NATIONAL TOXICOLOGY PROGRAM
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No. 308

TOXICOLOGY AND CARCINOGENESIS STUDIES OF CHLORINATED PARAFFINS

(C_{12}, 60% 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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NATIONAL TOXICOLOGY PROGRAM
P.O. Box 12233
Research Triangle Park, NC 27709

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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. Animal care and use were in accordance with the U.S. Public Health Service Policy on Humane Care and Use of Animals. 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 11

CONTRIBUTORS 13

PEER REVIEW PANEL 14

SUMMARY OF PEER REVIEW COMMENTS 15

I. INTRODUCTION 17

II. MATERIALS AND METHODS 21

PROCUREMENT AND CHARACTERIZATION OF CHLORINATED PARAFFINS (C_{12}, 60% CHLORINE) 22

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES 23

SINGLE-ADMINISTRATION STUDIES 23

SIXTEEN-DAY STUDIES 23

THIRTEEN-WEEK STUDIES 26

SIX-MONTH, TWELVE-MONTH, AND TWO-YEAR STUDIES 27

STUDY DESIGN 27

SOURCE AND SPECIFICATIONS OF ANIMALS 27

ANIMAL MAINTENANCE 27

CLINICAL EXAMINATIONS AND PATHOLOGY 27

STATISTICAL METHODS 28

III. RESULTS 31

RATS 32

SINGLE-ADMINISTRATION STUDIES 32

SIXTEEN-DAY STUDIES 32

THIRTEEN-WEEK STUDIES 33

SIX-MONTH AND TWELVE-MONTH STUDIES 34

TWO-YEAR STUDIES 35

BODY WEIGHTS AND CLINICAL SIGNS 35

SURVIVAL 38

PATHOLOGY AND STATISTICAL ANALYSES OF RESULTS 38

MICE 48

SINGLE-ADMINISTRATION STUDIES 48

SIXTEEN-DAY STUDIES 48

THIRTEEN-WEEK STUDIES 49

TWO-YEAR STUDIES 50

BODY WEIGHTS AND CLINICAL SIGNS 50

SURVIVAL 53

CONTENTS (Continued)

PAGE

PATHOLOGY AND STATISTICAL ANALYSES OF RESULTS 55

IV. DISCUSSION AND CONCLUSIONS 59

V. REFERENCES 65

TABLES

TABLE 1 PREPARATION AND STORAGE OF DOSE MIXTURES IN THE GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) 22

TABLE 2 SUMMARY OF RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) 23

TABLE 3 EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) 24

TABLE 4 SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE SIXTEEN-DAY GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) 32

TABLE 5 SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) 33

TABLE 6 LIVER WEIGHT TO BODY WEIGHT RATIOS FOR RATS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) 33

TABLE 7 ABSOLUTE AND RELATIVE ORGAN WEIGHTS FOR RATS IN THE SIX-MONTH AND TWELVE-MONTH GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) 34

TABLE 8 AVERAGE NUMBER OF HEPATOCYTES PER UNIT AREA OF LIVER IN RATS IN THE TWELVE-MONTH GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) 35

TABLE 9 INCIDENCES AND SEVERITY OF NEPHROPATHY IN RATS IN THE TWELVE-MONTH GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) 35

TABLE 10 MEAN BODY WEIGHTS AND SURVIVAL OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) 36

TABLE 11 SURVIVAL OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) 38

TABLE 12 NUMBERS OF RATS WITH LIVER LESIONS IN THE TWO-YEAR GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) 40

TABLE 13 ANALYSIS OF LIVER TUMORS IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) 41

TABLES (Continued)

PAGE

TABLE 14 ANALYSIS OF KIDNEY TUBULAR CELL LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) 42

TABLE 15 ANALYSIS OF THYROID GLAND FOLLICULAR CELL LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) 43

TABLE 16 ANALYSIS OF MONONUCLEAR CELL LEUKEMIA IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) 44

TABLE 17 CLASSIFICATION OF MONONUCLEAR CELL LEUKEMIA IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{12},, 60% Cl) 44

TABLE 18 NUMBERS OF RATS WITH STOMACH LESIONS IN THE TWO-YEAR GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) 45

TABLE 19 ANALYSIS OF PANCREATIC ACINAR CELL TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) 46

TABLE 20 ANALYSIS OF UTERINE TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) 47

TABLE 21 SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE SIXTEEN-DAY GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) 48

TABLE 22 SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE THIRTEEN-WEEK GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) 49

TABLE 23 LIVER WEIGHT TO BODY WEIGHT RATIOS FOR MICE IN THE THIRTEEN-WEEK GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) 50

TABLE 24 NUMBERS OF MICE WITH HYPERTROPHY OF HEPATOCYTES OR FOCAL NECROSIS OF THE LIVER IN THE THIRTEEN-WEEK GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) 50

TABLE 25 MEAN BODY WEIGHTS AND SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) 51

TABLE 26 SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) 53

TABLE 27 ANALYSIS OF HEPATOCELLULAR TUMORS IN MICE IN THE TW0-YEAR GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) 56

TABLE 28 ANALYSIS OF THYROID GLAND FOLLICULAR CELL LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) 57

TABLES (Continued)

PAGE

TABLE 29 ANALYSIS OF ALVEOLAR/BRONCHIOLAR LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) 58

TABLE 30 ANALYSIS OF HARDERIAN GLAND TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) 58

TABLE 31 INCIDENCES OF LIVER NEOPLASMS IN RATS AND MICE IN THE TWO-YEAR GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) 61

TABLE 32 INCIDENCES OF PROLIFERATIVE LESIONS OF THE THYROID GLAND FOLLICLES IN FEMALE RATS AND MICE IN THE TWO-YEAR GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) 62

FIGURES

FIGURE 1 GROWTH CURVES FOR RATS ADMINISTERED CHLORINATED PARAFFINS (C_{12}, 60% Cl) IN CORN OIL BY GAVAGE FOR TWO YEARS 37

FIGURE 2 KAPLAN-MEIER SURVIVAL CURVES FOR RATS ADMINISTERED CHLORINATED PARAFFINS (C_{12}, 60% Cl) IN CORN OIL BY GAVAGE FOR TWO YEARS 39

FIGURE 3 GROWTH CURVES FOR MICE ADMINISTERED CHLORINATED PARAFFINS (C_{12}, 60% Cl) IN CORN OIL BY GAVAGE FOR TWO YEARS 52

FIGURE 4 KAPLAN-MEIER SURVIVAL CURVES FOR MICE ADMINISTERED CHLORINATED PARAFFINS (C_{12}, 60% Cl) IN CORN OIL BY GAVAGE FOR TWO YEARS 54

FIGURE 5 INFRARED ABSORPTION SPECTRUM OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) (LOT NO. R-201-198) 171

FIGURE 6 NUCLEAR MAGNETIC RESONANCE SPECTRUM OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) (LOT NO. R-201-198) 173

APPENDIXES

PAGE

APPENDIX A SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) 69

TABLE A1 SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) 70

TABLE A2 SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) 73

TABLE A3 INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) 76

TABLE A4 INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) 82

APPENDIX B SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE IN THE TWO-YEAR GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) 89

TABLE B1 SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) 90

TABLE B2 SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) 93

TABLE B3 INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) 96

TABLE B4 INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) 102

APPENDIX C SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) 109

TABLE C1 SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) 110

TABLE C2 SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) 116

APPENDIX D SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE IN THE TWO-YEAR GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) 121

APPENDIXES

PAGE

TABLE D1 SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) 122

TABLE D2 SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) 127

APPENDIX E ANALYSES OF PRIMARY TUMORS IN RATS AND MICE IN THE TWO-YEAR GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) 133

TABLE E1 ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) 134

TABLE E2 ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) 140

TABLE E3 ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) 144

TABLE E4 ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) 148

APPENDIX F HISTORICAL INCIDENCES OF TUMORS IN F344/N RATS AND B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE 153

TABLE F1 HISTORICAL INCIDENCE OF LEUKEMIA IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE 154

TABLE F2 HISTORICAL INCIDENCE OF HEPATOCELLULAR TUMORS IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE 155

TABLE F3 HISTORICAL INCIDENCE OF KIDNEY TUBULAR CELL TUMORS IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE 155

TABLE F4 HISTORICAL INCIDENCE OF PANCREATIC ACINAR CELL TUMORS IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE 156

TABLE F5 HISTORICAL INCIDENCE OF LEUKEMIA IN FEMALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE 157

TABLE F6 HISTORICAL INCIDENCE OF HEPATOCELLULAR NEOPLASTIC NODULES IN FEMALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE 158

TABLE F7 HISTORICAL INCIDENCE OF PANCREATIC ACINAR CELL ADENOMAS IN FEMALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE 158

APPENDIXES (Continued)

PAGE

TABLE F8 HISTORICAL INCIDENCE OF THYROID GLAND FOLLICULAR CELL TUMORS IN FEMALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE 159

TABLE F9 HISTORICAL INCIDENCE OF UTERINE ENDOMETRIAL STROMAL TUMORS IN FEMALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE 160

TABLE F10 HISTORICAL INCIDENCE OF ALVEOLAR/BRONCHIOLAR TUMORS IN MALE B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE 161

TABLE F11 HISTORICAL INCIDENCE OF HEPATOCELLULAR TUMORS IN MALE B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE 162

TABLE F12 HISTORICAL INCIDENCE OF HEPATOCELLULAR TUMORS IN FEMALE B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE 163

TABLE F13 HISTORICAL INCIDENCE OF THYROID GLAND FOLLICULAR CELL TUMORS IN FEMALE B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE 164

TABLE F14 HISTORICAL INCIDENCE OF HARDERIAN GLAND TUMORS IN FEMALE B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE 165

APPENDIX G GENETIC TOXICOLOGY OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) 167

APPENDIX G1 MUTAGENICITY OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) IN *SALMONELLA TYPHIMURIUM* 168

APPENDIX H CHEMICAL CHARACTERIZATION OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) 169

APPENDIX I PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES 177

APPENDIX J METHODS OF ANALYSIS OF DOSE MIXTURES 183

APPENDIX K RESULTS OF ANALYSIS OF DOSE MIXTURES 187

TABLE K1 RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) 188

TABLE K2 RESULTS OF REFEREE ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) 189

APPENDIX L SENTINEL ANIMAL PROGRAM 191

TABLE L1 MURINE VIRUS ANTIBODY DETERMINATIONS FOR RATS AND MICE IN THE TWO-YEAR GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) 193

APPENDIX M INGREDIENTS, NUTRIENT COMPOSITION, AND CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION 195

APPENDIXES (Continued)

PAGE

TABLE M1 INGREDIENTS OF NIH 07 RAT AND MOUSE RATION 196

TABLE M2 VITAMINS AND MINERALS IN NIH 07 RAT AND MOUSE RATION 196

TABLE M3 NUTRIENT COMPOSITION OF NIH 07 RAT AND MOUSE RATION 197

TABLE M4 CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION 198

APPENDIX N ABSTRACT FROM THE NTP TECHNICAL REPORT ON CHLORINATED PARAFFINS (C_{23}, 43% CHLORINE) 201

APPENDIX O DATA AUDIT SUMMARY 205

$CH_3(CH_2CHClCH_2CHClCH_2)_2CH_2Cl$

(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.

CONTRIBUTORS

The NTP Technical Report on the Toxicology and Carcinogenesis Studies of Chlorinated Paraffins (C_{12}, 60% Chlorine) is based on the 13-week studies that began in November 1979 and ended in February 1980 and on the 2-year studies that began in September 1980 and ended in September 1982 at Southern Research Institute.

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PEER REVIEW PANEL

The members of the Peer Review Panel who evaluated the draft Technical Report on chlorinated paraffins (C_{12}, 60% Cl) 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.

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SUMMARY OF PEER REVIEW COMMENTS ON THE TOXICOLOGY AND CARCINOGENESIS STUDIES OF CHLORINATED PARAFFINS (C_{12}, 60% CHLORINE)

On August 14, 1985, the draft Technical Report on the toxicology and carcinogenesis studies of chlorinated paraffins (C_{12}, 60% Cl) 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, South Campus, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina.

Dr. Kotelchuck, a principal reviewer, suggested that there be discussion as well as consideration of further studies examining the differential metabolism and patterns of carcinogenicity for the C_{12} chlorinated paraffins as compared with the C_{23} chlorinated paraffins (NTP TR 305).

As a second principal reviewer, Dr. Tannenbaum agreed with the conclusions. He thought there was overt toxicity in both sexes and in almost all dose groups. He questioned why there was no examination of serum enzyme levels in view of the liver toxicity.

As a third principal reviewer, Dr. Hooper agreed with, and elaborated in detail on the findings supporting, the conclusions. He commented on the poor survival in rats but did not feel this jeopardized the validity of the findings.

Dr. Swenberg proposed stating in the Abstract that the maximum tolerated dose may have been exceeded in rats. Dr. Kociba said the doses in rats were excessive and the considerable toxicity made interpretation of the carcinogenesis results difficult; better doses might have been achieved if more parameters, such as serum enzyme levels, had been added to the short-term studies; for this reason, he thought the data in rats supported some evidence of carcinogenicity. Dr. J. Bucher, NTP, commented that most of the mortality in dosed male rats occurred after 80 weeks whereas overall survival in dosed female rats was reasonable compared with that in vehicle controls. Dr. J. Huff, NIEHS, added that of 26 male rats in the two dose groups with mononuclear cell leukemia, all but 2 died before the end of the study. Dr. E. McConnell, NIEHS, suggested that based on his experience with some solvents, the kidney lesions and attendant decreased survival would not have been predicted from the 13-week studies. Dr. Perera asked that increases in mononuclear cell leukemia in female rats, pancreatic acinar cell neoplasms in male rats, and alveolar/bronchiolar carcinomas in mice be mentioned in the Abstract.

Dr. Kotelchuck moved that the conclusions as written for both rats and mice, clear evidence of carcinogenicity, be accepted. Dr. Hooper seconded the motion, and the Technical Report on chlorinated paraffins (C_{12}, 60% Cl) was approved by nine affirmative votes; there was one negative vote (Dr. Kociba) and one abstention (Dr. Purchase).

Following the vote, there ensued discussion as to the definition of maximum tolerated dose. Dr. McConnell said that the NTP adhered to the definition in the Report of the Ad Hoc Panel on Chemical Carcinogenesis Testing and Evaluation. On that basis, the consensus of the Panel was that the maximum tolerated dose may have been exceeded in male and female rats. Dr. Hook said a statement to that effect should be added to the Abstract.

I. INTRODUCTION

Production and Use

Environmental Occurrence

Metabolism

Toxicity

Mutagenicity

Study Rationale

I. INTRODUCTION

$CH_3(CH_2CHClCH_2CHClCH_2)_2CH_2Cl$

(Approximation)

CHLORINATED PARAFFINS

Average chain length: C_{12}

Approximately 60% chlorine by weight

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

Molecular weight: 411 (average)

Chlorinated paraffins, saturated straight-chain hydrocarbons ranging from 10 to 30 carbons in length and containing 20%-70% chlorine by weight, are manufactured by the liquid-phase chlorination of various paraffinic stocks under controlled conditions of temperature and illumination (Hardie, 1964). Several types 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 and chlorinated naphthalenes (Howard et al., 1975). Most companies that produce chlorinated paraffins offer several different products distinguishable by the carbon chain length and the degree of chlorination.

The subject of this report is chlorinated paraffins produced from a C_{10-12} (average) paraffin feedstock chlorinated to approximately 60% by weight. The NTP has also performed toxicity and carcinogenicity evaluations on a longer chain paraffin, C_{23}, chlorinated to 43%. The results of the chlorinated paraffins (C_{23}, 43% chlorine) studies are reported separately (NTP, 1986).

Chlorinated paraffins (C_{12}, 60% 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, 1964). Small amounts of isoparaffins and aromatics may be present as contaminants; the content of aromatics in the C_{12} feedstock is typically 0.5%-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 material used in these studies.

Production and Use

Various chlorinated paraffins are manufactured by a large number of companies worldwide. Total global production was estimated to be greater than 250,000 metric tons (250×10^6 kg) per year in 1978 (Zitko, 1980). The commercial importance of chlorinated paraffins 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 polyvinyl chloride (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 used in place of polychlorinated biphenyls (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 (water) 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 the organisms 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 and found chlorinated paraffins in 13 of the 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, and 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 carbon-14 or chlorine-36 or have assayed 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 suspended in a fat emulsion was readily absorbed after oral administration and distributed to tissues that exhibit high metabolic activity, such as the intestinal mucosa, bone marrow, and exocrine glands (pancreas, salivary, and harderian) (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 on chlorinated paraffins (C_{12}, 60% chlorine) have been reported, but from studies of other highly 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 after oral administration is decreased. Thus, fecal excretion is a major route of elimination of highly chlorinated paraffins, and the fraction of compound metabolized to carbon dioxide or excreted via the urine is small (Darnerud et al., 1982). In C57BL female mice, a highly chlorinated paraffin (C_{16}, 69% chlorine) was initially distributed to the liver, kidney, and gallbladder after oral or intravenous administration and accumulated in the corpora lutea and fat over a 4-day period. 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. LC_{50} values (96 hours) 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 also with lower concentrations (40 mg/liter) of chlorinated paraffins in the

water (Howard et al., 1975; Svanberg et al., 1978). Lombardo et al. (1975) noted reduced growth in fingerling trout that were fed a diet containing 10 ppm chlorinated paraffins (C_{12}, 60% chlorine) for 82 days, but when adult rainbow trout were exposed to C_{20-30}, 42% chlorine, at 385 ppm in the feed for 35 days, no effects were observed (Madeley and Birtley, 1980).

Madeley and Birtley (1980) observed no toxicity in ducks and pheasants after single (oral gavage) and 5-day repeated-dose (feed) exposures to C_{14-17}, 52% chlorine, at doses up to 24.6 g/kg. No deaths resulted from the oral dosing of rats (strain unspecified) with C_{23}, 40% chlorine, at 11.7 g/kg, or with C_{24}, 70% chlorine, at 50 g/kg; the oral LD_{50} value for chlorinated paraffins (C_{12}, 58% chlorine) was determined to be greater than 29 g/kg (Howard et al., 1975). Death in these studies was apparently caused by physical obstruction due to the large volumes administered.

Low acute toxicity of several chlorinated paraffins in pathogen-free Wistar rats was reported by Birtley et al. (1980). Clinical signs observed in rats receiving over 4 g/kg were limited to piloerection, muscular incoordination, and urinary and fecal incontinence. Gross and histopathologic examinations revealed gastric inflammation, hepatocellular vacuolization with focal necrosis, 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 C_{14-17}, 52% chlorine, no effects were noted on survival, clinical signs, hematologic measurements, or 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 C_{14-17}, 52% chlorine, in dosed feed for 90 days, but no effects were seen in females (Birtley et al., 1980).

The various chlorinated paraffins exhibit little or no potential to irritate the skin of humans or rabbits but 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 manufacturing of chlorinated paraffins (Howard et al., 1975). No epidemiologic or animal studies were available which examine the potential of the chlorinated paraffins to cause carcinogenic, teratogenic, or reproductive effects.

Mutagenicity

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 rat or male Syrian hamster liver S9 when tested according to the preincubation protocol (Appendix G).

Study Rationale

Chlorinated paraffins (C_{12}, 60% chlorine and C_{23}, 43% chlorine) were nominated by the National Cancer Institute and the Consumer Product Safety Commission as representative examples of short- and long-chain 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 pattern of use. 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 the ITC recommendation.

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF CHLORINATED PARAFFINS (C_{12}, 60% CHLORINE)

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES

SINGLE-ADMINISTRATION STUDIES

SIXTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

SIX-MONTH, TWELVE-MONTH, AND 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_{12}, 60% CHLORINE)

Chlorinated paraffins (C_{12}, 60% chlorine) was provided by the Diamond Shamrock Co. (Dallas, Texas) as the commercial-grade material without stabilizers. The manufacturer reported the material to be a mixture of chlorinated paraffins (C_{10-12}) with an average molecular weight of 415 and 60% chlorine content. A single lot of the chemical was obtained in several containers. The contents from the various 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). The identity of the test material was confirmed by infrared spectra that were consistent with those in the literature and by ultraviolet/visible and nuclear magnetic resonance spectra that were consistent with those expected for the structure. Cumulative data from elemental analyses, Karl Fischer water analysis, and thin-layer chromatography indicated that the test material generally fit the manufacturer's specification for average molecular weight and chlorine content. Acid content (as hydrochloric acid) was determined to be 6.0 ppm.

The lot of chlorinated paraffins (C_{12}, 60% chlorine) used in these studies differed from commercial products in that it did not have added stabilizers and, therefore, was not stable at temperatures above 25° C (Appendix H). Chlorinated paraffins (C_{12}, 60% chlorine) was stored at −20°C. Results of routine periodic analysis of the bulk chemical by infrared spectroscopy and thin-layer chromatography indicated that no detectable degradation occurred during the studies (Appendix H).

TABLE 1. PREPARATION AND STORAGE OF DOSE MIXTURES IN THE GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{12}, 60% Cl)

Single-Administration Studies	Sixteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
Preparation			
Weighed aliquots of chlorinated paraffins (C_{12}, 60% Cl) added to measured amounts of corn oil in serum bottles. The bottles placed on preheated magnetic stirring hot plates and heated to 37° C.	Same as single-admistration studies	Mixed with corn oil; stirred with magnetic stirrer until homogeneous in appearance	Protected from light during all procedures. Chlorinated paraffins (C_{12}, 60% Cl) allowed to warm to room temperature and then weighed into a beaker; corn oil added by volume or after 6/15/81 by weight and mixed on a magnetic stirrer to produce visual homogeneity. After 1/26/81, a Polytron® with an anaerobic probe replaced the magnetic stirrer. Dose mixtures stirred continuously during dosing of animals.
Maximum Storage Time			
N/A	7 d	7 d	14 d
Storage Conditions			
N/A	Room temperature in the dark	Room temperature in the dark	0° ± 5° C in the dark in amber serum bottles for no longer than 14 d

TABLE 2. SUMMARY OF RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{12}, 60% Cl)

	Concentration of Chlorinated Paraffins (C_{12}, 60% Cl) in Corn Oil for Target Concentration (percent) (a)			
	1.25	2.50	6.24	12.50
Number of samples	26	23	26	24
Mean (percent)	1.33	2.54	6.25	12.38
Standard deviation	0.603	0.469	0.490	0.407
Coefficient of variation (percent)	45.8	18.5	7.8	3.3
Range (percent)	0.76-4.20	2.18-4.60	5.32-8.10	11.76-13.42
Number of samples greater than ± 10% of target	6	2	3	0

(a) Values given are percent weight/volume. The corresponding values for weight/weight percent are 1.35%, 2.72%, 6.79%, and 13.60%.

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES

Accurately weighed aliquots of chlorinated paraffins (C_{12}, 60% chlorine) and corn oil were mixed to give the desired concentrations (Table 1). As noted in Table 1, 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_{12}, 60% chlorine) mixtures. Chlorinated paraffins (C_{12}, 60% chlorine) in corn oil was found to be stable for 28 days in the dark at room temperature (Appendix I). Chlorinated paraffins (C_{12}, 60% chlorine)/corn oil mixtures were stored at 0° ± 5° C for no longer than 14 days. Routine periodic analysis of chemical/vehicle mixtures at the study laboratory was performed by either a gravimetric or hydrometric procedure (Appendix J). Occasionally, the study laboratory's analysis of dose mixtures indicated that a sample was not within ± 10% of the target concentration (Table 2). Because 88/99 of the dose mixtures analyzed were within ± 10% of the target concentration, it is estimated that the dose mixtures were prepared within specifications 89% of the time (Appendix K, Table K1).

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 study began. The animals were 8 weeks old when placed on study. Groups of five rats of each sex were administered a single dose of 816, 1,632, 3,400, 6,800, or 13,600 mg/kg chlorinated paraffins (C_{12}, 60% chlorine) in corn oil by gavage. Groups of five mice of each sex were administered 1,632, 3,264, 6,800, or 13,600 mg/kg in corn oil or 27,200 mg/kg as the neat chemical. Animals were observed twice per day for 15 days. Details of animal maintenance are presented in Table 3.

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, 469, 938, 1,875, 3,750, or 7,500 mg/kg chlorinated paraffins (C_{12}, 60% chlorine) in corn oil by gavage on 12 days over a 16-day period. Groups of five mice of each sex were administered 0, 938, 1,875, 3,750, 7,500, or 15,000 mg/kg on the same schedule. Because of the large volume of gavage material required, the 7,500 mg/kg group of rats and the 15,000 mg/kg group of mice were dosed twice per day (5 hours apart) with 3,750 and 7,500 mg/kg, respectively.

Animals were housed five per cage. Water and feed were freely available. The rats and mice were observed twice daily and weighed once per week. A necropsy was performed on all animals. Histologic evaluation was not performed. Details of animal maintenance are presented in Table 3.

TABLE 3. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{12}, 60% Cl)

Single-Administration Studies	Sixteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
EXPERIMENTAL DESIGN			
Study Laboratory			
Southern Research Institute	Southern Research Institute	Southern Research Institute	Southern Research Institute
Size of Test 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 added to each group for concurrent 6- and 12-month studies
Doses			
Rats--816, 1,632, 3,400, 6,800, or 13,600 mg/kg chlorinated paraffins (C_{12}, 60% Cl) in corn oil by gavage; dose vol: 10 ml/kg; mice--1,632, 3,264, 6,800, or 13,600 chlorinated paraffins (C_{12}, 60% Cl) in corn oil by gavage (dose vol: 20 ml/kg) or 27,200 mg/kg, neat	Rats--0, 469, 938, 1,875, 3,750, or 7,500 mg/kg chlorinated paraffins (C_{12}, 60% Cl) in corn oil by gavage; dose vol: 5 ml/kg; mice--0, 938, 1,875, 3,750, 7,500, or 15,000 mg/kg chlorinated paraffins (C_{12}, 60% Cl) in corn oil by gavage; dose vol: 10 ml/kg. Rats in 7,500 mg/kg and mice in 15,000 mg/kg groups given 2 doses per day, 5 h apart.	Rats--0, 313, 625, 1,250, 2,500, or 5,000 mg/kg chlorinated paraffins (C_{12}, 60% Cl) in corn oil by gavage; dose vol: 5 ml/kg; mice--0, 125, 250, 500, 1,000, or 2,000 mg/kg chlorinated paraffins (C_{12}, 60% Cl) in corn oil by gavage; dose vol: 10 ml/kg	Rats--0, 312, or 625 mg/kg chlorinated paraffins (C_{12}, 60% Cl) in corn oil by gavage; dose vol: 5 ml/kg; mice--0, 125, or 250 mg/kg chlorinated paraffins (C_{12}, 60% Cl) in corn oil by gavage; dose vol: 10 ml/kg
Date of First Dose			
6/6/79	8/12/79	11/28/79	Rats--9/12/80; mice--9/25/80
Date of Last Dose			
N/A	8/27/79	2/26/80	Rats--9/9/82; mice--9/15/82
Duration of Dosing			
Single administration only	Administered on 12 d over a 16-d period	5 d/wk for 13 wk	Rats--5 d/wk for 104 wk; mice--5 d/wk for 103 wk
Type and Frequency of Observation			
Observed 2 × d for 15 d; weighed before dosing	Observed 2 × d; weighed on d 1, 9, and 16	Observed 2 × d; weighed 1 × wk; clinical signs recorded at time of weighing	Observed 2 × d; weighed initially, 1 × wk for 12 wk, then monthly; clinical signs recorded at time of weighing; animals were palpated at time of weighing beginning d 298 (rats) and d 286 (mice)
Necropsy and Histologic Examination			
Necropsy not performed	Necropsy performed on all animals; histologic examination not performed	Necropsy performed on all animals; histologic examination performed on all male and female rats in the vehicle control and 5,000 mg/kg groups plus one male rat that died early in the 2,500 mg/kg group and on all mice in the vehicle control and 2,000 mg/kg groups plus 17 mice that died early in other groups. The following tissues were examined:	Necropsy and histologic examination performed on all animals; the following tissues were examined: gross lesions, tissue masses, mandibular and mesenteric lymph nodes, salivary glands, femur including marrow, thyroid gland, parathyroids, small intestine, colon, liver, seminal vesicles/prostate/testes/

TABLE 3. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) (Continued)

Single-Administration Studies	Sixteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
Necropsy and Histologic Examination (Continued)			
		skin, mandibular lymph node, mammary gland, salivary glands, thigh muscle, femur including marrow, thymus, trachea, lungs and bronchi, heart, thyroid gland, parathyroids, esophagus, stomach, small intestine, colon, mesenteric lymph node, liver, gall-bladder (mice), pancreas, spleen, kidneys, adrenal glands, urinary bladder, seminal vesicles/prostate/testes or ovaries/uterus, brain and pituitary gland. The livers of mice in 125, 250, 500, and 1,000 mg/kg groups were examined histologically.	epididymis or ovaries/uterus/oviduct, lungs with mainstem bronchi, skin, mammary gland, heart, esophagus, brain, thymus, trachea, pancreas, spleen, kidneys, adrenal glands, urinary bladder, pituitary gland, rectum, thigh muscle, inguinal lymph nodes, eyes if grossly abnormal. Rat tissues weighed in the 6- and 12-month studies: spleen, liver, thymus, adrenal glands, brain, kidneys, and heart. Histologic evaluation of the tissues indicated above also performed in the 6- and 12-month studies.
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 (Portage, MI)	Charles River Breeding Laboratories (Portage, MI)	Charles River Breeding Laboratories (Kingston, NY)
Time Held Before Test			
20 d	12 d	15 d	Rats--15 d; mice--21 d
Method of Animal Identification			
Ear punch	Ear punch	Ear punch	Ear punch
Age When Placed on Study			
8 wk	Rats--6 wk; mice--7 wk	Rats--6-7 wk; mice--6-8 wk	Rats--6-7 wk; mice--8-9 wk
Age When Killed			
10 wk	Rats--8 wk; mice--9 wk	Rats--19-21 wk; mice--19-22 wk	Rats--111-113 wk; mice--112-114 wk
Necropsy Dates			
6/21/79	8/28/79-8/31/79	2/27/80-3/6/80	Rats--9/17/82-9/23/82; mice--9/23/82-10/1/82
Method of Animal Distribution			
Animals grouped by weight stratification. Assigned to cages according to a random numbers table; then cages assigned to groups according to another table of random numbers	Same as single-administration studies	Same as single-administration studies	Animals grouped by weight stratification; then animals assigned to cages and cages assigned to groups by the same random numbers table

TABLE 3. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) (Continued)

Single-Administration Studies	Sixteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
ANIMALS AND ANIMAL MAINTENANCE (Continued)			
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 Test 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--33%-76%; fluorescent light 12 h/d; 15 room air changes/h	Temp--23° ± 1° C (92% of the time); humidity--50% ± 10% (90% of the time); fluorescent light 12 h/d; 15 room air changes/h

THIRTEEN-WEEK STUDIES

Thirteen-week studies were conducted to evaluate the cumulative toxic effects of repeated administration of chlorinated paraffins (C_{12}, 60% chlorine) and to facilitate selection of the doses to be used in the 2-year studies.

Groups of 10 rats of each sex were administered 0, 313, 625, 1,250, 2,500, or 5,000 mg/kg chlorinated paraffins (C_{12}, 60% chlorine) as a single dose in corn oil by gavage, 5 days per week for 13 weeks. Groups of 10 mice of each sex were administered 0, 125, 250, 500, 1,000, or 2,000 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 3.

Animals were checked twice daily; moribund animals were killed. Individual animal weights were recorded weekly. At the end of the 13-week studies, survivors were killed. A necropsy was performed on all animals, and histology slides were prepared except for those excessively autolyzed or cannibalized. Tissues and groups examined are listed in Table 3.

