	−
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinar cell carcinoma																									
Esophagus	+	+	+	+	+	−	+	+	+	−	−	+	+	+	+	+	+	+	+	−	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	−	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+
Carcinoma, NOS																							X		
Adenoma, NOS						X								X											X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma					X	X								X	X			X	X				X	X	
Pheochromocytoma, malignant																									
Thyroid	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell carcinoma																									
C-cell adenoma											X														
C-cell carcinoma																									
Parathyroid	−	−	+	−	−	−	+	−	+	+	+	−	+	−	−	+	−	−	−	+	+	+	−	−	−
Pancreatic islets	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell carcinoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	N	+	+	N	N	N	+	N	+	N	+	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	N
Carcinoma, NOS																									
Adenoma, NOS																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Ear	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell papilloma																									
Fibroma							X																		
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
C-cell carcinoma, metastatic																									
Mesothelioma, NOS									X																
Mesothelioma, malignant																									
Leukemia, mononuclear cell			X	X			X	X	X	X	X	X	X	X			X	X	X	X	X	X		X	X
Scrotum, NOS																									
Sarcoma, NOS					X																				

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: LOW DOSE (Continued)

ANIMAL NUMBER	031	035	041	016	046	001	004	007	010	011	012	014	018	023	024	027	028	029	033	042	043	044	045	047	049	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	099	101	101	103	103	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	*50
Basal cell tumor	X																									1
Basal cell carcinoma				X																						1
Trichoepithelioma									X																	1
Keratoacanthoma						X							X													2
Subcutaneous tissue	+	●	+	+	+	●	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	*50
Fibroma																					X					2
Fibrosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma															X											2
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																						X				2
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	−	+	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+	34
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule																X					X					2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Acinar cell carcinoma																									X	1
Esophagus	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Stomach	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	47
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Carcinoma, NOS																				X						2
Adenoma, NOS								X			X		X	X	X				X						X	10
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma	X			X			X		X	X		X		X				X		X	X			X		19
Pheochromocytoma, malignant			X																							1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell carcinoma	X						X			X	X							X								5
C-cell adenoma																			X							2
C-cell carcinoma				X																						1
Parathyroid	+	+	+	+	+	+	+	+	+	+	+	−	−	−	+	−	−	−	−	+	+	+	+	+	−	27
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islet cell carcinoma																				X						1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	N	N	+	+	N	+	+	+	N	N	N	N	+	+	+	N	+	N	N	+	N	+	+	N	*50
Fibroadenoma																								X		2
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell tumor	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	49
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS				X																						1
Adenoma, NOS																				X						1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Ear	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	*50
Squamous cell papilloma																					X					1
Fibroma																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
C-cell carcinoma, metastatic				X																						1
Mesothelioma, NOS																										1
Mesothelioma, malignant														X												1
Leukemia, mononuclear cell	X		X					X		X	X			X		X	X		X				X		X	29
Scrotum, NOS																										
Sarcoma, NOS																										1

* Animals necropsied

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF IODINATED GLYCEROL: HIGH DOSE

ANIMAL NUMBER	00 06	01 14	04 11	01 17	02 22	01 16	02 24	02 28	01 18	01 10	05 50	00 07	04 44	04 46	02 26	03 36	04 45	04 49	03 34	04 43	01 11	03 39	02 27	00 04	02 25
WEEKS ON STUDY	01 11	06 64	07 71	07 75	07 75	07 78	08 81	08 81	08 82	08 83	08 84	08 85	08 85	08 85	08 86	08 86	08 86	08 86	08 87	08 87	08 88	08 88	08 89	09 94	09 94
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma											X														
Keratoacanthoma									X			X													
Subcutaneous tissue	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nasal cavity	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	−	+	+	−	−	+	+	−	+	+	+	+	+	+	+	+	+	+	−	+	−	−	+	
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinar cell adenoma																									
Esophagus	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+	−
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenoma																									
Urinary bladder	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma, invasive												X													
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	−	−	+
Adenoma, NOS									X					X											
Adrenal	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Pheochromocytoma				X		X					X														X
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell carcinoma																									
C-cell adenoma																									
Parathyroid	+	+	−	+	−	−	−	−	+	−	−	−	−	−	+	+	+	−	+	+	+	+	−	+	−
REPRODUCTIVE SYSTEM																									
Mammary gland	N	+	N	+	N	N	N	N	N	N	+	+	+	+	N	N	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
Prostate	+	+	+	+	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Oligodendroglioma																									
SPECIAL SENSE ORGANS																									
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N
Carcinoma, NOS																				X					
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Mesothelioma, NOS								X																	
Mesothelioma, malignant												X													
Leukemia, mononuclear cell		X	X		X	X			X	X	X			X	X		X	X	X		X	X	X	X	X

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: HIGH DOSE (Continued)

ANIMAL NUMBER	0029	0037	0012	0023	0021	0042	0009	0001	0002	0003	0005	0015	0020	0031	0032	0035	0033	0040	0048	0008	0038	0113	0119	0030	0047	TOTAL:
WEEKS ON STUDY	094	094	095	095	096	096	098	099	099	099	099	099	099	099	099	099	100	100	101	102	102	104	104	105	105	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	*50
Squamous cell carcinoma																										1
Keratoacanthoma																										2
Subcutaneous tissue	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	*50
Fibroma									X																	1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma																	X									1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, NOS			X																					X		2
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	−	−	+	+	−	+	−	+	+	+	+	+	−	+	+	−	+	+	−	+	+	+	+	+	+	36
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule										X	X															2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Acinar cell adenoma														X												1
Esophagus	+	+	+	−	+	+	+	+	+	+	+	+	+	−	−	−	−	+	+	−	+	−	−	−	+	36
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tubular cell adenoma																									X	1
Urinary bladder	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Mesothelioma, invasive																										1
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Adenoma, NOS	X	X									X									X		X				7
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, NOS								X																		1
Pheochromocytoma					X		X					X				X		X					X			10
Thyroid	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell carcinoma																								X		1
C-cell adenoma																						X			X	2
Parathyroid	−	+	−	+	−	+	+	+	+	−	−	−	+	+	+	−	−	−	−	−	+	+	−	+	+	25
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	+	N	+	N	N	+	N	N	N	+	+	N	N	N	N	+	N	N	+	N	N	N	+	*50
Fibroadenoma												X									X					3
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell tumor	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	48
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS		X		X														X								3
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Oligodendroglioma											X															1
SPECIAL SENSE ORGANS																										
Zymbal gland	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS								X																		2
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Mesothelioma, NOS																										1
Mesothelioma, malignant																										1
Leukemia, mononuclear cell		X		X				X				X				X		X			X					24

* Animals necropsied

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

	Vehicle Control	125 mg/kg	250 mg/kg
Skin: Keratoacanthoma			
Overall Rates (a)	3/50 (6%)	2/50 (4%)	2/50 (4%)
Adjusted Rates (b)	10.7%	10.0%	4.9%
Terminal Rates (c)	3/28 (11%)	2/20 (10%)	0/4 (0%)
Week of First Observation	104	104	82
Life Table Tests (d)	P=0.314	P=0.654N	P=0.426
Incidental Tumor Tests (d)	P=0.434	P=0.654N	P=0.609
Cochran-Armitage Trend Test (d)	P=0.406N		
Fisher Exact Test (d)		P=0.500N	P=0.500N
Skin: Trichoepithelioma, Basal Cell Tumor, or Basal Cell Carcinoma			
Overall Rates (a)	1/50 (2%)	3/50 (6%)	0/50 (0%)
Adjusted Rates (b)	3.6%	12.4%	0.0%
Terminal Rates (c)	1/28 (4%)	1/20 (5%)	0/4 (0%)
Week of First Observation	104	99	
Life Table Tests (d)	P=0.472	P=0.212	P=0.872N
Incidental Tumor Tests (d)	P=0.467N	P=0.315	P=0.872N
Cochran-Armitage Trend Test (d)	P=0.378N		
Fisher Exact Test (d)		P=0.309	P=0.500N
Subcutaneous Tissue: Fibroma or Fibrosarcoma			
Overall Rates (a)	1/50 (2%)	3/50 (6%)	1/50 (2%)
Adjusted Rates (b)	3.1%	9.6%	5.6%
Terminal Rates (c)	0/28 (0%)	1/20 (5%)	0/4 (0%)
Week of First Observation	102	49	99
Life Table Tests (d)	P=0.328	P=0.240	P=0.490
Incidental Tumor Tests (d)	P=0.453N	P=0.555	P=0.566N
Cochran-Armitage Trend Test (d)	P=0.610		
Fisher Exact Test (d)		P=0.309	P=0.753
Subcutaneous Tissue: Fibroma, Fibrosarcoma, or Neurofibrosarcoma			
Overall Rates (a)	2/50 (4%)	3/50 (6%)	1/50 (2%)
Adjusted Rates (b)	6.6%	9.6%	5.6%
Terminal Rates (c)	1/28 (4%)	1/20 (5%)	0/4 (0%)
Week of First Observation	102	49	99
Life Table Tests (d)	P=0.455	P=0.398	P=0.564
Incidental Tumor Tests (d)	P=0.332N	P=0.685N	P=0.490N
Cochran-Armitage Trend Test (d)	P=0.399N		
Fisher Exact Test (d)		P=0.500	P=0.500N
Hematopoietic System: Mononuclear Cell Leukemia			
Overall Rates (a)	14/50 (28%)	29/50 (58%)	24/50 (48%)
Adjusted Rates (b)	35.9%	69.5%	65.2%
Terminal Rates (c)	6/28 (21%)	9/20 (45%)	0/4 (0%)
Week of First Observation	62	55	64
Life Table Tests (d)	P<0.001	P=0.001	P<0.001
Incidental Tumor Tests (d)	P=0.174	P=0.003	P=0.226
Cochran-Armitage Trend Test (d)	P=0.028		
Fisher Exact Test (d)		P=0.002	P=0.032
Anterior Pituitary Gland: Adenoma			
Overall Rates (a)	25/48 (52%)	10/47 (21%)	7/46 (15%)
Adjusted Rates (b)	67.6%	40.3%	48.4%
Terminal Rates (c)	16/27 (59%)	7/20 (35%)	1/4 (25%)
Week of First Observation	75	81	82
Life Table Tests (d)	P=0.178N	P=0.022N	P=0.471N
Incidental Tumor Tests (d)	P=0.002N	P=0.004N	P=0.006N
Cochran-Armitage Trend Test (d)	P<0.001N		
Fisher Exact Test (d)		P=0.002N	P<0.001N

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

	Vehicle Control	125 mg/kg	250 mg/kg
Anterior Pituitary Gland: Adenoma or Carcinoma			
Overall Rates (a)	26/48 (54%)	12/47 (26%)	7/46 (15%)
Adjusted Rates (b)	68.7%	46.8%	48.4%
Terminal Rates (c)	16/27 (59%)	8/20 (40%)	1/4 (25%)
Week of First Observation	75	81	82
Life Table Tests (d)	P=0.193N	P=0.050N	P=0.441N
Incidental Tumor Tests (d)	P=0.001N	P=0.008N	P=0.002N
Cochran-Armitage Trend Test (d)	P<0.001N		
Fisher Exact Test (d)		P=0.004N	P<0.001N
Adrenal Gland: Pheochromocytoma			
Overall Rates (a)	23/50 (46%)	19/50 (38%)	10/49 (20%)
Adjusted Rates (b)	59.7%	59.8%	52.0%
Terminal Rates (c)	13/28 (46%)	9/20 (45%)	1/4 (25%)
Week of First Observation	75	78	75
Life Table Tests (d)	P=0.277	P=0.468	P=0.257
Incidental Tumor Tests (d)	P=0.023N	P=0.343N	P=0.026N
Cochran-Armitage Trend Test (d)	P=0.005N		
Fisher Exact Test (d)		P=0.272N	P=0.006N
Adrenal Gland: *Malignant Pheochromocytoma*			
Overall Rates (a)	5/50 (10%)	1/50 (2%)	0/49 (0%)
Adjusted Rates (b)	16.6%	4.2%	0.0%
Terminal Rates (c)	4/28 (14%)	0/20 (0%)	0/4 (0%)
Week of First Observation	99	101	
Life Table Tests (d)	P=0.105N	P=0.194N	P=0.338N
Incidental Tumor Tests (d)	P=0.026N	P=0.121N	P=0.185N
Cochran-Armitage Trend Test (d)	P=0.011N		
Fisher Exact Test (d)		P=0.103N	P=0.030N
Adrenal Gland: Pheochromocytoma or Malignant Pheochromocytoma			
Overall Rates (a)	28/50 (56%)	20/50 (40%)	10/49 (20%)
Adjusted Rates (b)	71.2%	61.5%	52.0%
Terminal Rates (c)	17/28 (61%)	9/20 (45%)	1/4 (25%)
Week of First Observation	75	78	75
Life Table Tests (d)	P=0.479	P=0.459N	P=0.396
Incidental Tumor Tests (d)	P=0.002N	P=0.118N	P=0.005N
Cochran-Armitage Trend Test (d)	P<0.001N		
Fisher Exact Test (d)		P=0.081N	P<0.001N
Thyroid Gland: Follicular Cell Carcinoma			
Overall Rates (a)	0/49 (0%)	5/49 (10%)	1/49 (2%)
Adjusted Rates (b)	0.0%	22.8%	25.0%
Terminal Rates (c)	0/27 (0%)	4/20 (20%)	1/4 (25%)
Week of First Observation		99	104
Life Table Tests (d)	P=0.029	P=0.014	P=0.134
Incidental Tumor Tests (d)	P=0.056	P=0.020	P=0.134
Cochran-Armitage Trend Test (d)	P=0.399		
Fisher Exact Test (d)		P=0.028	P=0.500
Thyroid Gland: C-Cell Adenoma			
Overall Rates (a)	3/49 (6%)	2/49 (4%)	2/49 (4%)
Adjusted Rates (b)	9.6%	7.4%	50.0%
Terminal Rates (c)	2/27 (7%)	1/20 (5%)	2/4 (50%)
Week of First Observation	88	90	104
Life Table Tests (d)	P=0.287	P=0.587N	P=0.238
Incidental Tumor Tests (d)	P=0.446	P=0.541N	P=0.350
Cochran-Armitage Trend Test (d)	P=0.406N		
Fisher Exact Test (d)		P=0.500N	P=0.500N

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

	Vehicle Control	125 mg/kg	250 mg/kg
Thyroid Gland: C-Cell Carcinoma			
Overall Rates (a)	4/49 (8%)	1/49 (2%)	0/49 (0%)
Adjusted Rates (b)	14.8%	4.5%	0.0%
Terminal Rates (c)	4/27 (15%)	0/20 (0%)	0/4 (0%)
Week of First Observation	104	103	
Life Table Tests (d)	P=0.183N	P=0.276N	P=0.490N
Incidental Tumor Tests (d)	P=0.091N	P=0.228N	P=0.490N
Cochran-Armitage Trend Test (d)	P=0.026N		
Fisher Exact Test (d)		P=0.181N	P=0.059N
Thyroid Gland: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	7/49 (14%)	3/49 (6%)	2/49 (4%)
Adjusted Rates (b)	24.0%	11.6%	50.0%
Terminal Rates (c)	6/27 (22%)	1/20 (5%)	2/4 (50%)
Week of First Observation	88	90	104
Life Table Tests (d)	P=0.544N	P=0.273N	P=0.477
Incidental Tumor Tests (d)	P=0.293N	P=0.211N	P=0.588
Cochran-Armitage Trend Test (d)	P=0.048N		
Fisher Exact Test (d)		P=0.159N	P=0.080N
Pancreatic Islets: Islet Cell Adenoma			
Overall Rates (a)	3/49 (6%)	0/49 (0%)	0/49 (0%)
Adjusted Rates (b)	9.5%	0.0%	0.0%
Terminal Rates (c)	2/28 (7%)	0/20 (0%)	0/4 (0%)
Week of First Observation	92		
Life Table Tests (d)	P=0.109N	P=0.166N	P=0.407N
Incidental Tumor Tests (d)	P=0.065N	P=0.148N	P=0.264N
Cochran-Armitage Trend Test (d)	P=0.037N		
Fisher Exact Test (d)		P=0.121N	P=0.121N
Pancreatic Islets: Islet Cell Adenoma or Carcinoma			
Overall Rates (a)	5/49 (10%)	1/49 (2%)	0/49 (0%)
Adjusted Rates (b)	14.2%	5.0%	0.0%
Terminal Rates (c)	2/28 (7%)	1/20 (5%)	0/4 (0%)
Week of First Observation	88	104	
Life Table Tests (d)	P=0.071N	P=0.173N	P=0.202N
Incidental Tumor Tests (d)	P=0.013N	P=0.104N	P=0.025N
Cochran-Armitage Trend Test (d)	P=0.011N		
Fisher Exact Test (d)		P=0.102N	P=0.028N
Mammary Gland: Fibroadenoma			
Overall Rates (a)	3/50 (6%)	2/50 (4%)	3/50 (6%)
Adjusted Rates (b)	8.4%	7.2%	23.3%
Terminal Rates (c)	1/28 (4%)	1/20 (5%)	0/4 (0%)
Week of First Observation	80	83	85
Life Table Tests (d)	P=0.224	P=0.595N	P=0.236
Incidental Tumor Tests (d)	P=0.469N	P=0.484N	P=0.471N
Cochran-Armitage Trend Test (d)	P=0.588		
Fisher Exact Test (d)		P=0.500N	P=0.661
Preputial Gland: Carcinoma			
Overall Rates (a)	3/50 (6%)	1/50 (2%)	3/50 (6%)
Adjusted Rates (b)	9.7%	4.5%	18.1%
Terminal Rates (c)	2/28 (7%)	0/20 (0%)	0/4 (0%)
Week of First Observation	99	103	94
Life Table Tests (d)	P=0.178	P=0.414N	P=0.187
Incidental Tumor Tests (d)	P=0.514N	P=0.291N	P=0.680N
Cochran-Armitage Trend Test (d)	P=0.594		
Fisher Exact Test (d)		P=0.309N	P=0.661

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

	Vehicle Control	125 mg/kg	250 mg/kg
Preputial Gland: Adenoma or Carcinoma			
Overall Rates (a)	4/50 (8%)	2/50 (4%)	3/50 (6%)
Adjusted Rates (b)	12.5%	9.3%	18.1%
Terminal Rates (c)	2/28 (7%)	1/20 (5%)	0/4 (0%)
Week of First Observation	99	103	94
Life Table Tests (d)	P=0.217	P=0.488N	P=0.244
Incidental Tumor Tests (d)	P=0.363N	P=0.318N	P=0.413N
Cochran-Armitage Trend Test (d)	P=0.417N		
Fisher Exact Test (d)		P=0.339N	P=0.500N
Testis: Interstitial Cell Tumor			
Overall Rates (a)	46/50 (92%)	49/50 (98%)	48/50 (96%)
Adjusted Rates (b)	100.0%	100.0%	100.0%
Terminal Rates (c)	28/28 (100%)	20/20 (100%)	4/4 (100%)
Week of First Observation	62	49	64
Life Table Tests (d)	P<0.001	P=0.027	P<0.001
Incidental Tumor Tests (d)	P=0.026	P=0.026	P=0.026
Cochran-Armitage Trend Test (d)	P=0.238		
Fisher Exact Test (d)		P=0.181	P=0.339
All Sites: Benign Tumors			
Overall Rates (a)	50/50 (100%)	49/50 (98%)	48/50 (96%)
Adjusted Rates (b)	100.0%	100.0%	100.0%
Terminal Rates (c)	28/28 (100%)	20/20 (100%)	4/4 (100%)
Week of First Observation	62	49	64
Life Table Tests (d)	P<0.001	P=0.086	P<0.001
Incidental Tumor Tests (d)	P=0.268N	(e)	P=0.650N
Cochran-Armitage Trend Test (d)	P=0.142N		
Fisher Exact Test (d)		P=0.500N	P=0.248N
All Sites: Malignant Tumors			
Overall Rates (a)	29/50 (58%)	37/50 (74%)	29/50 (58%)
Adjusted Rates (b)	67.7%	83.0%	79.9%
Terminal Rates (c)	15/28 (54%)	13/20 (65%)	1/4 (25%)
Week of First Observation	62	49	64
Life Table Tests (d)	P<0.001	P=0.021	P<0.001
Incidental Tumor Tests (d)	P=0.336N	P=0.081	P=0.409N
Cochran-Armitage Trend Test (d)	P=0.541		
Fisher Exact Test (d)		P=0.069	P=0.580
All Sites: All Tumors			
Overall Rates (a)	50/50 (100%)	49/50 (98%)	49/50 (98%)
Adjusted Rates (b)	100.0%	100.0%	100.0%
Terminal Rates (c)	28/28 (100%)	20/20 (100%)	4/4 (100%)
Week of First Observation	62	49	64
Life Table Tests (d)	P<0.001	P=0.086	P<0.001
Incidental Tumor Tests (d)	P=0.638N	(e)	(e)
Cochran-Armitage Trend Test (d)	P=0.331N		
Fisher Exact Test (d)		P=0.500N	P=0.500N

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(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 is indicated by (N).
(e) No P value is reported because the tumor incidences in vehicle control and dosed groups were 100% in each of the four time intervals during which tumors were observed.

