NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 305

TOXICOLOGY AND CARCINOGENESIS STUDIES OF CHLORINATED PARAFFINS

(C_{23}, 43% CHLORINE)

(CAS NO. 63449-39-8)

IN F344/N RATS AND B6C3F$_1$ MICE

(GAVAGE STUDIES)

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

NATIONAL TOXICOLOGY PROGRAM

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

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

NTP TECHNICAL REPORT

ON THE

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(GAVAGE STUDIES)

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

May 1986

NTP TR 305

NIH Publication No. 86-2561

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

NOTE TO THE READER

These studies are designed and conducted to characterize and evaluate the toxicologic potential, including carcinogenic activity, of selected chemicals in laboratory animals (usually two species, rats and mice). Chemicals selected for testing in the NTP Carcinogenesis Program are chosen primarily on the bases of human exposure, level of production, and chemical structure. Selection per se is not an indicator of a chemical's carcinogenic potential. Negative results, in which the test animals do not have a greater incidence of cancer than control animals, do not necessarily mean that a test chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of conditions. Positive results demonstrate that a test chemical is carcinogenic for animals under the conditions of the test and indicate that exposure to the chemical has the potential for hazard to humans. The determination of the risk to humans from chemicals found to be carcinogenic in animals requires a wider analysis which extends beyond the purview of this study.

Five categories of interpretative conclusions were adopted for use in June 1983 in the Technical Reports series to specifically emphasize consistency and the concept of actual evidence of carcinogenicity. For each definitive study result (male rats, female rats, male mice, female mice), one of the following quintet will be 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 Carcinogenicity** is demonstrated by studies that are interpreted as showing a chemically related increased incidence of malignant neoplasms, studies that exhibit a substantially increased incidence of benign neoplasms, or studies that exhibit an increased incidence of a combination of malignant and benign neoplasms where each increases with dose.
- **Some Evidence of Carcinogenicity** is demonstrated by studies that are interpreted as showing a chemically related increased incidence of benign neoplasms, studies that exhibit marginal increases in neoplasms of several organs/tissues, or studies that exhibit a slight increase in uncommon malignant or benign neoplasms.
- **Equivocal Evidence of Carcinogenicity** is demonstrated by studies that are interpreted as showing a chemically related marginal increase of neoplasms.
- **No Evidence of Carcinogenicity** is demonstrated by studies that are interpreted as showing no chemically related increases in malignant or benign neoplasms.
- **Inadequate Study of Carcinogenicity** demonstrates that because of major qualitative or quantitative limitations, the studies cannot be interpreted as valid for showing either the presence or absence of a carcinogenic effect.

Additionally, the following concepts (as patterned from the International Agency for Research on Cancer Monographs) have been adopted by the NTP to give further clarification of these issues:

> The term *chemical carcinogenesis* generally means the induction by chemicals of neoplasms not usually observed, the earlier induction by chemicals of neoplasms that are commonly observed, or the induction by chemicals of more neoplasms than are generally found. Different mechanisms may be involved in these situations. Etymologically, the term *carcinogenesis* means induction of cancer, that is, of malignant neoplasms; however, the commonly accepted meaning is the induction of various types of neoplasms or of a combination of malignant and benign neoplasms. In the Technical Reports, the words *tumor* and *neoplasm* are used interchangeably.

This study was initiated by the National Cancer Institute's Carcinogenesis Bioassay Program, now part of the National Institute of Environmental Health Sciences, National Toxicology Program. The studies described in this Technical Report have been conducted in compliance with NTP chemical health and safety requirements and must meet or exceed all applicable Federal, state, and local health and safety regulations. All NTP toxicology and carcinogenesis studies are subjected to a data audit before being presented for peer review.

Although every effort is made to prepare the Technical Reports as accurately as possible, mistakes may occur. Readers are requested to identify any mistakes so that corrective action may be taken. Further, anyone who is aware of related ongoing or published studies not mentioned in this report is encouraged to make this information known to the NTP. Comments and questions about the National Toxicology Program Technical Reports on Toxicology and Carcinogenesis Studies should be directed to Dr. J.E. Huff, National Toxicology Program, P.O. Box 12233, Research Triangle Park, NC 27709 (919-541-3780).

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CONTENTS

PAGE

ABSTRACT 10

CONTRIBUTORS 12

PEER REVIEW PANEL 13

SUMMARY OF PEER REVIEW COMMENTS 14

I. INTRODUCTION 17

II. MATERIALS AND METHODS 21

PROCUREMENT AND CHARACTERIZATION OF CHLORINATED PARAFFINS (C_{23}, 43% CHLORINE) 22

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES 23

SINGLE-ADMINISTRATION STUDIES 24

SIXTEEN-DAY STUDIES 24

THIRTEEN-WEEK STUDIES 24

SIX-MONTH, TWELVE-MONTH, AND TWO-YEAR STUDIES 28

STUDY DESIGN 28

SOURCE AND SPECIFICATIONS OF ANIMALS 28

ANIMAL MAINTENANCE 28

CLINICAL EXAMINATIONS AND PATHOLOGY 29

STATISTICAL METHODS 29

III. RESULTS 31

RATS 32

SINGLE-ADMINISTRATION STUDIES 32

SIXTEEN-DAY STUDIES 32

THIRTEEN-WEEK STUDIES 33

SIX- AND TWELVE-MONTH STUDIES 34

TWO-YEAR STUDIES 38

BODY WEIGHTS AND CLINICAL SIGNS 38

SURVIVAL 41

PATHOLOGY AND STATISTICAL ANALYSES OF RESULTS 41

MICE 48

SINGLE-ADMINISTRATION STUDIES 48

SIXTEEN-DAY STUDIES 48

THIRTEEN-WEEK STUDIES 48

TWO-YEAR STUDIES 49

BODY WEIGHTS AND CLINICAL SIGNS 49

CONTENTS (Continued)

PAGE

SURVIVAL 52

PATHOLOGY AND STATISTICAL ANALYSES OF RESULTS 54

IV. DISCUSSION AND CONCLUSIONS 57

V. REFERENCES 63

TABLES

TABLE 1 IDENTITY AND SOURCE OF LOTS USED IN THE GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) 22

TABLE 2 PREPARATION AND STORAGE OF DOSE MIXTURES IN THE GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) 23

TABLE 3 SUMMARY OF RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) 24

TABLE 4 EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) 25

TABLE 5 SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE SIXTEEN-DAY GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) 32

TABLE 6 SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) 33

TABLE 7 INCIDENCES OF GRANULOMATOUS INFLAMMATION IN THE LIVER OF FEMALE RATS IN THE THIRTEEN-WEEK GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) 33

TABLE 8 EFFECT OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) ON LIVER WEIGHT TO BODY WEIGHT RATIOS IN RATS AFTER SIX AND TWELVE MONTHS OF DOSING 34

TABLE 9 EFFECT OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) ON THE INCIDENCE AND SEVERITY OF GRANULOMATOUS AND LYMPHOHISTIOCYTIC HEPATITIS IN RATS AFTER SIX AND TWELVE MONTHS OF DOSING 35

TABLE 10 CLINICAL CHEMISTRY VALUES FOR RATS DOSED WITH CHLORINATED PARAFFINS (C_{23}, 43% Cl) FOR SIX MONTHS 36

TABLE 11 CLINICAL CHEMISTRY VALUES FOR RATS DOSED WITH CHLORINATED PARAFFINS (C_{23}, 43% Cl) FOR TWELVE MONTHS 36

TABLE 12 MEAN HEMATOLOGIC VALUES FOR RATS DOSED WITH CHLORINATED PARAFFINS (C_{23}, 43% Cl) FOR SIX MONTHS 37

TABLES (Continued)

PAGE

TABLE 13 MEAN HEMATOLOGIC VALUES FOR RATS DOSED WITH CHLORINATED PARAFFINS (C_{23}, 43% Cl) FOR TWELVE MONTHS 38

TABLE 14 MEAN BODY WEIGHTS AND SURVIVAL OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) 39

TABLE 15 SURVIVAL OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) 41

TABLE 16 ANALYSIS OF ADRENAL GLAND (MEDULLA) LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) 43

TABLE 17 ANALYSIS OF PANCREATIC ACINAR CELL PROLIFERATIVE LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) 44

TABLE 18 ANALYSIS OF UTERINE TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) 45

TABLE 19 NUMBER OF RATS WITH SELECTED NONNEOPLASTIC LESIONS IN THE TWO-YEAR GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) 46

TABLE 20 SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE SIXTEEN-DAY GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) 48

TABLE 21 SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE THIRTEEN-WEEK GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) 49

TABLE 22 MEAN BODY WEIGHTS AND SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) 50

TABLE 23 SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) 52

TABLE 24 ANALYSIS OF MALIGNANT LYMPHOMAS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) 54

TABLE 25 ANALYSIS OF LIVER TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) 56

FIGURES

PAGE

FIGURE 1 GROWTH CURVES FOR RATS ADMINISTERED CHLORINATED PARAFFINS (C_{23}, 43% Cl) IN CORN OIL BY GAVAGE FOR TWO YEARS 40

FIGURE 2 KAPLAN-MEIER SURVIVAL CURVES FOR RATS ADMINISTERED CHLORINATED PARAFFINS (C_{23}, 43% Cl) IN CORN OIL BY GAVAGE FOR TWO YEARS 42

FIGURE 3 GROWTH CURVES FOR MICE ADMINISTERED CHLORINATED PARAFFINS (C_{23}, 43% Cl) IN CORN OIL BY GAVAGE FOR TWO YEARS 51

FIGURE 4 KAPLAN-MEIER SURVIVAL CURVES FOR MICE ADMINISTERED CHLORINATED PARAFFINS (C_{23}, 43% Cl) IN CORN OIL BY GAVAGE FOR TWO YEARS 53

FIGURE 5 INFRARED ABSORPTION SPECTRUM OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) (LOT NO. R-301-137F) 165

FIGURE 6 NUCLEAR MAGNETIC RESONANCE SPECTRUM OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) (LOT NO. R-301-137F) 167

FIGURE 7 INFRARED ABSORPTION SPECTRUM OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) (LOT NO. R-201-965) 170

FIGURE 8 NUCLEAR MAGNETIC RESONANCE SPECTRUM OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) (LOT NO. R-201-965) 171

APPENDIXES

APPENDIX A SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) 67

TABLE A1 SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) 68

TABLE A2 SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) 71

TABLE A3 INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) 74

TABLE A4 INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) 80

APPENDIX B SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE IN THE TWO-YEAR GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) 89

TABLE B1 SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) 90

APPENDIXES (Continued)

PAGE

TABLE B2 SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) 93

TABLE B3 INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) 96

TABLE B4 INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) 102

APPENDIX C SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) 109

TABLE C1 SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) 110

TABLE C2 SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) 116

APPENDIX D SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE IN THE TWO-YEAR GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) 123

TABLE D1 SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) 124

TABLE D2 SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) 130

APPENDIX E ANALYSES OF PRIMARY TUMORS IN RATS AND MICE IN THE TWO-YEAR GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) 135

TABLE E1 ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) 136

TABLE E2 ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) 140

TABLE E3 ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) 143

TABLE E4 ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) 148

APPENDIXES (Continued)

PAGE

APPENDIX F HISTORICAL INCIDENCES OF TUMORS IN F344/N RATS AND B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE 151

TABLE F1 HISTORICAL INCIDENCE OF ZYMBAL GLAND CARCINOMAS IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE 152

TABLE F2 HISTORICAL INCIDENCE OF PANCREATIC ISLET CELL TUMORS IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE 153

TABLE F3 HISTORICAL INCIDENCE OF PANCREATIC ACINAR CELL TUMORS IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE 154

TABLE F4 HISTORICAL INCIDENCE OF HEMATOPOIETIC SYSTEM TUMORS IN FEMALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE 155

TABLE F5 HISTORICAL INCIDENCE OF ADRENAL GLAND TUMORS IN FEMALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE 156

TABLE F6 HISTORICAL INCIDENCE OF UTERINE ENDOMETRIAL STROMAL TUMORS IN FEMALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE 157

TABLE F7 HISTORICAL INCIDENCE OF HEMATOPOIETIC SYSTEM TUMORS IN MALE B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE 158

TABLE F8 HISTORICAL INCIDENCE OF THYROID GLAND FOLLICULAR CELL TUMORS IN MALE B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE 159

TABLE F9 HISTORICAL INCIDENCE OF RENAL TUBULAR CELL TUMORS IN B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE 159

TABLE F10 HISTORICAL INCIDENCE OF HEPATOCELLULAR TUMORS IN FEMALE B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE 160

APPENDIX G MUTAGENICITY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) IN *SALMONELLA TYPHIMURIUM* 161

TABLE G1 MUTAGENICITY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) IN *SALMONELLA TYPHIMURIUM* 162

APPENDIX H CHEMICAL CHARACTERIZATION OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) 163

APPENDIX I PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES 175

APPENDIX J METHODS OF ANALYSIS OF DOSE MIXTURES 179

APPENDIX K RESULTS OF ANALYSIS OF DOSE MIXTURES 183

TABLE K1 RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE THIRTEEN-WEEK GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) 184

APPENDIXES (Continued)

PAGE

TABLE K2 RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) 185

TABLE K3 RESULTS OF REFEREE ANALYSIS IN THE TWO-YEAR GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) 186

APPENDIX L SENTINEL ANIMAL PROGRAM 187

APPENDIX M METHODS FOR SERUM ANALYSES 189

TABLE M1 METHODS FOR SERUM ANALYSES 190

APPENDIX N INGREDIENTS, NUTRIENT COMPOSITION, AND CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION 191

TABLE N1 INGREDIENTS OF NIH 07 RAT AND MOUSE RATION 192

TABLE N2 VITAMINS AND MINERALS IN NIH 07 RAT AND MOUSE RATION 192

TABLE N3 NUTRIENT COMPOSITION OF NIH 07 RAT AND MOUSE RATION 193

TABLE N4 CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION 194

APPENDIX O ABSTRACT FROM NTP TECHNICAL REPORT ON CHLORINATED PARAFFINS (C_{12}, 60% CHLORINE) 197

APPENDIX P DATA AUDIT SUMMARY 201

$CH_3CHCl(CHClCH_2CH_2CH_2)_5CH_2Cl$
(Approximation)

Chlorinated Paraffins
Average Chain Length: C_{23}
43% Chlorine by Weight

$C_{23}H_{41}Cl_7$ (average) **Molecular Weight 560 (average)**

ABSTRACT

Toxicology and carcinogenesis studies of chlorinated paraffins (C_{23}, 43% chlorine), an extreme-pressure lubricant and flame retardant, were conducted by administering the chemical in corn oil by gavage to groups of 50 F344/N rats and 50 B6C3F$_1$ mice of each sex, 5 days per week for 103 weeks. Additional groups of 10 rats per sex and dose were examined at 6 and at 12 months. Male rats received doses of 0, 1,875, or 3,750 mg/kg body weight; female rats were given 0, 100, 300, or 900 mg/kg. Male and female mice received 0, 2,500, or 5,000 mg/kg. Doses selected for the 2-year studies were based on the results from 13-week studies in which rats of each sex received 0 to 3,750 mg/kg, and mice of each sex, 0 to 7,500 mg/kg. No toxicity of chlorinated paraffins (C_{23}, 43% chlorine) was observed in male rats or in male or female mice in the 13-week studies. A dose-related inflammation of the liver was observed in female rats in the 13-week studies and in male and female rats at 6 and 12 months in the 2-year studies.

Chlorinated paraffins (C_{23}, 43% chlorine) administration did not influence mean body weights of rats during the 2-year studies, but both male and female low dose mice gained less weight than did vehicle controls or the high dose groups. Survival of dosed and vehicle control groups was similar for each sex and species (male rats: vehicle control, 30/50; low dose, 32/50; high dose, 27/50; female rats: 34/50; 30/50; 33/50; 31/50; male mice: 29/50; 36/50; 28/50; female mice: 21/50; 22/50; 20/50). For female mice, 60%-70% of the early deaths in each group were attributed to utero-ovarian infection. The lower survival for female mice may have decreased the sensitivity of this study to detect a carcinogenic effect.

Pheochromocytomas of the adrenal gland medulla occurred with an increased incidence in female rats exposed to chlorinated paraffins (C_{23}, 43% chlorine) (vehicle control, 1/50; low dose, 4/50; mid dose, 6/50; high dose, 7/50). However, adrenal gland medullary hyperplasia was not increased (6/50; 3/50; 1/50; 6/50). Malignant lymphomas were increased in dosed male mice (6/50; 12/50; 16/50). High dose female mice showed a marginal increase in the incidence of hepatocellular carcinomas (1/50; 1/49; 6/50) and in the incidence of adenomas or carcinomas (combined) (4/50; 3/49; 10/50).

The primary nonneoplastic lesion associated with chlorinated paraffins (C_{23}, 43% chlorine) administration was a diffuse lymphohistiocytic inflammation in the liver and in the pancreatic and mesenteric lymph nodes of male and female rats. Splenic congestion was a secondary effect. These lesions occurred earlier and at lower doses in female rats than in male rats. No significant nonneoplastic lesions were considered compound related in mice.

Chlorinated paraffins (C_{23}, 43% chlorine) was not mutagenic in strains TA100, TA1535, TA97, or TA98 of *Salmonella typhimurium* in the presence or absence of Aroclor 1254-induced male Sprague-Dawley rat or male Syrian hamster liver S9 when assayed according to the preincubation protocol.

An audit of the experimental data was conducted for these 2-year studies of chlorinated paraffins (C_{23}, 43% chlorine). No data discrepancies were found that influenced the final interpretations.

Under the conditions of these 2-year gavage studies, there was *no evidence of carcinogenicity** of chlorinated paraffins (C_{23}, 43% chlorine) for male F344/N rats given 1,875 or 3,750 mg/kg per day. There was *equivocal evidence of carcinogenicity* of chlorinated paraffins (C_{23}, 43% chlorine) for female F344/N rats as shown by an increased incidence of adrenal gland medullary pheochromocytomas. There was *clear evidence of carcinogenicity* of chlorinated paraffins (C_{23}, 43% chlorine) for male $B6C3F_1$ mice as shown by an increase in the incidence of malignant lymphomas. There was *equivocal evidence of carcinogenicity* of chlorinated paraffins (C_{23}, 43% chlorine) for female $B6C3F_1$ mice as shown by a marginal increase in the incidence of hepatocellular neoplasms.

*Categories of evidence of carcinogenicity are defined in the Note to the Reader on page 2.

CONTRIBUTORS

The NTP Technical Report on the Toxicology and Carcinogenesis Studies of Chlorinated Paraffins (C_{23}, 43% Chlorine) is based on the 13-week studies that began in October 1979 and ended in January 1980 and on the 2-year studies that began in August 1980 and ended in September 1982 at Southern Research Institute.

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

John R. Bucher, Ph.D., Chemical Manager

Gary A. Boorman, D.V.M., Ph.D.
Douglas Bristol, Ph.D.
Joseph K. Haseman, Ph.D.
James Huff, Ph.D.
C.W. Jameson, Ph.D.
W.M. Kluwe, Ph.D.
E.E. McConnell, D.V.M.
J.M. Mason, Ph.D.
G.N. Rao, D.V.M., Ph.D.
B.A. Schwetz, D.V.M., Ph.D.
Raymond W. Tennant, Ph.D.

NTP Pathology Working Group (for mice)
(Evaluated Slides and Prepared Pathology Report on 1/31/84)

Miriam Anver, D.V.M., Ph.D. (Chair)
Clement Associates, Inc.
Gary A. Boorman, D.V.M., Ph.D. (NTP)
Scot L. Eustis, D.V.M., Ph.D. (NTP)
T.C. Jones, D.V.M.
Harvard Medical School
Henk Solleveld, D.V.M., Ph.D. (NTP)
Frank Voelker, D.V.M.
Burroughs Wellcome
Katsuhiko Yoshitomi, D.V.M., Ph.D.
NTP Observer

NTP Pathology Working Group (for rats)
(Evaluated Slides and Prepared Pathology Report on 2/7/84)

Miriam Anver, D.V.M., Ph.D. (Chair)
Clement Associates, Inc.
Ken Ayers, D.V.M. (Burroughs Wellcome)
Gary A. Boorman, D.V.M., Ph.D. (NTP)
Scot L. Eustis, D.V.M., Ph.D. (NTP)
Leroy Hall, D.V.M., Ph.D. (NTP)
Kevin Morgan, Ph.D.
Chemical Industry Institute of Toxicology
Henk Solleveld, D.V.M., Ph.D. (NTP)
Marilyn Wolfe, D.V.M., Ph.D. (NTP)

Principal Contributors at Southern Research Institute
(Conducted Studies and Evaluated Tissues)

J. David Prejean, Ph.D.
Principal Investigator
Daniel Farnell, D.V.M., Ph.D.
Pathologist (for mice)
Ruby James, B.S.
Chemist
Roger Thompson, D.V.M.
Pathologist (for rats)

Principal Contributors at Experimental Pathology Laboratories
(Conducted Pathology Quality Assurance)

Melvin Hamlin, D.V.M.

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

William D. Theriault, Ph.D.
Project Manager
Abigail C. Jacobs, Ph.D.
Senior Scientist
John Warner, M.S.
Chemist/Statistician

PEER REVIEW PANEL

The members of the Peer Review Panel who evaluated the draft Technical Report on chlorinated paraffins (C_{23}, 43% chlorine) on August 14, 1985, 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

Jerry B. Hook, Ph.D. (Chair)
Vice President, Preclinical Research and Development
Smith Kline & French Laboratories
Philadelphia, Pennsylvania

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

James Swenberg, D.V.M., Ph.D.
Head, Department of Biochemical Toxicology and Pathobiology
Chemical Industry Institute of Toxicology
Research Triangle Park, North Carolina

Ad Hoc Subcommittee Panel of Experts

John J. Crowley, Ph.D.
Division of Public Health Science
The Fred Hutchinson Cancer Research Center
Seattle, Washington

Kim Hooper, Ph.D. (Principal Reviewer)
Chief, Hazard Evaluation System and Information Services
Department of Health Services
State of California
Berkeley, California

Thomas C. Jones, D.V.M.
Professor, Comparative Pathology
New England Regional Primate Research Center
Harvard Medical School
Southborough, Massachusetts

Richard J. Kociba, D.V.M., Ph.D.
Dow Chemical USA
Midland, Michigan

David Kotelchuck, Ph.D. (Principal Reviewer)
Environmental Health Science Program
Hunter School of Health Sciences
New York, New York

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

I.F.H. Purchase, Ph.D.
Central Toxicology Laboratory
Imperial Chemical Industries, PLC
Alderley Park, England

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

Steven R. Tannenbaum, Ph.D.
(Principal Reviewer)
Professor, Department of Nutrition and Food Science
Massachusetts Institute of Technology
Cambridge, Massachusetts

Bruce W. Turnbull, Ph.D.
Professor and Associate Director
College of Engineering
Cornell University, Ithaca, New York

*Unable to attend

SUMMARY OF PEER REVIEW COMMENTS ON THE TOXICOLOGY AND CARCINOGENESIS STUDIES OF CHLORINATED PARAFFINS (C_{23}, 43% CHLORINE)

On August 14, 1985, the draft Technical Report on the toxicology and carcinogenesis studies of chlorinated paraffins (C_{23}, 43% chlorine) received peer review by the National Toxicology Program Board of Scientific Counselors' Technical Reports Review Subcommittee and associated Panel of Experts. The review meeting began at 9:00 a.m. in the Conference Center, Building 101, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina.

Dr. Hooper, a principal reviewer, commented that although the high viscosity of the dosing vehicle may have prevented administration of maximum tolerated doses, the linear increase in liver weight indicated achievement of a biologically effective dose, at least in rats. However, the decreased survival in female mice due to a utero-ovarian infection may have limited the sensitivity of the study. He felt that more comparisons of the findings between these studies and those with chlorinated paraffins (C_{12}, 60%) (NTP TR 308) would be useful, especially with regard to liver changes in rats.

As a second principal reviewer, Dr. Tannenbaum agreed with the conclusions. He said that if serum enzyme changes were an indication of liver toxicity, then discussion was warranted as to whether the maximum tolerated dose may have been exceeded. Dr. J. Bucher, NTP, agreed that increases in serum enzyme levels reflected liver damage in male rats but noted that there were no effects on weight gain or survival and, in male rats, no chemically related tumors. With regard to chemical characterization, Dr. Tannenbaum stated that capillary gas chromatography for a mixture profile would have been preferable for both chlorinated paraffins (C_{23}, 43%, and C_{12}, 60%). Dr. T. Goehl, NIEHS, said earlier analytical studies indicated that the compounds do not chromatograph reproducibly and tend to dehalogenate when heated. Dr. Tannenbaum replied that recent technology allows analysis of thermolabile compounds through the use of capillary columns.

As a third principal reviewer, Dr. Kotelchuck agreed with the conclusions but suggested that there be more discussion in the Technical Report about why the marginal increases of pancreatic islet cell adenomas and neoplastic liver nodules in male rats were not considered to be chemically related. He observed that the striking difference in incidence and patterns of neoplastic lesions between these studies with the longer chain (C_{23}) and the shorter chain (C_{12}) paraffins suggested the need for further studies, especially in examining differential metabolism in mammalian species. In response to these comments, Dr. Bucher said that more comparisons of the results between the C_{23} and C_{12} compounds would be included in the Report [see page 60].

In other discussion, Dr. Mirer reported that these substances are used in 2%-5% concentrations in cutting fluids in machining operations. He said that there is considerable literature about increased incidences of cancer in workers exposed to machining and cutting fluids, although there is no good evidence pointing at specific constituents of the fluids. He said that more mention should be given to significant nontumor pathologic findings.

There was further discussion as to whether the conclusion in male mice should remain clear evidence of carcinogenicity or be changed to some evidence of carcinogenicity. Dr. Swenberg noted that malignant lymphoma is one of the more variable tumors and has a viral origin in many cases. Dr. Purchase commented that statistically significant trends were obtained only if the lymphocytic and histiocytic tumor types were combined. Dr. E. McConnell, NIEHS, said that this was done routinely. Dr. Hooper said support for the original conclusion derived from a clearly significant trend test, significant pairwise comparison at the high dose, and the fact that both low dose and high dose incidences of the tumor are above the historical control range.

Dr. Hooper moved that the conclusions as written for both rats and mice be accepted. Dr. Kotelchuck seconded the motion, and it carried by five affirmative votes (Dr. Crowley, Dr. Hooper, Dr. Kotelchuck, Dr. Mirer, and Dr. Perera) to four negative votes (Dr. Jones, Dr. Kociba, Dr. Swenberg, and Dr. Tannenbaum) with two abstentions (Dr. Purchase and Dr. Turnbull). Because of the closeness of the vote, Dr. Hook asked that separate votes be taken. Dr. Hooper moved that the conclusion for male rats, no evidence of carcinogenicity, and that for female rats, equivocal evidence of carcinogenicity, be accepted as written. Dr. Kotelchuck seconded the motion, and it was approved by 10 affirmative votes with one abstention (Dr. Purchase). Dr. Hooper then moved that the conclusion for female mice, equivocal evidence of carcinogenicity, be accepted as written. Dr. Kotelchuck seconded the motion, and it was approved by 10 affirmative votes with one abstention (Dr. Purchase). Dr. Hooper moved that the conclusion for male mice, clear evidence of carcinogenicity, be accepted as written. Dr. Perera seconded the motion, and it was approved by five affirmative votes (Dr. Crowley, Dr. Hooper, Dr. Kotelchuck, Dr. Mirer, and Dr. Perera) to four negative votes (Dr. Jones, Dr. Kociba, Dr. Swenberg, and Dr. Tannenbaum) with two abstentions (Dr. Purchase and Dr. Turnbull).

I. INTRODUCTION

I. INTRODUCTION

$CH_3CHCl(CHClCH_2CH_2CH_2)_5CH_2Cl$
(Approximation)

Chlorinated Paraffins
Average Chain Length: C_{23}
43% Chlorine by Weight

$C_{23}H_{41}Cl_7$ (average) **Molecular Weight 560 (average)**

Commercial chlorinated paraffins are saturated straight-chain hydrocarbons ranging from 10 to 30 carbons in length and containing 20%-70% chlorine by weight. These paraffins are manufactured by the liquid-phase chlorination of various paraffinic stocks under controlled conditions of temperature and illumination (Hardie, 1967). A variety of chlorinated isomers are generated from each paraffin present, and even the purest of these products is more complex than commercial mixtures of polychlorinated biphenyls (PCB's) and chlorinated naphthalenes (Howard et al., 1975). Most companies that produce chlorinated paraffins offer several different products distinguishable by the average carbon chain length and the degree of chlorination.

The subject of this report is the mixture of chlorinated paraffins produced from a C_{23} (average) paraffin feedstock chlorinated to approximately 43% by weight. The NTP has also performed toxicity and carcinogenicity evaluations on shorter chain paraffins, C_{12} (average), chlorinated to 60%; the results of those studies are reported separately (NTP, 1986).

Chlorinated paraffins (C_{23}, 43% chlorine) is a clear to slightly yellow, viscous liquid. It is soluble in mineral and lubricating oils, benzene, various chlorinated solvents, ether, ketones, esters, and a variety of aliphatic and aromatic hydrocarbons but is insoluble in water and alcohol (Hardie, 1967). Small amounts of isoparaffins and aromatics may be present as contaminants; the content of aromatics in the C_{23} feedstock is typically less than 0.1% (Zitko, 1980). Trace amounts of carbon tetrachloride, methylene chloride, chloroform, or tetrachloroethylene may remain from the manufacturing process. Epoxidized fatty acids, organotin compounds, lead oxide, or other compounds are usually added to the commercial product as stabilizers (Svanberg and Linden, 1979; Howard et al., 1975), but none of these substances was incorporated into the test material used in these studies.

Production and Uses

Various chlorinated paraffins are manufactured worldwide by a large number of companies. Total global production was estimated to be greater than 250,000 metric tons (250×10^6 kg) per year in 1978 (Zitko, 1980). Their commercial importance appears to be increasing as shown by a market growth of about 5% per year from 1972 to 1977 (Campbell and McConnell, 1980). Production of chlorinated paraffins in the United States in 1983 was 99 million pounds (45×10^6 kg) (USITC, 1984).

Chlorinated paraffins are used as extreme-pressure lubricant additives (45% of total production); as flame retardants in rubber, plastics, and paints (27%); and as secondary plasticizers, primarily in polyvinylchloride (24%) (Howard et al., 1975). Small amounts are also used in certain types of adhesives, plastics, caulks, and inks (Zitko, 1980). The viscosity of the chlorinated paraffins and their capacity to slowly release hydrogen chloride at high temperatures account for the lubricating and flame-retardant properties of these materials. For many applications, chlorinated paraffins are being used in place of PCB's (Svanberg and Linden, 1979).

Environmental Occurrence

Campbell and McConnell (1980) found chlorinated paraffins in marine and fresh waters and sediments in the United Kingdom. Concentrations in nonindustrialized areas ranged from less than 0.5 ppb to 2 ppb (waters) and from less than 0.5 ppb to 10 ppm (sediments). In industrialized areas, the upper values increased

to 6 ppb in water and to 15 ppm in sediments. The concentrations of chlorinated paraffins in aquatic organisms were generally similar to the concentrations in the sediments below the water in which they lived. Little evidence of bioaccumulation or biomagnification was found. Baldwin and Bennett (1974) examined 52 samples of 6 species of fish, 2 species of shellfish, and the eggs of 4 species of aquatic birds. They found chlorinated paraffins in 13 of these samples at concentrations of about 0.5 ppm.

Campbell and McConnell (1980) isolated chlorinated paraffins from human liver (up to 1.5 ppm) and adipose tissue (0.6 ppm). They estimated that the total body burden could range from 0 to 7 mg. These investigators also detected chlorinated paraffins in dairy products, vegetable oils, fruits, and vegetables.

Metabolism

The uptake and elimination of chlorinated paraffins have been studied in fish, birds, and rodents (Biessman et al., 1983; Lombardo et al., 1975; Svanberg et al., 1978). In general, these studies have employed chlorinated paraffins labeled with ^{14}C or ^{36}Cl or have assessed total tissue chloride. Attempts have been made to characterize labeled materials after isolation from tissues or excreta, but the metabolic pathways involved in the degradation of the chlorinated paraffins remain largely unknown.

In C57BL mice, a chlorinated paraffin with a chain length of 16 carbons and a chlorine content of 34% by weight (C_{16}, 34% chlorine) in a fat emulsion was readily absorbed after oral administration and distributed to tissues that exhibit high metabolic activity, e.g., the intestinal mucosa, bone marrow, and exocrine glands (Darnerud and Brandt, 1982). At least a portion of this chlorinated paraffin underwent β-oxidation, ultimately yielding carbon dioxide; a dechlorination reaction was required for β-oxidation to occur (Darnerud et al., 1982).

No metabolism studies have been reported for chlorinated paraffins (C_{23}, 43% chlorine), but from studies of other chlorinated paraffins, certain aspects of the metabolism of this material are suggested. As the chlorine content of the chlorinated paraffin is increased, the amount of compound that is absorbed following oral administration is decreased. Thus, fecal excretion is a major route of elimination of highly chlorinated paraffins, and the amount of compound metabolized to carbon dioxide or excreted via the urine is small (Darnerud et al., 1982). A highly chlorinated paraffin (C_{16}, 69% chlorine) was distributed initially to the liver, kidney, and gallbladder in C57BL female mice after oral or intravenous administration, and over a 4-day period it accumulated in the corpora lutea and fat. Poor absorption would account in part for the small amount of observed β-oxidation of the highly chlorinated paraffin, but the existence of other metabolic pathways for the absorbed paraffins was suggested by the observation of biliary excretion of labeled materials that were more polar than the parent compound (Biessmann et al., 1983). By following the disappearance of chlorine-36 after feeding ^{36}Cl-labeled $C_{14\text{-}17}$-*n*-paraffin (52% chlorine) to Wistar-derived rats for 10 weeks, Birtley et al. (1980) estimated the half-life for elimination of this chlorinated paraffin to be less than 1 week from liver and approximately 8 weeks from fat.

Toxicity

The acute toxicity of chlorinated paraffins is low. Ninety-six-hour LC_{50} values for various chlorinated paraffins (C_{23}, 40% chlorine; C_{20}, 34% chlorine; C_{24}, 48% chlorine; $C_{10\text{-}13}$, 58% chlorine) for rainbow trout and bluegill are greater than 300 mg/liter (Howard et al., 1975). However, a progressive loss of motor function and other evidence of possible neurotoxic effects were seen in bleaks and rainbow trout in feed studies of subacute effects and with lower concentrations (40 mg/liter) of chlorinated paraffins in the water (Howard et al., 1975; Svanberg et al., 1978). When adult rainbow trout were exposed to $C_{20\text{-}30}$, 42% chlorine, at 385 ppm in feed for 35 days, no effects were observed (Madeley and Birtley, 1980), but Lombardo et al. (1975) noted reduced growth of fingerling trout fed a diet containing 10 ppm $C_{10\text{-}12}$, 58% chlorine, for up to 82 days.

No toxicity was observed in ducks or pheasants after single (oral gavage) and 5-day repeated-dose exposures (feed) to $C_{14\text{-}17}$, 52% chlorine, at doses up to 24.6 g/kg (Madeley and Birtley, 1980). No deaths resulted from the oral dosing

of rats (unspecified strain) with chlorinated paraffins (C_{23}, 40% chlorine), at 10 ml/kg or with chlorinated paraffins (C_{24}, 70% chlorine), at 50 g/kg; the oral LD_{50} value for C_{10-12}, 58% chlorine, was determined to be greater than 21.5 ml/kg (Howard et al., 1975). Death in these studies was attributed to physical obstruction due to the large volumes administered.

The low acute toxicity of several chlorinated paraffins in pathogen-free Wistar rats was reported by Birtley et al. (1980). Clinical signs were observed in rats receiving over 4 g/kg but were limited to piloerection, muscular incoordination, and urinary and fecal incontinence. Gross and histologic examinations revealed gastric inflammation, hepatocellular vacuolation with occasional necrotic foci, and cloudy swelling of some inner cortical cells of the kidney.

In 90-day studies in which Wistar rats consumed feed containing up to 5,000 ppm chlorinated paraffins (C_{14-17}, 52% chlorine), no effects were noted on survival, clinical signs, hematologic measurement, or the efficiency of food utilization (Birtley et al., 1980). However, liver and kidney weights were elevated, and microscopic examination of the liver showed proliferation of smooth endoplasmic reticulum. Similar results were observed in male beagle dogs given up to 100 mg/kg chlorinated paraffins (C_{14-17}, 52% chlorine) in feed for 90 days, but no effects were seen in females.

The various chlorinated paraffins exhibit little or no potential to irritate the skin of humans or rabbits but can cause mild conjunctivitis when applied to the eyes of rabbits (Howard et al., 1975; Birtley et al., 1980). No incidents of human intoxication have been reported in workers involved in the handling or manufacture of chlorinated paraffins (Howard et al., 1975). No epidemiologic or animal studies were available that examined the potential of the chlorinated paraffins to cause carcinogenic, teratogenic, or reproductive effects.

Mutagenicity

Chlorinated paraffins (C_{23}, 43% chlorine) was not mutagenic in *Salmonella typhimurium* strains TA100, TA1535, TA97, or TA98 in the presence or absence of Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver S9 when tested according to the preincubation protocol (Appendix G). Birtley et al. (1980) also found that Cereclor 55® (C_{20-30}, 42% chlorine) was not mutagenic with or without metabolic activation in *S. typhimurium* and that the material did not induce morphologic transformation of BHK cells in vitro.

Study Rationale

Chlorinated paraffins (C_{23}, 43% chlorine) and chlorinated paraffins (C_{12}, 60% chlorine) were nominated by the National Cancer Institute and the Consumer Product Safety Commission as representative examples of chlorinated paraffins. Chlorinated paraffins were designated as priority chemicals by the Interagency Testing Committee (ITC) of the U.S. Environmental Protection Agency in October 1977 because of their large and growing market and their use pattern. The ITC recommended testing for carcinogenicity, mutagenicity, teratogenicity, and other chronic effects in mammals and for persistence, environmental fate, and chronic effects on aquatic organisms (42 FR 55026). The NTP toxicology, mutagenicity, and carcinogenesis studies, and a large independent research program on the chlorinated paraffins sponsored by a consortium of chlorinated paraffin manufacturers (47 FR 1017), were initiated in response to this recommendation.

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF CHLORINATED PARAFFINS (C_{23}, 43% CHLORINE)

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES

SINGLE-ADMINISTRATION STUDIES

SIXTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Study Design

Source and Specifications of Animals

Animal Maintenance

Clinical Examinations and Pathology

Statistical Methods

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF CHLORINATED PARAFFINS (C_{23}, 43% CHLORINE)

Chlorinated paraffins (C_{23}, 43% chlorine) was obtained in two lots from Diamond Shamrock Corporation as the commercial-grade material without stabilizers (Table 1). The material was reported by the manufacturer to be a mixture of chlorinated paraffins (C_{22-26}) with an average molecular weight of 560 and 43% chlorine content. Each lot was shipped in several containers. For each lot, the contents of the containers were combined, mixed, and returned to the original containers.

Purity and identity analyses were conducted at Midwest Research Institute (Kansas City, Missouri) (Appendix H). For both lots, infrared spectra were consistent with those in the literature, and ultraviolet/visible and nuclear magnetic resonance spectra were consistent with those expected for the structure.

For both lots, nos. R-301-137F and R201-965, cumulative data from elemental analyses, Karl Fischer water analysis, and thin-layer chromatography indicated that the study material fit the manufacturer's specifications for average molecular weight and chlorine content. Acid content (as hydrochloric acid) was determined to be 3 ppm for lot no. R-301-137F and 4.7 ppm for lot no. R-201-965. The chlorinated paraffins (C_{23}, 43% chlorine) used in these studies differed from the commercial product in that it did not have added stabilizers and therefore was not stable at temperatures above 25° C (Appendix H). Chlorinated paraffins (C_{23}, 43% chlorine) was stored at 5° C until September 4, 1979, and thereafter at −20° C. Results of periodic analyses of the bulk chemical by infrared spectroscopy and thin-layer chromatography indicated that no notable degradation occurred during the studies (Appendix H).

TABLE 1. IDENTITY AND SOURCE OF LOTS USED IN THE GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{23}, 43% Cl)

	Single-Administration Studies	Sixteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
Lot Numbers	R-301-137F	R-301-137F	R-301-137F	R-301-137F R-201-965
Date of Initial Use of Each Lot	6/5/79	N/A	N/A	8/12/81
Supplier	Diamond Shamrock Corp. (Dallas, TX)	Same as single-administration studies	Same as single-administration studies	Same as single-administration studies

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES

Accurately weighed aliquots of chlorinated paraffins (C_{23}, 43% chlorine) and corn oil were mixed (w/w) to give the desired concentrations (Table 2; Appendix I). The mixing procedure was changed during the second year of the 2-year studies to improve homogeneity and prevent separation of the corn oil/chlorinated paraffins (C_{23}, 43% chlorine) mixtures. Chlorinated paraffins (C_{23}, 43% chlorine) in corn oil was found to be stable for 28 days in the dark at room temperature. Before October 1980, chlorinated paraffins (C_{23}, 43% chlorine)/corn oil mixtures were stored at 0° ± 5° C for no longer than 8 days; thereafter, the mixtures were stored for 14 days at 0° ± 5° C.

Routine periodic analysis of chemical/vehicle mixtures at the study laboratory was performed by either a gravimetric or viscosity determination procedure (Appendix J). Because 185/196 of the mixes were formulated within the specified ± 10% of the target concentrations during the 2-year studies, the data can be extrapolated to indicate that 94% of the mixes were formulated within specifications (Table 3; Appendix K, Table K2).

TABLE 2. PREPARATION AND STORAGE OF DOSE MIXTURES IN THE GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{23}, 43% Cl)

	Single-Administration Studies	Sixteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
Preparation	Accurately weighed aliquots of chlorinated paraffins (C_{23}, 43% Cl) were added to corn oil in serum bottle. Bottle was placed on preheated magnetic stirring hot plate and heated to 37° C. Dose mixtures were stirred constantly during dosing period.	Chemical was protected from light during all procedures. After chemical was warmed to room temperature, it was measured into serum bottle followed by corn oil and then stirred on a magnetic stirrer until the mixture was visually homogenous.	Same as 16-d studies, except mixture was shaken manually for 1 min before being mixed on magnetic stirrer	Protected from light during all procedures. Chlorinated paraffins (C_{23}, 43% Cl) was allowed to come to room temperature and then weighed into a beaker; corn oil was added by volume and mixed on a magnetic stirrer. After 6/8/81, both chlorinated paraffins (C_{23}, 43% Cl) and corn oil were weighed into a beaker, then either mixed with high-speed stirrer to produce visual homogeneity or stirred on a magnetic stirrer, and then blended by a Polytron for 5 min.
Maximum Storage Time	N/A	8 d	7 d	7 d until 10/80, then 14 d to end of studies
Storage Conditions	N/A	Room temperature in the dark	Room temperature in the dark	Room temperature in the dark; amber serum bottle containing stirring bar

TABLE 3. SUMMARY OF RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{23}, 43% Cl)

	Determined Concentration for Target Concentration (percent weight/volume)						
	2	6	18	25	37.5	50	75
Mean (percent)	2.1	6.1	18.0	25.0	37.6	49.3	73.8
Standard deviation	0.36	0.62	0.83	1.04	1.84	2.37	5.85
Coefficent of variation (percent)	17.1	10.2	4.6	4.2	4.9	4.8	7.9
Range (percent)	1.6-3.7	5.4-7.9	16.4-19.8	23.2-27.8	34.2-41.2	46.1-54.8	49.2-80.7
Number of samples	29	28	29	27	28	27	28
Number of samples greater than ± 10% of target concentration	4	4	0	2	0	0	1

SINGLE-ADMINISTRATION STUDIES

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Harlan Industries and observed for 20 days before the studies began. The animals were 8-9 weeks old when placed on study.

Groups of five rats of each sex were administered a single dose of 702, 1,404, 2,925, 5,850, or 11,700 mg/kg chlorinated paraffins (C_{23}, 43% chlorine) in corn oil by gavage. Groups of five mice of each sex were administered 1,404, 2,808, 5,850, or 11,700 mg/kg in corn oil or 23,400 mg/kg as the neat chemical. Rats were fasted overnight, and mice were fasted 4 hours before dosing. Animals were observed twice per day for 14 days. Details of animal maintenance are presented in Table 4.

SIXTEEN-DAY STUDIES

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories and held for 12 days before the studies began. The animals were 6-7 weeks old when placed on study.

Groups of five rats of each sex were administered 0, 235, 469, 938, 1,875, or 3,750 mg/kg chlorinated paraffins (C_{23}, 43% chlorine) in corn oil by gavage for 5 days per week over a 16-day period (dosed on 12 days). Groups of mice of each sex were administered 0, 469, 938, 1,875, 3,750, or 7,500 mg/kg on the same schedule.

Animals were housed five per cage. Water and feed were freely available. The rats and mice were observed twice daily and were weighed once per week. A necropsy was performed on all animals. Tissues were not examined microscopically. Details of animal maintenance are presented in Table 4.

THIRTEEN-WEEK STUDIES

Thirteen-week studies were conducted to evaluate the cumulative toxic effects of repeated administration of chlorinated paraffins (C_{23}, 43% chlorine) and to determine the doses to be used in the 2-year studies.

Groups of 10 rats of each sex were administered 0, 235, 469, 938, 1,875, or 3,750 mg/kg chlorinated paraffins (C_{23}, 43% chlorine) in corn oil by gavage, 5 days per week for 13 weeks. Groups of 10 mice of each sex were administered 0, 469, 938, 1,875, 3,750, or 7,500 mg/kg on the same schedule. Rats and mice were housed five per cage in polycarbonate cages. Feed and water were available ad libitum. Further experimental details are summarized in Table 4.

Animals were checked twice daily; moribund animals were killed. Individual animal weights and clinical signs were recorded weekly.

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 4.