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

Study Design

Groups of 50 rats were administered 0, 312, or 625 mg/kg chlorinated paraffins (C_{12}, 60% chlorine) in corn oil by gavage, 5 days per week for 104 weeks. Groups of 50 mice of each sex were administered 0, 125, or 250 mg/kg, 5 days per week for 103 weeks. Additional groups of 20 male and 20 female rats were added to each dose group for concurrent 6-month and 12-month studies. The spleen, liver, thymus, adrenal glands, brain, kidney, and heart were weighed at necropsy in the 6- and 12-month studies.

Source and Specifications of Animals

The male and female F344/N rats and $B6C3F_1$ (C57BL/6N, female, × C3H/HeN MTV^-, male) mice used in these studies were produced under strict barrier conditions at Charles River Breeding Laboratories (Kingston, New York) 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 testing 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 laboratory 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).

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

Animals were housed five per cage. Feed and water were available ad libitum. Further details of animal maintenance are given in Table 3.

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 12 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 3.

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. When significant survival differences were detected, additional analyses using these procedures were carried out to determine the time point at which significant differences in the survival curves were first detected. All reported P values for the survival analysis are two-sided.

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

Analysis of Tumor Incidence: Three statistical methods are used to analyze tumor incidence data. The two that adjust for intercurrent mortality employ the classical method for combining contingency tables developed by Mantel and Haenszel (1959). Tests of significance included 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 vehicle control groups were compared in each of four time intervals: weeks 0-52, weeks 53-86, week 87 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 vehicle 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.

Multiple Comparisons with a Control: For comparisons of many (quantitative) means with the concurrent vehicle control mean, a technique discussed by Dunnett (1955) is used. 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, sec. 2.5.)

III. RESULTS

RATS

SINGLE-ADMINISTRATION STUDIES

FOURTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

SIX-MONTH AND TWELVE-MONTH STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

MICE

SINGLE-ADMINISTRATION STUDIES

FOURTEEN-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 mean body weights were not recorded. Animals were inactive and ataxic after dosing. Diarrhea was observed for 2-6 days after dosing in all groups of dosed male rats and in all but the 816 mg/kg group of females. No clear evidence of chemical-related toxicity was noted. A high dose of 7,500 mg/kg was selected for both males and females for the 16-day studies. A dose higher than 3,750 mg/kg was considered too viscous to be given repeatedly by gavage without causing deaths related to the gavage procedure. The high dose of 7,500 mg/kg was therefore given as two daily doses of 3,750 mg/kg, 5 hours apart, in the 16-day studies.

SIXTEEN-DAY STUDIES

One of five males and 2/5 females that received 7,500 mg/kg died before the end of the studies (Table 4). All rats that received the 7,500 mg/kg dose had diarrhea. Final mean body weights of rats that received 7,500 mg/kg were 22% lower than those of corresponding vehicle controls for males and 14% lower for females, and those of rats that received 3,750 mg/kg were 15% lower for males and 6% lower for females. Enlarged livers were observed in 3-5 animals in every dose group except the 469 mg/kg group of females. It could not be concluded from this study whether the deaths observed in the 7,500 mg/kg dose groups were due to chemical toxicity or to the large volume (10 ml/kg per day) of the chemical/corn oil mixture administered. For this reason, the high dose for the 13-week studies was set at 5,000 mg/kg given as a single daily dose for rats of each sex. This dose exceeded the earlier recommended limit of 3,750 mg/kg based on chemical viscosity, but it was considered preferable to giving more than the usual daily gavage volume during a 13-week study.

TABLE 4. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE SIXTEEN-DAY GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{12}, 60% 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	115 ± 1	178 ± 2	+63 ± 2	--
469	5/5	119 ± 2	186 ± 3	+67 ± 2	104
938	5/5	114 ± 1	175 ± 2	+61 ± 1	98
1,875	5/5	118 ± 2	173 ± 4	+55 ± 2	97
3,750	5/5	116 ± 3	152 ± 9	+36 ± 9	85
7,500	(d) 4/5	115 ± 1	139 ± 2	+24 ± 1	78
FEMALE					
0	5/5	91 ± 3	124 ± 3	+33 ± 1	--
469	5/5	91 ± 1	127 ± 2	+36 ± 2	102
938	5/5	94 ± 1	127 ± 2	+33 ± 2	102
1,875	5/5	92 ± 2	124 ± 2	+32 ± 2	100
3,750	5/5	91 ± 2	117 ± 3	+26 ± 1	94
7,500	(e) 3/5	90 ± 1	107 ± 4	+17 ± 4	86

(a) Number surviving/number in group
(b) Initial group mean 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 of the group ± standard error of the mean
(d) Day of death: 7
(e) Day of death: 3, 8

THIRTEEN-WEEK STUDIES

No compound-related deaths occurred (Table 5). The final mean body weights of males that received 2,500 mg/kg and 5,000 mg/kg were 11% and 12% lower than those of the vehicle controls. Final mean body weights of the female rats were not adversely affected by chlorinated paraffins (C_{12}, 60% chlorine). Animals in the 625, 1,250, 2,500, and 5,000 mg/kg groups were generally inactive after dosing. A dose-related increase in relative liver weights was observed for male and female rats (Table 6). Hypertrophy of hepatocytes was noted in the livers of all rats that received the 5,000 mg/kg dose and in 1/10 male and 0/10 female rats that received 2,500 mg/kg. Nephrosis (nephropathy) was present in 10/10 males and 3/10 females that received 5,000 mg/kg and in 8/10 male and 0/10 female vehicle controls. Nephropathy appeared more severe in the dosed males than in the vehicle controls.

Dose Selection Rationale: Doses selected for rats in the 2-year studies were 312 and 625 mg/kg chlorinated paraffins (C_{12}, 60% chlorine) to be administered in corn oil, 5 days per week. Higher doses were not selected because of the marked liver enlargement noted with these doses in the 13-week studies.

TABLE 5. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{12}, 60% 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	135 ± 4	359 ± 9	+224 ± 8	--
313	10/10	122 ± 3	348 ± 5	+226 ± 6	97
625	10/10	130 ± 5	337 ± 5	+207 ± 4	94
1,250	10/10	129 ± 4	334 ± 4	+205 ± 5	93
2,500	(d) 9/10	122 ± 4	318 ± 6	+200 ± 6	89
5,000	10/10	122 ± 4	317 ± 6	+195 ± 5	88
FEMALE					
0	10/10	97 ± 2	200 ± 2	+103 ± 1	--
313	10/10	99 ± 2	207 ± 3	+108 ± 3	104
625	10/10	96 ± 1	201 ± 2	+105 ± 3	101
1,250	10/10	101 ± 2	215 ± 5	+114 ± 4	107
2,500	10/10	101 ± 2	206 ± 3	+105 ± 3	103
5,000	10/10	101 ± 2	205 ± 1	+104 ± 3	103

(a) Number surviving/number in group; no compound-related deaths were observed.
(b) Initial group mean 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 of the group ± standard error of the mean
(d) Week of death: 11

TABLE 6. LIVER WEIGHT TO BODY WEIGHT RATIOS FOR RATS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) (a,b)

Dose (mg/kg)	Relative Liver Weight (mg/g) Male	Female
0	39.40 ± 2.91	33.80 ± 3.26
313	(c) 46.44 ± 2.88	45.60 ± 7.63
625	52.90 ± 2.92	44.60 ± 2.91
1,250	59.90 ± 6.95	52.00 ± 4.45
2,500	(c) 72.44 ± 3.81	72.00 ± 5.14
5,000	72.00 ± 5.33	75.80 ± 4.42

(a) Mean milligrams per gram ± standard deviation for 10 animals unless otherwise noted
(b) $P<0.01$ by Dunnett's test for all dosed groups vs the vehicle controls
(c) Nine animals

SIX-MONTH AND TWELVE-MONTH STUDIES

Mean body weights at 6 and 12 months for male rats that received 625 mg/kg were 11% and 12% lower than those of the vehicle controls; mean body weights at 6 and 12 months for male rats that received 312 mg/kg were 6% lower than those of the vehicle controls (Table 7). Sialodacryoadenitis was observed upon gross and microscopic examinations at 6 months but not at 12 months in 2-10 animals in all groups (male and female) including vehicle controls.

A dose-related increase in absolute and relative liver weight was observed at 6 and 12 months (Table 7). The relative liver weights at 12 months were not significantly greater than those at 6 months. The increase in liver weights was due at least in part to hypertrophy of hepatocytes. (Hepatocytes were larger and fewer per defined microscopic area relative to that of the vehicle controls [Table 8].) A dose-related increase in absolute and relative kidney weight was observed at 6 and 12 months (Table 7). The incidence and severity of lesions of the tubules and of interstitial inflammation were dose related. Nephropathy in the male rats was more severe than that in the female rats (Table 9). There were no chemical-related changes in organ-to-body weight ratios in males and females for the adrenal glands, thymus, heart, brain, or spleen.

TABLE 7. ABSOLUTE AND RELATIVE ORGAN WEIGHTS FOR RATS IN THE SIX-MONTH AND TWELVE-MONTH GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) (a)

Dose (mg/kg)	Mean Body Weight (grams)	Liver Weight (grams)	Liver Weight/ Body Weight (mg/g)	Kidney Weight (grams)	Kidney Weight/ Body Weight (mg/g)
SIX-MONTH STUDIES					
Male					
0	431 ± 13	14.56 ± 1.21	33.9 ± 3.5	2.75 ± 0.14	6.4 ± 0.4
312	404 ± 17	19.86 ± 1.45	49.3 ± 3.8	3.54 ± 0.29	8.8 ± 0.6
625	379 ± 19	22.81 ± 2.55	60.0 ± 5.0	3.44 ± 0.24	9.1 ± 0.5
Female					
0	222 ± 10	7.20 ± 0.61	32.4 ± 2.8	1.54 ± 0.11	7.0 ± 0.4
312	214 ± 9	11.40 ± 0.82	53.2 ± 3.4	1.84 ± 0.16	8.6 ± 0.7
625	222 ± 10	15.16 ± 1.04	68.2 ± 2.9	1.95 ± 0.13	8.8 ± 0.4
TWELVE-MONTH STUDIES					
Male					
0	508 ± 23	18.58 ± 1.74	36.5 ± 2.3	3.44 ± 0.31	6.8 ± 0.4
312	476 ± 20	24.24 ± 2.42	51.0 ± 4.8	4.22 ± 0.36	8.9 ± 1.0
625	453 ± 39	29.14 ± 2.30	64.4 ± 3.1	4.49 ± 0.34	9.9 ± 0.6
Female					
0	260 ± 16	8.92 ± 0.72	34.5 ± 3.3	1.90 ± 0.12	7.3 ± 0.4
312	265 ± 13	14.32 ± 1.46	53.9 ± 4.1	2.24 ± 0.12	8.5 ± 0.3
625	267 ± 18	20.01 ± 3.07	75.2 ± 12.5	2.61 ± 0.17	9.8 ± 0.7

(a) Mean ± standard deviation for 10 animals. All values for relative and absolute organ weights of dosed groups are significantly greater ($P < 0.01$ by Dunnett's test) than those for vehicle controls. Male body weights are significantly lower ($P < 0.01$) than those of the vehicle controls.

TABLE 8. AVERAGE NUMBER OF HEPATOCYTES PER UNIT AREA OF LIVER IN RATS IN THE TWELVE-MONTH GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{12}, 60% Cl)

Dose (mg/kg)	Male No. of Hepatocytes (a)	Male Mean Cell Size (b)	Female No. of Hepatocytes (a)	Female Mean Cell Size (b)
0	239 ± 25	498	311 ± 42	383
625	(c) 216 ± 24	551	(d) 257 ± 35	463

(a) Mean ± standard deviation for two independent measurements of 10 animals for hepatocytes per 0.119 mm^2
(b) Square microns
(c) *t*-test P = 0.007 vs vehicle control
(d) *t*-test P < 0.001 vs vehicle control

TABLE 9. INCIDENCES AND SEVERITY OF NEPHROPATHY IN RATS IN THE TWELVE-MONTH GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{12}, 60% Cl)

Dose (mg/kg)	Incidence	Severity (a) (average)
MALE		
0	9/10	1.6
312	10/10	2.5
625	10/10	3.4
FEMALE		
0	2/10	0.2
312	10/10	1.5
625	10/10	2.5

(a) Mean severity: 1 = minimal; 2 = mild; 3 = moderate; 4 = marked; 5 = severe

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of high dose male rats were more than 5% lower than those of the vehicle controls after week 17 and 10% or more lower than those of the vehicle controls after week 37 (Table 10 and Figure 1). The mean body weights of low dose male rats were approximately 5% lower than those of the vehicle controls after week 37. The mean body weights of high dose female rats were approximately 5% lower than those of the vehicle controls after week 42. Clinical observations revealed no chemical-related changes until approximately 90 weeks into the study. At this time, the dosed males and females were observed to have a decrease in activity in relation to the vehicle control animals. This condition persisted in a number of animals of both sexes and both dose groups until the end of the studies; however, it was most prominent in male rats. In addition, a number of the high dose females began showing distended or firm abdomens and the observation "backbone prominent" was recorded for a large number of high and low dose males. These conditions also persisted until the end of the studies. Other conditions associated with chlorinated paraffins (C_{12}, 60% chlorine) administration included pale skin and eyes at both doses in each sex; emaciation, stained and wet fur in the pelvic/perianal area in the males at both doses; and sunken or small eyes and abnormal breathing in high dose males only.

Cloudy or opaque eyes were also reported among the high and low dose males and among low dose females. This condition is attributed to the intensity of room lighting, the proximity of the cages to the light source, and the lack of cage rotation rather than to any effect of the chemical.

TABLE 10. MEAN BODY WEIGHTS AND SURVIVAL OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{12}, 60% Cl)

Weeks on Study	Vehicle Control		312 mg/kg			625 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	137	50	137	100	50	138	101	50
1	198	50	202	102	50	199	101	50
2	226	50	230	102	50	229	101	50
3	254	50	258	102	50	257	101	50
4	269	50	273	101	50	273	101	50
5	285	50	287	101	50	286	100	50
6	296	50	297	100	50	295	100	50
7	310	50	307	99	50	304	98	50
8	316	50	312	99	50	319	101	50
9	326	50	324	99	50	318	98	50
10	336	50	332	99	50	326	97	50
11	345	50	340	99	50	332	96	50
12	354	50	350	99	50	342	97	50
17	389	50	378	97	50	363	93	50
20	405	50	392	97	50	375	93	50
24	426	50	410	96	50	391	92	50
29	428	50	409	96	50	385	90	50
33	445	50	428	96	50	405	91	50
37	463	50	436	94	50	417	90	50
42	485	50	456	94	50	425	88	49
47	495	50	464	94	50	436	88	49
52	499	50	470	94	50	441	88	48
56	506	50	477	94	50	446	88	48
60	513	50	482	94	50	451	88	48
64	512	48	479	94	49	449	88	48
69	510	47	481	94	49	445	87	48
75	512	44	484	95	47	448	88	48
77	508	44	487	96	47	450	89	48
83	499	40	476	95	45	442	89	43
87	491	40	479	98	40	430	88	37
92	483	39	462	96	30	419	87	28
96	475	35	440	93	21	408	86	17
101	456	32	436	96	11	399	88	5
105	447	27	420	94	6	343	77	3
FEMALE								
0	88	50	89	101	50	89	101	50
1	131	50	135	103	50	132	101	50
2	147	50	151	103	50	150	102	50
3	159	50	164	103	50	163	103	50
4	168	50	171	102	50	171	102	50
5	174	50	180	103	50	180	103	50
6	179	50	185	103	50	186	104	50
7	184	50	189	103	50	190	103	50
8	185	50	188	102	50	191	103	50
9	189	50	194	103	50	196	104	50
10	193	50	198	103	50	199	103	50
11	197	50	201	102	50	203	103	50
12	200	50	205	103	50	205	103	50
17	211	50	215	102	50	213	101	50
20	217	50	218	100	50	219	101	50
24	226	50	226	100	50	225	100	50
29	225	50	227	101	50	226	100	49
33	232	50	235	101	50	235	101	49
37	241	50	247	102	50	246	102	49
42	255	50	253	99	50	247	97	49
47	261	50	262	100	50	253	97	49
52	268	50	268	100	50	258	96	49
56	275	49	274	100	50	266	97	49
60	284	49	287	101	49	275	97	49
64	292	49	293	100	48	280	96	48
69	301	49	304	101	48	287	95	47
75	313	49	315	101	48	294	94	47
77	315	49	318	101	48	301	96	46
83	317	48	322	102	44	307	97	44
87	323	47	330	102	40	308	95	42
92	326	46	336	103	35	314	96	38
96	327	44	337	103	33	318	97	34
101	329	36	336	102	27	313	95	31
105	327	34	330	101	23	302	92	29

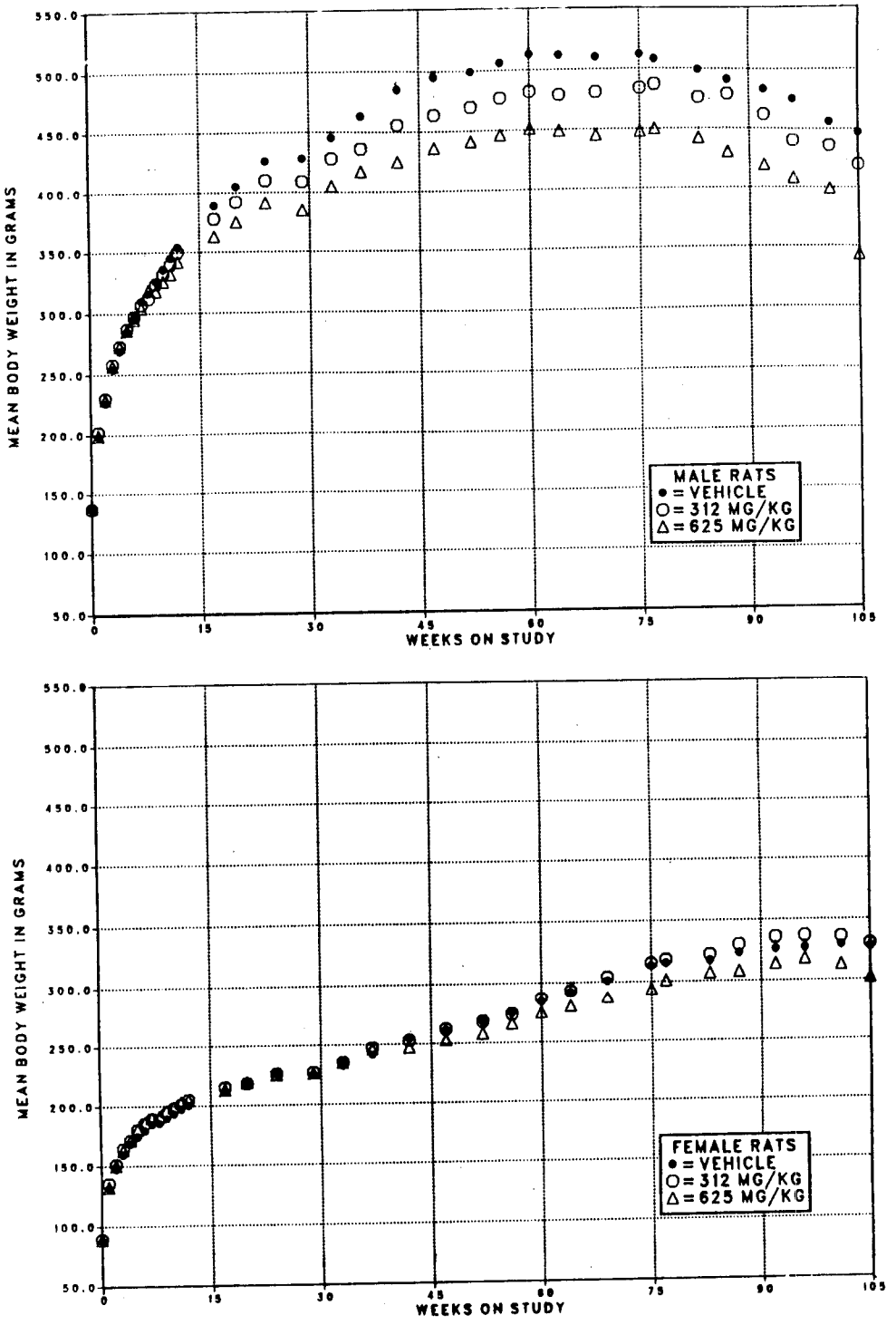


FIGURE 1. GROWTH CURVES FOR RATS ADMINISTERED CHLORINATED PARAFFINS (C_{12}, 60% Cl) IN CORN OIL BY GAVAGE FOR TWO YEARS

III. RESULTS: RATS

Survival

Estimates of the probabilities of survival for male and female rats administered chlorinated paraffins (C_{12}, 60% chlorine) at the doses used in these studies and for the vehicle controls are shown in the Kaplan and Meier curves in Figure 2. The survival of both the low dose (after week 92) and the high dose male groups (after week 89) were significantly lower than that of the vehicle controls (Table 12). Survival of the low dose group of female rats was significantly lower than that of the vehicle controls after week 92.

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 liver, kidney, thyroid gland, hematopoietic system, stomach, parathyroid, bone, pancreas, and uterus. 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 three 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. Because of low survival of dosed male rats, incidences of neoplasms in these groups which are significantly increased only by life table tests are not considered to be biologically meaningful unless the neoplasms in question were clearly a cause of death.

TABLE 11. SURVIVAL OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{12}, 60% Cl)

	Vehicle Control	312 mg/kg	625 mg/kg
MALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	19	43	46
Accidentally killed (c)	4	1	1
Killed at termination	27	6	3
Survival P values (d)	<0.001	<0.001	<0.001
FEMALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	16	26	20
Accidentally killed (c)	0	0	1
Killed at termination	34	23	29
Died during termination period	0	1	0
Survival P values (d)	0.300	0.035	0.333

(a) Terminal kill period: weeks 105-106
(b) Includes animals killed in a moribund condition
(c) All accidental deaths were due to gavage-related trauma.
(d) The result of the life table trend test is in the vehicle control column, and the results of the life table pairwise comparisons with the vehicle controls are in the dosed columns.

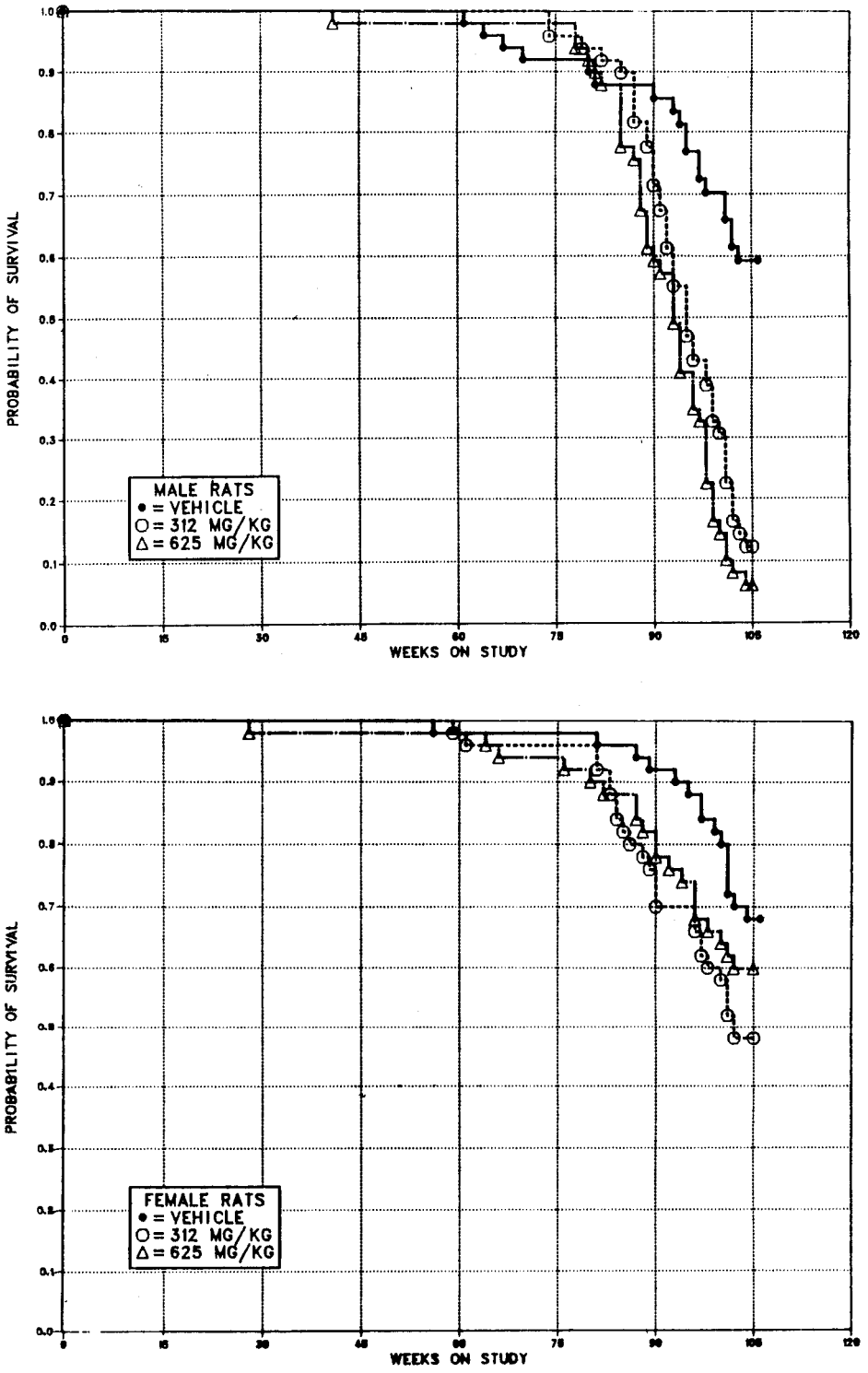


FIGURE 2. KAPLAN-MEIER SURVIVAL CURVES FOR RATS ADMINISTERED CHLORINATED PARAFFINS (C_{12}, 60% Cl) IN CORN OIL BY GAVAGE FOR TWO YEARS

Liver: Necrosis, focal cellular change, hypertrophy (of minimal severity), and angiectasis were observed at increased incidences in dosed male and female rats (Table 12). Focal and/or zonal necrosis was described as slight or minimal in all affected animals. The incidence of basophilic cytologic change was notably decreased in dosed female rats compared with that in the vehicle controls. This lesion may have been masked somewhat by hepatocyte hypertropy in dosed females. Neoplastic nodules or hepatocellular carcinomas (combined) occurred with positive trends in males and females. The incidences of hepatocellular carcinomas in low dose males and of neoplastic nodules and neoplastic nodules or hepatocellular carcinomas (combined) in dosed males and females were greater than those in the vehicle controls (Table 13).

The observed hepatocellular carcinomas were large, solid nodules that markedly compressed adjacent hepatic parenchyma. They were composed of enlarged anaplastic hepatocytes arranged in a trabecular pattern that distorted normal lobular architecture. Neoplastic nodules consisted of enlarged eosinophilic hepatocytes in an irregular arrangement. At least a portion of the circumference of these spherical lesions was sharply demarcated from the surrounding liver parenchyma by either compression of normal liver or lack of continuity between the plates of the nodule and adjacent tissue. The diagnosis of focal cellular change was used for hepatic lesions similar to the neoplastic nodules but smaller and with a less distinct zone of demarcation between the lesion and normal hepatic parenchyma.

TABLE 12. NUMBERS OF RATS WITH LIVER LESIONS IN THE TWO-YEAR GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{12}, 60% Cl)

	Male			Female		
Lesion	Vehicle Control	312 mg/kg	625 mg/kg	Vehicle Control	312 mg/kg	625 mg/kg
Number examined	50	50	48	50	50	50
Hepatocellular carcinoma	0	3	2	0	1	1
Neoplastic nodule	0	10	16	0	4	7
Focal cellular change	1	12	21	0	4	7
Hypertrophy	0	37	46	1	39	45
Necrosis	3	14	16	7	16	10
Angiectasis	0	11	10	0	7	7
Basophilic cytologic change	0	0	0	37	14	1

TABLE 13. ANALYSIS OF LIVER TUMORS IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) (a)

	Vehicle Control	312 mg/kg	625 mg/kg
MALE			
Neoplastic Nodule			
Overall Rates	0/50 (0%)	10/50 (20%)	16/48 (33%)
Adjusted Rates	0.0%	56.6%	86.4%
Terminal Rates	0/27 (0%)	2/6 (33%)	2/3 (67%)
Week of First Observation		90	78
Life Table Tests	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests	P<0.001	P=0.003	P<0.001
Hepatocellular Carcinoma			
Overall Rates	0/50 (0%)	3/50 (6%)	2/48 (4%)
Adjusted Rates	0.0%	39.4%	17.9%
Terminal Rates	0/27 (0%)	2/6 (33%)	0/3 (0%)
Week of First Observation		102	94
Life Table Tests	P=0.005	P=0.004	P=0.066
Incidental Tumor Tests	P=0.078	P=0.020	P=0.410
Neoplastic Nodule or Hepatocellular Carcinoma (b)			
Overall Rates	0/50 (0%)	13/50 (26%)	16/48 (33%)
Adjusted Rates	0.0%	80.5%	86.4%
Terminal Rates	0/27 (0%)	4/6 (67%)	2/3 (67%)
Week of First Observation		90	78
Life Table Tests	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests	P<0.001	P<0.001	P<0.001
FEMALE			
Neoplastic Nodule			
Overall Rates	0/50 (0%)	4/50 (8%)	7/50 (14%)
Adjusted Rates	0.0%	13.0%	21.7%
Terminal Rates	0/34 (0%)	2/24 (8%)	5/29 (17%)
Week of First Observation		81	90
Life Table Tests	P=0.004	P=0.038	P=0.005
Incidental Tumor Tests	P=0.005	P=0.080	P=0.008
Hepatocellular Carcinoma			
Overall Rates	0/50 (0%)	1/50 (2%)	1/50 (2%)
Neoplastic Nodule or Hepatocellular Carcinoma (c)			
Overall Rates	0/50 (0%)	5/50 (10%)	7/50 (14%)
Adjusted Rates	0.0%	14.9%	21.7%
Terminal Rates	0/34 (0%)	2/24 (8%)	5/29 (17%)
Week of First Observation		81	90
Life Table Tests	P=0.006	P=0.020	P=0.005
Incidental Tumor Tests	P=0.008	P=0.068	P=0.008

(a) The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix E (footnotes).
(b) Historical incidences at study laboratory (mean ± SD): 8/299 (3% ± 3%); historical incidences in NTP studies: 43/1,098 (4% ± 4%)
(c) Historical incidences at study laboratory (mean ± SD): 2/300 (0.7% ± 1%); historical incidences in NTP studies: 21/1,098 (2% ± 3%)

Kidney: Multiple cysts were observed in the cortex in 26/50 (52%) of low dose males and 27/49 (54%) of high dose males but in 0/50 vehicle controls. These lesions consisted primarily of severe tubular dilatation, with a marked thickening of the basement membrane, extensive protein casts, and interstitial fibrosis. The chronic nephropathy commonly observed in aged F344/N rats was subjectively judged to be more severe in dosed male rats than in vehicle controls, and the incidence of nephropathy was increased in dosed females (vehicle control, 33/50; low dose, 50/50; high dose, 48/50). Renal damage was so extensive in males that approximately 50% of dosed males developed a secondary parathyroid hyperplasia and subsequent fibrous osteodystrophy.