TABLE A4a. HISTORICAL INCIDENCE OF LEUKEMIA IN CONTROL MALE F344/N RATS (a)

Study	Incidence in Controls
Historical Incidence for All Water Gavage Vehicle Controls	
Iodinated glycerol (b)	14/50
Malonaldehyde, sodium salt (c)	7/50
Chlorpheniramine maleate (c)	25/50
Tetrakis(hydroxymethyl)phosphonium chloride (c)	19/50
Tetrakis(hydroxymethyl)phosphonium sulfate (c)	30/50
Methyl carbamate (d)	23/50
TOTAL	118/300 (39.3%)
SD (e)	16.48%
Range (f)	
High	30/50
Low	7/50
Overall Historical Incidence for Untreated Controls	
TOTAL	636/1,936 (32.9%)
SD (e)	14.62%
Range (f)	
High	36/50
Low	5/50

(a) Data as of April 29, 1987, for studies of at least 104 weeks (with revised data for iodinated glycerol)
(b) Study performed at EG&G Mason Research Institute
(c) Study performed at Battelle Columbus Laboratories
(d) Study performed at Microbiological Associates
(e) Standard deviation
(f) Range and SD are presented for groups of 35 or more animals.

TABLE A4b. HISTORICAL INCIDENCE OF THYROID GLAND FOLLICULAR CELL TUMORS IN CONTROL MALE F344/N RATS (a)

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence for All Water Gavage Vehicle Controls			
Iodinated glycerol (b)	0/49	0/49	0/49
Malonaldehyde, sodium salt (c)	3/50	1/50	4/50
Chlorpheniramine maleate (c)	0/50	1/50	1/50
Tetrakis(hydroxymethyl)phosphonium chloride (c)	0/47	0/47	0/47
Tetrakis(hydroxymethyl)phosphonium sulfate (c)	0/47	1/47	1/47
Methyl carbamate (d)	0/50	0/50	0/50
TOTAL	3/293 (1.0%)	3/293 (1.0%)	6/293 (2.0%)
SD (e)	2.45%	1.12%	3.10%
Range (f)			
High	3/50	1/47	4/50
Low	0/50	0/50	0/50
Overall Historical Incidence for Untreated Controls			
TOTAL	(g) 13/1,904 (0.7%)	(h)10/1,904 (0.5%)	(g,h) 23/1,904 (1.2%)
SD (e)	1.39%	0.90%	1.62%
Range (f)			
High	2/44	1/47	3/50
Low	0/50	0/50	0/50

(a) Data as of April 29, 1987, for studies of at least 104 weeks
(b) Study performed at EG&G Mason Research Institute
(c) Study performed at Battelle Columbus Laboratories
(d) Study performed at Microbiological Associates
(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
(h) Includes one papillary adenocarcinoma

TABLE A4c. HISTORICAL INCIDENCE OF NASAL CAVITY TUMORS IN CONTROL MALE F344/N RATS (a)

	No. Examined	No. of Tumors	Site	Diagnosis
Historical Incidence for All Water Gavage Vehicle Controls				
	300	0	--	--
Overall Historical Incidence for Untreated Controls				
		1	Nasal cavity	Squamous cell carcinoma
		1	Nose, NOS	Squamous cell papilloma
TOTAL	1,936	2 (0.1%)		

(a) Data as of April 29, 1987, for studies of at least 104 weeks. No more than one tumor was observed in any control group.

TABLE A4d. HISTORICAL INCIDENCE OF TESTICULAR INTERSTITIAL CELL TUMORS IN CONTROL MALE F344/N RATS (a)

Study	Incidence in Controls
Historical Incidence for All Water Gavage Vehicle Controls	
Iodinated glycerol (b)	46/50
Malonaldehyde, sodium salt (c)	40/50
Chlorpheniramine maleate (c)	44/49
Tetrakis(hydroxymethyl)phosphonium chloride (c)	44/50
Tetrakis(hydroxymethyl)phosphonium sulfate (c)	40/50
Methyl carbamate (d)	43/50
TOTAL	257/299 (86.0%)
SD (e)	5.03%
Range (f)	
High	46/50
Low	40/50
Overall Historical Incidence for Untreated Controls	
TOTAL	1,677/1,910 (87.8%)
SD (e)	7.70%
Range (f)	
High	49/50
Low	32/50

(a) Data as of April 29, 1987, for studies of at least 104 weeks
(b) Study performed at EG&G Mason Research Institute
(c) Study performed at Battelle Columbus Laboratories
(d) Study performed at Microbiological Associates
(e) Standard deviation
(f) Range and SD are presented for groups of 35 or more animals.

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

	Vehicle Control	Low Dose	High Dose
Animals initially in study	50	50	50
Animals necropsied	50	50	50
Animals examined histopathologically	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Inflammation, chronic			1 (2%)
Necrosis, NOS			1 (2%)
Acanthosis			1 (2%)
*Subcutaneous tissue	(50)	(50)	(50)
Abscess, NOS			1 (2%)
RESPIRATORY SYSTEM			
#Nasal cavity	(48)	(47)	(49)
Hamartoma		1 (2%)	
Foreign body, NOS			1 (2%)
Inflammation, suppurative	3 (6%)	12 (26%)	12 (24%)
Inflammation, chronic	6 (13%)	8 (17%)	2 (4%)
Hyperplasia, epithelial		5 (11%)	1 (2%)
Metaplasia, squamous		2 (4%)	2 (4%)
#Trachea	(49)	(50)	(50)
Inflammation, suppurative			1 (2%)
Inflammation, chronic		1 (2%)	
#Lung/bronchiole	(50)	(50)	(50)
Hyperplasia, focal	1 (2%)		
#Lung	(50)	(50)	(50)
Cyst, NOS	1 (2%)		
Congestion, NOS	2 (4%)	1 (2%)	
Inflammation, interstitial		1 (2%)	2 (4%)
Bronchopneumonia, acute			1 (2%)
Inflammation, acute	1 (2%)	2 (4%)	
Inflammation, chronic			1 (2%)
Pneumonia, interstitial chronic	1 (2%)		
Hyperplasia, adenomatous			1 (2%)
Hyperplasia, alveolar epithelium		2 (4%)	1 (2%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Leukocytosis, NOS		1 (2%)	
#Spleen	(50)	(50)	(50)
Congestion, NOS			1 (2%)
Fibrosis, focal			3 (6%)
Hyperplasia, stromal			1 (2%)
Hematopoiesis		1 (2%)	
#Lymph node	(49)	(49)	(50)
Cyst, NOS		1 (2%)	
#Mandibular lymph node	(49)	(49)	(50)
Cyst, NOS		1 (2%)	
Hyperplasia, NOS	1 (2%)		
#Mediastinal lymph node	(49)	(49)	(50)
Plasmacytosis	1 (2%)		
#Pancreatic lymph node	(49)	(49)	(50)
Hyperplasia, plasma cell		1 (2%)	
#Mesenteric lymph node	(49)	(49)	(50)
Cyst, NOS		1 (2%)	
Congestion, NOS	1 (2%)	1 (2%)	
Hemorrhage	1 (2%)		
Histiocytosis			1 (2%)

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

	Vehicle Control	Low Dose	High Dose
CIRCULATORY SYSTEM			
#Mesenteric lymph node	(49)	(49)	(50)
Lymphangiectasis	2 (4%)		
#Heart	(50)	(50)	(50)
Calcification, focal		1 (2%)	
#Heart/atrium	(50)	(50)	(50)
Thrombosis, NOS	3 (6%)	3 (6%)	
#Myocardium	(50)	(50)	(50)
Degeneration, NOS	38 (76%)	32 (64%)	31 (62%)
#Endocardium	(50)	(50)	(50)
Inflammation, chronic focal	1 (2%)		
*Aorta	(50)	(50)	(50)
Inflammation, chronic focal		1 (2%)	
Medial calcification		1 (2%)	
*Pulmonary vein	(50)	(50)	(50)
Embolus, fat			1 (2%)
#Pancreas	(49)	(49)	(49)
Periarteritis	2 (4%)	2 (4%)	2 (4%)
DIGESTIVE SYSTEM			
#Salivary gland	(48)	(50)	(49)
Hemorrhagic cyst	1 (2%)		
Inflammation, suppurative		2 (4%)	7 (14%)
Inflammation, chronic focal		2 (4%)	4 (8%)
Atrophy, focal	1 (2%)	10 (20%)	30 (61%)
Metaplasia, squamous		47 (94%)	48 (98%)
#Liver	(50)	(50)	(50)
Hernia, NOS		1 (2%)	
Congestion, NOS		1 (2%)	
Inflammation, acute focal			1 (2%)
Inflammation, chronic focal	4 (8%)		
Degeneration, cystic	9 (18%)	8 (16%)	11 (22%)
Necrosis, NOS	1 (2%)	2 (4%)	
Metamorphosis, fatty	14 (28%)	8 (16%)	6 (12%)
Basophilic cyto change	13 (26%)	6 (12%)	9 (18%)
Focal cellular change	1 (2%)		2 (4%)
Eosinophilic cyto change		1 (2%)	1 (2%)
Clear cell change	13 (26%)	8 (16%)	5 (10%)
Angiectasis	2 (4%)	8 (16%)	11 (22%)
#Liver/periportal	(50)	(50)	(50)
Calcification, NOS	1 (2%)		
#Liver/Kupffer cell	(50)	(50)	(50)
Hyperplasia, NOS			1 (2%)
#Bile duct	(50)	(50)	(50)
Hyperplasia, NOS	47 (94%)	42 (84%)	37 (74%)
#Pancreas	(49)	(49)	(49)
Inflammation, chronic	7 (14%)	1 (2%)	5 (10%)
Hyperplasia, focal	1 (2%)		
#Pancreatic acinus	(49)	(49)	(49)
Atrophy, NOS	9 (18%)	7 (14%)	3 (6%)
Hyperplasia, NOS	1 (2%)	1 (2%)	
#Glandular stomach	(49)	(49)	(50)
Cyst, NOS			1 (2%)
Calcification, NOS		1 (2%)	1 (2%)
#Forestomach	(49)	(49)	(50)
Ulcer, NOS			2 (4%)
Inflammation, acute		1 (2%)	
Calcification, NOS		1 (2%)	
Acanthosis			1 (2%)

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

	Vehicle Control	Low Dose	High Dose
DIGESTIVE SYSTEM (Continued)			
#Ileum	(50)	(49)	(50)
Parasitism		1 (2%)	
#Colon	(49)	(47)	(50)
Parasitism	12 (24%)	10 (21%)	7 (14%)
#Cecum	(49)	(47)	(50)
Inflammation, chronic			1 (2%)
Parasitism	1 (2%)		
Necrosis, NOS		1 (2%)	
URINARY SYSTEM			
#Kidney	(50)	(50)	(50)
Cyst, NOS	1 (2%)		
Nephrosis, NOS	50 (100%)	48 (96%)	49 (98%)
Calcification, NOS		1 (2%)	
#Kidney/cortex	(50)	(50)	(50)
Cyst, NOS		1 (2%)	
Necrosis, focal		1 (2%)	
#Kidney/tubule	(50)	(50)	(50)
Pigmentation, NOS	1 (2%)		
#Urinary bladder	(49)	(49)	(48)
Inflammation, chronic focal	1 (2%)		
ENDOCRINE SYSTEM			
#Pituitary	(48)	(47)	(46)
Necrosis, NOS	1 (2%)		
#Anterior pituitary	(48)	(47)	(46)
Cyst, NOS			1 (2%)
Hypertrophy, focal	1 (2%)		
Hyperplasia, focal	6 (13%)	6 (13%)	5 (11%)
Angiectasis	1 (2%)		
#Adrenal cortex	(50)	(50)	(49)
Degeneration, NOS	3 (6%)	2 (4%)	7 (14%)
Metamorphosis, fatty		1 (2%)	3 (6%)
Hypertrophy, focal			1 (2%)
Hyperplasia, focal	6 (12%)	3 (6%)	2 (4%)
#Adrenal medulla	(50)	(50)	(49)
Degeneration, NOS		1 (2%)	
Hyperplasia, focal	9 (18%)	3 (6%)	8 (16%)
#Thyroid	(49)	(49)	(49)
Inflammation, chronic focal			1 (2%)
Hyperplasia, cystic		6 (12%)	3 (6%)
Hyperplasia, C-cell	4 (8%)	8 (16%)	9 (18%)
Hyperplasia, follicular cell		1 (2%)	2 (4%)
#Parathyroid	(19)	(27)	(25)
Hyperplasia, NOS	4 (21%)	1 (4%)	4 (16%)
#Pancreatic islets	(49)	(49)	(49)
Hyperplasia, NOS		1 (2%)	1 (2%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Hyperplasia, NOS	4 (8%)	7 (14%)	1 (2%)
*Prepuce	(50)	(50)	(50)
Hyperkeratosis		1 (2%)	
Acanthosis		1 (2%)	
*Preputial gland	(50)	(50)	(50)
Inflammation, suppurative	1 (2%)	6 (12%)	7 (14%)
Inflammation, acute/chronic		3 (6%)	
Inflammation, chronic	22 (44%)	19 (38%)	16 (32%)
Hyperplasia, NOS		2 (4%)	

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

	Vehicle Control	Low Dose	High Dose
REPRODUCTIVE SYSTEM (Continued)			
#Prostate	(50)	(49)	(47)
Retention of content	1 (2%)		
Inflammation, suppurative	17 (34%)	13 (27%)	12 (26%)
Inflammation, chronic	1 (2%)	4 (8%)	
Cytoplasmic vacuolization			1 (2%)
Metaplasia, squamous			2 (4%)
*Seminal vesicle	(50)	(50)	(50)
Retention of content	1 (2%)		
Inflammation, chronic	1 (2%)		
#Testis	(50)	(50)	(50)
Atrophy, NOS	1 (2%)		
Hyperplasia, interstitial cell	7 (14%)		
#Testis/tubule	(50)	(50)	(50)
Degeneration, NOS	4 (8%)	1 (2%)	
Calcification, NOS		1 (2%)	
#Rete testis	(50)	(50)	(50)
Hyperplasia, NOS	1 (2%)		
*Epididymis	(50)	(50)	(50)
Calcification, NOS			1 (2%)
NERVOUS SYSTEM			
#Lateral ventricle	(50)	(50)	(50)
Hydrocephalus, NOS		1 (2%)	
#Cerebrum	(50)	(50)	(50)
Calcification, focal			1 (2%)
#Brain	(50)	(50)	(50)
Hemorrhage		1 (2%)	
SPECIAL SENSE ORGANS			
*Nasolacrimal duct	(50)	(50)	(50)
Inflammation, suppurative		1 (2%)	3 (6%)
Inflammation, chronic	2 (4%)	2 (4%)	1 (2%)
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
*Mesentery	(50)	(50)	(50)
Inflammation, chronic			1 (2%)
Necrosis, fat	1 (2%)		
ALL OTHER SYSTEMS			
None			
SPECIAL MORPHOLOGY SUMMARY			
None			

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

APPENDIX B

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

		PAGE
TABLE B1	SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF IODINATED GLYCEROL	97
TABLE B2	INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF IODINATED GLYCEROL	100
TABLE B3	ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF IODINATED GLYCEROL	106
TABLE B4	HISTORICAL INCIDENCE OF ANTERIOR PITUITARY GLAND TUMORS IN CONTROL FEMALE F344/N RATS	109
TABLE B5	SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF IODINATED GLYCEROL	110

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

	Vehicle Control	Low Dose	High Dose
Animals initially in study	50	50	50
Animals necropsied	50	50	50
Animals examined histopathologically	49	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Basal cell tumor		1 (2%)	
Keratoacanthoma	1 (2%)		
Fibroma			1 (2%)
Neurofibrosarcoma			1 (2%)
*Subcutaneous tissue	(50)	(50)	(50)
Fibroma	1 (2%)	1 (2%)	
Neurilemoma, malignant			1 (2%)
RESPIRATORY SYSTEM			
#Lung	(49)	(33)	(50)
Alveolar/bronchiolar adenoma	1 (2%)	1 (3%)	2 (4%)
Alveolar/bronchiolar carcinoma	1 (2%)		
C-cell carcinoma, metastatic	1 (2%)		
Pheochromocytoma, metastatic			1 (2%)
Choriocarcinoma, metastatic			1 (2%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Leukemia, mononuclear cell	15 (30%)	14 (28%)	14 (28%)
#Liver	(49)	(50)	(50)
Leukemia, mononuclear cell		4 (8%)	
CIRCULATORY SYSTEM			
#Spleen	(48)	(21)	(50)
Hemangiosarcoma	1 (2%)	1 (5%)	
*Mesentery	(50)	(50)	(50)
Hemangiosarcoma, metastatic	1 (2%)		
DIGESTIVE SYSTEM			
#Liver	(49)	(50)	(50)
Neoplastic nodule			1 (2%)
#Esophagus	(34)	(11)	(44)
Squamous cell carcinoma			1 (2%)
URINARY SYSTEM			
None			
ENDOCRINE SYSTEM			
#Anterior pituitary	(48)	(50)	(50)
Carcinoma, NOS		3 (6%)	1 (2%)
Adenoma, NOS	26 (54%)	24 (48%)	33 (66%)
#Adrenal	(49)	(50)	(50)
Cortical adenoma		2 (4%)	
#Adrenal medulla	(49)	(50)	(50)
Pheochromocytoma	1 (2%)	6 (12%)	4 (8%)
Pheochromocytoma, malignant	1 (2%)		1 (2%)
Ganglioneuroma			1 (2%)

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

	Vehicle Control	Low Dose	High Dose
ENDOCRINE SYSTEM (Continued)			
#Thyroid	(46)	(12)	(48)
Follicular cell carcinoma		1 (8%)	1 (2%)
C-cell adenoma		1 (8%)	1 (2%)
C-cell carcinoma	2 (4%)		2 (4%)
#Parathyroid	(20)	(7)	(22)
Adenoma, NOS			1 (5%)
#Pancreatic islets	(49)	(14)	(50)
Islet cell adenoma			2 (4%)
Islet cell carcinoma			1 (2%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Adenocarcinoma, NOS			1 (2%)
Fibroadenoma	13 (26%)	10 (20%)	11 (22%)
*Clitoral gland	(50)	(50)	(50)
Carcinoma, NOS	2 (4%)	1 (2%)	2 (4%)
Adenoma, NOS		1 (2%)	
#Uterus	(49)	(23)	(49)
Adenocarcinoma, NOS		1 (4%)	
Leiomyosarcoma	1 (2%)	1 (4%)	
Endometrial stromal polyp	14 (29%)	7 (30%)	9 (18%)
Endometrial stromal sarcoma		1 (4%)	
#Cervix uteri	(49)	(23)	(49)
Endometrial stromal sarcoma	1 (2%)		
#Ovary	(49)	(16)	(50)
Granulosa cell tumor	1 (2%)		
Choriocarcinoma			1 (2%)
NERVOUS SYSTEM			
#Brain	(49)	(10)	(50)
Oligodendroglioma			1 (2%)
SPECIAL SENSE ORGANS			
*Zymbal gland	(50)	(50)	(50)
Carcinoma, NOS			1 (2%)
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
None			
ALL OTHER SYSTEMS			
None			
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	4	11	5
Moribund sacrifice	14	9	18
Terminal sacrifice	31	30	27
Accidentally killed, nda	1		

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

	Vehicle Control	Low Dose	High Dose
TUMOR SUMMARY			
Total animals with primary tumors**	44	46	47
Total primary tumors	82	81	95
Total animals with benign tumors	36	40	40
Total benign tumors	57	54	65
Total animals with malignant tumors	23	21	26
Total malignant tumors	24	27	29
Total animals with secondary tumors##	2		2
Total secondary tumors	2		2
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 B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF IODINATED GLYCEROL: VEHICLE CONTROL