TABLE 4. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{23}, 43% Cl)

	Single-Administration Studies	Sixteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
EXPERIMENTAL DESIGN				
Study Laboratory	Southern Research Institute	Same as single-administration studies	Same as single-administration studies	Same as single-administration studies
Size of Study Groups	5 males and 5 females of each species	Same as single-administration studies	10 males and 10 females of each species	50 males and 50 females of each species; 20 rats of each sex added to dosed rat groups for concurrent 6- and 12-month studies
Doses	Rats--702, 1,404, 2,925, 5,850, or 11,700 mg/kg chlorinated paraffins (C_{23}, 43% Cl) in corn oil by gavage; dose vol: 10 ml/kg; mice--1,404, 2,808, 5,850, or 11,700 mg/kg in corn oil by gavage; dose vol: 20 ml/kg, or 23,400 mg/kg (neat) chlorinated paraffins (C_{23}, 43% Cl)	Rats--0, 235, 469, 938, 1,875, or 3,750 mg/kg chlorinated paraffins (C_{23}, 43% Cl) in corn oil by gavage; dose vol: 5 ml/kg; mice--0, 469, 938, 1,875, 3,750, or 7,500 mg/kg chlorinated paraffins (C_{23}, 43% Cl) in corn oil by gavage; dose vol: 10 ml/kg	Same as 16-d studies dose vol: 5 ml/kg	Male rats--0, 1,875, or 3,750 mg/kg chlorinated paraffins (C_{23}, 43% Cl) in corn oil by gavage; female rats--0, 100, 300, or 900 mg/kg chlorinated paraffins (C_{23}, 43% Cl) in corn oil by gavage (5 female rats in the 300 mg/kg group were dosed with 1,875 mg/kg on 10/20/81); dose vol: 5 ml/kg; mice--0, 2,500, or 5,000 mg/kg chlorinated paraffins (C_{23}, 43% Cl) in corn oil by gavage; dose vol: 10 ml/kg
Date of First Dose	6/5/79	8/12/79	10/24/79	Rats--8/7/80; mice--9/12/80
Date of Last Dose	N/A	8/27/79	1/22/80	Rats--7/30/82; mice--9/2/82
Duration of Dosing	One time only	Administered on 12 d over a 16-d period	5 d/wk for 13 wk	5 d/wk for 103 wk
Type and of Observation	Observed 2 × d; weighed before dosing	Observed 2 × d; weighed on d 1, 9, and 16	Weighed 1 × wk; observed 2 × d	Observed 2 × d; weighed initially, 1 × wk for 13 wk, then monthly. Clinical signs recorded at time of weighing. Palpated at weighing starting at wk 41
Necropsy and Histologic Examination	Necropsy not performed	Necropsy performed on all animals; tissues were not examined histologically	Necropsy performed on all animals; histologic exam performed on the following tissues of high dose and vehicle control groups and on all animals dying before the end of the studies: skin, mandibular lymph node, mammary gland, salivary gland, thigh	Necropsy performed on all animals; the following tissues examined histologically: gross lesions and tissue masses, mandibular and mesenteric lymph nodes, salivary gland, femur, including marrow, thyroid gland, parathyroids, small intestine, cecum, colon, liver, gallbladder (mice),

TABLE 4. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) (Continued)

	Single-Administration Studies	Sixteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
Necropsy and Histologic Exam (Continued)			muscle, femur including marrow, thymus, lungs and bronchi, heart, thyroid gland, parathyroids, esophagus, stomach, small intestine, colon, mesenteric lymph node, liver, pancreas, spleen, kidneys, adrenal glands, urinary bladder, seminal vesicles/prostate/testis or ovaries/uterus, brain, pituitary gland, gallbladder (mice). Livers also examined in all dosed female rats; spleens examined in the 938 mg/kg and 1,875 mg/kg female groups.	prostate/testis/epididymis or ovaries/uterus, lungs and mainstem bronchi, nasal cavity and turbinates, heart, esophagus, stomach, brain, thymus, trachea, pancreas, spleen, kidneys, adrenal glands, urinary bladder, skin, preputial or clitoral gland (rats). Ten rats per group killed at 6 or 12 mo for the following procedures: gross necropsy, histologic examination of tissues indicated above; spleen, liver, thymus, adrenal gland, brain, kidney, and heart weights; hematologic and clinical chemistry procedures: hematocrit, hemoglobin, red blood cell count, white blood cell count, differential count, total serum protein, serum albumin, serum globulin, serum albumin/globulin ratio, serum sorbitol dehydrogenase, serum alanine aminotransferase, and serum aspartate aminotransferase.
ANIMALS AND ANIMAL MAINTENANCE				
Strain and Species	F344/N rats; $B6C3F_1$ mice	F344/N rats; $B6C3F_1$ mice	F344/N rats; $B6C3F_1$ mice	F344/N rats; $B6C3F_1$ mice
Animal Source	Harlan Industries (Indianapolis, IN)	Charles River Breeding Laboratories	Charles River Breeding Laboratories (Portage, MI)	Rats--Charles River Breeding Laboratories (Kingston, NY); mice--Charles River Breeding Laboratories (Portage, MI)
Time Held Before Study	20 d	12 d	15 d	Rats--2 wk; mice--3 wk
Age When Placed on Study	8 wk	Rats--6 wk; mice--7 wk	8 wk	Rats--6-7 wk; mice--8-9 wk
Age When Killed	10 wk	Rats--8 wk; mice--9 wk	21 wk	Rats--111-112 wk; mice--113-114 wk

TABLE 4. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) (Continued)

	Single-Administration Studies	Sixteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
Necropsy or Kill Dates	6/20/79	8/28/79-8/31/79	Rats--1/22/80-1/28/80; mice--1/22/80-1/30/80	Rats--8/9/82-8/13/82; mice--9/10/82-9/15/82
Method of Animal Distribution	Animals grouped based on weight intervals. Assigned to cages by one table of random numbers, then to groups by another table	Same as single-administration studies	Same as single-administration studies	Same as single-administration studies
Animal Identification	Ear punch	Ear punch	Ear punch	Ear punch
Feed	Wayne Lab Blox® pellets (Allied Mills, Chicago, IL); available ad libitum	Same as single-administration studies	NIH 07 Rat and Mouse Ration (Zeigler Bros., Gardners, PA); available ad libitum	Same as 13-wk studies
Bedding	Beta Chips®--heat-treated hardwood chips (Northeastern Products Corp., Warrensburg, NY)	Same as single-administration studies	Same as single-administration studies	Same as single-administration studies
Water	Automatic watering system (Edstrom Industries, Waterford, WI); available ad libitum	Same as single-administration studies	Same as single-administration studies	Same as single-administration studies
Cages	Polycarbonate (Lab Products, Inc., Garfield, NJ)	Same as single-administration studies	Same as single-administration studies	Same as single-administration studies
Cage Filters	Reemay spun-bonded polyester filters (Snow Filtration, Cincinnati, OH)	Same as single-administration studies	Same as single-administration studies	Same as single-administration studies
Animals per Cage	5	5	5	5
Other Chemicals on Study in the Same Room	None	None	None	None
Animal Room Environment	Temp--22° ± 1° C; humidity--30%-50%; fluorescent light 12 h/d; 15 room air changes/h	Same as single-administration studies	Temp--23° ± 1° C; humidity--43%-50%; fluorescent light 12 h/d; 15 room air changes/h	Temp--23° ± 1° C; humidity--43%-60%; fluorescent light 12 h/d; 15 room air changes/h

II. MATERIALS AND METHODS

SIX-MONTH, TWELVE-MONTH, AND TWO-YEAR STUDIES

Study Design

Groups of 50 male rats were administered 0, 1,875, or 3,750 mg/kg chlorinated paraffins (C_{23}, 43% chlorine) in corn oil by gavage, 5 days per week for 103 weeks. Groups of 50 female rats were administered 0, 100, 300, or 900 mg/kg, and groups of 50 mice of each sex were administered 0, 2,500, or 5,000 mg/kg on the same schedule. Additional groups of 20 male and 20 female rats were added to each group for concurrent 6-month and 12-month studies. For the 6- and 12-month studies, blood was collected from the posterior vena cava of chloroform-anesthetized animals just before necropsy. The spleen, liver, thymus, adrenal glands, brain, kidneys, and heart were removed and weighed. Hematologic evaluations at 6 and 12 months included hematocrit, hemoglobin, erythrocyte count, leukocyte count, and differential count (Appendix M). Serum enzyme analyses included sorbitol dehydrogenase (SDH), aspartate aminotransferase (ASAT), and alanine aminotransferase (ALAT).

The 2-year studies in mice were started with doses of 3,750 and 7,500 mg/kg delivered by gavage via an 18-gauge needle. After 3 weeks of dosing, gavage-related accidents had killed 13 vehicle control, 10 low dose, and 14 high dose mice. For this reason, the studies in mice were restarted, and the dose was reduced to 2,500 and 5,000 mg/kg. The reduction in dose allowed delivery of the viscous chlorinated paraffins (C_{23}, 43% chlorine) corn oil mixture through a 20-gauge needle rather than the 18-gauge needle that had been used, a procedure that essentially eliminated dosing accidents.

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 this study were produced under strict barrier conditions at Charles River Breeding Laboratories (Kingston, New York, for rats and Portage, Michigan, for mice) under a contract to the Carcinogenesis Program. Breeding stock for the foundation colonies at the production facility originated at the National Institutes of Health Repository. Animals shipped for study were progeny of defined microflora-associated parents that were transferred from isolators to barrier-maintained rooms. Rats were shipped to the study laboratory at 4-5 weeks of age and mice at 5-6 weeks of age. The animals were quarantined at the study facility for 2 weeks (rats) or 3 weeks (mice). Thereafter, a complete necropsy was performed on five animals of each sex and species to assess their health status. The rats were placed on study at 6-7 weeks of age and the mice at 8-9 weeks of age. The health of the animals was monitored during the course of the study according to the protocols of the NTP Sentinel Animal Program (Appendix L), except that female sentinel F344/N rats were from Harlan Industries rather than from Charles River Breeding Laboratories.

A quality control skin grafting program has been in effect since early 1978 to monitor the genetic integrity of the inbred mice used to produce the hybrid $B6C3F_1$ test animal. In mid-1981, data were obtained that showed incompatibility between the NIH C3H reference colony and the C3H colony from a 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/6 mice were homogeneous at all loci tested. Eighty-five percent of the C3H mice monitored were variant at one to three loci, indicating some heterogeneity in the C3H line 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/6 colony were used as parents for the hybrid $B6C3F_1$ mice used in these studies. The influence of the potential genetic nonuniformity in the hybrid mice on these results is not known, but results of the studies are not affected because concurrent controls were included in each study.

Animal Maintenance

Rats and mice were housed five per cage. Water and feed were available ad libitum. Further

details of animal maintenance are given in Table 4.

Clinical Examinations and Pathology

All animals were observed twice daily, and clinical signs were recorded at each weighing. Body weights by cage were recorded once per week for the first 13 weeks of the study and once per month thereafter. Mean body weights were calculated for each group. Moribund animals were killed, as were animals that survived to the end of the study. A necropsy was performed on all animals, including those found dead unless they were excessively autolyzed or cannibalized. Thus, the number of animals from which particular organs or tissues were examined microscopically varies and is not necessarily equal to the number of animals that were placed on study in each group.

Examinations for grossly visible lesions were performed on major tissues or organs. Tissues were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Tissues examined microscopically are listed in Table 4.

When the pathology examination was completed, the slides, individual animal data records, and summary tables were sent to an independent quality assurance laboratory. Individual animal records and tables were compared for accuracy, slides and 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 assurance pathologist. Slides of all target tissues and those about which the original and quality assurance pathologists disagreed were submitted to the Chairperson of the Pathology Working Group (PWG) for evaluation. Representative coded slides selected by the Chairperson were reviewed by PWG pathologists, who reached a consensus and compared their findings with the original and quality assurance diagnoses. When diagnostic differences were found, the PWG sent the appropriate slides and comments to the original pathologist for review. 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. For subsequent evaluations, the diagnosed lesions for each tissue type are combined according to the guidelines of McConnell et al. (1986).

Nonneoplastic lesions are not examined routinely by the quality assurance pathologist or PWG. Certain nonneoplastic findings are reviewed by the quality assurance pathologist and PWG if they are considered part of the toxic response to a chemical or if they are deemed of special interest.

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 pathologic 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 dead of other than natural causes or were found to be missing; 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. 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. The two that adjust for intercurrent mortality employ the classical method for combining contingency tables developed by Mantel and Haenszel (1959). Tests of significance include pairwise comparisons of high dose and low dose groups with vehicle controls and tests for overall dose-response trends.

For studies in which compound administration 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. All reported P values for tumor analyses are one-sided.

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 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 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.)

Unadjusted Analyses--Primarily, survival-adjusted methods are used to evaluate tumor incidence. In addition, 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 appendix containing the analyses of primary 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) are included for those tumors appearing to show compound-related effects.

Quantitative Response Analyses: For comparisons of many (quantitative) means with the concurrent vehicle control mean, a technique discussed by Dunnett (1955) is utilized. The procedure is similar to the comparison between two means available with the usual *t*-test (Snedecor and Cochran, 1967) but is more appropriate for multiple comparisons with a control, since it takes the specialized experimental setting into account. For a complete description of this procedure, see Miller (1971).

III. RESULTS

RATS

SINGLE-ADMINISTRATION STUDIES

SIXTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

SIX- AND TWELVE-MONTH STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

MICE

SINGLE-ADMINISTRATION STUDIES

SIXTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

SINGLE-ADMINISTRATION STUDIES

None of the rats died before the end of the studies. Final body weights were not recorded. No compound-related toxic effects were observed during the studies or at necropsy. A high dose of 3,750 mg/kg was chosen for the 16-day studies because it was believed that any higher dose was too viscous to be given repeatedly by gavage without causing a large number of deaths related to the gavage procedure.

SIXTEEN-DAY STUDIES

None of the rats died before the end of the studies (Table 5). No adverse effect of chlorinated paraffins (C_{23}, 43% chlorine) on body weights was observed. No compound-related clinical signs or gross pathologic effects were observed. Therefore, the high dose of 3,750 mg/kg was used again in the 13-week studies for rats of each sex.

TABLE 5. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE SIXTEEN-DAY GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{23}, 43% Cl)

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	116 ± 2	186 ± 3	+ 70 ± 2	--
235	5/5	116 ± 2	190 ± 5	+ 74 ± 3	102
469	5/5	116 ± 2	191 ± 4	+ 75 ± 2	103
938	5/5	117 ± 2	192 ± 5	+ 75 ± 4	103
1,875	5/5	115 ± 1	190 ± 1	+ 75 ± 0	102
3,750	5/5	114 ± 1	188 ± 3	+ 74 ± 2	101
FEMALE					
0	5/5	89 ± 1	123 ± 1	+ 34 ± 2	--
235	5/5	89 ± 1	126 ± 1	+ 37 ± 1	102
469	5/5	92 ± 2	132 ± 2	+ 40 ± 1	107
938	5/5	94 ± 2	131 ± 2	+ 37 ± 1	107
1,875	5/5	92 ± 2	125 ± 3	+ 33 ± 2	102
3,750	5/5	91 ± 2	128 ± 3	+ 37 ± 2	104

(a) Number surviving/number in group
(b) Initial mean body weight ± standard error of the mean
(c) Mean body weight change of the group ± standard error of the mean

THIRTEEN-WEEK STUDIES

None of the rats died before the end of the studies (Table 6). The final mean body weights of male and female rats were not adversely affected by chlorinated paraffins (C_{23}, 43% chlorine). No compound-related clinical signs were observed during the study, and no gross lesions were observed at necropsy.

Histologic examination revealed dose-related granulomatous inflammation of the liver in all groups of dosed female rats (Table 7). Lesions were characterized by multiple, randomly distributed accumulations of histiocytes within the liver sinusoids, which usually compressed the adjacent liver parenchyma. The smaller lesions were usually nodular, whereas the larger, more extensive accumulations appeared to result from the coalescence of adjacent smaller nodules. Lymphoid cells were present in the center of some histiocytic foci but were most commonly seen at the periphery of the histiocytic accumulations. Large epithelioid cells were present near the center of some nodules. Numerous lesions contained a small number of hyaline acidophilic cells. Granulomatous inflammation was not observed in the male rats.

TABLE 6. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{23}, 43% Cl)

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	119 ± 2	360 ± 7	+241 ± 6	--
235	10/10	123 ± 4	357 ± 8	+234 ± 6	99
469	10/10	118 ± 2	362 ± 7	+244 ± 7	101
938	10/10	119 ± 3	354 ± 9	+235 ± 9	98
1,875	10/10	117 ± 3	359 ± 6	+242 ± 5	100
3,750	10/10	125 ± 3	371 ± 6	+246 ± 6	103
FEMALE					
0	10/10	102 ± 1	205 ± 2	+103 ± 3	--
235	10/10	114 ± 2	205 ± 2	+91 ± 2	100
469	10/10	115 ± 2	214 ± 4	+99 ± 3	104
938	10/10	115 ± 2	212 ± 4	+97 ± 3	103
1,875	10/10	114 ± 2	218 ± 5	+104 ± 4	106
3,750	10/10	114 ± 2	215 ± 5	+101 ± 3	105

(a) Number surviving/number in group
(b) Initial mean body weight ± standard error of the mean
(c) Mean weight change of the group ± standard error of the mean

TABLE 7. INCIDENCES OF GRANULOMATOUS INFLAMMATION IN THE LIVER OF FEMALE RATS IN THE THIRTEEN-WEEK GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl)

	Dose (mg/kg) 0	235	469	938	1,875	3,750
Incidence	0/10	1/10	4/10	9/10	8/10	9/10

Dose Selection Rationale: Because the granulomatous inflammation was considered to be potentially life threatening, doses selected for female rats in the 2-year studies were 100, 300, and 900 mg/kg chlorinated paraffins (C_{23}, 43% chlorine) to be administered in corn oil, 5 days per week for 103 weeks. Three doses were selected for female rats because of concern that toxic effects in the liver might affect survival at 900 mg/kg in the 2-year study. Since no toxicity was noted in male rats in the 13-week studies, the two highest doses, 1,875 and 3,750 mg/kg, were selected for the 2-year studies.

SIX- AND TWELVE-MONTH STUDIES

All designated animals survived to the scheduled 6-month kill, but three of the male rats (one high dose and two vehicle controls) predesignated to be killed at 12 months died early because of gavage accidents. Body weights of dosed animals did not differ from their respective controls at 6 or 12 months (data not shown).

Relative liver weights were increased in dosed male rats at 12 months and in dosed female rats at 6 and 12 months (Table 8). Except for male rats at 6 months, liver weights exhibited a dose-related increase at both time points. No change in relative kidney, adrenal gland, thymus, brain, or spleen weight was found at either 6 or 12 months in dosed male or female rats.

Progressive increases in the severity of granulomatous and lymphohistiocytic hepatitis were observed in both male and female rats dosed with chlorinated paraffins (C_{23}, 43% chlorine) (Table 9). The severity of the liver inflammation in females that received 900 mg/kg was subjectively greater than that in males that received 3,750 mg/kg, and the lesion appeared to be similar to that seen in the females in the 13-week study. Pancreatic and renal-celiac lymph nodes of female rats had granulomatous inflammatory lesions similar to those in the liver. The hepatic and lymphoid lesions were not neoplastic and did not appear to be preneoplastic. No other lesions appeared to be related to chlorinated paraffins (C_{23}, 43% chlorine) exposure. No compound-related clinical signs were observed.

TABLE 8. EFFECT OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) ON LIVER WEIGHT TO BODY WEIGHT RATIOS IN RATS AFTER SIX AND TWELVE MONTHS OF DOSING

Dose Group	Group Mean of Relative Liver Weights (a)	
	Six Month	Twelve Month
MALE		
Vehicle control	36.9 ± 4.1	32.1 ± 5.6
1,875 mg/kg	36.4 ± 2.2	36.2 ± 6.3
3,750 mg/kg	37.0 ± 2.1	(b) 41.0 ± 2.4
FEMALE		
Vehicle control	32.0 ± 3.4	32.9 ± 4.2
100 mg/kg	32.4 ± 2.8	36.7 ± 6.6
300 mg/kg	37.6 ± 8.2	(c) 41.0 ± 8.3
900 mg/kg	(b) 45.0 ± 12.1	(b) 52.0 ± 8.1

(a) Values are the mean × 10^3 ± standard deviation × 10^3 of those values obtained from analyses performed on 10 animals, except for the 12-month male vehicle control (n = 8) and 3,750 mg/kg (n = 9) groups. One value of 560 was deleted from the 6-month male 1,875 mg/kg group, so n = 9 for that group.
(b) $P<0.01$ versus the vehicle controls by Dunnett's test
(c) $P<0.05$ versus the vehicle controls by Dunnett's test

TABLE 9. EFFECT OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) ON THE INCIDENCE AND SEVERITY OF GRANULOMATOUS AND LYMPHOHISTIOCYTIC HEPATITIS IN RATS AFTER SIX AND TWELVE MONTHS OF DOSING

Dose Group	Six Month		Twelve Month	
	Incidence	Mean Severity (a)	Incidence	Mean Severity (a)
MALE				
Vehicle control	0/10	--	0/8	--
1,875 mg/kg	6/10	0.6	10/10	1.9
3,750 mg/kg	7/10	0.9	9/9	2.4
FEMALE				
Vehicle control	0/10	--	0/10	--
100 mg/kg	2/10	0.2	10/10	2.1
300 mg/kg	9/10	1.9	10/10	3.5
900 mg/kg	10/10	2.8	10/10	3.9

(a) The mean severity values were calculated by dividing the total of the severity scores for all animals in a group by the number of animals in that group; n = 10 except for the 12-month male vehicle control (n = 8) and the 3,750 mg/kg (n = 9) groups. The degree of severity: 1 = minimal; 2 = mild; 3 = moderate; 4 = marked; 5 = severe.

Activities of several serum enzymes were slightly elevated at both 6 and 12 months in dosed males and females (Tables 10 and 11). Serum albumin concentrations were decreased in high dose male rats and in mid dose and high dose female rats, and serum globulin levels were increased in mid dose and high dose female rats relative to vehicle controls. The albumin:globulin ratio was significantly lower in high dose males and in all groups of dosed females than in vehicle controls. Increases in serum sorbitol dehydrogenase and alanine aminotransferase activities are indicative of liver cell injury, and serum aspartate aminotransferase activity is a less specific indication of injury to a number of tissues, including heart, liver, muscle, kidney, and brain (Boyd, 1983). Decreases in serum total protein, and especially albumin, indicate impaired liver function, since most serum proteins are synthesized in the liver. However, certain globulins are often found increased in inflammatory or other disease states (Harper, 1975). Thus, the albumin:globulin ratio is a useful index for detecting the type of hepatic lesions observed in the short-term studies.

TABLE 10. CLINICAL CHEMISTRY VALUES FOR RATS DOSED WITH CHLORINATED PARAFFINS (C_{23}, 43% Cl) FOR SIX MONTHS (a)

MALE	Vehicle Control	1,875 mg/kg	3,750 mg/kg
Sorbitol dehydrogenase (U/liter)	29 ± 9	(b) 51 ± 20	(b) 70 ± 14
Aspartate aminotransferase (U/liter)	56 ± 10	(b) 148 ± 59	(b) 207 ± 63
Alanine aminotransferase (U/liter)	28 ± 6	(b) 65 ± 24	(b) 100 ± 24
Total protein (g/dl)	6.2 ± 0.3	6.2 ± 0.4	6.0 ± 0.3
Albumin (g/dl)	3.9 ± 0.1	3.8 ± 0.2	(b) 3.6 ± 0.2
Globulin (g/dl)	2.3 ± 0.2	2.4 ± 0.4	2.4 ± 0.2
Albumin:globulin ratio	1.7 ± 0.1	1.7 ± 0.3	(c) 1.5 ± 0.1

FEMALE	Vehicle Control	100 mg/kg	300 mg/kg	900 mg/kg
Sorbitol dehydrogenase (U/liter)	27 ± 7	26 ± 13	71 ± 52	(b) 111 ± 66
Aspartate aminotransferase (U/liter)	50 ± 11	51 ± 17	126 ± 107	(b) 200 ± 128
Alanine aminotransferase (U/liter)	19 ± 3	22 ± 7	(b) 44 ± 14	(b) 63 ± 22
Total protein (g/dl)	6.4 ± 0.3	6.4 ± 0.3	6.3 ± 0.4	6.4 ± 0.4
Albumin (g/dl)	4.3 ± 0.2	4.2 ± 0.2	(b) 3.9 ± 0.3	(b) 3.8 ± 0.3
Globulin (g/dl)	2.0 ± 0.2	2.2 ± 0.1	(b) 2.4 ± 0.2	(b) 2.5 ± 0.2
Albumin:globulin ratio	2.1 ± 0.2	(c) 1.9 ± 0.1	(b) 1.7 ± 0.2	(b) 1.5 ± 0.2

(a) All analyses were performed on serum; values are the mean ± standard deviation of 10 animals; P values are by Dunnett's test relative to the vehicle controls.
(b) $P<0.01$ relative to vehicle controls
(c) $P<0.05$ relative to vehicle controls

TABLE 11. CLINICAL CHEMISTRY VALUES FOR RATS DOSED WITH CHLORINATED PARAFFINS (C_{23}, 43% Cl) FOR TWELVE MONTHS (a)

MALE	Vehicle Control	1,875 mg/kg	3,750 mg/kg
Sorbitol dehydrogenase (U/liter)	62 ± 40	(b) 124 ± 39	(b) 155 ± 40
Aspartate aminotransferase (U/liter)	90 ± 49	(b) 206 ± 71	(b) 274 ± 34
Alanine aminotransferase (U/liter)	53 ± 35	112 ± 45	(b) 157 ± 73
Total protein (g/dl)	5.6 ± 0.2	5.7 ± 0.3	5.5 ± 0.4
Albumin(g/dl)	3.5 ± 0.2	3.5 ± 0.2	3.5 ± 0.2
Globulin(g/dl)	2.1 ± 0.2	2.2 ± 0.3	2.0 ± 0.4
Albumin:globulin ratio	1.7 ± 0.2	1.7 ± 0.4	1.8 ± 0.4

FEMALE	Vehicle Control	100 mg/kg	300 mg/kg	900 mg/kg
Sorbitol dehydrogenase (U/liter)	42 ± 21	75 ± 52	(c) 93 ± 45	(b) 116 ± 47
Aspartate aminotransferase (U/liter)	107 ± 80	117 ± 64	(c) 142 ± 58	(b) 178 ± 98
Alanine aminotransferase (U/liter)	36 ± 23	46 ± 17	48 ± 14	(b) 59 ± 17
Total protein(g/dl)	6.9 ± 1.0	6.3 ± 0.9	6.3 ± 1.0	(c) 6.0 ± 0.7
Albumin(g/dl)	4.6 ± 0.5	4.2 ± 0.5	(b) 3.9 ± 0.4	(b) 3.8 ± 0.4
Globulin(g/dl)	2.2 ± 0.6	2.1 ± 0.8	2.4 ± 0.6	2.3 ± 0.4
Albumin:globulin ratio	2.2 ± 0.5	2.4 ± 1.5	1.7 ± 0.3	1.7 ± 0.3

(a) All analyses were performed on serum; values are the mean ± standard deviation of 8 vehicle control males, 9 high dose males, and 10 of all other groups; P values are by Dunnett's test relative to the vehicle controls.
(b) $P<0.01$ relative to vehicle controls
(c) $P<0.05$ relative to vehicle controls

Packed cell volumes in high dose female rats at 12 months and hemoglobin concentration in high dose females at six months were significantly lower than those in the vehicle controls. Leukocyte and lymphocyte counts in high dose females at 6 months and mid dose and high dose females at 12 months, neutrophil counts in mid dose and high dose females at 12 months, and lymphocyte counts in mid dose males were significantly greater than those of the vehicle controls (Tables 12 and 13).

TABLE 12. MEAN HEMATOLOGIC VALUES FOR RATS DOSED WITH CHLORINATED PARAFFINS (C_{23}, 43% Cl) FOR SIX MONTHS (a)

MALE	Vehicle Control	1,875 mg/kg	3,750 mg/kg
Red blood cells/mm^3 ($\times 10^{-6}$)	9.21 ± 0.46	8.71 ± 0.71	8.77 ± 0.22
Hemoglobin (g/dl)	15.4 ± 0.84	14.60 ± 1.07	14.81 ± 0.72
Hematocrit (percent)	44.20 ± 2.25	42.17 ± 3.49	42.90 ± 2.17
Leukocytes/mm^3 ($\times 10^{-3}$)	8.78 ± 1.72	9.13 ± 4.57	8.80 ± 2.21
Neutrophils/mm^3 ($\times 10^{-3}$)	1.29 ± 0.30	1.21 ± 0.51	1.76 ± 1.08
Lymphocytes/mm^3 ($\times 10^{-3}$)	7.32 ± 1.50	7.77 ± 4.03	6.96 ± 1.22
Eosinophils/mm^3	169 ± 93	150 ± 118	77 ± 170

FEMALE	Vehicle Control	100 mg/kg	300 mg/kg	900 mg/kg
Red blood cells/mm^3 ($\times 10^{-6}$)	7.78 ± 0.34	7.79 ± 0.28	7.52 ± 0.31	7.67 ± 0.29
Hemoglobin (g/dl)	14.22 ± 0.39	14.06 ± 0.52	13.46 ± 0.79	(b) 13.08 ± 1.04
Hematocrit (percent)	39.58 ± 1.28	39.75 ± 1.75	38.81 ± 2.98	38.33 ± 2.42
Leukocytes/mm^3 ($\times 10^{-3}$)	4.92 ± 0.76	4.73 ± 0.34	9.29 ± 5.57	(c) 13.28 ± 5.71
Neutrophils/mm^3 ($\times 10^{-3}$)	1.06 ± 0.40	0.72 ± 0.23	1.48 ± 0.85	1.73 ± 0.72
Lymphocytes/mm^3 ($\times 10^{-3}$)	3.79 ± 0.43	3.98 ± 0.21	7.77 ± 4.98	(c) 11.52 ± 5.25
Eosinophils/mm^3	58 ± 53	30 ± 25	36 ± 42	36 ± 60

(a) P values are by Dunnett's test relative to vehicle controls. Values are the mean ± standard deviation for 10 male vehicle control, 9 male low dose, and 10 male high dose rats; values are the mean ± standard deviation for 6 female vehicle control, 8 female low dose, 8 female mid dose, and 6 female high dose rats.
(b) $P<0.05$ relative to vehicle controls
(c) $P<0.01$ relative to vehicle controls

TABLE 13. MEAN HEMATOLOGIC VALUES FOR RATS DOSED WITH CHLORINATED PARAFFINS (C_{23}, 43% Cl) FOR TWELVE MONTHS (a)

MALE	Vehicle Control	1,875 mg/kg	3,750 mg/kg
Red blood cells/mm^3 ($\times 10^{-6}$)	9.07 ± 0.66	8.99 ± 0.38	8.78 ± 0.52
Hemoglobin (g/dl)	16.0 ± 0.94	15.6 ± 0.87	14.9 ± 1.19
Hematocrit (percent)	41.4 ± 2.97	42.4 ± 2.27	38.7 ± 2.65
Leukocytes/mm^3 ($\times 10^{-3}$)	6.43 ± 1.19	8.97 ± 3.04	9.03 ± 2.83
Neutrophils/mm^3 ($\times 10^{-3}$)	1.52 ± 0.33	1.44 ± 0.69	1.51 ± 0.43
Lymphocytes/mm^3 ($\times 10^{-3}$)	4.62 ± 1.10	(b) 7.33 ± 2.63	7.17 ± 2.90
Eosinophils/mm^3	77 ± 46	61 ± 99	42 ± 63
Monocytes	215 ± 85	137 ± 182	284 ± 182

FEMALE	Vehicle Control	100 mg/kg	300 mg/kg	900 mg/kg
Red blood cells/mm^3 ($\times 10^{-6}$)	7.54 ± 0.93	7.82 ± 0.47	7.80 ± 0.83	8.16 ± 0.55
Hemoglobin (g/dl)	14.7 ± 1.51	15.3 ± 1.57	15.02 ± 1.20	13.64 ± 0.98
Hematocrit (percent)	40.0 ± 3.27	38.4 ± 2.17	39.1 ± 2.88	(b) 36.2 ± 3.08
Leukocytes/mm^3 ($\times 10^{-3}$)	4.18 ± 1.65	5.91 ± 2.81	(c) 10.41 ± 5.72	(c) 15.21 ± 5.26
Neutrophils/mm^3 ($\times 10^{-3}$)	0.84 ± 0.35	1.17 ± 0.61	(b) 1.69 ± 0.81	(c) 2.09 ± 0.77
Lymphocytes/mm^3 ($\times 10^{-3}$)	3.29 ± 1.38	4.70 ± 2.33	(c) 8.60 ± 5.04	(c) 12.90 ± 5.02
Eosinophils/mm^3	39 ± 42	31 ± 36	45 ± 76	39 ± 67
Monocytes	8 ± 17	13 ± 22	75 ± 150	167 ± 193

(a) Values are the mean ± standard deviation for 8 male vehicle control, 10 low dose, and 9 high dose animals, except for leukocytes, neutrophils, lymphocytes, eosinophils, and monocytes, which are for 8 high dose animals. All female values represent 10 animals.
(b) $P<0.05$ relative to the vehicle controls by Dunnett's test
(c) $P<0.01$ relative to the vehicle controls by Dunnett's test

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of low and high dose male rats were comparable to those of the vehicle controls throughout the 2-year study (Table 14 and Figure 1). Mean body weights of mid dose and high dose female rats were approximately 5% lower than those of the vehicle controls after week 69. After week 43, a number of low and high dose male rats were observed to have a brown stain around the mouth, which persisted until the end of the study. Dosed females showed a high incidence of distended abdomens during the latter part of the study.

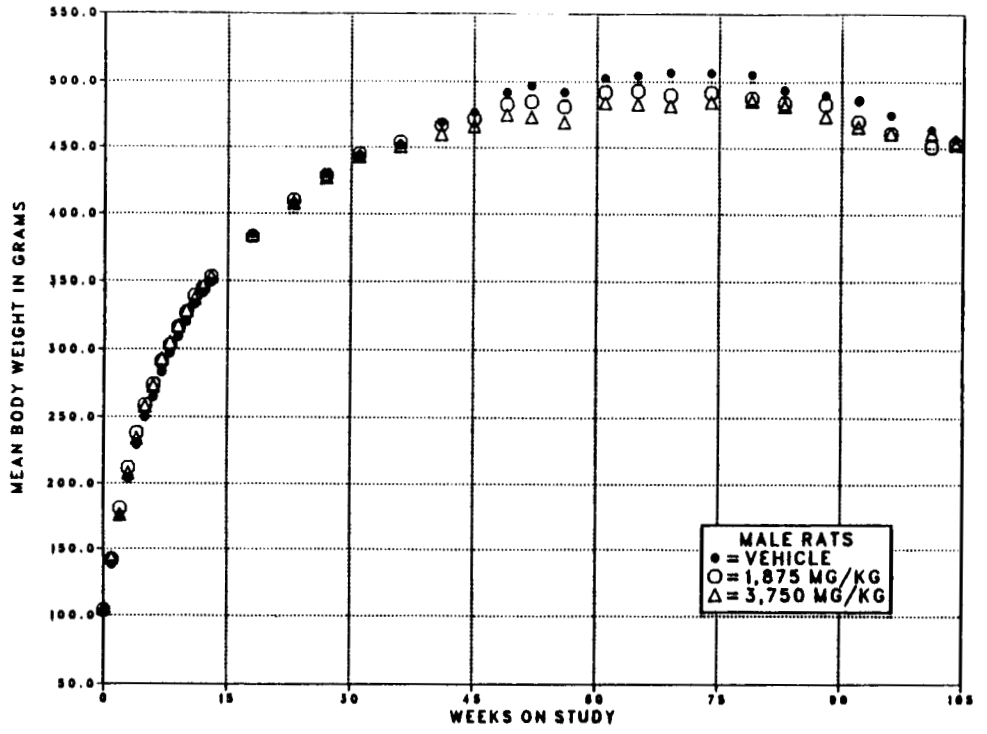
TABLE 14. MEAN BODY WEIGHTS AND SURVIVAL OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{23}, 43% Cl)

MALE

Weeks on Study	Av Wt (grams)	No. of Survivors	Av Wt (grams)	Wt (percent of veh controls)	No. of Survivors	Av Wt (grams)	Wt (percent of veh controls)	No. of Survivors
	Vehicle Control		1,875 mg/kg			3,750 mg/kg		
0	104	50	104	100	50	105	101	50
1	138	50	142	103	50	143	104	50
2	176	50	181	103	50	176	100	50
3	204	50	212	104	50	208	102	50
4	229	50	238	104	50	234	102	50
5	250	50	259	104	50	258	103	50
6	265	50	274	103	50	273	103	50
7	283	50	291	103	50	293	104	50
8	297	50	303	102	50	305	103	50
9	309	50	316	102	50	317	103	50
10	320	50	327	102	50	328	103	50
11	333	50	339	102	50	337	101	50
12	341	50	345	101	50	346	101	50
13	349	50	353	101	50	353	101	50
18	385	50	383	99	50	384	100	50
23	408	50	410	100	50	408	100	50
27	430	50	429	100	50	427	99	50
31	444	50	445	100	50	443	100	50
36	452	50	454	100	50	451	100	50
41	469	49	467	100	50	460	98	50
45	477	49	472	99	50	466	98	50
49	492	49	483	98	50	475	97	50
52	497	49	485	98	49	473	95	50
56	492	49	481	98	49	469	95	50
61	503	49	492	98	49	484	96	50
65	505	49	493	98	49	483	96	50
69	507	48	490	97	49	482	95	50
74	507	48	492	97	48	485	96	48
79	506	46	488	96	48	486	96	48
83	494	45	484	98	47	482	98	47
88	490	41	483	99	45	474	97	46
92	486	40	470	97	43	466	96	44
96	475	37	461	97	41	461	97	40
101	464	35	451	97	33	461	99	30
104	457	32	454	99	32	453	99	27

FEMALE

Weeks on Study	Av Wt (grams)	No. of Survivors	Av Wt (grams)	Wt (percent of veh cont)	No. of Survivors	Av Wt (grams)	Wt. (percent of veh cont)	No. of Survivors	Av Wt (grams)	Wt (percent of veh cont)	No. of Survivors
	Vehicle Control		100 mg/kg			300 mg/kg			900 mg/kg		
0	93	50	94	101	50	95	102	50	95	102	50
1	117	50	118	101	50	119	102	50	120	103	50
2	133	50	135	102	50	133	100	50	137	103	50
3	144	50	147	102	50	147	102	50	150	104	50
4	154	50	157	102	50	157	102	50	160	104	50
5	164	50	166	101	50	166	101	50	169	103	50
6	170	50	175	103	50	174	102	50	176	104	50
7	175	50	180	103	50	180	103	50	181	103	50
8	182	50	187	103	50	185	102	50	187	103	50
9	185	50	188	102	50	188	102	50	189	102	50
10	190	50	192	101	50	194	102	50	195	103	50
11	194	50	194	100	50	197	102	50	197	102	50
12	198	50	198	100	50	201	102	50	203	103	50
13	199	50	201	101	50	204	103	50	203	102	50
18	211	50	212	100	50	214	101	50	214	101	50
23	220	50	222	101	50	223	101	49	220	100	50
27	227	50	230	101	50	228	100	49	226	100	50
31	232	50	231	100	50	232	100	49	231	100	50
36	234	50	238	102	50	237	101	49	236	101	50
41	244	50	245	100	50	246	101	49	245	100	50
45	254	50	256	101	50	254	100	49	252	99	50
49	263	50	264	100	50	265	101	49	261	99	48
52	267	49	268	100	50	269	101	49	265	99	48
56	271	49	272	100	48	270	100	49	267	99	48
61	282	49	283	100	48	278	99	49	272	96	48
65	291	49	289	99	48	281	97	49	279	96	48
69	300	48	295	98	48	288	96	49	283	94	48
74	309	47	302	98	46	294	95	48	292	94	47
79	313	46	307	98	46	300	96	47	296	95	47
83	317	45	313	99	44	300	95	47	302	95	45
88	316	44	313	99	44	303	96	46	300	95	44
92	316	44	318	101	40	301	95	45	298	94	40
96	320	41	318	99	38	301	94	44	299	93	38
101	322	36	323	100	35	305	95	38	304	94	36
104	326	34	320	98	32	303	93	34	305	94	34



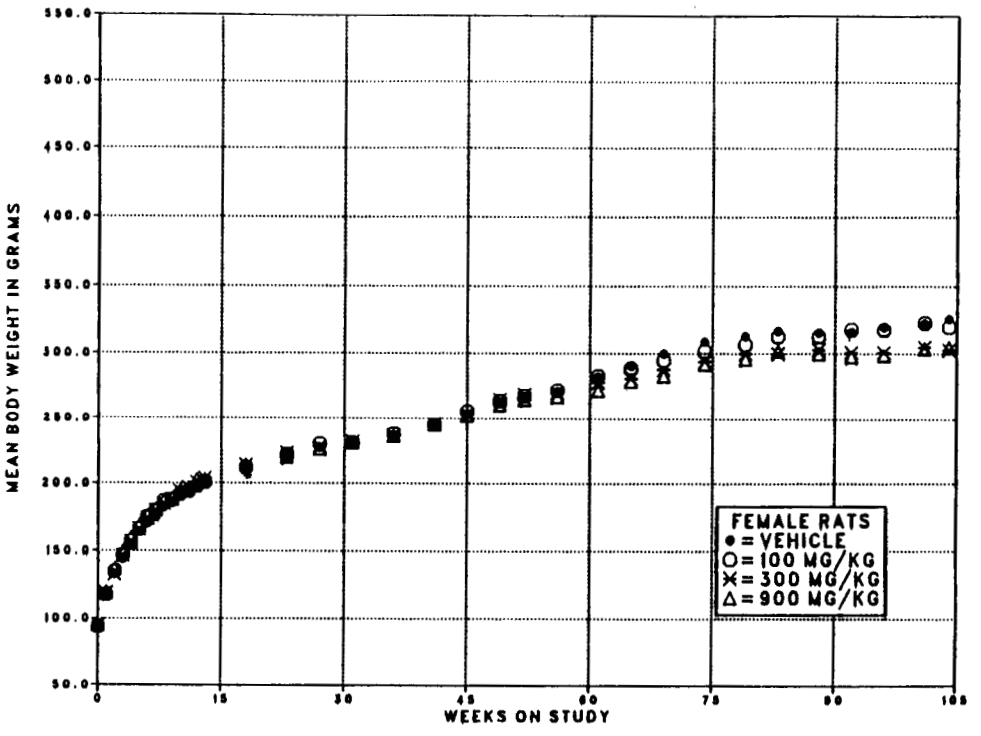


FIGURE 1. GROWTH CURVES FOR RATS ADMINISTERED CHLORINATED PARAFFINS (C_{23}, 43% Cl) IN CORN OIL BY GAVAGE FOR TWO YEARS

Survival

Estimates of the probabilities of survival for male and female rats administered chlorinated paraffins (C_{23}, 43% chlorine) at the doses used in these studies and for the vehicle controls are shown in the Kaplan and Meier curves in Figure 2. No significant differences in survival were observed between any groups of either sex (Table 15).

Pathology and Statistical Analyses of Results

This section describes the significant or noteworthy changes in the incidences of rats with neoplastic or nonneoplastic lesions of the adrenal gland, pancreas, uterus, Zymbal gland, hematopoietic system, spleen, liver, skin, kidney, nasal cavity, and eye. Histopathologic findings on neoplasms in rats are summarized in Appendix A (Tables A1 and A2); Appendix A (Tables A3 and A4) also gives the survival and tumor status for individual male and female rats. Findings on nonneoplastic lesions are summarized in Appendix C (Tables C1 and C2). Appendix E (Tables E1 and E2) contains the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the dose groups. The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix E (footnotes). Historical incidences of tumors in corn oil vehicle control animals are listed in Appendix F.

TABLE 15. SURVIVAL OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{23}, 43% Cl)

MALE (a)	Vehicle Control	1,875 mg/kg	3,750 mg/kg
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	20	15	23
Accidentally killed	0	3	0
Killed at termination	30	32	27
Survival P values (c)	0.677	0.457	0.740

FEMALE (a)	Vehicle Control	100 mg/kg	300 mg/kg	900 mg/kg
Animals initially in study	50	50	50	50
Nonaccidental deaths before termination (b)	16	19	17	18
Accidentally killed	0	1	0	1
Killed at termination	34	30	33	31
Survival P values (c)	0.917	0.631	0.940	0.786

(a) Terminal kill period: week 105
(b) Includes animals killed in a moribund condition
(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.

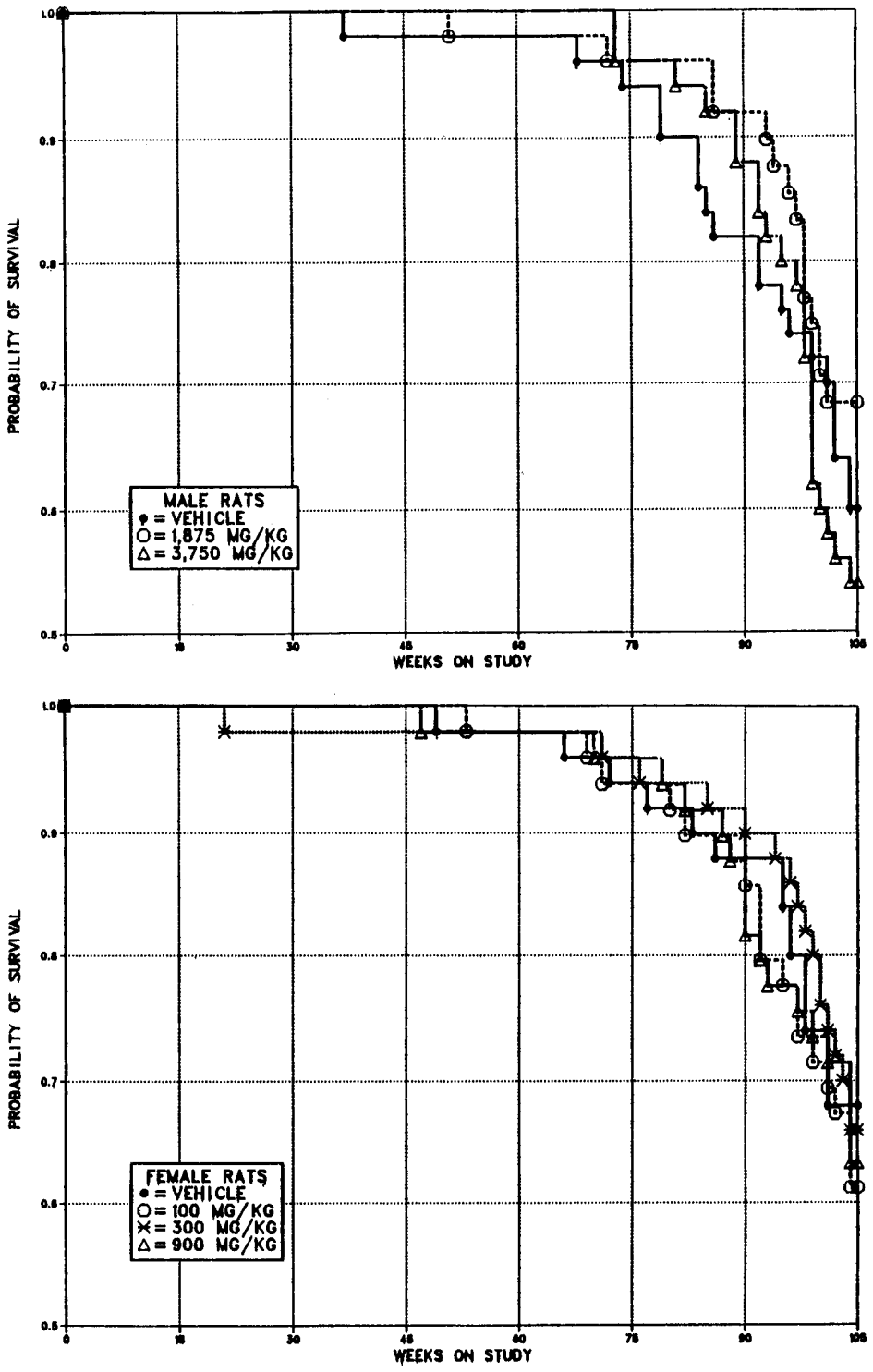


FIGURE 2. KAPLAN-MEIER SURVIVAL CURVES FOR RATS ADMINISTERED CHLORINATED PARAFFINS (C_{23}, 43% Cl) IN CORN OIL BY GAVAGE FOR TWO YEARS

Adrenal Gland: Pheochromocytomas or malignant pheochromocytomas (combined) in female rats occurred with a positive trend, and the incidence in the high dose group was greater than that in the vehicle controls (Table 16). The following incidences of pheochromocytomas or malignant pheochromocytomas (combined) were observed in male rats: vehicle control, 20/50 (43%); low dose, 16/50 (32%); high dose, 20/50 (43%).

Pancreas: Islet cell adenomas occurred with a positive trend in male rats, but the incidences in the dosed groups were not significantly greater than that in the vehicle controls (vehicle control: 0/49; low dose, 1/50, 2%; high dose, 4/50, 8%). The incidences of islet cell adenomas or carcinomas (combined) in dosed male rats were not significantly different from that in the vehicle controls (vehicle control, 1/49; low dose, 3/50; high dose, 4/50). Acinar cell adenomas and hyperplasias occurred with a negative trend in male rats (Table 17).