The incidence of tubular cell hyperplasia was increased in dosed male groups (Table 14). Tubular cell adenomas and tubular cell adenomas or adenocarcinomas (combined) in male rats occurred with a positive trend, and the incidence in the low dose group was greater than that in the vehicle controls. Tubular cell adenomas were well circumscribed and compressed the adjacent parenchyma. They were composed of variably sized cuboidal, columnar, or polygonal cells that formed solid lobules separated by connective tissue septa. Tubular cell adenocarcinomas were larger than adenomas and often invaded the adjacent parenchyma. The cells were often pleomorphic, and many contained large bizarre nuclei. Necrosis, hemorrhage, and cholesterol clefts were often present. Tubular cell hyperplasias were small, circumscribed lesions usually only a few hundred microns in diameter. The cells were small with poorly defined basophilic cytoplasm and round nuclei. These lesions consisted of nonseptated masses of cells which did not compress the surrounding parenchyma.

TABLE 14. ANALYSIS OF KIDNEY TUBULAR CELL LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{12}, 60% Cl)

	Vehicle Control	312 mg/kg	625 mg/kg
Hyperplasia			
Overall Rates	1/50 (2%)	9/50 (18%)	12/49 (24%)
Adenoma			
Overall Rates	0/50 (0%)	7/50 (14%)	3/49 (6%)
Adjusted Rates	0.0%	52.3%	10.5%
Terminal Rates	0/27 (0%)	2/6 (33%)	0/3 (0%)
Week of First Observation		93	82
Life Table Tests	P=0.007	P<0.001	P=0.080
Incidental Tumor Tests	P=0.170	P=0.013	P=0.238
Adenocarcinoma			
Overall Rates	0/50 (0%)	2/50 (4%)	0/49 (0%)
Adenoma or Adenocarcinoma (a)			
Overall Rates	0/50 (0%)	9/50 (18%)	3/49 (6%)
Adjusted Rates	0.0%	54.8%	10.5%
Terminal Rates	0/27 (0%)	2/6 (33%)	0/3 (0%)
Week of First Observation		87	82
Life Table Tests	P=0.012	P<0.001	P=0.080
Incidental Tumor Tests	P=0.253	P=0.008	P=0.238

(a) Historical incidences at study laboratory (mean): 1/300 (0.3%); historical incidences in NTP studies: 5/1,098, (0.5%)

Thyroid Gland: Follicular cell carcinomas and follicular cell adenomas or carcinomas (combined) in female rats occurred with positive trends (Table 15). The incidences of follicular cell adenomas in low dose females and of follicular cell adenomas or carcinomas (combined) in dosed females were greater than those of the vehicle controls. The following incidences of follicular cell adenomas or carcinomas (combined) were found in male rats: vehicle control, 3/50 (6%); low dose, 3/50 (6%); high dose 3/50 (6%).

TABLE 15. ANALYSIS OF THYROID GLAND FOLLICULAR CELL LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{12}, 60% Cl)

	Vehicle Control	312 mg/kg	625 mg/kg
Hyperplasia			
Overall Rates	0/50 (0%)	3/50 (6%)	3/50 (6%)
Adenoma			
Overall Rates	0/50 (0%)	6/50 (12%)	3/50 (6%)
Adjusted Rates	0.0%	18.9%	8.7%
Terminal Rates	0/34 (0%)	3/24 (13%)	0/29 (0%)
Week of First Observation		83	88
Life Table Tests	P=0.118	P=0.009	P=0.094
Incidental Tumor Tests	P=0.153	P=0.020	P=0.128
Carcinoma			
Overall Rates	0/50 (0%)	0/50 (0%)	3/50 (6%)
Adjusted Rates	0.0%	0.0%	10.3%
Terminal Rates	0/34 (0%)	0/24 (0%)	3/29 (10%)
Week of First Observation			105
Life Table Tests	P=0.033	(a)	P=0.094
Incidental Tumor Tests	P=0.033	(a)	P=0.094
Adenoma or Carcinoma (b)			
Overall Rates	0/50 (0%)	6/50 (12%)	6/50 (12%)
Adjusted Rates	0.0%	18.9%	18.1%
Terminal Rates	0/34 (0%)	3/24 (13%)	3/29 (10%)
Week of First Observation		83	88
Life Table Tests	P=0.016	P=0.009	P=0.011
Incidental Tumor Tests	P=0.020	P=0.020	P=0.016

(a) No P value is reported because no tumors were observed in the 312 mg/kg and vehicle control groups.
(b) Historical incidence at the study laboratory (mean ± SD): 3/297 (1% ± 1%); historical incidence in NTP studies: 15/1,076 (1% ± 2%)

Hematopoietic System: Mononuclear cell leukemia in male rats occurred with a positive trend; the incidences in dosed males and low dose females were greater than those in the vehicle controls (Table 16).

The diagnoses of mononuclear cell leukemia were classified according to the extent of the disease as stage 1 (early), stage 2 (intermediate), or stage 3 (advanced). The following criteria were used: In stage 1, the spleen was not enlarged or was only moderately enlarged, there were few suspicious cells surrounding the malpighian corpuscles of the spleen, and only very few neoplastic cells in the blood vessels of the lung. In stage 2, the disease was more severe; the spleen and/or liver only were moderately enlarged and neoplastic cells were detected in the liver sinusoids and the blood vessels of other organs. In stage 3, the spleen and liver were enlarged and many neoplastic cells were detected in the liver sinusoids and the blood vessels of other organs. The distribution of stages of mononuclear cell leukemia in male and female rats is summarized in Table 17.

TABLE 16. ANALYSIS OF MONONUCLEAR CELL LEUKEMIA IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{12}, 60% Cl)

	Vehicle Control	312 mg/kg	625 mg/kg
MALE (a)			
Overall Rates	7/50 (14%)	12/50 (24%)	14/50 (28%)
Adjusted Rates	19.2%	52.6%	51.5%
Terminal Rates	3/27 (11%)	2/6 (33%)	0/3 (0%)
Week of First Observation	61	74	78
Life Table Tests	P=0.001	P=0.021	P=0.003
Incidental Tumor Tests	P=0.102	P=0.121	P=0.208
FEMALE (b)			
Overall Rates	11/50 (22%)	22/50 (44%)	16/50 (32%)
Adjusted Rates	25.3%	50.9%	41.7%
Terminal Rates	4/34 (12%)	4/24 (17%)	7/29 (24%)
Week of First Observation	56	81	88
Life Table Tests	P=0.098	P=0.006	P=0.104
Incidental Tumor Tests	P=0.138	P=0.062	P=0.127

(a) Historical incidences at study laboratory (mean ± SD): 19/300 (6% ± 6%); historical incidences in NTP studies: 152/1,100 (14% ± 8%)
(b) Historical incidences at study laboratory (mean ±SD): 36/300 (12% ± 6%); historical incidences in NTP studies: 196/1,100 (18% ± 9%)

TABLE 17. CLASSIFICATION OF MONONUCLEAR CELL LEUKEMIA IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{12}, 60% Cl)

	Male			Female		
	Vehicle Control	312 mg/kg	625 mg/kg	Vehicle Control	312 mg/kg	625 mg/kg
Number Examined	50	50	50	50	50	50
Number of Rats with Mononuclear Cell Leukemia	7	12	(a) 13	11	22	16
Stage 1	0	0	3	0	2	3
Stage 2	2	6	0	3	3	3
Stage 3	5	6	10	8	17	10

(a) The tissues from one high dose male rat with leukemia were inadvertently not examined.

Stomach: Edema and erosion of the glandular stomach and ulcers, inflammation, epithelial hyperplasia, and hyperkeratosis of the forestomach were observed at noticeably increased incidences in dosed male rats (Table 18). Squamous cell papillomas of the forestomach were found in 2/49 high dose male rats. Erosions consisted of a loss of superficial epithelium, whereas ulcers were deeper and exposed submucosal tissues. Inflammation was generally of the chronic, active type, demonstrating healing (fibroplasia) concurrent with a pleomorphic cellular exudation and edema.

Parathyroid: Hyperplasia was observed at increased incidences in dosed male rats (vehicle control, 8/46, 17%; low dose, 27/48, 56%; high dose, 24/50, 48%). Hyperplasia was observed in 1/47 (2%) high dose female rats.

Bone: Fibrous osteodystrophy was observed at increased incidences in dosed male rats (vehicle control, 0/50; low dose, 31/50, 62%; high dose, 23/50, 46%). Fibrous osteodystrophy was present in 1/50 high dose female rats.

TABLE 18. NUMBERS OF RATS WITH STOMACH LESIONS IN THE TWO-YEAR GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{12}, 60% Cl)

	Male			Female		
Site/Lesion	Vehicle Control	312 mg/kg	625 mg/kg	Vehicle Control	312 mg/kg	625 mg/kg
Number Examined	50	50	49	50	50	50
Glandular Stomach						
Edema	1	9	9	0	1	3
Erosion	1	5	9	0	3	1
Ulcer	0	8	1	1	0	0
Forestomach						
Ulcer	1	13	13	1	2	2
Inflammation	3	19	21	2	4	2
Epithelial hyperplasia	5	23	27	4	7	3
Hyperkeratosis	5	23	27	4	6	2
Squamous cell papilloma	0	0	2	0	0	0

Pancreas: Acinar cell adenomas and adenomas or carcinomas (combined) in male rats occurred with positive trends by the life table test, and the incidences in dosed males were greater than that in the vehicle controls (Table 19). Acinar cell adenomas were generally rounded or nodular, discrete, and sharply demarcated from the surrounding tissue. They were usually 2 mm or larger in diameter and often were encapsulated. Acinar cell carcinomas were similar to adenomas but showed an admixture of growth patterns, including glandular, ductular, trabecular, and solid sheets.

Uterus: The incidence of endometrial stromal polyps in low dose female rats was greater than those in the vehicle controls (Table 20).

TABLE 19. ANALYSIS OF PANCREATIC ACINAR CELL TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{12}, 60% Cl)

	Vehicle Control	312 mg/kg	625 mg/kg
Adenoma (a)			
Overall Rate	11/50 (22%)	22/50 (44%)	15/49 (31%)
Adjusted Rate	36.5%	80.2%	77.0%
Terminal Rate	8/27 (30%)	3/6 (50%)	1/3 (33%)
Week of First Observation	101	87	88
Life Table Test	P<0.001	P<0.001	P<0.001
Incidental Tumor Test	P=0.268	P=0.049	P=0.236
Carcinoma			
Overall Rate	(b) 0/50 (0%)	0/50 (0%)	2/49 (4%)
Adenoma or Carcinoma (c)			
Overall Rates	11/50 (22%)	22/50 (44%)	17/49 (35%)
Adjusted Rate	36.5%	80.2%	78.1%
Terminal Rate	8/27 (30%)	3/6 (50%)	1/3 (33%)
Week of First Observation	101	87	85
Life Table Test	P<0.001	P<0.001	P<0.001
Incidental Tumor Test	P=0.142	P=0.049	P=0.115

(a) The incidences in female rats were vehicle control, 1/50 (2%); low dose, 5/48 (10%); high dose, 2/50 (4%).
(b) One carcinoma, NOS, was also observed. This tumor appeared to be of acinar or ductular origin and was clearly different from islet cell tumors.
(c) Historical incidence at study laboratory (mean ± SD): 14/298 (5% ± 9%); historical incidence in NTP studies: 47/1,098 (4% ± 7%)

TABLE 20. ANALYSIS OF UTERINE TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{12}, 60% Cl)

	Vehicle Control	312 mg/kg	625 mg/kg
Endometrial Stromal Polyp			
Overall Rates	5/50 (10%)	13/50 (26%)	11/50 (22%)
Adjusted Rates	13.1%	41.7%	32.8%
Terminal Rates	3/34 (9%)	7/24 (29%)	8/29 (28%)
Week of First Observation	95	90	66
Life Table Tests	P=0.045	P=0.007	P=0.048
Incidental Tumor Tests	P=0.067	P=0.015	P=0.089
Endometrial Stromal Sarcoma			
Overall Rates	1/50 (2%)	1/50 (2%)	0/50 (0%)
Endometrial Stromal Polyp or Sarcoma (a)			
Overall Rates	6/50 (12%)	14/50 (28%)	11/50 (22%)
Adjusted Rates	15.1%	45.1%	32.8%
Terminal Rates	3/34 (9%)	8/24 (33%)	8/29 (28%)
Week of First Observation	95	90	66
Life Table Tests	P=0.074	P=0.008	P=0.083
Incidental Tumor Tests	P=0.110	P=0.017	P=0.151

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

III. RESULTS: MICE

SINGLE-ADMINISTRATION STUDIES

No compound-related deaths occurred. Final body weights were not recorded. Animals were inactive and ataxic after dosing and had ruffled fur on days 2-6 after dosing. No evidence of chemical-related toxicity was noted. A high dose of 15,000 mg/kg was selected for both males and females for the 16-day studies. A dose higher than 7,500 mg/kg was considered too viscous to be given repeatedly by gavage. Therefore, the high dose of 15,000 mg/kg was given as two daily doses of 7,500 mg/kg, 5 hours apart, in the 16-day studies.

SIXTEEN-DAY STUDIES

All mice that received 3,750, 7,500, or 15,000 mg/kg and 4/5 males and 2/5 females that received 1,875 mg/kg died before the end of the studies (Table 21). Final mean body weights of male and female mice that survived were not affected by chlorinated paraffins (C_{12}, 60% chlorine). Diarrhea was present in all dosed groups except the female group administered 938 mg/kg. Livers appeared enlarged in dosed mice that lived to the end of the studies. The selection of 2,000 mg/kg as the high dose for both male and female mice for the 13-week studies was based on the incidence of deaths observed in the 16-day studies.

TABLE 21. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE SIXTEEN-DAY GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{12}, 60% 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	27.4 ± 0.6	29.0 ± 0.9	+1.6 ± 0.5	--
938	5/5	28.4 ± 0.7	30.2 ± 0.8	+1.8 ± 0.4	104.1
1,875	(d) 1/5	26.4 ± 0.8	29.0	0.0	100.0
3,750	(e) 0/5	28.2 ± 0.7	(f)	(f)	--
7,500	(g) 0/5	28.0 ± 0.3	(f)	(f)	--
15,000	(h) 0/5	27.6 ± 0.4	(f)	(f)	--
FEMALE					
0	5/5	21.6 ± 0.2	22.4 ± 0.2	+0.8 ± 0.2	--
938	5/5	21.6 ± 0.4	22.4 ± 0.4	+0.8 ± 0.4	100.0
1,875	(i) 3/5	22.8 ± 0.7	24.3 ± 1.2	+1.0 ± 0.6	108.5
3,750	(j) 0/5	20.8 ± 0.6	(f)	(f)	--
7,500	(k) 0/5	22.0 ± 0.3	(f)	(f)	--
15,000	(h) 0/5	23.0 ± 0.6	(f)	(f)	--

(a) Number surviving/number initially in group
(b) Initial group mean 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 of the group ± standard error of the mean
(d) Day of death: all 5
(e) Day of death: 3, 4, 4, 4, 5
(f) No data are presented due to the 100% mortality in this group.
(g) Day of death: 4, 4, 4, 4, 5
(h) Day of death: all 3
(i) Day of death: 4, 5
(j) Day of death: 1, 5, 5, 5, 7
(k) Day of death: 4, 4, 5, 5, 5

THIRTEEN-WEEK STUDIES

All deaths were considered to be due to gavage error, as shown by the observation of oil in the thoracic cavity or a hole in the esophagus (Table 22). The final mean body weights of male mice that received 1,000 or 2,000 mg/kg were 8% and 13% lower than that of the vehicle controls. Final mean body weights of female mice were not adversely affected by administration of chlorinated paraffins (C_{12}, 60% chlorine). Relative liver weights of male and female mice increased with dose (Table 23). The incidences of hypertrophy of hepatocytes and focal necrosis of the liver were increased in dosed male and female mice (Table 24). The large number of deaths from gavage-related trauma was probably from the use of a 20-gauge gavage needle rather than the smaller, 22-gauge needle used during the 16-day studies.

Dose Selection Rationale: Doses selected for mice in the 2-year studies were 125 and 250 mg/kg chlorinated paraffins (C_{12}, 60% chlorine), to be administered in corn oil by gavage, 5 days per week. Higher doses were not selected because of the marked liver enlargement noted with these doses in the 13-week studies and the accompanying hepatocyte hypertrophy and necrosis.

TABLE 22. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE THIRTEEN-WEEK GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{12}, 60% 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	25.9 ± 0.5	38.1 ± 0.9	+ 12.0 ± 0.8	--
125	9/10	25.2 ± 0.5	35.7 ± 0.6	+ 10.4 ± 0.4	93.7
250	9/10	25.8 ± 0.5	38.1 ± 0.7	+ 12.0 ± 0.5	100.0
500	9/10	26.0 ± 0.5	38.6 ± 1.0	+ 12.4 ± 0.8	101.3
1,000	10/10	25.0 ± 0.5	35.1 ± 0.4	+ 10.1 ± 0.5	92.1
2,000	6/10	24.9 ± 0.5	33.0 ± 0.8	+ 8.3 ± 0.7	86.6
FEMALE					
0	8/10	17.8 ± 0.4	27.3 ± 1.0	+ 9.5 ± 0.8	--
125	5/10	17.9 ± 0.5	27.6 ± 1.4	+ 10.2 ± 0.8	101.1
250	7/10	17.8 ± 0.2	26.6 ± 0.3	+ 9.1 ± 0.3	97.4
500	5/10	18.3 ± 0.4	27.8 ± 1.1	+ 10.0 ± 0.8	101.8
1,000	9/10	18.2 ± 0.4	27.6 ± 0.5	+ 9.4 ± 0.2	101.1
2,000	8/10	17.7 ± 0.4	29.1 ± 0.5	+ 11.5 ± 0.5	106.6

(a) Number surviving/number initially in group; all deaths judged accidental due to gavage error.
(b) Initial group mean 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 of the group ± standard error of the mean

TABLE 23. LIVER WEIGHT TO BODY WEIGHT RATIOS FOR MICE IN THE THIRTEEN-WEEK GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) (a)

Dose (mg/kg)	Relative Liver Weight (mg/g) Male	Female
0	45.3 ± 6.1 (9)	42.9 ± 3.5 (8)
125	48.7 ± 6.3 (9)	51.6 ± 2.7 (5)
250	51.6 ± 6.0 (9)	(b) 51.7 ± 3.6 (7)
500	(c) 62.7 ± 6.4 (9)	(c) 60.6 ± 6.8 (5)
1,000	(c) 74.5 ± 6.6 (10)	(c) 84.0 ± 6.7 (9)
2,000	(c) 108.7 ±14.1 (6)	(c) 116.5 ±10.1 (8)

(a) Mean ± standard deviation (number of animals)
(b) P<0.05 relative to vehicle controls by Dunnett's test
(c) P<0.01 relative to vehicle controls by Dunnett's test

TABLE 24. NUMBERS OF MICE WITH HYPERTROPHY OF HEPATOCYTES OR FOCAL NECROSIS OF THE LIVER IN THE THIRTEEN-WEEK GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) (a)

Dose (mg/kg)	Hypertrophy Male	Hypertrophy Female	Necrosis Male	Necrosis Female
0	0	0	0	0
125	0	0	1	0
250	4	1	0	0
500	4	2	3	0
1,000	10	3	2	0
2,000	8	8	7	3

(a) Ten animals were examined in each group. Hypertrophy of hepatocytes was based on a subjective analysis of tissues by light microscopy.

TWO-YEAR STUDIES

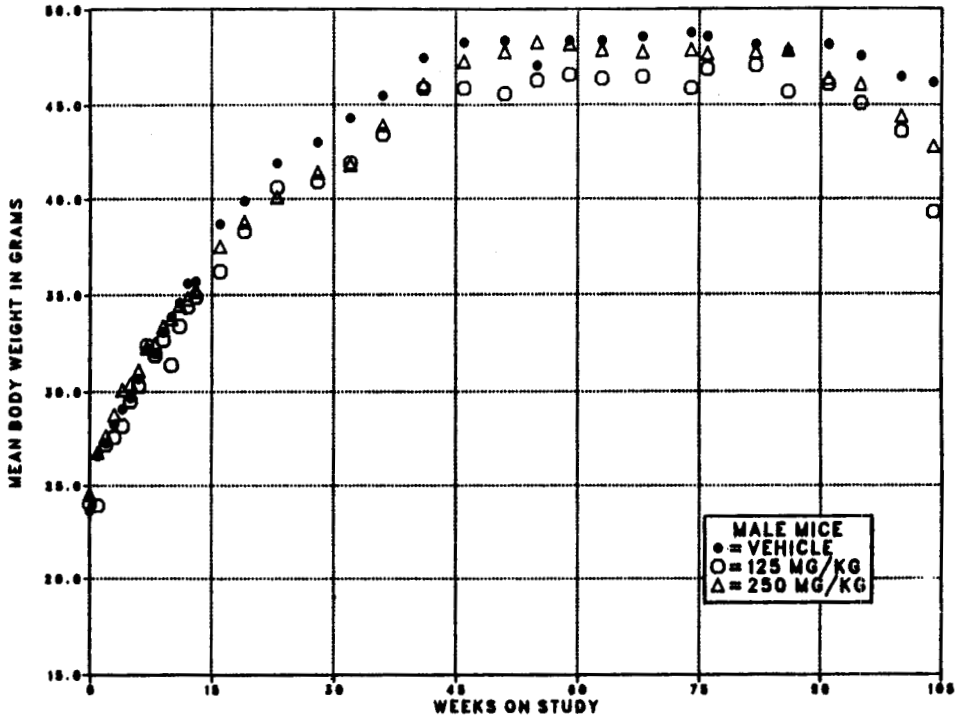
Body Weights and Clinical Signs

Mean body weights of dosed male mice were comparable to or slightly lower than those of the vehicle controls (Table 25 and Figure 3). Mean body weights of dosed female mice were 6%-12% lower than those of the vehicle controls after week 36.

No chemical-related observations were recorded until approximately week 81 of the study. At that time, a number of high dose males began to exhibit distended abdomens. By week 86, the condition had also become apparent in the high dose females and in the male and female vehicle control groups. Other observations recorded in the females included a decrease in activity, prominent backbones, and abnormal breathing in both dose groups and ruffled fur in the high dose group. Most of the observations reported for male mice were related to fighting among cage mates (e.g., external genitalia cannibalized) and not to chemical administration. However, the males also had decreased activity, prominent backbones, and abnormal breathing in both dose groups.

TABLE 25. MEAN BODY WEIGHTS AND SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{12}, 60% Cl)

Weeks on Study	Vehicle Control		125 mg/kg			250 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	23.6	50	24.0	102	50	24.5	104	50
1	26.6	49	23.9	90	50	26.8	101	50
2	27.3	49	27.2	100	50	27.7	101	50
3	28.3	49	27.6	98	50	28.8	102	50
4	29.1	49	28.2	97	50	30.1	103	50
5	29.7	49	29.5	99	50	30.4	102	50
6	30.7	49	30.3	99	50	31.1	101	50
7	32.2	49	32.4	101	50	32.3	100	50
8	32.0	49	31.9	100	50	32.5	102	50
9	33.1	49	32.7	99	50	33.4	101	50
10	33.9	49	31.4	93	50	33.8	100	50
11	34.6	49	33.4	97	50	34.5	100	50
12	35.6	49	34.4	97	50	34.8	98	50
13	35.7	49	34.9	98	50	35.2	99	50
16	38.7	49	36.2	94	50	37.5	97	50
19	39.9	49	38.3	96	50	38.8	97	50
23	41.9	49	40.6	97	50	40.1	96	50
28	43.0	49	40.9	95	50	41.4	96	49
32	44.3	49	41.9	95	50	41.8	94	49
36	45.5	49	43.4	95	50	43.9	96	49
41	47.5	49	45.9	97	50	46.1	97	49
46	48.3	49	45.9	95	50	47.3	98	49
51	48.4	49	45.6	94	49	47.8	99	49
55	47.1	49	46.3	98	49	48.3	103	49
59	48.4	49	46.6	96	47	48.2	100	49
63	48.4	49	46.4	96	47	47.9	99	49
68	48.6	49	46.5	96	47	47.8	98	47
74	48.8	49	45.9	94	46	47.9	98	46
76	48.6	49	46.9	97	44	47.7	98	46
82	48.2	49	47.1	98	44	47.8	99	43
86	47.9	49	45.7	95	44	47.9	100	42
91	48.2	41	46.1	96	39	46.4	96	38
95	47.6	41	45.1	95	38	46.1	97	36
100	46.5	41	43.6	94	36	44.4	95	35
104	46.2	34	39.3	85	31	42.8	93	31
FEMALE								
0	19.5	50	19.5	100	50	20.0	103	50
1	21.0	50	21.4	102	49	22.2	106	50
2	22.3	49	22.8	102	47	23.2	104	48
3	22.5	49	22.8	101	47	23.4	104	48
4	23.7	49	23.5	99	47	24.5	103	48
5	23.8	49	24.2	102	47	24.7	104	48
6	24.3	49	24.4	100	47	25.3	104	48
7	24.9	49	25.6	103	47	25.9	104	48
8	25.4	49	24.9	98	47	25.8	102	48
9	25.6	49	25.5	100	47	26.5	104	48
10	26.0	49	25.6	98	47	26.7	103	48
11	26.2	49	25.9	99	47	26.8	102	48
12	26.8	49	26.3	98	47	27.1	101	48
13	27.1	49	26.8	99	47	27.6	102	48
16	28.5	49	27.4	96	47	28.3	99	48
19	29.0	49	28.6	99	47	29.1	100	48
23	30.3	49	29.7	98	47	29.8	98	48
28	30.9	49	30.1	97	47	30.4	98	48
32	32.1	49	31.4	98	47	31.4	98	48
36	33.9	48	31.9	94	47	31.9	94	48
41	35.8	48	33.5	94	47	33.0	92	48
46	37.5	48	34.5	92	47	34.1	91	48
51	37.6	48	34.7	92	47	35.1	93	48
55	39.0	48	36.1	93	47	35.5	91	48
59	40.0	48	36.8	92	47	36.3	91	48
63	41.0	48	38.2	93	46	37.0	90	47
68	41.0	48	37.9	92	46	36.6	89	46
74	41.7	48	37.8	91	45	36.7	88	46
76	41.9	48	38.3	91	44	37.2	89	44
82	41.9	46	38.3	91	44	37.7	90	43
86	41.9	46	38.6	92	44	38.2	91	40
91	42.5	46	39.1	92	40	38.3	90	36
95	41.7	44	38.2	92	40	38.4	92	35
100	42.1	40	38.3	91	37	37.2	88	31
104	41.4	36	37.9	92	31	37.3	90	25



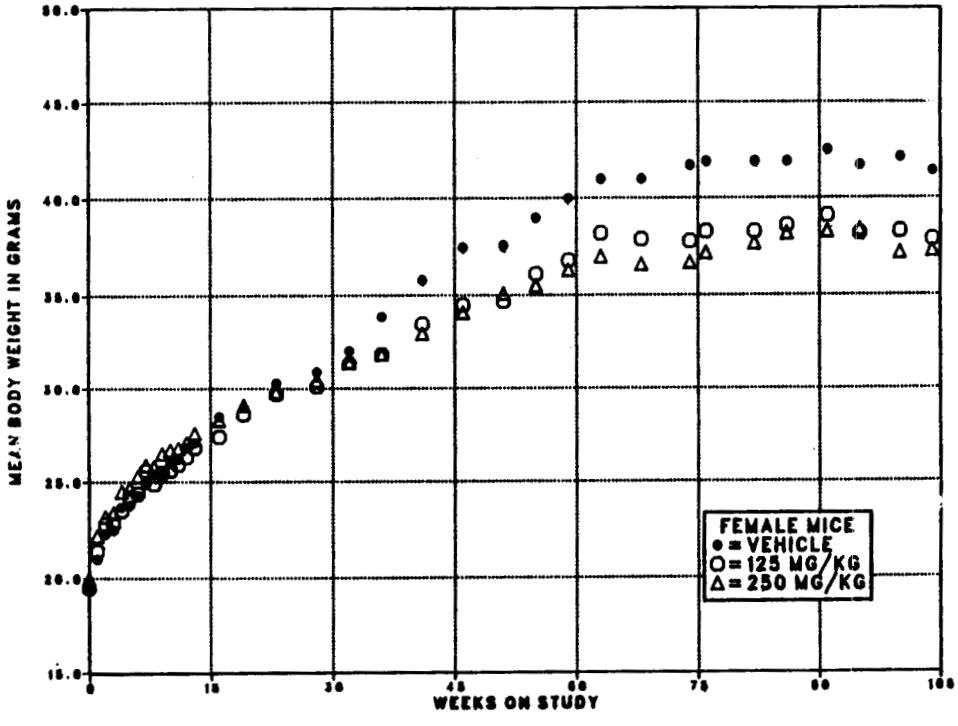


FIGURE 3. GROWTH CURVES FOR MICE ADMINISTERED CHLORINATED PARAFFINS (C_{12}, 60% Cl) IN CORN OIL BY GAVAGE FOR TWO YEARS

Survival

Estimates of the probabilities of survival for male and female mice administered chlorinated paraffins (C_{12}, 60% chlorine) at the doses used in these studies and for the vehicle controls are shown in the Kaplan and Meier curves in Figure 4. The survival of the high dose group of female mice was significantly lower than that of the vehicle controls after week 100. No other significant differences in survival were observed between any groups of either sex (Table 26). Several dosed and vehicle control female mice died of nonaccidental or undetermined causes during the first 40 weeks of study. These deaths may have been due to gavage-related trauma, but clear evidence of this was not found at necropsy.

TABLE 26. SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{12}, 60% Cl)

	Vehicle Control	125 mg/kg	250 mg/kg
MALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	15	19	18
Accidentally killed	1	0	1
Killed at termination	34	30	30
Died during termination period	0	1	1
Survival P values (c)	0.427	0.428	0.460
FEMALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	13	16	24
Accidentally killed	1	3	1
Killed at termination	35	31	25
Died during termination period	1	0	0
Survival P values (c)	0.018	0.551	0.024

(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.