ANIMAL NUMBER	00071	00181	00200	00226	00337	00244	00449	00288	00002	00011	00111	00339	00448	00227	00321	00122	00115	00330	00255	00033	00044	00055	00066	00088	00099
WEEKS ON STUDY	06021	07071	07072	07073	07075	07078	08083	08086	08087	08088	09094	09095	09095	09096	09096	09099	09099	09099	10010	10044	10044	10044	10044	10044	10044
INTEGUMENTARY SYSTEM																									
Skin	N	+	+	+	+	+	+	+	+	+	N	+	N	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																									
Subcutaneous tissue	N	+	+	+	+	+	+	+	+	+	N	+	N	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma						X																			
RESPIRATORY SYSTEM																									
Lungs and bronchi	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																									
C-cell carcinoma, metastatic																									
Trachea	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nasal cavity	A	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	−	+	+	+	+	+	−
HEMATOPOIETIC SYSTEM																									
Bone marrow	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	A	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma										X															
Lymph nodes	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	A	+	+	+	−	+	+	+	+	+	−	−	−	+	+	+	+	+	+	+	+	+	+	−	+
CIRCULATORY SYSTEM																									
Heart	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bile duct	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	A	+	+	−	+	+	+	−	+	+	+	−	+	−	+	−	+	+	+	+	+	+	−	−	+
Stomach	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	A	+	+	+	+	+	+	+	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	A	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS							X					X	X			X	X		X		X	X			X
Adrenal	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma																									
Pheochromocytoma, malignant															X										
Thyroid	A	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	−	+	+	+	−	+	+	+	+
C-cell carcinoma																								X	
Parathyroid	A	+	−	−	+	+	+	+	+	−	−	−	+	+	−	−	−	+	+	−	−	+	−	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	N	+	N	N	N	+	+	N	+	+	N	+	+	+	+	+	+	+	+	+	+	+	N	+	N
Fibroadenoma												X	X			X		X			X	X			
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																									
Uterus	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma																									
Endometrial stromal polyp		X						X	X	X		X		X						X		X			
Endometrial stromal sarcoma					X																				
Ovary	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor																									X
NERVOUS SYSTEM																									
Brain	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
BODY CAVITIES																									
Mesentery	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Hemangiosarcoma, metastatic										X															
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell		X		X				X			X			X				X	X			X	X	

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

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

ANIMAL NUMBER	0 1 0	0 1 3	0 1 4	0 1 7	0 1 9	0 2 1	0 2 2	0 2 3	0 2 9	0 3 1	0 3 3	0 3 4	0 3 5	0 4 0	0 4 1	0 4 2	0 4 3	0 4 4	0 4 5	0 4 7	0 1 6	0 3 6	0 3 8	0 4 6	0 5 0	TOTAL:
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 5	1 0 5	1 0 5	1 0 5	1 0 5	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	*50
Keratoacanthoma			X																							1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	*50
Fibroma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma																				X						1
Alveolar/bronchiolar carcinoma										X																1
C-cell carcinoma, metastatic															X											1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	48
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hemangiosarcoma																										1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	–	+	+	–	–	+	+	+	+	–	+	+	+	–	+	+	–	+	+	+	–	+	–	+	+	36
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	–	+	+	+	+	–	+	–	–	–	–	–	+	+	+	+	+	–	+	+	34
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Large intestine	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	47
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+		46
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma, NOS	X	X	X	X	X	X	X	X	X						X	X	X		X	X		X	X	X		26
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma																							X			1
Pheochromocytoma, malignant																										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
C-cell carcinoma															X											2
Parathyroid	+	–	–	+	–	–	–	–	–	+	–	–	+	–	+	–	–	–	–	+	–	–	–	+	–	20
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	+	+	+	+	+	+	+	+	+	+	+	N	+	+	N	N	N	+	N	+	+	+	N	*50
Fibroadenoma			X		X		X		X						X					X		X				13
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS														X									X			2
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leiomyosarcoma										X																1
Endometrial stromal polyp						X	X			X			X							X		X				14
Endometrial stromal sarcoma																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Granulosa cell tumor																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
BODY CAVITIES																										
Mesentery	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Hemangiosarcoma, metastatic																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leukemia, mononuclear cell		X	X						X									X		X		X				15

* Animals necropsied

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF IODINATED GLYCEROL: LOW DOSE

ANIMAL NUMBER	045	021	029	041	025	046	016	049	022	037	042	018	030	033	006	035	017	009	013	044	001	002	003	004	005
WEEKS ON STUDY	042	063	076	077	082	083	084	084	087	093	094	095	095	095	096	098	099	101	102	103	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	N	+	+	+	N	N	N	N	N	+	N	N	N	N	+	+	N	N	+
Basal cell tumor																					X				
Subcutaneous tissue	+	+	+	+	+	+	N	+	+	+	N	N	N	N	N	+	N	N	N	N	+	+	N	N	+
Fibroma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	−	+	−	+	+	+	+	−	+	+	+	+	+	−	−	−
Alveolar/bronchiolar adenoma																									
Trachea	+	+	+	+	−	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Nasal cavity	−	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Spleen	+	+	+	+	+	+	+	+	+	−	−	−	−	−	+	−	+	+	+	−	−	−	−	−	+
Hemangiosarcoma																			X						
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	−	+	+	−	+	+
Thymus	+	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia, mononuclear cell											X														
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	−	−	−	−	−	−	+	−	−	+	−	−	−	+	−	
Esophagus	+	+	+	+	−	+	+	+	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Stomach	+	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Small intestine	+	+	+	+	+	+	+	+	+	−	−	−	−	−	−	+	−	−	−	−	−	−	−	−	−
Large intestine	+	+	+	+	+	+	+	+	+	−	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Urinary bladder	+	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																				X					X
Adenoma, NOS	X					X	X	X	X		X		X	X	X				X				X	X	
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																									
Pheochromocytoma										X	X					X									X
Thyroid	+	+	+	+	−	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Follicular cell carcinoma																									
C-cell adenoma																									
Parathyroid	+	−	−	+	−	+	−	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	N	+	N	+	+	+	N	N	+	+	N	+	+	N	N	N	N	+	+	N	+
Fibroadenoma								X					X	X			X						X		
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS												X													
Adenoma, NOS																	X								
Uterus	+	+	+	+	+	+	+	+	+	−	−	−	−	−	−	+	−	−	−	−	−	+	−	−	−
Adenocarcinoma, NOS																									
Leiomyosarcoma																									
Endometrial stromal polyp		X																				X			
Endometrial stromal sarcoma																									
Ovary	+	+	+	+	+	+	+	+	+	−	−	−	−	−	−	+	−	−	+	−	−	−	−	−	−
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell		X	X	X			X							X	X	X	X	X	X						X

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: LOW DOSE (Continued)

ANIMAL NUMBER	00007	00008	00110	00111	00112	00114	00115	00119	00200	00223	00224	00226	00227	00228	00231	00232	00234	00236	00238	00239	00400	00433	00447	00448	00500	TOTAL:
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	+	+	+	N	N	N	N	N	N	*50
Basal cell tumor																										1
Subcutaneous tissue	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	+	+	+	N	N	N	N	N	N	*50
Fibroma																		X								1
RESPIRATORY SYSTEM																										
Lungs and bronchi	−	+	−	−	+	+	+	−	−	+	+	+	−	+	+	−	+	−	+	+	+	−	−	+	−	33
Alveolar/bronchiolar adenoma											X															1
Trachea	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	−	−	+	−	−	−	−	−	11
Nasal cavity	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	−	−	−	−	−	−	−	−	9
HEMATOPOIETIC SYSTEM																										
Bone marrow	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	−	−	−	−	−	−	−	−	9
Spleen	−	−	−	−	−	−	−	−	+	−	+	+	−	−	−	−	+	−	+	+	−	−	−	+	−	21
Hemangiosarcoma																										1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	46
Thymus	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	−	−	−	−	−	−	−	−	10
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia, mononuclear cell							X										X				X					4
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	−	−	−	−	−	−	−	−	−	−	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	14
Esophagus	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	−	−	+	−	−	−	+	−	11
Stomach	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	−	−	−	−	−	−	−	−	10
Small intestine	+	−	−	−	−	−	−	−	−	−	+	−	−	−	−	−	+	−	−	−	−	−	−	−	−	13
Large intestine	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	−	−	+	−	−	−	−	−	12
URINARY SYSTEM																										
Kidney	−	+	−	−	−	−	+	−	−	+	−	−	−	+	−	−	+	−	−	+	+	−	−	+	−	19
Urinary bladder	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	−	−	−	−	−	−	−	−	10
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS							X																			3
Adenoma, NOS	X	X	X			X		X								X	X	X	X		X	X	X			24
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma											X			X												2
Pheochromocytoma				X																					X	6
Thyroid	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	−	−	+	−	−	−	+	−	12
Follicular cell carcinoma																								X		1
C-cell adenoma																				X						1
Parathyroid	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	−	−	+	−	−	−	+	−	7
REPRODUCTIVE SYSTEM																										
Mammary gland	N	+	+	N	N	+	+	N	N	+	N	+	N	N	N	+	+	N	+	N	N	N	N	N	N	*50
Fibroadenoma						X	X			X		X				X										10
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS																										1
Adenoma, NOS																										1
Uterus	+	−	−	−	+	+	−	−	−	+	+	+	−	+	−	−	+	−	+	−	+	−	+	+	−	23
Adenocarcinoma, NOS	X																									1
Leiomyosarcoma											X															1
Endometrial stromal polyp					X	X				X		X									X					7
Endometrial stromal sarcoma																							X			1
Ovary	−	−	−	−	−	−	−	+	−	−	+	+	−	−	−	−	+	−	−	−	+	−	−	−	−	16
NERVOUS SYSTEM																										
Brain	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	−	−	−	−	−	−	−	−	10
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leukemia, mononuclear cell											X	X												X		14

* Animals necropsied

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF IODINATED GLYCEROL: HIGH DOSE

ANIMAL NUMBER	0311	0500	0401	0255	0002	0220	0004	0033	0199	0227	0336	0144	0337	0441	0266	0233	0449	0067	0112	0229	0334	0448	0111	0015	0005
WEEKS ON STUDY	071	077	081	087	088	088	090	091	091	091	091	094	094	096	097	099	099	100	102	102	102	102	103	105	105
INTEGUMENTARY SYSTEM																									
Skin	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma													X												
Neurofibrosarcoma																				X					
Subcutaneous tissue	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neurilemoma, malignant														X											
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Pheochromocytoma, metastatic									X																
Choriocarcinoma, metastatic		X																							
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nasal cavity	+	+	+	+	+	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	–	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	–	+	+	+	+	+	–	–
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	–	–	+	+	+	+	+	+
Squamous cell carcinoma				X																					
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																									X
Adenoma, NOS				X	X	X			X			X	X	X	X		X		X	X	X	X		X	
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma								X								X									
Pheochromocytoma, malignant									X																
Ganglioneuroma			X																						
Thyroid	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	–	+	+	+	+
Follicular cell carcinoma																									
C-cell adenoma												X													
C-cell carcinoma																									X
Parathyroid	–	+	–	–	+	+	–	–	–	–	–	+	+	+	–	+	+	–	–	–	–	–	+	+	+
Adenoma, NOS																									
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma														X											X
Islet cell carcinoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	+	+	+	+	N	N	+	N	+	+	+	+	+	+	N	N	N	+	N	+	+	N	+
Adenocarcinoma, NOS																									
Fibroadenoma					X				X		X		X							X					
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS			X																	X					
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp						X				X			X			X								X	
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Choriocarcinoma		X																							
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Oligodendroglioma																									
SPECIAL SENSE ORGANS																									
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N
Carcinoma, NOS																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell	X						X	X		X		X	X				X	X							

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: HIGH DOSE (Continued)

ANIMAL NUMBER	00007	00008	00009	00107	00113	00115	00116	00117	00118	00121	00122	00124	00128	00130	00132	00134	00135	00138	00139	00142	00143	00144	00145	00146	00147	TOTAL:
WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	*50
Fibroma																										1
Neurofibrosarcoma																										1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	*50
Neurilemoma, malignant																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma														X											X	2
Pheochromocytoma, metastatic																										1
Choriocarcinoma, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nasal cavity	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	−	+	+	+	+	−	+	+	+	−	+	+	+	−	−	+	+	+	+	+	−	+	−	+	−	37
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule				X																						1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	−	+	+	+	+	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	44
Squamous cell carcinoma																										1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS																										1
Adenoma, NOS	X	X	X	X	X	X		X	X	X			X	X	X	X	X	X		X	X			X	X	33
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma																	X							X		4
Pheochromocytoma, malignant																										1
Ganglioneuroma																										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Follicular cell carcinoma																		X								1
C-cell adenoma																										1
C-cell carcinoma											X															2
Parathyroid	−	−	+	+	−	−	−	+	+	+	+	+	+	−	−	−	+	−	−	+	+	−	−	−	−	22
Adenoma, NOS																				X						1
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet cell adenoma																										2
Islet cell carcinoma																		X								1
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	+	+	N	+	+	+	+	+	N	N	+	N	+	+	+	+	N	+	+	+	N	+	+	*50
Adenocarcinoma, NOS								X																		1
Fibroadenoma			X			X							X					X						X	X	11
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS																										2
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Endometrial stromal polyp					X	X												X	X							9
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Choriocarcinoma																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Oligodendroglioma					X																					1
SPECIAL SENSE ORGANS																										
Zymbal gland	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS			X																							1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leukemia, mononuclear cell										X		X		X				X			X		X			14

* Animals necropsied

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

	Vehicle Control	62 mg/kg	125 mg/kg
Hematopoietic System: Mononuclear Cell Leukemia			
Overall Rates (a)	15/50 (30%)	(b,c) 18/50 (36%)	14/50 (28%)
Adjusted Rates (d)	38.0%		36.5%
Terminal Rates (e)	8/31 (26%)		6/27 (22%)
Week of First Observation	71		71
Life Table Test (f)			P=0.560N
Incidental Tumor Test (f)			P=0.481N
Fisher Exact Test (f)			P=0.500N
Anterior Pituitary Gland: Adenoma			
Overall Rates (a)	26/48 (54%)	24/50 (48%)	33/50 (66%)
Adjusted Rates (d)	70.0%	58.5%	81.9%
Terminal Rates (e)	20/31 (65%)	14/30 (47%)	20/27 (74%)
Week of First Observation	83	42	87
Life Table Tests (f)	P=0.064	P=0.466N	P=0.064
Incidental Tumor Tests (f)	P=0.158	P=0.266N	P=0.141
Cochran-Armitage Trend Test (f)	P=0.136		
Fisher Exact Test (f)		P=0.342N	P=0.161
Anterior Pituitary Gland: Carcinoma			
Overall Rates (a)	0/48 (0%)	3/50 (6%)	1/50 (2%)
Adjusted Rates (d)	0.0%	9.7%	3.7%
Terminal Rates (e)	0/31 (0%)	2/30 (7%)	1/27 (4%)
Week of First Observation		103	104
Life Table Tests (f)	P=0.342	P=0.119	P=0.472
Incidental Tumor Tests (f)	P=0.372	P=0.130	P=0.472
Cochran-Armitage Trend Test (f)	P=0.395		
Fisher Exact Test (f)		P=0.129	P=0.510
Anterior Pituitary Gland: Adenoma or Carcinoma			
Overall Rates (a)	26/48 (54%)	27/50 (54%)	34/50 (68%)
Adjusted Rates (d)	70.0%	64.9%	84.5%
Terminal Rates (e)	20/31 (65%)	16/30 (53%)	21/27 (78%)
Week of First Observation	83	42	87
Life Table Tests (f)	P=0.043	P=0.461	P=0.042
Incidental Tumor Tests (f)	P=0.108	P=0.495N	P=0.092
Cochran-Armitage Trend Test (f)	P=0.097		
Fisher Exact Test (f)		P=0.574N	P=0.115
Adrenal Gland: Pheochromocytoma			
Overall Rates (a)	1/49 (2%)	6/50 (12%)	4/50 (8%)
Adjusted Rates (d)	3.2%	16.8%	12.1%
Terminal Rates (e)	1/31 (3%)	3/30 (10%)	2/27 (7%)
Week of First Observation	104	93	91
Life Table Tests (f)	P=0.151	P=0.060	P=0.163
Incidental Tumor Tests (f)	P=0.209	P=0.069	P=0.220
Cochran-Armitage Trend Test (f)	P=0.178		
Fisher Exact Test (f)		P=0.059	P=0.187
Adrenal Gland: Pheochromocytoma or Malignant Pheochromocytoma			
Overall Rates (a)	2/49 (4%)	6/50 (12%)	5/50 (10%)
Adjusted Rates (d)	5.8%	16.8%	14.2%
Terminal Rates (e)	1/31 (3%)	3/30 (10%)	2/27 (7%)
Week of First Observation	96	93	91
Life Table Tests (f)	P=0.173	P=0.136	P=0.207
Incidental Tumor Tests (f)	P=0.267	P=0.159	P=0.323
Cochran-Armitage Trend Test (f)	P=0.197		
Fisher Exact Test (f)		P=0.141	P=0.226

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

	Vehicle Control	62 mg/kg	125 mg/kg
Thyroid Gland: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	2/46 (4%)	(c) 1/12 (8%)	3/48 (6%)
Adjusted Rates (d)	6.7%		9.8%
Terminal Rates (e)	2/30 (7%)		2/27 (7%)
Week of First Observation	104		94
Life Table Test (f)			P=0.459
Incidental Tumor Test (f)			P=0.490
Fisher Exact Test (f)			P=0.520
Pancreatic Islets: Islet Cell Adenoma or Carcinoma			
Overall Rates (a)	0/49 (0%)	(c) 0/14 (0%)	3/50 (6%)
Adjusted Rates (d)	0.0%		9.9%
Terminal Rates (e)	0/31 (0%)		2/27 (7%)
Week of First Observation			96
Life Table Test (f)			P=0.107
Incidental Tumor Test (f)			P=0.122
Fisher Exact Test (f)			P=0.125
Mammary Gland: Fibroadenoma			
Overall Rates (a)	13/50 (26%)	10/50 (20%)	11/50 (22%)
Adjusted Rates (d)	36.5%	28.0%	31.5%
Terminal Rates (e)	9/31 (29%)	6/30 (20%)	6/27 (22%)
Week of First Observation	95	84	88
Life Table Tests (f)	P=0.447N	P=0.347N	P=0.496N
Incidental Tumor Tests (f)	P=0.274N	P=0.268N	P=0.320N
Cochran-Armitage Trend Test (f)	P=0.361N		
Fisher Exact Test (f)		P=0.318N	P=0.408N
Uterus: Endometrial Stromal Polyp			
Overall Rates (a)	14/49 (29%)	(c) 7/23 (30%)	9/49 (18%)
Adjusted Rates (d)	35.9%		26.3%
Terminal Rates (e)	8/31 (26%)		5/27 (19%)
Week of First Observation	71		88
Life Table Test (f)			P=0.229N
Incidental Tumor Test (f)			P=0.114N
Fisher Exact Test (f)			P=0.170N
All Sites: Benign Tumors			
Overall Rates (a)	36/50 (72%)	40/50 (80%)	40/50 (80%)
Adjusted Rates (d)	81.6%	90.7%	88.6%
Terminal Rates (e)	23/31 (74%)	26/30 (87%)	22/27 (81%)
Week of First Observation	71	42	81
Life Table Tests (f)	P=0.158	P=0.264	P=0.194
Incidental Tumor Tests (f)	P=0.398	P=0.365	P=0.494
Cochran-Armitage Trend Test (f)	P=0.203		
Fisher Exact Test (f)		P=0.241	P=0.241
All Sites: Malignant Tumors			
Overall Rates (a)	23/50 (46%)	21/50 (42%)	26/50 (52%)
Adjusted Rates (d)	55.0%	49.2%	60.9%
Terminal Rates (e)	13/31 (42%)	9/30 (30%)	12/27 (44%)
Week of First Observation	71	63	71
Life Table Tests (f)	P=0.274	P=0.453N	P=0.300
Incidental Tumor Tests (f)	P=0.290	P=0.477N	P=0.374
Cochran-Armitage Trend Test (f)	P=0.307		
Fisher Exact Test (f)		P=0.421N	P=0.345

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

	Vehicle Control	62 mg/kg	125 mg/kg
All Sites: All Tumors			
Overall Rates (a)	44/50 (88%)	46/50 (92%)	47/50 (94%)
Adjusted Rates (d)	91.7%	93.9%	95.9%
Terminal Rates (e)	27/31 (87%)	27/30 (90%)	25/27 (93%)
Week of First Observation	71	42	71
Life Table Tests (f)	P=0.203	P=0.391	P=0.232
Incidental Tumor Tests (f)	P=0.267	P=0.456	P=0.396
Cochran-Armitage Trend Test (f)	P=0.188		
Fisher Exact Test (f)		P=0.370	P=0.243

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Twenty-one spleens examined microscopically
(c) Incomplete sampling of tissues
(d) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(e) Observed tumor incidence at terminal kill
(f) 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 is indicated by (N).