TABLE 16. ANALYSIS OF ADRENAL GLAND (MEDULLA) LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) (a)

	Vehicle Control	100 mg/kg	300 mg/kg	900 mg/kg
Hyperplasia				
Overall Rates	6/50 (12%)	3/50 (6%)	1/50 (2%)	6/50 (12%)
Pheochromocytoma (All types) (b)				
Overall Rates	1/50 (2%)	(c) 4/50 (8%)	6/50 (12%)	7/50 (14%)
Adjusted Rates	2.7%	10.3%	17.6%	19.6%
Terminal Rates	0/34 (0%)	1/30 (3%)	5/33 (15%)	3/31 (10%)
Week of First Observation	101	82	104	97
Life Table Tests	P=0.049	P=0.169	P=0.059	P=0.033
Incidental Tumor Tests	P=0.046	P=0.301	P=0.065	P=0.014
Hyperplasia or Pheochromocytoma				
Overall Rates	7/50 (14%)	7/50 (14%)	7/50 (14%)	13/50 (26%)
Adjusted Rates	19.0%	17.6%	19.4%	34.2%
Terminal Raates	5/34 (15%)	2/30 (7%)	5/33 (15%)	7/31 (23%)
Week of First Observation	96	82	96	87
Life Table Tests	P=0.045	P=0.545	P=0.603	P=0.092
Incidental Tumor Tests	P=0.057	P=0.498N	P=0.590N	P=0.099

(a) The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix E (footnotes).
(b) Historical incidence of pheochromocytomas (all types) at study laboratory (mean ± SD): 16/300 (5% ± 3%); historical incidence in NTP studies: 65/1,093 (6% ± 3%)
(c) One female rat had a malignant pheochromocytoma.

TABLE 17. ANALYSIS OF PANCREATIC ACINAR CELL PROLIFERATIVE LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl)

	Vehicle Control	1,875 mg/kg	3,750 mg/kg
Acinar Cell Hyperplasia			
Overall Rates	9/49 (18%)	2/50 (4%)	1/50 (2%)
Acinar Cell Adenoma (a)			
Overall Rates	6/49 (12%)	1/50 (2%)	1/50 (2%)
Adjusted Rates	18.1%	3.1%	3.7%
Terminal Rates	4/29 (14%)	1/32 (3%)	1/27 (4%)
Week of First Observation	84	105	105
Life Table Tests	P=0.026N	P=0.051N	P=0.073N
Incidental Tumor Tests	P=0.024N	P=0.054N	P=0.062N
Acinar Cell Hyperplasia or Adenoma			
Overall Rates	15/49 (31%)	3/50 (6%)	1/50 (2%)
Adjusted Rates	44.2%	9.4%	3.7%
Terminal Rates	11/29 (38%)	3/32 (9%)	1/27 (4%)
Week of First Observation	84	105	105
Life Table Tests	P<0.001N	P=0.001N	P<0.001N
Incidental Tumor Tests	P<0.001N	P=0.001N	P<0.001N

(a) Historical incidence at study laboratory (mean ± SD): 14/298 (5% ± 9%); historical incidence in NTP studies: 14/1,086 (4% ± 7%)

Uterus: The incidences of endometrial stromal polyps and endometrial stromal polyps or sarcomas (combined) in the low dose female rats were greater than that in the vehicle controls (Table 18). Two endometrial stromal sarcomas were observed in the low dose group (one in an animal with a polyp), but none was noted in any other dose group or in the vehicle controls. The incidence of cystic hyperplasia (cystic endometrial glands) in dosed female rats was greater than that in vehicle control female rats (vehicle control, 11/50, 22%; low dose, 19/50, 38%; mid dose, 25/50, 50%; high dose, 22/50, 44%). Cystic hyperplasia was characterized by minimal to mild cystic dilatation of endometrial glands that were lined by flattened atrophic epithelium. This change was the result of fluid accumulation and did not represent a proliferative process.

Zymbal Gland: Carcinomas were found in 2/50 (4%) low dose and 2/50 (4%) high dose male rats. An adenoma was found in 1/50 (2%) low dose male rats. The incidence of adenomas or carcinomas (combined) in low dose male rats was not significantly greater than that in the vehicle controls (historical incidence at testing laboratory: 0/300; historical incidence in NTP studies: 8/1,100, 0.7% ± 1%).

TABLE 18. ANALYSIS OF UTERINE TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl)

	Vehicle Control	100 mg/kg	300 mg/kg	900 mg/kg
Endometrial Stromal Polyp				
Overall Rates	9/50 (18%)	17/50 (34%)	10/50 (20%)	10/50 (20%)
Adjusted Rates	23.9%	43.5%	29.2%	29.3%
Terminal Rates	7/34 (21%)	9/30 (30%)	9/33 (27%)	8/31 (26%)
Week of First Observation	49	80	101	47
Life Table Tests	P=0.366N	P=0.042	P=0.477	P=0.428
Incidental Tumor Tests	P=0.241N	P=0.047	P=0.485	P=0.549
Endometrial Stromal Sarcoma				
Overall Rates	0/50 (0%)	2/50 (4%)	0/50 (0%)	0/50 (0%)
Endometrial Stromal Polyp or Sarcoma (a)				
Overall Rates	9/50 (18%)	18/50 (36%)	10/50 (20%)	10/50 (20%)
Adjusted Rates	23.9%	44.7%	29.2%	29.3%
Terminal Rates	7/34 (21%)	9/30 (30%)	9/33 (27%)	8/31 (26%)
Week of First Observation	49	69	101	47
Life Table Tests	P=0.329N	P=0.029	P=0.477	P=0.428
Incidental Tumor Tests	P=0.230N	P=0.034	P=0.485	P=0.549

(a) Historical incidence at study laboratory (mean ± SD): 76/300 (25% ± 6%); historical incidence in NTP studies: 252/1,089 (23% ± 6%)

Hematopoietic System: Granulomatous inflammation (evident microscopically and often present grossly as tan or yellow masses 5 mm to 15 mm in diameter) and lymphoid hyperplasia of the pancreatic lymph nodes were observed in dosed rats of each sex but not in vehicle controls (Table 19). Granulomatous inflammation and lymphoid hyperplasia of the mesenteric lymph nodes were observed in low dose and high dose males and in mid dose and high dose females. These lesions were not noted in vehicle controls.

Spleen: Congestion was observed in dosed animals of each sex, but not in vehicle controls (Table 19).

Liver: Inflammatory Lesions--Lymphocytic infiltration, granulomatous inflammation, and pigmentation were observed in dosed male and female rats at incidences greater than those in the vehicle controls (Table 19). Microscopically, the liver lesions were characterized by a multifocal, randomly disseminated, granulomatous and lymphocytic inflammation that increased in severity with dose. The lesion was similar to those seen in female rats in the 13-week studies and in male and female rats at 6 and 12 months into the 2-year studies. The granulomatous component consisted of aggregates of histiocytes that had a finely vacuolated cytoplasm with various degrees of brownish pigmentation. In larger foci, the central histiocytic cells were fibrillar and spindle-shaped and sometimes had eosinophilic hyaline inclusions associated with degeneration or necrosis of cells. Frequently, large numbers of densely packed small lymphocytes and lesser numbers of other mononuclear inflammatory cells were clustered adjacent to the histiocytic aggregates. Examination of tissues stained with hematoxylin-eosin did not reveal deposits in the sinusoids. No refractive or crystalline deposits were observed with polarized light. Pigment within the macrophages did not fluoresce under ultraviolet light.

Hepatocellular Hyperplasia--Hepatocellular hyperplasia (diagnosed as nodular hyperplasia in Appendix C) was usually seen as multifocal, nodular lesions and less frequently as a single focus of hyperplasia. In view of the considerable inflammatory effects of chlorinated paraffins (C_{23}, 43% chlorine) in the liver, these nodular lesions might be considered a regenerative hyperplasia. Hepatocellular hyperplasia is also seen commonly in livers of F344 rats with mononuclear cell leukemia. In these instances

TABLE 19. NUMBER OF RATS WITH SELECTED NONNEOPLASTIC LESIONS IN THE TWO-YEAR GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{23}, 43% Cl)

	Dose (mg/kg)						
	Male			Female			
Site/Lesion	0	1,875	3,750	0	100	300	900
Number of rats examined	50	50	50	50	50	50	50
Pancreatic lymph node							
Granulomatous inflammation	0	29	23	0	19	21	20
Lymphoid hyperplasia	0	27	19	0	19	22	23
Mesenteric lymph node							
Granulomatous inflammation	0	8	11	0	1	4	6
Lymphoid hyperplasia	0	5	5	0	0	3	5
Spleen							
Congestion	0	30	32	0	21	32	33
Liver							
Lymphocytic inflammatory infiltrate	0	42	44	3	44	45	41
Granulomatous focal inflammation	0	49	49	4	48	49	50
Hepatocellular hyperplasia	0	0	6	0	4	6	5
Pigmentation	0	45	46	0	45	47	47
Skin							
Hyperkeratosis	1	0	0	1	1	0	16
Kidney							
Nephropathy	48	47	46	13	19	27	32
Pigmentation	0	3	3	2	20	30	29
Nasal Cavity							
Suppurative inflammation	5	14	11	1	4	0	3
Eye							
Retinopathy	2	24	24	16	2	5	3
Cataracts	1	22	19	12	1	4	1

of leukemia, whether the hepatocellular hyperplasia is focal or multifocal presumably depends on the degree of liver degeneration secondary to the anemia and resultant anoxia characteristic of mononuclear cell leukemia. Periportal fibrosis, macrophage accumulation, bile duct proliferation, and hepatocellular degeneration were often present in cases where multifocal hyperplasia was diagnosed.

The focal hyperplastic lesions consisted of spherical proliferations of hepatocytes without nuclear atypia. Some contained cytologic alterations similar to those observed in foci of cellular alteration. The hyperplastic cells occasionally were hypertrophic or contained intracytoplasmic vacuoles. In most instances, the hepatic lobular architecture was evident, albeit distorted, and portal triads were found within the areas of hyperplasia. Cells within a focus of hyperplasia were usually uniform and had a homogeneous growth pattern. The principal diagnostic feature distinguishing focal hyperplasia from foci of cellular alteration was evidence of mild compression of surrounding parenchyma in the former. Hyperplastic lesions reached several millimeters in diameter and were frequently seen as relatively distinct nodules in histologic sections.

Multifocal hepatocellular hyperplasia with associated fibrosis and bile duct hyperplasia may resemble cirrhosis as described in human pathology texts (Robbins and Cotran, 1979;

Rosai, 1981; Anderson and Kissane, 1977). This condition in rats is generally associated with less fibrosis than is typical in humans. The lesion in rats is seen in situations of repeated toxic injury to the liver and represents a combination of the reaction to injury and attempted regeneration of lost hepatic parenchyma.

Neoplastic Nodules--Neoplastic nodules occurred in male rats with an incidence of 0/50 in vehicle control, 3/50 in low dose, and 3/50 in high dose animals. The incidences in dosed male rats were not significantly greater than in controls. The following incidences of neoplastic nodules were observed in female rats: vehicle control, 1/50; low dose, 2/50; mid dose, 1/50; high dose, 2/50. These nodular proliferations are sharply demarcated by definite compression of surrounding liver parenchyma and usually also by virtue of tinctorial staining differences. The hepatic plates of the nodule are not usually continuous with the surrounding liver plates but impinge upon them at a sharp angle. There is loss of the usual lobular architecture. Neoplastic nodules are often characterized by an increased mitotic index, may contain small areas of cellular atypia (e.g., pleomorphic nuclei, coarsely clumped chromatin, large nucleoli, increased nuclear to cytoplasmic ratio, cytoplasmic basophilia, cytoplasmic pleomorphism, altered cell to cell relationship), and have an irregular growth pattern. The principal diagnostic features distinguishing the neoplastic nodules from hepatocellular hyperplasia in these studies are the degree and prominence of compression of surrounding hepatic parenchyma and loss of normal lobular architecture. Neoplastic nodules in these studies usually occurred as single nodular lesions.

Skin, Kidney, and Nasal Cavity: Incidences of hyperkeratosis of the skin in high dose female rats and nephropathy in mid dose and high dose female rats were greater than those in the vehicle controls (Table 19). Infection of the nasal cavity by *Aspergillus spp* with accompanying inflammatory changes was noted in both vehicle control and dosed rats. The incidence was somewhat greater in dosed male rats than in vehicle controls.

Eye: The incidence of retinopathy and cataracts in dosed male rats was greater than that in the vehicle controls; the incidence of retinopathy and cataracts in female vehicle controls was greater than that in the dosed groups (Table 19). This greater incidence was attributed to the proximity to fluorescent lighting throughout the studies. Low and high dose male and vehicle control female rats occupied the top positions of the cage racks. Cages were not rotated during the studies.

SINGLE-ADMINISTRATION STUDIES

None of the mice died before the end of the studies, and no compound-related toxic effects were observed. Final body weights were not recorded. A high dose of 7,500 mg/kg was selected for the 16-day studies because any higher dose was considered too viscous to be given repeatedly by gavage without causing a significant number of deaths related to the gavage procedure.

SIXTEEN-DAY STUDIES

No compound-related deaths occurred, and no toxic effects were observed (Table 20). Differences in final mean body weights were not considered compound related. No lesions noted at gross necropsy were considered related to chlorinated paraffins (C_{23}, 43% chlorine) administration. For these reasons, the high dose of 7,500 mg/kg was again used for the 13-week studies.

THIRTEEN-WEEK STUDIES

No compound-related deaths occurred; all 17 early deaths were due to gavage-related trauma (Table 21). The final mean body weights were not adversely affected by administration of chlorinated paraffins (C_{23}, 43% chlorine). High dose females gained more weight than did the vehicle controls. No compound-related clinical signs or toxic effects were observed on gross necropsy or by histopathologic examination of high dose and vehicle control mice and of mice that died before the end of the study.

Dose Selection Rationale: Doses initially selected for mice for the 2-year studies were 3,750 and 7,500 mg/kg chlorinated paraffins (C_{23}, 43% chlorine). Because of the large number of gavage-related deaths in the first 3 weeks of the 2-year studies, all male and female mice were killed and the studies were restarted with doses of 0, 2,500, and 5,000 mg/kg chlorinated paraffins (C_{23}, 43% chlorine).

TABLE 20. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE SIXTEEN-DAY GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{23}, 43% Cl)

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	27.0 ± 0.5	28.2 ± 0.8	+1.2 ± 0.4	--
469	5/5	26.4 ± 0.7	28.8 ± 0.7	+2.4 ± 0.2	102.1
938	5/5	26.6 ± 0.5	28.2 ± 1.0	+1.6 ± 0.7	100.0
1,875	4/5	29.2 ± 1.0	32.0 ± 1.4	+3.3 ± 0.3	113.5
3,750	5/5	26.6 ± 0.9	29.8 ± 1.2	+3.2 ± 0.9	105.7
7,500	5/5	26.4 ± 0.7	28.8 ± 1.0	+2.4 ± 0.5	102.1
FEMALE					
0	5/5	22.4 ± 0.7	24.0 ± 0.5	+1.6 ± 0.5	--
469	4/5	20.8 ± 0.4	23.5 ± 0.3	+3.0 ± 0.4	97.9
938	5/5	22.0 ± 0.3	22.6 ± 0.5	+0.6 ± 0.4	94.2
1,875	5/5	21.2 ± 0.5	23.0 ± 0.4	+1.8 ± 0.2	95.8
3,750	5/5	22.2 ± 0.5	23.4 ± 0.5	+1.2 ± 0.4	97.5
7,500	5/5	21.8 ± 0.4	22.8 ± 0.4	+1.0 ± 0.0	95.0

(a) Number surviving/number in group. All deaths were judged accidental.
(b) Initial mean group body weight ± standard error of the mean. Subsequent calculations are based on those animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean

TABLE 21. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE THIRTEEN-WEEK GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{23}, 43% Cl)

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	9/10	26.0 ± 0.6	37.4 ± 1.2	+ 11.4 ± 0.9	--
469	8/10	25.3 ± 0.8	37.0 ± 0.7	+ 11.1 ± 1.1	98.9
938	10/10	25.6 ± 0.6	37.7 ± 0.7	+ 12.1 ± 0.7	100.8
1,875	10/10	25.9 ± 0.6	38.1 ± 0.9	+ 12.2 ± 0.7	101.9
3,750	10/10	26.2 ± 1.0	37.2 ± 1.6	+ 11.0 ± 1.0	99.5
7,500	6/10	24.3 ± 0.5	37.3 ± 1.1	+ 12.7 ± 1.0	99.7
FEMALE					
0	9/10	18.9 ± 0.2	26.7 ± 0.4	+ 7.8 ± 0.4	--
469	8/10	20.5 ± 0.4	28.4 ± 0.8	+ 7.9 ± 0.5	106.4
938	10/10	19.9 ± 0.3	27.4 ± 0.6	+ 7.5 ± 0.5	102.6
1,875	9/10	20.3 ± 0.3	27.2 ± 0.5	+ 6.9 ± 0.4	101.9
3,750	8/10	19.5 ± 0.5	27.5 ± 0.8	+ 7.5 ± 0.7	103.0
7,500	6/10	19.8 ± 0.4	31.0 ± 1.2	+ 10.3 ± 1.0	116.1

(a) Number surviving/number in group; all deaths considered gavage accidents, which was confirmed by evidence of oil in the lung or a tear in the esophagus.
(b) Initial mean group body weight ± standard error of the mean. Subsequent calculations are based on those animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of high dose male mice were comparable to those of the vehicle controls, and body weights of high dose female mice were greater than those of vehicle controls after week 26 (Table 22 and Figure 3). Mean body weights of low dose male mice were slightly lower than those of the vehicle control and high dose mice after week 51. Mean body weights of low dose female mice were lower than those of the vehicle control and high dose female mice after week 13. There were no chemically related clinical signs observed in male or female mice during the studies.

TABLE 22. MEAN BODY WEIGHTS AND SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{23}, 43% Cl)

Weeks on Study	Vehicle Control		2,500 mg/kg			5,000 mg/kg		
	Av Wt (grams)	No. of Survivors	Av Wt (grams)	Wt (percent of veh controls)	No. of Survivors	Av Wt (grams)	Wt (percent of veh controls)	No. of Survivors
MALE								
0	25.2	50	25.2	100	50	25.4	101	50
1	27.3	50	27.7	101	50	27.6	101	50
2	28.8	49	28.9	100	50	29.2	101	50
3	29.7	49	29.0	98	50	29.9	101	50
4	30.6	49	30.4	99	50	31.3	102	50
5	32.1	49	31.8	99	50	32.6	102	50
6	32.6	49	32.6	100	50	33.1	102	50
7	33.1	49	32.7	99	49	34.0	103	50
8	34.7	49	34.1	98	48	35.3	102	50
9	35.0	49	34.0	97	48	35.3	101	50
10	36.4	49	35.9	99	48	36.3	100	50
11	35.9	49	35.3	98	48	36.5	102	50
12	37.4	49	36.3	97	48	37.6	101	50
13	37.9	49	36.9	97	48	38.0	100	50
18	41.4	49	38.8	94	48	40.9	99	50
22	42.4	49	40.4	95	48	42.5	100	50
26	43.4	49	42.6	98	48	43.2	100	50
31	43.0	49	41.4	96	48	43.8	102	50
36	45.7	49	43.1	94	48	45.9	100	50
40	45.5	48	44.0	97	48	46.2	102	50
44	46.4	48	45.3	98	48	46.3	100	50
47	46.9	48	44.6	95	48	47.3	101	49
51	46.8	48	44.7	96	48	47.4	101	48
56	47.4	47	44.1	93	48	47.7	101	48
60	47.9	47	44.1	92	48	47.5	99	48
64	47.7	47	45.0	94	48	48.6	102	47
69	48.8	47	45.9	94	48	48.2	99	46
74	48.3	46	45.7	95	46	48.3	100	46
78	47.1	45	44.3	94	46	47.9	102	45
83	46.9	42	43.8	93	46	47.9	102	42
87	46.2	42	44.3	96	46	48.0	104	39
91	45.7	41	43.7	96	44	47.5	104	36
96	45.9	33	43.5	95	42	46.3	101	33
101	44.3	32	42.8	97	38	46.0	104	30
104	42.5	29	39.7	93	36	45.5	107	28
FEMALE								
0	20.9	50	20.7	99	50	21.3	102	50
1	22.2	50	23.0	104	50	22.7	102	50
2	23.5	50	22.8	97	50	23.3	99	50
3	24.3	50	23.5	97	50	24.1	99	50
4	24.8	50	24.3	98	50	25.3	102	50
5	25.3	50	24.6	97	50	25.2	100	50
6	26.0	50	25.5	98	50	26.1	100	50
7	25.8	50	25.4	98	49	26.2	102	49
8	26.6	50	25.9	97	49	27.3	103	49
9	26.8	50	26.0	97	49	27.1	101	49
10	27.6	50	27.0	98	49	27.7	100	49
11	26.9	50	26.6	99	49	28.0	104	49
12	28.2	50	26.8	95	49	28.4	101	49
13	28.6	50	28.1	98	49	29.1	102	49
18	30.8	50	28.8	94	49	31.1	101	49
22	31.7	50	29.0	91	49	32.2	102	49
26	31.4	50	30.6	97	48	33.3	106	49
31	32.2	50	31.2	97	48	33.8	105	49
36	34.0	50	30.3	89	48	35.5	104	49
40	35.8	50	32.8	92	47	37.3	104	49
44	37.2	50	34.8	94	47	38.7	104	49
47	38.1	50	34.7	91	47	39.5	104	49
51	38.3	49	35.1	92	47	40.6	106	49
56	40.7	49	37.2	91	47	42.6	105	49
60	41.1	49	37.8	92	47	44.4	108	47
64	42.1	49	38.9	92	47	45.6	108	47
69	44.2	45	40.2	91	46	47.7	108	45
74	44.5	42	41.5	93	43	48.0	108	42
78	44.1	39	39.7	90	42	47.1	107	41
83	44.2	33	39.6	90	34	47.6	108	36
87	44.1	31	40.2	91	31	48.1	109	34
91	45.9	27	41.6	91	29	48.8	106	31
96	46.1	26	40.3	87	23	47.5	103	27
101	43.7	25	40.1	92	22	47.3	108	23
104	44.4	21	38.1	86	22	46.7	105	20

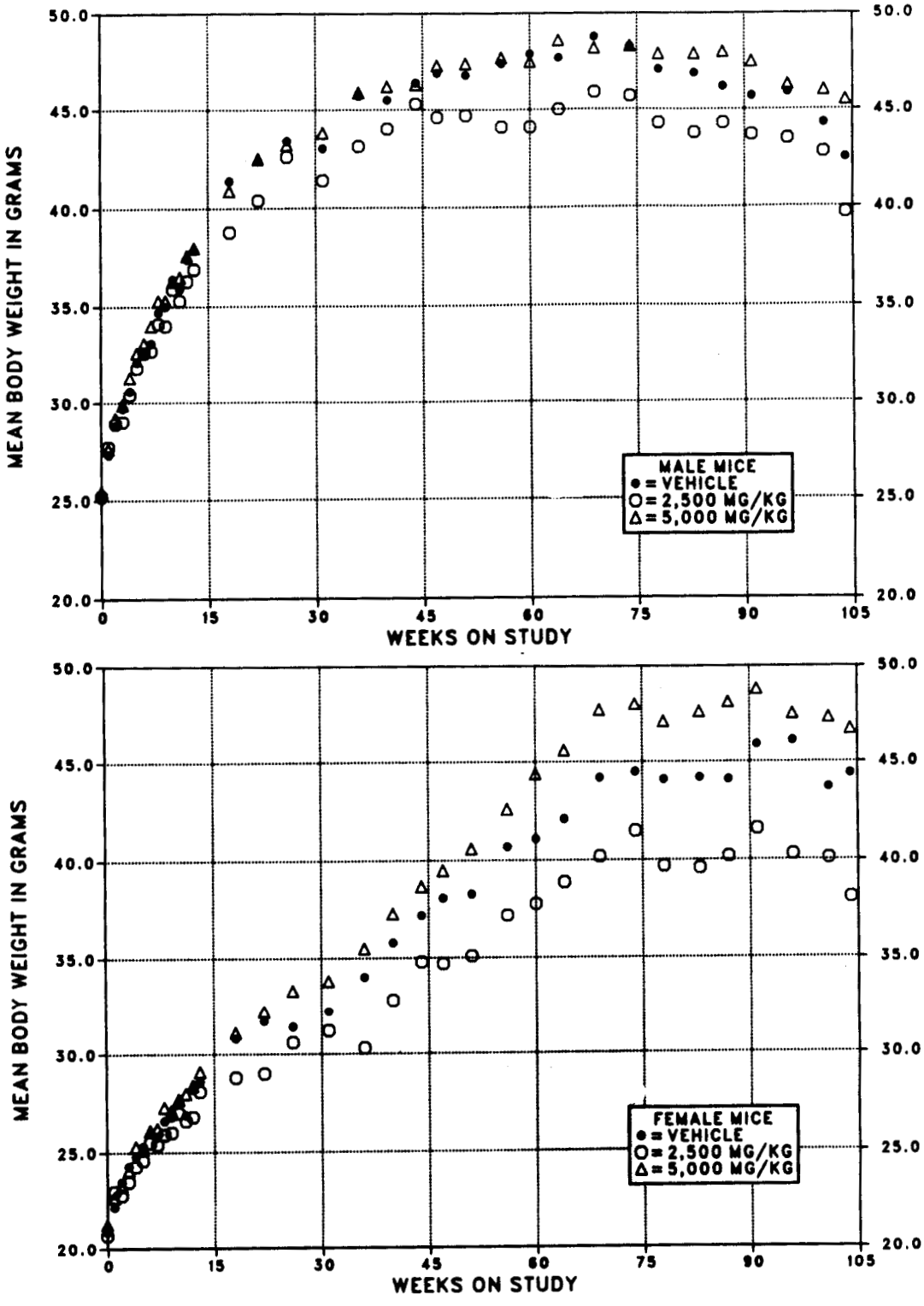


FIGURE 3. GROWTH CURVES FOR MICE ADMINISTERED CHLORINATED PARAFFINS (C_{23}, 43% Cl) IN CORN OIL BY GAVAGE FOR TWO YEARS

Survival

Estimates of the probabilities of survival for male and female mice administered chlorinated paraffins (C_{23}, 43% chlorine) at the doses used in these studies and for the vehicle controls are shown in the Kaplan and Meier curves in Figure 4. No significant differences in survival between dosed and vehicle control groups were observed (Table 23). Survival in all dosed and vehicle control groups of female mice was affected after week 65 by a *Klebsiella oxytoca* infection. Evidence of utero-ovarian infection was noted in 20/29 vehicle control, 19/27 low dose, and 17/29 high dose female mice that died before the end of the studies.

TABLE 23. SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{23}, 43% Cl)

	Vehicle Control	2,500 mg/kg	5,000 mg/kg
MALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	20	12	22
Accidentally killed	1	2	0
Killed at termination	28	36	28
Died during termination period	1	0	0
Survival P values (c)	0.707	0.115	0.787
FEMALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	29	27	29
Accidentally killed	0	1	1
Killed at termination	21	22	20
Survival P values (c)	0.934	0.822	0.911

(a) Terminal kill period: weeks 104-105
(b) Includes animals killed in a moribund condition
(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.

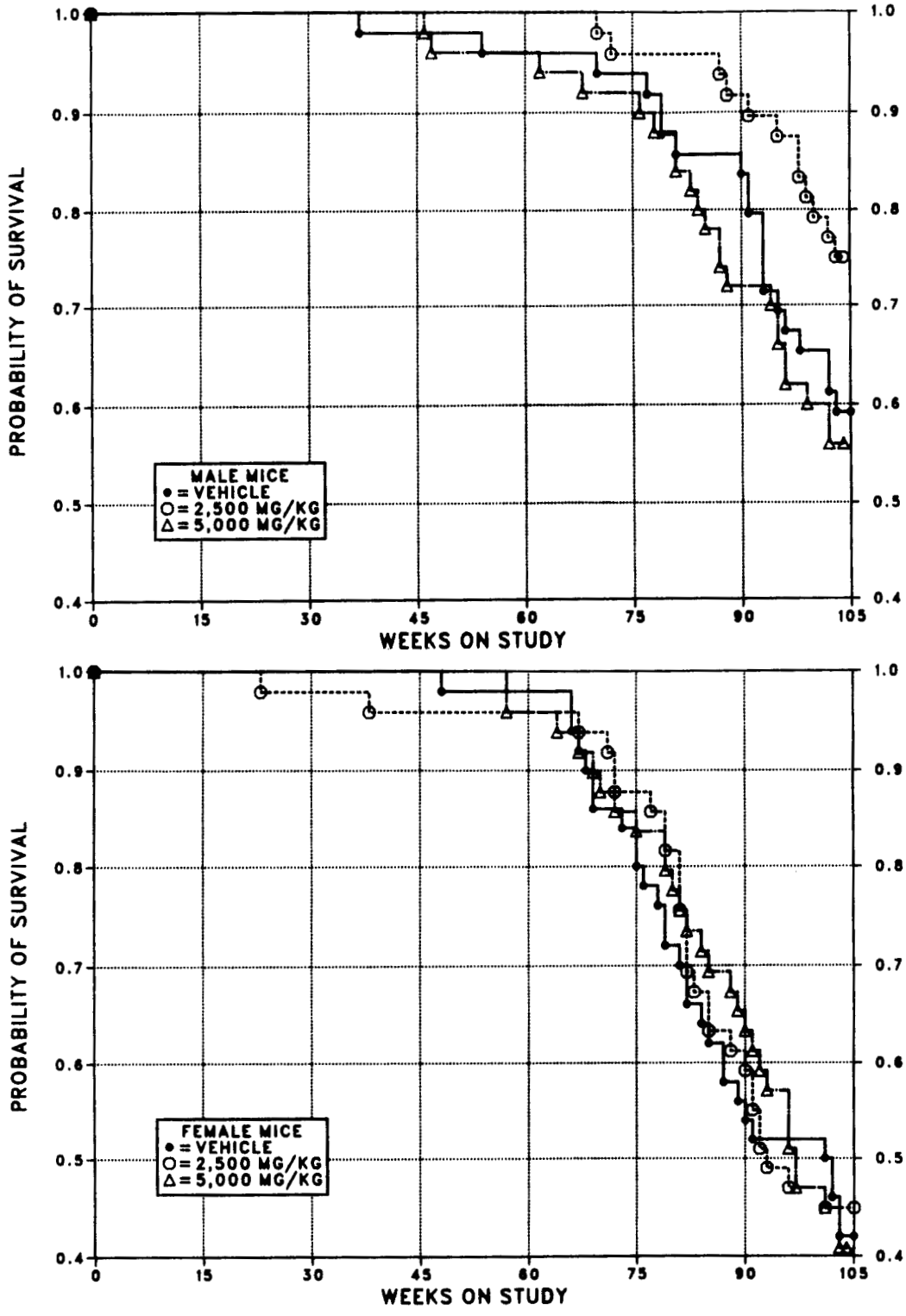


FIGURE 4. KAPLAN-MEIER SURVIVAL CURVES FOR MICE ADMINISTERED CHLORINATED PARAFFINS (C_{23}, 43% Cl) IN CORN OIL BY GAVAGE FOR TWO YEARS

Pathology and Statistical Analyses of Results

This section describes the significant or noteworthy changes in the incidences of mice with neoplastic or nonneoplastic lesions of the hematopoietic system, liver, thyroid gland, urinary system, circulatory system, nasal cavity, ovary, and brain. Histopathologic findings on neoplasms in mice are summarized in Appendix B (Tables B1 and B2); Appendix B (Tables B3 and B4) also gives the survival and tumor status for individual male and female mice. Findings on nonneoplastic lesions are summarized in Appendix D (Tables D1 and D2). Appendix E (Tables E3 and E4) contains the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the dose groups. The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix E (footnotes). Historical incidences of tumors in corn oil vehicle control animals are listed in Appendix F.

Hematopoietic System: Malignant lymphomas in male mice occurred with a significant positive trend, and the incidence in the high dose group was significantly greater than that in the vehicle controls (Table 24). The incidence of all malignant lymphomas in female mice was as follows: vehicle control, 15/50; low dose, 12/49; high dose, 20/50. No leukemia was observed in any group of male or female mice.

TABLE 24. ANALYSIS OF MALIGNANT LYMPHOMAS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) (a,b)

	Vehicle Control	2,500 mg/kg	5,000 mg/kg
Overall Rates	6/50 (12%)	12/50 (24%)	16/50 (32%)
Adjusted Rates	16.3%	31.4%	48.7%
Terminal Rates	2/29 (7%)	10/36 (28%)	12/28 (43%)
Week of First Observation	77	99	85
Life Table Tests	P=0.009	P=0.204	P=0.014
Incidental Tumor Tests	P=0.011	P=0.099	P=0.017

(a) The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix E (footnotes).
(b) Historical incidence at study laboratory (mean ± SD): 35/299 (12% ± 5%); historical incidence in NTP studies: 132/1,097 (12% ± 4%)

Liver: Hepatocellular carcinomas and hepatocellular adenomas or carcinomas (combined) in female mice occurred with significant positive trends, but the incidences in the dosed groups were not significantly greater than those in the vehicle controls (Table 25). An increased incidence of cytoplasmic vacuolization was observed in high dose male mice (vehicle control, 1/50; low dose, 1/50; high dose, 6/50). The following incidences of hepatocellular adenomas or carcinomas (combined) were observed in male mice: vehicle control, 18/50 (36%); low dose, 21/50 (42%); high dose, 23/50 (46%).

Thyroid Gland: Follicular cell carcinomas in male mice occurred with a positive trend (vehicle control, 0/49; low dose, 0/48; high dose, 3/49); the incidences of follicular cell adenomas or carcinomas (combined) were not significantly greater than that in the vehicle controls (vehicle control, 1/49, 2%; low dose, 3/48, 6%; high dose, 5/49, 10%). The incidences of follicular cell adenomas or carcinomas (combined) in female mice were as follows: vehicle control, 7/49 (14%); low dose, 6/47 (13%); high dose, 5/49 (10%) (historical incidence in male mice at testing laboratory: 25/292, 9% ± 5%; historical incidence in NTP studies: 43/1,009, 4% ± 5%).

Urinary System: A urinary bladder transitional cell papilloma was observed in 1/50 high dose male mice. Kidney tubular cell adenocarcinomas were observed in 1/50 high dose male mice and in 1/49 low dose and 1/50 high dose female mice (historical incidence in NTP studies: urinary bladder transitional cell neoplasms in male mice, 0/1,054; kidney tubular cell adenomas or adenocarcinomas in male mice, 4/1,091; kidney tubular cell adenomas or adenocarcinomas in female mice, 1/1,092).

Circulatory System: Hemangiosarcomas in male mice occurred with a significant negative trend (vehicle control, 7/50, 14%; low dose, 2/50, 4%; high dose, 2/50, 4%), but the incidences in the dosed groups were not significantly different from those in the vehicle controls.

Nasal Mucosa: The incidence of focal inflammation of the nasal mucosa was increased in high dose mice (male: vehicle control, 1/50, 2%; low dose, 2/50, 4%; high dose, 8/50, 16%; female: vehicle control, 3/50, 6%; low dose, 5/49, 10%; high dose, 14/50, 28%).

Ovary: Follicular cysts were observed at increased incidence in high dose female mice (vehicle control, 11/46, 24%; low dose, 15/42, 36%; high dose, 20/47, 43%).

Brain: Psammoma bodies in the thalamus were observed at increased incidences in dosed male mice and at decreased incidences in dosed female mice (male: vehicle control, 14/50, 28%; low dose, 21/50, 42%; high dose, 25/50, 50%; female: vehicle control, 30/50, 60%; low dose, 22/49, 45%; high dose, 16/50, 32%).

TABLE 25. ANALYSIS OF LIVER TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl)

	Vehicle Control	2,500 mg/kg	5,000 mg/kg
Hepatocellular Adenoma			
Overall Rates	3/50 (6%)	2/49 (4%)	7/50 (14%)
Adjusted Rates	14.3%	8.4%	27.0%
Terminal Rates	3/21 (14%)	1/22 (5%)	3/20 (15%)
Week of First Observation	104	93	67
Life Table Tests	P=0.093	P=0.487N	P=0.144
Incidental Tumor Tests	P=0.152	P=0.529N	P=0.201
Hepatocellular Carcinoma			
Overall Rates	1/50 (2%)	1/49 (2%)	6/50 (12%)
Adjusted Rates	4.8%	4.5%	23.3%
Terminal Rates	1/21 (5%)	1/22 (5%)	2/20 (10%)
Week of First Observation	104	104	90
Life Table Tests	P=0.022	P=0.753N	P=0.058
Incidental Tumor Tests	P=0.043	P=0.753N	P=0.098
Hepatocellular Adenoma or Carcinoma (a)			
Overall Rates	4/50 (8%)	3/49 (6%)	10/50 (20%)
Adjusted Rates	19.0%	12.7%	36.3%
Terminal Rates	4/21 (19%)	2/22 (9%)	4/20 (20%)
Week of First Observation	104	93	67
Life Table Tests	P=0.039	P=0.481N	P=0.069
Incidental Tumor Tests	P=0.071	P=0.518N	P=0.106

(a) Historical incidence at study laboratory (mean ± SD): 18/300 (6% ± 3%); historical incidence in NTP studies: 74/1,092 (7% ± 4%)

IV. DISCUSSION AND CONCLUSIONS

IV. DISCUSSION AND CONCLUSIONS

Studies of the toxicology and carcinogenesis of chlorinated paraffins (C_{23}, 43% chlorine) were conducted in F344/N rats and $B6C3F_1$ mice of each sex. For the 2-year studies, chlorinated paraffins (C_{23}, 43% chlorine) was administered 5 days per week by gavage in corn oil at doses of 0, 1,875, or 3,750 mg/kg body weight to male rats; at 0, 100, 300, or 900 mg/kg to female rats; and at 0, 2,500, or 5,000 mg/kg to male and female mice. Doses for the 2-year studies were selected based on results from single-administration, 16-day, and 13-week studies with rats and mice of each sex.

The doses of chlorinated paraffins (C_{23}, 43% chlorine) given during the 2-year studies to male rats and male and female mice were limited solely by the physical properties of the chemical. Because of the absence of chemically related toxicity in the short-term studies, these groups received the maximum amount of chlorinated paraffins (C_{23}, 43% chlorine) that could be administered by gavage based on the viscosity and total volume of the corn oil/chlorinated paraffins (C_{23}, 43% chlorine) mixture. The 2-year studies in mice were begun with a high dose of 7,500 mg/kg for each sex, but the 18-gauge needle required for delivery of this viscous dose contributed to many gavage-related deaths in young mice, causing the mouse study to be restarted with the dose and size of the gavage needle reduced. After this adjustment, no more than three gavage-related accidental deaths were recorded in any group of rats or mice during the 2-year studies.

In contrast to the absence of chemically related toxicity in the short-term studies with male rats and male and female mice, a diffuse inflammation of the liver was observed in the 13-week study in female rats. This lesion was observed in all dose groups (235 to 3,750 mg/kg), and the incidences were dose related. Since the effect of this lesion on survival of female rats during the 2-year study could not be predicted, two doses (300 and 900 mg/kg) anticipated to produce the lesion were selected for the 2-year study, and a third dose (100 mg/kg) was included in case survival of the high dose group was poor. Additional male and female rats to be killed at 6 and 12 months were added to all dosed and vehicle control groups to determine the onset and progress of this lesion. Although the results of the additional studies showed that the inflammatory liver lesion was present at 6 and 12 months, survival and body weight gain of these animals were not affected in the 2-year studies, and therefore the female rats may have been able to tolerate higher doses of chlorinated paraffins (C_{23}, 43% chlorine).

The survival of dosed and vehicle control male rats and male and female mice was similar in the 2-year studies. Body weight gains of dosed and vehicle control rats were similar, but low dose male mice had an average body weight as little as 92% of that of the vehicle controls and low dose female mice as little as 86% at various times during the 2-year studies. No reasons for these weight differences were apparent. A large number of deaths of female mice were observed after week 65 in both dosed and vehicle control groups. Evidence of utero-ovarian infection was noted in 69% of vehicle control, 70% of low dose, and 59% of high dose animals that died before the end of the study. Cultures taken from the ovaries or uterus of five affected mice were positive for *Klebsiella oxytoca*. Thus, female mice had an active Klebsiella infection during the second year of the study, and this infection was the primary cause of death of these animals. The low survival may have decreased the sensitivity of the study for detection of a carcinogenic effect in female mice.

There were no significant chemically related clinical signs in either rats or mice during the 2-year studies. However, certain organs or organ systems showed histopathologic changes in response to chlorinated paraffins (C_{23}, 43% chlorine) exposure in rats and mice of each sex.

Malignant lymphomas occurred with a dose-related positive trend in male mice (vehicle control, 6/50; low dose, 12/50; high dose, 16/50). The incidences in high dose male mice (32%) and in low dose male mice (24%) were greater than that in the vehicle controls (12%) and were greater than the highest incidence observed in historical corn oil vehicle control groups (22%) (Appendix F, Table F1). In that these incidences represent significant, dose-related increases in a malignant neoplasm, they represent clear evidence of carcinogenicity of chlorinated paraffins (C_{23}, 43% chlorine) in male mice.

Hepatocellular carcinomas and hepatocellular adenomas or carcinomas (combined) showed positive trends (life table analysis) in dosed female mice. Emphasis on the results of life table analysis is appropriate in this instance for two reasons. Survival of dosed and vehicle control female mice was similar, which precludes generation of an inappropriately low P value through shortened survival due to chemical toxicity. Also, the increased incidence of liver neoplasms in the high dose group was primarily accounted for by malignant, life-threatening tumors, i.e., hepatocellular carcinomas. The incidence of hepatocellular carcinomas in the high dose group (12%) was nearly twice the highest rate observed in vehicle corn oil controls in NTP studies and was about fourfold greater than the mean historical incidence (34/1,092; 3.1%) (Table F10). Nonetheless, there was only a marginal increase in the incidence of total liver neoplasms in dosed female mice (vehicle control, 4/50; low dose, 3/49; high dose, 10/50); hence the evidence of carcinogenicity of chlorinated paraffins (C_{23}, 43% chlorine) was considered equivocal in that group. Liver neoplastic nodules were observed in dosed male rats (vehicle control, 0/50; low dose, 3/50; high dose, 3/50), but the incidences were not statistically significant.

Adrenal gland medullary pheochromocytomas were observed with a dose-related positive trend in female rats, and the incidence in the high dose group (14%) was significantly greater than that in the vehicle controls (2%). The historical incidence of pheochromocytomas in corn oil vehicle controls is 5%-6% in female rats, with 12% being the greatest observed incidence (Table F5). If adrenal gland medullary hyperplasias are also considered, an increase in total proliferative lesions is seen only in the high dose group (hyperplasia or pheochromocytomas, combined: vehicle control, 7/50; low dose, 7/50; mid dose, 7/50; high dose, 13/50). With the exception of one malignant pheochromocytoma noted in a low dose female rat, the neoplasms were benign. These lesions were not increased in male rats. This small increase in benign tumors in female rats may be related to the administration of chlorinated paraffins (C_{23}, 43% chlorine).

The incidence of endometrial stromal polyps of the uterus was increased in the low dose female rats (17/50). In addition, two endometrial stromal sarcomas were found in this dose group (one in an animal with a polyp), but none was found in other group. Although the incidence of these neoplasms in the low dose group was greater than that in the vehicle controls (9/50) and the incidence is greater than the historical control rate (252/1,089, 23%), this increase is not considered to be related to chlorinated paraffins (C_{23}, 43% chlorine) exposure, since no increase was seen in the mid dose and high dose groups. Endometrial stromal polyps were observed in 3/50 vehicle control female mice but not in any dosed mice.

Dose-related changes in the incidence of acinar cell adenomas of the pancreas were observed in male rats administered chlorinated paraffins (C_{23}, 43% chlorine). Pancreatic acinar cell adenomas occurred with a negative trend, and acinar cell hyperplasia also followed this pattern (vehicle control, 18%; low dose, 4%; high dose, 2%). Acinar cell neoplasms are frequently noted at a greater incidence in male rat vehicle controls in corn oil gavage studies than in feed studies (Boorman and Eustis, 1984). The relative incidences observed in the present study may reflect the amount of corn oil administered to the respective dose groups. Vehicle controls received 5 ml of corn oil/kg per day, low dose animals, 3.4 ml/kg, and high dose, 1.8 ml/kg throughout the studies.

The primary nonneoplastic lesion in the rat attributed to chlorinated paraffins (C_{23}, 43% chlorine) administration was a lymphohistiocytic inflammation of the liver, with associated involvement of the pancreatic and mesenteric lymph nodes (see Table 19). In male and female rats, this granulomatous lesion caused an impairment of hepatic blood flow by obstruction of the sinusoids, which led to congestion of the spleen. Female rats appeared to develop the toxic liver lesion after administration of chlorinated paraffins (C_{23}, 43% chlorine) at lower doses for shorter periods of time than was required for the male rats. However, the results of the 6- and 12-month studies indicated that the lesion did occur in males as well as females.

A subjective assessment of the severity of lymphohistiocytic inflammation of the liver suggested an association with both the dose and the duration of administration of chlorinated

paraffins (C_{23}, 43% chlorine). The increases in relative liver weight appeared to reflect the severity of the lesion, and liver weights correlated well at 6 and 12 months with the doses given to female rats and at 12 months with the doses given to male rats. Grossly, the livers were enlarged and mottled and often had multiple nodules. Microscopically, diffuse foci of lymphohistiocytic inflammation were observed. Cellular necrosis was noted in the periphery of larger foci, and the moderate increases in serum ASAT, ALAT, and SDH activity at 6 and 12 months may have originated in these areas. (Clinical pathology assessments were not performed at the termination of the 2-year studies.) Although within normal ranges, the serum albumin concentrations were lower in the high dose female rats than in the vehicle controls at 6 and 12 months. The concentration of globulins was elevated in the mid dose and high dose groups at 6 months, and the albumin:globulin ratio was decreased at 6 months in all dosed female rats. Total serum protein was decreased in mid dose and high dose female rats at 12 months. All these changes are characteristic of a toxic liver lesion.

Hematologic parameters also showed changes consistent with a lymphohistiocytic inflammation. Leukocyte counts were elevated in the high dose female rats at both 6 and 12 months, with lymphocytes accounting for most of the increase. Monocytes, the precursors of the histiocytes, appeared elevated at 12 months in dosed female rats. Packed cell volumes (hematocrit), erythrocyte counts, and hemoglobin content were all within normal ranges, but the trends in the data were suggestive of a slight peripheral anemia. An anemia of chronic inflammation is often observed concurrently with a granulomatous lesion, possibly because of sequestration of iron by the macrophages (Wintrobe et al., 1981). Microcytic anemia can occur under these conditions, and calculations of mean corpuscular volume from the present hematologic data suggest a reduction in the red blood cell volume in high dose female rats at 12 months.

The mechanism(s) by which chlorinated paraffins (C_{23}, 43% chlorine) causes the hepatic inflammation are not known, and the reasons for the greater sensitivity of the female rat for development of the lesion are not understood. The appearance of the lesion is suggestive of a delayed tissue hypersensitivity reaction, although the strong dose response is not consistent with a primary allergic mechanism. Following short periods of administration, certain chlorinated paraffins are known to cause proliferation of hepatocyte smooth endoplasmic reticulum along with the induction of epoxide hydrolase, glutathione-*S*-transferase, certain cytochrome P-450's, and other enzymes (Nilsen et al., 1981; Meijer et al., 1981). Exposure in vivo to the shorter carbon chain paraffins also tends to increase the number and size of mitochondria and peroxisomes and induces the occurrence of autophagosomes and lysosomes (Nilsen et al., 1980, 1981). The extent of such biochemical changes after exposure to chlorinated paraffins (C_{23}, 43% chlorine) is not known, nor is it known if these changes are in any way involved in the development of the liver lesion.