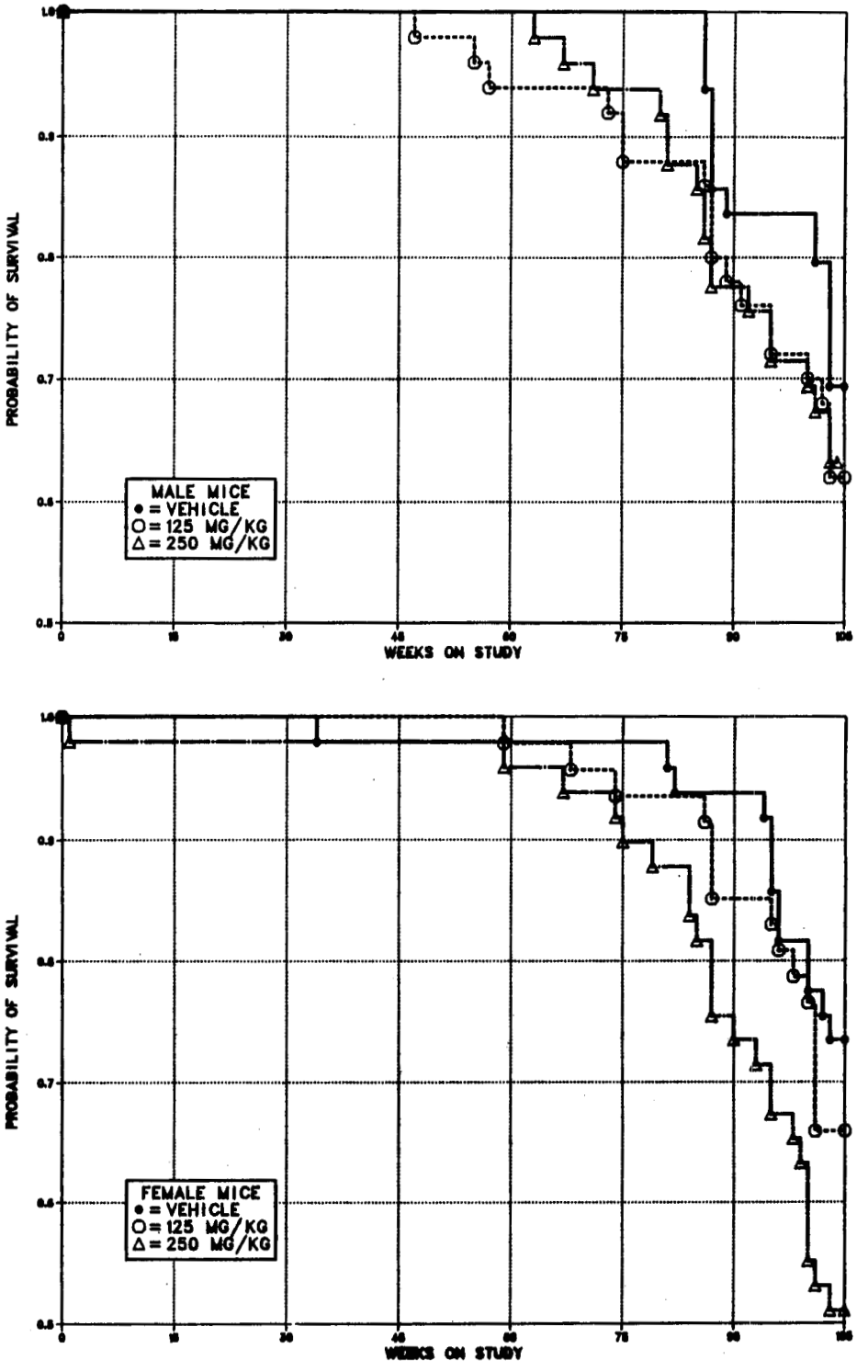


FIGURE 4. KAPLAN-MEIER SURVIVAL CURVES FOR MICE ADMINISTERED CHLORINATED PARAFFINS (C_{12}, 60% Cl) IN CORN OIL BY GAVAGE FOR TWO YEARS

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 liver, thyroid gland, lung, harderian gland, and kidney. 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 three 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.

Liver: Hepatocellular adenomas in male and female mice, hepatocellular carcinomas in female mice, and hepatocellular adenomas or carcinomas (combined) in male and female mice occurred with significant positive trends (Table 27). The incidences of hepatocellular adenomas in dosed male and dosed female mice, hepatocellular carcinomas in high dose female mice, and hepatocellular adenomas or carcinomas (combined) in dosed male and dosed female mice were significantly greater than those of the vehicle controls. Microscopically, hepatocellular adenomas were found to have well-defined borders that compressed the surrounding parenchyma. Both solid and trabecular types were seen, with the solid areas composed of closely packed cells that resembled normal hepatocytes but contained few sinusoids. The trabecular type had a clear cord structure, with sinusoids separating the cords.

Hepatocellular carcinomas resembled both the solid and the trabecular-type adenomas, but the cells comprising the solid neoplasms varied greatly in size with large hyperchromatic nuclei frequently seen. The trabecular pattern differed from that of the adenoma in that the cords were many cells thick. Dilation of the sinusoids produced disruption of the regular trabecular pattern, and necrosis and hemorrhage were common.

TABLE 27. ANALYSIS OF HEPATOCELLULAR TUMORS IN MICE IN THE TWO-YEAR GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) (a)

	Vehicle Control	125 mg/kg	250 mg/kg
MALE			
Adenoma			
Overall Rates	11/50 (22%)	20/50 (40%)	29/50 (58%)
Adjusted Rates	30.9%	52.9%	76.1%
Terminal Rates	10/34 (29%)	14/31 (45%)	22/31 (71%)
Week of First Observation	86	47	86
Life Table Tests	P<0.001	P=0.024	P<0.001
Incidental Tumor Tests	P<0.001	P=0.034	P<0.001
Carcinoma			
Overall Rates	11/50 (22%)	15/50 (30%)	17/50 (34%)
Adjusted Rates	24.4%	35.1%	39.8%
Terminal Rates	3/34 (9%)	6/31 (19%)	7/31 (23%)
Week of First Observation	86	47	71
Life Table Tests	P=0.084	P=0.198	P=0.095
Incidental Tumor Tests	P=0.245	P=0.394	P=0.285
Adenoma or Carcinoma (b)			
Overall Rates	20/50 (40%)	34/50 (68%)	38/50 (76%)
Adjusted Rates	46.4%	75.0%	86.2%
Terminal Rates	12/34 (35%)	20/31 (65%)	25/31 (81%)
Week of First Observation	86	47	71
Life Table Tests	P<0.001	P=0.006	P<0.001
Incidental Tumor Tests	P<0.001	P=0.009	P<0.001
Hepatoblastoma			
Overall Rates	0/50 (0%)	(c) 1/50 (2%)	(d) 1/50 (2%)
FEMALE			
Adenoma			
Overall Rates	0/50 (0%)	18/50 (36%)	22/50 (44%)
Adjusted Rates	0.0%	49.4%	65.4%
Terminal Rates	0/36 (0%)	13/31 (42%)	14/25 (56%)
Week of First Observation		87	84
Life Table Tests	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests	P<0.001	P<0.001	P<0.001
Carcinoma			
Overall Rates	3/50 (6%)	4/50 (8%)	9/50 (18%)
Adjusted Rates	8.3%	11.0%	26.9%
Terminal Rates	3/36 (8%)	2/31 (6%)	4/25 (16%)
Week of First Observation	105	68	75
Life Table Tests	P=0.014	P=0.435	P=0.022
Incidental Tumor Tests	P=0.067	P=0.508	P=0.093
Adenoma or Carcinoma (e)			
Overall Rates	3/50 (6%)	22/50 (44%)	28/50 (56%)
Adjusted Rates	8.3%	57.3%	74.8%
Terminal Rates	3/36 (8%)	15/31 (48%)	16/25 (64%)
Week of First Observation	105	68	75
Life Table Tests	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests	P<0.001	P<0.001	P<0.001

(a) The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix E (footnotes).
(b) Historical incidence at the study laboratory (mean ± SD): 109/298 (37% ± 12%); historical incidence in NTP studies: 357/1,091 (33% ± 10%)
(c) Observed in an animal with an adenoma
(d) Observed in an animal with a carcinoma
(e) Historical incidence at the study laboratory (mean ± SD): 18/300 (6% ± 3%); historical incidence in NTP studies: 74/1,092 (7% ± 4%)

Thyroid Gland: Follicular cell adenomas or carcinomas (combined) in female mice occurred with positive trends (Table 28). The incidences of follicular cell adenomas and follicular cell adenomas or carcinomas (combined) in high dose female mice were greater than those in the vehicle controls.

A spectrum of proliferative follicular cell lesions was present in all dose groups. The earliest form of hyperplasia was characterized by a single enlarged follicle lined by hypertrophied epithelial cells. These cells appeared to progress to multilayered, nipple-like projections that extended into the lumen. Further development resulted in papillary and/or follicular patterns of growth. Follicular cell adenomas were well-circumscribed masses compressing adjacent parenchyma. The neoplasms consisted of variably sized follicles and/or large cystic spaces, often with papillary fronds projecting into the lumen. The cells ranged from low cuboidal to columnar, with multilayed areas present. Follicular cell carcinomas were generally pleomorphic with solid, papillary, and/or follicular patterns. Some tumors were circumscribed, but most showed evidence of invasion. The cells were similar to those seen in the adenomas but were more pleomorphic and appeared to have a higher mitotic rate.

TABLE 28. ANALYSIS OF THYROID GLAND FOLLICULAR CELL LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{12}, 60% Cl)

	Vehicle Control	125 mg/kg	250 mg/kg
Hyperplasia			
Overall Rates	16/50 (32%)	27/49 (55%)	22/49 (45%)
Adenoma			
Overall Rates	8/50 (16%)	12/49 (24%)	13/49 (27%)
Adjusted Rates	20.7%	35.5%	44.2%
Terminal Rates	6/36 (17%)	9/30 (30%)	9/25 (36%)
Week of First Observation	95	95	95
Life Table Tests	P=0.024	P=0.128	P=0.033
Incidental Tumor Tests	P=0.063	P=0.162	P=0.082
Carcinoma			
Overall Rates	0/50 (6%)	0/49 (0%)	2/49 (4%)
Adenoma or Carcinoma (a)			
Overall Rates	8/50 (16%)	12/49 (24%)	15/49 (31%)
Adjusted Rates	20.7%	35.5%	49.1%
Terminal Rates	6/36 (17%)	9/30 (30%)	10/25 (40%)
Week of First Observation	95	95	90
Life Table Tests	P=0.007	P=0.128	P=0.011
Incidental Tumor Tests	P=0.024	P=0.162	P=0.033

(a) Historical incidence at the study laboratory (mean ± SD): 19/291 (7% ± 3%); historical incidence in NTP studies: 40/1,009 (4% ± 3%)

Lung: Alveolar/bronchiolar carcinomas 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 29). The incidences of alveolar/bronchiolar adenomas or carcinomas (combined) in dosed male mice were not significantly different from that in the vehicle control group.

Harderian Gland: The incidence of adenomas in low dose female mice was significantly greater than that in the vehicle controls (Table 30).

Kidney: The incidence of nephrosis was increased in high dose female mice (vehicle control, 4/50, 8%; low dose, 5/50, 10%; high dose, 12/50, 24%). The following incidences were observed in male mice: vehicle control, 40/50 (80%); low dose, 27/50 (54%); high dose, 26/50 (52%).

TABLE 29. ANALYSIS OF ALVEOLAR/BRONCHIOLAR LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{12}, 60% Cl)

	Vehicle Control	125 mg/kg	250 mg/kg
Alveolar Epithelial Hyperplasia			
Overall Rates	0/50 (0%)	0/50 (0%)	1/50 (2%)
Adenoma			
Overall Rates	5/50 (10%)	3/50 (6%)	3/50 (6%)
Carcinoma			
Overall Rates	0/50 (0%)	3/50 (6%)	6/50 (12%)
Adjusted Rates	0.0%	9.7%	17.9%
Terminal Rates	0/34 (0%)	3/31 (10%)	5/31 (16%)
Week of First Observation		104	71
Life Table Tests	P=0.008	P=0.105	P=0.014
Incidental Tumor Tests	P=0.011	P=0.105	P=0.021
Adenoma or Carcinoma (a)			
Overall Rates	5/50 (10%)	6/50 (12%)	9/50 (18%)
Adjusted Rates	13.5%	19.4%	25.1%
Terminal Rates	3/34 (9%)	6/31 (19%)	6/31 (19%)
Week of First Observation	103	104	71
Life Table Tests	P=0.114	P=0.430	P=0.149
Incidental Tumor Tests	P=0.145	P=0.447	P=0.205

(a) Historical incidence at the study laboratory (mean ± SD): 54/298 (18% ± 7%); historical incidence in NTP studies: 169/1,093 (15% ± 6%)

TABLE 30. ANALYSIS OF HARDERIAN GLAND TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{12}, 60% Cl)

	Vehicle Control	125 mg/kg	250 mg/kg
Adenoma (a)			
Overall Rates	1/50 (2%)	6/50 (12%)	2/50 (4%)
Adjusted Rates	2.8%	18.5%	18.0%
Terminal Rates	1/36 (3%)	5/31 (16%)	2/25 (8%)
Week of First Observation	104	101	104
Life Table Tests	P=0.251	P=0.040	P=0.373
Incidental Tumor Tests	P=0.286	P=0.044	P=0.373
Carcinoma			
Overall Rates	0/50 (0%)	(b) 1/50 (2%)	0/50 (0%)

(a) Historical incidence of adenomas or carcinomas at the study laboratory (mean ± SD): 5/300 (2% ± 2%); historical incidence in NTP studies: 21/1,096 (2% ± 3%)
(b) This tumor was present in an animal that also had an adenoma.

IV. DISCUSSION AND CONCLUSIONS

IV. DISCUSSION AND CONCLUSIONS

Toxicology and carcinogenesis studies of chlorinated paraffins (C_{12}, 60% chlorine) were conducted in F344/N rats and $B6C3F_1$ mice of each sex. Chlorinated paraffins (C_{12}, 60% chlorine) was administered by gavage in corn oil at doses of 0, 312, or 625 mg/kg body weight to male and female rats and at 0, 125, or 250 mg/kg body weight to male and female mice, 5 days per week for 2 years. Doses for the 2-year studies were based on results from the single-administration, 16-day, and 13-week studies with rats and mice of each sex.

Single large doses of chlorinated paraffins (C_{12}, 60% chlorine) were found to be nonlethal to rats and mice. Clinical signs of diarrhea and ataxia in nearly all dose groups after a single dose of up to 13,600 mg/kg to rats and 27,200 mg/kg to mice appeared related to the large volumes of gavage material administered rather than to chemical toxicity. However, in the 16-day studies, chemical-related deaths were noted among male and female rats given 7,500 mg/kg per day and male and female mice given doses of 1,875 mg/kg or higher. Rats and mice given lower doses showed increased liver weights. No chemical-related deaths were seen in the 13-week studies in rats given up to 5,000 mg/kg and in mice given up to 2,000 mg/kg. Increased liver weight in rats and mice and focal (centrilobular) liver necrosis in mice were the principal toxic lesions in the 13-week studies. In addition, high dose male rats showed a more severe nephropathy than was seen in vehicle controls, suggesting a chemical-related worsening of this age-associated condition. Doses for the 2-year studies were reduced from those given in the 13-week studies because the degree of liver enlargement was considered to be potentially life threatening over 2 years in rats given doses of 1,250 mg/kg or higher and in mice given 500 mg/kg or higher.

In an effort to determine the onset of liver and kidney lesions in rats in the 2-year studies, 10 male and 10 female rats were killed after 6 and 12 months of dosing. Dose-related increased liver weights were clearly evident in males and females both at 6 months and 12 months. Morphometric studies indicated an increase in the size of hepatocytes. Higher kidney weights were also noted in both males and females at 6 and 12 months. Interstitial inflammation and lesions in the kidney tubules consistent with nephropathy were more severe and were observed more frequently in dosed rats than in vehicle controls.

During the 2-year studies, the survival of dosed and vehicle control male rats was similar until about week 87, when survival sharply declined in dosed animals. Many of the early deaths of dosed male rats may have been due to a chemical-related worsening of the nephropathy commonly seen in aging male F344/N rats. This possibility is supported by the observation of increased incidences of parathyroid hyperplasia and fibrous osteodystrophy in dosed male rats, suggesting impaired kidney function. Low dose female rats had poorer survival than did vehicle controls, perhaps due to a higher incidence of mononuclear cell leukemia. The survival of high dose female rats and male mice was not affected, but deaths were increased in the high dose group of female mice relative to the vehicle controls. The cause of the early deaths of high dose female mice is not known. In another study conducted concurrently at the same laboratory, survival of female mice administered chlorinated paraffins (C_{23}, 43% chlorine) (NTP, 1986) was reduced, apparently due to an infection with Klebsiella. Uterine and ovarian lesions consistent with a Klebsiella infection were also noted in female mice administered chlorinated paraffins (C_{12}, 60% chlorine) in the current study. These lesions were found in all 13 early death vehicle control female mice, in 10/16 early death low dose female mice, and in 9/24 early death high dose female mice. Although an infection was probably active in these mice, it apparently was not present in a disproportionate number of dosed mice, and it would not appear to account for the reduced survival in the high dose group.

The administration of chlorinated paraffins (C_{12}, 60% chlorine) to rats and mice resulted in liver changes in both species. A dose-related hypertrophy, seen in rats and mice of each sex in the 13-week studies, was noted in rats but not in mice after 2 years of dosing. Minimal liver necrosis was observed in rats in the 2-year studies, and necrosis was probably associated with the neoplasms in mice. This finding is generally not recorded in NTP studies because chemical-related necrosis cannot be distinguished from that frequently seen in or near neoplasms.

Nonetheless, nonproliferative liver injury did not progress to cirrhosis and did not appear to be life threatening in either rats or mice. Similar liver changes (mild necrosis and enlargement) in rats have been observed by other investigators after single or repeated doses of chlorinated paraffins (Birtley et al., 1980; Nilsen et al., 1981). Short-chain chlorinated paraffins were found to cause a proliferation of smooth endoplastic reticulum, to increase the activity of certain forms of cytochrome P450, and to increase the number and size of mitochondria and peroxisomes and the occurrence of lysosomes (Nilsen et al., 1981).

In the present studies, rats and mice of each sex showed clear increases in the incidences of liver neoplasms (Table 31). Substantial increases in the incidences of benign hepatocellular neoplasms (neoplastic nodules or adenomas) were seen in all dose groups, and the incidences observed in high dose animals were greater than the historical mean and range for vehicle control groups in previous studies. In dosed mice, incidences of carcinomas were also clearly increased over vehicle control and historical control rates, although the incidence in the high dose males had been exceeded by that in some vehicle control groups in previous studies. The increased incidences of liver neoplasms in both sexes of both species make it unlikely that the frequencies were due to random biologic variation in any one group and support the conclusion that the administration of chlorinated paraffins (C_{12}, 60% chlorine) causes liver neoplasms in rats and mice.

The kidneys of dosed male rats showed increased incidences of both neoplastic and nonneoplastic lesions. Evidence of kidney toxicity was seen in both male and female rats at 6 and 12 months into the 2-year studies. Later in the studies, the incidence of nephropathy was increased in dosed females, and multiple cysts were frequently observed in the kidneys of dosed male rats. This lesion is most likely a marked expression of chronic nephropathy and cannot be considered a totally separate entity. The incidences of tubular cell hyperplasia were increased in dosed male rats (vehicle control, 1/50; low dose, 9/50; high dose, 12/49), and 12/99 dosed male rats were found to have kidney tubular cell adenomas or adenocarcinomas, neoplasms that have been observed with an incidence of 0.5% in historical corn oil vehicle controls. Tubular cell adenomas or adenocarcinomas (combined) were significantly increased in the low dose male rats but not in the high dose group. The reason for the lack of a dose response for tubular cell neoplasms is not clear. Survival of low dose and high dose groups was similar, and the time to observation of first neoplasm was about 85 weeks in each group. There was no clear association between the diagnosis of multiple cysts and the observation of a proliferative lesion in the dosed male rats.

TABLE 31. INCIDENCES OF LIVER NEOPLASMS IN RATS AND MICE IN THE TWO-YEAR GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{12}, 60% Cl)

MALE RATS	Vehicle Control	312 mg/kg	625 mg/kg	Historical Mean (range)
Neoplastic nodules	0/50	10/50	16/48	3.2% (0/50-7/50)
Carcinomas	0/50	3/50	2/48	0.7% (0/50-2/50)
FEMALE RATS				
Neoplastic nodules	0/50	4/50	7/50	1.9% (0/50-5/50)
Carcinomas	0/50	1/50	1/50	0%
MALE MICE	**Vehicle Control**	**125 mg/kg**	**250 mg/kg**	**Historical Mean (range)**
Adenomas	11/50	20/50	29/50	12.8% (0/50-14/50)
Carcinomas	11/50	15/50	17/50	21.8% (5/50-19/50)
FEMALE MICE				
Adenomas	0/50	18/50	22/50	3.8% (0/50-5/50)
Carcinomas	3/50	4/50	9/50	3.1% (0/50-4/50)

Proliferative lesions of the thyroid gland follicular cells were found with a greater incidence in dosed female rats and female mice than in the vehicle controls (Table 32). Adenomas were significantly increased in low dose female rats and occurred with a frequency twice that seen in any previous corn oil vehicle control group, and carcinomas showed a positive trend. In female mice, statistical significance was obtained only with adenomas or carcinomas (combined), but dose-related increases were observed in adenomas and carcinomas, and significant increases were seen even though the vehicle control incidence of 8/50 is the greatest ever observed in an NTP study. As with liver neoplasms, the observation of increased follicular cell neoplasms in dosed females of both species strengthens the association with administration of chlorinated paraffins (C_{12}, 60% chlorine).

The incidences of mononuclear cell leukemia were greater in dosed male and low dose female rats than in the vehicle controls. The results of staging of this lesion indicated that almost all lesions in both dosed and vehicle control animals were relatively advanced as shown by infiltration of mononuclear cells in various organs (see Table 17). This neoplasm is fatal (Stromberg and Vogtsberger, 1983); therefore, life table analysis is appropriate. In male rats, there was a clear dose-related trend in the incidence of mononuclear cell leukemia (vehicle control, 7/50; low dose, 12/50; high dose, 14/50). Low dose female rats showed a statistically significant increased incidence (vehicle control, 11/50; low dose, 22/50; high dose, 16/50), but the lower increase in the high dose group resulted in a lack of significance in the overall trend tests. The increased incidences of mononuclear cell leukemia in dosed rats of both sexes are suggestive of an association with chlorinated paraffins (C_{12}, 60% chlorine) dosing, but the absence of a dose response in females weakens the argument. The incidence in low dose females (44%) exceeded the greatest incidence previously seen in an NTP corn oil vehicle control group (42%), and 20/22 animals showed advanced leukemia (stage 2 or 3); but when only stage-2 or stage-3 leukemias are considered, high dose female rats had an incidence of 13/50 versus 11/50 in the vehicle controls. Thus, neither the incidence nor severity of the lesion was significantly increased in the high dose group.

Acinar cell tumors of the pancreas occurred at high incidences in dosed and vehicle control male rats. The incidence observed in vehicle controls in this study (11/50) was fivefold greater than the historical average (4.3%) but was within the historical range (0%-28%) observed with corn oil vehicle controls. The incidence of acinar cell adenomas was 22/50 in low dose and 15/49 in high dose males. Two other high dose male rats had acinar cell carcinomas. The high background rate, occasionally seen in studies that employ corn oil as a gavage vehicle (Boorman and Eustis, 1984), makes it difficult to assess the influence of chlorinated paraffins (C_{12}, 60% chlorine) administration on this tumor type. A dose-response relationship was not seen, even with the addition of acinar cell hyperplasia (vehicle control, 7/50; low dose, 13/50; high dose, 8/49). If chlorinated paraffins (C_{12}, 60% chlorine) distributes in a manner similar to the longer chain,

TABLE 32. INCIDENCES OF PROLIFERATIVE LESIONS OF THE THYROID GLAND FOLLICLES IN FEMALE RATS AND MICE IN THE TWO-YEAR GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{12}, 60% Cl)

	Vehicle Control	Low Dose	High Dose	Historical Mean (range)
RATS				
Hyperplasia	0/50	3/50	3/50	
Adenomas	0/50	6/50	3/50	0.9% (0/50-3/48)
Carcinomas	0/50	0/50	3/50	0.5% (0/50-1/46)
MICE				
Hyperplasia	16/50	27/49	22/49	
Adenomas	8/50	12/49	13/49	3.6% (0/49-5/50)
Carcinomas	0/50	0/49	2/49	0.5% (0/50-2/49)

less chlorinated paraffins (e.g., C_{16}, 34% chlorine) (Darnerud and Brandt, 1982), the pancreas would be expected to take up the chemical, and a toxic response could result. However, the current results suggest only moderate increases in tumors in dosed male rats, and an interaction of corn oil and chlorinated paraffins (C_{12}, 60% chlorine) cannot be ruled out.

Endometrial stromal polyps of the uterus were found more frequently in dosed female rats than in vehicle controls (vehicle control, 5/50; low dose, 13/50; high dose, 11/50), and the incidence of polyps or sarcomas (combined) was increased in low dose animals. Although these increases are statistically significant, it is unlikely that they are related to chlorinated paraffins (C_{12}, 60% chlorine) administration because the incidences are not dose related, and they are similar to the historical control rates for these neoplasms (Appendix F, Table F9).

Dosed male rats appeared more susceptible than did dosed females to the development of stomach lesions. Increased incidences of ulcers, hyperkeratosis, epithelial hyperplasia, and inflammation were associated with chlorinated paraffins (C_{12}, 60% chlorine) administration. Two squamous cell papillomas were observed in high dose male rats. Suppurative or ulcerative inflammation also was seen in 2/10 high dose male rats in the 13-week studies.

Tumors of the harderian gland were found at an increased incidence in low dose female mice compared with that in vehicle controls (vehicle control, 1/50; low dose, 6/50; high dose, 2/50). This tissue is examined microscopically only if a neoplasm is observed on gross examination; thus, the total incidence of tumors of the harderian gland is not known. The incidence in the low dose group exceeded the greatest incidence ever observed in corn oil vehicle controls in previous NTP studies (10%), but the lack of a dose response suggests that this result may be spurious.

Optimal doses for 2-year studies are those which when given for the duration of a study do not shorten the longevity of animals from any cause other than induction of neoplasms. Such doses should not cause morphologic evidence of toxicity in organs other than mild changes such as slight hypertrophy, hyperplasia, or inflammation or slight changes in serum enzymes (Board of Scientific Counselors, 1984). On these bases, it is clear that the doses used for male rats were overtly toxic. Survival of both low and high dose male rats was significantly lower than that of vehicle controls, probably as a result of chemically induced kidney injury. Marked liver hypertrophy was noted in both dosed male and female rats at 6 and 12 months into the 2-year studies. If this proliferative change is considered a toxic rather than an adaptive response, then the doses used may have been excessive in all groups of dosed female rats. However, survival of high dose females and weight gains of both low and high dose female rats did not differ from those of vehicle controls in the 2-year studies.

The NTP has found two chlorinated paraffins (C_{12}, 60% chlorine and C_{23}, 43% chlorine) to be nonmutagenic in the Salmonella/microsome test with and without metabolic activation (Appendix G; NTP, 1986). These results are in agreement with those of Birtley et al. (1980) who tested $C_{14\text{-}17}$, 52% chlorine; $C_{20\text{-}30}$, 42% chlorine; and $C_{10\text{-}13}$, 50% chlorine in similar assays. Birtley et al. (1980) also found that these chlorinated paraffins gave negative results in a cell transformation assay with BHK cells.

Similar toxicology and carcinogenicity studies were performed on a mixture of longer chain chlorinated paraffins (C_{23}, 43% chlorine). Full results from these studies are reported in a separate Technical Report (NTP, 1986), and the abstract from these studies is included as Appendix N in this Technical Report. The results of these studies were judged to provide clear evidence of carcinogenicity in male $B6C3F_1$ mice, as shown by an increased incidence of malignant lymphomas. Equivocal evidence of carcinogenicity was seen in female mice and in female rats, based on marginal increases in hepatocellular neoplasms in mice and in adrenal gland pheochromocytomas in rats. No evidence of carcinogenicity of chlorinated paraffins (C_{23}, 43% chlorine) was seen in male rats.

Nonneoplastic lesions seen in rats given the longer chain chlorinated paraffins primarily involved a lymphohistiocytic inflammation of the liver and the pancreatic and mesenteric lymph

nodes, with secondary congestion of the spleen. Liver enlargement was not apparent in rats or mice in the 13-week studies, but a moderate increase in liver weight was noted in rats killed 6 and 12 months into the 2-year studies. Thus, the pattern of hepatotoxicity and the extent of kidney toxicity clearly differed in rats given the different chain length paraffins. No significant nonneoplastic changes were seen in mice given the long-chain chlorinated paraffins.

On a molar basis, the doses used in the chlorinated paraffins (C_{23}, 43% chlorine) studies were, except in female rats, larger than those used in the chlorinated paraffins (C_{12}, 60% chlorine) studies. Absorption of the compounds may differ, but nonetheless, it would appear that the longer chain paraffins have a lower toxic and carcinogenic potential than do the shorter chain paraffins.

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 chlorinated 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 defined in the Note to the Reader on page 2.

V. REFERENCES

V. REFERENCES

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

2. Baldwin, M.; Bennett, D. (1974) Analysis of Biological Samples for Chlorinated Straight-Chain Paraffins. Group Research Report TLGR.0058.74. Tunstall Laboratory.

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

4. Biessmann, A.; Darnerud, P.; Brandt, I. (1983) Chlorinated paraffin: Disposition of highly chlorinated polychlorohexadecane in mice and quail. Arch. Toxicol. 53:79-86.

5. Birtley, R.; Conning, D.; Daniel, J.; Ferguson, D.; Longstaff, E.; Swan, A. (1980) The toxicological effects of chlorinated paraffin in mammals. Toxicol. Appl. Pharmacol. 54:514-525.

6. Boorman, G.; Eustis, S. (1984) Proliferative lesions of the exocrine pancreas in male F344/N rats. Environ. Health Perspect. 56:213-217.

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

8. Campbell, I.; McConnell, G. (1980) Chlorinated paraffin and the environment. I. Environmental occurrences. Environ. Sci. Tech. 14:1209-1214.

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

10. Darnerud, P.; Brandt, I. (1982) Studies on the distribution and metabolism of a ^{14}C-labelled chlorinated alkane in mice. Environ. Pollution (Series A) 27:45-56.

11. Darnerud, P.; Biessmann, A.; Brandt, I. (1982) Metabolic fate of chlorinated paraffin: Degree of chlorination of [^{14}C]-chlorododecanes in relation to degradation and excretion in mice. Arch. Toxicol. 50:217-226.

12. Dunnett, C. (1955) Multiple comparisons with a standard. Am. Soc. Qual. Control 9th Ann. Conv. Trans., pp. 485-492.

13. Gart, J.; Chu, K.; Tarone, R. (1979) Statistical issues in interpretation of chronic bioassay tests for carcinogenicity. J. Natl. Cancer Inst. 62(4):957-974.

14. Hardie, D., Ed. (1964) Kirk-Othmer Encyclopedia of Chemical Technology, 2nd ed., Vol. 5, 231-239.

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

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

17. Haworth, S.; Lawlor, T.; Mortelmans, K.; Speck, W.; Zeiger, E. (1983) Salmonella mutagenicity test results for 250 chemicals. Environ. Mutagen. (Suppl. 1) 5:3-142.

18. Howard, P.; Santodonato, J.; Saxena, J. (1975) Investigation of selected potential environmental contaminants: Chlorinated paraffins. Document EPA-560/2-75-007. Office of Toxic Substances, U.S. Environmental Protection Agency, Washington, DC.

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

20. Linhart, M.; Cooper, J.; Martin, R.; Page, N.; Peters, J. (1974) Carcinogenesis bioassay data system. Comp. Biomed. Res. 7:230-248.

21. Lombardo, P.; Dennison, J.; Johnson, W. (1975) Bioaccumulation of chlorinated paraffin residues in fish fed Chlorowax 500C. J. Assoc. Off. Anal. Chem. 58:707-710.

22. Madeley, J.; Birtley, R. (1980) Chlorinated paraffin and the environment. 2. Aquatic and avian toxicology. Environ. Sci. Tech. 14:1215-1221.

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

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

25. McConnell, E.; Solleveld, H.; Swenberg, J.; Boorman, G. (1986) Guidelines for combining neoplasms for evaluation of rodent carcinogenesis studies. J. Natl. Cancer Inst. (in press).

26. Miller, R. (1971) Simultaneous Statistical Inference, 2nd ed. New York: Springer-Verlag.

27. National Cancer Institute (NCI) (1976) Guidelines for Carcinogen Bioassay in Small Rodents. NCI Carcinogenesis Technical Report Series No. 1. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health.

28. National Institutes of Health (NIH) (1978) NIH Specification, NIH-11-133f, November 1.

29. National Toxicology Program (NTP) (1986) NTP Technical Report on the Toxicology and Carcinogenesis Studies of Chlorinated Paraffins (C_{23}, 43% Chlorine) in F344/N Rats and B6C3F$_1$ Mice. NTP TR 305. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health. 202 p.

30. Nilsen, O.; Toftgard, R.; Glaumann, H. (1981) Effects of chlorinated paraffins on rat liver microsomal activities and morphology. Arch. Toxicol. 49:1-13.