TABLE B4. HISTORICAL INCIDENCE OF ANTERIOR PITUITARY GLAND TUMORS IN CONTROL FEMALE F344/N RATS (a)

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence for All Water Gavage Vehicle Controls			
Iodinated glycerol (b)	26/48	0/48	26/48
Malonaldehyde, sodium salt (c)	16/49	2/49	18/49
Chlorpheniramine maleate (c)	24/48	1/48	25/48
Tetrakis(hydroxymethyl)phosphonium chloride (c)	24/49	0/49	24/49
Tetrakis(hydroxymethyl)phosphonium sulfate (c)	23/46	0/46	23/46
Methyl carbamate (d)	21/50	3/50	24/50
TOTAL	134/290 (46.2%)	6/290 (2.1%)	140/290 (48.3%)
SD (e)	7.76%	2.54%	6.10%
Range (f)			
High	26/48	3/50	26/48
Low	16/49	0/49	18/49
Overall Historical Incidence for Untreated Controls			
TOTAL	(g) 869/1,922 (45.2%)	(h) 72/1,922 (3.7%)	(g,h) 939/1,922 (48.9%)
SD (e)	11.77%	4.05%	11.34%
Range (f)			
High	33/47	8/49	33/47
Low	7/39	0/50	9/39

(a) Data as of April 29, 1987, for studies of at least 104 weeks
(b) Study performed at EG&G Mason Research Institute
(c) Study performed at Battelle Columbus Laboratories
(d) Study performed at Microbiological Associates
(e) Standard deviation
(f) Range and SD are presented for groups of 35 or more animals.
(g) Includes 102 chromophobe adenomas
(h) Includes three adenocarcinomas, NOS, and six chromophobe carcinomas

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

	Vehicle Control	Low Dose	High Dose
Animals initially in study	50	50	50
Animals necropsied	50	50	50
Animals examined histopathologically	49	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Hyperplasia, basal cell	1 (2%)		
Acanthosis	1 (2%)		
RESPIRATORY SYSTEM			
#Nasal cavity	(46)	(9)	(47)
Inflammation, suppurative		1 (11%)	3 (6%)
Inflammation, chronic	5 (11%)	3 (33%)	2 (4%)
#Trachea	(48)	(11)	(50)
Inflammation, acute/chronic			1 (2%)
Inflammation, chronic	1 (2%)		
#Lung	(49)	(33)	(50)
Congestion, NOS		12 (36%)	
Inflammation, interstitial	2 (4%)		
Bronchopneumonia, acute		1 (3%)	1 (2%)
Inflammation, chronic	3 (6%)		
Pneumonia, interstitial chronic			1 (2%)
Hyperplasia, alveolar epithelium		2 (6%)	
#Lung/alveoli	(49)	(33)	(50)
Hemorrhage	1 (2%)	1 (3%)	
Necrosis, NOS	1 (2%)		
HEMATOPOIETIC SYSTEM			
#Spleen	(48)	(21)	(50)
Inflammation, granulomatous		1 (5%)	1 (2%)
Granuloma, NOS			1 (2%)
Fibrosis, focal			1 (2%)
Hemosiderosis	1 (2%)		
Hyperplasia, lymphoid			1 (2%)
Hematopoiesis	2 (4%)		
#Lymph node	(49)	(46)	(50)
Cyst, NOS		1 (2%)	
#Mandibular lymph node	(49)	(46)	(50)
Hyperplasia, plasma cell		1 (2%)	
#Mediastinal lymph node	(49)	(46)	(50)
Congestion, NOS		2 (4%)	
Pigmentation, NOS	1 (2%)	1 (2%)	
#Mesenteric lymph node	(49)	(46)	(50)
Congestion, NOS	1 (2%)	2 (4%)	
Hemorrhage			1 (2%)
Inflammation, granulomatous	1 (2%)		1 (2%)
CIRCULATORY SYSTEM			
#Heart	(49)	(50)	(50)
Inflammation, chronic focal		1 (2%)	1 (2%)
Periarteritis		1 (2%)	
#Myocardium	(49)	(50)	(50)
Degeneration, NOS	26 (53%)	12 (24%)	17 (34%)
*Coronary artery	(50)	(50)	(50)
Inflammation, chronic	1 (2%)		
Inflammation, chronic focal			1 (2%)

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

	Vehicle Control	Low Dose	High Dose
CIRCULATORY SYSTEM (Continued)			
#Pancreas	(49)	(14)	(50)
Periarteritis	1 (2%)	1 (7%)	
*Mesentery	(50)	(50)	(50)
Periarteritis		1 (2%)	
DIGESTIVE SYSTEM			
#Salivary gland	(49)	(50)	(50)
Cyst, NOS			1 (2%)
Inflammation, suppurative			2 (4%)
Inflammation, acute			1 (2%)
Inflammation, chronic	1 (2%)	2 (4%)	3 (6%)
Atrophy, focal		4 (8%)	11 (22%)
Metaplasia, squamous	1 (2%)	48 (96%)	49 (98%)
#Parotid gland	(49)	(50)	(50)
Atrophy, focal		2 (4%)	
#Liver	(49)	(50)	(50)
Hemorrhage		1 (2%)	
Inflammation, chronic focal	22 (45%)	20 (40%)	20 (40%)
Sclerosis	1 (2%)		
Peliosis hepatis		1 (2%)	
Necrosis, NOS	1 (2%)		1 (2%)
Necrosis, focal		2 (4%)	1 (2%)
Metamorphosis, fatty	19 (39%)	13 (26%)	22 (44%)
Basophilic cyto change	35 (71%)	33 (66%)	33 (66%)
Ground glass cyto change			1 (2%)
Focal cellular change	1 (2%)		2 (4%)
Eosinophilic cyto change		1 (2%)	
Clear cell change	2 (4%)		2 (4%)
Angiectasis	1 (2%)		1 (2%)
#Hepatic capsule	(49)	(50)	(50)
Fibrosis, focal	1 (2%)		
#Liver/centrilobular	(49)	(50)	(50)
Congestion, NOS		1 (2%)	
#Bile duct	(49)	(50)	(50)
Hyperplasia, NOS	24 (49%)	26 (52%)	26 (52%)
#Pancreas	(49)	(14)	(50)
Inflammation, chronic	6 (12%)	2 (14%)	5 (10%)
#Pancreatic acinus	(49)	(14)	(50)
Atrophy, NOS	6 (12%)	1 (7%)	7 (14%)
#Glandular stomach	(49)	(10)	(49)
Necrosis, focal			1 (2%)
#Forestomach	(49)	(10)	(49)
Ulcer, NOS	1 (2%)		2 (4%)
Inflammation, acute		1 (10%)	1 (2%)
Inflammation, chronic	2 (4%)		
Hyperplasia, basal cell			1 (2%)
Hyperkeratosis	1 (2%)		1 (2%)
Acanthosis	2 (4%)		
#Colon	(47)	(12)	(50)
Parasitism	11 (23%)		5 (10%)
#Cecum	(47)	(12)	(50)
Dilatation, NOS		1 (8%)	
Parasitism			2 (4%)
URINARY SYSTEM			
#Kidney	(49)	(19)	(50)
Nephrosis, NOS	43 (88%)	15 (79%)	45 (90%)
Necrosis, cortical	1 (2%)		
#Kidney/tubule	(49)	(19)	(50)
Calcification, NOS		1 (5%)	

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

	Vehicle Control	Low Dose	High Dose
URINARY SYSTEM (Continued)			
#Kidney/pelvis	(49)	(19)	(50)
Inflammation, chronic			1 (2%)
Hyperplasia, epithelial			1 (2%)
#Urinary bladder	(46)	(10)	(49)
Hyperplasia, epithelial			1 (2%)
ENDOCRINE SYSTEM			
#Anterior pituitary	(48)	(50)	(50)
Cyst, NOS	3 (6%)		2 (4%)
Multiple cysts	5 (10%)	6 (12%)	3 (6%)
Cytomegaly	1 (2%)		
Hyperplasia, focal	2 (4%)	1 (2%)	1 (2%)
Angiectasis	3 (6%)	1 (2%)	4 (8%)
#Adrenal	(49)	(50)	(50)
Hyperplasia, focal	1 (2%)		
#Adrenal cortex	(49)	(50)	(50)
Accessory structure			3 (6%)
Necrosis, focal	2 (4%)	2 (4%)	
Metamorphosis, fatty	1 (2%)	1 (2%)	
Hypertrophy, focal	11 (22%)	9 (18%)	16 (32%)
Hyperplasia, focal	22 (45%)	19 (38%)	18 (36%)
Angiectasis	1 (2%)	2 (4%)	
#Adrenal medulla	(49)	(50)	(50)
Cyst, NOS	1 (2%)		
Hyperplasia, focal	4 (8%)	2 (4%)	5 (10%)
#Thyroid	(46)	(12)	(48)
Cystic follicles			1 (2%)
Hyperplasia, C-cell	4 (9%)		5 (10%)
Hyperplasia, follicular cell		1 (8%)	1 (2%)
#Parathyroid	(20)	(7)	(22)
Hyperplasia, NOS			2 (9%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Inflammation, suppurative	1 (2%)		
Hyperplasia, NOS	13 (26%)	10 (20%)	11 (22%)
*Clitoral gland	(50)	(50)	(50)
Inflammation, suppurative	4 (8%)	2 (4%)	6 (12%)
Inflammation, chronic	2 (4%)		6 (12%)
Hyperplasia, NOS		2 (4%)	1 (2%)
Hyperplasia, focal	1 (2%)		
*Vagina	(50)	(50)	(50)
Inflammation, suppurative		2 (4%)	
#Uterus	(49)	(23)	(49)
Hydrometra			1 (2%)
Hemorrhage		1 (4%)	1 (2%)
Inflammation, suppurative	1 (2%)	1 (4%)	
Inflammation, acute	1 (2%)		
#Uterus/endometrium	(49)	(23)	(49)
Hyperplasia, cystic	7 (14%)	1 (4%)	2 (4%)
#Ovary	(49)	(16)	(50)
Cyst, NOS	7 (14%)	1 (6%)	10 (20%)
Inflammation, suppurative	1 (2%)		
Inflammation, chronic	1 (2%)		
Hyperplasia, focal	1 (2%)		

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

	Vehicle Control	Low Dose	High Dose
NERVOUS SYSTEM			
#Brain	(49)	(10)	(50)
Hydrocephalus, NOS	1 (2%)		
SPECIAL SENSE ORGANS			
None			
MUSCULOSKELETAL SYSTEM			
*Muscle of thorax	(50)	(50)	(50)
Cyst, NOS			1 (2%)
BODY CAVITIES			
*Abdominal cavity	(50)	(50)	(50)
Hematoma, NOS		1 (2%)	
*Mesentery	(50)	(50)	(50)
Inflammation, chronic focal			1 (2%)
Necrosis, fat	3 (6%)		3 (6%)
ALL OTHER SYSTEMS			
Site unknown			
Necrosis, NOS		1	
Adipose tissue			
Hemorrhage			1
Necrosis, NOS	2		1
SPECIAL MORPHOLOGY SUMMARY			
Autolysis/necropsy/no histology	1		

* 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 IODINATED GLYCEROL

		PAGE
TABLE C1	SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF IODINATED GLYCEROL	117
TABLE C2	INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF IODINATED GLYCEROL	120
TABLE C3	ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF IODINATED GLYCEROL	126
TABLE C4	SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF IODINATED GLYCEROL	130

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

	Vehicle Control	Low Dose	High Dose
Animals initially in study	50	50	50
Animals necropsied	50	50	50
Animals examined histopathologically	50	50	50
INTEGUMENTARY SYSTEM			
*Subcutaneous tissue	(50)	(50)	(50)
Fibroma	3 (6%)	4 (8%)	
Fibrosarcoma	8 (16%)	12 (24%)	4 (8%)
Liposarcoma	1 (2%)		
#Nasopharynx	(45)	(3)	(38)
Fibrous histiocytoma	1 (2%)		
RESPIRATORY SYSTEM			
#Lung	(50)	(19)	(50)
Hepatocellular carcinoma, metastatic			1 (2%)
Alveolar/bronchiolar adenoma	8 (16%)	6 (32%)	10 (20%)
Alveolar/bronchiolar carcinoma	1 (2%)		
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Malignant lymphoma, lymphocytic type	2 (4%)	1 (2%)	1 (2%)
Malignant lymphoma, histiocytic type	1 (2%)	1 (2%)	
Malignant lymphoma, mixed type	6 (12%)	2 (4%)	1 (2%)
#Spleen	(50)	(16)	(50)
Malignant lymphoma, mixed type			1 (2%)
#Mesenteric lymph node	(48)	(22)	(49)
Malignant lymphoma, lymphocytic type	1 (2%)		
*Periodontal tissues	(50)	(50)	(50)
Mast cell tumor	1 (2%)		
CIRCULATORY SYSTEM			
#Liver	(50)	(19)	(50)
Hemangiosarcoma		1 (5%)	1 (2%)
DIGESTIVE SYSTEM			
#Liver	(50)	(19)	(50)
Hepatocellular adenoma	8 (16%)	8 (42%)	7 (14%)
Hepatocellular carcinoma	2 (4%)	1 (5%)	6 (12%)
Mixed hepato/cholangio carcinoma	2 (4%)		
#Bile duct	(50)	(19)	(50)
Bile duct carcinoma	1 (2%)		
#Jejunum	(50)	(6)	(49)
Adenocarcinoma, NOS		1 (17%)	
URINARY SYSTEM			
#Kidney	(50)	(8)	(50)
Tubular cell adenoma	1 (2%)		

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

	Vehicle Control	Low Dose	High Dose
ENDOCRINE SYSTEM			
#Anterior pituitary	(44)	(42)	(45)
Adenoma, NOS		1 (2%)	1 (2%)
#Adrenal/capsule	(50)	(4)	(50)
Adenoma, NOS	1 (2%)		1 (2%)
#Adrenal medulla	(50)	(4)	(50)
Pheochromocytoma			3 (6%)
Pheochromocytoma, malignant	1 (2%)		
#Thyroid	(48)	(50)	(50)
Follicular cell adenoma	3 (6%)	6 (12%)	
#Pancreatic islets	(50)	(6)	(50)
Islet cell adenoma			1 (2%)
REPRODUCTIVE SYSTEM			
#Testis	(50)	(4)	(50)
Interstitial cell tumor	1 (2%)		1 (2%)
NERVOUS SYSTEM			
None			
SPECIAL SENSE ORGANS			
#Harderian gland	(50)	(44)	(50)
Carcinoma, NOS		2 (5%)	
Adenoma, NOS	4 (8%)	4 (9%)	4 (8%)
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
None			
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Bile duct carcinoma, metastatic	1 (2%)		
Hepatocellular carcinoma, metastatic	1 (2%)		
Mixed hepato/cholangio carcinoma, metastatic	1 (2%)		
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	7	5	9
Moribund sacrifice	7	5	10
Terminal sacrifice	36	40	31

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

	Vehicle Control	Low Dose	High Dose
TUMOR SUMMARY			
Total animals with primary tumors**	33	29	29
Total primary tumors	57	50	42
Total animals with benign tumors	23	16	22
Total benign tumors	30	29	28
Total animals with malignant tumors	22	19	14
Total malignant tumors	26	21	14
Total animals with secondary tumors##	2		1
Total secondary tumors	3		1
Total animals with tumors-- uncertain benign or malignant	1		
Total uncertain tumors	1		

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

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

ANIMAL NUMBER	031	050	020	017	008	037	006	023	010	002	014	022	035	048	001	003	004	009	011	012	013	015	016	018	019
WEEKS ON STUDY	045	050	075	082	091	092	093	093	094	098	098	099	102	102	105	105	105	105	105	105	105	105	105	105	105
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+
Fibroma																									
Fibrosarcoma						X						X	X											X	
Liposarcoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma						X								X											
Alveolar/bronchiolar carcinoma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nasal cavity	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma																									
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+
Malignant lymphoma, lymphocytic type													X												
Thymus	–	+	–	–	+	–	–	+	–	–	+	+	–	–	+	+	+	+	+	–	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Mast cell tumor																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma											X		X		X									X	
Hepatocellular carcinoma								X		X															
Mixed hepato/cholangio carcinoma			X	X																					
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bile duct carcinoma								X																	
Gallbladder & common bile duct	+	N	N	+	+	+	+	+	N	N	+	+	+	+	+	+	N	+	+	+	N	+	+	N	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenoma																			X						
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	–
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS					X																				
Pheochromocytoma, malignant										X															
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma										X															
Parathyroid	+	–	+	–	+	–	+	–	+	+	+	+	–	+	–	+	+	+	+	–	+	+	+	–	+
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor											X														
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS														X											
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Bile duct carcinoma, metastatic								X																	
Hepatocellular carcinoma, metastatic								X																	
Mixed hepato/cholangio carcinoma, metastatic				X																					
Malignant lymphoma, lymphocytic type																									
Malignant lymphoma, histiocytic type																									
Malignant lymphoma, mixed type											X													X	

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

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

ANIMAL NUMBER	0021	0024	0025	0026	0027	0028	0029	0030	0033	0034	0036	0038	0040	0041	0042	0043	0044	0045	0046	0049	0050	0057	0032	0039	0047	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	106	106	106	106	106	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	*50
Fibroma								X			X		X													3
Fibrosarcoma	X											X							X					X		8
Liposarcoma																									X	1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma		X										X			X	X	X				X					8
Alveolar/bronchiolar carcinoma											X															1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nasal cavity	+	+	–	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	–	45
Fibrous histiocytoma																			X							1
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Malignant lymphoma, lymphocytic type																										1
Thymus	–	+	+	–	+	+	–	+	–	+	+	+	+	+	+	–	+	+	+	+	+	–	–	–	–	31
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Mast cell tumor																			X							1
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma						X	X								X	X										8
Hepatocellular carcinoma																										2
Mixed hepato/cholangio carcinoma																										2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bile duct carcinoma																										1
Gallbladder & common bile duct	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	47
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tubular cell adenoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	–	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+		44
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS																										1
Pheochromocytoma, malignant																										1
Thyroid	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Follicular cell adenoma										X			X													3
Parathyroid	–	–	–	+	–	–	+	+	+	–	–	+	–	–	–	+	+	–	+	+	+	+	–	+	+	30
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell tumor																										1
Prostate	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	–	+	+	46
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS							X								X			X								4
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Bile duct carcinoma, metastatic																										1
Hepatocellular carcinoma, metastatic																										1
Mixed hepato/cholangio carcinoma, meta																										1
Malignant lymphoma, lymphocytic type						X							X													2
Malignant lymphoma, histiocytic type		X																								1
Malignant lymphoma, mixed type			X	X					X							X										6

* Animals necropsied

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF IODINATED GLYCEROL: LOW DOSE

ANIMAL NUMBER	0117	0113	0227	0112	0447	0115	0442	0444	0220	0228	0001	0002	0003	0004	0005	0006	0007	0008	0009	0110	0111	0114	0116	0118	0119
WEEKS ON STUDY	086	087	088	091	095	097	098	099	103	103	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	N	+	+	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	+	N	N	N	N
Fibroma								X																X	
Fibrosarcoma	X	X	X	X		X	X	X	X					X						X					X
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	−	−	+	−	+	−	−	+	−	+	+	−	−	+	−	+	+	−	+	+
Alveolar/bronchiolar adenoma			X					X													X			X	
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nasal cavity	+	−	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Spleen	+	+	+	+	+	+	+	+	+	+	−	−	−	+	−	−	−	−	−	+	+	−	−	−	−
Lymph nodes	+	+	+	+	+	+	+	−	+	−	−	−	−	+	−	+	+	−	−	−	+	+	+	+	+
Thymus	−	−	−	+	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	−	−	−	−	−	−
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Liver	+	+	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	+	−	−
Hepatocellular adenoma	X		X																						
Hepatocellular carcinoma							X																		
Hemangiosarcoma																							X		
Bile duct	+	+	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	+	−	−
Gallbladder & common bile duct	+	+	+	+	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	+	+	+	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Esophagus	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Adenocarcinoma, NOS																									
Large intestine	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
URINARY SYSTEM																									
Kidney	+	+	+	+	+	−	+	+	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Urinary bladder	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	−	+	−	−	−	−
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																					X				
Adrenal	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma	X																X				X				
Parathyroid	+	−	−	−	+	+	+	+	−	+	+	−	+	−	+	−	−	−	+	−	+	+	−	−	+
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Testis	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Prostate	+	−	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
NERVOUS SYSTEM																									
Brain	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
SPECIAL SENSE ORGANS																									
Harderian gland	−	−	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS					X																				
Adenoma, NOS																	X				X				
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, lymphocytic type																					X				
Malignant lymphoma, histiocytic type										X															
Malignant lymphoma, mixed type						X																			