Other nonneoplastic lesions that may have been related to chlorinated paraffins (C_{23}, 43% chlorine) exposure included pigmentation in the kidneys of female rats, pigmentation in the livers of male and female rats, and an increase in inflammation of the nasal cavity of male rats and male and female mice. Follicular cysts of the ovary were observed at an increased incidence in female mice, but the presence of a Klebsiella infection makes this difficult to interpret.

Similar toxicology and carcinogenesis studies were carried out on chlorinated paraffins (C_{12}, 60% chlorine), a mixture of shorter chain paraffins chlorinated to approximately 60% by weight. Complete details of these studies are reported separately (NTP, 1986), and a copy of the abstract from the Technical Report is included as Appendix O in this Report. The shorter chain paraffin material was judged to exhibit clear evidence of carcinogenicity in rats and mice of each sex. Dosed male and female rats and mice showed increased incidences of liver tumors, dosed male rats had increased incidences of kidney tubular cell hyperplasia and adenomas or adenocarcinomas (combined), and dosed female rats and female mice showed increased thyroid gland follicular cell neoplasms. Mononuclear cell leukemia was increased in dosed male rats, but malignant lymphomas were not increased in male mice, in contrast to the results with chlorinated paraffins (C_{23}, 43% chlorine).

The shorter chain chlorinated paraffins caused a marked hepatocyte hypertrophy and corresponding liver enlargement in rats and mice, but no evidence of a lymphohistiocytic inflammation was noted in males or females of either species. In addition, the shorter chain material caused kidney enlargement and a worsening of nephropathy in dosed male and female rats; the longer chain paraffins appeared to cause only a moderate increase in the terminal incidence of nephropathy and pigmentation of the kidney in female rats. Administration of short-chain paraffins caused inflammation and ulceration of the stomach of male rats, effects not seen in any of the groups given the longer chain chlorinated paraffins (C_{23}, 43% chlorine).

Comparisons of the effects of administration of these materials to rats and mice must include a consideration of the molar doses used in the two sets of studies and the likelihood of differences in absorption. With the exception of the low and mid doses of chlorinated paraffins (C_{23}, 43% chlorine) given to female rats, molar doses of the longer chain paraffins were higher than those of the shorter chain materials. Lower absorption of longer chain paraffins may have partially offset the differences in the administered doses. Given this uncertainty, it would nonetheless appear that the shorter chain, highly chlorinated paraffins have a greater potential for toxicity and carcinogenicity in rodents than do the longer chain paraffins (NTP, 1986).

Conclusions: Under the conditions of these 2-year gavage studies, there was *no evidence of carcinogenicity** of chlorinated paraffins (C_{23}, 43% chlorine) for male F344/N rats given 1,875 or 3,750 mg/kg per day. There was *equivocal evidence of carcinogenicity* of chlorinated paraffins (C_{23}, 43% chlorine) for female F344/N rats as shown by an increased incidence of adrenal gland medullary pheochromocytomas. There was *clear evidence of carcinogenicity* of chlorinated paraffins (C_{23}, 43% chlorine) for male $B6C3F_1$ mice as shown by an increase in the incidence of malignant lymphomas. There was *equivocal evidence of carcinogenicity* of chlorinated paraffins (C_{23}, 43% chlorine) for female $B6C3F_1$ mice as shown by a marginal increase in the incidence of hepatocellular neoplasms.

*Categories of evidence of carcinogenicity are defined in the Note to the Reader on page 2.

V. REFERENCES

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APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{23}, 43% CHLORINE)

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl)

	CONTROL (VEH)	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	3 (6%)	2 (4%)	
Basal cell tumor	2 (4%)		1 (2%)
Trichoepithelioma		1 (2%)	1 (2%)
Keratoacanthoma	4 (8%)	1 (2%)	2 (4%)
*Subcutaneous tissue	(50)	(50)	(50)
Sarcoma, NOS		1 (2%)	
Fibroma	3 (6%)	6 (12%)	3 (6%)
Neurofibrosarcoma			1 (2%)
*Mesentery	(50)	(50)	(50)
Fibrous histiocytoma, malignant	1 (2%)		
RESPIRATORY SYSTEM			
*Nasal cavity	(50)	(50)	(50)
Papillary adenoma	1 (2%)		
#Lung	(50)	(50)	(50)
Alveolar/bronchiolar adenoma		1 (2%)	
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Malignant lymphoma, lymphocytic type		1 (2%)	
Malignant lymphoma, histiocytic type			2 (4%)
Leukemia, mononuclear cell	9 (18%)	8 (16%)	14 (28%)
#Spleen	(50)	(50)	(50)
Fibroma	1 (2%)		1 (2%)
Leukemia, mononuclear cell		1 (2%)	
CIRCULATORY SYSTEM			
*Subcutaneous tissue	(50)	(50)	(50)
Hemangiopericytoma, NOS	1 (2%)		
DIGESTIVE SYSTEM			
*Tongue	(50)	(50)	(50)
Squamous cell papilloma		1 (2%)	
#Liver	(50)	(50)	(50)
Neoplastic nodule		3 (6%)	3 (6%)
#Pancreas	(49)	(50)	(50)
Acinar cell adenoma	6 (12%)	1 (2%)	1 (2%)
#Small intestine	(50)	(50)	(50)
Mucinous adenocarcinoma	1 (2%)		
URINARY SYSTEM			
#Kidney	(50)	(50)	(50)
Tubular cell adenoma	1 (2%)		
Tubular cell adenocarcinoma		1 (2%)	
#Urinary bladder	(50)	(50)	(48)
Transitional cell carcinoma	2 (4%)	1 (2%)	

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM			
#Pituitary	(49)	(49)	(47)
Craniopharyngioma		1 (2%)	
#Pituitary intermedia	(49)	(49)	(47)
Craniopharyngioma	1 (2%)		
#Anterior pituitary	(49)	(49)	(47)
Carcinoma, NOS	2 (4%)	1 (2%)	2 (4%)
Adenoma, NOS	13 (27%)	6 (12%)	10 (21%)
#Pituitary posterior	(49)	(49)	(47)
Adenoma, NOS		1 (2%)	
#Adrenal	(50)	(50)	(50)
Cortical adenoma		2 (4%)	
#Adrenal medulla	(50)	(50)	(50)
Pheochromocytoma	20 (40%)	15 (30%)	20 (40%)
Pheochromocytoma, malignant		2 (4%)	
#Thyroid	(50)	(50)	(49)
Follicular cell adenoma		1 (2%)	
Follicular cell carcinoma	1 (2%)	2 (4%)	
C-cell adenoma	7 (14%)	4 (8%)	5 (10%)
C-cell carcinoma	4 (8%)	5 (10%)	3 (6%)
#Pancreatic islets	(49)	(50)	(50)
Islet cell adenoma		1 (2%)	4 (8%)
Islet cell carcinoma	1 (2%)	2 (4%)	
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Fibroadenoma	4 (8%)	1 (2%)	
*Preputial gland	(50)	(50)	(50)
Carcinoma, NOS	1 (2%)	2 (4%)	1 (2%)
Adenoma, NOS	1 (2%)	3 (6%)	
#Testis	(50)	(50)	(50)
Interstitial cell tumor	41 (82%)	43 (86%)	39 (78%)
*Spermatic cord	(50)	(50)	(50)
Mesothelioma, NOS		2 (4%)	
NERVOUS SYSTEM			
#Brain/meninges	(50)	(50)	(49)
Granular cell tumor, NOS	1 (2%)		
#Cerebrum	(50)	(50)	(49)
Granular cell tumor, NOS	1 (2%)		
#Brain/thalamus	(50)	(50)	(49)
Astrocytoma	1 (2%)		
SPECIAL SENSE ORGANS			
*Zymbal gland	(50)	(50)	(50)
Carcinoma, NOS		2 (4%)	2 (4%)
Adenoma, NOS		1 (2%)	
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
*Mesentery	(50)	(50)	(50)
Carcinoma, NOS	1 (2%)		
*Tunica vaginalis	(50)	(50)	(50)
Mesothelioma, NOS	1 (2%)	1 (2%)	

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Mesothelioma, NOS			1 (2%)
Osteosarcoma	1 (2%)		
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	6	4	5
Moribund sacrifice	14	11	18
Terminal sacrifice	30	32	27
Dosing accident		3	
TUMOR SUMMARY			
Total animals with primary tumors**	48	47	48
Total primary tumors	137	127	116
Total animals with benign tumors	46	46	48
Total benign tumors	107	91	87
Total animals with malignant tumors	23	25	24
Total malignant tumors	25	29	25
Total animals with tumors uncertain--benign or malignant	5	6	4
Total uncertain tumors	5	7	4

* Number of animals necropsied
** Primary tumors: all tumors except secondary tumors
# Number of animals with tissue examined microscopically

TABLE A2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl)

	CONTROL (VEH)	LOW DOSE	MID DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS NECROPSIED	50	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50	50
INTEGUMENTARY SYSTEM				
*Skin	(50)	(50)	(50)	(50)
Squamous cell papilloma		1 (2%)		
Squamous cell carcinoma				1 (2%)
Basal cell tumor	1 (2%)			
Keratoacanthoma	1 (2%)			1 (2%)
*Subcutaneous tissue	(50)	(50)	(50)	(50)
C-cell carcinoma, invasive			1 (2%)	
Sarcoma, NOS		1 (2%)		1 (2%)
Fibroma		1 (2%)	1 (2%)	1 (2%)
Fibrosarcoma		1 (2%)		
RESPIRATORY SYSTEM				
#Trachea	(50)	(50)	(50)	(50)
C-cell carcinoma, invasive			1 (2%)	
#Lung	(50)	(50)	(49)	(50)
Squamous cell carcinoma, metastatic			1 (2%)	
Alveolar/bronchiolar adenoma	1 (2%)		2 (4%)	1 (2%)
Alveolar/bronchiolar carcinoma			1 (2%)	1 (2%)
C-cell carcinoma, metastatic			1 (2%)	
Pheochromocytoma, metastatic		1 (2%)		
HEMATOPOIETIC SYSTEM				
#Cerebrum	(50)	(50)	(50)	(50)
Malignant reticulosis				1 (2%)
*Multiple organs	(50)	(50)	(50)	(50)
Malignant lymphoma, lymphocytic type				1 (2%)
Leukemia, mononuclear cell	7 (14%)	9 (18%)	7 (14%)	8 (16%)
#Spleen	(50)	(50)	(50)	(50)
Osteosarcoma, metastatic			1 (2%)	
Malignant lymphoma, histiocytic type		1 (2%)		
Leukemia, mononuclear cell	1 (2%)	1 (2%)		
#Mandibular l. node	(50)	(50)	(50)	(50)
Sarcoma, NOS, invasive		1 (2%)		
#Kidney	(50)	(50)	(50)	(50)
Malignant lymphoma, histiocytic type				1 (2%)
CIRCULATORY SYSTEM				
*Muscle of thorax	(50)	(50)	(50)	(50)
Hemangiosarcoma	1 (2%)			
DIGESTIVE SYSTEM				
#Liver	(50)	(50)	(50)	(50)
Neoplastic nodule	1 (2%)	2 (4%)	1 (2%)	2 (4%)
#Forestomach	(50)	(50)	(50)	(50)
Squamous cell papilloma			1 (2%)	
#Cecum	(50)	(49)	(50)	(49)
Leiomyosarcoma			1 (2%)	

TABLE A2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) (Continued)

	CONTROL (VEH)	LOW DOSE	MID DOSE	HIGH DOSE
URINARY SYSTEM				
#Urinary bladder	(50)	(50)	(50)	(50)
Transitional cell carcinoma				1 (2%)
Endometrial stromal sarcoma, invasive		1 (2%)		
ENDOCRINE SYSTEM				
#Anterior pituitary	(50)	(50)	(50)	(50)
Carcinoma, NOS	3 (6%)	2 (4%)	1 (2%)	2 (4%)
Adenoma, NOS	22 (44%)	18 (36%)	18 (36%)	18 (36%)
#Adrenal	(50)	(50)	(50)	(50)
Cortical adenoma	1 (2%)			1 (2%)
#Adrenal medulla	(50)	(50)	(50)	(50)
Pheochromocytoma	1 (2%)	3 (6%)	6 (12%)	7 (14%)
Pheochromocytoma, malignant		1 (2%)		
#Thyroid	(50)	(48)	(50)	(50)
Follicular cell carcinoma	1 (2%)	1 (2%)		
C-cell adenoma	5 (10%)	5 (10%)	5 (10%)	3 (6%)
C-cell carcinoma	4 (8%)	5 (10%)	2 (4%)	1 (2%)
#Pancreatic islets	(50)	(50)	(50)	(50)
Islet cell adenoma				1 (2%)
REPRODUCTIVE SYSTEM				
*Mammary gland	(50)	(50)	(50)	(50)
Adenoma, NOS	1 (2%)			
Adenocarcinoma, NOS	3 (6%)	2 (4%)		
Fibroadenoma	14 (28%)	13 (26%)	8 (16%)	8 (16%)
*Clitoral gland	(50)	(50)	(50)	(50)
Carcinoma, NOS	1 (2%)		1 (2%)	1 (2%)
Squamous cell carcinoma			1 (2%)	
#Uterus	(50)	(50)	(50)	(50)
Endometrial stromal polyp	9 (18%)	17 (34%)	10 (20%)	10 (20%)
Endometrial stromal sarcoma		2 (4%)		
#Uterus/endometrium	(50)	(50)	(50)	(50)
Squamous cell carcinoma		1 (2%)		
Adenoma, NOS	1 (2%)			
#Ovary	(50)	(50)	(50)	(50)
Granulosa cell carcinoma			1 (2%)	
NERVOUS SYSTEM				
#Cerebrum	(50)	(50)	(50)	(50)
Carcinoma, NOS, invasive	1 (2%)			
#Brain	(50)	(50)	(50)	(50)
Carcinoma, NOS, invasive				1 (2%)
SPECIAL SENSE ORGANS				
None				
MUSCULOSKELETAL SYSTEM				
*Muscle of back	(50)	(50)	(50)	(50)
Osteosarcoma			1 (2%)	
BODY CAVITIES				
None				

TABLE A2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) (Continued)

	CONTROL (VEH)	LOW DOSE	MID DOSE	HIGH DOSE
ALL OTHER SYSTEMS				
*Multiple organs	(50)	(50)	(50)	(50)
Squamous cell carcinoma	1 (2%)			
C-cell carcinoma, metastatic			1 (2%)	
Broad ligament				
Fibroma			1	
ANIMAL DISPOSITION SUMMARY				
Animals initially in study	50	50	50	50
Natural death	6	6	4	8
Moribund sacrifice	10	13	13	10
Terminal sacrifice	34	30	33	31
Accidentally killed, NOS		1		1
TUMOR SUMMARY				
Total animals with primary tumors**	46	45	40	41
Total primary tumors	80	87	69	72
Total animals with benign tumors	39	39	36	34
Total benign tumors	57	58	52	51
Total animals with malignant tumors	19	22	13	17
Total malignant tumors	22	27	16	19
Total animals with secondary tumors##	1	3	3	1
Total secondary tumors	1	3	6	1
Total animals with tumors uncertain--benign or malignant	1	2	1	2
Total uncertain tumors	1	2	1	2

* Number of animals necropsied
** Primary tumors: all tumors except secondary tumors
\# Number of animals with tissue examined microscopically
Secondary tumors: metastatic tumors or tumors invasive into an adjacent organ

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl): VEHICLE CONTROL

ANIMAL NUMBER	020	027	004	046	047	017	018	014	016	013	021	006	042	030	009	001	037	043	043	045	002	005	007	008	010
WEEKS ON STUDY	037	068	074	079	079	084	084	085	086	092	092	095	096	099	101	102	102	104	104	105	105	105	105	105	105
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma		X																							
Basal cell tumor																									
Keratoacanthoma						X				X										X					
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																									
Hemangiopericytoma, NOS																X									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nasal cavity	N	N	N	N	N	N	N	N	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papillary adenoma																									
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																									
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinar cell adenoma						X												X							
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mucinous adenocarcinoma													X												
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional cell carcinoma		X																							
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS					X												X								
Adenoma, NOS									X	X		X												X	
Craniopharyngioma													X												
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma									X	X		X		X						X		X	X	X	X
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell carcinoma																									
C-cell adenoma								X		X		X			X			X							
C-cell carcinoma													X								X				
Parathyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell carcinoma															X										
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma										X							X						X		
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor			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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granular cell tumor, NOS																									
Astrocytoma								X																	
BODY CAVITIES																									
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma, NOS						X																			
Mesentery	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																									
Fibrous histiocytoma, malignant												X													
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Osteosarcoma							X																		
Leukemia, mononuclear cell			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 A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: VEHICLE CONTROL (Continued)

ANIMAL NUMBER	011	012	015	019	022	023	024	025	026	028	029	031	032	033	034	035	036	038	039	040	041	044	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																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell papilloma													X			X										3
Basal cell tumor																X			X							2
Keratoacanthoma																			X							4
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma						X															X		X			3
Hemangiopericytoma, NOS																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Papillary adenoma										X																1
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroma								X																		1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Pancreas	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Acinar cell adenoma																		X	X	X		X				6
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mucinous adenocarcinoma																										1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tubular cell adenoma																	X									1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Transitional cell carcinoma	X																									2
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, NOS																										2
Adenoma, NOS			X	X		X	X				X			X								X		X	X	13
Craniopharyngioma																										1
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma			X		X	X		X	X	X			X		X	X			X						X	20
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell carcinoma				X																						1
C-cell adenoma					X							X														7
C-cell carcinoma																							X	X		4
Parathyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreatic islets	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islet cell carcinoma																										1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroadenoma														X												4
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	41
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																										1
Adenoma, NOS																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granular cell tumor, NOS																							X	X		2
Astrocytoma																										1
BODY CAVITIES																										
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Mesothelioma, NOS																										1
Mesentery	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS			X																							1
Fibrous histiocytoma, malignant																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Osteosarcoma																										1
Leukemia, mononuclear cell							X																		X	9

* Animals necropsied

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl): LOW DOSE

ANIMAL NUMBER	002	005	026	015	046	013	034	043	047	031	039	030	035	042	028	014	027	024	001	002	003	004	006	007	008
WEEKS ON STUDY	051	072	081	086	086	090	090	093	094	096	097	098	098	098	099	100	100	101	105	105	105	105	105	105	105
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																						X			
Trichoepithelioma																						X			
Keratoacanthoma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																									
Fibroma										X			X			X									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia, mononuclear cell																									
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	–	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell papilloma																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																X									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinar cell adenoma																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenocarcinoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional cell carcinoma																									
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+
Carcinoma, NOS								X																	
Adenoma, NOS					X													X			X		X	X	
Craniopharyngioma																			X						
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																									
Pheochromocytoma						X					X								X	X					
Pheochromocytoma, malignant																							X		
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma				X																					
Follicular cell carcinoma				X																					
C-cell adenoma				X		X						X													
C-cell carcinoma								X							X							X			
Parathyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																						X			
Islet cell carcinoma										X															
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+
Fibroadenoma																									X
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor			X			X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X		X	X
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													
Vas deferens, spermatic cord	N	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																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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
Carcinoma, NOS										X														X	
Adenoma, NOS																									
BODY CAVITIES																									
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma, NOS																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malig lymphoma, lymphocytic type																									
Leukemia, mononuclear cell									X		X	X		X		X	X			X					

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: LOW DOSE (Continued)

ANIMAL NUMBER	009	010	011	012	016	017	018	019	020	021	023	025	029	032	033	036	037	038	040	041	044	045	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																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell papilloma																									X	2
Trichoepithelioma																										1
Keratoacanthoma																			X							1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS													X													1
Fibroma							X							X						X						6
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma					X																					1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia, mononuclear cell						X																				1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell papilloma		X																								1
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule				X							X															3
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Acinar cell adenoma															X											1
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tubular cell adenocarcinoma																			X							1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Transitional cell carcinoma																								X		1
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, NOS																										1
Adenoma, NOS										X							X									7
Craniopharyngioma																										1
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma														X					X							2
Pheochromocytoma	X						X				X					X	X			X	X	X	X	X	X	15
Pheochromocytoma, malignant																					X					2
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell adenoma																										1
Follicular cell carcinoma																									X	2
C-cell adenoma				X																						4
C cell carcinoma	X									X																5
Parathyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet cell adenoma																										1
Islet cell carcinoma						X																				2
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroadenoma																										1
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	43
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS														X												2
Adenoma, NOS	X														X											3
Vas deferens, spermatic cord	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Mesothelioma, NOS																				X					X	2
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Zymbal gland	N	N	N	N	+	+	+	N	+	+	N	N	N	N	N	N	+	+	N	N	N	N	N	N	N	*50
Carcinoma, NOS																										2
Adenoma, NOS										X																1
BODY CAVITIES																										
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Mesothelioma, 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
Malig lymphoma, lymphocytic type		X																								1
Leukemia, mononuclear cell												X														8

* Animals necropsied

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl): HIGH DOSE

ANIMAL NUMBER	008	035	005	027	020	048	006	024	002	034	042	003	021	044	011	026	036	037	050	012	041	039	017	001	004
WEEKS ON STUDY	073	073	081	085	089	089	092	092	093	095	097	098	099	098	099	099	099	099	099	100	101	102	104	105	105
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell tumor																			X						
Trichoepithelioma						X																			
Keratoacanthoma																	X								
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma							X								X										
Neurofibrosarcoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																									
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule											X						X						X		
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinar cell adenoma																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	−	+	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+
Carcinoma, NOS																X									
Adenoma, NOS																				X					
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma						X						X	X			X	X				X				
Thyroid	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell adenoma			X																				X		
C-cell carcinoma																			X						
Parathyroid	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma									X		X														
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor	X	X	X	X		X	X	X	X	X	X	X		X		X	X	X	X		X	X		X	X
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS													X												
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Zymbal gland	+	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							
Malig lymphoma, histiocytic type		X																					X		
Leukemia, mononuclear cell	X			X		X	X		X		X		X	X	X		X				X				

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: HIGH DOSE (Continued)

ANIMAL NUMBER	007	009	010	013	014	015	016	018	019	022	023	025	028	029	030	031	032	033	038	040	043	045	046	047	049	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																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Basal cell tumor																										1
Trichoepithelioma																										1
Keratoacanthoma	X																									2
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma								X																		3
Neurofibrosarcoma							X																			1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroma										X																1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	−	+	−	+	+	−	−	−	+	−	+	+	+	+	+	+	+	+	−	+	+	+	41
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule																										3
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Acinar cell adenoma				X																						1
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	−	+	+	+	48
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Carcinoma, NOS									X																	2
Adenoma, NOS						X	X						X	X		X		X	X				X		X	10
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma	X		X			X	X		X				X	X	X	X		X		X		X	X		X	20
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell adenoma										X						X								X		5
C-cell carcinoma																	X						X			3
Parathyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet cell adenoma									X															X		4
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell tumor	X	X	X	X	X			X	X	X	X	X	X		X	X	X		X	X		X	X	X		39
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	49
SPECIAL SENSE ORGANS																										
Zymbal gland	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
Malig lymphoma, histiocytic type																										2
Leukemia, mononuclear cell				X	X	X																				14

*Animals necropsied

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl): VEHICLE CONTROL

ANIMAL NUMBER	014	012	016	009	048	022	021	049	003	031	006	026	036	027	040	050	001	002	004	005	007	008	010	011	013
WEEKS ON STUDY	049	066	072	077	083	086	095	095	096	096	098	098	098	101	101	101	105	105	105	105	105	105	105	105	105
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell tumor																									
Keratoacanthoma																							X		
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia, mononuclear cell																					X				
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule											X														
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																									
Pheochromocytoma															X										
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell carcinoma																									X
C-cell adenoma																									
C cell carcinoma											X										X	X		X	
Parathyroid	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Adenocarcinoma, NOS																									X
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																			
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Endometrial stromal polyp	X					X													X						
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, invasive														X											
MUSCULOSKELETAL SYSTEM																									
Muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																X									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell carcinoma			X																						
Leukemia, mononuclear cell									X	X		X			X	X				X					

+	Tissue Examined Microscopically		No Tissue Information Submitted
–	Required Tissue Not Examined Microscopically	C	Necropsy, No Histology Due To Protocol
X	Tumor Incidence	A	Autolysis
N	Necropsy, No Autolysis, No Microscopic Examination	M	Animal Missing
S	Animal Missexed	B	No Necropsy Performed

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: VEHICLE CONTROL (Continued)

ANIMAL NUMBER	015	017	018	019	020	023	024	025	028	029	030	032	033	034	035	037	038	039	041	042	043	044	045	046	047	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																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Basal cell tumor													X													1
Keratoacanthoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma					X																					1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia, mononuclear cell																										1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS														X												3
Adenoma, NOS			X			X	X				X	X			X			X	X			X	X		X	22
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma		X																								1
Pheochromocytoma																										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell carcinoma																										1
C-cell adenoma						X	X			X					X					X						5
C-cell carcinoma																										4
Parathyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	46
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenoma, NOS			X																							1
Adenocarcinoma, NOS			X															X								3
Fibroadenoma	X	X				X		X	X				X					X		X			X			14
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS													X													1
Endometrial stromal polyp				X	X				X						X	X								X		9
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS, invasive																										1
MUSCULOSKELETAL SYSTEM																										
Muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Hemangiosarcoma																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell carcinoma																										1
Leukemia, mononuclear cell						X																				7

* Animals necropsied

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl): LOW DOSE

ANIMAL NUMBER	022	037	020	046	003	001	010	023	029	032	034	039	007	011	050	045	025	027	036	048	002	004	005	006	008
WEEKS ON STUDY	053	053	069	071	080	082	090	090	092	092	092	095	097	097	099	101	102	104	104	104	105	105	105	105	105
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS		X																							
Fibroma																									
Fibrosarcoma																X									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma, metastatic						X																			
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malig. lymphoma, histiocytic type								X																	
Leukemia, mononuclear cell																									X
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS, invasive		X																							
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule											X									X					
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal sarcoma, in			X																						
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS											X							X							
Adenoma, NOS								X	X			X				X	X		X	X	X	X	X		
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma											X				X										
Pheochromocytoma, malignant						X																			
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell carcinoma																	X								
C-cell adenoma				X						X		X													
C-cell carcinoma					X							X													
Parathyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																	X					X			
Fibroadenoma				X						X							X	X			X		X	X	
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																				X					
Endometrial stromal polyp					X	X				X			X	X			X	X		X	X				
Endometrial stromal sarcoma			X											X											
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					

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: LOW DOSE (Continued)

ANIMAL NUMBER	009	012	013	014	015	016	017	018	019	021	024	026	028	030	031	033	035	038	040	041	042	043	044	047	049	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																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell papilloma					X																					1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS																										1
Fibroma																								X		1
Fibrosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Malig. lymphoma, histiocytic type																										1
Leukemia, mononuclear cell																										1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, NOS, invasive																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	–	+	+	+	–	+	+	–	+	+	46
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule																										2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endometrial stromal sarcoma, invas																										1
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS																										2
Adenoma, NOS	X	X	X		X		X													X				X	X	18
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma								X																		3
Pheochromocytoma, malignant																										1
Thyroid	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Follicular cell carcinoma																										1
C-cell adenoma																		X					X			5
C-cell carcinoma					X				X							X										5
Parathyroid	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenocarcinoma, NOS																										2
Fibroadenoma	X		X			X				X		X			X											13
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma																										1
Endometrial stromal polyp			X		X			X						X	X		X		X			X				17
Endometrial stromal sarcoma																										2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leukemia, mononuclear cell								X		X				X												9

* Animals necropsied

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl): MID DOSE

ANIMAL NUMBER	007	033	029	002	040	045	049	003	047	006	034	036	043	041	001	024	025	004	005	008	009	010	011	012	013
WEEKS ON STUDY	021	071	076	085	090	094	096	097	098	099	100	100	101	102	103	104	104	105	105	105	105	105	105	105	105
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell carcinoma, invasive																									
Fibroma																		X							
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+
Squamous cell carcinoma, metastatic																			X						
Alveolar/bronchiolar adenoma															X										
Alveolar/bronchiolar carcinoma												X													
C-cell carcinoma, metastatic																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell carcinoma, invasive																									
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic																			X						
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule													X												
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma									X																
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma												X													
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS									X																
Adenoma, NOS		X	X	X	X					X			X	X	X		X						X		X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma																	X		X						
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell adenoma				X																					
C-cell carcinoma																									
Parathyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma									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												
Squamous cell carcinoma																			X						
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																									
Endometrial stromal polyp													X							X				X	
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell carcinoma																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MUSCULOSKELETAL SYSTEM																									
Muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma																			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																									
Leukemia, mononuclear cell						X	X	X					X	X	X								X		

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: MID DOSE (Continued)

ANIMAL NUMBER	014	015	016	017	018	019	020	021	022	023	026	027	028	030	031	032	035	037	038	039	042	044	046	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	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
C-cell carcinoma, invasive																X										1
Fibroma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell carcinoma, metastatic																										1
Alveolar/bronchiolar adenoma																X										2
Alveolar/bronchiolar carcinoma																										1
C-cell carcinoma, metastatic																X										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell carcinoma, invasive																X										1
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma, metastatic																										1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																										1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma																										1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS																										1
Adenoma, NOS							X		X	X		X									X		X		X	18
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma														X				X			X	X				6
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell adenoma			X															X		X			X			5
C-cell carcinoma														X		X										2
Parathyroid	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	48
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroadenoma					X							X										X		X		8
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS																										1
Squamous cell carcinoma																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroma					X																					1
Endometrial stromal polyp	X		X	X				X			X				X						X					10
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa cell carcinoma									X																	1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
MUSCULOSKELETAL SYSTEM																										
Muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Osteosarcoma																										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
Leukemia, mononuclear cell																										7

*Animals necropsied

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl): HIGH DOSE

ANIMAL NUMBER	021	008	030	004	047	011	034	013	015	029	002	044	037	036	039	020	038	043	046	003	005	006	007	009	010
WEEKS ON STUDY	045	047	070	079	082	087	088	090	090	090	092	093	097	099	101	104	104	104	104	105	105	105	105	105	105
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																				X					
Keratoacanthoma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS					X																				
Fibroma																		X							
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																							X		
Alveolar/bronchiolar carcinoma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	–
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule									X													X			
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malig. lymphoma, histiocytic type																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional cell carcinoma																									
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS														X											
Adenoma, NOS							X	X	X		X		X		X		X		X	X				X	
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																			X						
Pheochromocytoma													X			X	X	X							
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell adenoma																									
C-cell carcinoma																		X							
Parathyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma							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																					
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp		X												X						X					X
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, invasive														X											
Malignant reticulosis										X															
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malig. lymphoma, lymphocytic type																									
Leukemia, mononuclear cell		X					X		X		X	X			X										

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: HIGH DOSE (Continued)

ANIMAL NUMBER	011	012	014	016	017	018	019	022	023	024	025	026	027	028	031	032	033	035	040	041	042	045	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																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell carcinoma																										1
Keratoacanthoma					X																					1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS																										1
Fibroma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										1
Alveolar/bronchiolar carcinoma								X																		1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	45
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule																										2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Malig. lymphoma, histiocytic type	X																									1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Transitional cell carcinoma																					X					1
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS							X																			2
Adenoma, NOS						X					X			X					X	X	X	X		X		18
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma																										1
Pheochromocytoma										X		X			X											7
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell adenoma		X																				X	X			3
C-cell carcinoma																										1
Parathyroid	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet cell adenoma					X																					1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroadenoma															X			X			X		X			8
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endometrial stromal polyp	X			X	X										X	X				X						10
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS, invasive																										1
Malignant reticulosis																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malig. lymphoma, lymphocytic type								X																		1
Leukemia, mononuclear cell					X		X																			8

*Animals necropsied

APPENDIX B

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE IN THE TWO-YEAR GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{23}, 43% CHLORINE)

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl)

	CONTROL (VEH)	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%)		
Sebaceous adenoma			1 (2%)
Rhabdomyosarcoma			1 (2%)
*Subcutaneous tissue	(50)	(50)	(50)
Sarcoma, NOS	2 (4%)	4 (8%)	3 (6%)
Fibroma	2 (4%)	6 (12%)	2 (4%)
Fibrosarcoma	5 (10%)	5 (10%)	3 (6%)
Neurofibrosarcoma	1 (2%)		
Neurilemoma		1 (2%)	
RESPIRATORY SYSTEM			
#Lung	(50)	(50)	(50)
Carcinoma, NOS, metastatic	1 (2%)		
Hepatocellular carcinoma, metastatic	2 (4%)	1 (2%)	3 (6%)
Alveolar/bronchiolar adenoma	9 (18%)	5 (10%)	9 (18%)
Alveolar/bronchiolar carcinoma	2 (4%)	5 (10%)	5 (10%)
Follicular cell carcinoma, metastatic			1 (2%)
Sarcoma, NOS, metastatic		1 (2%)	
Fibrosarcoma, metastatic	1 (2%)		1 (2%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Malignant lymphoma, lymphocytic type		1 (2%)	2 (4%)
Malignant lymphoma, histiocytic type			3 (6%)
Malignant lymphoma, mixed type	4 (8%)	6 (12%)	8 (16%)
#Spleen	(49)	(49)	(50)
Malignant lymphoma, mixed type		2 (4%)	1 (2%)
#Mandibular lymph node	(50)	(50)	(50)
Carcinoma, NOS, metastatic	1 (2%)		
#Mediastinal lymph node	(50)	(50)	(50)
Sarcoma, NOS, metastatic		1 (2%)	
#Mesenteric lymph node	(50)	(50)	(50)
Malignant lymphoma, lymphocytic type		1 (2%)	1 (2%)
Malignant lymphoma, mixed type	1 (2%)	2 (4%)	
#Inguinal lymph node	(50)	(50)	(50)
Fibrosarcoma, metastatic	1 (2%)		
#Liver	(50)	(50)	(50)
Malignant lymphoma, NOS	1 (2%)		
#Small intestine	(47)	(50)	(48)
Malignant lymphoma, mixed type			1 (2%)
CIRCULATORY SYSTEM			
*Multiple organs	(50)	(50)	(50)
Hemangiosarcoma	1 (2%)		
*Skin	(50)	(50)	(50)
Hemangiosarcoma	1 (2%)		
#Spleen	(49)	(49)	(50)
Hemangiosarcoma	1 (2%)	2 (4%)	2 (4%)
#Heart	(50)	(49)	(50)
Hemangiosarcoma	1 (2%)		
#Liver	(50)	(50)	(50)
Hemangiosarcoma	3 (6%)		

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
#Salivary gland	(50)	(49)	(49)
Myoepithelioma			1 (2%)
#Liver	(50)	(50)	(50)
Hepatocellular adenoma	10 (20%)	14 (28%)	14 (28%)
Hepatocellular carcinoma	9 (18%)	12 (24%)	12 (24%)
Hepatoblastoma			1 (2%)
#Forestomach	(50)	(50)	(50)
Squamous cell papilloma		1 (2%)	
#Ileum	(47)	(50)	(48)
Adenocarcinoma, NOS		1 (2%)	
URINARY SYSTEM			
#Kidney	(50)	(50)	(50)
Tubular cell adenocarcinoma			1 (2%)
#Urinary bladder	(50)	(50)	(50)
Transitional cell papilloma			1 (2%)
ENDOCRINE SYSTEM			
#Adrenal	(49)	(50)	(47)
Cortical adenoma			2 (4%)
#Adrenal/capsule	(49)	(50)	(47)
Adenoma, NOS	4 (8%)		2 (4%)
#Adrenal medulla	(49)	(50)	(47)
Pheochromocytoma	1 (2%)	4 (8%)	1 (2%)
#Thyroid	(49)	(48)	(49)
Follicular cell adenoma	1 (2%)	3 (6%)	2 (4%)
Follicular cell carcinoma			3 (6%)
#Pancreatic islets	(50)	(50)	(50)
Islet cell adenoma			1 (2%)
REPRODUCTIVE SYSTEM			
#Testis	(50)	(50)	(50)
Interstitial cell tumor		1 (2%)	
NERVOUS SYSTEM			
None			
SPECIAL SENSE ORGANS			
*Harderian gland	(50)	(50)	(50)
Adenoma, NOS	3 (6%)	3 (6%)	2 (4%)
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
*Mediastinum	(50)	(50)	(50)
Hepatocellular carcinoma, metastatic			1 (2%)
*Mesentery	(50)	(50)	(50)
Hepatocellular carcinoma, invasive			1 (2%)
Sarcoma, NOS		1 (2%)	

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Carcinoma, NOS			1 (2%)
Hepatocellular carcinoma, metastatic		1 (2%)	
Alveolar/bronchiolar ca, metastatic	1 (2%)		
Mesothelioma, malignant		1 (2%)	
Orbital region			
Carcinoma, NOS	1		
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	10	6	11
Moribund sacrifice	11	6	11
Terminal sacrifice	28	36	28
Accidentally killed, NOS	1	2	
TUMOR SUMMARY			
Total animals with primary tumors**	43	41	43
Total primary tumors	65	81	86
Total animals with benign tumors	26	28	30
Total benign tumors	32	38	38
Total animals with malignant tumors	29	32	37
Total malignant tumors	33	43	48
Total animals with secondary tumors##	6	3	5
Total secondary tumors	7	4	7

* Number of animals necropsied
** Primary tumors: all tumors except secondary tumors
\# Number of animals with tissue examined microscopically
Secondary tumors: metastatic tumors or tumors invasive into an adjacent organ

TABLE B2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	49	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	49	50
INTEGUMENTARY SYSTEM			
*Subcutaneous tissue	(50)	(49)	(50)
Sarcoma, NOS	1 (2%)		
Fibrosarcoma	1 (2%)		1 (2%)
Neurilemoma, malignant			1 (2%)
RESPIRATORY SYSTEM			
#Lung	(50)	(49)	(50)
Adenocarcinoma, NOS, metastatic			1 (2%)
Alveolar/bronchiolar adenoma	1 (2%)	2 (4%)	3 (6%)
Alveolar/bronchiolar carcinoma	2 (4%)	1 (2%)	
Sarcoma, NOS, invasive	1 (2%)		
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(49)	(50)
Malignant lymphoma, undiffer type			1 (2%)
Malignant lymphoma, lymphocytic type	5 (10%)	2 (4%)	6 (12%)
Malignant lymphoma, histiocytic type			2 (4%)
Malignant lymphoma, mixed type	10 (20%)	9 (18%)	8 (16%)
#Spleen	(49)	(49)	(50)
Malignant lymphoma, NOS			1 (2%)
Malignant lymphoma, mixed type			1 (2%)
#Liver	(50)	(49)	(50)
Malignant lymphoma, mixed type		1 (2%)	
#Small intestine	(48)	(46)	(50)
Malignant lymphoma, mixed type			1 (2%)
CIRCULATORY SYSTEM			
*Vaginal mucosa	(50)	(49)	(50)
Hemangiosarcoma	1 (2%)		
#Uterus	(50)	(48)	(50)
Hemangioma	1 (2%)	1 (2%)	
Hemangiosarcoma, unc prim or met			1 (2%)
DIGESTIVE SYSTEM			
#Parotid gland	(48)	(49)	(49)
Adenocarcinoma, NOS			1 (2%)
#Liver	(50)	(49)	(50)
Hepatocellular adenoma	3 (6%)	2 (4%)	7 (14%)
Hepatocellular carcinoma	1 (2%)	1 (2%)	6 (12%)
#Esophagus	(49)	(49)	(50)
Squamous cell carcinoma			1 (2%)
#Glandular stomach	(49)	(47)	(50)
Squamous cell carcinoma, invasive			1 (2%)
#Forestomach	(49)	(47)	(50)
Squamous cell papilloma		2 (4%)	1 (2%)
#Duodenal mucosa	(48)	(46)	(50)
Adenocarcinoma, NOS	1 (2%)		
Adenomatous polyp, NOS	1 (2%)		

TABLE B2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
URINARY SYSTEM			
#Kidney	(50)	(49)	(50)
Tubular cell adenocarcinoma		1 (2%)	1 (2%)
ENDOCRINE SYSTEM			
#Pituitary	(46)	(46)	(45)
Acidophil adenoma	1 (2%)		
#Anterior pituitary	(46)	(46)	(45)
Carcinoma, NOS		1 (2%)	
Adenoma, NOS	12 (26%)	8 (17%)	15 (33%)
#Adrenal	(50)	(49)	(50)
Cortical adenoma	1 (2%)		
#Adrenal/capsule	(50)	(49)	(50)
Adenoma, NOS			1 (2%)
#Adrenal medulla	(50)	(49)	(50)
Pheochromocytoma	1 (2%)	1 (2%)	1 (2%)
#Thyroid	(49)	(47)	(49)
Follicular cell adenoma	7 (14%)	4 (9%)	5 (10%)
Follicular cell carcinoma		2 (4%)	
#Pancreatic islets	(49)	(48)	(50)
Islet cell adenoma		1 (2%)	
Islet cell carcinoma	1 (2%)		
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(49)	(50)
Adenocarcinoma, NOS	1 (2%)	1 (2%)	1 (2%)
Adenosquamous carcinoma			1 (2%)
#Uterus	(50)	(48)	(50)
Leiomyosarcoma	1 (2%)		
Endometrial stromal polyp	3 (6%)		
#Cervix uteri	(50)	(48)	(50)
Leiomyoma			1 (2%)
Endometrial stromal sarcoma	1 (2%)		
#Ovary	(46)	(42)	(47)
Teratoma, NOS		1 (2%)	
NERVOUS SYSTEM			
#Brain	(50)	(49)	(50)
Carcinoma, NOS, invasive		1 (2%)	
SPECIAL SENSE ORGANS			
*Harderian gland	(50)	(49)	(50)
Carcinoma, NOS		1 (2%)	
Adenoma, NOS	4 (8%)	2 (4%)	1 (2%)
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
*Mediastinum	(50)	(49)	(50)
Sarcoma, NOS	1 (2%)		

TABLE B2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ALL OTHER SYSTEMS			
None			
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	16	16	15
Moribund sacrifice	13	11	14
Terminal sacrifice	21	22	20
Accidentally killed, NOS		1	1
TUMOR SUMMARY			
Total animals with primary tumors**	32	29	38
Total primary tumors	62	44	69
Total animals with benign tumors	22	18	24
Total benign tumors	35	23	35
Total animals with malignant tumors	23	18	27
Total malignant tumors	27	20	33
Total animals with secondary tumors##	1	1	2
Total secondary tumors	1	1	2
Total animals with tumors uncertain--benign or malignant		1	
Total uncertain tumors		1	
Total animals with tumors uncertain--primary or metastatic			1
Total uncertain tumors			1

* Number of animals necropsied
** Primary tumors: all tumors except secondary tumors
\# Number of animals with tissue examined microscopically
Secondary tumors: metastatic tumors or tumors invasive into an adjacent organ

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl): VEHICLE CONTROL

ANIMAL NUMBER	546	501	543	510	549	502	548	513	542	519	536	506	528	530	541	545	531	526	503	502	539	533	504	505	507
WEEKS ON STUDY	001	037	054	070	077	079	079	081	090	091	091	093	093	093	093	095	096	098	102	102	103	104	105	105	105
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																X									
Hemangiosarcoma																									
Subcutaneous tissue	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																	X								
Fibroma																									X
Fibrosarcoma													X		X										
Neurofibrosarcoma										X															
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, metastatic																						X			
Hepatocellular carcinoma, metastatic								X						X											
Alveolar/bronchiolar adenoma				X																					
Alveolar/bronchiolar carcinoma							X																		X
Fibrosarcoma, metastatic															X										
Trachea	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, metastatic																						X			
Fibrosarcoma, metastatic																									
Malignant lymphoma, mixed type																									X
Thymus	+	+	+	+	–	–	+	+	+	–	+	+	–	–	–	–	+	+	+	+	–	+	+	+	–
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma				X											X									X	
Hepatocellular carcinoma		X	X			X		X						X				X			X				
Hemangiosarcoma																		X	X						
Malignant lymphoma, NOS									X																
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	N	+	N	+	N	+	N	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+
Large intestine	+	+	+	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	–	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																							X		
Pheochromocytoma																									
Thyroid	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																									
Parathyroid	+	+	+	+	–	–	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS								X																	
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
Alveolar/bronchiolar ca, metastatic							X																		
Hemangiosarcoma															X										
Malignant lymphoma, mixed type					X											X				X					
Orbital region																									
Carcinoma, NOS																						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 B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: VEHICLE CONTROL (Continued)

ANIMAL NUMBER	508	509	511	512	514	515	516	517	518	521	522	523	524	525	527	529	532	534	535	537	538	540	544	547	550	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																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell papilloma							X																			2
Hemangiosarcoma																	X									1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS									X																	2
Fibroma													X													2
Fibrosarcoma														X								X	X			5
Neurofibrosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS, metastatic																										1
Hepatocellular carcinoma, metastatic																										2
Alveolar/bronchiolar adenoma									X			X	X	X	X		X		X		X					9
Alveolar/bronchiolar carcinoma																										2
Fibrosarcoma, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	47
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma													X													1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS, metastatic																										1
Fibrosarcoma, metastatic														X												1
Malignant lymphoma, mixed type																										1
Thymus	–	–	–	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	–	+	–	–	34
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma					X																					1
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma		X			X							X	X	X										X	X	10
Hepatocellular carcinoma																						X		X		9
Hemangiosarcoma											X															3
Malignant lymphoma, NOS																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	N	N	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	–	–	+	+	+	+	–	+	+	+	+	+	–	+	+	+	43
Adrenal	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, NOS								X			X							X								4
Pheochromocytoma																					X					1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell adenoma						X																				1
Parathyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	–	+	–	+	43
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS	X																						X			3
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Alveolar/bronchiolar ca, metastatic																										1
Hemangiosarcoma																										1
Malignant lymphoma, mixed type			X																							4
Orbital region																										
Carcinoma, NOS																										1

* Animals necropsied

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl): LOW DOSE

ANIMAL NUMBER	518	507	511	546	514	512	503	516	519	524	526	502	549	501	504	505	506	508	509	510	513	515	517	520	521
WEEKS ON STUDY	006	007	070	072	087	088	091	095	098	098	099	100	102	103	104	104	104	104	104	104	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS						X	X							X											
Fibroma													X												
Fibrosarcoma			X						X	X			X											X	
Neurilemoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic																			X						
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																	X	X							X
Sarcoma, NOS, metastatic						X																			
Trachea	+	+	–	–	+	+	–	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Malignant lymphoma, mixed type																									
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS, metastatic						X																			
Malig lymphoma, lymphocytic type																			X						
Malignant lymphoma, mixed type												X													
Thymus	+	–	+	–	+	–	–	+	–	+	–	+	–	+	–	+	+	+	+	+	+	–	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma												X										X			
Hepatocellular carcinoma				X	X					X	X	X							X			X			
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																		X							
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																									
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	–	+	+	+	+	+	+
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma																		X						X	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
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor														X											
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																			X				X		
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
Sarcoma, NOS																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Hepatocellular carcinoma, metastatic											X														
Mesothelioma, malignant					X																				
Malig lymphoma, lymphocytic type																									
Malignant lymphoma, mixed type											X														

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: LOW DOSE (Continued)