31. Sadtler Standard Spectra, Sadtler Research Laboratories, Philadelphia, Pennsylvania, IR No. G4081.

32. Snedecor, G.; Cochran, W. (1967) Statistical Methods, 6th ed. Ames, IA: State University Press.

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

34. Svanberg, O.; Linden, E. (1979) Chlorinated paraffins--an environmental hazard? Ambio 8:206-209.

35. Svanberg, O.; Bengtsson, B-E.; Linden, E.; Lunde, G.; Baumann, E. (1978) Paraffins--A case for accumulation and toxicity to fish. Ambio 7:64-65.

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

37. U.S. International Trade Commission (USITC) (1984) Synthetic Organic Chemicals, United States Production and Sales 1983. USITC Publication No. 1588, Washington, DC: Government Printing Office.

38. Zitko, V. (1980) Chlorinated paraffins. The Handbook of Environmental Chemistry, Vol. 3, Part A, Anthropogenic Compounds. Berlin: Springer-Verlag, pp. 149-156.

APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{12}, 60% Chlorine)

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{12}, 60% 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%)	3 (6%)	2 (4%)
Squamous cell carcinoma	1 (2%)	2 (4%)	
Basal cell tumor		1 (2%)	
Trichoepithelioma	2 (4%)		1 (2%)
Sebaceous adenoma			1 (2%)
Adenosquamous carcinoma		1 (2%)	
Keratoacanthoma	3 (6%)	†2 (4%)	1 (2%)
Fibroma		1 (2%)	
*Subcutaneous tissue	(50)	(50)	(50)
Sarcoma, NOS	1 (2%)		
Fibroma	3 (6%)	4 (8%)	1 (2%)
Fibrosarcoma	2 (4%)	1 (2%)	1 (2%)
Fibrous histiocytoma			1 (2%)
Lipoma		1 (2%)	
Osteosarcoma	1 (2%)		
Neurofibrosarcoma			1 (2%)
Neurilemoma		1 (2%)	
RESPIRATORY SYSTEM			
#Lung	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	1 (2%)		1 (2%)
Alveolar/bronchiolar carcinoma		1 (2%)	
Osteosarcoma, metastatic	1 (2%)		
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Leukemia, mononuclear cell	7 (14%)	12 (24%)	13 (26%)
#Spleen	(50)	(50)	(49)
Sarcoma, NOS		1 (2%)	
Leukemia, mononuclear cell			1 (2%)
CIRCULATORY SYSTEM			
*Mesentery	(50)	(50)	(50)
Hemangiosarcoma			1 (2%)
DIGESTIVE SYSTEM			
*Hard palate	(50)	(50)	(50)
Squamous cell papilloma		1 (2%)	
*Lip	(50)	(50)	(50)
Squamous cell papilloma	1 (2%)		
*Tongue	(50)	(50)	(50)
Squamous cell papilloma	1 (2%)	1 (2%)	
*Gum	(50)	(50)	(50)
Squamous cell papilloma	1 (2%)		
#Liver	(50)	(50)	(48)
Neoplastic nodule		10 (20%)	16 (33%)
Hepatocellular carcinoma		3 (6%)	2 (4%)
#Pancreas	(50)	(50)	(49)
Carcinoma, NOS	1 (2%)		
Acinar cell adenoma	11 (22%)	22 (44%)	15 (31%)
Acinar cell carcinoma			2 (4%)

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM (Continued)			
#Forestomach	(50)	(50)	(49)
Squamous cell papilloma			2 (4%)
#Small intestine	(49)	(50)	(49)
Adenocarcinoma, NOS		1 (2%)	
#Ileum	(49)	(50)	(49)
Sarcoma, NOS	1 (2%)		
URINARY SYSTEM			
#Kidney	(50)	(50)	(49)
Tubular cell adenoma		7 (14%)	3 (6%)
Tubular cell adenocarcinoma		2 (4%)	
#Urinary bladder	(50)	(49)	(48)
Transitional cell papilloma			1 (2%)
ENDOCRINE SYSTEM			
#Anterior pituitary	(50)	(48)	(49)
Adenoma, NOS	16 (32%)	10 (21%)	5 (10%)
#Adrenal	(50)	(50)	(49)
Cortical adenoma		1 (2%)	
#Adrenal medulla	(50)	(50)	(49)
Pheochromocytoma	14 (28%)	15 (30%)	15 (31%)
Pheochromocytoma, malignant	2 (4%)		
#Thyroid	(50)	(50)	(50)
Follicular cell adenoma	2 (4%)	1 (2%)	2 (4%)
Follicular cell carcinoma	1 (2%)	2 (4%)	1 (2%)
C-cell adenoma	8 (16%)	8 (16%)	2 (4%)
C-cell carcinoma	2 (4%)	3 (6%)	2 (4%)
#Pancreatic islets	(50)	(50)	(49)
Islet cell adenoma	2 (4%)	2 (4%)	1 (2%)
Islet cell carcinoma			1 (2%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Fibroadenoma	2 (4%)	4 (8%)	2 (4%)
*Preputial gland	(50)	(50)	(50)
Carcinoma, NOS	5 (10%)	1 (2%)	2 (4%)
Adenoma, NOS	4 (8%)	3 (6%)	7 (14%)
#Prostate	(48)	(48)	(49)
Adenoma, NOS		1 (2%)	
#Testis	(50)	(49)	(49)
Interstitial cell tumor	48 (96%)	49 (100%)	47 (96%)
NERVOUS SYSTEM			
#Brain	(50)	(50)	(50)
Astrocytoma	1 (2%)		
*Paraganglion	(50)	(50)	(50)
Paraganglioma, NOS			1 (2%)
SPECIAL SENSE ORGANS			
None			
MUSCULOSKELETAL SYSTEM			
None			

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
BODY CAVITIES			
*Mediastinum	(50)	(50)	(50)
Mesothelioma, NOS	1 (2%)		
*Mesentery	(50)	(50)	(50)
Mesothelioma, NOS	1 (2%)		
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Squamous cell carcinoma	1 (2%)		
Mesothelioma, NOS	2 (4%)		
Diaphragm			
Acinar cell carcinoma, metastatic			1
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	9	8	8
Moribund sacrifice	10	35	38
Terminal sacrifice	27	6	3
Dosing accident	4	1	
Accidentally killed, NOS			1
TUMOR SUMMARY			
Total animals with primary tumors**	50	49	48
Total primary tumors	151	179	154
Total animals with benign tumors	49	49	48
Total benign tumors	121	139	110
Total animals with malignant tumors	20	23	22
Total malignant tumors	26	30	27
Total animals with secondary tumors##	1		1
Total secondary tumors	1		1
Total animals with tumors uncertain--benign or malignant	4	10	17
Total uncertain tumors	4	10	17

* 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
† Multiple occurrence of morphology in the same organ tissues is counted once only

TABLE A2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{12}, 60% 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%)
Basal cell tumor	1 (2%)		
Trichoepithelioma			1 (2%)
Keratoacanthoma		2 (4%)	1 (2%)
Neurofibrosarcoma			1 (2%)
*Subcutaneous tissue	(50)	(50)	(50)
Fibroma		1 (2%)	1 (2%)
Fibrous histiocytoma, malignant	1 (2%)		
RESPIRATORY SYSTEM			
#Lung	(50)	(50)	(50)
Carcinoma, NOS, metastatic	1 (2%)		
Squamous cell carcinoma		1 (2%)	
Alveolar/bronchiolar adenoma			1 (2%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Leukemia, mononuclear cell	11 (22%)	22 (44%)	16 (32%)
CIRCULATORY SYSTEM			
#Kidney	(50)	(50)	(50)
Hemangioma			1 (2%)
DIGESTIVE SYSTEM			
*Tongue	(50)	(50)	(50)
Squamous cell papilloma			1 (2%)
#Liver	(50)	(50)	(50)
Neoplastic nodule		4 (8%)	7 (14%)
Hepatocellular carcinoma		1 (2%)	1 (2%)
#Pancreas	(50)	(48)	(50)
Acinar cell adenoma	1 (2%)	5 (10%)	2 (4%)
Acinar cell carcinoma			1 (2%)
#Ileum	(50)	(50)	(50)
Neurilemoma	1 (2%)		
URINARY SYSTEM			
None			
ENDOCRINE SYSTEM			
#Anterior pituitary	(49)	(49)	(49)
Carcinoma, NOS	3 (6%)	1 (2%)	
Adenoma, NOS	27 (55%)	19 (39%)	26 (53%)
#Adrenal	(50)	(50)	(50)
Cortical adenoma	3 (6%)	1 (2%)	1 (2%)
#Adrenal medulla	(50)	(50)	(50)
Pheochromocytoma	1 (2%)	3 (6%)	3 (6%)
Pheochromocytoma, malignant	1 (2%)		1 (2%)

TABLE A2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM (Continued)			
#Thyroid	(50)	(50)	(50)
Follicular cell adenoma		6 (12%)	3 (6%)
Follicular cell carcinoma			3 (6%)
C-cell adenoma	15 (30%)	5 (10%)	5 (10%)
C-cell carcinoma			2 (4%)
#Pancreatic islets	(50)	(48)	(50)
Islet cell adenoma	1 (2%)		1 (2%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Adenoma, NOS			1 (2%)
Adenocarcinoma, NOS	2 (4%)		1 (2%)
Fibroadenoma	19 (38%)	18 (36%)	9 (18%)
*Clitoral gland	(50)	(50)	(50)
Carcinoma, NOS		1 (2%)	2 (4%)
Adenoma, NOS	1 (2%)	3 (6%)	
#Uterus	(50)	(50)	(50)
Adenoma, NOS		1 (2%)	
Endometrial stromal polyp	5 (10%)	13 (26%)	11 (22%)
Endometrial stromal sarcoma	1 (2%)	1 (2%)	
NERVOUS SYSTEM			
#Brain	(50)	(50)	(49)
Carcinoma, NOS, invasive	1 (2%)	1 (2%)	
Granular cell tumor, NOS	1 (2%)		
*Paraganglion	(50)	(50)	(50)
Paraganglioma, NOS	1 (2%)		
SPECIAL SENSE ORGANS			
*Zymbal gland	(50)	(50)	(50)
Carcinoma, NOS			1 (2%)
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
None			
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Sarcoma, NOS	1 (2%)		
Fibrosarcoma		1 (2%)	
Mesothelioma, malignant	1 (2%)		
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	3	6	4
Moribund sacrifice	13	21	16
Terminal sacrifice	34	23	29
Dosing accident			1

TABLE A2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
Total animals with primary tumors**	48	45	46
Total primary tumors	98	109	106
Total animals with benign tumors	41	34	40
Total benign tumors	75	77	70
Total animals with malignant tumors	19	25	24
Total malignant tumors	21	28	29
Total animals with secondary tumors##	2	1	
Total secondary tumors	2	1	
Total animals with tumors uncertain--benign or malignant	2	4	7
Total uncertain tumors	2	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 A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{12}, 60% Cl): VEHICLE CONTROL

ANIMAL NUMBER	006	048	010	036	020	050	034	045	008	025	031	013	041	011	005	012	015	035	004	042	033	049	017	011	002
WEEKS ON STUDY	061	064	067	070	071	074	080	080	081	081	090	093	094	095	095	097	097	098	101	101	102	102	103	105	106
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																								X	
Squamous cell carcinoma																									
Trichoepithelioma													X												
Keratoacanthoma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS											X														
Fibroma																									X
Fibrosarcoma																									
Osteosarcoma																						X			
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Osteosarcoma, metastatic																						X			
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	–	+	+	+	+	+	+	–	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell papilloma									X												X				
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																							X		
Acinar cell adenoma																				X		X	X		
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																		X							
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS				X		X									X						X		X		X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma													X	X		X							X		
Pheochromocytoma, malignant																									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																					X				
Follicular cell carcinoma											X														
C-cell adenoma											X											X			X
C-cell carcinoma																									
Parathyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																			X						
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma																			X						
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																				X		X			
Adenoma, NOS																	X								
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma																									
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
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
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
Squamous cell carcinoma											X														
Mesothelioma, NOS														X											
Leukemia, mononuclear cell	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	003	007	009	014	016	018	019	021	022	023	024	026	027	028	029	030	032	037	038	039	040	043	044	046	047	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell papilloma						X																				2
Squamous cell carcinoma										X																1
Trichoepithelioma				X																						2
Keratoacanthoma												X								X		X				3
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS																										1
Fibroma													X	X												3
Fibrosarcoma						X				X																2
Osteosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma			X																							1
Osteosarcoma, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	−	+	+	+	−	+	+	+	−	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	42
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell papilloma																		X								3
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS																										1
Acinar cell adenoma	X										X		X			X			X	X				X	X	11
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Sarcoma, NOS																										1
Large intestine	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS		X	X				X	X		X		X							X			X	X	X		16
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma	X				X					X		X	X				X	X				X	X	X		14
Pheochromocytoma, malignant		X										X														2
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell adenoma																						X				2
Follicular cell carcinoma																										1
C-cell adenoma	X						X			X					X	X										8
C-cell carcinoma		X																			X					2
Parathyroid	+	+	−	+	+	+	+	+	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	−	+	46
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet cell adenoma								X																		2
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroadenoma																								X		2
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell tumor	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	48
Prostate	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	48
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS	X		X																X							5
Adenoma, NOS		X																		X	X					4
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma															X											1
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
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
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
Squamous cell carcinoma																										1
Mesothelioma, NOS				X																						2
Leukemia, mononuclear cell						X								X			X									7

* Animals Necropsied

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{12}, 60% Cl): LOW DOSE

ANIMAL NUMBER	007	012	049	014	025	008	009	029	041	047	013	044	027	028	039	005	018	001	011	036	004	040	042	022	023
WEEKS ON STUDY	063	074	074	079	082	085	087	087	087	087	089	089	090	090	090	091	091	092	092	092	093	093	093	095	095
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																					X				
Squamous cell carcinoma		X																							
Basal cell tumor																									
Adenosquamous carcinoma																X									
Keratoacanthoma											X@														
Fibroma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																			X		X				
Fibrosarcoma																									
Lipoma																								X	
Neurilemoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma																		X							
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS			X																						
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									X		X	
Hepatocellular carcinoma																									
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		X	X	X				X		X				X
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																									
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	–	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenoma																					X				
Tubular cell adenocarcinoma							X											X							
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	–	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS												X	X												
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																								X	
Pheochromocytoma		X											X	X	X	X									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																								X	
Follicular cell carcinoma																									
C-cell adenoma								X		X		X	X												
C-cell carcinoma																			X						X
Parathyroid	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	+	+	N	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma																									
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+
Interstitial cell tumor	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+
Adenoma, NOS										X															
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																									
Adenoma, NOS			X																						
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell		X				X	X			X	X						X	X					X		

@ : Multiple Occurrence of Morphology

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

ANIMAL NUMBER	043	045	034	050	031	048	017	033	037	002	003	006	010	026	016	019	035	038	021	015	020	024	030	032	046	TOTAL TISSUES TUMORS
WEEKS ON STUDY	095	095	096	096	098	098	099	099	099	100	101	101	101	101	102	102	102	103	104	105	105	105	105	105	105	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell papilloma															X				X							3
Squamous cell carcinoma				X																						2
Basal cell tumor																	X									1
Adenosquamous carcinoma																										1
Keratoacanthoma																			X							2
Fibroma																					X					1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma				X																X						4
Fibrosarcoma																	X									1
Lipoma																										1
Neurilemoma	X																									1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, NOS																										1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	–	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	–	47
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell papilloma	X										X															2
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule			X		X								X	X	X						X				X	10
Hepatocellular carcinoma																X				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	X			X	X	X	X	X			X	X		X	X				X	X		X			22
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS																							X			1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	–	+	+	+	+	46
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tubular cell adenoma			X				X						X					X			X	X				7
Tubular cell adenocarcinoma																										2
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma, NOS					X				X		X	X									X		X	X	X	10
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma																										1
Pheochromocytoma						X	X	X	X			X	X				X	X				X			X	15
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell adenoma																										1
Follicular cell carcinoma					X													X								2
C-cell adenoma											X									X	X				X	8
C-cell carcinoma																X										3
Parathyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	48
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet cell adenoma												X					X									2
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroadenoma				X																		X		X	X	4
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Interstitial cell tumor	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	49
Prostate	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma, NOS																										1
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS					X																					1
Adenoma, NOS								X															X			3
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				X		12

* Animals Necropsied

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{12}, 60% Cl): HIGH DOSE

ANIMAL NUMBER	041	002	013	029	004	030	035	005	021	022	023	038	008	031	034	042	046	001	012	016	019	010	027	033
WEEKS ON STUDY	041	048	078	078	080	081	082	085	085	085	085	085	087	088	088	088	088	089	089	089	090	091	093	093
INTEGUMENTARY SYSTEM																								
Skin	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma						X																		
Trichoepithelioma																								
Sebaceous adenoma																								
Keratoacanthoma																								
Subcutaneous tissue	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																								
Fibrosarcoma																								
Fibrous histiocytoma														X										
Neurofibrosarcoma																								
RESPIRATORY SYSTEM																								
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma		X																						
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																								
Bone marrow	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia, mononuclear cell																								
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	–	+	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																								
Salivary gland	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule				X											X					X			X	
Hepatocellular carcinoma																								
Bile duct	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinar cell adenoma																X		X		X		X	X	X
Acinar cell carcinoma												X	X											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma							X	X																
Small intestine	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																								
Kidney	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenoma							X																	
Urinary bladder	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional cell papilloma				X																				
ENDOCRINE SYSTEM																								
Pituitary	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS											X													
Adrenal	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma										X								X		X		X		X
Paraganglion	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Paraganglioma, NOS						X																		
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																		X	X					
Follicular cell carcinoma								X																
C-cell adenoma																					X			
C-cell carcinoma																								
Parathyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreatic islets	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																								
Islet cell carcinoma																					X			
REPRODUCTIVE SYSTEM																								
Mammary gland	N	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma																								
Testis	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor			X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prostate	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																								
Adenoma, NOS			X									X						X						
NERVOUS SYSTEM																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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
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
Leukemia, mononuclear cell			X				X			X			X	X			X			X		X		X
Diaphragm NOS																								
Acinar cell carcinoma, metastatic												X												

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

ANIMAL NUMBER	037	020	026	032	036	007	009	024	043	014	018	025	028	049	011	015	045	039	044	047	017	003	040	048	050	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	093	094	094	094	094	096	096	096	097	098	098	098	098	098	099	099	099	100	101	101	102	104	105	105	105	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell papilloma																		X								2
Trichoepithelioma																			X							1
Sebaceous adenoma																X										1
Keratoacanthoma																								X		1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma							X																			1
Fibrosarcoma																	X									1
Fibrous histiocytoma																										1
Neurofibrosarcoma																	X									1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia, mononuclear cell											X															1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Neoplastic nodule	X		X						X	X	X		X	X	X	X			X					X	X	16
Hepatocellular carcinoma			X																X							2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
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			X				X	X	X				X	15
Acinar cell carcinoma																										2
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell papilloma																										2
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	48
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tubular cell adenoma	X					X																				3
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Transitional cell papilloma																										1
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, NOS		X	X														X							X		5
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma			X		X				X	X				X			X	X	X				X		X	15
Paraganglion	N	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
Paraganglioma, NOS																										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell adenoma																										2
Follicular cell carcinoma																										1
C-cell adenoma																	X									2
C-cell carcinoma																		X	X							2
Parathyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islet cell adenoma	X																									1
Islet cell carcinoma																										1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	N	+	+	+	*50
Fibroadenoma									X												X					2
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Interstitial cell tumor	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	47
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS					X								X													2
Adenoma, NOS									X			X						X					X			7
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
BODY CAVITIES																										
Mesentery	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Hemangiosarcoma																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leukemia, mononuclear cell								X				X						X		X						13
Diaphragm NOS																										
Acinar cell carcinoma, metastatic																										1

*Animals Necropsied

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{12}, 60% Cl): VEHICLE CONTROL

ANIMAL NUMBER	028	018	019	025	047	039	014	031	036	026	003	005	009	049	027	048	010	042	001	002	004	006	007	008	011
WEEKS ON STUDY	056	081	087	089	093	095	097	097	099	100	101	101	101	101	102	104	105	105	106	106	106	106	106	106	106
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell tumor																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, malignant																	X								
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, metastatic													X												
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinar cell adenoma																									X
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neurilemoma																									
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																						X			
Pheochromocytoma																									
Pheochromocytoma, malignant																									
Paraganglion	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Paraganglioma, NOS																									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell adenoma								X							X				X						X
Parathyroid	–	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																X									
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																								X	
Fibroadenoma		X						X		X	X							X		X					X
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp						X						X													
Endometrial stromal sarcoma								X																	
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, invasive																									
Granular cell tumor, 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
Sarcoma, NOS									X																
Mesothelioma, malignant				X																					
Leukemia, mononuclear cell	X		X		X	X					X			X		X	X	X							

+ : Tissue Examined Microscopically
– : Required Tissue Not Examined Microscopically
X : Tumor Incidence
N : Necropsy, No Autolysis, No Microscopic Examination
S : Animal Missexed

: No Tissue Information Submitted
C : Necropsy, No Histology Due To Protocol
A : Autolysis
M : Animal Missing
B : No Necropsy Performed

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

ANIMAL NUMBER	012	013	015	016	017	020	021	022	023	024	029	030	032	033	034	035	037	038	040	041	043	044	045	046	050	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Basal cell tumor			X																							1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibrous histiocytoma, malignant																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	–	+	–	+	+	+	47
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Acinar cell adenoma																										1
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neurilemoma																		X								1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, NOS																				X						3
Adenoma, NOS	X		X	X			X	X	X		X		X			X	X		X		X	X	X	X	X	27
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma							X					X														3
Pheochromocytoma						X																				1
Pheochromocytoma, malignant																						X				1
Paraganglion	N	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
Paraganglioma, NOS																		X								1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell adenoma	X	X			X					X	X			X					X	X	X		X		X	15
Parathyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet cell adenoma																										1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenocarcinoma, NOS							X																			2
Fibroadenoma		X						X	X		X	X	X			X	X		X			X	X	X		19
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS											X															1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endometrial stromal polyp								X			X						X									5
Endometrial stromal sarcoma																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS, invasive																				X						1
Granular cell tumor, NOS																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Sarcoma, NOS																										1
Mesothelioma, malignant																										1
Leukemia, mononuclear cell		X								X																11

* Animals Necropsied

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{12}, 60% Cl): LOW DOSE

ANIMAL NUMBER	020	026	003	047	017	033	012	014	036	004	024	044	013	035	048	019	032	002	005	006	028	023	029	049	021
WEEKS ON STUDY	059	061	081	081	083	083	084	084	085	086	088	089	090	090	090	096	096	097	097	098	100	101	101	101	102
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma															X										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																							X		
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule			X															X							
Hepatocellular carcinoma								X																	
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	+	+	+	+	+	−	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+
Acinar cell adenoma																				X					
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																				X					
Adenoma, NOS													X		X			X			X	X		X	X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																									
Pheochromocytoma							X																		
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma					X									X	X										
C-cell adenoma																									
Parathyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma			X		X							X								X		X	X	X	X
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS							X																		
Adenoma, NOS						X																			
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Endometrial stromal polyp													X	X						X	X			X	X
Endometrial stromal sarcoma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, 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
Fibrosarcoma		X																							
Leukemia, mononuclear cell				X		X		X	X	X	X	X	X		X	X		X	X	X	X		X	X	X

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

ANIMAL NUMBER	002	001	007	008	009	010	011	015	016	018	025	027	030	031	034	037	038	039	040	041	042	043	045	046	050	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	102	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
Keratoacanthoma												X														2
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma			X																							1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	–	+	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	–	+	43
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule						X													X							4
Hepatocellular carcinoma																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Acinar cell adenoma								X					X			X	X									5
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, NOS																										1
Adenoma, NOS		X	X		X		X	X				X		X	X		X	X	X		X					19
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma																X										1
Pheochromocytoma					X																		X			3
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell adenoma		X	X																				X			6
C-cell adenoma			X		X							X							X				X			5
Parathyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroadenoma			X	X			X			X		X	X		X		X						X	X		18
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								X											X							3
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS																X										1
Endometrial stromal polyp		X		X	X							X	X			X				X						13
Endometrial stromal sarcoma																								X		1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS, 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
Fibrosarcoma																										1
Leukemia, mononuclear cell	X					X					X	X				X										22

* Animals Necropsied

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{12}, 60% Cl): HIGH DOSE

ANIMAL NUMBER	010	007	050	034	037	033	005	043	039	042	047	009	038	023	027	029	048	002	019	020	008	001	003	004	006
WEEKS ON STUDY	028	064	066	076	080	082	087	087	088	090	090	092	094	096	096	096	098	100	100	101	102	105	105	105	105
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Trichoepithelioma																									
Keratoacanthoma																									
Neurofibrosarcoma									X																
Subcutaneous tissue	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma								X																	
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	–	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell papilloma					X																				
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule											X								X						
Hepatocellular carcinoma																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinar cell adenoma																									
Acinar cell carcinoma																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS				X		X		X	X		X	X		X				X		X	X	X	X	X	
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																									
Pheochromocytoma																								X	X
Pheochromocytoma, malignant																									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma									X											X	X				
Follicular cell carcinoma																									
C-cell adenoma																				X					
C-cell carcinoma													X												
Parathyroid	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	–	+	+	+	+	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Adenocarcinoma, NOS																									
Fibroadenoma																	X				X			X	
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																			X					X	
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp			X			X													X						X
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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	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
Leukemia, mononuclear cell									X	X					X	X	X	X	X	X	X		X		

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

ANIMAL NUMBER	011	012	013	014	015	016	017	018	021	022	024	025	026	028	030	031	032	035	036	040	041	044	045	046	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									X	2
Trichoepithelioma																								X		1
Keratoacanthoma				X																						1
Neurofibrosarcoma																										1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																					X					1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell papilloma																										1
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule				X							X						X	X	X							7
Hepatocellular carcinoma																			X							1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Acinar cell adenoma																			X	X						2
Acinar cell carcinoma														X												1
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma																					X					1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, NOS			X		X			X	X		X		X	X			X	X		X	X	X	X			26
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma								X																		1
Pheochromocytoma								X																		3
Pheochromocytoma, malignant																		X								1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell adenoma																										3
Follicular cell carcinoma											X			X								X				3
C-cell adenoma					X															X	X			X		5
C-cell carcinoma												X														2
Parathyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet cell adenoma																							X			1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenoma, NOS										X																1
Adenocarcinoma, NOS													X													1
Fibroadenoma		X							X				X			X	X					X				9
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS																										2
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endometrial stromal polyp	X	X						X			X				X								X		X	11
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
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	N	+	N	N	N	+	N	*50
Carcinoma, NOS																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leukemia, mononuclear cell							X		X			X	X			X									X	16

*Animals Necropsied

APPENDIX B

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE IN THE TWO-YEAR GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{12}, 60% Chlorine)

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{12}, 60% 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)
Sebaceous adenoma	1 (2%)		
*Subcutaneous tissue	(50)	(50)	(50)
Sarcoma, NOS	1 (2%)	3 (6%)	2 (4%)
Fibroma		1 (2%)	
Fibrosarcoma		1 (2%)	1 (2%)
RESPIRATORY SYSTEM			
#Lung	(50)	(50)	(50)
Hepatocellular carcinoma, metastatic	4 (8%)	4 (8%)	3 (6%)
Alveolar/bronchiolar adenoma	5 (10%)	3 (6%)	3 (6%)
Alveolar/bronchiolar carcinoma		3 (6%)	6 (12%)
Adenosquamous carcinoma			1 (2%)
Sarcoma, NOS, metastatic			1 (2%)
Fibrosarcoma, metastatic		1 (2%)	
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Malignant lymphoma, NOS			1 (2%)
Malignant lymphoma, undiffer type		1 (2%)	
Malignant lymphoma, lymphocytic type	1 (2%)		1 (2%)
Malignant lymphoma, histiocytic type	3 (6%)	1 (2%)	
Malignant lymphoma, mixed type		4 (8%)	2 (4%)
#Mandibular lymph node	(49)	(49)	(50)
Carcinoma, NOS, metastatic	1 (2%)		
#Mesenteric lymph node	(49)	(49)	(50)
Malignant lymphoma, mixed type	1 (2%)		
#Jejunum	(50)	(50)	(48)
Malignant lymphoma, mixed type	1 (2%)		1 (2%)
CIRCULATORY SYSTEM			
*Multiple organs	(50)	(50)	(50)
Hemangiosarcoma		1 (2%)	1 (2%)
*Subcutaneous tissue	(50)	(50)	(50)
Hemangiosarcoma	1 (2%)	1 (2%)	
#Spleen	(50)	(49)	(50)
Hemangiosarcoma		3 (6%)	
#Liver	(50)	(50)	(50)
Hemangiosarcoma	1 (2%)	3 (6%)	3 (6%)
DIGESTIVE SYSTEM			
#Liver	(50)	(50)	(50)
Adenocarcinoma, NOS, metastatic	1 (2%)		
Hepatocellular adenoma	11 (22%)	20 (40%)	29 (58%)
Hepatocellular carcinoma	11 (22%)	15 (30%)	17 (34%)
Hepatoblastoma		1 (2%)	1 (2%)
#Gastric fundal gland	(50)	(50)	(50)
Adenocarcinoma, NOS	1 (2%)		
#Forestomach	(50)	(50)	(50)
Squamous cell papilloma		2 (4%)	1 (2%)
Squamous cell carcinoma			1 (2%)
#Small intestine	(50)	(50)	(48)
Adenocarcinoma, NOS	2 (4%)		1 (2%)

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM (Continued)			
#Jejunal mucosa	(50)	(50)	(48)
Adenocarcinoma, NOS		1 (2%)	
#Ileal mucosa	(50)	(50)	(48)
Adenocarcinoma, NOS			1 (2%)
URINARY SYSTEM			
#Kidney	(50)	(50)	(50)
Tubular cell adenocarcinoma			1 (2%)
ENDOCRINE SYSTEM			
#Anterior pituitary	(45)	(47)	(47)
Adenoma, NOS			1 (2%)
#Adrenal	(50)	(48)	(49)
Cortical adenoma			1 (2%)
#Adrenal/capsule	(50)	(48)	(49)
Adenoma, NOS	3 (6%)	3 (6%)	3 (6%)
#Periadrenal tissue	(50)	(48)	(49)
Alveolar/bronchiolar ca, metastatic		1 (2%)	
#Thyroid	(49)	(50)	(49)
Follicular cell adenoma	2 (4%)	3 (6%)	2 (4%)
Follicular cell carcinoma	1 (2%)	1 (2%)	1 (2%)
#Pancreatic islets	(49)	(50)	(49)
Islet cell adenoma		1 (2%)	
REPRODUCTIVE SYSTEM			
#Testis	(50)	(49)	(50)
Interstitial cell tumor			1 (2%)
NERVOUS SYSTEM			
#Brain	(50)	(50)	(50)
Neurilemoma, malignant			1 (2%)
SPECIAL SENSE ORGANS			
*Harderian gland	(50)	(50)	(50)
Carcinoma, NOS	1 (2%)		
Adenoma, NOS	3 (6%)	2 (4%)	4 (8%)
MUSCULOSKELETAL SYSTEM			
*Skeletal muscle	(50)	(50)	(50)
Sarcoma, NOS			1 (2%)
BODY CAVITIES			
*Epicardium	(50)	(50)	(50)
Sarcoma, NOS		1 (2%)	
*Mesentery	(50)	(50)	(50)
Hepatocellular carcinoma, invasive		1 (2%)	
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Squamous cell carcinoma, invasive			1 (2%)
Alveolar/bronchiolar carcinoma, metastatic			1 (2%)
Sarcoma, NOS	1 (2%)		
Sarcoma, NOS, invasive			1 (2%)