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: LOW DOSE (Continued)

ANIMAL NUMBER	021	022	023	024	025	026	029	030	031	032	033	034	035	036	037	038	039	040	041	043	045	046	048	049	050	TOTAL TISSUES TUMORS
WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	*50
Fibroma										X											X					4
Fibrosarcoma																				X						12
RESPIRATORY SYSTEM																										
Lungs and bronchi	–	+	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–	+	–	–	–	19
Alveolar/bronchiolar adenoma																				X		X				6
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nasal cavity	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	3
HEMATOPOIETIC SYSTEM																										
Bone marrow	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	4
Spleen	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	+	+	16
Lymph nodes	–	–	–	–	–	–	–	–	–	–	–	–	+	–	+	–	–	–	–	–	+	–	–	+	+	22
Thymus	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	2
CIRCULATORY SYSTEM																										
Heart	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	5
DIGESTIVE SYSTEM																										
Salivary gland	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	4
Liver	+	+	–	–	–	+	–	–	–	–	–	+	–	+	–	–	+	–	–	–	+	–	–	+	–	19
Hepatocellular adenoma	X	X				X						X		X							X					8
Hepatocellular carcinoma																										1
Hemangiosarcoma																										1
Bile duct	+	+	–	–	–	+	–	–	–	–	–	+	–	+	–	–	+	–	–	–	+	–	–	+	–	19
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	+	N	*50
Pancreas	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	6
Esophagus	–	+	+	+	–	+	+	+	+	–	+	+	–	+	+	+	+	+	+	+	+	–	+	+	+	44
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Small intestine	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–	6
Adenocarcinoma, NOS																								X		1
Large intestine	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	4
URINARY SYSTEM																										
Kidney	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	8
Urinary bladder	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–		7
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	–	–	+	–	–	+	–	+	+	+	+	+	+	+	+	+	+	+	–	+	+	–	42
Adenoma, NOS																										1
Adrenal	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	4
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell adenoma		X				X		X																		6
Parathyroid	+	–	–	+	–	+	–	–	+	–	+	–	+	+	+	+	–	–	+	–	–	+	–	–	+	25
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Testis	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	4
Prostate	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	3
NERVOUS SYSTEM																										
Brain	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	4
SPECIAL SENSE ORGANS																										
Harderian gland	+	+	+	+	+	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Carcinoma, NOS						X																				2
Adenoma, NOS		X																				X				4
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malignant lymphoma, lymphocytic type																										1
Malignant lymphoma, histiocytic type																										1
Malignant lymphoma, mixed type																									X	2

* Animals necropsied

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF IODINATED GLYCEROL: HIGH DOSE

ANIMAL NUMBER	0191	0311	0355	0399	0411	0011	0255	0181	0099	0422	0477	0044	0222	0088	0388	0144	0266	0400	0002	0033	0055	0066	0077	0110	0111
WEEKS ON STUDY	0002	0113	0133	0337	0337	0551	0667	0774	0779	0885	0885	0889	0889	0992	0994	1000	1003	1033	1044	1044	1044	1044	1044	1044	1044
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	N	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma									X							X		X			X				
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic														X											
Alveolar/bronchiolar adenoma		X												X											
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nasal cavity	–	–	–	–	–	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, mixed type																								X	
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	–	+	+	+	+	–	–	+	–	+	–	–	+	+	–	–	+	+	+	+	–	+	–	–
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma								X							X				X	X				
Hepatocellular carcinoma							X			X	X			X			X								
Hemangiosarcoma																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	N	+	N	+	N	N	+	+	N	N	N	+	+	+	+	N	+	+	+	+	+	+	+	N
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	+	+	+	+	+
Adenoma, NOS								X																	
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Pheochromocytoma											X						X							X	
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid	+	–	–	–	+	–	–	–	–	+	+	+	–	–	+	–	–	–	–	–	–	–	–	+	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma										X															
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor								X																	
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																					X	X			
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, lymphocytic type														X											
Malignant lymphoma, mixed type																									

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: HIGH DOSE (Continued)

ANIMAL NUMBER	0012	0013	0015	0016	0017	0020	0021	0023	0024	0027	0029	0028	0030	0032	0033	0034	0036	0037	0043	0044	0045	0046	0048	0049	0050	TOTAL:
WEEKS ON STUDY	1004	1004	1004	1004	1004	1004	1004	1004	1004	1004	1004	1005	1005	1005	1005	1005	1005	1005	1005	1005	1005	1005	1005	1005	1005	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibrosarcoma																										4
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic																										1
Alveolar/bronchiolar adenoma	X					X	X					X		X			X		X	X						10
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nasal cavity	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	–	+	38
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Malignant lymphoma, mixed type																										1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	–	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	36
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma																	X	X			X					7
Hepatocellular carcinoma																								X		6
Hemangiosarcoma												X														1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	N	+	+	+	N	N	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Large intestine	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	–	–	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Adenoma, NOS																										1
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS												X														1
Pheochromocytoma																										3
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid	+	–	+	–	–	–	+	–	+	+	+	–	–	+	+	–	+	–	–	–	–	–	+	–	+	19
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet cell adenoma																										1
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell tumor																										1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	49
SPECIAL SENSE ORGANS																										
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS			X			X																				4
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malignant lymphoma, lymphocytic type																										1
Malignant lymphoma, mixed type																			X							1

* Animals necropsied

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

	Vehicle Control	125 mg/kg	250 mg/kg
Subcutaneous Tissue: Fibroma			
Overall Rates (a)	3/50 (6%)	4/50 (8%)	0/50 (0%)
Adjusted Rates (b)	8.3%	9.7%	0.0%
Terminal Rates (c)	3/36 (8%)	3/40 (7%)	0/32 (0%)
Week of First Observation	104	99	
Life Table Tests (d)	P=0.138N	P=0.556	P=0.142N
Incidental Tumor Tests (d)	P=0.158N	P=0.527	P=0.142N
Cochran-Armitage Trend Test (d)	P=0.118N		
Fisher Exact Test (d)		P=0.500	P=0.121N
Subcutaneous Tissue: Fibrosarcoma			
Overall Rates (a)	8/50 (16%)	12/50 (24%)	4/50 (8%)
Adjusted Rates (b)	20.1%	24.6%	10.8%
Terminal Rates (c)	5/36 (14%)	4/40 (10%)	1/32 (3%)
Week of First Observation	92	86	79
Life Table Tests (d)	P=0.253N	P=0.315	P=0.248N
Incidental Tumor Tests (d)	P=0.204N	P=0.232	P=0.262N
Cochran-Armitage Trend Test (d)	P=0.170N		
Fisher Exact Test (d)		P=0.227	P=0.178N
Subcutaneous Tissue: Fibroma or Fibrosarcoma			
Overall Rates (a)	11/50 (22%)	15/50 (30%)	4/50 (8%)
Adjusted Rates (b)	27.9%	30.8%	10.8%
Terminal Rates (c)	8/36 (22%)	7/40 (18%)	1/32 (3%)
Week of First Observation	92	86	79
Life Table Tests (d)	P=0.102N	P=0.355	P=0.084N
Incidental Tumor Tests (d)	P=0.069N	P=0.286	P=0.083N
Cochran-Armitage Trend Test (d)	P=0.052N		
Fisher Exact Test (d)		P=0.247	P=0.045N
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	8/50 (16%)	(e) 6/19 (32%)	10/50 (20%)
Adjusted Rates (b)	20.7%		28.5%
Terminal Rates (c)	6/36 (17%)		8/32 (25%)
Week of First Observation	92		13
Life Table Test (d)			P=0.296
Incidental Tumor Test (d)			P=0.397
Fisher Exact Test (d)			P=0.397
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	9/50 (18%)	(e) 6/19 (32%)	10/50 (20%)
Adjusted Rates (b)	23.3%		28.5%
Terminal Rates (c)	7/36 (19%)		8/32 (25%)
Week of First Observation	92		13
Life Table Test (d)			P=0.387
Incidental Tumor Test (d)			P=0.495
Fisher Exact Test (d)			P=0.500
Hematopoietic System: Malignant Lymphoma, Lymphocytic Type			
Overall Rates (a)	3/50 (6%)	(e,f) 1/50 (2%)	1/50 (2%)
Adjusted Rates (b)	8.0%		2.6%
Terminal Rates (c)	2/36 (6%)		0/32 (0%)
Week of First Observation	102		89
Life Table Test (d)			P=0.354N
Incidental Tumor Test (d)			P=0.324N
Fisher Exact Test (d)			P=0.309N

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

	Vehicle Control	125 mg/kg	250 mg/kg
Hematopoietic System: Malignant Lymphoma, Mixed Type			
Overall Rates (a)	6/50 (12%)	(e,f) 2/50 (4%)	2/50 (4%)
Adjusted Rates (b)	16.0%		6.2%
Terminal Rates (c)	5/36 (14%)		2/32 (6%)
Week of First Observation	98		104
Life Table Test (d)			P=0.177N
Incidental Tumor Test (d)			P=0.201N
Fisher Exact Test (d)			P=0.135N
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	10/50 (20%)	(e,f) 4/50 (8%)	3/50 (6%)
Adjusted Rates (b)	26.1%		8.7%
Terminal Rates (c)	8/36 (22%)		2/32 (6%)
Week of First Observation	98		89
Life Table Test (d)			P=0.064N
Incidental Tumor Test (d)			P=0.064N
Fisher Exact Test (d)			P=0.036N
Liver: Hepatocellular Adenoma			
Overall Rates (a)	8/50 (16%)	(e) 8/19 (42%)	7/50 (14%)
Adjusted Rates (b)	20.8%		19.9%
Terminal Rates (c)	6/36 (17%)		5/32 (16%)
Week of First Observation	98		74
Life Table Test (d)			P=0.599N
Incidental Tumor Test (d)			P=0.577
Fisher Exact Test (d)			P=0.500N
Liver: Hepatocellular Carcinoma			
Overall Rates (a)	2/50 (4%)	(e) 1/19 (5%)	6/50 (12%)
Adjusted Rates (b)	4.7%		15.0%
Terminal Rates (c)	0/36 (0%)		1/32 (3%)
Week of First Observation	93		67
Life Table Test (d)			P=0.106
Incidental Tumor Test (d)			P=0.134
Fisher Exact Test (d)			P=0.134
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	10/50 (20%)	(e) 9/19 (47%)	13/50 (26%)
Adjusted Rates (b)	24.6%		32.3%
Terminal Rates (c)	6/36 (17%)		6/32 (19%)
Week of First Observation	93		67
Life Table Test (d)			P=0.226
Incidental Tumor Test (d)			P=0.222
Fisher Exact Test (d)			P=0.317
Adrenal Gland: Pheochromocytoma			
Overall Rates (a)	0/50 (0%)	(e) 0/4 (0%)	3/50 (6%)
Adjusted Rates (b)	0.0%		8.3%
Terminal Rates (c)	0/36 (0%)		1/32 (3%)
Week of First Observation			85
Life Table Test (d)			P=0.108
Incidental Tumor Test (d)			P=0.108
Fisher Exact Test (d)			P=0.121
Adrenal Gland: Pheochromocytoma or Malignant Pheochromocytoma			
Overall Rates (a)	1/50 (2%)	(e) 0/4 (0%)	3/50 (6%)
Adjusted Rates (b)	2.4%		8.3%
Terminal Rates (c)	0/36 (0%)		1/32 (3%)
Week of First Observation	98		85
Life Table Test (d)			P=0.270
Incidental Tumor Test (d)			P=0.228
Fisher Exact Test (d)			P=0.309

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

	Vehicle Control	125 mg/kg	250 mg/kg
Thyroid Gland: Follicular Cell Adenoma			
Overall Rates (a)	3/48 (6%)	6/50 (12%)	0/50 (0%)
Adjusted Rates (b)	8.0%	14.2%	0.0%
Terminal Rates (c)	2/35 (6%)	5/40 (13%)	0/32 (0%)
Week of First Observation	98	86	
Life Table Tests (d)	P=0.171N	P=0.308	P=0.144N
Incidental Tumor Tests (d)	P=0.155N	P=0.306	P=0.168N
Cochran-Armitage Trend Test (d)	P=0.134N		
Fisher Exact Test (d)		P=0.264	P=0.114N
Harderian Gland: Adenoma			
Overall Rates (a)	4/50 (8%)	4/44 (9%)	4/50 (8%)
Adjusted Rates (b)	10.7%	10.5%	12.5%
Terminal Rates (c)	3/36 (8%)	4/38 (11%)	4/32 (13%)
Week of First Observation	102	104	104
Life Table Tests (d)	P=0.508	P=0.610N	P=0.578
Incidental Tumor Tests (d)	P=0.479	P=0.637N	P=0.538
Cochran-Armitage Trend Test (d)	P=0.572		
Fisher Exact Test (d)		P=0.569	P=0.643
Harderian Gland: Adenoma or Carcinoma			
Overall Rates (a)	4/50 (8%)	6/44 (14%)	4/50 (8%)
Adjusted Rates (b)	10.7%	15.0%	12.5%
Terminal Rates (c)	3/36 (8%)	5/38 (13%)	4/32 (13%)
Week of First Observation	102	95	104
Life Table Tests (d)	P=0.495	P=0.412	P=0.578
Incidental Tumor Tests (d)	P=0.444	P=0.361	P=0.538
Cochran-Armitage Trend Test (d)	P=0.567		
Fisher Exact Test (d)		P=0.291	P=0.643
All Sites: Benign Tumors			
Overall Rates (a)	23/50 (46%)	16/50 (32%)	22/50 (44%)
Adjusted Rates (b)	54.5%	36.7%	55.6%
Terminal Rates (c)	17/36 (47%)	13/40 (33%)	15/32 (47%)
Week of First Observation	91	86	13
Life Table Tests (d)	P=0.435	P=0.066N	P=0.446
Incidental Tumor Tests (d)	P=0.523N	P=0.063N	P=0.550
Cochran-Armitage Trend Test (d)	P=0.459N		
Fisher Exact Test (d)		P=0.109N	P=0.500N
All Sites: Malignant Tumors			
Overall Rates (a)	22/50 (44%)	19/50 (38%)	14/50 (28%)
Adjusted Rates (b)	49.5%	38.0%	33.6%
Terminal Rates (c)	14/36 (39%)	9/40 (23%)	5/32 (16%)
Week of First Observation	75	86	67
Life Table Tests (d)	P=0.166N	P=0.251N	P=0.194N
Incidental Tumor Tests (d)	P=0.057N	P=0.368N	P=0.076N
Cochran-Armitage Trend Test (d)	P=0.060N		
Fisher Exact Test (d)		P=0.343N	P=0.072N
All Sites: All Tumors			
Overall Rates (a)	33/50 (66%)	29/50 (58%)	29/50 (58%)
Adjusted Rates (b)	71.6%	58.0%	65.7%
Terminal Rates (c)	23/36 (64%)	19/40 (48%)	17/32 (53%)
Week of First Observation	75	86	13
Life Table Tests (d)	P=0.501N	P=0.169N	P=0.548N
Incidental Tumor Tests (d)	P=0.323N	P=0.222N	P=0.370N
Cochran-Armitage Trend Test (d)	P=0.237N		
Fisher Exact Test (d)		P=0.269N	P=0.269N

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

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(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 is indicated by (N).
(e) Incomplete sampling of tissues
(f) Sixteen spleens and 19 livers were examined microscopically.

TABLE C4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF IODINATED GLYCEROL

	Vehicle Control	Low Dose	High Dose
Animals initially in study	50	50	50
Animals necropsied	50	50	50
Animals examined histopathologically	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Inflammation, NOS	1 (2%)		1 (2%)
Ulcer, NOS	5 (10%)	1 (2%)	1 (2%)
Hyperplasia, NOS	1 (2%)		
*Subcutaneous tissue	(50)	(50)	(50)
Inflammation, NOS		1 (2%)	
Fibrosis	2 (4%)	3 (6%)	
RESPIRATORY SYSTEM			
#Nasopharynx	(45)	(3)	(38)
Inflammation, NOS	5 (11%)	1 (33%)	4 (11%)
#Lung/bronchus	(50)	(19)	(50)
Foreign body, NOS			1 (2%)
#Lung	(50)	(19)	(50)
Bronchiectasis	10 (20%)	1 (5%)	6 (12%)
Congestion, NOS		2 (11%)	
Hemorrhage		1 (5%)	
Inflammation, NOS	2 (4%)	8 (42%)	1 (2%)
Histiocytosis		2 (11%)	
#Lung/alveoli	(50)	(19)	(50)
Metaplasia, NOS	19 (38%)	6 (32%)	18 (36%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Hematopoiesis			1 (2%)
#Bone marrow	(50)	(4)	(50)
Hyperplasia, neutrophilic	13 (26%)	1 (25%)	2 (4%)
#Spleen	(50)	(16)	(50)
Congestion, NOS	1 (2%)		3 (6%)
Hemosiderosis	2 (4%)		8 (16%)
Hyperplasia, lymphoid		2 (13%)	
Hematopoiesis	30 (60%)	12 (75%)	21 (42%)
#Lymph node	(48)	(22)	(49)
Plasma cell infiltrate	1 (2%)		
Hyperplasia, lymphoid	1 (2%)		
#Mandibular lymph node	(48)	(22)	(49)
Pigmentation, NOS	1 (2%)		
#Lumbar lymph node	(48)	(22)	(49)
Plasma cell infiltrate			1 (2%)
Histiocytosis	1 (2%)		
#Mesenteric lymph node	(48)	(22)	(49)
Congestion, NOS	20 (42%)	13 (59%)	14 (29%)
Inflammation, NOS			1 (2%)
Histiocytosis		1 (5%)	
Hyperplasia, lymphoid		1 (5%)	
Hematopoiesis		4 (18%)	4 (8%)
#Axillary lymph node	(48)	(22)	(49)
Plasma cell infiltrate			1 (2%)
#Inguinal lymph node	(48)	(22)	(49)
Plasma cell infiltrate	1 (2%)		
#Liver	(50)	(19)	(50)
Hematopoiesis	1 (2%)		
#Peyer's patch	(50)	(6)	(49)
Hyperplasia, lymphoid	1 (2%)		

TABLE C4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF IODINATED GLYCEROL (Continued)

	Vehicle Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM (Continued)			
#Thymus	(31)	(2)	(36)
Cyst, NOS		1 (50%)	
Hyperplasia, lymphoid			1 (3%)
CIRCULATORY SYSTEM			
#Lung	(50)	(19)	(50)
Perivasculitis	1 (2%)		
#Heart	(50)	(5)	(50)
Inflammation, acute focal	2 (4%)		
Periarteritis	1 (2%)		2 (4%)
#Myocardium	(50)	(5)	(50)
Degeneration, NOS	48 (96%)	3 (60%)	35 (70%)
#Endocardium	(50)	(5)	(50)
Fibrosis			1 (2%)
*Aorta	(50)	(50)	(50)
Thrombosis, NOS	1 (2%)		
DIGESTIVE SYSTEM			
*Tooth	(50)	(50)	(50)
Inflammation, acute	6 (12%)		1 (2%)
Abscess, NOS	4 (8%)		1 (2%)
#Salivary gland	(50)	(4)	(49)
Dilatation/ducts			1 (2%)
Inflammation, NOS	2 (4%)		3 (6%)
Hypertrophy, NOS			1 (2%)
#Liver	(50)	(19)	(50)
Hernia, NOS		1 (5%)	
Congestion, NOS			4 (8%)
Hemorrhage		1 (5%)	
Inflammation, chronic focal			1 (2%)
Necrosis, focal	4 (8%)	2 (11%)	6 (12%)
Metamorphosis, fatty	3 (6%)		1 (2%)
Cytoplasmic change, NOS	3 (6%)	1 (5%)	4 (8%)
*Gallbladder	(50)	(50)	(50)
Dilatation, NOS			1 (2%)
#Pancreatic acinus	(50)	(6)	(50)
Cytoplasmic vacuolization	1 (2%)		
Hyperplasia, focal	2 (4%)		
#Periesophageal tissue	(48)	(44)	(49)
Inflammation, chronic			1 (2%)
#Glandular stomach	(49)	(49)	(50)
Ulcer, NOS			1 (2%)
Metaplasia, squamous	1 (2%)		
#Forestomach	(49)	(49)	(50)
Inflammation, NOS			1 (2%)
Ulcer, NOS			2 (4%)
Hyperkeratosis			5 (10%)
Acanthosis		1 (2%)	5 (10%)
#Jejunum	(50)	(6)	(49)
Inflammation, NOS		1 (17%)	1 (2%)
Ulcer, NOS			1 (2%)
Abscess, NOS	1 (2%)		