ANIMAL NUMBER	522	523	525	527	528	529	530	531	532	533	534	535	536	537	538	539	540	541	542	543	544	545	547	548	550	TOTAL TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS															X											4
Fibroma						X		X	X			X					X									6
Fibrosarcoma																										5
Neurilemoma																			X							1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic																										1
Alveolar/bronchiolar adenoma					X	X															X	X		X		5
Alveolar/bronchiolar carcinoma															X				X							5
Sarcoma, NOS, metastatic																										1
Trachea	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma	X						X																			2
Malignant lymphoma, mixed type										X										X						2
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, NOS, metastatic																										1
Malig lymphoma, lymphocytic type																										1
Malignant lymphoma, mixed type																						X				2
Thymus	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	–	38
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma		X	X	X		X		X		X	X	X										X	X	X	X	14
Hepatocellular carcinoma		X	X									X		X						X						12
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	N	+	+	N	+	+	+	+	+	N	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																										1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS																								X		1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	47
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma																	X									4
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Follicular cell adenoma													X	X												3
Parathyroid	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	–	–	+	+	+	+	43
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	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell tumor																										1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS																	X									3
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
Sarcoma, NOS												X														1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Hepatocellular carcinoma, metastatic																										1
Mesothelioma, malignant																										1
Malig lymphoma, lymphocytic type									X																	1
Malignant lymphoma, mixed type			X												X						X		X	X		6

* Animals necropsied

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl): HIGH DOSE

ANIMAL NUMBER	533	529	534	527	540	510	501	535	513	542	504	518	525	528	511	520	547	530	532	507	546	549	502	503	505
WEEKS ON STUDY	046	047	062	068	076	078	081	081	083	084	085	087	087	088	094	095	095	096	096	099	102	102	104	104	104
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sebaceous adenoma																									
Rhabdomyosarcoma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS														X							X				
Fibroma																			X						
Fibrosarcoma				X											X										
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic						X										X				X					
Alveolar/bronchiolar adenoma											X						X			X	X				
Alveolar/bronchiolar carcinoma						X															X		X		
Follicular cell carcinoma, metastatic									X																
Fibrosarcoma, metastatic				X																					
Trachea	+	+	+	−	+	−	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	−	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																					X				
Malignant lymphoma, mixed type																									
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malig lymphoma, lymphocytic type																									
Thymus	+	+	+	+	+	−	+	+	+	+	+	+	−	−	+	+	+	+	+	+	−	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
Myoepithelioma																									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma								X								X				X		X			X
Hepatocellular carcinoma					X	X	X	X		X						X			X	X	X				
Hepatoblastoma						X																			
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	N	N	+	N	N	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, mixed type																									
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenocarcinoma																						X			
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional cell papilloma																									
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	−	+	+
Adrenal	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																								X	
Cortical adenoma																									
Pheochromocytoma																									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																					X				
Follicular cell carcinoma									X						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	N	N	N	N
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS															X										
BODY CAVITIES																									
Mediastinum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Hepatocellular carcinoma, metastatic						X																			
Mesentery	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Hepatocellular carcinoma, invasive																X									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																			X						
Malig lymphoma, lymphocytic type											X														
Malig lymphoma, histiocytic type												X					X								
Malignant lymphoma, mixed type													X												

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: HIGH DOSE (Continued)

ANIMAL NUMBER	506	508	509	512	514	515	516	517	519	521	522	523	524	526	531	536	537	538	539	541	543	544	545	548	550	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sebaceous adenoma												X														1
Rhabdomyosarcoma																			X							1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS																						X				3
Fibroma	X																									2
Fibrosarcoma				X																						3
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic																										3
Alveolar/bronchiolar adenoma								X			X							X				X	X			9
Alveolar/bronchiolar carcinoma	X											X														5
Follicular cell carcinoma, metastatic																										1
Fibrosarcoma, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	–	+	+	+	–	+	43
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma													X													2
Malignant lymphoma, mixed type						X																				1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Malig. lymphoma, lymphocytic type																	X									1
Thymus	–	–	–	+	–	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	–	+	–	39
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Myoepithelioma																		X								1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma		X	X		X								X	X		X	X						X		X	14
Hepatocellular carcinoma									X	X														X		12
Hepatoblastoma																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	N	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Malignant lymphoma, mixed type											X															1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tubular cell adenocarcinoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Transitional cell papilloma										X																1
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	–	+	+	+	–	44
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	47
Adenoma, NOS																							X			2
Cortical adenoma				X								X														2
Pheochromocytoma					X																					1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	49
Follicular cell adenoma																									X	2
Follicular cell carcinoma																						X				3
Parathyroid	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	+	+	+	–	+	38
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
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS									X																	2
BODY CAVITIES																										
Mediastinum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Hepatocellular carcinoma, metastatic																										1
Mesentery	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Hepatocellular carcinoma, invasive																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS																										1
Malig. lymphoma, lymphocytic type								X																		2
Malig. lymphoma, histiocytic type	X																									3
Malignant lymphoma, mixed type			X							X						X					X	X	X		X	8

*Animals necropsied

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl): VEHICLE CONTROL

ANIMAL NUMBER	502	502	510	520	518	515	544	539	511	548	505	513	505	544	532	526	537	506	534	524	549	501	517	536	514
WEEKS ON STUDY	048	066	066	067	068	069	069	073	075	075	076	078	079	079	081	082	082	084	085	087	087	089	090	091	101
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																			X						
Fibrosarcoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																									
Sarcoma, NOS, invasive																									
Trachea	+	+	+	+	–	–	–	–	–	+	+	–	–	–	+	+	+	+	–	–	+	+	–	–	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	–	+	+	+	+	–	+	–	+	–	+	–	+	–	+	+	+	–	+	+	+	–
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Hepatocellular carcinoma																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	+	+	+	+	N	N	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	–	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																							X		
Adenomatous polyp, NOS																									
Large intestine	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	–	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	+
Adenoma, NOS								X										X	X						
Acidophil adenoma																									X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																									
Pheochromocytoma																									
Thyroid	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																									
Parathyroid	+	+	+	+	–	+	–	+	–	+	+	–	–	–	+	+	+	–	–	+	+	+	–	–	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell carcinoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																									
Vagina	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Hemangiosarcoma																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma																									
Endometrial stromal polyp																									
Endometrial stromal sarcoma																									
Hemangioma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS			X																						
BODY CAVITIES																									
Mediastinum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Sarcoma, NOS																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malig. lymphoma, lymphocytic type							X																		
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 B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: VEHICLE CONTROL (Continued)

ANIMAL NUMBER	530	531	541	546	503	504	507	508	509	512	516	519	521	522	523	527	528	529	533	535	538	540	543	545	547	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	102	102	103	103	104	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS																										1
Fibrosarcoma														X												1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																X										1
Alveolar/bronchiolar carcinoma	X																				X					2
Sarcoma, NOS, invasive	X																									1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	37
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	–	+	+	+	+	+	–	+	–	+	+	+	+	+	–	+	+	–	+	+	+	37
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma								X																X	X	3
Hepatocellular carcinoma																						X				1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	N	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenocarcinoma, NOS																										1
Adenomatous polyp, NOS																									X	1
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	12
Acidophil adenoma																										1
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma																			X							1
Pheochromocytoma													X													1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell adenoma								X		X			X						X	X	X				X	7
Parathyroid	+	+	+	+	+	+	+	+	+	+	–	+	+	–	+	+	+	+	+	+	–	+	+	+	+	37
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islet cell carcinoma													X													1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenocarcinoma, NOS								X																		1
Vagina	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Hemangiosarcoma																									X	1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma																						X				1
Endometrial stromal polyp			X																X			X				3
Endometrial stromal sarcoma																		X								1
Hemangioma																					X					1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	–	+	+	+	–	+	–	+	+	46
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS							X								X						X					4
BODY CAVITIES																										
Mediastinum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Sarcoma, NOS	X																									1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malig. lymphoma, lymphocytic type				X	X		X																	X		5
Malignant lymphoma, mixed type						X			X		X			X					X	X		X	X			10

* Animals necropsied

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl): LOW DOSE

ANIMAL NUMBER	544	515	516	502	537	513	514	524	522	525	507	546	549	512	529	536	510	518	531	506	517	519	541	527	550
WEEKS ON STUDY	006	023	038	067	071	072	077	079	079	079	081	081	081	082	082	082	083	085	085	088	090	091	091	092	092
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma									X		X														
Alveolar/bronchiolar carcinoma																									
Trachea	–	A	+	+	+	+	+	–	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	A	+	+	+	+	–	+	+	–	+	+	+	+	+	+	+	–	+	–	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Hepatocellular carcinoma																									
Malignant lymphoma, mixed type																					X				
Bile duct	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	A	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	N	+	+
Pancreas	+	A	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	A	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Small intestine	+	A	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+
Large intestine	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+
URINARY SYSTEM																									
Kidney	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenocarcinoma				X																					
Urinary bladder	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	–	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																									
Adenoma, NOS																									
Adrenal	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma																								X	
Thyroid	+	A	–	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																									
Follicular cell carcinoma																									
Parathyroid	–	A	–	+	+	+	+	–	–	–	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+
Pancreatic islets	+	A	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																									X
REPRODUCTIVE SYSTEM																									
Mammary gland	+	A	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+
Adenocarcinoma, NOS																									
Uterus	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Ovary	+	A	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Teratoma, NOS			X																						
NERVOUS SYSTEM																									
Brain	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, invasive																									
SPECIAL SENSE ORGANS																									
Harderian gland	N	A	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																									
Adenoma, NOS																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	A	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malig. lymphoma, lymphocytic type																									
Malignant lymphoma, mixed type																			X			X		X	

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: LOW DOSE (Continued)

ANIMAL NUMBER	503	545	540	532	501	503	504	505	508	509	511	520	521	523	526	528	530	533	538	539	542	543	547	548	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	093	096	101	104	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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma																									2
Alveolar/bronchiolar carcinoma												X													1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	48
Thymus	−	+	−	+	+	−	+	+	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	40
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular adenoma	X																		X						2
Hepatocellular carcinoma																				X					1
Malignant lymphoma, mixed type																									1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	N	+	+	N	+	+	+	N	N	+	+	+	+	+	*49
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Squamous cell papilloma																			X			X			2
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tubular cell adenocarcinoma																									1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	+	+	+	+	+	+	46
Carcinoma, NOS																					X				1
Adenoma, NOS	X					X				X		X		X	X					X			X		8
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma																									1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Follicular cell adenoma						X									X		X							X	4
Follicular cell carcinoma														X						X					2
Parathyroid	+	+	+	+	−	+	+	+	+	−	−	−	−	+	−	+	+	+	+	+	+	+	+	+	37
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Islet cell adenoma																									1
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*49
Adenocarcinoma, NOS																	X								1
Uterus	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hemangioma										X															1
Ovary	+	+	+	+	+	+	+	+	+	−	−	−	+	+	−	+	−	+	+	+	+	+	+	+	42
Teratoma, NOS																									1
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, NOS, invasive																					X				1
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*49
Carcinoma, NOS																							X		1
Adenoma, NOS							X										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	*49
Malig. lymphoma, lymphocytic type								X	X																2
Malignant lymphoma, mixed type			X				X				X								X		X			X	9

* Animals necropsied

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl): HIGH DOSE

ANIMAL NUMBER	546	516	521	528	541	535	522	520	540	503	538	542	505	515	523	525	524	545	513	544	502	504	509	512	530
WEEKS ON STUDY	006	057	057	064	067	069	070	072	075	079	079	080	081	082	084	085	088	089	090	091	092	093	096	096	096
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																									
Neurilemoma, malignant																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS, metastatic																	X								
Alveolar/bronchiolar adenoma															X										
Trachea	+	+	+	+	–	+	+	+	+	–	–	+	+	+	+	–	+	+	+	–	+	+	+	–	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, NOS																									
Malignant lymphoma, mixed type																									
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	–	–	+	+	–	–	+	+	+	+	+	+	+	+	+	–	–	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+
Adenocarcinoma, NOS																	X								
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma					X																				
Hepatocellular carcinoma																			X						
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																									
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Squamous cell carcinoma, invasive																									
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, mixed type																									
Large intestine	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenocarcinoma			X																						
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	–	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	–	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	–	+	–	+	+	+	+	+	–
Adenoma, NOS						X							X											X	
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Pheochromocytoma																									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																									
Parathyroid	–	–	–	+	+	+	+	+	+	+	–	+	+	+	+	–	–	+	+	–	+	+	+	–	–
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																									
Adenosquamous carcinoma							X																		
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma																									
Hemangiosarcoma, unc prim or metas																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malig. lymphoma, undiffer type																									
Malig. lymphoma, lymphocytic type																						X			
Malig. lymphoma, histiocytic type				X																X					
Malignant lymphoma, mixed type																									X

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: HIGH DOSE (Continued)

ANIMAL NUMBER	507	539	517	511	527	501	506	508	510	514	518	519	526	529	531	532	533	534	536	537	543	547	548	549	550	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	097	097	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																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibrosarcoma										X																1
Neurilemoma, malignant																X										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS, metastatic																										1
Alveolar/bronchiolar adenoma	X																			X						3
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Malignant lymphoma, NOS	X																									1
Malignant lymphoma, mixed type						X																				1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	–	+	+	+	+	–	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	41
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma, NOS																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma	X	X		X							X		X					X								7
Hepatocellular carcinoma	X	X	X			X							X													6
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma		X																								1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma				X																						1
Squamous cell carcinoma, invasive		X																								1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Malignant lymphoma, mixed type										X																1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tubular cell adenocarcinoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Adenoma, NOS		X		X		X	X		X							X			X	X	X	X		X	X	15
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS								X																		1
Pheochromocytoma																				X						1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell adenoma						X	X								X		X				X					5
Parathyroid	+	+	+	–	+	+	–	+	+	+	+	–	+	+	–	+	+	+	+	+	+	+	+	+	+	37
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenocarcinoma, NOS															X											1
Adenosquamous carcinoma																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyoma																				X						1
Hemangiosarcoma, unc prim or metas													X													1
Ovary	+	+	+	+	+	+	–	+	–	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	47
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS		X																								1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malig. lymphoma, undiffer type														X												1
Malig. lymphoma, lymphocytic type				X			X	X	X									X								6
Malig. lymphoma, histiocytic type																										2
Malignant lymphoma, mixed type					X							X	X			X					X	X		X		8

* Animals necropsied

APPENDIX C

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{23}, 43% CHLORINE)

TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl)

	CONTROL (VEH)	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%)	
Hyperkeratosis	1 (2%)		
*Subcutaneous tissue	(50)	(50)	(50)
Edema, NOS	1 (2%)		
Hemorrhage	1 (2%)		1 (2%)
Hemorrhagic cyst	1 (2%)		
Inflammation, suppurative			1 (2%)
Inflammation, pyogranulomatous	1 (2%)		
Necrosis, ischemic		1 (2%)	
RESPIRATORY SYSTEM			
*Nasal cavity	(50)	(50)	(50)
Foreign body, NOS		3 (6%)	3 (6%)
Inflammation, suppurative	5 (10%)	14 (28%)	11 (22%)
Inflammation, chronic		1 (2%)	
Infection, fungal	4 (8%)	11 (22%)	7 (14%)
Hyperplasia, NOS	1 (2%)		
Hyperplasia, epithelial	2 (4%)	4 (8%)	2 (4%)
Metaplasia, squamous	2 (4%)		2 (4%)
#Peritracheal tissue	(50)	(50)	(49)
Necrosis, NOS			1 (2%)
#Lung	(50)	(50)	(50)
Congestion, NOS		2 (4%)	1 (2%)
Hemorrhage			2 (4%)
Lymphocytic inflammatory infiltrate			1 (2%)
Inflammation, interstitial		1 (2%)	
Pneumonia, aspiration	1 (2%)	2 (4%)	4 (8%)
Inflammation, acute suppurative	1 (2%)		
Inflammation, granulomatous focal	1 (2%)	2 (4%)	
Alveolar macrophages		8 (16%)	
Hyperplasia, adenomatous	3 (6%)	2 (4%)	
#Lung/alveoli	(50)	(50)	(50)
Histiocytosis	1 (2%)	1 (2%)	
HEMATOPOIETIC SYSTEM			
#Bone marrow	(50)	(50)	(50)
Atrophy, NOS	1 (2%)	1 (2%)	
Myelofibrosis		1 (2%)	1 (2%)
Hyperplasia, hematopoietic			1 (2%)
Hyperplasia, granulocytic		1 (2%)	
#Spleen	(50)	(50)	(50)
Accessory structure	1 (2%)		1 (2%)
Congestion, NOS		30 (60%)	32 (64%)
Hemorrhage		1 (2%)	
Fibrosis, focal	1 (2%)		5 (10%)
Fibrosis, diffuse		1 (2%)	
Pigmentation, NOS	2 (4%)		
Hyperplasia, nodular		1 (2%)	1 (2%)
Hyperplasia, stromal	1 (2%)		1 (2%)
Metaplasia, osseous			1 (2%)
Hyperplasia, lymphoid		2 (4%)	2 (4%)
Hematopoiesis	3 (6%)	1 (2%)	

TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
HEMATOPOIETIC SYSTEM (Continued)			
#Mandibular lymph node	(50)	(50)	(50)
Inflammation, suppurative		1 (2%)	
Hyperplasia, lymphoid	1 (2%)	5 (10%)	
#Mediastinal lymph node	(50)	(50)	(50)
Inflammation, granulomatous		1 (2%)	
Pigmentation, NOS		1 (2%)	1 (2%)
Hyperplasia, lymphoid			3 (6%)
#Celiac lymph node	(50)	(50)	(50)
Hyperplasia, lymphoid	1 (2%)		
#Pancreatic lymph node	(50)	(50)	(50)
Edema, NOS		1 (2%)	
Inflammation, granulomatous		29 (58%)	23 (46%)
Pigmentation, NOS			1 (2%)
Angiectasis			1 (2%)
Hyperplasia, lymphoid		27 (54%)	19 (38%)
#Mesenteric lymph node	(50)	(50)	(50)
Congestion, NOS			1 (2%)
Inflammation, granulomatous		8 (16%)	11 (22%)
Pigmentation, NOS		4 (8%)	2 (4%)
Angiectasis			1 (2%)
Hyperplasia, lymphoid		5 (10%)	5 (10%)
#Adrenal	(50)	(50)	(50)
Hematopoiesis		1 (2%)	
#Adrenal cortex	(50)	(50)	(50)
Hematopoiesis	1 (2%)		1 (2%)
CIRCULATORY SYSTEM			
*Multiple organs	(50)	(50)	(50)
Periarteritis		1 (2%)	1 (2%)
*Tail	(50)	(50)	(50)
Thrombosis, NOS		1 (2%)	
#Mandibular lymph node	(50)	(50)	(50)
Lymphangiectasis		2 (4%)	2 (4%)
#Mediastinal lymph node	(50)	(50)	(50)
Lymphangiectasis		1 (2%)	2 (4%)
#Pancreatic lymph node	(50)	(50)	(50)
Lymphangiectasis			1 (2%)
#Mesenteric lymph node	(50)	(50)	(50)
Lymphangiectasis	1 (2%)		1 (2%)
#Renal lymph node	(50)	(50)	(50)
Lymphangiectasis		1 (2%)	
#Inguinal lymph node	(50)	(50)	(50)
Lymphangiectasis		2 (4%)	
#Heart	(50)	(50)	(50)
Periarteritis			2 (4%)
#Heart/atrium	(50)	(50)	(50)
Thrombosis, NOS		1 (2%)	
Thrombus, mural		1 (2%)	7 (14%)
#Auricular appendage	(50)	(50)	(50)
Thrombus, mural	1 (2%)		
#Myocardium	(50)	(50)	(50)
Inflammation, acute/chronic		1 (2%)	
Inflammation, chronic	41 (82%)	47 (94%)	41 (82%)
*Pulmonary artery	(50)	(50)	(50)
Mineralization		1 (2%)	
Thrombosis, NOS			1 (2%)
Thrombus, mural			1 (2%)

TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
CIRCULATORY SYSTEM (Continued)			
*Sup. panc-duod. artery	(50)	(50)	(50)
Thrombosis, NOS			1 (2%)
Periarteritis		1 (2%)	
Arteriosclerosis, NOS			5 (10%)
Hypertrophy, NOS		1 (2%)	
*Mesenteric artery	(50)	(50)	(50)
Mineralization			1 (2%)
*Renal artery	(50)	(50)	(50)
Thrombosis, NOS		1 (2%)	
*Hepatic vein	(50)	(50)	(50)
Dilatation, NOS	1 (2%)		
Thrombus, mural			1 (2%)
#Salivary gland	(50)	(50)	(50)
Periarteritis			1 (2%)
#Liver	(50)	(50)	(50)
Thrombosis, NOS			1 (2%)
#Pancreas	(49)	(50)	(50)
Periarteritis	1 (2%)	2 (4%)	2 (4%)
#Stomach	(50)	(50)	(50)
Periarteritis		2 (4%)	5 (10%)
*Mesentery	(50)	(50)	(50)
Periarteritis	1 (2%)	1 (2%)	1 (2%)
DIGESTIVE SYSTEM			
*Soft palate	(50)	(50)	(50)
Hyperplasia, epithelial	1 (2%)		
Hyperkeratosis	1 (2%)		
#Salivary gland	(50)	(50)	(50)
Inflammation, chronic	1 (2%)		
#Liver	(50)	(50)	(50)
Deformity, NOS	1 (2%)	2 (4%)	
Cyst, NOS			1 (2%)
Multiple cysts		1 (2%)	
Hemorrhage			1 (2%)
Lymphocytic inflammatory infiltrate		42 (84%)	44 (88%)
Inflammation, granulomatous focal		49 (98%)	49 (98%)
Cholangiofibrosis	1 (2%)		3 (6%)
Degeneration, cystic	1 (2%)		
Pigmentation, NOS		45 (90%)	46 (92%)
Cytoplasmic vacuolization	2 (4%)		
Focal cellular change	1 (2%)	1 (2%)	
Hyperplasia, nodular			6 (12%)
Angiectasis			1 (2%)
#Liver/centrilobular	(50)	(50)	(50)
Degeneration, NOS	1 (2%)	1 (2%)	1 (2%)
Necrosis, coagulative	2 (4%)		1 (2%)
Cytoplasmic vacuolization	5 (10%)		1 (2%)
#Liver/periportal	(50)	(50)	(50)
Fibrosis, multifocal		1 (2%)	
#Bile duct	(50)	(50)	(50)
Hyperplasia, NOS	42 (84%)	36 (72%)	34 (68%)
Hyperplasia, focal		1 (2%)	
#Pancreas	(49)	(50)	(50)
Inflammation, chronic focal			2 (4%)
Fibrosis, focal			1 (2%)
#Pancreatic acinus	(49)	(50)	(50)
Atrophy, NOS	12 (24%)	11 (22%)	9 (18%)
Atrophy, focal		1 (2%)	
Hyperplasia, NOS	8 (16%)	2 (4%)	
Hyperplasia, focal	1 (2%)		1 (2%)

TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM (Continued)			
#Glandular stomach	(50)	(50)	(50)
Edema, NOS			1 (2%)
#Gastric submucosa	(50)	(50)	(50)
Edema, NOS	2 (4%)	1 (2%)	
Inflammation, chronic			1 (2%)
Inflammation, granulomatous			1 (2%)
#Forestomach	(50)	(50)	(50)
Edema, NOS			1 (2%)
Ulcer, NOS	1 (2%)	1 (2%)	1 (2%)
Inflammation, chronic	2 (4%)	1 (2%)	1 (2%)
Inflammation, chronic focal			1 (2%)
Necrosis, NOS			1 (2%)
Hyperplasia, epithelial	4 (8%)		1 (2%)
Hyperplasia, papillary			1 (2%)
Hyperkeratosis	1 (2%)		
#Colon	(50)	(50)	(50)
Edema, NOS			1 (2%)
Parasitism	3 (6%)	4 (8%)	4 (8%)
#Colonic submucosa	(50)	(50)	(50)
Inflammation, acute/chronic			1 (2%)
#Cecum	(50)	(50)	(50)
Edema, NOS			1 (2%)
Parasitism	1 (2%)	3 (6%)	2 (4%)
*Rectum	(50)	(50)	(50)
Parasitism		1 (2%)	1 (2%)
URINARY SYSTEM			
#Kidney	(50)	(50)	(50)
Hydronephrosis	1 (2%)		
Inflammation, suppurative		1 (2%)	
Scar	1 (2%)		
Nephropathy	48 (96%)	47 (94%)	46 (92%)
Infarct, NOS		1 (2%)	
Pigmentation, NOS			1 (2%)
#Kidney/cortex	(50)	(50)	(50)
Cyst, NOS	1 (2%)	1 (2%)	
#Kidney/medulla	(50)	(50)	(50)
Cyst, NOS	1 (2%)		
#Kidney/tubule	(50)	(50)	(50)
Pigmentation, NOS		3 (6%)	2 (4%)
#Kidney/pelvis	(50)	(50)	(50)
Hemorrhage			1 (2%)
#Urinary bladder	(50)	(50)	(48)
Mucocele			1 (2%)
Hemorrhage		1 (2%)	
Fibrosis	1 (2%)		
Hyperplasia, epithelial	1 (2%)	1 (2%)	
Metaplasia, squamous	1 (2%)		
ENDOCRINE SYSTEM			
#Pituitary	(49)	(49)	(47)
Angiectasis	1 (2%)		
#Pituitary intermedia	(49)	(49)	(47)
Cyst, NOS		1 (2%)	
#Anterior pituitary	(49)	(49)	(47)
Cyst, NOS	5 (10%)	6 (12%)	2 (4%)
Multiple cysts		1 (2%)	
Hyperplasia, focal	7 (14%)	4 (8%)	5 (11%)
Angiectasis	12 (24%)	7 (14%)	10 (21%)

TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM (Continued)			
#Adrenal	(50)	(50)	(50)
Lymphocytic inflammatory infiltrate			1 (2%)
Hypertrophy, focal	1 (2%)		
Angiectasis	1 (2%)	1 (2%)	
#Adrenal cortex	(50)	(50)	(50)
Lymphocytic inflammatory infiltrate			1 (2%)
Degeneration, cystic		1 (2%)	1 (2%)
Degeneration, lipoid	5 (10%)	3 (6%)	1 (2%)
Pigmentation, NOS			1 (2%)
Cytoplasmic vacuolization		2 (4%)	3 (6%)
Hyperplasia, focal		1 (2%)	1 (2%)
Angiectasis		1 (2%)	
#Adrenal medulla	(50)	(50)	(50)
Hyperplasia, focal	7 (14%)	8 (16%)	5 (10%)
Angiectasis	2 (4%)	1 (2%)	
#Thyroid	(50)	(50)	(49)
Embryonal duct cyst	1 (2%)		
Cystic follicles	1 (2%)	1 (2%)	
Hyperplasia, cystic		1 (2%)	
Hyperplasia, C-cell	3 (6%)	2 (4%)	3 (6%)
#Thyroid follicle	(50)	(50)	(49)
Follicular cyst, NOS		1 (2%)	
#Parathyroid	(50)	(50)	(49)
Hyperplasia, NOS			1 (2%)
Angiectasis		1 (2%)	
#Pancreatic islets	(49)	(50)	(50)
Hyperplasia, focal	1 (2%)		
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Cystic ducts	6 (12%)	4 (8%)	3 (6%)
Adenosis		1 (2%)	
*Mammary lobule	(50)	(50)	(50)
Hyperplasia, NOS	3 (6%)	3 (6%)	
*Preputial gland	(50)	(50)	(50)
Cystic ducts	1 (2%)	8 (16%)	1 (2%)
Lymphocytic inflammatory infiltrate	1 (2%)	1 (2%)	
Inflammation, suppurative	3 (6%)	4 (8%)	2 (4%)
Inflammation, acute/chronic			1 (2%)
Inflammation, chronic	1 (2%)	3 (6%)	5 (10%)
Inflammation, chronic focal			1 (2%)
Atrophy, NOS	1 (2%)	2 (4%)	1 (2%)
Hyperplasia, NOS	1 (2%)	1 (2%)	
#Prostate	(49)	(50)	(50)
Cyst, NOS	1 (2%)		
Inflammation, suppurative	12 (24%)	9 (18%)	17 (34%)
Inflammation, chronic	2 (4%)	1 (2%)	
Inflammation, chronic suppurative	3 (6%)	2 (4%)	
Hyperplasia, epithelial	1 (2%)	2 (4%)	
*Seminal vesicle	(50)	(50)	(50)
Dilatation, NOS			1 (2%)
#Testis	(50)	(50)	(50)
Necrosis, focal		1 (2%)	
Atrophy, NOS	18 (36%)	13 (26%)	8 (16%)
Hyperplasia, interstitial cell	2 (4%)	3 (6%)	3 (6%)
*Epididymis	(50)	(50)	(50)
Inflammation, chronic focal		1 (2%)	
*Spermatic cord	(50)	(50)	(50)
Steatitis	5 (10%)	1 (2%)	4 (8%)

TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
NERVOUS SYSTEM			
#Cerebrum	(50)	(50)	(49)
Status spongiosus	1 (2%)		
#Brain	(50)	(50)	(49)
Deformity, NOS		1 (2%)	1 (2%)
Hemorrhage			2 (4%)
SPECIAL SENSE ORGANS			
*Eye	(50)	(50)	(50)
Retinopathy	2 (4%)	24 (48%)	24 (48%)
Cataract	1 (2%)	22 (44%)	19 (38%)
Phthisis bulbi		1 (2%)	
*Vitreous body	(50)	(50)	(50)
Hemorrhage		1 (2%)	
*External ear	(50)	(50)	(50)
Inflammation, suppurative		1 (2%)	
MUSCULOSKELETAL SYSTEM			
*Skull	(50)	(50)	(50)
Hyperostosis		1 (2%)	
BODY CAVITIES			
*Mediastinum	(50)	(50)	(50)
Lymphocytic inflammatory infiltrate			1 (2%)
*Mesentery	(50)	(50)	(50)
Steatitis	4 (8%)	5 (10%)	2 (4%)
Lymphocytic inflammatory infiltrate			3 (6%)
Inflammation, acute/chronic			1 (2%)
Reaction, foreign body	1 (2%)		
Pigmentation, NOS	1 (2%)		
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Lymphocytic inflammatory infiltrate			1 (2%)
Tail			
Epidermal inclusion cyst		1	
Foot			
Inflammation, acute/chronic			1
Hyperkeratosis			1
Omentum			
Steatitis	1	1	
SPECIAL MORPHOLOGY SUMMARY			
None			

Number of animals with tissue examined microscopically
* Number of animals necropsied

TABLE C2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl)

	CONTROL (VEH)	LOW DOSE	MID DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS NECROPSIED	50	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50	50
INTEGUMENTARY SYSTEM				
*Skin	(50)	(50)	(50)	(50)
Epidermal inclusion cyst				2 (4%)
Ulcer, NOS				1 (2%)
Inflammation, suppurative			1 (2%)	2 (4%)
Inflammation, chronic				6 (12%)
Ulcer, chronic			1 (2%)	
Fibrosis				1 (2%)
Hyperplasia, NOS				1 (2%)
Hyperplasia, epithelial				2 (4%)
Hyperplasia, focal				1 (2%)
Hyperkeratosis	1 (2%)	1 (2%)		16 (32%)
Acanthosis		1 (2%)		
*Subcutaneous tissue	(50)	(50)	(50)	(50)
Hemorrhage		1 (2%)		
Steatitis			1 (2%)	
Inflammation, chronic				2 (4%)
Abscess, chronic				1 (2%)
RESPIRATORY SYSTEM				
*Nasal cavity	(50)	(50)	(50)	(50)
Foreign body, NOS				1 (2%)
Ulcer, NOS		1 (2%)		1 (2%)
Inflammation, suppurative	1 (2%)	4 (8%)		3 (6%)
Infection, fungal	1 (2%)	4 (8%)		2 (4%)
Hyperplasia, epithelial		2 (4%)		2 (4%)
Metaplasia, squamous		1 (2%)		
#Lung	(50)	(50)	(49)	(50)
Atelectasis			1 (2%)	
Congestion, NOS	1 (2%)	1 (2%)		2 (4%)
Lymphocytic inflammatory infiltrate				1 (2%)
Inflammation, interstitial				1 (2%)
Pneumonia, aspiration		1 (2%)	1 (2%)	4 (8%)
Bronchopneumonia, acute			1 (2%)	
Inflammation, acute/chronic				1 (2%)
Inflammation, granulomatous focal				1 (2%)
Pigmentation, NOS		2 (4%)		2 (4%)
Hemosiderosis				1 (2%)
Alveolar macrophages		2 (4%)	1 (2%)	3 (6%)
Hyperplasia, adenomatous		1 (2%)		1 (2%)
#Lung/alveoli	(50)	(50)	(49)	(50)
Edema, NOS				1 (2%)
Hemorrhage			1 (2%)	
Histiocytosis			1 (2%)	
HEMATOPOIETIC SYSTEM				
*Multiple organs	(50)	(50)	(50)	(50)
Hyperplasia, lymphoid			1 (2%)	
#Bone marrow	(49)	(50)	(50)	(50)
Atrophy, diffuse				1 (2%)
Myelofibrosis	1 (2%)			
Hyperplasia, reticulum cell		1 (2%)		

TABLE C2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) (Continued)

	CONTROL (VEH)	LOW DOSE	MID DOSE	HIGH DOSE
HEMATOPOIETIC SYSTEM (Continued)				
#Spleen	(50)	(50)	(50)	(50)
Ectopia			1 (2%)	
Congestion, NOS		21 (42%)	32 (64%)	33 (66%)
Fibrosis	1 (2%)			
Pigmentation, NOS	2 (4%)			
Hyperplasia, nodular				2 (4%)
Hyperplasia, lymphoid		1 (2%)	8 (16%)	
Hematopoiesis	2 (4%)	2 (4%)	2 (4%)	4 (8%)
#Mandibular lymph node	(50)	(50)	(50)	(50)
Hyperplasia, lymphoid			2 (4%)	4 (8%)
#Cervical lymph node	(50)	(50)	(50)	(50)
Hyperplasia, NOS	1 (2%)			
#Mediastinal lymph node	(50)	(50)	(50)	(50)
Inflammation, granulomatous				1 (2%)
Pigmentation, NOS				1 (2%)
Hyperplasia, lymphoid		1 (2%)	3 (6%)	2 (4%)
#Celiac lymph node	(50)	(50)	(50)	(50)
Inflammation, granulomatous			1 (2%)	
Hyperplasia, lymphoid			1 (2%)	
#Pancreatic lymph node	(50)	(50)	(50)	(50)
Congestion, NOS				2 (4%)
Edema, NOS		1 (2%)	2 (4%)	
Inflammation, granulomatous		19 (38%)	21 (42%)	20 (40%)
Pigmentation, NOS		7 (14%)	2 (4%)	1 (2%)
Angiectasis			2 (4%)	2 (4%)
Hyperplasia, lymphoid		19 (38%)	22 (44%)	23 (46%)
#Mesenteric lymph node	(50)	(50)	(50)	(50)
Inflammation, granulomatous		1 (2%)	4 (8%)	6 (12%)
Pigmentation, NOS		1 (2%)		2 (4%)
Angiectasis	3 (6%)		1 (2%)	
Hyperplasia, lymphoid			3 (6%)	5 (10%)
#Inguinal lymph node	(50)	(50)	(50)	(50)
Hyperplasia, lymphoid				1 (2%)
#Lung	(50)	(50)	(49)	(50)
Leukocytosis, NOS			1 (2%)	
#Peyer's patch	(49)	(49)	(50)	(50)
Hyperplasia, lymphoid		2 (4%)		
#Uterus	(50)	(50)	(50)	(50)
Hyperplasia, lymphoid			1 (2%)	
#Adrenal cortex	(50)	(50)	(50)	(50)
Hematopoiesis	1 (2%)			
CIRCULATORY SYSTEM				
#Mesenteric lymph node	(50)	(50)	(50)	(50)
Lymphangiectasis			2 (4%)	
#Heart	(50)	(50)	(50)	(50)
Endocarditis, bacterial		1 (2%)		
#Heart/atrium	(50)	(50)	(50)	(50)
Thrombus, mural			2 (4%)	
#Myocardium	(50)	(50)	(50)	(50)
Lymphocytic inflammatory infiltrate				1 (2%)
Inflammation, acute/chronic				1 (2%)
Inflammation, chronic	33 (66%)	36 (72%)	31 (62%)	34 (68%)
Inflammation, chronic focal		1 (2%)	1 (2%)	
#Liver	(50)	(50)	(50)	(50)
Periarteritis		1 (2%)		
#Pancreas	(50)	(50)	(50)	(50)
Periarteritis			1 (2%)	
*Mesentery	(50)	(50)	(50)	(50)
Periarteritis			1 (2%)	

TABLE C2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) (Continued)

	CONTROL (VEH)	LOW DOSE	MID DOSE	HIGH DOSE
DIGESTIVE SYSTEM				
#Salivary gland	(50)	(50)	(50)	(50)
Cystic ducts				1 (2%)
Inflammation, chronic			1 (2%)	
Atrophy, focal				1 (2%)
#Liver	(50)	(50)	(50)	(50)
Deformity, NOS	3 (6%)	3 (6%)	2 (4%)	2 (4%)
Cyst, NOS			1 (2%)	1 (2%)
Multiple cysts				1 (2%)
Congestion, NOS				2 (4%)
Lymphocytic inflammatory infiltrate	3 (6%)	44 (88%)	45 (90%)	41 (82%)
Inflammation, granulomatous focal	4 (8%)	48 (96%)	49 (98%)	50 (100%)
Cholangiofibrosis				4 (8%)
Degeneration, NOS				2 (4%)
Degeneration, cystic			1 (2%)	
Necrosis, focal		1 (2%)		
Necrosis, coagulative			2 (4%)	1 (2%)
Pigmentation, NOS		45 (90%)	47 (94%)	47 (94%)
Cytoplasmic vacuolization	2 (4%)		2 (4%)	
Focal cellular change	1 (2%)	1 (2%)		
Cytologic alteration, NOS			1 (2%)	1 (2%)
Hyperplasia, nodular		4 (8%)	6 (12%)	5 (10%)
Angiectasis		1 (2%)	1 (2%)	
#Liver/centrilobular	(50)	(50)	(50)	(50)
Degeneration, NOS	2 (4%)	1 (2%)		1 (2%)
Necrosis, NOS		1 (2%)		
#Bile duct	(50)	(50)	(50)	(50)
Dilatation, NOS			1 (2%)	
Retention of content				1 (2%)
Cyst, NOS			1 (2%)	
Multiple cysts		1 (2%)		1 (2%)
Cystic ducts				1 (2%)
Hyperplasia, NOS	1 (2%)	1 (2%)	2 (4%)	3 (6%)
Hyperplasia, cystic			4 (8%)	2 (4%)
#Pancreas	(50)	(50)	(50)	(50)
Lymphocytic inflammatory infiltrate			1 (2%)	1 (2%)
#Pancreatic acinus	(50)	(50)	(50)	(50)
Atrophy, NOS	2 (4%)	1 (2%)	1 (2%)	4 (8%)
Atrophy, focal	2 (4%)		1 (2%)	4 (8%)
Hyperplasia, NOS				5 (10%)
Hyperplasia, focal	2 (4%)		1 (2%)	
#Glandular stomach	(50)	(50)	(50)	(50)
Inflammation, acute/chronic			1 (2%)	
Inflammation, chronic				1 (2%)
#Gastric submucosa	(50)	(50)	(50)	(50)
Cyst, NOS	1 (2%)			
Edema, NOS				1 (2%)
Inflammation, chronic				1 (2%)
#Forestomach	(50)	(50)	(50)	(50)
Edema, NOS	1 (2%)		1 (2%)	
Ulcer, NOS		1 (2%)		
Inflammation, acute/chronic			1 (2%)	
Inflammation, chronic		3 (6%)	2 (4%)	2 (4%)
Ulcer, chronic				1 (2%)
Inflammation, chronic focal		1 (2%)		
Inflammation, chronic diffuse			1 (2%)	
Hyperplasia, epithelial		1 (2%)	3 (6%)	4 (8%)
Hyperkeratosis			1 (2%)	
#Colon	(50)	(49)	(50)	(49)
Parasitism	6 (12%)	3 (6%)	1 (2%)	4 (8%)
#Colonic mucosa	(50)	(49)	(50)	(49)
Hyperplasia, epithelial				1 (2%)

TABLE C2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) (Continued)

	CONTROL (VEH)	LOW DOSE	MID DOSE	HIGH DOSE
DIGESTIVE SYSTEM (Continued)				
#Cecum	(50)	(49)	(50)	(49)
Parasitism	1 (2%)	6 (12%)	2 (4%)	1 (2%)
*Rectum	(50)	(50)	(50)	(50)
Parasitism				2 (4%)
URINARY SYSTEM				
#Kidney	(50)	(50)	(50)	(50)
Pyelonephritis, NOS			1 (2%)	
Lymphocytic inflammatory infiltrate		1 (2%)	2 (4%)	
Inflammation, chronic			1 (2%)	
Nephropathy	13 (26%)	19 (38%)	27 (54%)	32 (64%)
Necrosis, ischemic		1 (2%)		
Pigmentation, NOS				4 (8%)
#Kidney/tubule	(50)	(50)	(50)	(50)
Pigmentation, NOS	2 (4%)	20 (40%)	30 (60%)	25 (50%)
#Kidney/pelvis	(50)	(50)	(50)	(50)
Mineralization	1 (2%)			
Hyperplasia, epithelial	1 (2%)			
#Urinary bladder	(50)	(50)	(50)	(50)
Lymphocytic inflammatory infiltrate		1 (2%)		
Inflammation, chronic			1 (2%)	
Hyperplasia, epithelial		1 (2%)	1 (2%)	
ENDOCRINE SYSTEM				
#Pituitary	(50)	(50)	(50)	(50)
Cyst, NOS	2 (4%)	1 (2%)		1 (2%)
Hyperplasia, focal	4 (8%)			
Angiectasis	7 (14%)			
#Anterior pituitary	(50)	(50)	(50)	(50)
Cyst, NOS	7 (14%)	5 (10%)	8 (16%)	3 (6%)
Multiple cysts		1 (2%)	1 (2%)	1 (2%)
Hemorrhagic cyst		1 (2%)		
Hyperplasia, NOS	1 (2%)		1 (2%)	
Hyperplasia, focal	2 (4%)	3 (6%)	5 (10%)	3 (6%)
Angiectasis	16 (32%)	21 (42%)	19 (38%)	19 (38%)
#Adrenal	(50)	(50)	(50)	(50)
Hemorrhage		1 (2%)		
Lymphocytic inflammatory infiltrate				1 (2%)
Degeneration, NOS			1 (2%)	
Pigmentation, NOS			1 (2%)	
Angiectasis		1 (2%)	2 (4%)	2 (4%)
#Adrenal cortex	(50)	(50)	(50)	(50)
Accessory structure	1 (2%)			
Cyst, NOS		1 (2%)	1 (2%)	
Lymphocytic inflammatory infiltrate			1 (2%)	
Degeneration, NOS			2 (4%)	
Degeneration, cystic			1 (2%)	
Degeneration, lipoid	5 (10%)	4 (8%)	5 (10%)	
Cytoplasmic vacuolization	1 (2%)	1 (2%)	2 (4%)	2 (4%)
Atrophy, NOS			1 (2%)	
Hypertrophy, focal		1 (2%)	1 (2%)	
Hyperplasia, NOS			3 (6%)	1 (2%)
Hyperplasia, focal		2 (4%)		
Angiectasis			4 (8%)	3 (6%)
#Adrenal medulla	(50)	(50)	(50)	(50)
Hyperplasia, focal	6 (12%)	3 (6%)	1 (2%)	6 (12%)

TABLE C2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) (Continued)

	CONTROL (VEH)	LOW DOSE	MID DOSE	HIGH DOSE
ENDOCRINE SYSTEM (Continued)				
#Thyroid	(50)	(48)	(50)	(50)
Embryonal duct cyst	2 (4%)			1 (2%)
Cystic follicles		1 (2%)		
Hemorrhage				1 (2%)
Hyperplasia, C-cell	4 (8%)	5 (10%)	5 (10%)	6 (12%)
REPRODUCTIVE SYSTEM				
*Mammary gland	(50)	(50)	(50)	(50)
Cystic ducts	27 (54%)	16 (32%)	14 (28%)	11 (22%)
Hyperplasia, cystic	3 (6%)	2 (4%)	1 (2%)	2 (4%)
Adenosis	4 (8%)			
*Mammary lobule	(50)	(50)	(50)	(50)
Hyperplasia, NOS	4 (8%)	5 (10%)	2 (4%)	1 (2%)
*Clitoral gland	(50)	(50)	(50)	(50)
Cystic ducts	4 (8%)	2 (4%)	1 (2%)	4 (8%)
Lymphocytic inflammatory infiltrate		1 (2%)		
Inflammation, suppurative	1 (2%)	1 (2%)		
Fibrosis		1 (2%)		
Hyperplasia, NOS	1 (2%)			1 (2%)
Hyperplasia, epithelial				1 (2%)
#Uterus	(50)	(50)	(50)	(50)
Dilatation, NOS	3 (6%)	2 (4%)		1 (2%)
#Cervix uteri	(50)	(50)	(50)	(50)
Inflammation, suppurative	1 (2%)			
#Uterus/endometrium	(50)	(50)	(50)	(50)
Cyst, NOS		2 (4%)	1 (2%)	4 (8%)
Hemorrhage				1 (2%)
Inflammation, suppurative				1 (2%)
Inflammation, chronic			1 (2%)	
Hyperplasia, epithelial	3 (6%)		1 (2%)	1 (2%)
Hyperplasia, cystic	11 (22%)	19 (38%)	25 (50%)	22 (44%)
Decidual alteration, NOS		1 (2%)		
#Ovary	(50)	(50)	(50)	(50)
Cyst, NOS		1 (2%)		1 (2%)
Cystic follicles	2 (4%)			1 (2%)
Follicular cyst, NOS			1 (2%)	
NERVOUS SYSTEM				
#Brain/meninges	(50)	(50)	(50)	(50)
Inflammation, chronic	1 (2%)			
#Cerebrum	(50)	(50)	(50)	(50)
Hemorrhage		1 (2%)		
Hemorrhagic cyst	1 (2%)			
Gliosis	1 (2%)			
Angiectasis	1 (2%)			
#Brain	(50)	(50)	(50)	(50)
Deformity, NOS	1 (2%)		2 (4%)	
Hydrocephalus, internal		1 (2%)		
Hemorrhage				1 (2%)
SPECIAL SENSE ORGANS				
*Eye	(50)	(50)	(50)	(50)
Retinopathy	16 (32%)	2 (4%)	5 (10%)	3 (6%)
Cataract	12 (24%)	1 (2%)	4 (8%)	1 (2%)
Phthisis bulbi	2 (4%)			
*Vitreous body	(50)	(50)	(50)	(50)
Hemorrhage				1 (2%)
Inflammation, chronic			1 (2%)	

TABLE C2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) (Continued)

	CONTROL (VEH)	LOW DOSE	MID DOSE	HIGH DOSE
SPECIAL SENSE ORGANS (Continued)				
*Eye/crystalline lens	(50)	(50)	(50)	(50)
Mineralization		1 (2%)	1 (2%)	1 (2%)
*Harderian gland	(50)	(50)	(50)	(50)
Degeneration, NOS	1 (2%)			
MUSCULOSKELETAL SYSTEM				
*Bone	(50)	(50)	(50)	(50)
Osteosclerosis		1 (2%)		
*Skull	(50)	(50)	(50)	(50)
Hyperostosis	3 (6%)	2 (4%)	2 (4%)	1 (2%)
*Tarsal joint	(50)	(50)	(50)	(50)
Inflammation, chronic				1 (2%)
BODY CAVITIES				
*Mesentery	(50)	(50)	(50)	(50)
Ectopia		1 (2%)		
Hemorrhage			1 (2%)	
Steatitis	2 (4%)	1 (2%)	2 (4%)	7 (14%)
Lymphocytic inflammatory infiltrate			1 (2%)	
Inflammation, chronic			1 (2%)	
ALL OTHER SYSTEMS				
*Multiple organs	(50)	(50)	(50)	(50)
Pigmentation, NOS		1 (2%)		
Adipose tissue				
Steatitis		1		
Omentum				
Hemorrhage				1
Steatitis	1		1	1
Inflammation, chronic				1
Broad ligament				
Steatitis	2	6	10	6
SPECIAL MORPHOLOGY SUMMARY				
None				

Number of animals with tissue examined microscopically
* Number of animals necropsied

APPENDIX D

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE IN THE TWO-YEAR GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{23}, 43% CHLORINE)

TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl)

	CONTROL (VEH)	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)
Hemorrhage		1 (2%)	
Inflammation, NOS		1 (2%)	
Ulcer, NOS		3 (6%)	2 (4%)
Inflammation, focal	1 (2%)		
Inflammation, suppurative		1 (2%)	
Inflammation, chronic	†11 (22%)	4 (8%)	†6 (12%)
Ulcer, chronic	1 (2%)	3 (6%)	1 (2%)
Fibrosis		1 (2%)	
Atrophy, NOS		1 (2%)	
*Subcutaneous tissue	(50)	(50)	(50)
Epidermal inclusion cyst			1 (2%)
Congestion, NOS			1 (2%)
Inflammation, NOS			2 (4%)
Inflammation, suppurative			1 (2%)
Abscess, NOS			1 (2%)
Inflammation, chronic			1 (2%)
Degeneration, cystic	1 (2%)		
Necrosis, fat	1 (2%)		
Metaplasia, osseous		1 (2%)	1 (2%)
RESPIRATORY SYSTEM			
*Nasal cavity	(50)	(50)	(50)
Inflammation, NOS		1 (2%)	
*Nasal mucosa	(50)	(50)	(50)
Inflammation, focal	1 (2%)	2 (4%)	8 (16%)
*Nasal gland	(50)	(50)	(50)
Inflammation, suppurative			1 (2%)
#Lung	(50)	(50)	(50)
Congestion, NOS	1 (2%)	2 (4%)	4 (8%)
Inflammation, multifocal		1 (2%)	
Inflammation, granulomatous		1 (2%)	
Hyperplasia, alveolar epithelium		1 (2%)	1 (2%)
#Lung/alveoli	(50)	(50)	(50)
Histiocytosis	1 (2%)	1 (2%)	
HEMATOPOIETIC SYSTEM			
*Mediastinum	(50)	(50)	(50)
Leukocytosis, NOS			1 (2%)
#Bone marrow	(50)	(50)	(50)
Angiectasis			1 (2%)
Hyperplasia, granulocytic	3 (6%)	1 (2%)	1 (2%)
#Spleen	(49)	(49)	(50)
Amyloid, NOS		1 (2%)	
Atrophy, NOS		1 (2%)	
Leukemoid reaction	1 (2%)		
Hyperplasia, lymphoid	1 (2%)	1 (2%)	2 (4%)
Hematopoiesis	10 (20%)	11 (22%)	8 (16%)
#Splenic red pulp	(49)	(49)	(50)
Atrophy, NOS		1 (2%)	3 (6%)
#Mandibular lymph node	(50)	(50)	(50)
Hyperplasia, NOS		2 (4%)	1 (2%)
#Mediastinal lymph node	(50)	(50)	(50)
Hyperplasia, lymphoid	1 (2%)		

TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
HEMATOPOIETIC SYSTEM (Continued)			
#Pancreatic lymph node	(50)	(50)	(50)
Hyperplasia, lymphoid	1 (2%)		
#Mesenteric lymph node	(50)	(50)	(50)
Congestion, NOS	3 (6%)	1 (2%)	4 (8%)
Hyperplasia, NOS		1 (2%)	
Angiectasis	23 (46%)	21 (42%)	14 (28%)
Hyperplasia, lymphoid	1 (2%)	3 (6%)	1 (2%)
Hematopoiesis		3 (6%)	
#Iliac lymph node	(50)	(50)	(50)
Hyperplasia, NOS			1 (2%)
#Inguinal lymph node	(50)	(50)	(50)
Congestion, NOS			1 (2%)
Degeneration, cystic			1 (2%)
Pigmentation, NOS	1 (2%)		
Hyperplasia, NOS			1 (2%)
Angiectasis		1 (2%)	
Hyperplasia, lymphoid		1 (2%)	1 (2%)
#Lung	(50)	(50)	(50)
Leukocytosis, NOS		2 (4%)	2 (4%)
Hyperplasia, lymphoid	1 (2%)		
#Liver	(50)	(50)	(50)
Leukocytosis, NOS		2 (4%)	1 (2%)
Hematopoiesis		1 (2%)	
#Peyer's patch	(47)	(50)	(48)
Hyperplasia, lymphoid	1 (2%)	2 (4%)	
#Kidney	(50)	(50)	(50)
Hyperplasia, lymphoid	1 (2%)	2 (4%)	
#Perirenal tissue	(50)	(50)	(50)
Hyperplasia, lymphoid		1 (2%)	
#Thymus	(34)	(38)	(39)
Embryonal duct cyst			1 (3%)
Hyperplasia, epithelial	1 (3%)		
#Thymic lymphocytes	(34)	(38)	(39)
Necrosis, NOS		1 (3%)	
CIRCULATORY SYSTEM			
*Multiple organs	(50)	(50)	(50)
Periarteritis		1 (2%)	
*Mediastinum	(50)	(50)	(50)
Periarteritis			1 (2%)
#Mesenteric lymph node	(50)	(50)	(50)
Thrombosis, NOS	1 (2%)		
#Heart	(50)	(49)	(50)
Thrombosis, NOS		1 (2%)	
Embolus, septic			1 (2%)
#Base of heart	(50)	(49)	(50)
Inflammation, focal	1 (2%)		
Necrosis, focal	1 (2%)		
#Heart/ventricle	(50)	(49)	(50)
Thrombosis, NOS	1 (2%)		
#Myocardium	(50)	(49)	(50)
Fibrosis, focal	1 (2%)	1 (2%)	
#Liver	(50)	(50)	(50)
Thrombosis, NOS	2 (4%)	1 (2%)	1 (2%)
Embolus, septic			1 (2%)
#Glandular stomach	(50)	(50)	(50)
Periarteritis			1 (2%)

TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
*Root of tooth	(50)	(50)	(50)
Deformity, NOS			1 (2%)
Inflammation, suppurative			1 (2%)
Granuloma, NOS	1 (2%)		
Dysplasia, NOS	2 (4%)		
#Salivary gland	(50)	(49)	(49)
Inflammation, chronic	1 (2%)		
#Liver	(50)	(50)	(50)
Cyst, NOS	1 (2%)		
Hemorrhage			2 (4%)
Fibrosis	1 (2%)		
Fibrosis, focal		1 (2%)	
Necrosis, NOS	3 (6%)		
Necrosis, focal	6 (12%)		4 (8%)
Infarct, NOS	2 (4%)	1 (2%)	
Amyloidosis	1 (2%)		
Fibrosiderotic nodule	1 (2%)		
Nuclear size alteration		1 (2%)	
Cytoplasmic vacuolization	1 (2%)	1 (2%)	6 (12%)
Angiectasis	4 (8%)		1 (2%)
Histiocytosis			1 (2%)
#Liver/centrilobular	(50)	(50)	(50)
Necrosis, NOS		1 (2%)	
Metamorphosis, fatty			1 (2%)
Cytoplasmic vacuolization		1 (2%)	1 (2%)
#Liver/kupffer cell	(50)	(50)	(50)
Hyperplasia, focal			1 (2%)
#Bile duct	(50)	(50)	(50)
Hyperplasia, NOS	1 (2%)		
#Pancreas	(50)	(50)	(50)
Cystic ducts			1 (2%)
Basophilic cyto change		1 (2%)	
Atrophy, NOS			1 (2%)
Atrophy, focal			2 (4%)
#Esophagus	(50)	(50)	(50)
Wound, NOS		1 (2%)	
Hyperplasia, epithelial		1 (2%)	
#Glandular stomach	(50)	(50)	(50)
Hyperplasia, epithelial		1 (2%)	
#Forestomach	(50)	(50)	(50)
Cyst, NOS		1 (2%)	1 (2%)
Ulcer, NOS	2 (4%)		
Inflammation, focal	1 (2%)	2 (4%)	1 (2%)
Hyperplasia, epithelial	3 (6%)		1 (2%)
#Jejunum	(47)	(50)	(48)
Inflammation, suppurative	1 (2%)		
#Jejunal mucosa	(47)	(50)	(48)
Hyperplasia, adenomatous		1 (2%)	
*Rectum	(50)	(50)	(50)
Inflammation, chronic		1 (2%)	
Necrosis, focal		1 (2%)	
Hyperplasia, focal		1 (2%)	
Dysplasia, NOS		1 (2%)	

TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
URINARY SYSTEM			
#Kidney	(50)	(50)	(50)
Pyelonephritis, NOS			1 (2%)
Pyelonephritis, focal	1 (2%)		
Inflammation, chronic			1 (2%)
Fibrosis, focal			1 (2%)
Nephrosis, NOS	16 (32%)	21 (42%)	14 (28%)
Amyloidosis	1 (2%)		
Atrophy, NOS			1 (2%)
#Kidney/cortex	(50)	(50)	(50)
Accessory structure	1 (2%)		
Cyst, NOS			2 (4%)
#Kidney/medulla	(50)	(50)	(50)
Congestion, NOS		1 (2%)	
#Renal corpuscle	(50)	(50)	(50)
Dilatation, NOS			1 (2%)
#Kidney/tubule	(50)	(50)	(50)
Degeneration, hyaline			1 (2%)
Cytoplasmic vacuolization			1 (2%)
#Kidney/pelvis	(50)	(50)	(50)
Dilatation, NOS			1 (2%)
ENDOCRINE SYSTEM			
#Anterior pituitary	(43)	(47)	(44)
Embryonal duct cyst	1 (2%)	1 (2%)	1 (2%)
#Adrenal/capsule	(49)	(50)	(47)
Hyperplasia, focal	6 (12%)	1 (2%)	5 (11%)
#Adrenal cortex	(49)	(50)	(47)
Accessory structure			1 (2%)
Amyloidosis	1 (2%)		
Cytoplasmic vacuolization	1 (2%)		
Ground glass cyto change			1 (2%)
Hypertrophy, focal			1 (2%)
Hyperplasia, focal		1 (2%)	2 (4%)
#Adrenal medulla	(49)	(50)	(47)
Fibrosis, focal		1 (2%)	
Hyperplasia, focal	1 (2%)	2 (4%)	1 (2%)
#Thyroid	(49)	(48)	(49)
Embryonal duct cyst			3 (6%)
Cystic follicles	2 (4%)	2 (4%)	
Inflammation, focal	1 (2%)		
Lymphocytic inflammatory infiltrate	2 (4%)		
Degeneration, cystic	4 (8%)	5 (10%)	5 (10%)
Hyperplasia, follicular cell	2 (4%)	3 (6%)	4 (8%)
#Thyroid follicle	(49)	(48)	(49)
Degeneration, cystic			2 (4%)
Hyperplasia, cystic	1 (2%)		1 (2%)
#Parathyroid	(43)	(43)	(38)
Cyst, NOS		1 (2%)	
REPRODUCTIVE SYSTEM			
*Preputial gland	(50)	(50)	(50)
Cystic ducts			2 (4%)
Inflammation, NOS	3 (6%)	1 (2%)	4 (8%)
Inflammation, suppurative	6 (12%)	1 (2%)	6 (12%)
Inflammation, chronic suppurative	1 (2%)		
Degeneration, cystic	2 (4%)		
Atrophy, NOS			1 (2%)
Hyperplasia, NOS			1 (2%)

TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM (Continued)			
#Prostate	(49)	(50)	(50)
Inflammation, suppurative	1 (2%)		
Inflammation, chronic suppurative	1 (2%)		1 (2%)
Hyperplasia, epithelial	1 (2%)		
*Seminal vesicle	(50)	(50)	(50)
Dilatation, NOS	1 (2%)	1 (2%)	2 (4%)
Distention			1 (2%)
Inflammation, suppurative			2 (4%)
Inflammation, chronic			2 (4%)
*Coagulating gland	(50)	(50)	(50)
Dilatation, NOS	1 (2%)		2 (4%)
#Testis	(50)	(50)	(50)
Atrophy, NOS		3 (6%)	1 (2%)
*Epididymis	(50)	(50)	(50)
Inflammation, focal		1 (2%)	
Granuloma, spermatic			1 (2%)
*Spermatic cord	(50)	(50)	(50)
Necrosis, fat	2 (4%)		
NERVOUS SYSTEM			
#Brain/thalamus	(50)	(50)	(50)
Psammoma bodies	14 (28%)	21 (42%)	25 (50%)
SPECIAL SENSE ORGANS			
*Eye	(50)	(50)	(50)
Retinopathy			1 (2%)
Cataract			1 (2%)
*Nasolacrimal duct	(50)	(50)	(50)
Inflammation, NOS	1 (2%)	2 (4%)	
Inflammation, chronic	1 (2%)		
*Harderian gland	(50)	(50)	(50)
Inflammation, chronic	1 (2%)		
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
*Mediastinum	(50)	(50)	(50)
Hemorrhage	1 (2%)		
Inflammation, acute suppurative		2 (4%)	
Reaction, foreign body		2 (4%)	
*Abdominal wall	(50)	(50)	(50)
Hemorrhage	1 (2%)		
*Peritoneum	(50)	(50)	(50)
Hemorrhage, chronic	1 (2%)		
*Pleura	(50)	(50)	(50)
Inflammation, necrotizing		1 (2%)	
*Epicardium	(50)	(50)	(50)
Fibrosis, focal			1 (2%)
*Mesentery	(50)	(50)	(50)
Inflammation, suppurative	1 (2%)		
Necrosis, fat	1 (2%)	1 (2%)	2 (4%)
Fibrosiderotic nodule	1 (2%)		1 (2%)
Angiectasis	1 (2%)		

TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Inflammation, suppurative	1 (2%)		
Perineum			
Inflammation, chronic suppurative	1		
Metaplasia, osseous	1		
Diaphragm			
Inflammation, granulomatous focal		1	
Infection, fungal		1	
Foot			
Edema, NOS			1
Sole of foot			
Callus		1	
SPECIAL MORPHOLOGY SUMMARY			
None			

Number of animals with tissue examined microscopically
* Number of animals necropsied
† Multiple occurrence of morphology in the same organ. Tissue is counted once only.

TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	49	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	49	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(49)	(50)
Inflammation, NOS		1 (2%)	2 (4%)
Inflammation, suppurative	1 (2%)		
Inflammation, chronic			1 (2%)
Atrophy, focal			1 (2%)
*Subcutaneous tissue	(50)	(49)	(50)
Edema, NOS	2 (4%)		1 (2%)
Inflammation, NOS			1 (2%)
RESPIRATORY SYSTEM			
*Nasal cavity	(50)	(49)	(50)
Inflammation, NOS	1 (2%)		
Inflammation, suppurative	2 (4%)	2 (4%)	
*Nasal mucosa	(50)	(49)	(50)
Inflammation, focal	3 (6%)	5 (10%)	14 (28%)
#Lung	(50)	(49)	(50)
Congestion, NOS	1 (2%)		
Hemorrhage			1 (2%)
Inflammation, interstitial			1 (2%)
Hyperplasia, alveolar epithelium	1 (2%)	3 (6%)	
#Lung/alveoli	(50)	(49)	(50)
Histiocytosis	2 (4%)	2 (4%)	
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(49)	(50)
Leukocytosis, NOS	2 (4%)	1 (2%)	3 (6%)
Hyperplasia, lymphoid		1 (2%)	
Hematopoiesis	2 (4%)	1 (2%)	3 (6%)
*Mediastinum	(50)	(49)	(50)
Hyperplasia, lymphoid		1 (2%)	
*Subcutaneous tissue	(50)	(49)	(50)
Mastocytosis	2 (4%)		
#Bone marrow	(50)	(49)	(50)
Hyperplasia, granulocytic	8 (16%)	5 (10%)	6 (12%)
Hyperplasia, reticulum cell			1 (2%)
#Spleen	(49)	(49)	(50)
Fibrosiderotic nodule	1 (2%)		
Leukemoid reaction	1 (2%)		
Hyperplasia, lymphoid	3 (6%)	3 (6%)	3 (6%)
Hematopoiesis	18 (37%)	23 (47%)	20 (40%)
#Lymph node	(50)	(48)	(50)
Hyperplasia, NOS	1 (2%)	2 (4%)	4 (8%)
Hyperplasia, lymphoid	1 (2%)		1 (2%)
#Mandibular lymph node	(50)	(48)	(50)
Hyperplasia, NOS	1 (2%)	2 (4%)	1 (2%)
Angiectasis			1 (2%)
Hyperplasia, lymphoid	1 (2%)		
#Bronchial lymph node	(50)	(48)	(50)
Hyperplasia, NOS			1 (2%)
#Mediastinal lymph node	(50)	(48)	(50)
Hyperplasia, NOS	7 (14%)	3 (6%)	3 (6%)
Angiectasis			1 (2%)
#Abdominal lymph node	(50)	(48)	(50)
Hyperplasia, NOS		1 (2%)	

TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
HEMATOPOIETIC SYSTEM (Continued)			
#Celiac lymph node	(50)	(48)	(50)
Hyperplasia, NOS		2 (4%)	
#Pancreatic lymph node	(50)	(48)	(50)
Hyperplasia, NOS	1 (2%)	1 (2%)	
Hyperplasia, lymphoid			1 (2%)
#Mesenteric lymph node	(50)	(48)	(50)
Congestion, NOS		1 (2%)	
Hyperplasia, NOS	3 (6%)	1 (2%)	2 (4%)
Angiectasis	3 (6%)	1 (2%)	4 (8%)
Hyperplasia, lymphoid	1 (2%)		
#Renal lymph node	(50)	(48)	(50)
Abscess, chronic	1 (2%)		
Hyperplasia, NOS	10 (20%)	7 (15%)	3 (6%)
Angiectasis		1 (2%)	
#Iliac lymph node	(50)	(48)	(50)
Hyperplasia, NOS	6 (12%)	7 (15%)	3 (6%)
Angiectasis		1 (2%)	1 (2%)
#Inguinal lymph node	(50)	(48)	(50)
Hyperplasia, NOS		1 (2%)	
#Lung	(50)	(49)	(50)
Leukocytosis, NOS	3 (6%)	7 (14%)	4 (8%)
#Liver	(50)	(49)	(50)
Leukocytosis, NOS	8 (16%)	11 (22%)	7 (14%)
Hematopoiesis	10 (20%)	14 (29%)	11 (22%)
#Peyer's patch	(48)	(46)	(50)
Hyperplasia, lymphoid	1 (2%)		
#Kidney	(50)	(49)	(50)
Leukocytosis, NOS	1 (2%)		
#Urinary bladder	(50)	(48)	(48)
Hyperplasia, lymphoid			1 (2%)
#Adrenal	(50)	(49)	(50)
Hematopoiesis			1 (2%)
#Adrenal cortex	(50)	(49)	(50)
Hematopoiesis		1 (2%)	3 (6%)
CIRCULATORY SYSTEM			
#Myocardium	(50)	(49)	(50)
Inflammation, NOS	1 (2%)		
Inflammation, focal	1 (2%)		
Fibrosis, focal	1 (2%)		
*Pulmonary artery	(50)	(49)	(50)
Hypertrophy, NOS		1 (2%)	
#Urinary bladder	(50)	(48)	(48)
Periarteritis	1 (2%)		
#Uterus	(50)	(48)	(50)
Thrombosis, NOS		1 (2%)	
#Ovary	(46)	(42)	(47)
Periarteritis			1 (2%)
DIGESTIVE SYSTEM			
#Liver	(50)	(49)	(50)
Cyst, NOS			2 (4%)
Congestion, NOS	1 (2%)		1 (2%)
Inflammation, chronic focal			1 (2%)
Lipogranuloma		1 (2%)	
Fibrosis, multifocal		1 (2%)	

TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
#Liver (Continued)	(50)	(49)	(50)
Necrosis, focal	2 (4%)	1 (2%)	2 (4%)
Infarct, NOS			1 (2%)
Metamorphosis, fatty	2 (4%)		1 (2%)
Cholesterol deposit		1 (2%)	
Pigmentation, NOS			1 (2%)
Cytoplasmic vacuolization	2 (4%)		2 (4%)
Angiectasis	2 (4%)	1 (2%)	
Histiocytosis	1 (2%)	(50)	(49) (50)
#Liver/centrilobular	(50)	(49)	(50)
Necrosis, coagulative			1 (2%)
Metamorphosis, fatty	1 (2%)		
#Pancreas	(49)	(48)	(50)
Cyst, NOS	1 (2%)		
Edema, NOS	1 (2%)		
Inflammation, chronic		1 (2%)	
Infarct, NOS		1 (2%)	
Atrophy, NOS			1 (2%)
Atrophy, focal	1 (2%)	1 (2%)	2 (4%)
#Pancreatic duct	(49)	(48)	(50)
Hyperplasia, focal	1 (2%)		
#Gastric mucosa	(49)	(47)	(50)
Ulcer, NOS	1 (2%)		
#Gastric fundal gland	(49)	(47)	(50)
Dilatation, NOS		1 (2%)	
#Glandular stomach	(49)	(47)	(50)
Congestion, NOS		1 (2%)	
Inflammation, focal			1 (2%)
#Forestomach	(49)	(47)	(50)
Inflammation, focal	2 (4%)	3 (6%)	2 (4%)
Hyperplasia, epithelial	1 (2%)	2 (4%)	3 (6%)
#Duodenal mucosa	(48)	(46)	(50)
Atrophy, focal			1 (2%)
#Jejunal mucosa	(48)	(46)	(50)
Amyloidosis	1 (2%)		
#Ileal mucosa	(48)	(46)	(50)
Amyloidosis			1 (2%)
#Large intestine	(48)	(48)	(48)
Edema, NOS	1 (2%)	1 (2%)	
*Perirectal tissue	(50)	(49)	(50)
Fibrosis			1 (2%)
URINARY SYSTEM			
#Kidney	(50)	(49)	(50)
Hydronephrosis			1 (2%)
Cyst, NOS			4 (8%)
Congestion, NOS	1 (2%)		
Inflammation, NOS			1 (2%)
Inflammation, focal		1 (2%)	
Inflammation, suppurative			1 (2%)
Pyelonephritis, acute	1 (2%)		
Nephrosis, NOS	7 (14%)	2 (4%)	9 (18%)
Necrosis, medullary	1 (2%)	3 (6%)	1 (2%)
#Kidney/medulla	(50)	(49)	(50)
Cyst, NOS			1 (2%)
*Ureter	(50)	(49)	(50)
Hyperplasia, epithelial			1 (2%)
#Urinary bladder	(50)	(48)	(48)
Inflammation, NOS			1 (2%)

TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM			
#Pituitary	(46)	(46)	(45)
Cyst, NOS	1 (2%)		
Congestion, NOS	1 (2%)		
Focal cellular change			1 (2%)
Hyperplasia, focal			1 (2%)
Angiectasis			1 (2%)
#Pituitary intermedia	(46)	(46)	(45)
Hyperplasia, focal	1 (2%)		
#Anterior pituitary	(46)	(46)	(45)
Hyperplasia, focal	6 (13%)	4 (9%)	5 (11%)
Angiectasis	1 (2%)	2 (4%)	3 (7%)
#Adrenal	(50)	(49)	(50)
Depletion, lipid	1 (2%)		
#Adrenal/capsule	(50)	(49)	(50)
Hyperplasia, diffuse	1 (2%)	1 (2%)	
#Adrenal cortex	(50)	(49)	(50)
Accessory structure		2 (4%)	1 (2%)
Depletion, lipid	1 (2%)		1 (2%)
Hyperplasia, focal	1 (2%)		
#Adrenal medulla	(50)	(49)	(50)
Pigmentation, NOS		1 (2%)	
Hyperplasia, focal		2 (4%)	
#Thyroid	(49)	(47)	(49)
Cystic follicles		2 (4%)	1 (2%)
Inflammation, focal	1 (2%)		
Lymphocytic inflammatory infiltrate	2 (4%)	4 (9%)	4 (8%)
Degeneration, cystic	6 (12%)	1 (2%)	7 (14%)
Hyperplasia, follicular cell	12 (24%)	7 (15%)	14 (29%)
#Thyroid follicle	(49)	(47)	(49)
Hyperplasia, cystic			1 (2%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(49)	(50)
Cystic disease	20 (40%)	25 (51%)	23 (46%)
#Uterus	(50)	(48)	(50)
Hydrometra	1 (2%)		
Inflammation, suppurative	5 (10%)	3 (6%)	1 (2%)
Abscess, NOS		1 (2%)	
#Uterine serosa	(50)	(48)	(50)
Angiectasis			1 (2%)
#Cervix uteri	(50)	(48)	(50)
Polyp, NOS		1 (2%)	
#Uterus/endometrium	(50)	(48)	(50)
Cyst, NOS	1 (2%)		1 (2%)
Hyperplasia, cystic	42 (84%)	42 (88%)	37 (74%)
#Fallopian tube	(50)	(48)	(50)
Dilatation, NOS			1 (2%)
#Ovary	(46)	(42)	(47)
Cystic follicles		1 (2%)	
Follicular cyst, NOS	11 (24%)	14 (33%)	20 (43%)
Parovarian cyst		2 (5%)	
Abscess, chronic	1 (2%)		

TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
NERVOUS SYSTEM			
#Brain	(50)	(49)	(50)
Hemorrhage		1 (2%)	
Necrosis, focal		1 (2%)	
#Cerebral basal surface	(50)	(49)	(50)
Displacement, NOS		2 (4%)	1 (2%)
Atrophy, pressure			1 (2%)
#Brain/thalamus	(50)	(49)	(50)
Psammoma bodies	30 (60%)	22 (45%)	16 (32%)
SPECIAL SENSE ORGANS			
*Eye	(50)	(49)	(50)
Phthisis bulbi	1 (2%)		
*Nasolacrimal duct	(50)	(49)	(50)
Inflammation, NOS	2 (4%)	2 (4%)	2 (4%)
Inflammation, suppurative	1 (2%)		
*Harderian gland	(50)	(49)	(50)
Inflammation, focal	1 (2%)		
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
*Thoracic cavity	(50)	(49)	(50)
Inflammation, suppurative		1 (2%)	1 (2%)
Reaction, foreign body		1 (2%)	1 (2%)
*Mediastinum	(50)	(49)	(50)
Hemorrhage			1 (2%)
*Peritoneum	(50)	(49)	(50)
Necrosis, fat			1 (2%)
*Mesentery	(50)	(49)	(50)
Multiple cysts	1 (2%)		
Necrosis, fat	2 (4%)	1 (2%)	
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(49)	(50)
Inflammation, suppurative	19 (38%)	18 (37%)	18 (36%)
Broad ligament			
Necrosis, fat	2	3	
SPECIAL MORPHOLOGY SUMMARY			
Autolysis/no necropsy		1	

Number of animals with tissue examined microscopically
* Number of animals necropsied

APPENDIX E

ANALYSES OF PRIMARY TUMORS IN RATS AND MICE IN THE TWO-YEAR GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{23}, 43% CHLORINE)

TABLE E1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl)

	Vehicle Control	1,875 mg/kg	3,750 mg/kg
Skin: Squamous Cell Papilloma			
Overall Rates (a)	3/50 (6%)	2/50 (4%)	0/50 (0%)
Adjusted Rates (b)	8.6%	6.3%	0.0%
Terminal Rates (c)	2/30 (7%)	2/32 (6%)	0/27 (0%)
Week of First Observation	68	105	
Life Table Tests (d)	P=0.090N	P=0.477N	P=0.134N
Incidental Tumor Tests (d)	P=0.095N	P=0.538N	P=0.135N
Cochran-Armitage Trend Test (d)	P=0.082N		
Fisher Exact Test (d)		P=0.500N	P=0.121N
Skin: Keratoacanthoma			
Overall Rates (a)	4/50 (8%)	1/50 (2%)	2/50 (4%)
Adjusted Rates (b)	10.7%	3.1%	6.4%
Terminal Rates (c)	1/30 (3%)	1/32 (3%)	1/27 (4%)
Week of First Observation	84	105	99
Life Table Tests (d)	P=0.258N	P=0.172N	P=0.360N
Incidental Tumor Tests (d)	P=0.236N	P=0.216N	P=0.319N
Cochran-Armitage Trend Test (d)	P=0.238N		
Fisher Exact Test (d)		P=0.181N	P=0.339N
Subcutaneous Tissue: Fibroma			
Overall Rates (a)	3/50 (6%)	6/50 (12%)	3/50 (6%)
Adjusted Rates (b)	10.0%	16.3%	8.5%
Terminal Rates (c)	3/30 (10%)	3/32 (9%)	1/27 (4%)
Week of First Observation	105	96	92
Life Table Tests (d)	P=0.538	P=0.273	P=0.632
Incidental Tumor Tests (d)	P=0.523N	P=0.299	P=0.646
Cochran-Armitage Trend Test (d)	P=0.573		
Fisher Exact Test (d)		P=0.243	P=0.661
Subcutaneous Tissue: Fibroma, Sarcoma, or Neurofibrosarcoma			
Overall Rates (a)	3/50 (6%)	7/50 (14%)	4/50 (8%)
Adjusted Rates (b)	10.0%	19.2%	12.0%
Terminal Rates (c)	3/30 (10%)	4/32 (13%)	2/27 (7%)
Week of First Observation	105	96	92
Life Table Tests (d)	P=0.392	P=0.186	P=0.463
Incidental Tumor Tests (d)	P=0.469	P=0.204	P=0.476
Cochran-Armitage Trend Test (d)	P=0.432		
Fisher Exact Test (d)		P=0.159	P=0.500
Hematopoietic System: Mononuclear Cell Leukemia			
Overall Rates (a)	9/50 (18%)	9/50 (18%)	14/50 (28%)
Adjusted Rates (b)	25.6%	22.8%	32.8%
Terminal Rates (c)	5/30 (17%)	3/32 (9%)	3/27 (11%)
Week of First Observation	74	94	73
Life Table Tests (d)	P=0.135	P=0.566N	P=0.169
Incidental Tumor Tests (d)	P=0.266	P=0.519N	P=0.282
Cochran-Armitage Trend Test (d)	P=0.136		
Fisher Exact Test (d)		P=0.603N	P=0.171
Liver: Neoplastic Nodule			
Overall Rates (a)	0/50 (0%)	3/50 (6%)	3/50 (6%)
Adjusted Rates (b)	0.0%	8.9%	8.6%
Terminal Rates (c)	0/30 (0%)	2/32 (6%)	0/27 (0%)
Week of First Observation		100	97
Life Table Tests (d)	P=0.090	P=0.129	P=0.119
Incidental Tumor Tests (d)	P=0.163	P=0.143	P=0.218
Cochran-Armitage Trend Test (d)	P=0.101		
Fisher Exact Test (d)		P=0.121	P=0.121

TABLE E1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) (Continued)

	Vehicle Control	1,875 mg/kg	3,750 mg/kg
Pancreas: Acinar Cell Adenoma			
Overall Rates (a)	6/49 (12%)	1/50 (2%)	1/50 (2%)
Adjusted Rates (b)	18.1%	3.1%	3.7%
Terminal Rates (c)	4/29 (14%)	1/32 (3%)	1/27 (4%)
Week of First Observation	84	105	105
Life Table Tests (d)	P=0.026N	P=0.051N	P=0.073N
Incidental Tumor Tests (d)	P=0.024N	P=0.054N	P=0.062N
Cochran-Armitage Trend Test (d)	P=0.021N		
Fisher Exact Test (d)		P=0.053N	P=0.053N
Pituitary: Adenoma			
Overall Rates (a)	13/49 (27%)	6/49 (12%)	10/47 (21%)
Adjusted Rates (b)	38.1%	17.0%	35.5%
Terminal Rates (c)	10/30 (33%)	4/32 (13%)	9/27 (33%)
Week of First Observation	86	86	100
Life Table Tests (d)	P=0.330N	P=0.050N	P=0.402N
Incidental Tumor Tests (d)	P=0.336N	P=0.061N	P=0.413N
Cochran-Armitage Trend Test (d)	P=0.296N		
Fisher Exact Test (d)		P=0.062N	P=0.359N
Pituitary: Adenoma or Carcinoma			
Overall Rates (a)	15/49 (31%)	7/49 (14%)	12/47 (26%)
Adjusted Rates (b)	41.2%	18.9%	40.8%
Terminal Rates (c)	10/30 (33%)	4/32 (13%)	10/27 (37%)
Week of First Observation	79	86	99
Life Table Tests (d)	P=0.351N	P=0.041N	P=0.424N
Incidental Tumor Tests (d)	P=0.316N	P=0.046N	P=0.393N
Cochran-Armitage Trend Test (d)	P=0.312N		
Fisher Exact Test (d)		P=0.044N	P=0.373N
Adrenal: Pheochromocytoma			
Overall Rates (a)	20/50 (40%)	15/50 (30%)	20/50 (40%)
Adjusted Rates (b)	56.3%	43.4%	59.2%
Terminal Rates (c)	15/30 (50%)	13/32 (41%)	14/27 (52%)
Week of First Observation	86	90	89
Life Table Tests (d)	P=0.429	P=0.143N	P=0.460
Incidental Tumor Tests (d)	P=0.518	P=0.159N	P=0.580N
Cochran-Armitage Trend Test (d)	P=0.541		
Fisher Exact Test (d)		P=0.201N	P=0.581N
Adrenal: Pheochromocytoma or Pheochromocytoma, Malignant			
Overall Rates (a)	20/50 (40%)	16/50 (32%)	20/50 (40%)
Adjusted Rates (b)	56.3%	46.4%	59.2%
Terminal Rates (c)	15/30 (50%)	14/32 (44%)	14/27 (52%)
Week of First Observation	86	90	89
Life Table Tests (d)	P=0.426	P=0.194N	P=0.460
Incidental Tumor Tests (d)	P=0.515	P=0.215N	P=0.580N
Cochran-Armitage Trend Test (d)	P=0.541		
Fisher Exact Test (d)		P=0.266N	P=0.581N
Thyroid: C-Cell Adenoma			
Overall Rates (a)	7/50 (14%)	4/50 (8%)	5/49 (10%)
Adjusted Rates (b)	18.2%	9.7%	16.1%
Terminal Rates (c)	2/30 (7%)	1/32 (3%)	3/27 (11%)
Week of First Observation	85	86	81
Life Table Tests (d)	P=0.344N	P=0.249N	P=0.427N
Incidental Tumor Tests (d)	P=0.311N	P=0.301N	P=0.358N
Cochran-Armitage Trend Test (d)	P=0.326N		
Fisher Exact Test (d)		P=0.263N	P=0.394N

TABLE E1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) (Continued)

	Vehicle Control	1,875 mg/kg	3,750 mg/kg
Thyroid: C-Cell Carcinoma			
Overall Rates (a)	4/50 (8%)	5/50 (10%)	3/49 (6%)
Adjusted Rates (b)	12.4%	13.9%	10.0%
Terminal Rates (c)	3/30 (10%)	3/32 (9%)	2/27 (7%)
Week of First Observation	96	93	99
Life Table Tests (d)	P=0.463N	P=0.536	P=0.539N
Incidental Tumor Tests (d)	P=0.379N	P=0.569	P=0.473N
Cochran-Armitage Trend Test (d)	P=0.438N		
Fisher Exact Test (d)		P=0.500	P=0.511N
Thyroid: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	11/50 (22%)	9/50 (18%)	8/49 (16%)
Adjusted Rates (b)	28.8%	22.5%	25.2%
Terminal Rates (c)	5/30 (17%)	4/32 (13%)	5/27 (19%)
Week of First Observation	85	86	81
Life Table Tests (d)	P=0.310N	P=0.365N	P=0.371N
Incidental Tumor Tests (d)	P=0.232N	P=0.393N	P=0.274N
Cochran-Armitage Trend Test (d)	P=0.276N		
Fisher Exact Test (d)		P=0.402N	P=0.323N
Pancreatic Islets: Islet Cell Adenoma			
Overall Rates (a)	0/49 (0%)	1/50 (2%)	4/50 (8%)
Adjusted Rates (b)	0.0%	3.1%	11.9%
Terminal Rates (c)	0/29 (0%)	1/32 (3%)	2/27 (7%)
Week of First Observation		105	93
Life Table Tests (d)	P=0.024	P=0.520	P=0.066
Incidental Tumor Tests (d)	P=0.034	P=0.520	P=0.092
Cochran-Armitage Trend Test (d)	P=0.027		
Fisher Exact Test (d)		P=0.505	P=0.061
Pancreatic Islets: Islet Cell Adenoma or Carcinoma			
Overall Rates (a)	1/49 (2%)	3/50 (6%)	4/50 (8%)
Adjusted Rates (b)	2.8%	8.5%	11.9%
Terminal Rates (c)	0/29 (0%)	2/32 (6%)	2/27 (7%)
Week of First Observation	101	96	93
Life Table Tests (d)	P=0.126	P=0.324	P=0.174
Incidental Tumor Tests (d)	P=0.193	P=0.360	P=0.267
Cochran-Armitage Trend Test (d)	P=0.138		
Fisher Exact Test (d)		P=0.316	P=0.187
Mammary Gland: Fibroadenoma			
Overall Rates (a)	4/50 (8%)	1/50 (2%)	0/50 (0%)
Adjusted Rates (b)	11.5%	3.1%	0.0%
Terminal Rates (c)	2/30 (7%)	1/32 (3%)	0/27 (0%)
Week of First Observation	92	105	
Life Table Tests (d)	P=0.030N	P=0.174N	P=0.077N
Incidental Tumor Tests (d)	P=0.027N	P=0.186N	P=0.064N
Cochran-Armitage Trend Test (d)	P=0.026N		
Fisher Exact Test (d)		P=0.181N	P=0.059N
Preputial Gland: Adenoma			
Overall Rates (a)	1/50 (2%)	3/50 (6%)	0/50 (0%)
Adjusted Rates (b)	2.6%	8.7%	0.0%
Terminal Rates (c)	0/30 (0%)	2/32 (6%)	0/27 (0%)
Week of First Observation	96	98	
Life Table Tests (d)	P=0.386N	P=0.331	P=0.490N
Incidental Tumor Tests (d)	P=0.313N	P=0.354	P=0.398N
Cochran-Armitage Trend Test (d)	P=0.378N		
Fisher Exact Test (d)		P=0.309	P=0.500N

TABLE E1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) (Continued)

	Vehicle Control	1,875 mg/kg	3,750 mg/kg
Preputial Gland: Adenoma or Carcinoma			
Overall Rates (a)	2/50 (4%)	5/50 (10%)	1/50 (2%)
Adjusted Rates (b)	5.4%	13.8%	2.6%
Terminal Rates (c)	0/30 (0%)	3/32 (9%)	0/27 (0%)
Week of First Observation	96	93	98
Life Table Tests (d)	P=0.428N	P=0.242	P=0.510N
Incidental Tumor Tests (d)	P=0.283N	P=0.274	P=0.320N
Cochran-Armitage Trend Test (d)	P=0.412N		
Fisher Exact Test (d)		P=0.218	P=0.500N
Testis: Interstitial Cell Tumor			
Overall Rates (a)	41/50 (82%)	43/50 (86%)	39/50 (78%)
Adjusted Rates (b)	93.2%	95.5%	86.0%
Terminal Rates (c)	27/30 (90%)	30/32 (94%)	21/27 (78%)
Week of First Observation	74	81	73
Life Table Tests (d)	P=0.485	P=0.565N	P=0.519
Incidental Tumor Tests (d)	P=0.229N	P=0.599	P=0.288N
Cochran-Armitage Trend Test (d)	P=0.348N		
Fisher Exact Test (d)		P=0.393	P=0.402N
Zymbal Gland: Adenoma or Carcinoma			
Overall Rates (a)	0/50 (0%)	3/50 (6%)	2/50 (4%)
Adjusted Rates (b)	0.0%	8.5%	7.4%
Terminal Rates (c)	0/30 (0%)	2/32 (6%)	2/27 (7%)
Week of First Observation		96	105
Life Table Tests (d)	P=0.180	P=0.135	P=0.215
Incidental Tumor Tests (d)	P=0.204	P=0.143	P=0.215
Cochran-Armitage Trend Test (d)	P=0.202		
Fisher Exact Test (d)		P=0.121	P=0.247

(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).

TABLE E2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl)

	Vehicle Control	100 mg/kg	300 mg/kg	900 mg/kg
Subcutaneous Tissue: Fibroma, Fibrosarcoma, or Sarcoma				
Overall Rates (a)	0/50 (0%)	3/50 (6%)	1/50 (2%)	2/50 (4%)
Adjusted Rates (b)	0.0%	8.0%	3.0%	5.0%
Terminal Rates (c)	0/34 (0%)	1/30 (3%)	1/33 (3%)	0/31 (0%)
Week of First Observation		53	105	82
Life Table Tests (d)	P=0.425	P=0.115	P=0.494	P=0.243
Incidental Tumor Tests (d)	P=0.391	P=0.126	P=0.494	P=0.344
Cochran-Armitage Trend Test (d)	P=0.429			
Fisher Exact Test (d)		P=0.121	P=0.500	P=0.247
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma				
Overall Rates (a)	1/50 (2%)	0/50 (0%)	3/49 (6%)	2/50 (4%)
Adjusted Rates (b)	2.9%	0.0%	8.2%	6.5%
Terminal Rates (c)	1/34 (3%)	0/30 (0%)	1/32 (3%)	2/31 (6%)
Week of First Observation	105		100	105
Life Table Tests (d)	P=0.289	P=0.525N	P=0.309	P=0.468
Incidental Tumor Tests (d)	P=0.262	P=0.525N	P=0.327	P=0.468
Cochran-Armitage Trend Test (d)	P=0.297			
Fisher Exact Test (d)		P=0.500N	P=0.301	P=0.500
Hematopoietic System: Mononuclear Cell Leukemia				
Overall Rates (a)	8/50 (16%)	10/50 (20%)	7/50 (14%)	8/50 (16%)
Adjusted Rates (b)	19.9%	25.5%	16.6%	19.2
Terminal Rates (c)	3/34 (9%)	4/30 (13%)	1/33 (3%)	2/31 (6%)
Week of First Observation	96	80	94	47
Life Table Tests (d)	P=0.507N	P=0.337	P=0.480N	P=0.546N
Incidental Tumor Tests (d)	P=0.364N	P=0.479	P=0.380N	P=0.485N
Cochran-Armitage Trend Test (d)	P=0.473N			
Fisher Exact Test (d)		P=0.397	P=0.500N	P=0.607N
Pituitary: Adenoma				
Overall Rates (a)	22/50 (44%)	18/50 (36%)	18/50 (36%)	18/50 (36%)
Adjusted Rates (b)	54.4%	47.9%	41.7%	45.1%
Terminal Rates (c)	16/34 (47%)	11/30 (37%)	9/33 (27%)	10/31 (32%)
Week of First Observation	83	90	71	88
Life Table Tests (d)	P=0.402N	P=0.432N	P=0.300N	P=0.392N
Incidental Tumor Tests (d)	P=0.325N	P=0.302N	P=0.261N	P=0.210N
Cochran-Armitage Trend Test (d)	P=0.338N			
Fisher Exact Test (d)		P=0.270N	P=0.270N	P=0.270N
Pituitary: Carcinoma				
Overall Rates (a)	3/50 (6%)	2/50 (4%)	1/50 (2%)	2/50 (4%)
Adjusted Rates (b)	7.6%	5.3%	2.4%	5.8%
Terminal Rates (c)	1/34 (3%)	0/30 (0%)	0/33 (0%)	1/31 (3%)
Week of First Observation	77	92	98	99
Life Table Tests (d)	P=0.509N	P=0.525N	P=0.305N	P=0.519N
Incidental Tumor Tests (d)	P=0.554N	P=0.402N	P=0.311N	P=0.648N
Cochran-Armitage Trend Test (d)	P=0.500N			
Fisher Exact Test (d)		P=0.500N	P=0.309N	P=0.500N
Pituitary: Adenoma or Carcinoma				
Overall Rates (a)	25/50 (50%)	20/50 (40%)	19/50 (38%)	20/50 (40%)
Adjusted Rates (b)	59.1%	50.8%	43.1%	49.1%
Terminal Rates (c)	17/34 (50%)	11/30 (37%)	9/33 (27%)	11/31 (35%)
Week of First Observation	77	90	71	88
Life Table Tests (d)	P=0.369N	P=0.377N	P=0.199N	P=0.338N
Incidental Tumor Tests (d)	P=0.299N	P=0.205N	P=0.150N	P=0.204N
Cochran-Armitage Trend Test (d)	P=0.297N			
Fisher Exact Test (d)		P=0.211N	P=0.157N	P=0.211N

TABLE E2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) (Continued)

	Vehicle Control	100 mg/kg	300 mg/kg	900 mg/kg
Adrenal: Pheochromocytoma				
Overall Rates (a)	1/50 (2%)	3/50 (6%)	6/50 (12%)	7/50 (14%)
Adjusted Rates (b)	2.7%	8.3%	17.6%	19.6%
Terminal Rates (c)	0/34 (0%)	1/30 (3%)	5/33 (15%)	3/31 (10%)
Week of First Observation	101	92	104	97
Life Table Tests (d)	P=0.031	P=0.286	P=0.059	P=0.033
Incidental Tumor Tests (d)	P=0.023	P=0.373	P=0.065	P=0.014
Cochran-Armitage Trend Test (d)	P=0.031			
Fisher Exact Test (d)		P=0.309	P=0.056	P=0.030
Adrenal: Pheochromocytoma or Pheochromocytoma, Malignant				
Overall Rates (a)	1/50 (2%)	4/50 (8%)	6/50 (12%)	7/50 (14%)
Adjusted Rates (b)	2.7%	10.3%	17.6%	19.6%
Terminal Rates (c)	0/34 (0%)	1/30 (3%)	5/33 (15%)	3/31 (10%)
Week of First Observation	101	82	104	97
Life Table Tests (d)	P=0.049	P=0.169	P=0.059	P=0.033
Incidental Tumor Tests (d)	P=0.046	P=0.301	P=0.065	P=0.014
Cochran-Armitage Trend Test (d)	P=0.048			
Fisher Exact Test (d)		P=0.181	P=0.056	P=0.030
Thyroid: C-Cell Adenoma				
Overall Rates (a)	5/50 (10%)	5/48 (10%)	5/50 (10%)	3/50 (6%)
Adjusted Rates (b)	14.7%	13.6%	14.0%	9.7%
Terminal Rates (c)	5/34 (15%)	2/28 (7%)	4/33 (12%)	3/31 (10%)
Week of First Observation	105	71	85	105
Life Table Tests (d)	P=0.289N	P=0.530	P=0.617	P=0.406N
Incidental Tumor Tests (d)	P=0.262N	P=0.627	P=0.614	P=0.406N
Cochran-Armitage Trend Test (d)	P=0.265N			
Fisher Exact Test (d)		P=0.603	P=0.630N	P=0.358N
Thyroid: C-Cell Carcinoma				
Overall Rates (a)	4/50 (8%)	5/48 (10%)	2/50 (4%)	1/50 (2%)
Adjusted Rates (b)	11.1%	14.9%	6.1%	2.9%
Terminal Rates (c)	3/34 (9%)	3/28 (11%)	2/33 (6%)	0/31 (0%)
Week of First Observation	98	80	105	104
Life Table Tests (d)	P=0.093N	P=0.406	P=0.345N	P=0.203N
Incidental Tumor Tests (d)	P=0.083N	P=0.482	P=0.335N	P=0.226N
Cochran-Armitage Trend Test (d)	P=0.083N			
Fisher Exact Test (d)		P=0.474	P=0.339N	P=0.181N
Thyroid: C-Cell Adenoma or Carcinoma				
Overall Rates (a)	9/50 (18%)	9/48 (19%)	7/50 (14%)	4/50 (8%)
Adjusted Rates (b)	25.4%	25.2%	19.9%	12.3%
Terminal Rates (c)	8/34 (24%)	5/28 (18%)	6/33 (18%)	3/31 (10%)
Week of First Observation	98	71	85	104
Life Table Tests (d)	P=0.082N	P=0.459	P=0.409N	P=0.151N
Incidental Tumor Tests (d)	P=0.065N	P=0.593	P=0.404N	P=0.163N
Cochran-Armitage Trend Test (d)	P=0.068N			
Mammary Gland: Fibroadenoma				
Overall Rates (a)	14/50 (28%)	13/50 (26%)	8/50 (16%)	8/50 (16%)
Adjusted Rates (b)	37.5%	37.1%	21.4%	22.6%
Terminal Rates (c)	11/34 (32%)	9/30 (30%)	5/33 (15%)	5/31 (16%)
Week of First Observation	98	71	98	88
Life Table Tests (d)	P=0.108N	P=0.549	P=0.125N	P=0.164N
Incidental Tumor Tests (d)	P=0.109N	P=0.573N	P=0.098N	P=0.146N
Cochran-Armitage Trend Test (d)	P=0.086N			
Fisher Exact Test (d)		P=0.500N	P=0.114N	P=0.114N
Fisher Exact Test (d)		P=0.565	P=0.393N	P=0.117N

TABLE E2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) (Continued)

	Vehicle Control	100 mg/kg	300 mg/kg	900 mg/kg
Mammary Gland: Adenocarcinoma				
Overall Rates (a)	(e) 3/50 (6%)	2/50 (4%)	0/50 (0%)	0/50 (0%)
Adjusted Rates (b)	8.8%	6.2%	0.0%	0.0%
Terminal Rates (c)	3/34 (9%)	1/30 (3%)	0/33 (0%)	0/31 (0%)
Week of First Observation	105	102		
Life Table Tests (d)	P=0.075N	P=0.545N	P=0.126N	P=0.137N
Incidental Tumor Tests (d)	P=0.078N	P=0.555N	P=0.126N	P=0.137N
Cochran-Armitage Trend Test (d)	P=0.072N			
Fisher Exact Test (d)		P=0.500N	P=0.121N	P=0.121N
Mammary Gland: Adenocarcinoma or Fibroadenoma				
Overall Rates (a)	16/50 (32%)	14/50 (28%)	8/50 (16%)	8/50 (16%)
Adjusted Rates (b)	42.9%	40.1%	21.4%	22.6%
Terminal Rates (c)	13/34 (38%)	10/30 (33%)	5/33 (15%)	5/31 (16%)
Week of First Observation	98	71	98	88
Life Table Tests (d)	P=0.053N	P=0.553N	P=0.058N	P=0.082N
Incidental Tumor Tests (d)	P=0.052N	P=0.500N	P=0.043N	P=0.069N
Cochran-Armitage Trend Test (d)	P=0.039N			
Fisher Exact Test (d)		P=0.414N	P=0.050N	P=0.050N
Uterus: Endometrial Stromal Polyp				
Overall Rates (a)	9/50 (18%)	17/50 (34%)	10/50 (20%)	10/50 (20%)
Adjusted Rates (b)	23.9%	43.5%	29.2%	29.3%
Terminal Rates (c)	7/34 (21%)	9/30 (30%)	9/33 (27%)	8/31 (26%)
Week of First Observation	49	80	101	47
Life Table Tests (d)	P=0.366N	P=0.042	P=0.477	P=0.428
Incidental Tumor Tests (d)	P=0.241N	P=0.047	P=0.485	P=0.549
Cochran-Armitage Trend Test (d)	P=0.324N			
Fisher Exact Test (d)		P=0.055	P=0.500	P=0.500
Uterus: Endometrial Stromal Polyp or Sarcoma				
Overall Rates (a)	9/50 (18%)	18/50 (36%)	10/50 (20%)	10/50 (20%)
Adjusted Rates (b)	23.9%	44.7%	29.2%	29.3%
Terminal Rates (c)	7/34 (21%)	9/30 (30%)	9/33 (27%)	8/31 (26%)
Week of First Observation	49	69	101	47
Life Table Tests (d)	P=0.329N	P=0.029	P=0.477	P=0.428
Incidental Tumor Tests (d)	P=0.230N	P=0.034	P=0.485	P=0.549
Cochran-Armitage Trend Test (d)	P=0.287N			
Fisher Exact Test		P=0.035	P=0.500	P=0.500

(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) An adenoma was also observed in one animal.