TABLE C4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF IODINATED GLYCEROL (Continued)

	Vehicle Control	Low Dose	High Dose
URINARY SYSTEM			
#Kidney	(50)	(8)	(50)
Mineralization	1 (2%)		2 (4%)
Glomerulonephritis, NOS	44 (88%)	8 (100%)	34 (68%)
Inflammation, acute focal	2 (4%)		
Abscess, NOS		1 (13%)	
Inflammation, chronic focal	3 (6%)		3 (6%)
Scar	3 (6%)		6 (12%)
Nephrosis, NOS	2 (4%)		
Necrosis, focal	1 (2%)		
Cytomegaly			1 (2%)
#Kidney/tubule	(50)	(8)	(50)
Cast, NOS			2 (4%)
Pigmentation, NOS	1 (2%)		
Regeneration, NOS	10 (20%)		16 (32%)
#Urinary bladder	(50)	(7)	(49)
Calculus, unknown gross or microscopic		1 (14%)	
Calculus, gross observation only		2 (29%)	1 (2%)
Calculus, microscopic examination			2 (4%)
Hemorrhage			1 (2%)
Inflammation, acute/chronic	1 (2%)		
ENDOCRINE SYSTEM			
#Anterior pituitary	(44)	(42)	(45)
Cyst, NOS	1 (2%)	2 (5%)	5 (11%)
Hyperplasia, focal		1 (2%)	5 (11%)
#Pituitary/basophil cell	(44)	(42)	(45)
Cytoplasmic vacuolization			1 (2%)
#Adrenal cortex	(50)	(4)	(50)
Focal cellular change	5 (10%)		5 (10%)
Hyperplasia, focal			2 (4%)
#Adrenal medulla	(50)	(4)	(50)
Hyperplasia, focal	2 (4%)		1 (2%)
#Thyroid	(48)	(50)	(50)
Mineralization		1 (2%)	
Inflammation, NOS	2 (4%)		1 (2%)
Hyperplasia, follicular cell	3 (6%)	46 (92%)	34 (68%)
#Thyroid follicle	(48)	(50)	(50)
Dilatation, NOS		28 (56%)	32 (64%)
#Parathyroid	(30)	(25)	(19)
Cyst, NOS	1 (3%)	1 (4%)	
#Pancreatic islets	(50)	(6)	(50)
Hyperplasia, NOS			1 (2%)
REPRODUCTIVE SYSTEM			
*Penis	(50)	(50)	(50)
Abscess, NOS		1 (2%)	
Inflammation, active chronic	2 (4%)		
*Preputial gland	(50)	(50)	(50)
Mineralization		1 (2%)	
Dilatation, NOS	1 (2%)	2 (4%)	2 (4%)
Inflammation, NOS	13 (26%)	15 (30%)	16 (32%)
Abscess, NOS	8 (16%)	6 (12%)	4 (8%)
#Prostate	(46)	(3)	(50)
Inflammation, NOS	2 (4%)		1 (2%)
Abscess, NOS			1 (2%)
Atrophy, NOS			1 (2%)
*Seminal vesicle	(50)	(50)	(50)
Dilatation, NOS	1 (2%)	4 (8%)	1 (2%)
Atrophy, NOS	1 (2%)	1 (2%)	1 (2%)

TABLE C4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF IODINATED GLYCEROL (Continued)

	Vehicle Control	Low Dose	High Dose
REPRODUCTIVE SYSTEM (Continued)			
*Coagulating gland	(50)	(50)	(50)
Dilatation, NOS		1 (2%)	
#Testis	(50)	(4)	(50)
Mineralization	5 (10%)		2 (4%)
Hypospermatogenesis	1 (2%)		2 (4%)
Hyperplasia, interstitial cell			2 (4%)
#Testis/tubule	(50)	(4)	(50)
Atrophy, focal	5 (10%)		4 (8%)
*Epididymis	(50)	(50)	(50)
Inflammation, NOS			1 (2%)
Granuloma, foreign body	1 (2%)		
Aspermatogenesis	2 (4%)		1 (2%)
*Scrotum	(50)	(50)	(50)
Abscess, NOS			1 (2%)
NERVOUS SYSTEM			
#Brain	(50)	(4)	(49)
Mineralization	26 (52%)	3 (75%)	18 (37%)
*Spinal cord	(50)	(50)	(50)
Degeneration, NOS			1 (2%)
SPECIAL SENSE ORGANS			
#Harderian gland	(50)	(44)	(50)
Inflammation, NOS	1 (2%)	1 (2%)	
Hyperplasia, NOS	1 (2%)		3 (6%)
Hyperplasia, focal		1 (2%)	
MUSCULOSKELETAL SYSTEM			
*Tarsal joint	(50)	(50)	(50)
Ankylosis	41 (82%)	33 (66%)	29 (58%)
Hemorrhage		2 (4%)	
Inflammation, chronic		2 (4%)	
*Muscle of leg	(50)	(50)	(50)
Degeneration, NOS			1 (2%)
BODY CAVITIES			
*Abdominal cavity	(50)	(50)	(50)
Cyst, NOS		1 (2%)	
*Pelvis	(50)	(50)	(50)
Abscess, NOS			1 (2%)
*Pleura	(50)	(50)	(50)
Inflammation, acute			1 (2%)
*Pericardium	(50)	(50)	(50)
Inflammation, acute			1 (2%)
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Congestion, NOS			1 (2%)
Inflammation, chronic focal	40 (80%)	4 (8%)	41 (82%)
Perineum			
Steatitis	1		
Omentum			
Necrosis, fat		4	2

TABLE C4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF IODINATED GLYCEROL (Continued)

	Vehicle Control	Low Dose	High Dose
SPECIAL MORPHOLOGY SUMMARY			
None			

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

APPENDIX D

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

		PAGE
TABLE D1	SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF IODINATED GLYCEROL	137
TABLE D2	INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF IODINATED GLYCEROL	140
TABLE D3	ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF IODINATED GLYCEROL	146
TABLE D4a	HISTORICAL INCIDENCE OF ANTERIOR PITUITARY GLAND TUMORS IN CONTROL FEMALE B6C3F$_1$ MICE	149
TABLE D4b	HISTORICAL INCIDENCE OF HARDERIAN GLAND TUMORS IN CONTROL FEMALE B6C3F$_1$ MICE	150
TABLE D4c	HISTORICAL INCIDENCE OF HEPATOCELLULAR TUMORS IN CONTROL FEMALE B6C3F$_1$ MICE	151
TABLE D4d	HISTORICAL INCIDENCE OF STOMACH TUMORS IN CONTROL FEMALE B6C3F$_1$ MICE	152
TABLE D5	SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF IODINATED GLYCEROL	153

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

	Vehicle Control	Low Dose	High Dose
Animals initially in study	50	50	50
Animals necropsied	50	50	50
Animals examined histopathologically	50	50	50
INTEGUMENTARY SYSTEM			
*Subcutaneous tissue	(50)	(50)	(50)
Fibrosarcoma		1 (2%)	
RESPIRATORY SYSTEM			
#Lung	(50)	(15)	(50)
Hepatocellular carcinoma, metastatic		1 (7%)	1 (2%)
Alveolar/bronchiolar adenoma	3 (6%)		4 (8%)
Alveolar/bronchiolar carcinoma	1 (2%)		2 (4%)
Pheochromocytoma, metastatic	1 (2%)		
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Malignant lymphoma, undifferentiated type	1 (2%)	1 (2%)	1 (2%)
Malignant lymphoma, lymphocytic type	15 (30%)	5 (10%)	14 (28%)
Malignant lymphoma, histiocytic type	2 (4%)	1 (2%)	1 (2%)
Malignant lymphoma, mixed type	7 (14%)	4 (8%)	8 (16%)
#Spleen	(50)	(31)	(50)
Malignant lymphoma, lymphocytic type			4 (8%)
Malignant lymphoma, mixed type	1 (2%)		3 (6%)
#Thymus	(41)	(7)	(40)
Malignant lymphoma, lymphocytic type			1 (3%)
CIRCULATORY SYSTEM			
#Mesenteric lymph node	(48)	(19)	(47)
Hemangiosarcoma			1 (2%)
#Uterus	(50)	(27)	(50)
Hemangiosarcoma		1 (4%)	
#Uterus/endometrium	(50)	(27)	(50)
Hemangioma	1 (2%)		
#Ovary	(48)	(29)	(49)
Hemangiosarcoma	1 (2%)		
DIGESTIVE SYSTEM			
#Liver	(50)	(50)	(50)
Hepatocellular adenoma		4 (8%)	3 (6%)
Hepatocellular carcinoma		1 (2%)	1 (2%)
#Forestomach	(49)	(50)	(49)
Squamous cell papilloma	1 (2%)	2 (4%)	5 (10%)
#Jejunum	(50)	(12)	(50)
Adenocarcinoma, NOS	1 (2%)		
URINARY SYSTEM			
None			
ENDOCRINE SYSTEM			
#Pituitary intermedia	(47)	(45)	(46)
Adenoma, NOS	1 (2%)		
#Anterior pituitary	(47)	(45)	(46)
Adenoma, NOS	10 (21%)	15 (33%)	24 (52%)

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

	Vehicle Control	Low Dose	High Dose
ENDOCRINE SYSTEM (Continued)			
#Adrenal medulla	(49)	(13)	(50)
Pheochromocytoma	2 (4%)		
Pheochromocytoma, malignant	1 (2%)		
#Thyroid	(48)	(48)	(48)
Follicular cell adenoma	2 (4%)	3 (6%)	4 (8%)
C-cell adenoma	1 (2%)		
#Pancreatic islets	(50)	(9)	(49)
Islet cell adenoma	1 (2%)		1 (2%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Adenosquamous carcinoma			1 (2%)
#Uterus	(50)	(27)	(50)
Leiomyosarcoma			1 (2%)
Endometrial stromal polyp			2 (4%)
#Cervix uteri	(50)	(27)	(50)
Adenocarcinoma, NOS		1 (4%)	
#Uterus/endometrium	(50)	(27)	(50)
Adenocarcinoma, NOS		1 (4%)	
#Ovary	(48)	(29)	(49)
Cystadenoma, NOS	1 (2%)		1 (2%)
Luteoma			1 (2%)
NERVOUS SYSTEM			
None			
SPECIAL SENSE ORGANS			
#Harderian gland	(50)	(40)	(50)
Carcinoma, NOS			1 (2%)
Adenoma, NOS	6 (12%)	8 (20%)	13 (26%)
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
None			
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Leiomyosarcoma, metastatic			1 (2%)
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	6	9	4
Moribund sacrifice	6	8	8
Terminal sacrifice	38	33	38

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

	Vehicle Control	Low Dose	High Dose
TUMOR SUMMARY			
Total animals with primary tumors**	37	30	45
Total primary tumors	59	48	97
Total animals with benign tumors	23	23	37
Total benign tumors	29	32	58
Total animals with malignant tumors	30	15	34
Total malignant tumors	30	16	39
Total animals with secondary tumors##	1	1	2
Total secondary tumors	1	1	2

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

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

ANIMAL NUMBER	035	021	007	031	048	045	020	042	030	046	001	002	003	004	005	009	010	036	041	006	008	011	012	013	014
WEEKS ON STUDY	086	087	090	093	098	100	101	101	104	104	105	105	105	105	105	105	105	105	105	106	106	106	106	106	106
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma												X										X			
Alveolar/bronchiolar carcinoma																									
Pheochromocytoma, metastatic			X																						
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	–	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, mixed type																									
Lymph nodes	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	–	+	+	+	+	+	+	–	+	–	+	+	+	+	+	+	+	–	–	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	N	+	N	N	+	N	+	+	N	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																X									
Large intestine	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+
Adenoma, NOS		X							X												X				
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma		X																							
Pheochromocytoma, malignant			X																						
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																									
C-cell adenoma		X																							
Parathyroid	+	–	+	+	–	+	–	–	+	–	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma		X																							
REPRODUCTIVE SYSTEM																									
Mammary gland	N	+	N	N	N	+	N	+	N	N	N	N	N	N	N	N	N	+	N	N	+	N	+	N	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Ovary	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma, NOS																									
Hemangiosarcoma																									X
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS									X							X									X
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, undifferentiated type																									
Malignant lymphoma, lymphocytic type										X	X		X		X						X	X		X	
Malignant lymphoma, histiocytic type	X						X																		
Malignant lymphoma, mixed type					X							X					X						X		

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

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

ANIMAL NUMBER	0 1 5	0 1 6	0 1 7	0 1 8	0 1 9	0 2 2	0 2 3	0 2 4	0 2 5	0 2 6	0 2 7	0 2 8	0 2 9	0 3 2	0 3 3	0 3 4	0 3 7	0 3 8	0 3 9	0 4 0	0 4 3	0 4 4	0 4 7	0 4 9	0 5 0	TOTAL:
WEEKS ON STUDY	1 0 6	1 0 6	1 0 6	1 0 6	1 0 6	1 0 6	1 0 6	1 0 6	1 0 6	1 0 6	1 0 6	1 0 6	1 0 6	1 0 6	1 0 6	1 0 6	1 0 6	1 0 6	1 0 6	1 0 6	1 0 6	1 0 6	1 0 6	1 0 6	1 0 6	TISSUES TUMORS
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	X	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																			X						3
Alveolar/bronchiolar carcinoma																									1
Pheochromocytoma, metastatic																									1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	49
Nasal cavity	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	–	46
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Malignant lymphoma, mixed type																							X		1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	48
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–	+	+	+	41
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	+	+	+	+	46
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell papilloma										X															1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS																									1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+	–	+	+	+	47
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	–	+	+	+	+	+	+	47
Adenoma, NOS			X					X				X		X		X				X		X	X		11
Adrenal	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma									X																2
Pheochromocytoma, malignant																									1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	48
Follicular cell adenoma								X									X								2
C-cell adenoma																									1
Parathyroid	–	+	+	–	+	+	+	–	–	+	–	+	+	+	+	+	–	–	+	–	+	+	+	–	35
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet cell adenoma																									1
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	+	+	N	N	N	N	N	N	*50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma				X																					1
Ovary	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Cystadenoma, NOS							X																		1
Hemangiosarcoma																									1
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																									
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS	X				X				X																6
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malignant lymphoma, undiffer type																X									1
Malignant lymphoma, lymphocytic type	X		X	X	X	X			X	X												X			15
Malignant lymphoma, histiocytic type																									2
Malignant lymphoma, mixed type								X					X					X							7

* Animals necropsied

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF IODINATED GLYCEROL: LOW DOSE

ANIMAL NUMBER	025	041	045	010	001	021	004	008	034	035	002	039	018	016	040	044	013	003	005	006	007	009	011	012	014
WEEKS ON STUDY	001	039	048	053	073	079	081	086	089	090	092	092	093	096	096	100	104	105	105	105	105	105	105	105	105
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	N	+	+	+	+	+	+	+	+	+	N	N	N	N	N	N	N	N	+	N	N	N	N	
Fibrosarcoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	+	−	−	−	−	−	−	−	−	−
Hepatocellular carcinoma, metastatic				X																					
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+
Nasal cavity	−	−	−	−	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Spleen	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	−	+	+	+	+	+	−	−
Lymph nodes	+	+	+	−	+	+	+	+	+	+	+	−	−	−	+	−	+	−	−	+	+	−	−	−	−
Thymus	−	+	+	−	−	−	+	−	+	−	−	−	−	−	−	−	−	+	−	−	+	−	−	+	−
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−
DIGESTIVE SYSTEM																									
Salivary gland	−	+	+	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																			X	X					
Hepatocellular carcinoma				X																					
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	−	+	+	−	+	+	+	−	+	+	−	−	−	+	−	−	−	−	−	−	−	−	−	−
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Small intestine	+	+	+	+	+	+	+	+	+	+	+	−	−	−	−	−	+	−	−	−	−	−	−	−	−
Large intestine	+	+	+	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	−	−	−	−	+	−	−	−	−	−	−	−	−	−
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+
Adenoma, NOS									X						X	X	X	X			X	X			
Adrenal	+	+	+	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Thyroid	−	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																					X				
Parathyroid	−	−	+	+	−	−	−	+	+	+	−	−	+	−	−	+	+	−	+	+	+	−	−	+	−
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	+	N	+	+	N	+	N	+	N	N	N	N	+	N	N	N	N	N	N	N	N	N
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	+	+	−	−
Adenocarcinoma, NOS																									
Hemangiosarcoma			X																						
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	−	+	+	+	−	−
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	−	−	−	+	+	−	−	−	−	−	−	−	−	−
SPECIAL SENSE ORGANS																									
Harderian gland	−	−	−	+	−	−	−	−	−	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS												X	X											X	
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, undifferentiated type								X																	
Malignant lymphoma, lymphocytic type												X													
Malignant lymphoma, histiocytic type																									
Malignant lymphoma, mixed type																	X			X	X				

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: LOW DOSE (Continued)

ANIMAL NUMBER	0151	0171	0191	0200	0222	0233	0244	0266	0277	0288	0299	0300	0311	0322	0333	0366	0377	0388	0422	0433	0466	0477	0488	0499	0500	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Fibrosarcoma									X																	1
RESPIRATORY SYSTEM																										
Lungs and bronchi	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	15
Hepatocellular carcinoma, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Nasal cavity	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	7
HEMATOPOIETIC SYSTEM																										
Bone marrow	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	11
Spleen	+	+	+	+	–	–	–	+	–	–	–	–	+	+	–	–	+	+	–	–	–	–	–	+	+	31
Lymph nodes	–	+	–	–	–	–	–	–	–	–	–	–	+	+	–	–	–	+	–	–	–	–	–	–	+	19
Thymus	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	7
CIRCULATORY SYSTEM																										
Heart	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	11
DIGESTIVE SYSTEM																										
Salivary gland	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	11
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma							X																		X	4
Hepatocellular carcinoma																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	*50
Pancreas	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	9
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	–	+	–	+	47
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma	X										X															2
Small intestine	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	12
Large intestine	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	11
URINARY SYSTEM																										
Kidney	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	13
Urinary bladder	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	11
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	–	+	+	–	+	45
Adenoma, NOS	X						X				X	X						X	X			X			X	15
Adrenal	+	–	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	13
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Follicular cell adenoma											X														X	3
Parathyroid	–	+	+	–	+	+	–	+	+	–	+	+	+	+	+	+	+	+	+	+	–	–	+	–	–	29
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Uterus	+	+	+	+	+	–	+	–	+	–	–	+	–	–	–	–	–	–	–	–	+	+	+	–	–	27
Adenocarcinoma, NOS	X								X																	2
Hemangiosarcoma																										1
Ovary	+	+	+	–	+	–	–	+	+	–	–	–	+	–	–	–	+	–	–	–	–	–	+	–	–	29
NERVOUS SYSTEM																										
Brain	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	13
SPECIAL SENSE ORGANS																										
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Adenoma, NOS				X			X	X													X				X	8
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malignant lymphoma, undiffer type																										1
Malignant lymphoma, lymphocytic type								X									X	X							X	5
Malignant lymphoma, histiocytic type													X													1
Malignant lymphoma, mixed type														X												4

* Animals necropsied

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF IODINATED GLYCEROL: HIGH DOSE