TABLE E3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl)

	Vehicle Control	2,500 mg/kg	5,000 mg/kg
Subcutaneous Tissue: Fibroma			
Overall Rates (a)	2/50 (4%)	6/50 (12%)	2/50 (4%)
Adjusted Rates (b)	6.9%	16.2%	6.5%
Terminal Rates (c)	2/29 (7%)	5/36 (14%)	1/28 (4%)
Week of First Observation	104	102	96
Life Table Tests (d)	P=0.564	P=0.211	P=0.682
Incidental Tumor Tests (d)	P=0.542	P=0.184	P=0.664
Cochran-Armitage Trend Test (d)	P=0.579		
Fisher Exact Test (d)		P=0.134	P=0.691
Subcutaneous Tissue: Fibrosarcoma			
Overall Rates (a)	5/50 (10%)	5/50 (10%)	3/50 (6%)
Adjusted Rates (b)	14.9%	11.7%	8.2%
Terminal Rates (c)	3/29 (10%)	1/36 (3%)	1/28 (4%)
Week of First Observation	93	70	68
Life Table Tests (d)	P=0.317N	P=0.517N	P=0.378N
Incidental Tumor Tests (d)	P=0.334N	P=0.548	P=0.393N
Cochran-Armitage Trend Test (d)	P=0.297N		
Fisher Exact Test (d)		P=0.630	P=0.357N
Subcutaneous Tissue: Fibroma or Fibrosarcoma			
Overall Rates (a)	7/50 (14%)	10/50 (20%)	5/50 (10%)
Adjusted Rates (b)	21.5%	24.3%	14.3%
Terminal Rates (c)	5/29 (17%)	6/36 (17%)	2/28 (7%)
Week of First Observation	93	70	68
Life Table Tests (d)	P=0.363N	P=0.461	P=0.406N
Incidental Tumor Tests (d)	P=0.384N	P=0.305	P=0.429N
Cochran-Armitage Trend Test (d)	P=0.336N		
Fisher Exact Test (d)		P=0.298	P=0.380N
Subcutaneous Tissue: Fibrosarcoma or Neurofibrosarcoma			
Overall Rates (a)	6/50 (12%)	5/50 (10%)	3/50 (6%)
Adjusted Rates (b)	17.0%	11.7%	8.2%
Terminal Rates (c)	3/29 (10%)	1/36 (3%)	1/28 (4%)
Week of First Observation	91	70	68
Life Table Tests (d)	P=0.216N	P=0.391N	P=0.272N
Incidental Tumor Tests (d)	P=0.214N	P=0.627N	P=0.258N
Cochran-Armitage Trend Test (d)	P=0.195N		
Fisher Exact Test (d)		P=0.500N	P=0.243N
Subcutaneous Tissue: Sarcoma, Fibrosarcoma, or Neurofibrosaarcoma			
Overall Rates (a)	8/50 (16%)	9/50 (18%)	6/50 (12%)
Adjusted Rates (b)	22.6%	20.3%	16.9%
Terminal Rates (c)	4/29 (14%)	2/36 (6%)	2/28 (7%)
Week of First Observation	91	70	68
Life Table Tests (d)	P=0.385N	P=0.560N	P=0.429N
Incidental Tumor Tests (d)	P=0.349N	P=0.308	P=0.412N
Cochran-Armitage Trend Test (d)	P=0.339N		
Fisher Exact Test (d)		P=0.500	P=0.387N
Subcutaneous Tissue: Fibroma, Sarcoma, Fibrosarcoma, or Neurofibrosarcoma			
Overall Rates (a)	10/50 (20%)	14/50 (28%)	8/50 (16%)
Adjusted Rates (b)	28.8%	32.0%	22.5%
Terminal Rates (c)	6/29 (21%)	7/36 (19%)	3/28 (11%)
Week of First Observation	91	70	68
Life Table Tests (d)	P=0.407N	P=0.427	P=0.443N
Incidental Tumor Tests (d)	P=0.382N	P=0.168	P=0.437N
Cochran-Armitage Trend Test (d)	P=0.357N		
Fisher Exact Test (d)		P=0.241	P=0.398N

TABLE E3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) (Continued)

	Vehicle Control	2,500 mg/kg	5,000 mg/kg
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	9/50 (18%)	5/50 (10%)	9/50 (18%)
Adjusted Rates (b)	29.1%	13.9%	27.2%
Terminal Rates (c)	8/29 (28%)	5/36 (14%)	5/28 (18%)
Week of First Observation	70	104	85
Life Table Tests (d)	P=0.529	P=0.096N	P=0.570
Incidental Tumor Tests (d)	P=0.533	P=0.107N	P=0.575
Cochran-Armitage Trend Test (d)	P=0.555		
Fisher Exact Test (d)		P=0.194N	P=0.603N
Lung: Alveolar/Bronchiolar Carcinoma			
Overall Rates (a)	2/50 (4%)	5/50 (10%)	5/50 (10%)
Adjusted Rates (b)	5.6%	13.9%	15.6%
Terminal Rates (c)	1/29 (3%)	5/36 (14%)	3/28 (11%)
Week of First Observation	79	104	78
Life Table Tests (d)	P=0.160	P=0.299	P=0.209
Incidental Tumor Tests (d)	P=0.183	P=0.252	P=0.233
Cochran-Armitage Trend Test (d)	P=0.178		
Fisher Exact Test (d)		P=0.218	P=0.218
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	11/50 (22%)	10/50 (20%)	13/50 (26%)
Adjusted Rates (b)	34.0%	27.8%	38.1%
Terminal Rates (c)	9/29 (31%)	10/36 (28%)	8/28 (29%)
Week of First Observation	70	104	78
Life Table Tests (d)	P=0.324	P=0.300N	P=0.375
Incidental Tumor Tests (d)	P=0.350	P=0.350N	P=0.402
Cochran-Armitage Trend Test (d)	P=0.360		
Fisher Exact Test (d)		P=0.500N	P=0.408
Hematopoietic System: Malignant Lymphoma, Lymphocytic Type			
Overall Rates (a)	0/50 (0%)	2/50 (4%)	3/50 (6%)
Adjusted Rates (b)	0.0%	5.6%	9.5%
Terminal Rates (c)	0/29 (0%)	2/36 (6%)	2/28 (7%)
Week of First Observation		104	85
Life Table Tests (d)	P=0.070	P=0.287	P=0.116
Incidental Tumor Tests (d)	P=0.087	P=0.287	P=0.135
Cochran-Armitage Trend Test (d)	P=0.082		
Fisher Exact Test (d)		P=0.247	P=0.121
Hematopoietic System: Malignant Lymphoma, Histiocytic Type			
Overall Rates (a)	0/50 (0%)	0/50 (0%)	3/50 (6%)
Adjusted Rates (b)	0.0%	0.0%	8.7%
Terminal Rates (c)	0/29 (0%)	0/36 (0%)	1/28 (4%)
Week of First Observation			87
Life Table Tests (d)	P=0.032	(e)	P=0.118
Incidental Tumor Tests (d)	P=0.045	(e)	P=0.124
Cochran-Armitage Trend Test (d)	P=0.037		
Fisher Exact Test (d)		(e)	P=0.121
Hematopoietic System: Malignant Lymphoma, Mixed Type			
Overall Rates (a)	5/50 (10%)	10/50 (20%)	10/50 (20%)
Adjusted Rates (b)	14.3%	26.1%	33.9%
Terminal Rates (c)	2/29 (7%)	8/36 (22%)	9/28 (32%)
Week of First Observation	77	99	87
Life Table Tests (d)	P=0.093	P=0.246	P=0.118
Incidental Tumor Tests (d)	P=0.095	P=0.140	P=0.125
Cochran-Armitage Trend Test (d)	P=0.114		
Fisher Exact Test (d)		P=0.131	P=0.131

TABLE E3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) (Continued)

	Vehicle Control	2,500 mg/kg	5,000 mg/kg
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	6/50 (12%)	12/50 (24%)	16/50 (32%)
Adjusted Rates (b)	16.3%	31.4%	48.7%
Terminal Rates (c)	2/29 (7%)	10/36 (28%)	12/28 (43%)
Week of First Observation	77	99	85
Life Table Tests (d)	P=0.009	P=0.204	P=0.014
Incidental Tumor Tests (d)	P=0.011	P=0.099	P=0.017
Cochran-Armitage Trend Test (d)	P=0.012		
Fisher Exact Test (d)		P=0.096	P=0.014
Circulatory System: Hemangiosarcoma			
Overall Rates (a)	7/50 (14%)	2/50 (4%)	2/50 (4%)
Adjusted Rates (b)	21.1%	5.6%	6.8%
Terminal Rates (c)	4/29 (14%)	2/36 (6%)	1/28 (4%)
Week of First Observation	93	104	102
Life Table Tests (d)	P=0.044N	P=0.046N	P=0.099N
Incidental Tumor Tests (d)	P=0.054N	P=0.073N	P=0.109N
Cochran-Armitage Trend Test (d)	P=0.042N		
Fisher Exact Test (d)		P=0.080N	P=0.080N
Liver: Hepatocellular Adenoma			
Overall Rates (a)	10/50 (20%)	14/50 (28%)	14/50 (28%)
Adjusted Rates (b)	30.9%	37.7%	42.9%
Terminal Rates (c)	8/29 (28%)	13/36 (36%)	10/28 (36%)
Week of First Observation	70	100	81
Life Table Tests (d)	P=0.173	P=0.444	P=0.215
Incidental Tumor Tests (d)	P=0.168	P=0.377	P=0.205
Cochran-Armitage Trend Test (d)	P=0.210		
Fisher Exact Test (d)		P=0.241	P=0.241
Liver: Hepatocellular Carcinoma			
Overall Rates (a)	9/50 (18%)	12/50 (24%)	(f) 12/50 (24%)
Adjusted Rates (b)	22.1%	28.5%	29.9%
Terminal Rates (c)	2/29 (7%)	7/36 (19%)	3/28 (11%)
Week of First Observation	37	72	76
Life Table Tests (d)	P=0.265	P=0.470	P=0.311
Incidental Tumor Tests (d)	P=0.289	P=0.193	P=0.331
Cochran-Armitage Trend Test (d)	P=0.273		
Fisher Exact Test (d)		P=0.312	P=0.312
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	18/50 (36%)	21/50 (42%)	23/50 (46%)
Adjusted Rates (b)	45.0%	50.7%	59.4%
Terminal Rates (c)	9/29 (31%)	16/36 (44%)	13/28 (46%)
Week of First Observation	37	72	76
Life Table Tests (d)	P=0.171	P=0.541N	P=0.209
Incidental Tumor Tests (d)	P=0.176	P=0.331	P=0.205
Cochran-Armitage Trend Test (d)	P=0.180		
Fisher Exact Test (d)		P=0.341	P=0.208
Adrenal: Adenoma			
Overall Rates (a)	4/49 (8%)	0/50 (0%)	2/47 (4%)
Adjusted Rates (b)	14.3%	0.0%	7.4%
Terminal Rates (c)	4/28 (14%)	0/36 (0%)	2/27 (7%)
Week of First Observation	104		104
Life Table Tests (d)	P=0.219N	P=0.035N	P=0.351N
Incidental Tumor Tests (d)	P=0.219N	P=0.035N	P=0.351N
Cochran-Armitage Trend Test (d)	P=0.233N		
Fisher Exact Test (d)		P=0.056N	P=0.359N

TABLE E3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) (Continued)

	Vehicle Control	2,500 mg/kg	5,000 mg/kg
Adrenal: Adenoma or Cortical Adenoma			
Overall Rates (a)	4/49 (8%)	0/50 (0%)	4/47 (9%)
Adjusted Rates (b)	14.3%	0.0%	14.8%
Terminal Rates (c)	4/28 (14%)	0/36 (0%)	4/27 (15%)
Week of First Observation	104		104
Life Table Tests (d)	P=0.577	P=0.035N	P=0.627
Incidental Tumor Tests (d)	P=0.577	P=0.035N	P=0.627
Cochran-Armitage Trend Test (d)	P=0.570		
Fisher Exact Test (d)		P=0.056N	P=0.619
Adrenal: Pheochromocytoma			
Overall Rates (a)	1/49 (2%)	4/50 (8%)	1/47 (2%)
Adjusted Rates (b)	3.6%	11.1%	3.7%
Terminal Rates (c)	1/28 (4%)	4/36 (11%)	1/27 (4%)
Week of First Observation	104	104	104
Life Table Tests (d)	P=0.593	P=0.261	P=0.754
Incidental Tumor Tests (d)	P=0.593	P=0.261	P=0.754
Cochran-Armitage Trend Test (d)	P=0.585		
Fisher Exact Test (d)		P=0.187	P=0.742
Thyroid: Follicular Cell Adenoma			
Overall Rates (a)	1/49 (2%)	3/48 (6%)	2/49 (4%)
Adjusted Rates (b)	3.4%	8.8%	6.9%
Terminal Rates (c)	1/29 (3%)	3/34 (9%)	1/27 (4%)
Week of First Observation	104	104	102
Life Table Tests (d)	P=0.370	P=0.363	P=0.476
Incidental Tumor Tests (d)	P=0.359	P=0.363	P=0.458
Cochran-Armitage Trend Test (d)	P=0.400		
Fisher Exact Test (d)		P=0.301	P=0.500
Thyroid: Follicular Cell Carcinoma			
Overall Rates (a)	0/49 (0%)	0/48 (0%)	3/49 (6%)
Adjusted Rates (b)	0.0%	0.0%	8.6%
Terminal Rates (c)	0/29 (0%)	0/34 (0%)	1/27 (4%)
Week of First Observation			83
Life Table Tests (d)	P=0.034	(e)	P=0.122
Incidental Tumor Tests (d)	P=0.048	(e)	P=0.132
Cochran-Armitage Trend Test (d)	P=0.038		
Fisher Exact Test (d)		(e)	P=0.121
Thyroid: Follicular Cell Adenoma or Carcinoma			
Overall Rates (a)	1/49 (2%)	3/48 (6%)	5/49 (10%)
Adjusted Rates (b)	3.4%	8.8%	15.1%
Terminal Rates (c)	1/29 (3%)	3/34 (9%)	2/27 (7%)
Week of First Observation	104	104	83
Life Table Tests (d)	P=0.059	P=0.363	P=0.099
Incidental Tumor Tests (d)	P=0.065	P=0.363	P=0.097
Cochran-Armitage Trend Test (d)	P=0.071		
Fisher Exact Test (d)		P=0.301	P=0.102
Harderian Gland: Adenoma			
Overall Rates (a)	3/50 (6%)	3/50 (6%)	2/50 (4%)
Adjusted Rates (b)	9.1%	8.3%	6.3%
Terminal Rates (c)	2/29 (7%)	3/36 (8%)	1/28 (4%)
Week of First Observation	81	104	94
Life Table Tests (d)	P=0.418N	P=0.572N	P=0.505N
Incidental Tumor Tests (d)	P=0.416N	P=0.632N	P=0.504N
Cochran-Armitage Trend Test (d)	P=0.412N		
Fisher Exact Test (d)		P=0.661	P=0.500N

TABLE E3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) (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) No P value is reported because no tumors were observed in the 2,500 mg/kg and vehicle control groups.
(f) A hepatoblastoma was also observed in one animal.

TABLE E4. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl)

	Vehicle Control	2,500 mg/kg	5,000 mg/kg
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	1/50 (2%)	2/49 (4%)	3/50 (6%)
Adjusted Rates (b)	4.8%	4.8%	11.3%
Terminal Rates (c)	1/21 (5%)	0/22 (0%)	1/20 (5%)
Week of First Observation	104	79	84
Life Table Tests (d)	P=0.229	P=0.529	P=0.303
Incidental Tumor Tests (d)	P=0.251	P=0.586	P=0.349
Cochran-Armitage Trend Test (d)	P=0.223		
Fisher Exact Test (d)		P=0.492	P=0.309
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	3/50 (6%)	3/49 (6%)	3/50 (6%)
Adjusted Rates (b)	13.1%	9.1%	11.3%
Terminal Rates (c)	2/21 (10%)	1/22 (5%)	1/20 (5%)
Week of First Observation	102	79	84
Life Table Tests (d)	P=0.574	P=0.644N	P=0.643
Incidental Tumor Tests (d)	P=0.516N	P=0.637N	P=0.584N
Cochran-Armitage Trend Test (d)	P=0.583		
Fisher Exact Test (d)		P=0.651	P=0.661
Hematopoietic System: Malignant Lymphoma, Lymphocytic Type			
Overall Rates (a)	5/50 (10%)	2/49 (4%)	6/50 (12%)
Adjusted Rates (b)	19.8%	9.1%	26.3%
Terminal Rates (c)	3/21 (14%)	2/22 (9%)	4/20 (20%)
Week of First Observation	69	105	93
Life Table Tests (d)	P=0.410	P=0.205N	P=0.480
Incidental Tumor Tests (d)	P=0.491	P=0.276N	P=0.569
Cochran-Armitage Trend Test (d)	P=0.430		
Fisher Exact Test (d)		P=0.227N	P=0.500
Hematopoietic System: Malignant Lymphoma, Mixed Type			
Overall Rates (a)	10/50 (20%)	10/49 (20%)	10/50 (20%)
Adjusted Rates (b)	41.7%	35.6%	44.8%
Terminal Rates (c)	8/21 (38%)	5/22 (23%)	8/20 (40%)
Week of First Observation	67	85	96
Life Table Tests (d)	P=0.526	P=0.571N	P=0.559
Incidental Tumor Tests (d)	P=0.502N	P=0.590N	P=0.575N
Cochran-Armitage Trend Test (d)	P=0.550		
Fisher Exact Test (d)		P=0.579	P=0.599N
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	15/50 (30%)	12/49 (24%)	20/50 (40%)
Adjusted Rates (b)	58.1%	43.2%	73.1%
Terminal Rates (c)	11/21 (52%)	7/22 (32%)	13/20 (65%)
Week of First Observation	67	85	64
Life Table Tests (d)	P=0.144	P=0.295N	P=0.158
Incidental Tumor Tests (d)	P=0.210	P=0.351N	P=0.231
Cochran-Armitage Trend Test (d)	P=0.166		
Fisher Exact Test (d)		P=0.349N	P=0.201
Liver: Hepatocellular Adenoma			
Overall Rates (a)	3/50 (6%)	2/49 (4%)	7/50 (14%)
Adjusted Rates (b)	14.3%	8.4%	27.0%
Terminal Rates (c)	3/21 (14%)	1/22 (5%)	3/20 (15%)
Week of First Observation	104	93	67
Life Table Tests (d)	P=0.093	P=0.487N	P=0.144
Incidental Tumor Tests (d)	P=0.152	P=0.529N	P=0.201
Cochran-Armitage Trend Test (d)	P=0.099		
Fisher Exact Test (d)		P=0.510N	P=0.159

TABLE E4. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) (Continued)

	Vehicle Control	2,500 mg/kg	5,000 mg/kg
Liver: Hepatocellular Carcinoma			
Overall Rates (a)	1/50 (2%)	1/49 (2%)	6/50 (12%)
Adjusted Rates (b)	4.8%	4.5%	23.3%
Terminal Rates (c)	1/21 (5%)	1/22 (5%)	2/20 (10%)
Week of First Observation	104	104	90
Life Table Tests (d)	P=0.022	P=0.753N	P=0.058
Incidental Tumor Tests (d)	P=0.043	P=0.753N	P=0.098
Cochran-Armitage Trend Test (d)	P=0.023		
Fisher Exact Test (d)		P=0.747	P=0.056
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	4/50 (8%)	3/49 (6%)	10/50 (20%)
Adjusted Rates (b)	19.0%	12.7%	36.3%
Terminal Rates (c)	4/21 (19%)	2/22 (9%)	4/20 (20%)
Week of First Observation	104	93	67
Life Table Tests (d)	P=0.039	P=0.481N	P=0.069
Incidental Tumor Tests (d)	P=0.071	P=0.518N	P=0.106
Cochran-Armitage Trend Test (d)	P=0.042		
Fisher Exact Test (d)		P=0.511N	P=0.074
Pituitary: Adenoma			
Overall Rates (a)	13/46 (28%)	8/46 (17%)	15/45 (33%)
Adjusted Rates (b)	51.5%	37.6%	58.0%
Terminal Rates (c)	9/20 (45%)	7/20 (35%)	10/20 (50%)
Week of First Observation	73	93	69
Life Table Tests (d)	P=0.361	P=0.154N	P=0.410
Incidental Tumor Tests (d)	P=0.411	P=0.166N	P=0.448
Cochran-Armitage Trend Test (d)	P=0.337		
Fisher Exact Test (d)		P=0.160N	P=0.383
Pituitary: Adenoma or Carcinoma			
Overall Rates (a)	13/46 (28%)	9/46 (20%)	15/45 (33%)
Adjusted Rates (b)	51.5%	42.4%	58.0%
Terminal Rates (c)	9/20 (45%)	8/20 (40%)	10/20 (50%)
Week of First Observation	73	93	69
Life Table Tests (d)	P=0.361	P=0.224N	P=0.410
Incidental Tumor Tests (d)	P=0.411	P=0.242N	P=0.448
Cochran-Armitage Trend Test (d)	P=0.338		
Fisher Exact Test (d)		P=0.232N	P=0.383
Thyroid: Follicular Cell Adenoma			
Overall Rates (a)	7/49 (14%)	4/47 (9%)	5/49 (10%)
Adjusted Rates (b)	33.3%	18.2%	25.0%
Terminal Rates (c)	7/21 (33%)	4/22 (18%)	5/20 (25%)
Week of First Observation	104	104	104
Life Table Tests (d)	P=0.329N	P=0.218N	P=0.405N
Incidental Tumor Tests (d)	P=0.329N	P=0.218N	P=0.405N
Cochran-Armitage Trend Test (d)	P=0.314N		
Fisher Exact Test (d)		P=0.287N	P=0.380N
Thyroid: Follicular Cell Adenoma or Carcinoma			
Overall Rates (a)	7/49 (14%)	6/47 (13%)	5/49 (10%)
Adjusted Rates (b)	33.3%	27.3%	25.0%
Terminal Rates (c)	7/21 (33%)	6/22 (27%)	5/20 (25%)
Week of First Observation	104	104	104
Life Table Tests (d)	P=0.339N	P=0.460N	P=0.405N
Incidental Tumor Tests (d)	P=0.339N	P=0.460N	P=0.405N
Cochran-Armitage Trend Test (d)	P=0.323N		
Fisher Exact Test (d)		P=0.533N	P=0.380N

TABLE E4. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) (Continued)

	Vehicle Control	2,500 mg/kg	5,000 mg/kg
Uterus: Endometrial Stromal Polyp			
Overall Rates (a)	3/50 (6%)	0/48 (0%)	0/50 (0%)
Adjusted Rates (b)	13.5%	0.0%	0.0%
Terminal Rates (c)	2/21 (10%)	0/21 (0%)	0/20 (0%)
Week of First Observation	103		
Life Table Tests (d)	P=0.040N	P=0.125N	P=0.131N
Incidental Tumor Tests (d)	P=0.030N	P=0.152N	P=0.093N
Cochran-Armitage Trend Test (d)	P=0.038N		
Fisher Exact Test (d)		P=0.129N	P=0.121N
Harderian Gland: Adenoma			
Overall Rates (a)	4/50 (8%)	2/49 (4%)	1/50 (2%)
Adjusted Rates (b)	16.0%	9.1%	4.0%
Terminal Rates (c)	3/21 (14%)	2/22 (9%)	0/20 (0%)
Week of First Observation	66	104	97
Life Table Tests (d)	P=0.128N	P=0.321N	P=0.197N
Incidental Tumor Tests (d)	P=0.119N	P=0.375N	P=0.173N
Cochran-Armitage Trend Test (d)	P=0.119N		
Fisher Exact Test (d)		P=0.349N	P=0.181N
Harderian Gland: Adenoma or Carcinoma			
Overall Rates (a)	4/50 (8%)	3/49 (6%)	1/50 (2%)
Adjusted Rates (b)	16.0%	13.6%	4.0%
Terminal Rates (c)	3/21 (14%)	3/22 (14%)	0/20 (0%)
Week of First Observation	66	104	97
Life Table Tests (d)	P=0.143N	P=0.481N	P=0.197N
Incidental Tumor Tests (d)	P=0.133N	P=0.538N	P=0.173N
Cochran-Armitage Trend Test (d)	P=0.134N		
Fisher Exact Test (d)		P=0.511N	P=0.181N

(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).

APPENDIX F

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

TABLE F1. HISTORICAL INCIDENCE OF ZYMBAL GLAND CARCINOMAS IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

Historical Incidence at Southern Research Institute	
All studies	0/300
Overall Historical Incidence	
TOTAL (b)	8/1,100 (0.7%)
SD (c)	1.16%
Range (d)	
High	2/50
Low	0/50

(a) Data as of August 3, 1984, for studies of at least 104 weeks
(b) Includes four carcinomas, NOS, two squamous cell carcinomas, one sebaceous adenocarcinoma of the Zymbal gland, and one sebaceous adenocarcinoma of the ear canal. No benign tumors have been observed.
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.

TABLE F2. HISTORICAL INCIDENCE OF PANCREATIC ISLET CELL TUMORS IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Southern Research Institute			
Ethyl acrylate	1/49	4/49	5/49
Benzyl acetate	2/50	1/50	3/50
Allyl isovalerate	2/50	1/50	3/50
HC Red No. 3	3/50	1/50	4/50
Allyl isothiocyanate	2/50	1/50	3/50
Geranyl acetate	3/49	1/49	4/49
TOTAL	13/298 (4.4%)	9/298 (3.0%)	22/298 (7.4%)
SD (b)	1.52%	2.51%	1.71%
Range (c)			
High	3/49	4/49	5/49
Low	1/49	1/50	3/50
Overall Historical Incidence			
TOTAL	43/1,086 (4.0%)	20/1,086 (1.8%)	63/1,086 (5.8%)
SD (b)	2.82%	2.07%	3.08%
Range (c)			
High	5/50	4/49	5/49
Low	0/50	0/50	0/49

(a) Data as of August 3, 1984, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE F3. HISTORICAL INCIDENCE OF PANCREATIC ACINAR CELL TUMORS IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Southern Research Institute			
Ethyl acrylate	0/49	0/49	0/49
Benzyl acetate	1/50	0/50	1/50
Allyl isovalerate	1/50	0/50	1/50
HC Red No. 3	11/50	1/50	11/50
Allyl isothiocyanate	(b) 1/50	0/50	1/50
Geranyl acetate	3/49	1/49	4/49
TOTAL	14/298 (4.7%)	1/298 (0.3%)	14/298 (4.7%)
SD (c)	8.55%	0.82%	8.55%
Range (d)			
High	11/50	1/50	11/50
Low	0/49	0/50	0/49
Overall Historical Incidence			
TOTAL	(e) 46/1,086 (4.2%)	2/1,086 (0.2%)	47/1,086 (4.3%)
SD (c)	7.38%	0.59%	7.37%
Range (d)			
High	14/50	1/49	14/50
Low	0/50	0/50	0/50

(a) Data as of August 3, 1984, for studies of at least 104 weeks
(b) Diagnosed as adenoma, NOS
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.
(e) Includes one adenoma, NOS

TABLE F4. HISTORICAL INCIDENCE OF HEMATOPOIETIC SYSTEM TUMORS IN FEMALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls	
	Lymphoma	Leukemia
Historical Incidence at Southern Research Institute		
Ethyl acrylate	0/50	5/50
Benzyl acetate	0/50	2/50
Allyl isovalerate	1/50	4/50
HC Red No. 3	0/50	10/50
Allyl isothiocyanate	1/50	7/50
Geranyl acetate	0/50	8/50
TOTAL	2/300 (0.7%)	36/300 (12.0%)
SD (b)	1.03%	5.80%
Range (c)		
High	1/50	10/50
Low	0/50	2/50
Overall Historical Incidence		
TOTAL	10/1,100 (0.9%)	196/1,100 (17.8%)
SD (b)	1.60%	8.94%
Range (c)		
High	3/50	(d) 21/50
Low	0/50	2/50

(a) Data as of August 3, 1984, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.
(d) Second highest incidence: 16/50

TABLE F5. HISTORICAL INCIDENCE OF ADRENAL GLAND TUMORS IN FEMALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls		
	Pheochromocytoma	Pheochromocytoma, Malignant	Pheochromocytoma or Pheochromocytoma, Malignant
Historical Incidence at Southern Research Institute			
Ethyl acrylate	3/50	0/50	3/50
Benzyl acetate	1/50	0/50	1/50
Allyl isovalerate	5/50	0/50	5/50
HC Red No. 3	3/50	0/50	3/50
Allyl isothiocyanate	1/50	1/50	2/50
Geranyl acetate	2/50	0/50	2/50
TOTAL	15/300 (5.0%)	1/300 (0.3%)	16/300 (5.3%)
SD (b)	3.03%	0.82%	2.73%
Range (c)			
High	5/50	1/50	5/50
Low	1/50	0/50	1/50
Overall Historical Incidence			
TOTAL	64/1,093 (5.9%)	2/1,093 (0.2%)	65/1,093 (5.9%)
SD (b)	3.08%	0.59%	2.99%
Range (c)			
High	6/50	1/50	6/50
Low	1/50	0/50	1/50

(a) Data as of August 3, 1984, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE F6. HISTORICAL INCIDENCE OF UTERINE ENDOMETRIAL STROMAL TUMORS IN FEMALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls		
	Polyps	Sarcomas	Polyps or Sarcomas
Historical Incidence at Southern Research Institute			
Ethyl acrylate	17/50	0/50	17/50
Benzyl acetate	12/50	1/50	13/50
Allyl isovalerate	11/50	2/50	12/50
HC Red No. 3	10/50	3/50	12/50
Allyl isothiocyanate	14/50	1/50	14/50
Geranyl acetate	8/50	1/50	8/50
TOTAL	72/300 (24.0%)	8/300 (2.7%)	76/300 (25.3%)
SD (b)	6.32%	2.07%	5.89%
Range (c)			
High	17/50	3/50	17/50
Low	8/50	0/50	8/50
Overall Historical Incidence			
TOTAL	234/1,089 (21.5%)	25/1,089 (2.3%)	252/1,089 (23.1%)
SD (b)	6.31%	1.99%	6.32%
Range (c)			
High	17/50	3/49	17/50
Low	6/50	0/50	6/48

(a) Data as of August 3, 1984, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE F7. HISTORICAL INCIDENCE OF HEMATOPOIETIC SYSTEM TUMORS IN MALE B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls		
	Lymphoma	Leukemia	Lymphoma or Leukemia
Historical Incidence at Southern Research Institute			
Ethyl acrylate	9/49	0/49	9/49
Benzyl acetate	5/50	0/50	5/50
Allyl isovalerate	4/50	0/50	4/50
HC Red No. 3	7/50	0/50	7/50
Allyl isothiocyanate	3/50	0/50	3/50
Geranyl acetate	7/50	0/50	7/50
TOTAL	35/299 (11.7%)	0/299 (0.0%)	35/299 (11.7%)
SD (b)	4.56%	0.00%	4.56%
Range (c)			
High	9/49	0/50	9/49
Low	3/50	0/50	3/50
Overall Historical Incidence			
TOTAL	132/1,097 (12.0%)	3/1,097 (0.3%)	135/1,097 (12.3%)
SD (b)	4.40%	0.94%	4.30%
Range (c)			
High	11/50	2/50	11/50
Low	3/50	0/50	3/50

(a) Data as of August 3, 1984, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE F8. HISTORICAL INCIDENCE OF THYROID GLAND FOLLICULAR CELL TUMORS IN MALE B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls	
	Adenoma	Adenoma or Carcinoma
Historical Incidence at Southern Research Institute		
Ethyl acrylate	4/49	4/49
Benzyl acetate	1/49	1/49
Allyl isovalerate	5/47	5/47
HC Red No.3	8/48	8/48
Allyl isothiocyanate	3/50	3/50
Geranyl acetate	4/49	4/49
TOTAL	25/292 (8.6%)	25/292 (8.6%)
SD (b)	4.89%	4.89%
Range (c)		
High	8/48	8/48
Low	1/49	1/49
Overall Historical Incidence		
TOTAL	42/1,009 (4.2%)	(d) 43/1,009 (4.3%)
SD (b)	4.55%	4.52%
Range (c)		
High	8/48	8/48
Low	0/49	0/49

(a) Data as of August 3, 1984, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.
(d) Includes 41 follicular cell adenomas, 1 papillary adenoma, and 1 follicular cell carcinoma

TABLE F9. HISTORICAL INCIDENCES OF RENAL TUBULAR CELL TUMORS IN B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

	Male			Female		
	No. of Animals at Risk	No. of Tumors	Diagnosis	No. of Animals at Risk	No. of Tumors	Diagnosis
Historical Incidence at Southern Research Institute						
	298	(b) 1(0.3%)	Adenocarcinoma	300	(c) 1 (0.3%)	Adenocarcinoma
Overall Historical Incidences						
	1,091	2	Adenoma	1,092	1	Adenocarcinoma
		2	Adenocarcinoma			
TOTAL		4/1,091 (0.4%)			1/1,092 (0.1%)	

(a) Data as of August 3, 1984, for studies of at least 104 weeks
(b) Observed in the HC Red No. 3 study
(c) Observed in the ethyl acrylate study

TABLE F10. HISTORICAL INCIDENCE OF HEPATOCELLULAR TUMORS IN FEMALE $B6C3F_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Southern Research Institute			
Ethyl acrylate	1/50	2/50	3/50
Benzyl acetate	0/50	1/50	1/50
Allyl isovalerate	2/50	1/50	3/50
HC Red No. 3	4/50	0/50	4/50
Allyl isothiocyanate	2/50	0/50	2/50
Geranyl acetate	2/50	3/50	5/50
TOTAL	11/300 (3.7%)	7/300 (2.3%)	18/300 (6.0%)
SD (b)	2.66%	2.34%	2.83%
Range (c)			
High	4/50	3/50	5/50
Low	0/50	0/50	1/50
Overall Historical Incidence			
TOTAL	41/1,092 (3.8%)	34/1,092 (3.1%)	74/1,092 (6.8%)
SD (b)	2.65%	2.29%	3.63%
Range (c)			
High	5/50	4/50	7/50
Low	0/50	0/50	1/50

(a) Data as of August 3, 1984, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

APPENDIX G

MUTAGENICITY OF CHLORINATED PARAFFINS (C_{23}, 43% CHLORINE) IN *SALMONELLA TYPHIMURIUM*

TABLE G1. MUTAGENICITY OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) IN *SALMONELLA TYPHIMURIUM*

Strain	Dose (µg/plate)	Revertants/plate (a, b)		
		−S9	+S9 (rat)	+S9 (hamster)
TA100	0	144 ± 12.1	175 ± 14.3	140 ± 9.5
	100	140 ± 21.3	180 ± 4.0	174 ± 29.2
	333	165 ± 7.5	213 ± 15.7	189 ± 11.4
	1,000	169 ± 13.5	191 ± 16.2	209 ± 12.8
	3,333	155 ± 8.5	191 ± 7.0	193 ± 9.1
	10,000	138 ± 11.1	176 ± 5.5	158 ± 11.5
TA1535	0	5 ± 1.3	7 ± 2.3	9 ± 0.7
	100	5 ± 1.7	10 ± 3.7	11 ± 1.9
	333	3 ± 1.8	7 ± 2.4	8 ± 3.2
	1,000	5 ± 0.7	8 ± 3.5	10 ± 1.5
	3,333	5 ± 1.5	5 ± 2.3	8 ± 2.3
	10,000	4 ± 1.3	9 ± 2.5	8 ± 2.1
TA97	0	3 ± 0.7	8 ± 0.3	8 ± 1.3
	100	5 ± 1.5	8 ± 0.7	4 ± 1.5
	33	5 ± 0.5	10 ± 1.5	7 ± 1.7
	1,000	3 ± 1.0	10 ± 2.4	9 ± 2.2
	333	4 ± 1.3	14 ± 4.0	9 ± 1.9
	10,000	2 ± 1.5	10 ± 2.5	11 ± 2.5
TA98	0	18 ± 2.4	19 ± 2.2	24 ± 2.3
	100	14 ± 0.9	25 ± 4.4	24 ± 3.0
	333	15 ± 3.0	22 ± 2.6	23 ± 2.8
	1,000	15 ± 0.9	17 ± 1.8	21 ± 3.5
	3,333	15 ± 2.5	20 ± 2.6	24 ± 1.8
	10,000	18 ± 1.7	18 ± 3.2	25 ± 1.8

(a) The S9 fractions were prepared from the livers of Aroclor 1254-induced male Sprague-Dawley rats and male Syrian hamsters. Cells and test compound or solvent (DMSO) were incubated for 20 minutes at 37° C in the presence of either S9 or buffer. After the addition of soft agar, the contents of each tube were poured onto minimal medium, and the plates were incubated at 37° C for 48 hours (Haworth et al., 1983). The experiment was performed twice, each in triplicate; because the results were similar, data from only one experiment are shown.
(b) Mean ± standard error

APPENDIX H

CHEMICAL CHARACTERIZATION OF CHLORINATED PARAFFINS (C_{23}, 43% CHLORINE)

I. Identity and Purity Determinations of Chlorinated Paraffins (C_{23}, 43% Chlorine) Performed by the Analytical Chemistry Laboratory

	Determined	Literature Values
A. Lot no. R-301-137F		
1. Physical properties		
Appearance:	Very viscous, pale yellow liquid	
2. Spectral data		
a. Infrared		
Instrument:	Beckman IR-12	
Cell:	Thin film between silver chloride plates	
Results:	See Figure 5	Consistent with literature spectrum (Sadtler Standard Spectra)
b. Ultraviolet/visible		
Instrument:	Cary 118	
Solvent:	Hexanes	
Results:	No maximum absorbance between 800 and 350 nm at 1.0% concentration, although there was a gradual increase in absorbance toward 350 nm. Between 350 and 215 nm there was one shoulder and an increase in absorbance toward the solvent cutoff which did not resolve into a maximum at 0.04% concentration.	No literature spectrum found. Spectrum consistent with structure.

λ_{max} (nm)	ε
283 (shoulder)	13.9 ± 0.3(δ)

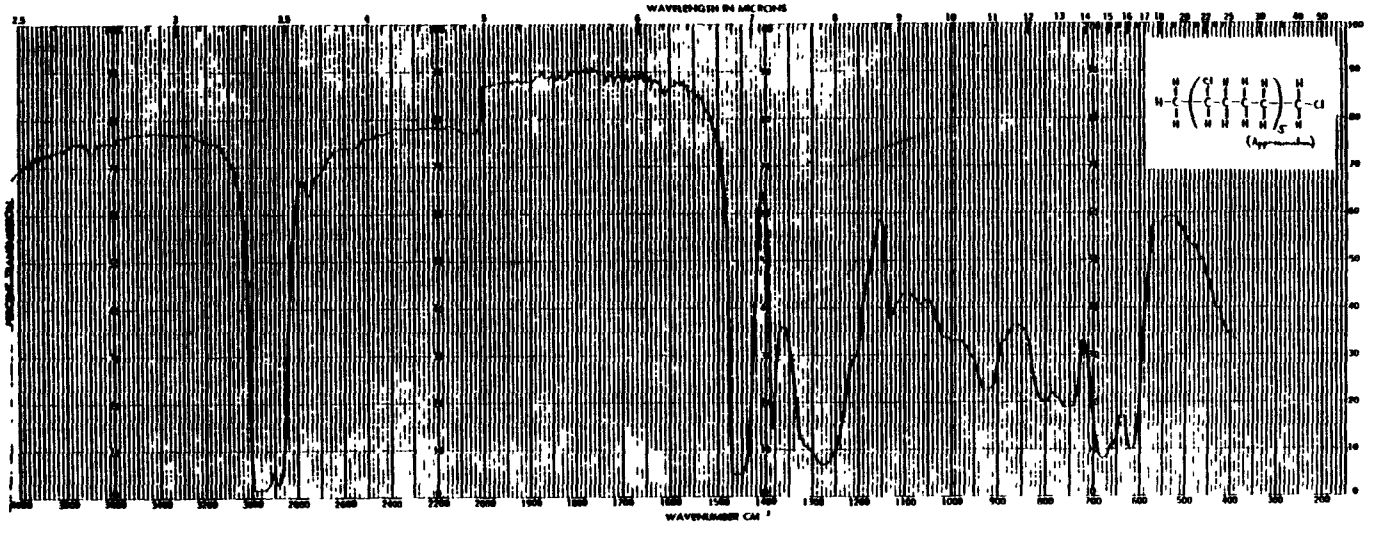

FIGURE 5. INFRARED ABSORPTION SPECTRUM OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) (LOT NO. R-301-137F)

	Determined	Literature Values
c. Nuclear magnetic resonance		
Instrument:	Varian EM-360-A	
Solvent:	Deuterated chloroform with tetramethylsilane internal standard	
Assignments:	See Figure 6	No literature reference found. Spectrum consistent with structure.
Chemical shift (δ):	a 0.83-1.20 ppm b 1.20-2.47 ppm c 3.33-4.43 ppm	
Integration ratios:	a 5.15 b 31.32 c 5.58	

3. **Water analysis (Karl Fischer):** 0.081% ± 0.004(δ)%

4. **Elemental analyses:** Theoretical values are based on the empirical formula, $C_{23}H_{41}Cl_7$.

Element	C	H	Cl
Theory (T)	48.82	7.30	43.87
Determined (D)	48.68 48.59	7.21 7.24	44.29 44.21
Percent D/T	99.62	98.97	100.87

5. **Titration for acidic components:** An aqueous extract of a solution of chlorinated paraffins (C_{23}, 43% chlorine) and carbon tetrachloride titrated with sodium hydroxide

   3.0 ± 1.2 ppm (assumed to be hydrochloric acid)

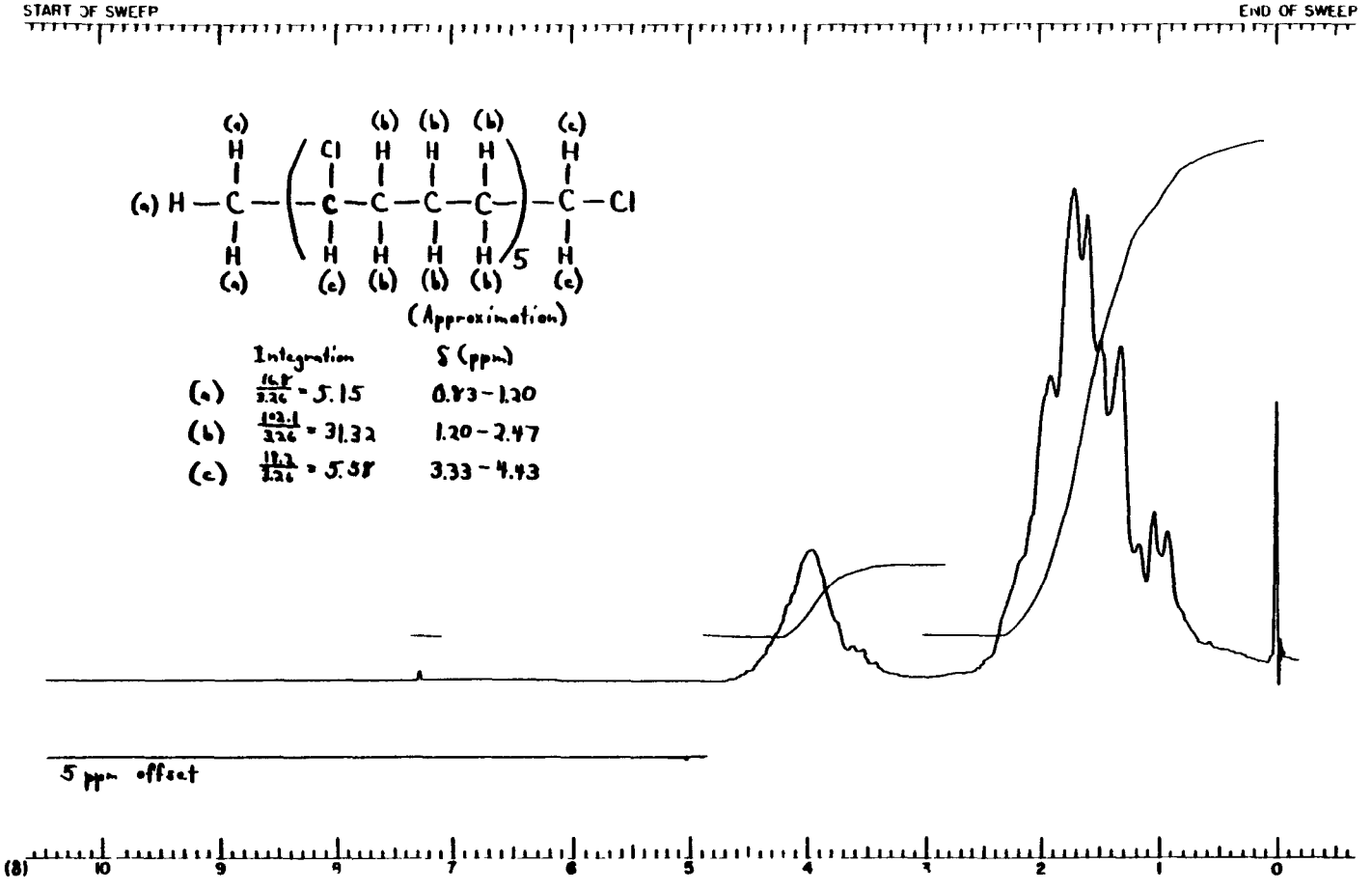

FIGURE 6. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) (LOT NO. R-301-137F)

6. **Chromatographic analyses: thin-layer chromatography**

Amount spotted: 100 and 300 µg (20 µg/µl in diethyl ether)
Reference standard: Hexachlorocyclopentadiene, 50 µg (10 µg/µl in diethyl ether)
Visualization: Potassium dichromate spray (5% in water), then heated for 15 to 20 minutes at 110° C, for sample. Ultraviolet light (254 nm) was used for the reference before the plate was sprayed.

System 1

Solvent: 100% Toluene
Plates: Aluminum oxide, Type E, F-254 (heated to 110° C for 30 minutes, before use)

R_f: 0.85
R_{st}: 0.99

System 2

Solvent: Methanol:ethyl acetate (70:30)
Plates: Whatman KC_{18} reverse-phase F-254

R_f: 0.61
R_{st}: 0.88

7. **Conclusions:** The results of the elemental analyses for carbon, hydrogen, and chlorine agreed with the theoretical values for an empirical formula of $C_{23}H_{41}Cl_7$, which best fit the manufacturer's specifications of 43% chlorine and average molecular weight of 560. Water content was 0.081% ± 0.004(δ)% by Karl Fischer analysis. Titration for acidic components indicated 3.0 ± 1.2 ppm (assumed to be hydrochloric acid) as compared with 5 ppm listed on the manufacturer's label. Thin-layer chromatography by two systems each indicated a single major spot. The infrared, ultraviolet/visible, and nuclear magnetic resonance spectra were consistent with the structure.

B. Lot no. R-201-965

	Determined	Literature Values
1. Physical properties		
Appearance:	Very viscous, pale yellow liquid	
2. Spectral data		
a. Infrared		
Instrument:	Perkin-Elmer 283	
Cell:	Thin film between silver chloride plates	
Results:	See Figure 7	Consistent with literature spectrum (Sadtler Standard Spectra)
b. Ultraviolet/visible		
Instrument:	Cary 118	
Solvent:	Hexanes	
Results:	No absorbance from 800 to 350 nm at a concentration of 0.8% (w/v). No maximum from 350 to 215 nm but a gradual increase in absorbance toward 215 nm at a concentration of 0.7% (w/v). (A small shoulder was observed at 278 nm with an ε_{max} value of approximately 3.)	No literature found. Spectrum consistent with structure of chlorinated paraffins (C_{23}, 43% chlorine).
c. Nuclear magnetic resonance		
Instrument:	Varian EM-360-A	
Solvent:	Deuterated chloroform with tetramethylsilane internal standard	
Assignments:	See Figure 8	No literature found. Spectrum consistent with structure of chlorinated paraffins (C_{23}, 43% chlorine).
Chemical shift (δ):	a 0.7-1.2 ppm b 1.2-3.0 ppm c 3.3-4.5 ppm	

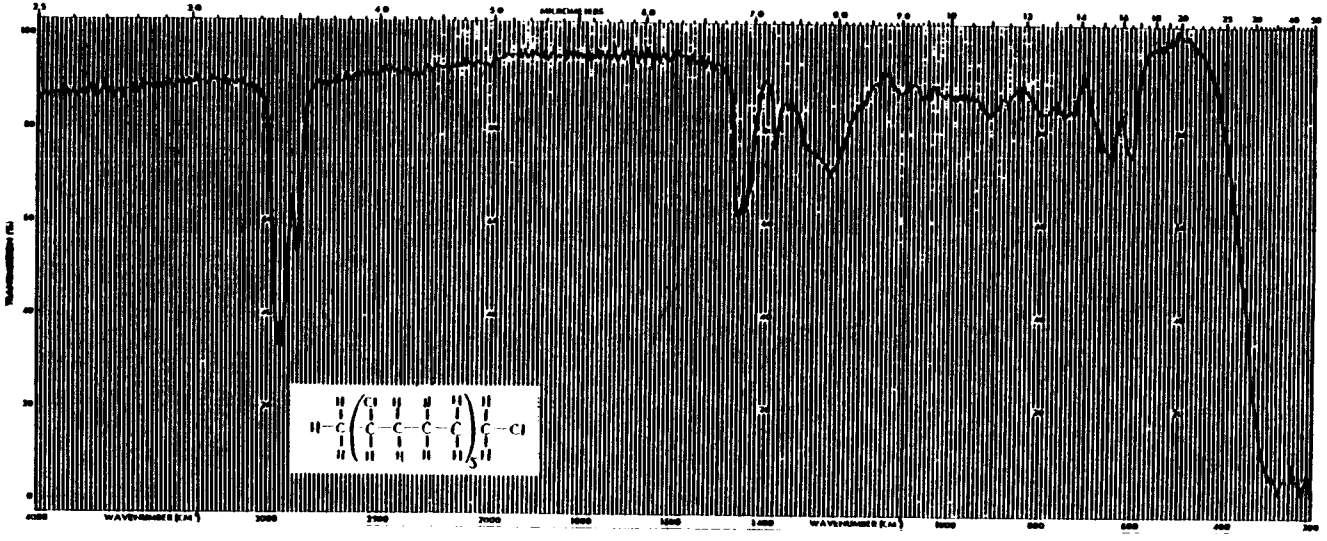

FIGURE 7. INFRARED ABSORPTION SPECTRUM OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) (LOT NO. R-201-965)

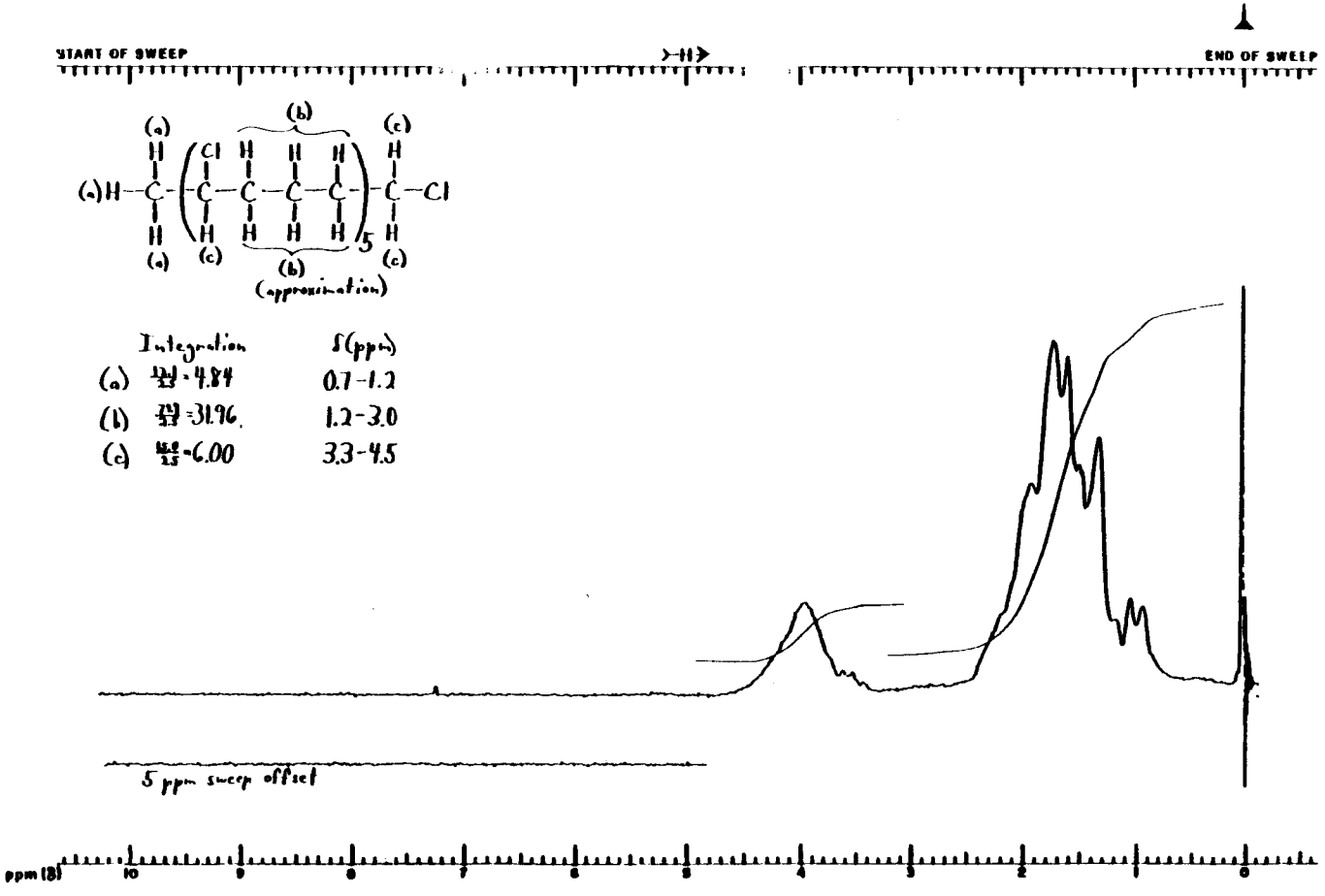

FIGURE 8. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF CHLORINATED PARAFFINS (C_{23}, 43% Cl) (LOT NO. R-201-965)

Integration ratios:	a	4.85
	b	31.96
	c	6.00

3. **Water analysis (Karl Fischer):** <0.03%

4. **Elemental analyses:** Theoretical values are based on the empirical formula, $C_{23}H_{41}Cl_7$.

Element	C	H	Cl
Theory (T)	48.82	7.30	43.87
Determined (D)	49.80	7.33	41.61
	50.01	7.31	41.41
Percent D/T	102.22	100.27	94.62

5. **Titration for acidic components:** An aqueous extract of a solution of chlorinated paraffins (C_{23}, 43% chlorine) and carbon tetrachloride titrated with 0.02N sodium hydroxide to the methyl red:bromcresol green mixed indicator endpoint

   4.7 ± 0.1 ppm (assumed to be hydrochloric acid)

6. **Chromatographic analyses: thin-layer chromatography**

   Amount spotted: 100 and 300 µg (5 and 15 µl of a 20 µg/µl solution in diethyl ether)
   Reference standard: Hexachlorocyclopentadiene, 50 µg (5 µl of a 10 µg/µl solution in diethyl ether)
   Visualization: Potassium dichromate spray (5% in water), then heated for 15 to 20 minutes at 110° C for the sample. Ultraviolet light was used for the reference before the plate was sprayed.

   System 1

   Solvent: 100% Toluene
   Plates: Aluminum oxide, Type E, F-254 (heated to 110° C for 30 minutes, before use)

   R_f: 0.76 (major), 0.80 (reference)
   R_{st}: 0.95 (major)

   System 2

   Solvent: Methanol:ethyl acetate (70:30)
   Plates: Whatman KC_{18} reverse-phase, F-254

   R_f: 0.49 (major), 0.57 (reference)
   R_{st}: 0.86

7. **Conclusions:** The results of the elemental analysis for carbon were slightly high, for chlorine low, and for hydrogen in agreement with the theoretical values for an empirical formula of $C_{23}H_{41}Cl_7$, which best fits the manufacturer's specifications of 43% chlorine and molecular weight of 560. Karl Fischer analysis indicated less than 0.03% water. Titration for acidic components indicated 4.7 ± 0.1(δ) ppm (assumed to be hydrochloric acid) as compared with 6.8 ppm listed on the manufacturer's label. Thin-layer chromatography with two systems each indicated a major spot only. The infrared, ultraviolet/visible, and nuclear magnetic resonance spectra were consistent with the structure of chlorinated paraffins (C_{23}, 43% chlorine).

II. Chemical Stability Study of Lot No. R-301-137F Performed by the Analytical Chemistry Laboratory

A. **Sample storage:** Chlorinated paraffins (C_{23}, 43% chlorine) samples were stored for 2 weeks at −20°, 5°, 25°, and 60° C in amber bottles with polyseal lids.

B. **Analytical method:** Aqueous extracts of the chlorinated paraffins (C_{23}, 43% chlorine) samples dissolved in carbon tetrachloride were titrated with sodium hydroxide. (Hydrochloric acid is an expected decomposition product of chlorinated paraffins (C_{23}, 43% chlorine).) The values found for acidic components in each storage temperature were compared with the value for the −20° C sample.

C. **Results**

Storage Temperature	Acidity (ppm) (assumed to be hydrochloric acid)
−20° C	3.0 ± 1.2
5° C	2.6 ± 1.2
25° C	3.6 ± 1.2
60° C	17.4 ± 1.2

D. **Conclusion:** Chlorinated paraffins (C_{23}, 43% chlorine) shows evidence of instability after storage for 2 weeks at 60° C. No significant instability was observed after storage for 2 weeks at 25° C.

III. Chemical Stability Study of Lot No. R-301-137F Performed by the Study Laboratory

A. Storage conditions: – 20° C

B. Analytical methods

1. **Thin-layer chromatography**

Plates: Brinkman aluminum oxide, type T, F-254, 0.25 mm, 5 × 20 cm. The analysis of May 19, 1981, was also performed with Whatman KC_{18} reversed-phase, fluorescent indicator, 0.20 mm, 5 × 20 cm plates.
Amount spotted: 100 and 300 µg of solution diluted to 10 mg/ml in diethyl ether
Detection: Visualized with 254 nm ultraviolet before the plates were sprayed with 5% aqueous potassium dichromate and heated on a hot plate.
Solvent: System I--toluene; System II--*o*-xylene.

The plates were developed for the 5/19/81 analysis by the following system:

Solvent: System I: acetone:water (85:15); System II: *o*-Xylene

2. **Infrared spectroscopy:** The infrared spectra of these samples were run as a thin film between potassium bromide plates with a Perkin-Elmer 621.

C. Results

1. **Thin-layer chromatography**

Sample size: 100 µg

Date	R_{st}		
8/19/80	0.9	xylene	No measurable impurities present
	1.00	toluene	No measurable impurities present
1/29/81	0.99	xylene	No measurable impurities present
	0.98	toluene	No measurable impurities present
4/24/81	0.99	xylene	No measurable impurities present
	0.96	toluene	No measurable impurities present

2. **Infrared spectroscopy:** The infrared spectra were consistent with that provided by the analytical laboratory.

D. Conclusion: No noticeable degradation occurred during the studies.

APPENDIX I

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES

APPENDIX I. PREPARATION AND CHARACTERIZATION

The studies were conducted at the analytical chemistry laboratory.

I. Sample preparation and storage: Chlorinated paraffins (C_{23}, 43% chlorine) (10.00 g) were dissolved in approximately 50 ml of corn oil in a 100-ml volumetric flask and diluted to 100 ml. After a thorough mixing, the solution was allowed to stand to permit bubbles to rise to the surface. Then the volume was adjusted with corn oil, and the contents were remixed thoroughly. The target concentration of the chemical in the corn oil solution was 10% (w/v). The corn oil solution was maintained at room temperature (approximately 24° C) in the dark and was sampled at weekly intervals over 4 weeks.

II. Viscosity determination

A. Special equipment

A 4-liter beaker, supported on a magnetic stirrer motor unit with approximately 1/4-inch insulating air space between the beaker and stirrer, was used as a temperature-controlled water bath capable of maintaining ± 0.1° C at room temperature. The beaker was equipped with a 3-inch magnetic stirring bar to provide circulation. A ring stand assembly with clamps to hold a thermometer and viscosity tube also was used.

Uncalibrated Kinematic Viscometer, Cannon-Fenske type, ASTM No. 300, 50-250 Centistokes range, available from Fisher Scientific Company.

Thermometer, graduated in 0.2° C divisions. A titer test thermometer, ASTM No. 36C, range −2° to 68° C, available from Fisher Scientific Company.

Timer, either mechanical or electric, capable of measuring to 0.1 second. A Precision Scientific Company "Time It" electric stopwatch was used.

B. Procedure: An empirical method was used and was based on the assumption that the viscosity of the corn oil solution will change if degradation of chlorinated paraffins (C_{23}, 43% chlorine) occurs during storage. No attempt to define viscosity in absolute units was made. Readings were expressed in seconds of elapsed time under controlled temperature conditions, and stability was computed relative to the zero time readings.

A carefully cleaned and dried viscometer tube was filled with 10 ml of chlorinated paraffins (C_{23}, 43% chlorine)/corn oil solution (into the large-bore filling tube of the viscometer from a 10-ml graduated cylinder). The cylinder was allowed to drain for 30 seconds while being held at a 45° angle.

The viscometer tube with sample was placed in a 24° C water bath to a depth at which the entire measuring section was immersed. The unit was clamped in a vertical position and was allowed to equilibrate for 15 minutes.

When the solution had equilibrated, the vertical alignment of the tube was checked. Then the corn oil solution was drawn with a rubber bulb into the graduated tube of the viscometer to a point just above the upper calibration mark. The stopwatch was set at zero, the rubber bulb was removed, and the corn oil solution was allowed to flow by gravity. As the meniscus of the corn oil solution passed the upper calibration mark, the timer was started, and as the meniscus reached the lower calibration mark, the timer was stopped. After the reading was recorded, the timer was reset to zero, and the operation was repeated twice more.

C. Results

Number of Days Stored at Room Temperature	Elapsed Time (seconds)			Mean of Elapsed Time (seconds)	Compound Stablity Relative to Zero Time (percent)
0	313.8	314.1	313.6	313.8	100.0
7	315.2	315.5	315.4	315.4	100.5
14	315.2	314.8	315.2	315.1	100.4
21	314.5	314.6	314.4	314.5	100.2
28	314.9	314.7	314.9	314.8	100.3

III. **Conclusions:** A 10% (w/v) chlorinated paraffins (C_{23}, 43% chlorine)/corn oil solution showed no measurable change in viscosity, within the limits of the test error (0.5%) after 4 weeks of storage at room temperature. Stability of the chemical was inferred on the basis of the stable viscosity readings over 4 weeks.

APPENDIX J

METHODS OF ANALYSIS OF DOSE MIXTURES

APPENDIX J. METHODS OF ANALYSIS

I. Study Laboratory

Periodic analysis of dose mixtures was carried out by one or more of the following methods.

A. Gravimetric method

1. **Weighing bottle procedure:** Prepared samples and standards were carefully poured into preweighed, clean, and dry 10-ml volumetric flasks, with specially drawn funnels. Care was taken to get none of the corn oil solution on the sides of the flasks. The filled flasks were then weighed, and the density of the samples and standards was then calculated from the weights of these 10.00-ml volumes.

   Standards of the chlorinated paraffins (C_{23}, 43% chlorine) in corn oil were prepared over the concentration range of 4%-75% (w/v). These standards were then weighed, the density calculated, and a standard curve prepared (density vs concentration).

2. **Hydrometer method:** Standards were prepared by weighing an amount of chlorinated paraffins (C_{23}, 40% chlorine) into a 200-ml volumetric flask. Corn oil was added with stirring over a period of hours until the standard was diluted to volume.

   The prepared standards and samples were shaken for 30 minutes on a New Brunswick® gyratory shaker and stirred for an additional 30 minutes in a constant temperature water bath. The samples and standards were then allowed to equilibrate in an ambient, constant-temperature water bath for 1 hour. Approximately 150 ml of the sample or standard was then poured into a glass-stoppered tube, 32 mm × 305 mm. An appropriate hydrometer was immersed into the corn oil solution, so that it floated freely without touching the sides of the tube. After equilibration (10 minutes), density measurements were made from the hydrometer. The hydrometer was tapped down into the corn oil solution and allowed to equilibrate again for two additional density measurements.

   A standard curve was obtained from the measured density of the standard and corn oil and their known concentrations. The sample concentrations were then obtained from the measured density of the sample as compared to the standard curve.

B. Viscosity method:

Ten milliliters of a standard or sample was carefully delivered from a 10-ml graduated cylinder into the large bore filling tube of the viscometer. The graduated cylinder was allowed to drain for 30 seconds while being held at a 45° angle. The filled viscometer was clamped in the water bath and equilibrated for at least 15 minutes at 24.0° ± 0.1° C.

When the solution had equilibrated, the vertical alignment of the tube was checked. Then with a flow of nitrogen, the corn oil solution was forced up into the viscometer to a point just above the upper calibration mark. A stopwatch was set at zero, and the corn oil solution allowed to flow by gravity. As the meniscus of the corn oil solution passed the upper calibration mark, the timer was started, and as the meniscus reached the lower calibration mark, the timer was stopped.

Standards of the chlorinated paraffins (C_{23}, 43% chlorine) in corn oil were prepared over the concentration range of 4%-75% (w/v). The viscosity of these standards was measured, and a standard curve was prepared.

II. Analytical Chemistry Laboratory

A. Preparation of standard spiked corn oil: Five or six corn oil standards were prepared by weighing quantities of chlorinated paraffins (C_{23}, 43% chlorine) into 10-ml volumetric flasks and diluting to volume with undosed corn oil. The flasks were wrapped with foil and thoroughly shaken. A 10-ml volumetric flask containing only the undosed corn oil was used for a blank. These standards bracketed the specified concentration range of the referee sample.

B. Preparation of referee sample: Two 10-ml portions of the dosed referee corn oil sample were transferred to individual 10-ml volumetric flasks that were wrapped in foil to protect the solutions from light. The samples and the spiked corn oil standards were analyzed immediately by the procedure below.

C. Analysis

See Appendix I, II. A and B.

D. Quality assurance measures: The referee corn oil sample was analyzed in duplicate and the undosed corn oil sample was analyzed once. Individually spiked portions of undosed corn oil (five or six levels bracketing the specified concentration range of the sample) were prepared from six independently weighed standards and were treated like the referee samples for obtaining standard data. Triplicate time readings of each standard and sample were made on the viscometer. The temperature of the water bath was controlled to ± 0.1° C.

APPENDIX K

RESULTS OF ANALYSIS OF DOSE MIXTURES

TABLE K1. RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE THIRTEEN-WEEK GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{23}, 43% Cl)

Date Mixed	Target Concentration (a) of Chlorinated Paraffins (C_{23}, 43% Cl) in Corn Oil (percent w/v)				
	4.7	9.38	18.76	37.5	75.0
11/13/79 (a)	3.8	13.6.	22.3	35.0	66.4
	7.0	12.5	20.5	33.0	75.2
12/11/79 (b)	(c) 15.0	10.0	19.6	39.7	74.7
	5.0	10.0	19.6	39.6	78.0
12/11/79 (a)	7.0	9.6	21.1	39.9	81.0
	7.2	10.0	20.0	37.8	76.2

(a) Determined by viscosity method
(b) Determined by density method
(c) Suspected mixing error

TABLE K2. RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{23}, 43% Cl)

Date Mixed	Concentration (a) of Chlorinated Paraffins (C_{23}, 43% Cl) in Corn Oil for Target Concentration (percent w/v)						
	2	6	18	25	37.5	50	75
08/06/80	1.8	5.8	18.8		40.1		
09/03/80	(b) 3.7		19.8				(b) 49.2
09/05/80	(c) 2.6						(c) 74.8
10/01/80		(b) 7.6		(b) 27.4	41.2		
10/02/80		(c) 7.2		(c) 27.0			
10/29/80	2.0		19.4			54.8	75.4
11/26/80		(b) 7.4		(b) 27.8	40.6		
12/02/80		(c) 5.7		(c) 26.8			
12/10/80	(b) 1.6		18.8			54.5	78.4
12/12/80	(c) 1.9						
01/21/81	2.0	6.0	17.5	24.4	36.4	48.4	74.0
01/28/81	(b) 2.4	5.6	17.5	24.6	35.8	48.6	75.0
02/02/81	(c) 1.8						
02/04/81	2.1	6.4	17.6	24.9	36.1	48.0	73.2
02/11/80	2.2	6.3	18.3	24.6	37.4	49.0	70.0
02/18/81	2.2	5.7	18.2	24.5	37.0	49.7	73.1
02/25/81	2.2	5.8	16.8	23.9	34.2	46.7	68.2
03/04/81	(b) 1.6	6.0	19.0	27.0	40.8	54.6	80.0
03/06/81	(c) 2.0						
03/11/81	1.8	5.4	17.2	23.5	36.0	48.4	71.4
03/18/81	2.2	5.8	18.4	25.2	37.5	49.8	75.1
03/25/81	2.2	6.5	19.0	26.0	40.0	52.9	80.7
04/01/81	2.0	5.6	17.9	25.0	37.3	48.6	73.0
04/08/81	2.0	6.0	18.8	25.3	38.7	49.6	75.3
04/15/81	2.2	6.1	18.0	24.7	36.8	46.1	71.0
04/22/81	1.8	5.7	17.9	25.3	34.5	47.7	72.2
04/29/81	2.0	6.2	18.3	25.2	37.3	48.1	71.6
05/06/81	1.9	6.1	18.1	25.1	37.3	47.1	71.8
05/13/81	2.0	5.9	18.2	25.1	36.7	47.0	71.4
05/20/81	2.0	6.0	18.3	25.3	37.8	47.1	72.1
(d) 06/10/81	1.9		17.8			51.0	75.6
07/08/81		6.2		25.0	38.9		
08/05/81	2.1		16.5			50.3	76.8
09/02/81		(b) 7.9		25.0	38.0		
09/08/81		(e) 7.8					
09/09/81		(c) 5.4					
09/30/81	1.8		17.9			49.5	79.8
10/28/81		6.0		25.0	38.9		
11/18/81	2.0		17.6			48.0	76.6
12/16/81		5.8		25.1	39.3		
01/20/82	2.2	5.7	17.1	24.2	35.8	49.3	78.8
03/17/82	2.0	(f) 5.4	16.4	23.2	36.3	48.1	77.5
05/12/82	2.0	5.7	17.2	24.1	37.0	49.2	79.2
Mean (percent)	2.1	6.1	18.0	25.0	37.6	49.3	73.8
Standard deviation	0.36	0.62	0.83	1.04	1.84	2.37	5.85
Coefficient of variation (percent)	17.1	10.2	4.6	4.2	4.9	4.8	7.9
Range (percent)	1.6-3.7	5.4-7.9	16.4-19.8	23.2-27.8	34.2-41.2	46.1-54.8	49.2-80.7
Number of samples	29	28	29	27	28	27	28
Number of samples greater than ±10% of target concentration	4	4	0	2	0	0	1

(a) Results of duplicate analysis
(b) Out of specifications. Not used in the studies.
(c) Remix. Not included in the mean.
(d) All mixes beginning on 6/10/81 were prepared on a w/w rather than a w/v basis, making the concentrations 2.2%, 6.5%, 19.6%, 27.2%, 40.8%, 54.4%, and 81.6%. To allow comparisons with the w/v percentages, all determined w/w values were divided by the conversion factor 1.088, except the 2.2% and 6.5% (w/w) values that were divided by 1.10 and 1.083, respectively.
(e) Remix out of specifications. Not used in the studies or included in the mean.
(f) Out of specifications. Used in the studies.

TABLE K3. RESULTS OF REFEREE ANALYSIS IN THE TWO-YEAR GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{23}, 43% Cl)

Date Mixed	Target Concentration (percent w/v)	Determined Concentration (a) Study Laboratory	Determined Concentration (a) Referee Laboratory
08/06/80	37.5	40.1	37.3
02/18/81	18.0	18.2	17.7
07/08/81	6.0	(b) 6.2	5.8
		(c) 6.0	6.0
01/20/82	75.0	(b) 78.8	90.0
		(c) 78.8	89.9

(a) Results of duplicate analysis
(b) Samples were taken from the formulation room before dosing.
(c) Animal room samples were taken after dosing.

APPENDIX L

SENTINEL ANIMAL PROGRAM

APPENDIX L. SENTINEL ANIMAL PROGRAM

I. 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 test results. The Sentinel Animal Program is part of the periodic monitoring of animal health that occurs during the toxicologic evaluation of chemical compounds. Under this program, the disease state of the rodents is monitored via viral serology on sera from extra (sentinel) animals in the test rooms. These animals are untreated, and these animals and the test 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 are selected at the time of randomization and allocation of the animals to the various study groups. Five animals of each designated sentinel group are killed at 6, 12, and 18 months on study. Data from animals surviving 24 months are collected from 5/50 randomly selected control animals of each sex and species. The blood from each animal is collected and clotted, and the serum is separated. The serum is cooled on ice and shipped to Microbiological Associates' Comprehensive Animal Diagnostic Service for determination of the viral antibody titers. The following tests are 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) (6, 12 mo)	MHV (mouse hepatitis virus) (18, 24 mo)
Rats	PVM KRV (Kilham rat virus) H-1 (Toolan's H-1 virus) Sendai	RCV (rat coronavirus)	

II. Results

One of 10 mice examined at 12 months had a positive serologic reaction for MHV. No other positive reactions were observed.

APPENDIX M

METHODS FOR SERUM ANALYSES

The packed cell volume (hematocrit) was determined with heparinized microhematocrit tubes (Todd-Stanford, 1969). Hemoglobin was determined with a Coulter hemoglobinometer. Erythrocyte and leukocyte counts were made with a Coulter Counter®, Model ZBI, with an aperture of 1,000 microns. For differential counts, blood films were stained with Camco Quik stain (buffered Wright's stain) and evaluated by light microscopy. Clinical chemistry included total protein, albumin, globulin, albumin/globulin ratio, sorbitol dehydrogenase (SDH), aspartate aminotransferase, and alanine aminotransferase determinations in serum. Serum chemistry determinations were performed with a Union Carbide CentrifiChem® 500 centrifugal analyzer. The SDH activity was determined by the method of Dooley et al., 1979.

Results are presented in Table M1.

TABLE M1. METHODS FOR SERUM ANALYSES

Assay	Technique/Method	Reference
Total protein	Biuret technique	CentrifiChem Methodology Sheet (Union Carbide Revised 1/80)
Albumin	Bromcresol green method	CentrifiChem Methodology Sheet (Union Carbide Revised 3/79)
Globulin	Calculated by subtracting albumin value from total protein	
Albumin/globulin ratio	Calculated using albumin and globulin values	
Aspartate aminotransferase	Modified Karmen technique	CentrifiChem Methodology Sheet (Union Carbide Revised 1/80)
Alanine aminotransferase	Modified Wroblewski and LaDue technique	CentrifiChem Methodology Sheet (Union Carbide Revised 1/80)

APPENDIX N

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

Pelleted Diet: June 1980 to July 1982

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

TABLE N1. 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
Brewer's dried 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) NIH, 1978; NCI, 1976
(b) Ingredients should be ground to pass through a U.S. Standard Screen No. 16 before being mixed.

TABLE N2. 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 activity
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 N3. NUTRIENT COMPOSITION OF NIH 07 RAT AND MOUSE RATION (a)

Nutrient	Mean	Range	Number of Samples
Crude protein	24.04 ± 0.75	22.7-25.1	24
Crude fat (percent by weight)	4.84 ± 0.80	4.1-5.7	24
Crude fiber (percent by weight)	3.40 ± 0.29	2.9-4.3	24
Ash (percent by weight)	6.56 ± 0.50	5.7-7.43	24
Essential Amino Acids (percent of total diet)			
Arginine	1.260	1.21-1.31	2
Cystine	0.395	0.39-0.40	2
Glycine	1.175	1.15-1.20	2
Histidine	0.553	0.530-0.576	2
Isoleucine	0.908	0.881-0.934	2
Leucine	1.905	1.85-1.96	2
Lysine	1.250	1.20-1.30	2
Methionine	0.310	0.306-0.314	2
Phenylalanine	0.967	0.960-0.974	2
Threonine	0.834	0.827-0.840	2
Tryptophan	0.175	0.171-0.178	2
Tyrosine	0.587	0.566-0.607	2
Valine	1.085	1.05-1.12	2
Essential Fatty Acids (percent of total diet)			
Linoleic	2.37		1
Linolenic	0.308		1
Arachidonic	0.008		1
Vitamins			
Vitamin A (IU/kg)	11,146 ± 2,291	7,200-17,000	24
Vitamin D (IU/kg)	6,300		1
α-Tocopherol (ppm)	37.6	31.1-44.0	2
Thiamine (ppm)	17.6 ± 3.3	7.4-27.0	(b) 23
Riboflavin (ppm)	6.9	6.1-7.4	2
Niacin (ppm)	75	65-85	2
Pantothenic acid (ppm)	30.2	29.8-30.5	2
Pyridoxine (ppm)	7.2	5.6-8.8	2
Folic acid (ppm)	2.1	1.8-2.4	2
Biotin (ppm)	0.24	0.21-0.27	2
Vitamin B_{12} (ppb)	12.8	10.6-15.0	2
Choline (ppm)	3,315	3,200-3,430	2
Minerals			
Calcium (percent)	1.29 ± 0.21	0.81-1.69	24
Phosphorous (percent)	1.00 ± 0.07	0.86-1.10	24
Potassium (percent)	0.809	0.772-0.846	2
Chloride (percent)	0.557	0.479-0.635	2
Sodium (percent)	0.304	0.258-0.349	2
Magnesium (percent)	0.172	0.166-0.177	2
Sulfur (percent)	0.278	0.270-0.285	2
Iron (ppm)	418	409-426	2
Manganese (ppm)	90.8	86.0-95.5	2
Zinc (ppm)	55.1	54.2-56.0	2
Copper (ppm)	12.68	9.65-15.70	2
Iodine (ppm)	2.58	1.52-3.64	2
Chromium (ppm)	1.86	1.79-1.93	2
Cobalt (ppm)	0.57	0.49-0.65	2

(a) One or two batches of feed analyzed for nutrients reported in this table were manufactured in January and/or April 1983.
(b) One batch (July 22, 1981) was not analyzed for thiamine.

TABLE N4. CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION

Contaminant	Mean ± Standard Deviation	Range	Number of Samples
Arsenic (ppm)	0.42 ± 0.21	<0.05-1.06	24
Cadmium (ppm)	0.09 ± 0.02	<0.05-0.10	24
Lead (ppm)	0.99 ± 0.72	0.42-3.37	24
Mercury (ppm) (a)	< 0.05		
Selenium (ppm)	0.31 ± 0.08	0.14-0.52	24
Aflatoxins (ppb) (a,b)	<10	<5.0-<10.0	24
Nitrate nitrogen (ppm) (c)	8.15 ± 3.65	2.1-17.0	24
Nitrite nitrogen (ppm) (c)	2.23 ± 1.59	0.4-6.9	24
BHA (ppm) (d, e)	4.55 ± 3.59	<0.4-13.0	24
BHT (ppm) (d)	2.55 ± 1.40	0.8-5.9	24
Aerobic plate count (CFU/g)	40,592 ± 32,056	4,900-120,000	24
Coliform (MPN/g) (f)	30.3 ± 53.2	<3-240	23
Coliform (MPN/g) (g)	74.8 ± 224.5	<3-1,100	24
E. Coli (MPN/g)	<3		24
Total nitrosamines (ppb) (h, i)	7.20 ± 7.04	0.8-24.5	21
Total nitrosamines (ppb) (i, j)	29.40 ± 64.76	0.8-273.3	24
N-Nitrosodimethylamine (ppb) (h, i)	5.67 ± 6.49	0.8-20.0	21
N-Nitrosodimethylamine (ppb) (i, j)	27.67 ± 64.38	0.8-272	24
N-Nitrosopyrrolidine (ppb)	1.35 ± 0.92	0-3.5	24
Pesticides (ppm)			
α-BHC (a, k)	<0.01		24
β-BHC (a)	<0.02		24
γ-BHC-Lindane (a)	<0.01		24
δ-BHC (a)	<0.01		24
Heptachlor (a)	<0.01		24
Aldrin (a)	<0.01		24
Heptachlor epoxide (a)	<0.01		24
DDE (a)	<0.01		24
DDD (a)	<0.01		24
DDT (a)	<0.01		24
HCB (a)	<0.01		24
Mirex (a)	<0.01		24
Methoxychlor (a, l)	<0.05	0.09 (8/26/81)	24
Dieldrin (a)	<0.01		24
Endrin (a)	<0.01		24
Telodrin (a)	<0.01		24
Chlordane (a)	<0.05		24
Toxaphene (a)	<0.1		24
Estimated PCB's (a)	<0.2		24
Ronnel (a)	<0.01		24
Ethion (a)	<0.02		24
Trithion (a)	<0.05		24
Diazinon (a, m)	<0.1	0.2 (4/27/81)	24
Methyl parathion (a)	<0.02		24
Ethyl parathion (a)	<0.02		24
Malathion (a, m)	0.09 ± 0.06	<0.05-0.27	24
Endosulfan I (a)	<0.01		24
Endosulfan II (a)	<0.01		24
Endosulfan sulfate (a)	<0.03		24

TABLE N4. CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION (Continued)

(a) All values were less than the detection limit, which is given in the table as the mean.
(b) 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) Two batches contained less than 0.5 ppm.
(f) Mean, standard deviation, and range exclude one very high value of 1,100 obtained in the batch produced on 12/16/80.
(g) Mean, standard deviation, and range include the high values listed in footnote (f).
(h) Mean, standard deviation, and range exclude three extreme values in the range of 115-273.2 ppb obtained in batches produced on 1/26/81, 2/23/81, and 4/27/81.
(i) All values were corrected for percent recovery.
(j) Mean, standard deviation, and range include the extreme value given in footnote h.
(k) BHC, hexachlorocyclohexane or benzene hexachloride
(l) One observation was above the detection limit. The value and the date it was obtained are listed under the range.
(m) Eleven batches contained more than 0.05 ppm.

APPENDIX O

ABSTRACT FROM NTP TECHNICAL REPORT ON

CHLORINATED PARAFFINS

(C_{12}, 60% CHLORINE)

NTP TR 308

NIH PUBLICATION NO. 86-2564

APPENDIX O. ABSTRACT FROM NTP TR 308

$CH_3(CH_2CHClCH_2CHClCH_2)_2CH_2Cl$

(Approximation)

CHLORINATED PARAFFINS

Average chain length: C_{12}

Approximately 60% chlorine by weight

$C_{12}H_{19}Cl_7$ (average)

Molecular weight: 411 (average)

ABSTRACT

Toxicology and carcinogenesis assessments of chlorinated paraffins (C_{12}, 60% chlorine), a material widely used as a flame retardant and extreme-pressure lubricant, were conducted in male and female F344/N rats and male and female $B6C3F_1$ mice in single-administration, 16-day, 13-week, and 2-year studies. Doses used in the 2-year studies were 0, 312, or 625 mg/kg body weight per day administered by gavage in corn oil five times per week to groups of 70 male and female rats and 0, 125, or 250 mg/kg administered to groups of 50 male and female mice. Ten male and 10 female rats were killed after 6 and 12 months of dosing and examined for toxicity.

No chemically related toxicity was observed in single-administration studies in which male and female rats received doses of chlorinated paraffins (C_{12}, 60% chlorine) up to 13,600 mg/kg body weight and male and female mice up to 27,200 mg/kg. In 16-day studies, deaths did occur in groups of male and female rats given 7,500 mg/kg and in groups of male and female mice given doses of 1,875 mg/kg or higher. In 13-week studies, no chemically related deaths occurred among male and female rats given up to 5,000 mg/kg or mice given up to 2,000 mg/kg. Increased liver weights were noted in dosed rats and mice of each sex in the short-term studies, and dosed male rats showed more severe nephropathy than did vehicle controls. Doses selected for the 2-year studies were those that caused a minimal increase in liver weight in the short-term studies.

Liver and kidney weights were increased in dosed rats killed at 6 and 12 months. Morphometric measurements demonstrated hepatocyte hypertrophy in the livers of dosed rats. Lesions of the kidney tubules and interstitial inflammation increased with dose in male and female rats.

During the 2-year studies, body weights of high dose male rats were 8%-12% lower than those of vehicle controls after week 20, and body weights of dosed female mice were about 10% lower than those of vehicle controls during the second year. Survival of dosed male rats was lower than that of vehicle controls after about week 85, perhaps due to toxicity to the kidney (final survival: vehicle control, 27/50; low dose, 6/50; high dose, 3/50). Survival of low dose female rats was lower than that of vehicle controls (34/50; 24/50; 29/50). Survival of dosed male mice was not significantly different from that of vehicle controls (34/50; 31/50; 31/50). Survival of high dose female mice was lower than that of vehicle controls after about week 75 (final survival: 36/50; 31/50; 25/50).

Chemically related nonneoplastic lesions consisted of hypertrophy and minimal focal necrosis of the liver in rats; erosion, inflammation, and ulceration of the glandular stomach and forestomach in male rats; and formation of multiple cysts in the kidney tubules of male rats. The incidence of nephropathy was also increased in dosed female rats and mice. The maximum tolerated dose may have been exceeded in male and female rats.

Neoplastic lesions associated with chlorinated paraffins (C_{12}, 60% chlorine) administration were found in the liver of rats and mice of each sex:

	Vehicle Control	Low Dose	High Dose
Male rats			
Neoplastic nodules	0/50	10/50	16/48
Carcinomas	0/50	3/50	2/48
Female rats			
Neoplastic nodules	0/50	4/50	7/50
Carcinomas	0/50	1/50	1/50
Male mice			
Adenomas	11/50	20/50	29/50
Carcinomas	11/50	15/50	17/50
Female mice			
Adenomas	0/50	18/50	22/50
Carcinomas	3/50	4/50	9/50

Dosed male rats showed increased incidences of kidney tubular cell hyperplasia (1/50; 9/50; 12/49) and of tubular cell adenomas (0/50; 7/50; 3/49); two low dose males had tubular cell adenocarcinomas. The incidences of mononuclear cell leukemia were increased in dosed male rats (7/50; 12/50; 14/50) and in low dose female rats (11/50; 22/50; 16/50). Pancreatic acinar cell tumors occurred at increased incidences in low dose male rats (11/50; 22/50; 17/50). Follicular cell adenomas or carcinomas (combined) of the thyroid gland were found at increased incidences in both female rats (0/50; 6/50; 6/50) and female mice (8/50; 12/49; 15/49).

Chlorinated paraffins (C_{12}, 60% chlorine) was not mutagenic in *Salmonella typhimurium* strains TA97, TA98, TA100, or TA1535 in the presence or absence of Aroclor 1254-induced male Sprague-Dawley or male Syrian hamster liver S9 when tested according to the preincubation protocol.

An audit of the experimental data was conducted for these 2-year studies on chlorinated paraffins (C_{12}, 60% chlorine). No data discrepancies were found that influenced the final interpretations.

Under the conditions of these 2-year gavage studies, there was *clear evidence of carcinogenicity** of chlorinated paraffins (C_{12}, 60% chlorine) for F344/N rats based on increased incidences of hepatocellular neoplasms (primarily neoplastic nodules) in male and female rats, of adenomas or adenocarcinomas (combined) of the kidney tubular cells in male rats, and of follicular cell adenomas or carcinomas (combined) of the thyroid gland in female rats. Mononuclear cell leukemia in dosed male rats may have been related to administration of chorinated paraffins (C_{12}, 60% chlorine). There was *clear evidence of carcinogenicity* of chlorinated paraffins (C_{12}, 60% chlorine) for $B6C3F_1$ mice as shown by increased incidences of hepatocellular adenomas and of adenomas or carcinomas (combined) in dosed male and female mice and increased incidences of adenomas and of adenomas or carcinomas (combined) of thyroid gland follicular cells in dosed female mice.

*Categories of evidence of carcinogenicity are presented in the Note to the Reader on page 2.

APPENDIX P

DATA AUDIT SUMMARY

APPENDIX P. DATA AUDIT SUMMARY

The experimental data for the NTP Technical Report on the Toxicology and Carcinogenesis Studies of Chlorinated Paraffins (C_{23}, 43% Chlorine) were examined for completeness, consistency, and accuracy and for procedures consistent with Good Laboratory Practice requirements. The audit was conducted during December 1984 at the National Toxicology Program Archives, Rockville, Maryland, by the following personnel of ImmuQuest Laboratories, Inc., and Pathology Associates, Inc.: P.H. Errico, M.A.; K.M. Witkin, Ph.D.; C.S. Reese; L.H. Brennecke, D.V.M.; and C.S. Corson, HT (ASCP). The 2-year studies in $B6C3F_1$ mice and F344/N rats were conducted by Southern Research Institute, Birmingham, Alabama, from August 1980 to August 1982.

The full audit report has been reviewed and approved by NTP personnel and is on file at NIEHS. The audit involved a review of all prestudy data (i.e., receipt, quarantine, randomization, protocol, correspondence) and a complete review of data (body weight, clinical observation, necropsy, and pathology) for 10% of the animals in each group. Ten percent of the dosing volume records and all of the chemistry and mortality data were audited. A slide/block match was conducted for all high dose and vehicle control animals. Wet tissue examination and animal identification were performed on a random 10% sample of rats and mice, and the correlation between gross and microscopic diagnoses was audited for 10% of the rats and mice.

The inlife data for the 2-year studies of chlorinated paraffins (C_{23}, 43% chlorine) were found to be in generally good order. Randomization data were not available for review nor were quarantine data for the rats. Some dosing discrepancies (detailed in the Technical Report) were noted by the laboratory, but these had no significant impact on the studies. These discrepancies included use of incorrect dosing volumes as well as dosing a group (or part of a group) with the wrong concentration. Periodic reanalyses of the bulk chemical by thin-layer chromatography and infrared spectral analysis indicated no degradation during the studies, but the imprecise nature of these methods did not allow absolute confirmation that chemical purity was maintained.

Comparison of gross and microscopic diagnoses revealed 31 potential lesions in nontarget organs in rats and 22 potential nontarget organ lesions in mice. Further examination of slides and wet tissues resolved all but seven discrepancies in rats and one in mice. These eight lesions were distributed between tissues and dose groups such that their resolution would have no impact on the results of the study; therefore, no further action was taken.

In summary, the audit of the data for the 2-year studies of chlorinated paraffins (C_{23}, 43% chlorine) revealed some uncertainties relating to bulk chemical analyses. Other minor problems noted during the audit, but not considered to influence the interpretation of the results, were not necessarily pursued to conclusion but are noted in the full audit report. In conclusion, the data presented in the Technical Report are considered adequate to meet the objectives of these studies.

☆U.S. GOVERNMENT PRINTING OFFICE: 1986-491-292:41084