ANIMAL NUMBER	0 3 0	0 3 4	0 4 7	0 2 4	0 2 3	0 0 6	0 4 6	0 1 3	0 0 3	0 1 0	0 1 6	0 4 9	0 0 1	0 0 2	0 0 4	0 0 5	0 0 7	0 0 8	0 0 9	0 1 1	0 1 2	0 1 4	0 1 5	0 1 7	0 1 8
WEEKS ON STUDY	0 5 4	0 7 0	0 8 5	0 9 3	0 9 7	0 9 8	0 9 9	1 0 0	1 0 1	1 0 3	1 0 3	1 0 4	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic																						X			
Alveolar/bronchiolar adenoma																		X					X		
Alveolar/bronchiolar carcinoma																									X
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nasal cavity	−	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	−	−	+	+	+	−	+	+	−
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, lymphocytic type														X											
Malignant lymphoma, mixed type																							X		
Lymph nodes	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									X
Thymus	+	−	−	−	+	+	−	−	+	−	+	+	+	+	+	+	+	+	−	+	+	+	−	+	+
Malignant lymphoma, lymphocytic type																									
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma				X																					
Hepatocellular carcinoma																							X		
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	N	N	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+
Pancreas	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma										X	X														
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	−	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS				X				X	X	X	X	X	X					X	X					X	X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+
Follicular cell adenoma												X										X		X	
Parathyroid	−	−	+	+	−	+	+	−	+	+	−	−	+	−	−	−	−	+	+	−	+	−	−	−	+
Pancreatic islets	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	+	N	+	N	+	N	N	+	+	+	N	N	N	+	N	+	+	N	N	N	+	N
Adenosquamous carcinoma																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma	X																								
Endometrial stromal polyp																									X
Ovary	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma, NOS									X																
Luteoma																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																									
Adenoma, NOS					X							X				X				X		X	X	X	
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leiomyosarcoma, metastatic	X																								
Malignant lymphoma, undifferentiated type			X																						
Malignant lymphoma, lymphocytic type												X					X	X				X	X		
Malignant lymphoma, histiocytic type		X																							
Malignant lymphoma, mixed type				X						X	X		X						X						

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: HIGH DOSE (Continued)

ANIMAL NUMBER	019	020	021	022	025	026	027	028	029	031	032	033	035	036	037	038	039	040	041	042	043	044	045	048	050	TOTAL TISSUES TUMORS
WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic																										1
Alveolar/bronchiolar adenoma						X			X																	4
Alveolar/bronchiolar carcinoma									X																	2
Trachea	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Nasal cavity	+	+	+	+	+	–	+	+	+	+	+	+	–	+	+	+	+	+	+	+	–	+	–	+	+	40
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Malignant lymphoma, lymphocytic type						X								X		X										4
Malignant lymphoma, mixed type																				X				X		3
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	47
Hemangiosarcoma																										1
Thymus	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Malignant lymphoma, lymphocytic type														X												1
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma				X			X																			3
Hepatocellular carcinoma																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	47
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell papilloma		X										X	X													5
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Adenoma, NOS	X	X	X	X			X	X	X				X	X		X	X			X				X		24
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thyroid	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Follicular cell adenoma											X															4
Parathyroid	–	+	–	+	–	+	+	+	–	–	–	+	–	–	+	–	+	–	–	+	+	+	+	–	+	24
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islet cell adenoma																	X									1
REPRODUCTIVE SYSTEM																										
Mammary gland	N	+	N	N	N	N	N	+	N	N	N	N	+	N	+	+	N	N	+	N	N	+	N	N	+	*50
Adenosquamous carcinoma																			X							1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma																										1
Endometrial stromal polyp													X													2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cystadenoma, NOS																										1
Luteoma				X																						1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS							X																			1
Adenoma, NOS										X			X								X	X	X		X	13
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leiomyosarcoma, metastatic																										1
Malignant lymphoma, undiffer type																										1
Malignant lymphoma, lymphocytic type			X		X		X	X	X		X	X					X		X							14
Malignant lymphoma, histiocytic type																										1
Malignant lymphoma, mixed type																					X		X		X	8

* Animals necropsied

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

	Vehicle Control	62 mg/kg	125 mg/kg
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	3/50 (6%)	(b) 0/15 (0%)	4/50 (8%)
Adjusted Rates (c)	7.5%		10.5%
Terminal Rates (d)	3/40 (7%)		4/38 (11%)
Week of First Observation	105		105
Life Table Test (e)			P=0.472
Incidental Tumor Test (e)			P=0.472
Fisher Exact Test (e)			P=0.500
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	4/50 (8%)	(b) 0/15 (0%)	5/50 (10%)
Adjusted Rates (c)	10.0%		13.2%
Terminal Rates (d)	4/40 (10%)		5/38 (13%)
Week of First Observation	105		105
Life Table Test (e)			P=0.468
Incidental Tumor Test (e)			P=0.468
Fisher Exact Test (e)			P=0.500
Hematopoietic System: Malignant Lymphoma, Lymphocytic Type			
Overall Rates (a)	15/50 (30%)	(b,f) 5/50 (10%)	19/50 (38%)
Adjusted Rates (c)	36.5%		48.7%
Terminal Rates (d)	14/40 (35%)		18/38 (47%)
Week of First Observation	104		104
Life Table Test (e)			P=0.198
Incidental Tumor Test (e)			P=0.218
Fisher Exact Test (e)			P=0.263
Hematopoietic System: Malignant Lymphoma, Mixed Type			
Overall Rates (a)	8/50 (16%)	(b,f) 4/50 (8%)	11/50 (22%)
Adjusted Rates (c)	19.3%		26.5%
Terminal Rates (d)	7/40 (18%)		8/38 (21%)
Week of First Observation	98		93
Life Table Test (e)			P=0.274
Incidental Tumor Test (e)			P=0.316
Fisher Exact Test (e)			P=0.305
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	26/50 (52%)	(b,f) 11/50 (22%)	32/50 (64%)
Adjusted Rates (c)	58.8%		72.5%
Terminal Rates (d)	22/40 (55%)		26/38 (68%)
Week of First Observation	86		70
Life Table Test (e)			P=0.115
Incidental Tumor Test (e)			P=0.136
Fisher Exact Test (e)			P=0.155
Liver: Hepatocellular Adenoma			
Overall Rates (a)	0/50 (0%)	4/50 (8%)	3/50 (6%)
Adjusted Rates (c)	0.0%	12.1%	7.3%
Terminal Rates (d)	0/40 (0%)	4/33 (12%)	2/38 (5%)
Week of First Observation		105	93
Life Table Tests (e)	P=0.117	P=0.041	P=0.117
Incidental Tumor Tests (e)	P=0.127	P=0.041	P=0.131
Cochran-Armitage Trend Test (e)	P=0.120		
Fisher Exact Test (e)		P=0.059	P=0.121

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

	Vehicle Control	62 mg/kg	125 mg/kg
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	0/50 (0%)	5/50 (10%)	4/50 (8%)
Adjusted Rates (c)	0.0%	14.0%	9.9%
Terminal Rates (d)	0/40 (0%)	4/33 (12%)	3/38 (8%)
Week of First Observation		53	93
Life Table Tests (e)	P=0.071	P=0.022	P=0.060
Incidental Tumor Tests (e)	P=0.103	P=0.041	P=0.068
Cochran-Armitage Trend Test (e)	P=0.071		
Fisher Exact Test (e)		P=0.028	P=0.059
Forestomach: Squamous Cell Papilloma			
Overall Rates (a)	1/49 (2%)	2/50 (4%)	5/49 (10%)
Adjusted Rates (c)	2.5%	6.1%	12.4%
Terminal Rates (d)	1/40 (3%)	2/33 (6%)	3/38 (8%)
Week of First Observation	105	105	103
Life Table Tests (e)	P=0.060	P=0.433	P=0.097
Incidental Tumor Tests (e)	P=0.077	P=0.433	P=0.127
Cochran-Armitage Trend Test (e)	P=0.059		
Fisher Exact Test (e)		P=0.508	P=0.102
Anterior Pituitary Gland: Adenoma			
Overall Rates (a)	10/47 (21%)	15/45 (33%)	24/46 (52%)
Adjusted Rates (c)	25.0%	44.4%	58.0%
Terminal Rates (d)	8/37 (22%)	11/29 (38%)	18/35 (51%)
Week of First Observation	87	89	93
Life Table Tests (e)	P=0.002	P=0.059	P=0.003
Incidental Tumor Tests (e)	P=0.001	P=0.068	P=0.002
Cochran-Armitage Trend Test (e)	P=0.001		
Fisher Exact Test (e)		P=0.143	P=0.002
Adrenal Gland: Pheochromocytoma or Malignant Pheochromocytoma			
Overall Rates (a)	3/49 (6%)	(b) 0/13 (0%)	0/50 (0%)
Adjusted Rates (c)	6.5%		0.0%
Terminal Rates (d)	1/39 (3%)		0/38 (0%)
Week of First Observation	87		
Life Table Test (e)			P=0.129N
Incidental Tumor Test (e)			P=0.243N
Fisher Exact Test (e)			P=0.118N
Thyroid Gland: Follicular Cell Adenoma			
Overall Rates (a)	2/48 (4%)	3/48 (6%)	4/48 (8%)
Adjusted Rates (c)	5.3%	9.1%	10.7%
Terminal Rates (d)	2/38 (5%)	3/33 (9%)	3/36 (8%)
Week of First Observation	105	105	104
Life Table Tests (e)	P=0.245	P=0.435	P=0.312
Incidental Tumor Tests (e)	P=0.264	P=0.435	P=0.336
Cochran-Armitage Trend Test (e)	P=0.264		
Fisher Exact Test (e)		P=0.500	P=0.339
Harderian Gland: Adenoma			
Overall Rates (a)	6/50 (12%)	8/40 (20%)	13/50 (26%)
Adjusted Rates (c)	14.6%	22.4%	32.3%
Terminal Rates (d)	5/40 (13%)	6/33 (18%)	11/38 (29%)
Week of First Observation	104	92	97
Life Table Tests (e)	P=0.041	P=0.251	P=0.052
Incidental Tumor Tests (e)	P=0.041	P=0.201	P=0.062
Cochran-Armitage Trend Test (e)	P=0.050		
Fisher Exact Test (e)		P=0.227	P=0.062

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

	Vehicle Control	62 mg/kg	125 mg/kg
Harderian Gland: Adenoma or Carcinoma			
Overall Rates (a)	6/50 (12%)	8/40 (20%)	14/50 (28%)
Adjusted Rates (c)	14.6%	22.4%	34.8%
Terminal Rates (d)	5/40 (13%)	6/33 (18%)	12/38 (32%)
Week of First Observation	104	92	97
Life Table Tests (e)	P=0.025	P=0.251	P=0.032
Incidental Tumor Tests (e)	P=0.024	P=0.201	P=0.039
Cochran-Armitage Trend Test (e)	P=0.030		
Fisher Exact Test (e)		P=0.227	P=0.039
All Sites: Benign Tumors			
Overall Rates (a)	23/50 (46%)	23/50 (46%)	37/50 (74%)
Adjusted Rates (c)	54.6%	58.8%	82.2%
Terminal Rates (d)	21/40 (53%)	17/33 (52%)	30/38 (79%)
Week of First Observation	87	89	93
Life Table Tests (e)	P=0.003	P=0.252	P=0.003
Incidental Tumor Tests (e)	P=0.002	P=0.319	P=0.002
Cochran-Armitage Trend Test (e)	P=0.003		
Fisher Exact Test (e)		P=0.579	P=0.004
All Sites: Malignant Tumors			
Overall Rates (a)	30/50 (60%)	15/50 (30%)	34/50 (68%)
Adjusted Rates (c)	66.4%	38.3%	75.3%
Terminal Rates (d)	25/40 (63%)	10/33 (30%)	27/38 (71%)
Week of First Observation	86	48	54
Life Table Tests (e)	P=0.192	P=0.032N	P=0.202
Incidental Tumor Tests (e)	P=0.250	P=0.002N	P=0.266
Cochran-Armitage Trend Test (e)	P=0.236		
Fisher Exact Test (e)		P=0.003N	P=0.266
All Sites: All Tumors			
Overall Rates (a)	37/50 (74%)	30/50 (60%)	45/50 (90%)
Adjusted Rates (c)	78.6%	71.1%	93.7%
Terminal Rates (d)	30/40 (75%)	21/33 (64%)	35/38 (92%)
Week of First Observation	86	48	54
Life Table Tests (e)	P=0.049	P=0.522N	P=0.044
Incidental Tumor Tests (e)	P=0.041	P=0.178N	P=0.028
Cochran-Armitage Trend Test (e)	P=0.041		
Fisher Exact Test (e)		P=0.101N	P=0.033

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Incomplete sampling of tissues
(c) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(d) Observed tumor incidence at terminal kill
(e) 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 is indicated by (N).
(f) Thirty-one spleens were examined microscopically.

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

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence for All Water Gavage Vehicle Controls			
Iodinated glycerol (b)	4/46	1/46	5/46
Chlorpheniramine maleate (c)	5/46	0/46	5/46
Tetrakis(hydroxymethyl)phosphonium chloride (c)	11/50	0/50	11/50
Malonaldehyde, sodium salt (c)	2/43	0/43	2/43
Tetrakis(hydroxymethyl)phosphonium sulfate (c)	8/43	0/43	8/43
Methyl carbamate (d)	9/49	0/49	9/49
Chlorinated trisodium phosphate (b)	8/45	0/45	8/45
TOTAL	47/322 (14.6%)	1/322 (0.3%)	48/322 (14.9%)
SD (e)	6.36%	0.82%	6.08%
Range (f)			
High	11/50	1/46	11/50
Low	2/43	0/50	2/43
Overall Historical Incidence for Untreated Controls			
TOTAL	(g) 231/1,782 (13.0%)	(h) 13/1,782 (0.7%)	(g,h) 244/1,782 (13.7%)
SD (e)	10.20%	1.34%	10.58%
Range (f)			
High	18/49	3/50	19/49
Low	0/48	0/49	0/48

(a) Data as of April 29, 1987, for studies of at least 104 weeks
(b) Study performed at EG&G Mason Research Institute
(c) Study performed at Battelle Columbus Laboratories
(d) Study performed at Microbiological Associates
(e) Standard deviation
(f) Range and SD are presented for groups of 35 or more animals.
(g) Includes eight chromophobe adenomas
(h) Includes three adenocarcinomas, NOS, and one chromophobe carcinoma

TABLE D4b. HISTORICAL INCIDENCE OF HARDERIAN GLAND TUMORS IN CONTROL FEMALE $B6C3F_1$ MICE (a)

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence for All Water Gavage Vehicle Controls			
Iodinated glycerol (b)	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	(d) 2/50
Methyl carbamate (e)	1/50	0/50	1/50
Chlorinated trisodium phosphate (b)	0/50	1/50	1/50
TOTAL	9/350 (2.6%)	3/350 (0.9%)	12/350 (3.4%)
SD (f)	4.43%	1.57%	4.12%
Range (g)			
High	6/50	2/50	6/50
Low	0/50	0/50	0/50
Overall Historical Incidence for Untreated Controls			
TOTAL	(h) 41/2,040 (2.0%)	(i) 7/2,040 (0.3%)	(h,i) 48/2,040 (2.4%)
SD (f)	2.06%	0.88%	2.19%
Range (g)			
High	4/50	2/50	4/50
Low	0/50	0/50	0/50

(a) Data as of April 29, 1987, for studies of at least 104 weeks
(b) Study performed at EG&G Mason Research Institute
(c) Study performed at Battelle Columbus Laboratories
(d) Papillary adenocarcinomas
(e) Study performed at Microbiological Associates
(f) Standard deviation
(g) Range and SD are presented for groups of 35 or more animals.
(h) Includes three papillary adenomas, one cystadenoma, NOS, and two papillary cystadenomas, NOS
(i) Includes one adenocarcinoma, NOS, two papillary adenocarcinomas, and one papillary cystadenocarcinoma, NOS

TABLE D4c. HISTORICAL INCIDENCE OF HEPATOCELLULAR TUMORS IN CONTROL FEMALE B6C3F$_1$ MICE (a)

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence for All Water Gavage Vehicle Controls			
Iodinated glycerol (b)	0/50	0/50	0/50
Chlorpheniramine maleate (c)	4/50	2/50	6/50
Tetrakis(hydroxymethyl)phosphonium chloride (c)	3/49	1/49	4/49
Malonaldehyde, sodium salt (c)	0/50	2/50	2/50
Tetrakis(hydroxymethyl)phosphonium sulfate (c)	5/50	3/50	7/50
Methyl carbamate (d)	4/49	1/49	4/49
Chlorinated trisodium phosphate (b)	6/50	0/50	6/50
TOTAL	22/348 (6.3%)	9/348 (2.6%)	29/348 (8.3%)
SD (e)	4.69%	2.22%	4.95%
Range (f)			
High	6/50	3/50	7/50
Low	0/50	0/50	0/50
Overall Historical Incidence for Untreated Controls			
TOTAL	107/2,032 (5.3%)	(g) 81/2,032 (4.0%)	(g)184/2,032 (9.1%)
SD (e)	4.34%	2.42%	4.70%
Range (f)			
High	9/49	4/48	10/49
Low	0/50	0/50	1/50

(a) Data as of April 29, 1987, for studies of at least 104 weeks
(b) Study performed at EG&G Mason Research Institute
(c) Study performed at Battelle Columbus Laboratories
(d) Study performed at Microbiological Associates
(e) Standard deviation
(f) Range and SD are presented for groups of 35 or more animals.
(g) A hepatoblastoma was also observed.

TABLE D4d. HISTORICAL INCIDENCE OF STOMACH TUMORS IN CONTROL FEMALE B6C3F$_1$ MICE (a)

Study	No. Examined	No. of Tumors	Site	Diagnosis
Historical Incidence for All Water Gavage Vehicle Controls				
Iodinated glycerol (b)	49	1	Forestomach	Squamous cell papilloma
Tetrakis(hydroxymethyl)phosphonium chloride (c)	49	2	Forestomach	Squamous cell papilloma
Malonaldehyde, sodium salt (c)	46	1	Cardiac stomach	Squamous cell papilloma
All others	195	0	--	--
TOTAL	339	4 (1.2%)		
Overall Historical Incidence for Untreated Controls				
		1	Stomach, NOS	Papilloma, NOS
		3	Stomach, NOS	Papillomatoses
		3	Stomach, NOS	Squamous cell papilloma
		9	Forestomach	Squamous cell papilloma
		1	Cardiac stomach	Squamous cell papilloma
		1	Stomach, NOS	Squamous cell carcinoma
TOTAL	1,994	18 (0.9%)		

(a) Data as of April 29, 1987, for studies of at least 104 weeks; the greatest observed incidence in any control group is 4/50.
(b) Study performed at EG&G Mason Research Institute
(c) Study performed at Battelle Columbus Laboratories

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

	Vehicle Control	Low Dose	High Dose
Animals initially in study	50	50	50
Animals necropsied	50	50	50
Animals examined histopathologically	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Ulcer, NOS	1 (2%)		
Inflammation, chronic diffuse		1 (2%)	
RESPIRATORY SYSTEM			
#Nasopharynx	(46)	(7)	(40)
Inflammation, NOS	5 (11%)	1 (14%)	4 (10%)
#Trachea	(49)	(48)	(49)
Inflammation, chronic		1 (2%)	
#Lung	(50)	(15)	(50)
Congestion, NOS		1 (7%)	
Hemorrhage		1 (7%)	
Bronchopneumonia, NOS		1 (7%)	
Inflammation, NOS	1 (2%)	3 (20%)	
#Lung/alveoli	(50)	(15)	(50)
Metaplasia, NOS	15 (30%)		6 (12%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Hyperplasia, lymphoid		1 (2%)	
Hematopoiesis	5 (10%)	7 (14%)	2 (4%)
#Bone marrow	(49)	(11)	(50)
Fibrosis	33 (67%)		34 (68%)
Hyperplasia, neutrophilic	4 (8%)	7 (64%)	5 (10%)
#Spleen	(50)	(31)	(50)
Congestion, NOS			1 (2%)
Plasma cell infiltrate	1 (2%)		
Infarct, focal			2 (4%)
Hemosiderosis	2 (4%)		
Depletion, lymphoid		1 (3%)	
Hyperplasia, lymphoid		3 (10%)	
Hematopoiesis	18 (36%)	18 (58%)	24 (48%)
#Lymph node	(48)	(19)	(47)
Plasma cell infiltrate	2 (4%)	4 (21%)	
Histiocytosis	1 (2%)		
#Mediastinal lymph node	(48)	(19)	(47)
Abscess, NOS		1 (5%)	
Plasma cell infiltrate		1 (5%)	
#Lumbar lymph node	(48)	(19)	(47)
Hyperplasia, NOS	1 (2%)		
#Mesenteric lymph node	(48)	(19)	(47)
Congestion, NOS	3 (6%)	1 (5%)	1 (2%)
Inflammation, acute			1 (2%)
Plasma cell infiltrate	1 (2%)		1 (2%)
Hyperplasia, NOS	1 (2%)		
Histiocytosis		1 (5%)	
Hematopoiesis	1 (2%)		
#Renal lymph node	(48)	(19)	(47)
Abscess, NOS	1 (2%)		
Plasma cell infiltrate	1 (2%)		
Hyperplasia, NOS		1 (5%)	

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

	Vehicle Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM (Continued)			
#Inguinal lymph node	(48)	(19)	(47)
Inflammation, acute		1 (5%)	
#Liver	(50)	(50)	(50)
Hematopoiesis	1 (2%)	1 (2%)	
#Glandular stomach	(49)	(50)	(49)
Hyperplasia, lymphoid		1 (2%)	
#Adrenal	(49)	(13)	(50)
Hematopoiesis		1 (8%)	
#Thymus	(41)	(7)	(40)
Hyperplasia, lymphoid		2 (29%)	
CIRCULATORY SYSTEM			
#Inguinal lymph node	(48)	(19)	(47)
Lymphangiectasis		1 (5%)	
#Lung	(50)	(15)	(50)
Perivasculitis		1 (7%)	
#Heart	(50)	(11)	(50)
Mineralization	1 (2%)		
Perivasculitis		1 (9%)	1 (2%)
#Myocardium	(50)	(11)	(50)
Degeneration, NOS	41 (82%)	6 (55%)	42 (84%)
*Pulmonary artery	(50)	(50)	(50)
Mineralization		1 (2%)	
#Liver	(50)	(50)	(50)
Perivasculitis		2 (4%)	
#Urinary bladder	(47)	(11)	(50)
Perivasculitis			1 (2%)
DIGESTIVE SYSTEM			
*Tooth	(50)	(50)	(50)
Inflammation, acute			1 (2%)
#Salivary gland	(50)	(11)	(50)
Inflammation, NOS		1 (9%)	
#Liver	(50)	(50)	(50)
Inflammation, chronic		9 (18%)	
Necrosis, focal	3 (6%)	9 (18%)	3 (6%)
Metamorphosis, fatty	8 (16%)	15 (30%)	13 (26%)
Cytoplasmic change, NOS			3 (6%)
Multinucleate giant cell			1 (2%)
#Hepatic serosa	(50)	(50)	(50)
Inflammation, acute		1 (2%)	
*Gallbladder	(50)	(50)	(50)
Dilatation, NOS		2 (4%)	
Inflammation, acute		1 (2%)	
#Pancreas	(50)	(9)	(49)
Dilatation/ducts			1 (2%)
Inflammation, acute		1 (11%)	
Fibrosis, focal	1 (2%)	1 (11%)	
Atrophy, NOS	1 (2%)		
#Stomach	(49)	(50)	(49)
Ectopia		1 (2%)	
Ulcer, NOS	1 (2%)	1 (2%)	1 (2%)
#Glandular stomach	(49)	(50)	(49)
Mineralization	1 (2%)		1 (2%)
Inflammation, NOS	4 (8%)	5 (10%)	2 (4%)
Ulcer, NOS	1 (2%)		

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

	Vehicle Control	Low Dose	High Dose
DIGESTIVE SYSTEM (Continued)			
#Forestomach	(49)	(50)	(49)
Inflammation, NOS	2 (4%)		1 (2%)
Ulcer, NOS		1 (2%)	
Abscess, NOS	1 (2%)		
Hyperplasia, basal cell		1 (2%)	
Hyperkeratosis	6 (12%)	2 (4%)	3 (6%)
Acanthosis	5 (10%)	4 (8%)	2 (4%)
URINARY SYSTEM			
#Kidney	(50)	(13)	(50)
Mineralization			5 (10%)
Cast, NOS			1 (2%)
Glomerulonephritis, NOS	47 (94%)	9 (69%)	48 (96%)
Inflammation, NOS	1 (2%)	1 (8%)	2 (4%)
Scar	1 (2%)		
Nephropathy	2 (4%)	1 (8%)	1 (2%)
Necrosis, focal			1 (2%)
Metaplasia, osseous			1 (2%)
#Kidney/tubule	(50)	(13)	(50)
Regeneration, NOS	1 (2%)		1 (2%)
#Urinary bladder	(47)	(11)	(50)
Inflammation, chronic focal	3 (6%)	3 (27%)	3 (6%)
ENDOCRINE SYSTEM			
#Pituitary intermedia	(47)	(45)	(46)
Hyperplasia, focal	1 (2%)	1 (2%)	
#Anterior pituitary	(47)	(45)	(46)
Cyst, NOS	1 (2%)		2 (4%)
Hypertrophy, focal			1 (2%)
Hyperplasia, focal	21 (45%)	18 (40%)	18 (39%)
Hyperplasia, diffuse			1 (2%)
Angiectasis	2 (4%)	1 (2%)	1 (2%)
Vascularization	1 (2%)		
#Adrenal	(49)	(13)	(50)
Inflammation, acute focal	1 (2%)	1 (8%)	
#Adrenal/capsule	(49)	(13)	(50)
Hyperplasia, NOS		1 (8%)	
#Adrenal cortex	(49)	(13)	(50)
Cytoplasmic vacuolization			2 (4%)
Focal cellular change	2 (4%)		
#Adrenal medulla	(49)	(13)	(50)
Hyperplasia, NOS			1 (2%)
#Thyroid	(48)	(48)	(48)
Inflammation, chronic focal	1 (2%)		1 (2%)
Hyperplasia, C-cell		1 (2%)	
Hyperplasia, follicular cell	2 (4%)	25 (52%)	35 (73%)
#Thyroid follicle	(48)	(48)	(48)
Dilatation, NOS	4 (8%)	11 (23%)	10 (21%)
#Parathyroid	(35)	(29)	(24)
Ectopia	1 (3%)		
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Lactation	2 (4%)	1 (2%)	4 (8%)
*Clitoral gland	(50)	(50)	(50)
Dilatation, NOS		1 (2%)	1 (2%)
Inflammation, NOS			1 (2%)
*Vagina	(50)	(50)	(50)
Keratin pearl formation	1 (2%)		

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

	Vehicle Control	Low Dose	High Dose
REPRODUCTIVE SYSTEM (Continued)			
#Uterus	(50)	(27)	(50)
Dilatation, NOS		1 (4%)	1 (2%)
Pyometra		3 (11%)	
Abscess, NOS	1 (2%)		
Atrophy, NOS	3 (6%)		2 (4%)
#Uterus/endometrium	(50)	(27)	(50)
Inflammation, acute	4 (8%)		1 (2%)
Hyperplasia, cystic	33 (66%)	19 (70%)	38 (76%)
Metaplasia, squamous		2 (7%)	2 (4%)
#Tubo ovarian site	(50)	(27)	(50)
Abscess, NOS	5 (10%)	10 (37%)	3 (6%)
#Ovary	(48)	(29)	(49)
Cyst, NOS	11 (23%)	14 (48%)	17 (35%)
Congestion, NOS		1 (3%)	
Inflammation, acute		1 (3%)	
NERVOUS SYSTEM			
#Brain	(50)	(13)	(50)
Mineralization	21 (42%)		22 (44%)
Deformity, NOS		1 (8%)	
Hydrocephalus, NOS	2 (4%)	1 (8%)	
#Cerebellum	(50)	(13)	(50)
Cytoplasmic vacuolization			1 (2%)
SPECIAL SENSE ORGANS			
*Eye	(50)	(50)	(50)
Synechia, anterior			2 (4%)
#Harderian gland	(50)	(40)	(50)
Dilatation, NOS		1 (3%)	
Inflammation, NOS	36 (72%)	23 (58%)	30 (60%)
Hyperplasia, NOS		1 (3%)	
Hyperplasia, focal	1 (2%)		1 (2%)
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
*Abdominal cavity	(50)	(50)	(50)
Inflammation, acute		1 (2%)	
Abscess, NOS			1 (2%)
*Peritoneum	(50)	(50)	(50)
Inflammation, acute	1 (2%)	2 (4%)	
Inflammation, acute/chronic			1 (2%)
*Pleura	(50)	(50)	(50)
Empyema	2 (4%)		
Inflammation, acute		1 (2%)	
*Pericardium	(50)	(50)	(50)
Inflammation, acute	2 (4%)	1 (2%)	
*Mesentery	(50)	(50)	(50)
Inflammation, acute/chronic		1 (2%)	

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

	Vehicle Control	Low Dose	High Dose
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Plasma cell infiltrate		1 (2%)	
Inflammation, chronic focal	40 (80%)	5 (10%)	40 (80%)
Omentum			
Necrosis, fat	2	2	1
SPECIAL MORPHOLOGY SUMMARY			
None			

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

APPENDIX E

SENTINEL ANIMAL PROGRAM

		PAGE
TABLE E1	MURINE ANTIBODY DETERMINATIONS FOR RATS AND MICE IN THE TWO-YEAR GAVAGE STUDIES OF IODINATED GLYCEROL	161

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 serology on sera from extra (sentinel) animals in the study rooms. These animals are untreated, and these animals and the study animals are both subject to identical environmental conditions. The sentinel animals come from the same production source and weanling groups as the animals used for the studies of chemical compounds.

Fifteen B6C3F$_1$ mice and 15 F344/N rats of each sex were selected at the time of randomization and allocation of the animals to the various study groups. Five animals of each designated sentinel group were killed at 6, 12, and 18 months on study. Data from animals surviving 24 months were collected from 5/50 randomly selected 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 antibody titers. The following tests were performed:

	Hemagglutination Inhibition	Complement Fixation	ELISA
Mice	PVM (pneumonia virus of mice) Reo 3 (reovirus type 3) GDVII (Theiler's encephalomyelitis virus) Poly (polyoma virus) MVM (minute virus of mice) Ectro (infectious ectromelia) Sendai	M. Ad. (mouse adenovirus) LCM (lymphocytic choriomeningitis virus)	MHV (mouse hepatitis virus) *M. pul.* (*Mycoplasma pulmonis*)
Rats	PVM KRV (Kilham rat virus) H-1 (Toolan's H-1 virus) Sendai	RCV (rat coronavirus)	*M. pul.*

Results

Results are presented in Table E1.

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

Interval (months)	No. of Animals	Positive Serologic Reaction for
RATS		
6	--	None positive
12	9/10	Sendai
18	9/10	Sendai
24	8/10	PVM
	4/10	Sendai
	5/8	*M. pul.* (b)
MICE		
6	--	None positive
12	10/10	Sendai
18	5/5	Sendai
	1/5	MHV
24	1/5	*M. pul.* (b)
	8/10	Sendai
	2/10	MHV

(a) Blood samples were taken from sentinel animals at 6, 12, and 18 months after the start of dosing and from the vehicle control animals just before they were killed; samples were sent to Microbiological Associates (Bethesda, MD) for determination of antibody titers.
(b) Further evaluation of this assay indicated that it was not specific for *M. pulmonis*, and these results were considered to be false positive.

APPENDIX F

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

Meal Diet: April 1981 to April 1983

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

		PAGE
TABLE F1	INGREDIENTS OF NIH 07 RAT AND MOUSE RATION	164
TABLE F2	VITAMINS AND MINERALS IN NIH 07 RAT AND MOUSE RATION	164
TABLE F3	NUTRIENT COMPOSITION OF NIH 07 RAT AND MOUSE RATION	165
TABLE F4	CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION	166

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

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

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

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

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

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

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

Nutrients	Mean ± Standard Deviation	Range	Number of Samples
Crude protein (percent by weight)	24.19 ± 1.07	22.4-26.3	25
Crude fat (percent by weight)	5.02 ± 0.47	4.2-6.0	25
Crude fiber (percent by weight)	3.37 ± 0.37	2.4-4.2	25
Ash (percent by weight)	6.54 ± 0.26	5.97-7.03	25
Amino Acids (percent of total diet) (a)			
Arginine	1.300	1.21-1.38	3
Cystine	0.340	0.23-0.40	3
Glycine	1.137	1.06-1.20	3
Histidine	0.561	0.530-0.578	3
Isoleucine	0.899	0.881-0.934	3
Leucine	1.930	1.85-1.98	3
Lysine	1.243	1.20-1.30	3
Methionine	0.329	0.306-0.368	3
Phenylalanine	0.991	0.960-1.04	3
Threonine	0.851	0.827-0.886	3
Tryptophan	0.187	0.171-0.211	3
Tyrosine	0.647	0.566-0.769	3
Valine	1.090	1.05-1.12	3
Essential Fatty Acids (percent of total diet) (a)			
Linoleic	2.40	2.37-2.44	2
Linolenic	0.284	0.259-0.308	2
Vitamins (a)			
Vitamin A (IU/kg)	11,936 ± 2,547	8,900-22,000	25
Vitamin D (IU/kg)	5,220	4,140-6,300	2
α-Tocopherol (ppm)	39.1	31.1-44.0	3
Thiamine (ppm)	18.7 ± 3.20	14.0-26.0	(b) 24
Riboflavin (ppm)	7.3	6.1-8.1	3
Niacin (ppm)	82	65-97	3
Pantothenic acid (ppm)	30.2	23.0-30.5	3
Pyridoxine (ppm)	7.7	5.6-8.8	3
Folic acid (ppm)	2.5	1.8-3.4	3
Biotin (ppm)	0.27	0.21-0.32	3
Vitamin B_{12} (ppb)	21.2	10.6-38.0	3
Choline (ppm)	3,337	3,200-3,430	3
Minerals (a)			
Calcium (percent)	1.22 ± 0.10	1.10-1.45	25
Phosphorus (percent)	0.96 ± 0.05	0.84-1.10	25
Potassium (percent)	0.809	0.772-0.846	2
Chloride (percent)	0.581	0.479-0.635	3
Sodium (percent)	0.307	0.258-0.349	3
Magnesium (percent)	0.165	0.151-0.177	3
Sulfur (percent)	0.292	0.270-0.290	3
Iron (ppm)	420	409-431	3
Manganese (ppm)	87.7	81.7-95.5	3
Zinc (ppm)	52.1	46.1-56.0	3
Copper (ppm)	11.15	8.09-15.70	3
Iodine (ppm)	2.66	1.52-3.64	3
Chromium (ppm)	1.72	1.44-1.93	3
Cobalt (ppm)	0.64	0.49-0.78	3

(a) Two or three lots of feed analyzed for nutrients reported in this table were manufactured in 1983 or 1984.
(b) One lot (7/22/81) 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)	0.45 ± 0.11	0.21-0.65	25
Cadmium (ppm) (a)	<0.1		25
Lead (ppm)	0.95 ± 0.78	0.27-2.93	25
Mercury (ppm) (a)	<0.05		25
Selenium (ppm)	0.28 ± 0.06	0.16-0.40	25
Aflatoxins (ppb) (a,b)	<10	<5.0-10.0	25
Nitrate nitrogen (ppm) (c)	9.85 ± 4.55	0.6-19.0	25
Nitrite nitrogen (ppm) (c)	1.92 ± 1.28	0.4-5.3	25
BHA (ppm) (d)	5.67 ± 5.07	1.5-20.0	25
BHT (ppm) (d)	3.35 ± 2.55	<1.0-13.0	25
Aerobic plate count (CFU/g) (e)	121,420 ± 94,844	7,000-420,000	25
Coliform (MPN/g) (f)	965 ± 991	<3-2,400	25
E. coli (MPN/g) (g)	6.76 ± 7.06	<3-23	24
E. coli (MPN/g) (h)	12.64 ± 29.46	<3-150	25
Total nitrosamines (ppb) (i, j)	4.40 ± 3.16	<1.2-12.9	24
Total nitrosamines (ppb) (i,k)	8.29 ± 19.41	1.2-100.3	25
N-Nitrosodimethylamine (ppb) (i,l)	3.05 ± 3.05	0.6-12.0	24
N-Nitrosodimethylamine (ppb) (i,m)	6.89 ± 19.42	0.6-99.0	25
N-Nitrosopyrrolidine (ppb)	1.20 ± 0.62	<0.3-2.4	25
Pesticides (ppm)			
α-BHC (a,n)	<0.01		25
β-BHC (a)	<0.02		25
γ-BHC-Lindane (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 (o)	<0.01	0.05 (7/14/81)	25
DDD (a)	<0.01		25
DDT (a)	<0.01		25
HCB (a)	<0.01		25
Mirex (a)	<0.01		25
Methoxychlor (p)	<0.05	0.13 (8/25/81); 0.6 (6/29/82)	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 (q)	0.08 ± 0.05	<0.05-0.25	25
Endosulfan I (r)	<0.01		17
Endosulfan II (r)	<0.01		17
Endosulfan sulfate (r)	<0.03		17

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

(a) All values were less than the detection limit, given in the table as the mean.
(b) The detection limit was reduced from 10 ppb to 5 ppb after 7/81.
(c) Source of contamination: alfalfa, grains, and fish meal
(d) Source of contamination: soy oil and fish meal
(e) CFU = colony-forming unit
(f) MPN = most probable number
(g) Mean, standard deviation, and range exclude one high value of 150 obtained for the lot produced on 8/26/82.
(h) Mean, standard deviation, and range include the high value given in footnote (g).
(i) All values were corrected for percent recovery.
(j) Mean, standard deviation, and range exclude one value of 100.3 obtained for the lot produced on 4/27/81.
(k) Mean, standard deviation, and range include the high value given in footnote (j).
(l) Mean, standard deviation, and range exclude one high value of 99.0 obtained for the lot produced on 4/27/81.
(m) Mean, standard deviation, and range include the high value given in footnote (l).
(n) BHC = hexachlorocyclohexane or benzene hexachloride
(o) One observation was above the detection limit. The value and the date it was obtained are listed under the range.
(p) Two observations were above the detection limit. The values and the dates they were obtained are listed under the range.
(q) Ten lots contained more than 0.05 ppm.
(r) Analysis for endosulfan I, endosulfan II, and endosulfan sulfate was started on 12/23/81.

APPENDIX G

AUDIT SUMMARY

APPENDIX G. AUDIT SUMMARY

The pathology specimens, experimental data, study documents, and draft NTP Technical Report No. 340 for the 2-year studies of iodinated glycerol in rats and mice were audited for the National Institute of Environmental Health Sciences (NIEHS) at the National Toxicology Program (NTP) Archives by Dynamac Corporation. 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 chemistry 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, and correlations between gross observations and microscopic diagnoses.

(6) All wet tissue bags for inventory, and 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 to examine for untrimmed potential lesions.

(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.

(8) Necropsy record forms for data entry errors, and correlation between original, updated, and final microscopic diagnoses for a random 10% sample of animals to verify computer data entry of all diagnoses.

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

Procedures and events during the exposure phase of the studies were documented adequately by the archival records, with the exception of some or all of the records for observations during quarantine, disposition of surplus animals, balance calibration, cage and rack changes, relative humidity measurements for 52 days, room light cycle, and room air changes. Records documented that doses were prepared, stored, analyzed, and administered to animals properly. Recalculation of group mean body weights for 20% of the measurement dates plus 4 possible outlier values showed 4 errors of small magnitude (2.2% to 4.9%) out of 97 values checked. Observations of clinical signs and masses were made consistently. Of the masses noted in the inlife records, 63/70 in rats and 54/55 in mice correlated with necropsy observations. Survival records for all unscheduled-death animals were reviewed and found to be complete and accurate.

Individual animal identifiers (marked ears) were present and correct for 64/72 rats and 57/78 mice examined. Review of data trails for animals with less than complete and correct wet tissue identifiers indicated that the integrity of individual identity had been preserved for all of the rats and for all but four mice. From comparison of the evidence of lesions and gender present in the residual tissues with written study records, it appeared that tissue bags for one pair of low dose male mice may have been cross-labeled and that a second pair of low dose male mice may have been exchanged at the time of

necropsy; there was no evidence to indicate that animals in the studies had been mixed up prior to necropsy or between study groups. Residual wet tissues contained 15 untrimmed potential lesions in 72 rats and 4 in 78 mice examined; the untrimmed potential lesions involved a variety of organs and were distributed across all study groups of rats and in high dose groups of mice. The comparison between gross observations recorded at necropsy or trimming and microscopic diagnoses revealed 7 noncorrelations in rats and 12 in mice, distributed across organs and study groups. Tissue blocks and slides were labeled correctly and corresponding sections matched.

Full details about these and other audit findings are presented in audit reports on file at the NIEHS. In conclusion, the data and factual information in the draft Technical Report are supported by the study records at the NTP Archives.

☆ U.S. GOVERNMENT PRINTING OFFICE : 1990 O - 265-776 : QL 3