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	4	7	6
Moribund sacrifice	11	13	13
Terminal sacrifice	34	30	30
Accidentally killed, NOS	1		1
TUMOR SUMMARY			
Total animals with primary tumors**	37	44	46
Total primary tumors	51	75	89
Total animals with benign tumors	23	25	35
Total benign tumors	25	35	45
Total animals with malignant tumors	22	34	30
Total malignant tumors	26	40	44
Total animals with secondary tumors##	6	6	5
Total secondary tumors	6	7	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_{12}, 60% 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 carcinoma	1 (2%)		
Sebaceous adenoma	1 (2%)	1 (2%)	
Adenosquamous carcinoma			1 (2%)
RESPIRATORY SYSTEM			
#Lung	(50)	(49)	(50)
Adenocarcinoma, NOS, metastatic	1 (2%)		
Hepatocellular carcinoma, metastatic			1 (2%)
Alveolar/bronchiolar adenoma	1 (2%)	4 (8%)	1 (2%)
Alveolar/bronchiolar carcinoma	2 (4%)		
Follicular cell carcinoma, metastatic			1 (2%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Malignant lymphoma, lymphocytic type		3 (6%)	6 (12%)
Malignant lymphoma, histiocytic type	2 (4%)		1 (2%)
Malignant lymphoma, mixed type	9 (18%)	6 (12%)	8 (16%)
Lymphocytic leukemia			1 (2%)
#Spleen	(50)	(50)	(50)
Malignant lymphoma, mixed type		1 (2%)	
#Mesenteric lymph node	(50)	(49)	(49)
Malignant lymphoma, mixed type		1 (2%)	
#Liver	(50)	(50)	(50)
Malignant lymphoma, histiocytic type	1 (2%)		
#Kidney	(50)	(50)	(50)
Malignant lymphoma, mixed type		1 (2%)	
CIRCULATORY SYSTEM			
*Skin	(50)	(50)	(50)
Hemangioma		1 (2%)	
#Spleen	(50)	(50)	(50)
Hemangiosarcoma	2 (4%)	1 (2%)	1 (2%)
#Liver	(50)	(50)	(50)
Hemangioma			1 (2%)
Hemangiosarcoma	1 (2%)		1 (2%)
DIGESTIVE SYSTEM			
#Liver	(50)	(50)	(50)
Hepatocellular adenoma		18 (36%)	22 (44%)
Hepatocellular carcinoma	3 (6%)	4 (8%)	9 (18%)
#Pancreas	(50)	(50)	(50)
Acinar cell adenoma	1 (2%)		
#Esophagus	(50)	(50)	(49)
Squamous cell carcinoma	1 (2%)		
#Forestomach	(50)	(50)	(50)
Squamous cell papilloma	2 (4%)	5 (10%)	
URINARY SYSTEM			
None			

TABLE B2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM			
#Anterior pituitary	(49)	(47)	(46)
Carcinoma, NOS			1 (2%)
Adenoma, NOS	18 (37%)	14 (30%)	9 (20%)
#Adrenal	(50)	(49)	(50)
Hepatocellular carcinoma, invasive			1 (2%)
Pheochromocytoma		1 (2%)	
#Adrenal/capsule	(50)	(49)	(50)
Adenoma, NOS	1 (2%)		
#Thyroid	(50)	(49)	(49)
Follicular cell adenoma	8 (16%)	12 (24%)	13 (27%)
Follicular cell carcinoma			2 (4%)
#Pancreatic islets	(50)	(50)	(50)
Islet cell adenoma		1 (2%)	
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Adenocarcinoma, NOS	5 (10%)		4 (8%)
#Uterus	(50)	(50)	(50)
Fibroma	1 (2%)		
Leiomyoma			1 (2%)
Leiomyosarcoma		2 (4%)	1 (2%)
Endometrial stromal polyp	4 (8%)	2 (4%)	3 (6%)
Endometrial stromal sarcoma			2 (4%)
#Uterus/endometrium	(50)	(50)	(50)
Adenocarcinoma, NOS			1 (2%)
#Ovary	(49)	(41)	(45)
Luteoma	1 (2%)		
Granulosa cell carcinoma		1 (2%)	
Tubular adenoma	1 (2%)		
NERVOUS SYSTEM			
#Brain	(50)	(50)	(49)
Carcinoma, NOS, metastatic			1 (2%)
SPECIAL SENSE ORGANS			
*Harderian gland	(50)	(50)	(50)
Carcinoma, NOS		1 (2%)	
Adenoma, NOS	1 (2%)	6 (12%)	2 (4%)
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
*Peritoneum	(50)	(50)	(50)
Granulosa cell carcinoma, invasive		1 (2%)	
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Endometrial stromal sarcoma, invasive			1 (2%)

TABLE B2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	10	5	6
Moribund sacrifice	4	11	18
Terminal sacrifice	35	31	25
Accidentally killed, NOS	1	3	1
TUMOR SUMMARY			
Total animals with primary tumors**	40	42	42
Total primary tumors	67	86	91
Total animals with benign tumors	25	40	31
Total benign tumors	40	65	52
Total animals with malignant tumors	24	18	30
Total malignant tumors	27	21	39
Total animals with secondary tumors##	1	1	5
Total secondary tumors	1	1	5

* 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_{12}, 60% Cl): VEHICLE CONTROL

ANIMAL NUMBER	050	037	042	044	024	039	045	046	006	002	021	012	041	043	048	049	001	003	004	005	007	008	009	010	011
WEEKS ON STUDY	000	086	086	086	087	087	087	087	089	101	101	103	103	103	103	103	105	105	105	105	105	105	105	105	105
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sebaceous adenoma																X									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS													X												
Hemangiosarcoma											X														
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic		X	X		X															X					
Alveolar/bronchiolar adenoma													X		X										
Trachea	+	+	–	+	+	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+
Carcinoma, NOS, metastatic									X																
Malignant lymphoma, mixed type																									
Thymus	+	+	–	+	–	+	+	–	+	–	+	+	–	–	–	+	+	+	+	–	+	+	–	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS, metastatic																			X						
Hepatocellular adenoma				X															X	X		X			X
Hepatocellular carcinoma		X	X	X	X	X						X		X	X			X		X				X	
Hemangiosarcoma																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	N	+	N	N	+	+
Pancreas	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																			X						
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS									X																
Malignant lymphoma, mixed type																									
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+
Follicular cell adenoma																									
Follicular cell carcinoma																									
Parathyroid	+	+	–	–	+	–	+	+	–	+	+	–	+	–	+	+	+	–	+	+	–	+	–	–	–
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	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													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
Sarcoma, NOS										X															
Malig. lymphoma, lymphocytic type								X																	
Malig. lymphoma, histiocytic type											X														

+ : Tissue Examined Microscopically
– : Required Tissue Not Examined Microscopically
X : Tumor Incidence
N : Necropsy, No Autolysis, No Microscopic Examination
S : Animal 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	013	014	015	016	017	018	019	020	022	023	025	026	027	028	029	030	031	032	033	034	035	036	038	040	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
Sebaceous adenoma																										1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS																										1
Hemangiosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic																										4
Alveolar/bronchiolar adenoma						X											X						X			5
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, NOS, metastatic																										1
Malignant lymphoma, mixed type											X															1
Thymus	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	39
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS, metastatic																										1
Hepatocellular adenoma	X				X		X				X				X				X							11
Hepatocellular carcinoma																										11
Hemangiosarcoma											X															1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	N	+	+	+	N	N	+	+	+	N	+	+	+	+	+	N	+	N	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS																										1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS				X																						2
Malignant lymphoma, mixed type								X																		1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	–	+	+	+	+	+	+	45
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS												X		X										X		3
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell adenoma													X							X						2
Follicular cell carcinoma																									X	1
Parathyroid	+	+	+	–	+	+	+	–	+	+	+	+	+	+	–	+	+	+	–	+	+	+	–	+	–	33
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	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
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
Carcinoma, NOS																										1
Adenoma, NOS																			X							3
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Sarcoma, NOS																										1
Malig. lymphoma, lymphocytic type																										1
Malig. lymphoma, histiocytic type				X																			X			3

* Animals Necropsied

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{12}, 60% Cl): LOW DOSE

ANIMAL NUMBER	006	023	044	043	024	028	027	004	014	046	012	032	001	037	002	025	016	018	020	017	019	039	003	005	007
WEEKS ON STUDY	047	055	057	073	075	075	086	087	087	087	089	091	095	095	100	102	103	103	103	104	104	104	105	105	105
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS											X			X											
Fibroma																X									
Fibrosarcoma													X												
Hemangiosarcoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic	X							X																	
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																									
Fibrosarcoma, metastatic													X												
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+
Hemangiosarcoma																X									
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	–	–	+	+	+	–	+	+	–	+	–	+	+	+	+	–	–	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma	X		X									X	X	X			X			X				X	
Hepatocellular carcinoma	X			X	X	X	X	X		X								X	X						
Hepatoblastoma																									
Hemangiosarcoma																X									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	N	+	+	+	N	N	+	+	+	+	+	+	+	N	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																									
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	–	+	+
Adenoma, NOS														X											
Alveolar/bronchiolar ca, metastatic																									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																						X			
Follicular cell carcinoma																									
Parathyroid	+	+	–	+	–	+	+	+	–	–	–	+	+	+	–	+	–	+	–	–	+	–	+	–	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	+	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	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																									
BODY CAVITIES																									
Pericardium	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Sarcoma, NOS																									
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																									
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
Hemangiosarcoma									X																
Malig. lymphoma, undiffer type															X										
Malig. lymphoma, histiocytic type		X																							
Malignant lymphoma, mixed type												X										X	X		

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

ANIMAL NUMBER	008	009	010	011	013	015	021	022	026	029	030	031	033	034	035	036	038	040	041	042	045	047	048	049	050	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS				X																						3
Fibroma																										1
Fibrosarcoma																										1
Hemangiosarcoma	X																									1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic											X	X														4
Alveolar/bronchiolar adenoma		X			X				X																	3
Alveolar/bronchiolar carcinoma											X							X	X							3
Fibrosarcoma, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma			X												X											3
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	−	+	−	−	+	+	+	+	+	+	−	−	+	+	+	+	−	+	+	+	+	+	+	+	+	37
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma	X	X	X	X	X		X						X					X		X	X	X			X	20
Hepatocellular carcinoma											X	X			X		X						X	X		15
Hepatoblastoma																									X	1
Hemangiosarcoma															X									X		3
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	N	+	+	+	+	+	+	N	N	N	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																		X				X				2
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS		X																								1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma, NOS													X										X			3
Alveolar/bronchiolar ca, metastatic																		X								1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell adenoma											X														X	3
Follicular cell carcinoma													X													1
Parathyroid	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	37
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet cell adenoma	X																									1
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	+	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
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												2
BODY CAVITIES																										
Pericardium	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Sarcoma, NOS					X																					1
Mesentery	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Hepatocellular carcinoma, invasive											X															1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Hemangiosarcoma																										1
Malig. lymphoma, undiffer type																										1
Malig. lymphoma, histiocytic type																										1
Malignant lymphoma, mixed type																									X	4

* Animals Necropsied

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{12}, 60% Cl): HIGH DOSE

ANIMAL NUMBER	015	004	008	007	041	048	050	016	014	021	002	045	046	009	030	013	038	020	026	001	003	005	006	010	011
WEEKS ON STUDY	026	063	067	071	080	081	081	085	086	086	087	087	092	095	095	100	101	103	103	104	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS			X									X													
Fibrosarcoma																							X		
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic							X									X									
Alveolar/bronchiolar adenoma					X														X		X				
Alveolar/bronchiolar carcinoma				X																					
Adenosquamous carcinoma																	X								
Sarcoma, NOS, metastatic				X																					
Trachea	+	+	+	+	+	+	+	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	–	–	–	+	+	+	+	–	+	–	+	+	+	–	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma									X			X	X		X	X		X	X	X	X	X	X	X	X
Hepatocellular carcinoma				X		X	X	X	X	X		X		X		X		X			X				
Hepatoblastoma						X																			
Hemangiosarcoma											X										X				
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	+	+	N	N	+	+	+	+	N	N	+	+	+	+	N	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																			X						
Squamous cell carcinoma								X																	
Small intestine	+	+	+	+	+	+	+	+	+	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																X									
Malignant lymphoma, mixed type						X																			
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenocarcinoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+
Adenoma, NOS							X																		
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																						X			
Cortical adenoma																									X
Thyroid	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																							X		
Follicular cell carcinoma				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
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor																			X						
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neurilemoma, malignant					X																				
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																				X			X		
MUSCULOSKELETAL SYSTEM																									
Muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, 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
Squamous cell carcinoma, invasive								X																	
Alveolar/bronchiolar ca, metastatic				X																					
Sarcoma, NOS, invasive				X																					
Hemangiosarcoma																	X								
Malignant lymphoma, NOS													X												
Malig. lymphoma, lymphocytic type																									
Malignant lymphoma, mixed type																		X							

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

ANIMAL NUMBER	012	017	018	019	022	023	024	025	027	028	029	031	032	033	034	035	036	037	039	040	042	043	044	047	049	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS																										2
Fibrosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic																						X				3
Alveolar/bronchiolar adenoma																										3
Alveolar/bronchiolar carcinoma					X	X					X				X	X										6
Adenosquamous carcinoma																										1
Sarcoma, NOS, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	–	–	+	–	+	+	+	+	–	+	+	+	+	–	+	+	+	+	+	–	–	+	+	37
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma		X		X			X	X		X	X					X	X	X	X	X	X	X	X	X	X	29
Hepatocellular carcinoma					X		X		X				X						X			X				17
Hepatoblastoma																										1
Hemangiosarcoma			X																							3
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	+	N	N	+	+	+	+	+	+	+	N	+	+	+	+	+	N	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																										1
Squamous cell carcinoma																										1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenocarcinoma, NOS																			X							2
Malignant lymphoma, mixed type																										1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tubular cell adenocarcinoma		X																								1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	47
Adenoma, NOS																										1
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, NOS															X						X					3
Cortical adenoma																										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell adenoma			X																							2
Follicular cell carcinoma																										1
Parathyroid	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
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
Neurilemoma, malignant																										1
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS					X							X														4
MUSCULOSKELETAL SYSTEM																										
Muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell carcinoma, invasive																										1
Alveolar/bronchiolar ca, metastatic																										1
Sarcoma, NOS, invasive																										1
Hemangiosarcoma																										1
Malignant lymphoma, NOS																										1
Malig. lymphoma, lymphocytic type													X													1
Malignant lymphoma, mixed type								X																		2

*Animals Necropsied

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{12}, 60% Cl): VEHICLE CONTROL

ANIMAL NUMBER	019	014	015	041	049	096	096	033	011	038	043	050	009	031	002	003	004	005	007	008	010	012	013	017	018
WEEKS ON STUDY	001	034	081	082	094	095	095	095	096	096	100	100	102	103	105	105	105	105	105	105	105	105	105	105	105
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																							X		
Sebaceous adenoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS, metastatic			X																						
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																									
Trachea	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	–	+	+	–	+	–	+	–	+	+	+	+	+	+	+	–	+	+	+	+	+	+	–
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																									
Hemangiosarcoma																									X
Malig. lymphoma, histiocytic type						X																			
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	+	N	+	+	N	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinar cell adenoma																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																						X			
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																			X						
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS								X			X		X	X		X			X	X	X	X			
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma						X								X								X			
Parathyroid	+	+	–	+	+	–	+	+	+	+	+	+	–	+	–	–	–	+	+	+	+	+	+	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+
Adenocarcinoma, NOS			X																	X			X		
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																									
Endometrial stromal polyp															X						X				X
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Luteoma																				X					
Tubular adenoma																									
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, histiocytic type					X									X											
Malignant lymphoma, mixed type				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 B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: VEHICLE CONTROL (Continued)

ANIMAL NUMBER	020	021	022	023	024	025	026	027	028	029	030	032	034	035	036	037	039	040	041	042	044	045	046	047	048	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
Sebaceous adenoma		X																								1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS, metastatic																										1
Alveolar/bronchiolar adenoma												X														1
Alveolar/bronchiolar carcinoma														X									X			2
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma									X	X																2
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	–	+	+	+	+	+	+	42
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma			X																X						X	3
Hemangiosarcoma																										1
Malig. lymphoma, histiocytic type																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	N	+	N	+	+	+	+	+	+	+	+	+	N	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Acinar cell adenoma									X																	1
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma																										1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma			X																							2
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, NOS		X	X			X			X		X	X								X	X			X		18
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS			X																							1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell adenoma		X			X							X						X					X			8
Parathyroid	+	–	+	+	+	+	+	+	+	+	+	+	–	+	+	+	–	+	+	+	+	+	–	+	+	40
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenocarcinoma, NOS	X											X														5
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroma						X																				1
Endometrial stromal polyp													X													4
Ovary	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Luteoma																										1
Tubular adenoma					X																					1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS																							X			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, histiocytic type																										2
Malignant lymphoma, mixed type							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_{12}, 60% Cl): LOW DOSE

ANIMAL NUMBER	033	041	003	009	020	048	038	018	026	047	019	049	024	006	001	002	008	021	045	010	027	004	005	007	011
WEEKS ON STUDY	001	001	002	059	068	074	086	087	087	087	095	096	098	100	101	101	101	101	101	104	104	105	105	105	105
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sebaceous adenoma																									
Hemangioma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma												X													
Trachea	+	+	+	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Malignant lymphoma, mixed type																									
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, mixed type																								X	
Thymus	+	+	+	+	+	+	+	−	−	+	−	−	−	+	+	+	+	+	+	+	−	+	+	+	−
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma								X					X		X		X	X					X	X	X
Hepatocellular carcinoma					X														X						
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	N	+	+	N	+	+	+	+	+	+	+	+	N	+	+	+	N	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma							X			X															
Small intestine	+	+	+	+	−	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, mixed type																							X		
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+
Adenoma, NOS													X	X	X				X				X	X	X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+
Pheochromocytoma										X															
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma											X						X		X	X		X		X	
Parathyroid	+	+	+	+	+	+	+	−	−	+	+	−	+	+	+	+	−	−	+	−	+	−	−	+	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																X									
REPRODUCTIVE SYSTEM																									
Mammary gland	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma					X														X						
Endometrial stromal polyp																		X					X		
Ovary	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	−	+	+	+	+	+	+
Granulosa cell carcinoma																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																									
Adenoma, NOS															X					X				X	
BODY CAVITIES																									
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Granulosa cell carcinoma, invasive																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malig. lymphoma, lymphocytic type											X										X				
Malignant lymphoma, mixed type								X						X			X			X					

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

ANIMAL NUMBER	012	013	014	015	016	017	022	023	025	028	029	030	031	032	034	035	036	037	039	040	042	043	044	046	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
Sebaceous adenoma														X												1
Hemangioma											X															1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma						X							X										X			4
Trachea	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma											X															1
Malignant lymphoma, mixed type														X												1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Malignant lymphoma, mixed type																										1
Thymus	+	+	+	–	+	–	–	–	+	–	–	–	+	+	+	+	+	+	–	+	+	+	+	+	–	34
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	–	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma	X		X	X					X			X			X	X	X							X	X	18
Hepatocellular carcinoma											X							X								4
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	N	+	+	+	N	+	+	N	+	+	+	N	+	+	+	+	+	+	N	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma		X								X														X		5
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Large intestine	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Malignant lymphoma, mixed type																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	49
ENDOCRINE SYSTEM																										
Pituitary	–	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma, NOS								X					X				X	X	X		X	X				14
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma																										1
Thyroid	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell adenoma		X	X	X																X	X		X			12
Parathyroid	+	–	+	+	+	–	+	–	+	+	–	+	+	+	+	–	–	–	+	–	+	+	+	–	+	33
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet cell adenoma																										1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma																										2
Endometrial stromal polyp																										2
Ovary	+	+	+	+	+	–	+	–	+	+	+	–	+	–	+	+	+	+	–	+	+	–	–	+	+	41
Granulosa cell carcinoma																									X	1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS										X																1
Adenoma, NOS								X		X										X						6
BODY CAVITIES																										
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Granulosa cell carcinoma, invasive																									X	1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malig. lymphoma, lymphocytic type	X																									3
Malignant lymphoma, mixed type						X											X									6

* Animals Necropsied

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{12}, 60% Cl): HIGH DOSE

ANIMAL NUMBER	036	047	020	032	018	030	012	022	041	034	013	024	043	017	008	001	016	023	010	014	021	028	046	005	011
WEEKS ON STUDY	001	001	059	067	074	075	079	084	084	085	087	087	087	090	093	095	095	098	099	100	100	100	100	101	103
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenosquamous carcinoma													X												
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic						X																			
Alveolar/bronchiolar adenoma																									
Follicular cell carcinoma, metastatic																									
Trachea	+	+	+	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma											X														
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	–	–	–	+	–	+	+	+	+	+	–	+	+	+	–	–	–	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma								X							X	X	X	X	X		X		X		
Hepatocellular carcinoma						X	X	X														X		X	
Hemangioma																									
Hemangiosarcoma																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	N	+	+	+	+	+	N	N	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	–	+	–	+	+	+
Carcinoma, NOS														X											
Adenoma, NOS				X													X								X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, invasive																								X	
Thyroid	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																	X	X						X	X
Follicular cell carcinoma														X											
Parathyroid	–	–	+	+	–	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	N	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS									X								X	X							X
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																									
Leiomyoma																									X
Leiomyosarcoma																	X								
Endometrial stromal polyp									X																X
Endometrial stromal sarcoma								X																	
Ovary	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, metastatic														X											
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																									
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
Endometrial stromal sarcoma, invas								X																	
Malig. lymphoma, lymphocytic type										X		X									X				
Malig. lymphoma, histiocytic type																									
Malignant lymphoma, mixed type																X			X						X
Lymphocytic leukemia							X																		

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

ANIMAL NUMBER	003	004	006	007	009	015	019	022	025	026	027	029	031	033	035	037	038	039	040	042	044	045	048	049	050	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenosquamous carcinoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic																										1
Alveolar/bronchiolar adenoma									X																	1
Follicular cell carcinoma, metastatic			X																							1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	–	+	+	+	+	+	46
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	–	–	–	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	38
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma	X	X	X	X	X		X			X	X	X	X	X		X	X				X					22
Hepatocellular carcinoma	X					X				X					X											9
Hemangioma							X																			1
Hemangiosarcoma										X																1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	N	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Carcinoma, NOS																										1
Adenoma, NOS									X				X		X		X		X		X					9
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, invasive																										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell adenoma	X	X							X			X	X		X			X	X					X		13
Follicular cell carcinoma			X																							2
Parathyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	–	+	+	43
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenocarcinoma, NOS																										4
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS									X																	1
Leiomyoma																										1
Leiomyosarcoma																										1
Endometrial stromal polyp			X																							3
Endometrial stromal sarcoma																									X	2
Ovary	+	+	+	+	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+	–	+	+	+	–	45
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, NOS, metastatic																										1
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS																X					X					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
Endometrial stromal sarcoma, invas																										1
Malig. lymphoma, lymphocytic type	X		X													X										6
Malig. lymphoma, histiocytic type									X																	1
Malignant lymphoma, mixed type				X										X			X				X		X			8
Lymphocytic leukemia																										1

* Animals Necropsied

APPENDIX C

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{12}, 60% Chlorine)

TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{12}, 60% 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, acute focal	1 (2%)		
Inflammation, acute suppurative			1 (2%)
Inflammation, acute/chronic		1 (2%)	
Alopecia		5 (10%)	2 (4%)
Hyperplasia, epithelial	1 (2%)		
Hyperkeratosis	1 (2%)		
*Subcutaneous tissue	(50)	(50)	(50)
Hemorrhage		1 (2%)	
Inflammation, acute suppurative		1 (2%)	
RESPIRATORY SYSTEM			
*Nasal cavity	(50)	(50)	(50)
Foreign body, NOS	1 (2%)	2 (4%)	
Lymphocytic inflammatory infiltrate	28 (56%)	34 (68%)	26 (52%)
Inflammation, suppurative		1 (2%)	
Inflammation, acute suppurative	8 (16%)	6 (12%)	3 (6%)
Infection, fungal	6 (12%)	2 (4%)	1 (2%)
*Nose	(50)	(50)	(50)
Lymphocytic inflammatory infiltrate			1 (2%)
#Lung	(50)	(50)	(50)
Foreign body, NOS	4 (8%)	1 (2%)	1 (2%)
Congestion, NOS	7 (14%)	2 (4%)	1 (2%)
Hemorrhage	2 (4%)	1 (2%)	
Lymphocytic inflammatory infiltrate	1 (2%)		2 (4%)
Pneumonia, aspiration	1 (2%)		
Bronchopneumonia, acute	1 (2%)		
Inflammation, acute focal			1 (2%)
Inflammation, acute suppurative		1 (2%)	
Fibrosis, multifocal	1 (2%)		
Necrosis, focal	1 (2%)		1 (2%)
Cholesterol deposit			1 (2%)
Foreign material, NOS	1 (2%)		
Hyperplasia, alveolar epithelium	4 (8%)	1 (2%)	4 (8%)
Histiocytosis	2 (4%)	1 (2%)	1 (2%)
HEMATOPOIETIC SYSTEM			
#Bone marrow	(50)	(49)	(49)
Atrophy, NOS		1 (2%)	
Hyperplasia, NOS		1 (2%)	
Myelofibrosis		1 (2%)	
#Spleen	(50)	(50)	(49)
Fibrosis	1 (2%)		
Fibrosis, focal	3 (6%)	8 (16%)	8 (16%)
Scar			1 (2%)
Necrosis, focal	1 (2%)		
Atrophy, NOS	1 (2%)		1 (2%)
Hematopoiesis	4 (8%)	2 (4%)	1 (2%)
#Mediastinal lymph node	(50)	(50)	(50)
Congestion, NOS	1 (2%)		
Angiectasis			1 (2%)
#Mesenteric lymph node	(50)	(50)	(50)
Congestion, NOS			1 (2%)
Angiectasis		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_{12}, 60% Cl) (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
HEMATOPOIETIC SYSTEM (Continued)			
#Renal lymph node	(50)	(50)	(50)
Cyst, NOS		1 (2%)	
Angiectasis		1 (2%)	1 (2%)
#Inguinal lymph node	(50)	(50)	(50)
Inflammation, acute suppurative	1 (2%)		
Hyperplasia, NOS	1 (2%)		
#Adrenal	(50)	(50)	(49)
Hematopoiesis			1 (2%)
#Adrenal cortex	(50)	(50)	(49)
Hematopoiesis	1 (2%)		
#Thymus	(42)	(47)	(47)
Cyst, NOS		1 (2%)	1 (2%)
CIRCULATORY SYSTEM			
#Mandibular lymph node	(50)	(50)	(50)
Lymphangiectasis	1 (2%)	1 (2%)	1 (2%)
#Pancreatic lymph node	(50)	(50)	(50)
Lymphangiectasis			1 (2%)
#Lumbar lymph node	(50)	(50)	(50)
Lymphangiectasis		1 (2%)	
#Mesenteric lymph node	(50)	(50)	(50)
Lymphangiectasis	1 (2%)		1 (2%)
#Inguinal lymph node	(50)	(50)	(50)
Lymphangiectasis			1 (2%)
#Heart	(50)	(50)	(50)
Mineralization		1 (2%)	
Thrombus, mural	1 (2%)	2 (4%)	1 (2%)
Inflammation, acute suppurative	1 (2%)		
Fibrosis		5 (10%)	
Fibrosis, focal	12 (24%)	10 (20%)	27 (54%)
Fibrosis, multifocal	23 (46%)	20 (40%)	4 (8%)
Periarteritis	1 (2%)		
Degeneration, NOS		3 (6%)	1 (2%)
#Heart/atrium	(50)	(50)	(50)
Thrombus, mural	1 (2%)		
*Mesenteric artery	(50)	(50)	(50)
Inflammation, fibrinoid	1 (2%)		
#Liver	(50)	(50)	(48)
Lymphangiectasis			1 (2%)
Thrombosis, NOS			1 (2%)
#Pancreas	(50)	(50)	(49)
Periarteritis	1 (2%)		1 (2%)
DIGESTIVE SYSTEM			
*Tongue	(50)	(50)	(50)
Foreign body, NOS	1 (2%)		
Inflammation, granulomatous focal	1 (2%)		
Hyperplasia, epithelial	1 (2%)		
Hyperkeratosis	1 (2%)		
#Salivary gland	(50)	(50)	(49)
Ranular cyst	1 (2%)		
Atrophy, focal			1 (2%)
#Liver	(50)	(50)	(48)
Mineralization		1 (2%)	
Malposition, NOS	2 (4%)		1 (2%)
Congestion, NOS			1 (2%)
Inflammation, acute suppurative		1 (2%)	2 (4%)
Fibrosis, focal			2 (4%)

TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
#Liver (Continued)	(50)	(50)	(48)
Cholangiofibrosis	1 (2%)	1 (2%)	
Degeneration, cystic		3 (6%)	1 (2%)
Necrosis, NOS		5 (10%)	2 (4%)
Necrosis, focal	1 (2%)	7 (14%)	12 (25%)
Necrosis, zonal	2 (4%)	2 (4%)	2 (4%)
Cytoplasmic change, NOS	1 (2%)		
Focal cellular change	1 (2%)	12 (24%)	21 (44%)
Eosinophilic cyto change			1 (2%)
Cytologic alteration, NOS		2 (4%)	1 (2%)
Hypertrophy, NOS		37 (74%)	45 (94%)
Hypertrophy, diffuse			1 (2%)
Hyperplasia, nodular		1 (2%)	
Angiectasis		11 (22%)	10 (21%)
#Hepatic capsule	(50)	(50)	(48)
Mineralization			1 (2%)
Inflammation, chronic	1 (2%)		
Fibrosis, focal			1 (2%)
Pigmentation, NOS	1 (2%)		
#Bile duct	(50)	(50)	(48)
Dilatation, NOS			1 (2%)
Hyperplasia, NOS	35 (70%)	15 (30%)	13 (27%)
#Pancreas	(50)	(50)	(49)
Ectopia		1 (2%)	
Inflammation, acute/chronic		1 (2%)	
Necrosis, focal		1 (2%)	
Atrophy, focal	7 (14%)	5 (10%)	2 (4%)
Hyperplasia, focal	7 (14%)	13 (26%)	8 (16%)
#Glandular stomach	(50)	(50)	(49)
Multiple cysts		1 (2%)	
Edema, NOS	1 (2%)	9 (18%)	9 (18%)
Ulcer, NOS		8 (16%)	1 (2%)
Inflammation, acute/chronic	1 (2%)	1 (2%)	1 (2%)
Erosion	1 (2%)	5 (10%)	9 (18%)
Hyperplasia, epithelial			1 (2%)
#Forestomach	(50)	(50)	(49)
Foreign body, NOS			1 (2%)
Cyst, NOS		1 (2%)	1 (2%)
Edema, NOS		1 (2%)	1 (2%)
Hemorrhage			1 (2%)
Ulcer, NOS	1 (2%)	13 (26%)	13 (27%)
Inflammation, acute			1 (2%)
Inflammation, acute focal		1 (2%)	2 (4%)
Inflammation, acute suppurative		1 (2%)	1 (2%)
Inflammation, acute/chronic	3 (6%)	16 (32%)	16 (33%)
Inflammation, chronic		1 (2%)	1 (2%)
Erosion	1 (2%)	1 (2%)	1 (2%)
Perforation, inflammatory		3 (6%)	1 (2%)
Adhesion, fibrous		1 (2%)	
Necrosis, focal			1 (2%)
Hyperplasia, epithelial	5 (10%)	23 (46%)	27 (55%)
Hyperkeratosis	5 (10%)	23 (46%)	27 (55%)
#Duodenum	(49)	(50)	(49)
Ulcer, NOS		1 (2%)	
Inflammation, acute		1 (2%)	
Erosion		3 (6%)	1 (2%)
#Jejunum	(49)	(50)	(49)
Intussusception			1 (2%)
#Ileum	(49)	(50)	(49)
Inflammation, chronic	1 (2%)		
Fibrosis, focal	1 (2%)		

TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM (Continued)			
#Colon	(48)	(46)	(48)
Ulcer, NOS		1 (2%)	
Inflammation, acute/chronic			1 (2%)
Inflammation, chronic		1 (2%)	
Parasitism	1 (2%)	1 (2%)	
#Cecum	(48)	(46)	(48)
Ulcer, NOS		1 (2%)	
Inflammation, acute			1 (2%)
Inflammation, acute/chronic		1 (2%)	
*Rectum	(50)	(50)	(50)
Inflammation, acute suppurative			1 (2%)
Parasitism	1 (2%)	3 (6%)	
URINARY SYSTEM			
#Kidney	(50)	(50)	(49)
Multiple cysts		2 (4%)	2 (4%)
Inflammation, acute suppurative	1 (2%)		
Nephropathy	49 (98%)	50 (100%)	49 (100%)
Hyperplasia, tubular cell	1 (2%)	9 (18%)	12 (24%)
#Kidney/cortex	(50)	(50)	(49)
Cyst, NOS		1 (2%)	1 (2%)
Multiple cysts		24 (48%)	25 (51%)
#Kidney/pelvis	(50)	(50)	(49)
Inflammation, acute suppurative	1 (2%)		2 (4%)
Hyperplasia, epithelial			1 (2%)
ENDOCRINE SYSTEM			
#Pituitary intermedia	(50)	(48)	(49)
Cyst, NOS		1 (2%)	
#Anterior pituitary	(50)	(48)	(49)
Cyst, NOS	2 (4%)	1 (2%)	4 (8%)
Hemosiderosis		3 (6%)	
Hyperplasia, NOS		1 (2%)	
Hyperplasia, focal		2 (4%)	2 (4%)
Angiectasis	10 (20%)	7 (15%)	6 (12%)
#Adrenal cortex	(50)	(50)	(49)
Cyst, NOS			1 (2%)
Hemorrhage		1 (2%)	
Degeneration, lipoid	1 (2%)	3 (6%)	1 (2%)
Necrosis, focal		1 (2%)	
Cytoplasmic vacuolization		1 (2%)	1 (2%)
Hyperplasia, focal	1 (2%)	1 (2%)	3 (6%)
Angiectasis	1 (2%)		3 (6%)
#Adrenal medulla	(50)	(50)	(49)
Necrosis, focal	1 (2%)		
Hyperplasia, NOS	1 (2%)		
Hyperplasia, focal	9 (18%)	4 (8%)	10 (20%)
Angiectasis	2 (4%)		
#Thyroid	(50)	(50)	(50)
Embryonal duct cyst	3 (6%)		2 (4%)
Cystic follicles	2 (4%)	9 (18%)	4 (8%)
Follicular cyst, NOS			1 (2%)
Hemosiderosis			1 (2%)
Hyperplasia, C-cell	6 (12%)	1 (2%)	2 (4%)
Hyperplasia, follicular cell		2 (4%)	1 (2%)
Angiectasis	1 (2%)		
#Parathyroid	(46)	(48)	(50)
Hyperplasia, NOS	8 (17%)	27 (56%)	24 (48%)

TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Cyst, NOS	1 (2%)		
Cystic ducts	16 (32%)	10 (20%)	5 (10%)
Adenosis	1 (2%)	2 (4%)	1 (2%)
*Mammary duct	(50)	(50)	(50)
Multiple cysts	1 (2%)		
*Preputial gland	(50)	(50)	(50)
Foreign body, NOS	1 (2%)		
Cystic ducts	5 (10%)	5 (10%)	6 (12%)
Inflammation, suppurative	1 (2%)		
Inflammation, acute		1 (2%)	1 (2%)
Inflammation, acute suppurative	6 (12%)	4 (8%)	7 (14%)
Inflammation, acute/chronic	1 (2%)		
Inflammation, chronic	1 (2%)		1 (2%)
Fibrosis			1 (2%)
Atrophy, NOS	19 (38%)	27 (54%)	22 (44%)
Hyperplasia, NOS	1 (2%)		
Hyperplasia, epithelial		2 (4%)	1 (2%)
#Prostate	(48)	(48)	(49)
Inflammation, acute suppurative	14 (29%)	6 (13%)	6 (12%)
Inflammation, acute/chronic	2 (4%)		1 (2%)
Inflammation, chronic	1 (2%)		
Fibrosis, focal		1 (2%)	
#Testis	(50)	(49)	(49)
Atrophy, NOS			1 (2%)
*Spermatic cord	(50)	(50)	(50)
Ectopia			1 (2%)
NERVOUS SYSTEM			
#Brain	(50)	(50)	(50)
Compression, NOS	1 (2%)		
Hemorrhage			2 (4%)
Necrosis, NOS	1 (2%)		
#Hippocampus	(50)	(50)	(50)
Necrosis, focal		1 (2%)	
SPECIAL SENSE ORGANS			
*Eye	(50)	(50)	(50)
Microphthalmia		1 (2%)	
Hemorrhage		1 (2%)	2 (4%)
Retinopathy	14 (28%)	14 (28%)	15 (30%)
Cataract	13 (26%)	14 (28%)	15 (30%)
*Eye/cornea	(50)	(50)	(50)
Fibrosis		1 (2%)	
*Nasolacrimal duct	(50)	(50)	(50)
Cyst, NOS	1 (2%)		
Inflammation, acute suppurative	2 (4%)		
*Harderian gland	(50)	(50)	(50)
Lymphocytic inflammatory infiltrate	3 (6%)		
MUSCULOSKELETAL SYSTEM			
*Bone	(50)	(50)	(50)
Fibrous osteodystrophy		31 (62%)	23 (46%)

TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
BODY CAVITIES			
*Mediastinum	(50)	(50)	(50)
Foreign body, NOS		1 (2%)	
Hemorrhage			1 (2%)
*Peritoneal cavity	(50)	(50)	(50)
Hemorrhage			1 (2%)
*Mesentery	(50)	(50)	(50)
Congestion, NOS			1 (2%)
Hemorrhage			1 (2%)
Necrosis, fat	9 (18%)	2 (4%)	3 (6%)
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Inflammation, suppurative	1 (2%)		
Inflammation, acute suppurative		1 (2%)	
Foot			
Inflammation, acute/chronic	1		
SPECIAL MORPHOLOGY SUMMARY			
No lesion reported			1

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_{12}, 60% 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)
Epidermal inclusion cyst			1 (2%)
Inflammation, acute suppurative	1 (2%)		
Inflammation, acute/chronic	1 (2%)		
Hyperplasia, NOS			1 (2%)
Hyperplasia, epithelial			2 (4%)
Hyperkeratosis			3 (6%)
RESPIRATORY SYSTEM			
*Nasal cavity	(50)	(50)	(50)
Lymphocytic inflammatory infiltrate	37 (74%)	35 (70%)	20 (40%)
Inflammation, acute suppurative	3 (6%)	2 (4%)	
Infection, fungal	3 (6%)	2 (4%)	
#Lung	(50)	(50)	(50)
Foreign body, NOS			1 (2%)
Congestion, NOS	1 (2%)	2 (4%)	2 (4%)
Hemorrhage		2 (4%)	1 (2%)
Lymphocytic inflammatory infiltrate			2 (4%)
Inflammation, chronic focal			2 (4%)
Inflammation, granulomatous focal		1 (2%)	
Cholesterol deposit			1 (2%)
Hyperplasia, alveolar epithelium	3 (6%)		1 (2%)
Histiocytosis	1 (2%)		2 (4%)
HEMATOPOIETIC SYSTEM			
#Spleen	(50)	(50)	(50)
Hemorrhage			1 (2%)
Fibrosis, focal		1 (2%)	1 (2%)
Fibrosis, multifocal			1 (2%)
Necrosis, NOS		1 (2%)	1 (2%)
Necrosis, focal		2 (4%)	
Hemosiderosis			1 (2%)
Atrophy, NOS			1 (2%)
Hematopoiesis	5 (10%)	3 (6%)	1 (2%)
#Mesenteric lymph node	(50)	(50)	(50)
Angiectasis		4 (8%)	
#Liver	(50)	(50)	(50)
Leukemoid reaction		1 (2%)	
#Adrenal medulla	(50)	(50)	(50)
Hematopoiesis	1 (2%)		
#Thymus	(47)	(43)	(47)
Hemorrhage			1 (2%)
CIRCULATORY SYSTEM			
#Mandibular lymph node	(50)	(50)	(50)
Lymphangiectasis	1 (2%)		
#Heart	(50)	(50)	(50)
Thrombus, mural		1 (2%)	1 (2%)
Lymphocytic inflammatory infiltrate			2 (4%)
Inflammation, chronic focal	1 (2%)		
Fibrosis			2 (4%)
Fibrosis, focal	1 (2%)	6 (12%)	4 (8%)
Fibrosis, multifocal	24 (48%)	11 (22%)	16 (32%)
Degeneration, NOS		1 (2%)	

TABLE C2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
CIRCULATORY SYSTEM (Continued)			
#Pancreas	(50)	(48)	(50)
Periarteritis			1 (2%)
#Stomach	(50)	(50)	(50)
Periarteritis		1 (2%)	
DIGESTIVE SYSTEM			
#Liver	(50)	(50)	(50)
Congenital malformation, NOS		1 (2%)	
Malposition, NOS	1 (2%)	3 (6%)	1 (2%)
Hemorrhage		1 (2%)	
Granuloma, NOS			1 (2%)
Inflammation, granulomatous focal	7 (14%)		1 (2%)
Fibrosis			1 (2%)
Degeneration, cystic		1 (2%)	1 (2%)
Necrosis, NOS	2 (4%)	6 (12%)	4 (8%)
Necrosis, focal	3 (6%)	3 (6%)	2 (4%)
Necrosis, zonal	2 (4%)	7 (14%)	4 (8%)
Mitotic alteration	1 (2%)		
Cytoplasmic vacuolization	5 (10%)	3 (6%)	1 (2%)
Basophilic cyto change	37 (74%)	14 (28%)	1 (2%)
Focal cellular change		4 (8%)	7 (14%)
Clear cell change			2 (4%)
Hypertrophy, NOS	1 (2%)	39 (78%)	45 (90%)
Angiectasis		7 (14%)	7 (14%)
#Bile duct	(50)	(50)	(50)
Hyperplasia, NOS	30 (60%)	29 (58%)	18 (36%)
#Pancreas	(50)	(48)	(50)
Ectopia		3 (6%)	2 (4%)
Atrophy, NOS			1 (2%)
Atrophy, focal	4 (8%)	4 (8%)	7 (14%)
Hyperplasia, focal	3 (6%)	7 (15%)	2 (4%)
#Glandular stomach	(50)	(50)	(50)
Mineralization	1 (2%)		
Edema, NOS		1 (2%)	3 (6%)
Ulcer, NOS	1 (2%)		
Inflammation, acute/chronic			1 (2%)
Erosion		3 (6%)	1 (2%)
#Forestomach	(50)	(50)	(50)
Foreign body, NOS	1 (2%)		
Mineralization	1 (2%)		
Cyst, NOS	1 (2%)		
Ulcer, NOS	1 (2%)	2 (4%)	2 (4%)
Inflammation, acute suppurative		1 (2%)	
Inflammation, acute/chronic		3 (6%)	2 (4%)
Inflammation, chronic focal	1 (2%)		
Inflammation, granulomatous focal	1 (2%)		
Perforation, inflammatory	1 (2%)		
Hyperplasia, epithelial	4 (8%)	7 (14%)	3 (6%)
Hyperkeratosis	4 (8%)	6 (12%)	2 (4%)
#Duodenum	(50)	(50)	(50)
Erosion			2 (4%)
#Colon	(49)	(50)	(49)
Parasitism	2 (4%)	2 (4%)	2 (4%)
#Cecum	(49)	(50)	(49)
Distention			1 (2%)
Edema, NOS			1 (2%)
Ulcer, NOS	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_{12}, 60% Cl) (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM (Continued)			
*Rectum	(50)	(50)	(50)
Edema, NOS		1 (2%)	
Inflammation, acute/chronic		1 (2%)	
Parasitism	5 (10%)	4 (8%)	4 (8%)
URINARY SYSTEM			
#Kidney	(50)	(50)	(50)
Inflammation, acute suppurative			1 (2%)
Nephropathy	33 (66%)	50 (100%)	48 (96%)
#Kidney/cortex	(50)	(50)	(50)
Cyst, NOS	1 (2%)	1 (2%)	
Multiple cysts			1 (2%)
#Urinary bladder	(50)	(50)	(50)
Calculus, gross observation only	1 (2%)		
ENDOCRINE SYSTEM			
#Anterior pituitary	(49)	(49)	(49)
Cyst, NOS	15 (31%)	15 (31%)	8 (16%)
Multiple cysts		6 (12%)	2 (4%)
Hemorrhage	2 (4%)		4 (8%)
Hemosiderosis	7 (14%)	11 (22%)	5 (10%)
Hyperplasia, NOS			1 (2%)
Hyperplasia, focal	2 (4%)	2 (4%)	2 (4%)
Angiectasis	30 (61%)	20 (41%)	24 (49%)
#Adrenal cortex	(50)	(50)	(50)
Accessory structure	1 (2%)		
Cyst, NOS			1 (2%)
Congestion, NOS		1 (2%)	2 (4%)
Degeneration, lipoid	4 (8%)	1 (2%)	2 (4%)
Necrosis, focal	1 (2%)	2 (4%)	2 (4%)
Necrosis, hemorrhagic		1 (2%)	
Hypertrophy, focal	1 (2%)	1 (2%)	2 (4%)
Hyperplasia, focal	3 (6%)	1 (2%)	2 (4%)
Angiectasis		2 (4%)	5 (10%)
#Adrenal medulla	(50)	(50)	(50)
Necrosis, focal			1 (2%)
Hyperplasia, NOS			1 (2%)
Hyperplasia, focal	1 (2%)	2 (4%)	2 (4%)
#Thyroid	(50)	(50)	(50)
Embryonal duct cyst		2 (4%)	3 (6%)
Cystic follicles	2 (4%)	5 (10%)	4 (8%)
Hyperplasia, cystic			1 (2%)
Hyperplasia, C-cell	4 (8%)	1 (2%)	1 (2%)
Hyperplasia, follicular cell		3 (6%)	3 (6%)
Angiectasis		1 (2%)	
#Parathyroid	(48)	(49)	(47)
Hyperplasia, NOS			1 (2%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Cystic ducts	42 (84%)	42 (84%)	32 (64%)
Adenosis	7 (14%)	5 (10%)	5 (10%)
*Mammary duct	(50)	(50)	(50)
Multiple cysts			3 (6%)

TABLE C2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM (Continued)			
*Clitoral gland	(50)	(50)	(50)
Cystic ducts	3 (6%)	1 (2%)	1 (2%)
Hemorrhage		1 (2%)	
Inflammation, acute suppurative	1 (2%)	1 (2%)	1 (2%)
Inflammation, acute/chronic		2 (4%)	
Inflammation, granulomatous focal	1 (2%)		
Necrosis, NOS		1 (2%)	
Atrophy, NOS	15 (30%)	11 (22%)	3 (6%)
Hyperplasia, NOS			1 (2%)
#Uterus	(50)	(50)	(50)
Prolapse			1 (2%)
Hydrometra	1 (2%)	2 (4%)	
Cyst, NOS	2 (4%)		
Hemorrhage		1 (2%)	
Inflammation, acute suppurative			1 (2%)
Necrosis, focal		1 (2%)	
#Cervix uteri	(50)	(50)	(50)
Cyst, NOS		1 (2%)	
Polyp, NOS		1 (2%)	
#Ovary	(50)	(50)	(50)
Cyst, NOS	2 (4%)	3 (6%)	1 (2%)
Parovarian cyst	2 (4%)	1 (2%)	2 (4%)
NERVOUS SYSTEM			
#Brain	(50)	(50)	(49)
Compression, NOS	5 (10%)	1 (2%)	2 (4%)
Hemorrhage		1 (2%)	3 (6%)
#Cerebellum	(50)	(50)	(49)
Angiectasis		1 (2%)	
SPECIAL SENSE ORGANS			
*Eye	(50)	(50)	(50)
Retinopathy	3 (6%)	15 (30%)	2 (4%)
Cataract	3 (6%)	15 (30%)	2 (4%)
*Nasolacrimal duct	(50)	(50)	(50)
Dilatation, NOS	5 (10%)		
Inflammation, acute suppurative	6 (12%)	2 (4%)	
*Harderian gland	(50)	(50)	(50)
Lymphocytic inflammatory infiltrate	2 (4%)		5 (10%)
*Ear	(50)	(50)	(50)
Inflammation, acute suppurative			1 (2%)
*Middle ear	(50)	(50)	(50)
Compression, NOS		1 (2%)	
MUSCULOSKELETAL SYSTEM			
*Bone	(50)	(50)	(50)
Fibrous osteodystrophy			1 (2%)
*Skull	(50)	(50)	(50)
Hyperostosis	1 (2%)		1 (2%)
BODY CAVITIES			
*Mesentery	(50)	(50)	(50)
Torsion			1 (2%)
Congestion, NOS			1 (2%)
Hemorrhage			1 (2%)
Necrosis, fat	5 (10%)	8 (16%)	4 (8%)

TABLE C2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Inflammation, acute suppurative		1 (2%)	
SPECIAL MORPHOLOGY SUMMARY			
None			

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

APPENDIX D

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE IN THE TWO-YEAR GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{12}, 60%, Chlorine)

TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{12}, 60% 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)
Mineralization		1 (2%)	
Ulcer, NOS	1 (2%)	2 (4%)	1 (2%)
Inflammation, chronic		3 (6%)	6 (12%)
Acanthosis			1 (2%)
*Subcutaneous tissue	(50)	(50)	(50)
Inflammation, focal	2 (4%)	2 (4%)	1 (2%)
RESPIRATORY SYSTEM			
*Nasal cavity	(50)	(50)	(50)
Inflammation, suppurative	6 (12%)	6 (12%)	6 (12%)
Reaction, foreign body	4 (8%)	7 (14%)	7 (14%)
Infection, fungal	1 (2%)	2 (4%)	
*Nasal mucosa	(50)	(50)	(50)
Inflammation, focal			1 (2%)
#Lung/bronchus	(50)	(50)	(50)
Hyperplasia, epithelial	1 (2%)		
#Lung/bronchiole	(50)	(50)	(50)
Inflammation, suppurative	1 (2%)		
#Lung	(50)	(50)	(50)
Aspiration, foreign body	1 (2%)		
Congestion, NOS	4 (8%)	4 (8%)	5 (10%)
Inflammation, chronic focal		1 (2%)	
Hyperplasia, alveolar epithelium			1 (2%)
#Lung/alveoli	(50)	(50)	(50)
Histiocytosis	1 (2%)	1 (2%)	1 (2%)
HEMATOPOIETIC SYSTEM			
#Bone marrow	(50)	(49)	(50)
Hyperplasia, granulocytic			1 (2%)
#Spleen	(50)	(49)	(50)
Congestion, NOS			1 (2%)
Amyloidosis			1 (2%)
Hyperplasia, lymphoid	2 (4%)	1 (2%)	3 (6%)
Hematopoiesis	10 (20%)	11 (22%)	10 (20%)
#Splenic red pulp	(50)	(49)	(50)
Atrophy, NOS		1 (2%)	
#Mandibular lymph node	(49)	(49)	(50)
Hyperplasia, NOS		1 (2%)	1 (2%)
Hyperplasia, lymphoid	2 (4%)	1 (2%)	1 (2%)
#Bronchial lymph node	(49)	(49)	(50)
Hyperplasia, lymphoid		1 (2%)	
#Mediastinal lymph node	(49)	(49)	(50)
Hyperplasia, lymphoid		1 (2%)	
#Mesenteric lymph node	(49)	(49)	(50)
Depletion, lymphoid			1 (2%)
Hyperplasia, NOS			1 (2%)
Angiectasis	10 (20%)	15 (31%)	5 (10%)
Hyperplasia, lymphoid		2 (4%)	
#Iliac lymph node	(49)	(49)	(50)
Abscess, NOS			1 (2%)
Hyperplasia, NOS			1 (2%)
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_{12}, 60% Cl) (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
HEMATOPOIETIC SYSTEM (Continued)			
#Inguinal lymph node	(49)	(49)	(50)
Pigmentation, NOS		1 (2%)	
Hyperplasia, NOS	1 (2%)	1 (2%)	
#Lung	(50)	(50)	(50)
Leukocytosis, NOS			1 (2%)
Hyperplasia, lymphoid	1 (2%)	1 (2%)	
#Liver	(50)	(50)	(50)
Leukocytosis, NOS		1 (2%)	
#Peyers patch	(50)	(50)	(48)
Hyperplasia, lymphoid	1 (2%)	1 (2%)	1 (2%)
#Kidney	(50)	(50)	(50)
Hyperplasia, lymphoid	1 (2%)	2 (4%)	
#Urinary bladder	(50)	(50)	(49)
Hyperplasia, lymphoid			1 (2%)
*Epididymis	(50)	(50)	(50)
Hyperplasia, lymphoid			1 (2%)
#Thymus	(39)	(37)	(37)
Embryonal duct cyst	1 (3%)		
Hyperplasia, epithelial	1 (3%)		1 (3%)
Hyperplasia, lymphoid		1 (3%)	
CIRCULATORY SYSTEM			
*Mediastinum	(50)	(50)	(50)
Periarteritis	1 (2%)		
#Spleen	(50)	(49)	(50)
Thrombosis, NOS		1 (2%)	
#Heart	(50)	(50)	(50)
Fibrosis		1 (2%)	1 (2%)
#Heart/atrium	(50)	(50)	(50)
Thrombosis, NOS			1 (2%)
*Aorta	(50)	(50)	(50)
Metaplasia, cartilaginous		1 (2%)	
#Liver	(50)	(50)	(50)
Thrombosis, NOS	2 (4%)	1 (2%)	3 (6%)
*Mesentery	(50)	(50)	(50)
Periarteritis	1 (2%)		
DIGESTIVE SYSTEM			
*Root of tooth	(50)	(50)	(50)
Inflammation, suppurative	1 (2%)	2 (4%)	2 (4%)
Necrosis, focal	1 (2%)		
Dysplasia, NOS	13 (26%)	2 (4%)	7 (14%)
#Salivary gland	(50)	(50)	(49)
Atrophy, NOS	1 (2%)		
#Liver	(50)	(50)	(50)
Cyst, NOS		1 (2%)	
Inflammation, focal	1 (2%)		
Necrosis, focal	2 (4%)	2 (4%)	2 (4%)
Necrosis, central			1 (2%)
Infarct, NOS	2 (4%)	4 (8%)	4 (8%)
Pigmentation, NOS		2 (4%)	2 (4%)
Nuclear alteration		1 (2%)	
Cytoplasmic vacuolization	2 (4%)		3 (6%)
Hepatocytomegaly		1 (2%)	3 (6%)
Atrophy, focal			1 (2%)
Angiectasis			2 (4%)
Histiocytosis			2 (4%)

TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM (Continued)			
#Liver/centrilobular	(50)	(50)	(50)
Metamorphosis, fatty	2 (4%)		
#Liver/hepatocytes	(50)	(50)	(50)
Depletion, glycogen			1 (2%)
*Gallbladder	(50)	(50)	(50)
Hyperplasia, epithelial		1 (2%)	
#Pancreas	(49)	(50)	(49)
Cystic ducts			1 (2%)
Atrophy, focal	1 (2%)	4 (8%)	
#Gastric cardiac gland	(50)	(50)	(50)
Dilatation, NOS	1 (2%)		
#Gastric fundal gland	(50)	(50)	(50)
Dilatation, NOS			1 (2%)
Hyperplasia, cystic			2 (4%)
#Glandular stomach	(50)	(50)	(50)
Erosion		1 (2%)	
#Forestomach	(50)	(50)	(50)
Ulcer, NOS	1 (2%)	1 (2%)	1 (2%)
Inflammation, focal	2 (4%)	5 (10%)	4 (8%)
Erosion			1 (2%)
Hyperplasia, epithelial	8 (16%)	7 (14%)	9 (18%)
Hyperkeratosis	1 (2%)		
#Small intestine	(50)	(50)	(48)
Amyloidosis			1 (2%)
#Jejunum	(50)	(50)	(48)
Intussusception	1 (2%)		
Inflammation, pyogranulomatous	1 (2%)		
URINARY SYSTEM			
#Kidney	(50)	(50)	(50)
Mineralization	1 (2%)	3 (6%)	
Hydronephrosis			1 (2%)
Nephrosis, NOS	40 (80%)	27 (54%)	26 (52%)
Atrophy, focal			1 (2%)
Metaplasia, osseous		1 (2%)	
#Kidney/cortex	(50)	(50)	(50)
Cyst, NOS			1 (2%)
#Kidney/tubule	(50)	(50)	(50)
Degeneration, hyaline	1 (2%)		
#Kidney/pelvis	(50)	(50)	(50)
Dilatation, NOS	1 (2%)		
#Urinary bladder	(50)	(50)	(49)
Congestion, NOS	1 (2%)		
#Urinary bladder/mucosa	(50)	(50)	(49)
Inflammation, NOS	1 (2%)		
ENDOCRINE SYSTEM			
#Anterior pituitary	(45)	(47)	(47)
Embryonal duct cyst	1 (2%)		
Hyperplasia, focal		1 (2%)	
#Adrenal/capsule	(50)	(48)	(49)
Hyperplasia, focal	6 (12%)	1 (2%)	2 (4%)
Hyperplasia, diffuse	1 (2%)		
#Adrenal cortex	(50)	(48)	(49)
Cytoplasmic vacuolization		1 (2%)	1 (2%)
Eosinophilic cyto change		1 (2%)	

TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM (Continued)			
#Adrenal medulla	(50)	(48)	(49)
Hyperplasia, focal	1 (2%)	1 (2%)	1 (2%)
#Thyroid	(49)	(50)	(49)
Cystic follicles	2 (4%)		1 (2%)
Inflammation, focal			1 (2%)
Degeneration, cystic	4 (8%)	5 (10%)	
Hyperplasia, follicular cell	5 (10%)	6 (12%)	12 (24%)
#Thyroid follicle	(49)	(50)	(49)
Crystals, NOS		1 (2%)	
#Pancreatic islets	(49)	(50)	(49)
Hyperplasia, NOS	1 (2%)		
REPRODUCTIVE SYSTEM			
*Preputial gland	(50)	(50)	(50)
Inflammation, suppurative	4 (8%)	7 (14%)	
Degeneration, cystic	7 (14%)	5 (10%)	5 (10%)
#Prostate	(48)	(49)	(50)
Inflammation, suppurative		1 (2%)	
*Seminal vesicle	(50)	(50)	(50)
Dilatation, NOS	4 (8%)		
Inflammation, chronic	1 (2%)		
Fibrosis		1 (2%)	
Atrophy, focal	1 (2%)		
*Coagulating gland	(50)	(50)	(50)
Dilatation, NOS			1 (2%)
#Testis	(50)	(49)	(50)
Mineralization		1 (2%)	
Atrophy, NOS	2 (4%)	1 (2%)	1 (2%)
*Epididymis	(50)	(50)	(50)
Dilatation, NOS			1 (2%)
Inflammation, chronic		1 (2%)	
*Spermatic cord	(50)	(50)	(50)
Necrosis, fat			2 (4%)
NERVOUS SYSTEM			
#Brain/thalamus	(50)	(50)	(50)
Psammoma bodies	33 (66%)	20 (40%)	21 (42%)
SPECIAL SENSE ORGANS			
*Nasolacrimal duct	(50)	(50)	(50)
Inflammation, NOS	2 (4%)	1 (2%)	3 (6%)
Hyperplasia, NOS		2 (4%)	
MUSCULOSKELETAL SYSTEM			
None			

TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
BODY CAVITIES			
*Mediastinum	(50)	(50)	(50)
Foreign body, NOS	1 (2%)		
Inflammation, acute	1 (2%)		
*Peritoneum	(50)	(50)	(50)
Hemorrhage		1 (2%)	
Inflammation, NOS			1 (2%)
*Mesentery	(50)	(50)	(50)
Steatitis			1 (2%)
Necrosis, fat			1 (2%)
Angiectasis	1 (2%)		
*Tunica vaginalis	(50)	(50)	(50)
Inflammation, chronic		1 (2%)	
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Inflammation, suppurative		1 (2%)	
Amyloidosis	1 (2%)	1 (2%)	
SPECIAL MORPHOLOGY SUMMARY			
No lesion reported			1

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

TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{12}, 60% 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)
Ulcer, NOS			1 (2%)
Inflammation, focal	1 (2%)		3 (6%)
*Subcutaneous tissue	(50)	(50)	(50)
Congestion, NOS			1 (2%)
Edema, NOS	1 (2%)		
Inflammation, chronic	1 (2%)		1 (2%)
RESPIRATORY SYSTEM			
*Nasal cavity	(50)	(50)	(50)
Inflammation, suppurative	14 (28%)	12 (24%)	14 (28%)
Reaction, foreign body	18 (36%)	12 (24%)	14 (28%)
*Nasal mucosa	(50)	(50)	(50)
Inflammation, focal	1 (2%)		
#Lung	(50)	(49)	(50)
Aspiration, foreign body			3 (6%)
Congestion, NOS	3 (6%)	4 (8%)	1 (2%)
Pigmentation, NOS	1 (2%)		
Hyperplasia, alveolar epithelium			1 (2%)
#Lung/alveoli	(50)	(49)	(50)
Histiocytosis	1 (2%)	1 (2%)	
HEMATOPOIETIC SYSTEM			
#Brain	(50)	(50)	(49)
Leukocytosis, NOS	1 (2%)		
*Multiple organs	(50)	(50)	(50)
Hyperplasia, lymphoid			2 (4%)
*Mediastinum	(50)	(50)	(50)
Hyperplasia, lymphoid			1 (2%)
#Bone marrow	(50)	(49)	(50)
Hyperplasia, granulocytic		1 (2%)	1 (2%)
#Spleen	(50)	(50)	(50)
Hemorrhage	1 (2%)		
Hyperplasia, lymphoid	3 (6%)	3 (6%)	3 (6%)
Hematopoiesis	15 (30%)	20 (40%)	17 (34%)
#Lymph node	(50)	(49)	(49)
Hyperplasia, NOS	1 (2%)		
#Mandibular lymph node	(50)	(49)	(49)
Hyperplasia, NOS	1 (2%)		
Angiectasis			1 (2%)
Hyperplasia, lymphoid			1 (2%)
#Bronchial lymph node	(50)	(49)	(49)
Hyperplasia, NOS	1 (2%)		
#Mediastinal lymph node	(50)	(49)	(49)
Hyperplasia, NOS	2 (4%)		
#Mesenteric lymph node	(50)	(49)	(49)
Hyperplasia, NOS	1 (2%)	2 (4%)	
Angiectasis	4 (8%)	2 (4%)	2 (4%)
Hyperplasia, lymphoid	3 (6%)		1 (2%)
#Renal lymph node	(50)	(49)	(49)
Hyperplasia, NOS	4 (8%)	1 (2%)	1 (2%)
Angiectasis	1 (2%)		
Hyperplasia, lymphoid		1 (2%)	

TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
HEMATOPOIETIC SYSTEM (Continued)			
#Iliac lymph node	(50)	(49)	(49)
Hyperplasia, NOS	2 (4%)	2 (4%)	2 (4%)
Angiectasis	1 (2%)		
Hyperplasia, lymphoid		1 (2%)	
#Inguinal lymph node	(50)	(49)	(49)
Hyperplasia, NOS			1 (2%)
#Lung	(50)	(49)	(50)
Leukocytosis, NOS	4 (8%)	1 (2%)	1 (2%)
Hyperplasia, lymphoid	3 (6%)	1 (2%)	
#Liver	(50)	(50)	(50)
Leukocytosis, NOS	4 (8%)	1 (2%)	1 (2%)
Hyperplasia, lymphoid	1 (2%)		4 (8%)
Hematopoiesis	2 (4%)	5 (10%)	5 (10%)
#Kidney	(50)	(50)	(50)
Hyperplasia, lymphoid	4 (8%)	5 (10%)	4 (8%)
#Urinary bladder	(50)	(49)	(50)
Hyperplasia, lymphoid		1 (2%)	
#Adrenal cortex	(50)	(49)	(50)
Hematopoiesis		1 (2%)	
#Thymus	(42)	(34)	(38)
Hyperplasia, lymphoid	1 (2%)		
CIRCULATORY SYSTEM			
*Subcutaneous tissue	(50)	(50)	(50)
Periarteritis		1 (2%)	
#Spleen	(50)	(50)	(50)
Thrombosis, NOS			1 (2%)
#Lung	(50)	(49)	(50)
Thrombosis, NOS	1 (2%)		
Periarteritis	1 (2%)		
#Heart	(50)	(49)	(50)
Endocarditis, bacterial			1 (2%)
Inflammation, focal	2 (4%)		1 (2%)
Periarteritis			1 (2%)
#Heart/atrium	(50)	(49)	(50)
Thrombosis, NOS	2 (4%)		
*Mesentery	(50)	(50)	(50)
Periarteritis			1 (2%)
#Adrenal	(50)	(49)	(50)
Thrombosis, NOS			2 (4%)
DIGESTIVE SYSTEM			
*Root of tooth	(50)	(50)	(50)
Inflammation, suppurative	1 (2%)	1 (2%)	
Dysplasia, NOS	1 (2%)	1 (2%)	1 (2%)
#Salivary gland capsule	(49)	(48)	(47)
Fibrosis			1 (2%)
#Liver	(50)	(50)	(50)
Mineralization		2 (4%)	
Deformity, NOS	1 (2%)		1 (2%)
Cyst, NOS			2 (4%)
Hemorrhage	1 (2%)		
Inflammation, focal	2 (4%)		2 (4%)
Fibrosis	1 (2%)	2 (4%)	
Fibrosis, focal			1 (2%)
Necrosis, focal	5 (10%)	3 (6%)	2 (4%)
Necrosis, central	1 (2%)		2 (4%)
Infarct, NOS	1 (2%)	4 (8%)	2 (4%)

TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
#Liver (Continued)	(50)	(50)	(50)
Pigmentation, NOS	1 (2%)		1 (2%)
Fibrosiderotic nodule	1 (2%)		
Cytoplasmic vacuolization			2 (4%)
Basophilic cyto change			1 (2%)
Angiectasis		2 (4%)	1 (2%)
#Liver/centrilobular	(50)	(50)	(50)
Degeneration, NOS			1 (2%)
Metamorphosis, fatty	1 (2%)		
#Liver/hepatocytes	(50)	(50)	(50)
Eosinophilic cyto change			1 (2%)
*Gallbladder	(50)	(50)	(50)
Hyperplasia, epithelial			1 (2%)
#Pancreas	(50)	(50)	(50)
Cystic ducts	1 (2%)	1 (2%)	
Edema, NOS			1 (2%)
Inflammation, chronic	1 (2%)	1 (2%)	
Necrosis, NOS		1 (2%)	
Infarct, NOS		1 (2%)	
Atrophy, focal		2 (4%)	
#Gastric fundal gland	(50)	(50)	(50)
Mineralization	1 (2%)		
#Forestomach	(50)	(50)	(50)
Epidermal inclusion cyst	1 (2%)		
Ulcer, NOS		1 (2%)	2 (4%)
Inflammation, focal	5 (10%)	6 (12%)	2 (4%)
Abscess, NOS	1 (2%)		
Hyperplasia, epithelial	8 (16%)	9 (18%)	10 (20%)
#Jejunal mucosa	(50)	(48)	(49)
Hyperplasia, epithelial		1 (2%)	
Hyperplasia, adenomatous	1 (2%)		
#Ileal mucosa	(50)	(48)	(49)
Amyloidosis			1 (2%)
*Rectal crypt of Lieberkuhn	(50)	(50)	(50)
Dilatation, NOS			1 (2%)
URINARY SYSTEM			
#Kidney	(50)	(50)	(50)
Mineralization	1 (2%)		
Congestion, NOS	1 (2%)	1 (2%)	1 (2%)
Glomerulonephritis, acute			1 (2%)
Nephrosis, NOS	4 (8%)	5 (10%)	12 (24%)
Atrophy, focal	2 (4%)		
#Kidney/glomerulus	(50)	(50)	(50)
Amyloidosis			1 (2%)
#Kidney/pelvis	(50)	(50)	(50)
Dilatation, NOS	1 (2%)		
#Urinary bladder	(50)	(49)	(50)
Inflammation, chronic	1 (2%)		
ENDOCRINE SYSTEM			
#Anterior pituitary	(49)	(47)	(46)
Hyperplasia, focal	6 (12%)	5 (11%)	4 (9%)
Angiectasis		3 (6%)	3 (7%)
#Adrenal	(50)	(49)	(50)
Angiectasis	1 (2%)		1 (2%)
#Adrenal/capsule	(50)	(49)	(50)
Hyperplasia, focal	1 (2%)		2 (4%)

TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM (Continued)			
#Adrenal cortex	(50)	(49)	(50)
Accessory structure			1 (2%)
Cytoplasmic vacuolization	2 (4%)	2 (4%)	1 (2%)
#Adrenal medulla	(50)	(49)	(50)
Hyperplasia, focal	1 (2%)	1 (2%)	2 (4%)
#Thyroid	(50)	(49)	(49)
Cystic follicles	1 (2%)		
Degeneration, cystic	2 (4%)	6 (12%)	5 (10%)
Hyperplasia, follicular-cell	16 (32%)	27 (55%)	22 (45%)
#Thyroid follicle	(50)	(49)	(49)
Crystals, NOS		1 (2%)	
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Cystic ducts	10 (20%)	8 (16%)	4 (8%)
Fibrosis	1 (2%)		
Hyperplasia, NOS			1 (2%)
*Vagina	(50)	(50)	(50)
Mineralization	1 (2%)		
Inflammation, suppurative	1 (2%)		
Hyperplasia, epithelial	1 (2%)	1 (2%)	
#Uterus	(50)	(50)	(50)
Hematometra	1 (2%)	1 (2%)	
Inflammation, suppurative	7 (14%)	9 (18%)	8 (16%)
Angiectasis	1 (2%)	1 (2%)	1 (2%)
#Cervix uteri	(50)	(50)	(50)
Hyperplasia, epithelial			1 (2%)
#Uterus/endometrium	(50)	(50)	(50)
Hemorrhage		1 (2%)	
Hyperplasia, cystic	45 (90%)	42 (84%)	42 (84%)
#Ovary/parovarian	(49)	(41)	(45)
Lipogranuloma	1 (2%)		
#Ovary	(49)	(41)	(45)
Follicular cyst, NOS	13 (27%)	14 (34%)	20 (44%)
Parovarian cyst			1 (2%)
Hemorrhage, chronic	2 (4%)		
Inflammation, suppurative		2 (5%)	2 (4%)
Hemosiderosis	1 (2%)		
NERVOUS SYSTEM			
#Brain	(50)	(50)	(49)
Hemorrhage	1 (2%)		
Necrosis, focal	1 (2%)		
#Cerebral basal surfa	(50)	(50)	(49)
Displacement, NOS		1 (2%)	
#Brain/thalamus	(50)	(50)	(49)
Psammoma bodies	26 (52%)	19 (38%)	23 (47%)
SPECIAL SENSE ORGANS			
*Eye/cornea	(50)	(50)	(50)
Inflammation, chronic		1 (2%)	
*Nasolacrimal duct	(50)	(50)	(50)
Inflammation, NOS	1 (2%)	1 (2%)	3 (6%)
*Harderian gland	(50)	(50)	(50)
Inflammation, suppurative		1 (2%)	

TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
MUSCULOSKELETAL SYSTEM			
*Skull	(50)	(50)	(50)
Exostosis			1 (2%)
*Tibia	(50)	(50)	(50)
Fracture, NOS		1 (2%)	
BODY CAVITIES			
*Mediastinum	(50)	(50)	(50)
Foreign body, NOS		2 (4%)	1 (2%)
Inflammation, acute	1 (2%)	3 (6%)	2 (4%)
Reaction, foreign body	2 (4%)	1 (2%)	
*Peritoneum	(50)	(50)	(50)
Inflammation, NOS	1 (2%)	4 (8%)	2 (4%)
*Mesentery	(50)	(50)	(50)
Fibrosis, multifocal	1 (2%)		
Necrosis, fat	2 (4%)	2 (4%)	
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Inflammation, suppurative	6 (12%)	4 (8%)	2 (4%)
Periorbital region			
Inflammation, suppurative	1		
Broad ligament			
Inflammation, suppurative		1	
Angiectasis		1	
SPECIAL MORPHOLOGY SUMMARY			
None			

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_{12}, 60% Chlorine)

TABLE E1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{12}, 60% Cl)

	Vehicle Control	312 mg/kg	625 mg/kg
Skin: Squamous Cell Papilloma			
Overall Rates (a)	2/50 (4%)	3/50 (6%)	2/50 (4%)
Adjusted Rates (b)	7.4%	24.7%	14.4%
Terminal Rates (c)	2/27 (7%)	0/6 (0%)	0/3 (0%)
Week of First Observation	105	93	81
Life Table Tests (d)	P=0.092	P=0.097	P=0.223
Incidental Tumor Tests (d)	P=0.541	P=0.543	P=0.464
Cochran-Armitage Trend Test (d)	P=0.594N		
Fisher Exact Test (d)		P=0.500	P=0.691
Skin: Squamous Cell Papilloma or Carcinoma			
Overall Rates (a)	3/50 (6%)	5/50 (10%)	2/50 (4%)
Adjusted Rates (b)	11.1%	29.4%	14.4%
Terminal Rates (c)	3/27 (11%)	0/6 (0%)	0/3 (0%)
Week of First Observation	105	74	81
Life Table Tests (d)	P=0.153	P=0.042	P=0.276
Incidental Tumor Tests (d)	P=0.539N	P=0.304	P=0.514
Cochran-Armitage Trend Test (d)	P=0.420N		
Fisher Exact Test (d)		P=0.357	P=0.500N
Skin: Keratoacanthoma			
Overall Rates (a)	3/50 (6%)	2/50 (4%)	1/50 (2%)
Adjusted Rates (b)	11.1%	16.4%	33.3%
Terminal Rates (c)	3/27 (11%)	0/6 (0%)	1/3 (33%)
Week of First Observation	105	89	105
Life Table Tests (d)	P=0.300	P=0.393	P=0.430
Incidental Tumor Tests (d)	P=0.589	P=0.699N	P=0.430
Cochran-Armitage Trend Test (d)	P=0.222N		
Fisher Exact Test (d)		P=0.500N	P=0.309N
Subcutaneous Tissue: Fibroma			
Overall Rates (a)	3/50 (6%)	4/50 (8%)	1/50 (2%)
Adjusted Rates (b)	11.1%	25.3%	5.0%
Terminal Rates (c)	3/27 (11%)	1/6 (17%)	0/3 (0%)
Week of First Observation	105	92	96
Life Table Tests (d)	P=0.351	P=0.094	P=0.593
Incidental Tumor Tests (d)	P=0.531N	P=0.303	P=0.759N
Cochran-Armitage Trend Test (d)	P=0.252N		
Fisher Exact Test (d)		P=0.500	P=0.309N
Subcutaneous Tissue: Sarcoma or Fibrosarcoma			
Overall Rates (a)	3/50 (6%)	1/50 (2%)	(e) 1/50 (2%)
Adjusted Rates (b)	9.7%	9.1%	9.1%
Terminal Rates (c)	2/27 (7%)	0/6 (0%)	0/3 (0%)
Week of First Observation	90	102	99
Life Table Tests (d)	P=0.549	P=0.672N	P=0.689
Incidental Tumor Tests (d)	P=0.265N	P=0.332N	P=0.416N
Cochran-Armitage Trend Test (d)	P=0.202N		
Fisher Exact Test (d)		P=0.309N	P=0.309N
Subcutaneous Tissue: Fibroma, Sarcoma, or Fibrosarcoma			
Overall Rates (a)	6/50 (12%)	5/50 (10%)	2/50 (4%)
Adjusted Rates (b)	20.6%	32.1%	13.6%
Terminal Rates (c)	5/27 (19%)	1/6 (17%)	0/3 (0%)
Week of First Observation	90	92	96
Life Table Tests (d)	P=0.334	P=0.163	P=0.519
Incidental Tumor Tests (d)	P=0.286N	P=0.598N	P=0.424N
Cochran-Armitage Trend Test (d)	P=0.107N		
Fisher Exact Test (d)		P=0.500N	P=0.134N

TABLE E1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) (Continued)

	Vehicle Control	312 mg/kg	625 mg/kg
Integumentary System: Fibroma			
Overall Rates (a)	3/50 (6%)	5/50 (10%)	1/50 (2%)
Adjusted Rates (b)	11.1%	40.2%	5.0%
Terminal Rates (c)	3/27 (11%)	2/6 (33%)	0/3 (0%)
Week of First Observation	105	92	96
Life Table Tests (d)	P=0.246	P=0.025	P=0.593
Incidental Tumor Tests (d)	P=0.541	P=0.108	P=0.759N
Cochran-Armitage Trend Test (d)	P=0.263N		
Fisher Exact Test (d)		P=0.357	P=0.309N
Integumentary System: Fibroma, Sarcoma, or Fibrosarcoma			
Overall Rates (a)	6/50 (12%)	6/50 (12%)	2/50 (4%)
Adjusted Rates (b)	20.6%	45.7%	13.6%
Terminal Rates (c)	5/27 (19%)	2/6 (33%)	0/3 (0%)
Week of First Observation	90	92	96
Life Table Tests (d)	P=0.248	P=0.063	P=0.519
Incidental Tumor Tests (d)	P=0.394N	P=0.351	P=0.424N
Cochran-Armitage Trend Test (d)	P=0.114N		
Fisher Exact Test (d)		P=0.620	P=0.134N
Hematopoietic System: Mononuclear Cell Leukemia			
Overall Rates (a)	7/50 (14%)	12/50 (24%)	14/50 (28%)
Adjusted Rates (b)	19.2%	52.6%	51.5%
Terminal Rates (c)	3/27 (11%)	2/6 (33%)	0/3 (0%)
Week of First Observation	61	74	78
Life Table Tests (d)	P=0.001	P=0.021	P=0.003
Incidental Tumor Tests (d)	P=0.102	P=0.121	P=0.208
Cochran-Armitage Trend Test (d)	P=0.058		
Fisher Exact Test (d)		P=0.154	P=0.070
Oral Cavity: Squamous Cell Papilloma			
Overall Rates (a)	3/50 (6%)	2/50 (4%)	0/50 (0%)
Adjusted Rates (b)	9.1%	10.1%	0.0%
Terminal Rates (c)	1/27 (4%)	0/6 (0%)	0/3 (0%)
Week of First Observation	81	95	
Life Table Tests (d)	P=0.346N	P=0.582	P=0.351N
Incidental Tumor Tests (d)	P=0.053N	P=0.381N	P=0.129N
Cochran-Armitage Trend Test (d)	P=0.082N		
Fisher Exact Test (d)		P=0.500N	P=0.121N
Liver: Neoplastic Nodule			
Overall Rates (a)	0/50 (0%)	10/50 (20%)	16/48 (33%)
Adjusted Rates (b)	0.0%	56.6%	86.4%
Terminal Rates (c)	0/27 (0%)	2/6 (33%)	2/3 (67%)
Week of First Observation		90	78
Life Table Tests (d)	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests (d)	P<0.001	P=0.006	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P<0.001	P<0.001
Liver: Hepatocellular Carcinoma			
Overall Rates (a)	0/50 (0%)	3/50 (6%)	2/48 (4%)
Adjusted Rates (b)	0.0%	39.4%	17.9%
Terminal Rates (c)	0/27 (0%)	2/6 (33%)	0/3 (0%)
Week of First Observation		102	94
Life Table Tests (d)	P=0.005	P=0.004	P=0.066
Incidental Tumor Tests (d)	P=0.082	P=0.022	P=0.473
Cochran-Armitage Trend Test (d)	P=0.191		
Fisher Exact Test (d)		P=0.121	P=0.237

TABLE E1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) (Continued)

	Vehicle Control	312 mg/kg	625 mg/kg
Liver: Neoplastic Nodule or Hepatocellular Carcinoma			
Overall Rates (a)	0/50 (0%)	13/50 (26%)	16/48 (33%)
Adjusted Rates (b)	0.0%	80.5%	86.4%
Terminal Rates (c)	0/27 (0%)	4/6 (67%)	2/3 (67%)
Week of First Observation		90	78
Life Table Tests (d)	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests (d)	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P<0.001	P<0.001
Pancreas: Acinar Cell Adenoma			
Overall Rates (a)	11/50 (22%)	22/50 (44%)	15/49 (31%)
Adjusted Rates (b)	36.5%	80.2%	77.0%
Terminal Rates (c)	8/27 (30%)	3/6 (50%)	1/3 (33%)
Week of First Observation	101	87	88
Life Table Tests (d)	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests (d)	P=0.268	P=0.049	P=0.236
Cochran-Armitage Trend Test (d)	P=0.206		
Fisher Exact Test (d)		P=0.016	P=0.228
Pancreas: Acinar Cell Adenoma or Carcinoma			
Overall Rates (a)	(f) 11/50 (22%)	22/50 (44%)	17/49 (35%)
Adjusted Rates (b)	36.5%	80.2%	78.1%
Terminal Rates (c)	8/27 (30%)	3/6 (50%)	1/3 (33%)
Week of First Observation	101	87	85
Life Table Tests (d)	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests (d)	P=0.142	P=0.049	P=0.128
Cochran-Armitage Trend Test (d)	P=0.107		
Fisher Exact Test (d)		P=0.016	P=0.119
Kidney: Tubular Cell Adenoma			
Overall Rates (a)	0/50 (0%)	7/50 (14%)	3/49 (6%)
Adjusted Rates (b)	0.0%	52.3%	10.5%
Terminal Rates (c)	0/27 (0%)	2/6 (33%)	0/3 (0%)
Week of First Observation		93	82
Life Table Tests (d)	P=0.007	P<0.001	P=0.080
Incidental Tumor Tests (d)	P=0.170	P=0.013	P=0.238
Cochran-Armitage Trend Test (d)	P=0.152		
Fisher Exact Test (d)		P=0.006	P=0.117
Kidney: Tubular Cell Adenoma or Adenocarcinoma			
Overall Rates (a)	0/50 (0%)	9/50 (18%)	3/49 (6%)
Adjusted Rates (b)	0.0%	54.8%	10.5%
Terminal Rates (c)	0/27 (0%)	2/6 (33%)	0/3 (0%)
Week of First Observation		87	82
Life Table Tests (d)	P=0.012	P<0.001	P=0.080
Incidental Tumor Tests (d)	P=0.253	P=0.008	P=0.238
Cochran-Armitage Trend Test (d)	P=0.171		
Fisher Exact Test (d)		P=0.001	P=0.117
Pituitary Gland: Adenoma			
Overall Rates (a)	16/50 (32%)	10/48 (21%)	5/49 (10%)
Adjusted Rates (b)	48.6%	75.3%	45.7%
Terminal Rates (c)	11/27 (41%)	4/6 (67%)	1/3 (33%)
Week of First Observation	70	89	85
Life Table Tests (d)	P=0.216	P=0.104	P=0.472
Incidental Tumor Tests (d)	P=0.197N	P=0.600N	P=0.167N
Cochran-Armitage Trend Test (d)	P=0.006N		
Fisher Exact Test (d)		P=0.153N	P=0.007N

TABLE E1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) (Continued)

	Vehicle Control	312 mg/kg	625 mg/kg
Adrenal Gland: Pheochromocytoma			
Overall Rates (a)	14/50 (28%)	15/50 (30%)	15/49 (31%)
Adjusted Rates (b)	44.1%	67.7%	85.3%
Terminal Rates (c)	10/27 (37%)	2/6 (33%)	2/3 (67%)
Week of First Observation	94	74	85
Life Table Tests (d)	P<0.001	P=0.005	P<0.001
Incidental Tumor Tests (d)	P=0.233	P=0.495	P=0.254
Cochran-Armitage Trend Test (d)	P=0.431		
Fisher Exact Test (d)		P=0.500	P=0.474
Adrenal Gland: Pheochromocytoma or Pheochromocytoma, Malignant			
Overall Rates (a)	15/50 (30%)	15/50 (30%)	15/49 (31%)
Adjusted Rates (b)	47.4%	67.7%	85.3%
Terminal Rates (c)	11/27 (41%)	2/6 (33%)	2/3 (67%)
Week of First Observation	94	74	85
Life Table Tests (d)	P<0.001	P=0.006	P<0.001
Incidental Tumor Tests (d)	P=0.262	P=0.534	P=0.273
Cochran-Armitage Trend Test (d)	P=0.517		
Fisher Exact Test (d)		P=0.586N	P=0.560
Thyroid: Follicular Cell Adenoma or Carcinoma			
Overall Rates (a)	3/50 (6%)	3/50 (6%)	3/50 (6%)
Adjusted Rates (b)	9.2%	19.8%	8.2%
Terminal Rates (c)	1/27 (4%)	0/6 (0%)	0/3 (0%)
Week of First Observation	90	95	85
Life Table Tests (d)	P=0.195	P=0.318	P=0.355
Incidental Tumor Tests (d)	P=0.383N	P=0.344N	P=0.494N
Cochran-Armitage Trend Test (d)	P=0.584		
Fisher Exact Test (d)		P=0.661	P=0.661
Thyroid: C-Cell Adenoma			
Overall Rates (a)	8/50 (16%)	8/50 (16%)	2/50 (4%)
Adjusted Rates (b)	26.7%	57.7%	12.2%
Terminal Rates (c)	6/27 (22%)	3/6 (50%)	0/3 (0%)
Week of First Observation	90	87	91
Life Table Tests (d)	P=0.334	P=0.045	P=0.624
Incidental Tumor Tests (d)	P=0.243N	P=0.330	P=0.175N
Cochran-Armitage Trend Test (d)	P=0.045N		
Fisher Exact Test (d)		P=0.607	P=0.046N
Thyroid Gland: C-Cell Carcinoma			
Overall Rates (a)	2/50 (4%)	3/50 (6%)	2/50 (4%)
Adjusted Rates (b)	7.4%	15.1%	25.0%
Terminal Rates (c)	2/27 (7%)	0/6 (0%)	0/3 (0%)
Week of First Observation	105	92	100
Life Table Tests (d)	P=0.086	P=0.159	P=0.092
Incidental Tumor Tests (d)	P=0.600	P=0.543	P=0.584
Cochran-Armitage Trend Test (d)	P=0.594N		
Fisher Exact Test (d)		P=0.500	P=0.691
Thyroid Gland: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	10/50 (20%)	11/50 (22%)	4/50 (8%)
Adjusted Rates (b)	33.7%	64.1%	34.2%
Terminal Rates (c)	8/27 (30%)	3/6 (50%)	0/3 (0%)
Week of First Observation	90	87	91
Life Table Tests (d)	P=0.100	P=0.011	P=0.204
Incidental Tumor Tests (d)	P=0.279N	P=0.261	P=0.297N
Cochran-Armitage Trend Test (d)	P=0.070N		
Fisher Exact Test (d)		P=0.500	P=0.074N

TABLE E1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) (Continued)

	Vehicle Control	312 mg/kg	625 mg/kg
Mammary Gland: Fibroadenoma			
Overall Rates (a)	2/50 (4%)	4/50 (8%)	2/50 (4%)
Adjusted Rates (b)	6.7%	52.2%	24.7%
Terminal Rates (c)	1/27 (4%)	3/6 (50%)	0/3 (0%)
Week of First Observation	101	96	97
Life Table Tests (d)	P=0.031	P=0.020	P=0.162
Incidental Tumor Tests (d)	P=0.266	P=0.090	P=0.603N
Cochran-Armitage Trend Test (d)	P=0.588N		
Fisher Exact Test (d)		P=0.339	P=0.691
Preputial Gland: Adenoma			
Overall Rates (a)	4/50 (8%)	3/50 (6%)	7/50 (14%)
Adjusted Rates (b)	13.7%	22.7%	52.3%
Terminal Rates (c)	3/27 (11%)	1/6 (17%)	1/3 (33%)
Week of First Observation	97	74	78
Life Table Tests (d)	P=0.003	P=0.327	P=0.006
Incidental Tumor Tests (d)	P=0.047	P=0.534	P=0.132
Cochran-Armitage Trend Test (d)	P=0.195		
Fisher Exact Test (d)		P=0.500N	P=0.262
Preputial Gland: Carcinoma			
Overall Rates (a)	5/50 (10%)	1/50 (2%)	2/50 (4%)
Adjusted Rates (b)	16.8%	4.8%	10.2%
Terminal Rates (c)	3/27 (11%)	0/6 (0%)	0/3 (0%)
Week of First Observation	101	98	94
Life Table Tests (d)	P=0.470	P=0.492N	P=0.434
Incidental Tumor Tests (d)	P=0.169N	P=0.096N	P=0.236N
Cochran-Armitage Trend Test (d)	P=0.133N		
Fisher Exact Test (d)		P=0.102N	P=0.218N
Preputial Gland: Adenoma or Carcinoma			
Overall Rates (a)	9/50 (18%)	4/50 (8%)	9/50 (18%)
Adjusted Rates (b)	29.2%	26.3%	57.3%
Terminal Rates (c)	6/27 (22%)	1/6 (17%)	1/3 (33%)
Week of First Observation	97	74	78
Life Table Tests (d)	P=0.008	P=0.505	P=0.007
Incidental Tumor Tests (d)	P=0.255	P=0.266N	P=0.440
Cochran-Armitage Trend Test (d)	P=0.556		
Fisher Exact Test (d)		P=0.117N	P=0.602
Testis: Interstitial Cell Tumor			
Overall Rates (a)	48/50 (96%)	49/49 (100%)	47/49 (96%)
Adjusted Rates (b)	98.0%	100.0%	100.0%
Terminal Rates (c)	26/27 (96%)	6/6 (100%)	3/3 (100%)
Week of First Observation	61	63	78
Life Table Tests (d)	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests (d)	P=0.230	P=0.463	P=0.450
Cochran-Armitage Trend Test (d)	P=0.615N		
Fisher Exact Test (d)		P=0.252	P=0.684N
All Sites: Mesothelioma			
Overall Rates (a)	4/50 (8%)	0/50 (0%)	0/50 (0%)
Adjusted Rates (b)	13.5%	0.0%	0.0%
Terminal Rates (c)	3/27 (11%)	0/6 (0%)	0/3 (0%)
Week of First Observation	95		
Life Table Tests (d)	P=0.163N	P=0.283N	P=0.414N
Incidental Tumor Tests (d)	P=0.082N	P=0.155N	P=0.215N
Cochran-Armitage Trend Test (d)	P=0.015N		
Fisher Exact Test (d)		P=0.059N	P=0.059N

TABLE E1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{12}, 60% 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) A neurofibrosarcoma also was observed in this animal.
(f) A carcinoma, NOS, was also observed in one of these animals.

TABLE E2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{12}, 60% Cl)

	Vehicle Control	312 mg/kg	625 mg/kg
Hematopoietic System: Mononuclear Cell Leukemia			
Overall Rates (a)	11/50 (22%)	22/50 (44%)	16/50 (32%)
Adjusted Rates (b)	25.3%	50.9%	41.7%
Terminal Rates (c)	4/34 (12%)	4/24 (17%)	7/29 (24%)
Week of First Observation	56	81	88
Life Table Tests (d)	P=0.098	P=0.006	P=0.104
Incidental Tumor Tests (d)	P=0.191	P=0.062	P=0.174
Cochran-Armitage Trend Test (d)	P=0.169		
Fisher Exact Test (d)		P=0.016	P=0.184
Liver: Neoplastic Nodule			
Overall Rates (a)	0/50 (0%)	4/50 (8%)	7/50 (14%)
Adjusted Rates (b)	0.0%	13.0%	21.7%
Terminal Rates (c)	0/34 (0%)	2/24 (8%)	5/29 (17%)
Week of First Observation		81	90
Life Table Tests (d)	P=0.004	P=0.038	P=0.005
Incidental Tumor Tests (d)	P=0.006	P=0.080	P=0.007
Cochran-Armitage Trend Test (d)	P=0.006		
Fisher Exact Test (d)		P=0.059	P=0.006
Liver: Neoplastic Nodule or Hepatocellular Carcinoma			
Overall Rates (a)	0/50 (0%)	5/50 (10%)	7/50 (14%)
Adjusted Rates (b)	0.0%	14.9%	21.7%
Terminal Rates (c)	0/34 (0%)	2/24 (8%)	5/29 (17%)
Week of First Observation		81	90
Life Table Tests (d)	P=0.006	P=0.020	P=0.005
Incidental Tumor Tests (d)	P=0.008	P=0.068	P=0.007
Cochran-Armitage Trend Test (d)	P=0.008		
Fisher Exact Test (d)		P=0.028	P=0.006
Pancreas: Acinar Cell Adenoma			
Overall Rates (a)	1/50 (2%)	5/48 (10%)	2/50 (4%)
Adjusted Rates (b)	2.9%	19.4%	6.9%
Terminal Rates (c)	1/34 (3%)	4/24 (17%)	2/29 (7%)
Week of First Observation	105	98	105
Life Table Tests (d)	P=0.338	P=0.043	P=0.444
Incidental Tumor Tests (d)	P=0.353	P=0.051	P=0.444
Cochran-Armitage Trend Test (d)	P=0.413		
Fisher Exact Test (d)		P=0.093	P=0.500
Pancreas: Acinar Cell Adenoma or Carcinoma			
Overall Rates (a)	1/50 (2%)	5/48 (10%)	3/50 (6%)
Adjusted Rates (b)	2.9%	19.4%	10.3%
Terminal Rates (c)	1/34 (3%)	4/24 (17%)	3/29 (10%)
Week of First Observation	105	98	105
Life Table Tests (d)	P=0.204	P=0.043	P=0.249
Incidental Tumor Tests (d)	P=0.214	P=0.051	P=0.249
Cochran-Armitage Trend Test (d)	P=0.266		
Fisher Exact Test (d)		P=0.093	P=0.309
Pituitary: Adenoma			
Overall Rates (a)	27/49 (55%)	19/49 (39%)	26/49 (53%)
Adjusted Rates (b)	68.7%	60.3%	67.2%
Terminal Rates (c)	21/33 (64%)	12/24 (50%)	16/28 (57%)
Week of First Observation	97	90	76
Life Table Tests (d)	P=0.302	P=0.509N	P=0.328
Incidental Tumor Tests (d)	P=0.455	P=0.283N	P=0.525
Cochran-Armitage Trend Test (d)	P=0.460N		
Fisher Exact Test (d)		P=0.078N	P=0.500N

TABLE E2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) (Continued)

	Vehicle Control	312 mg/kg	625 mg/kg
Pituitary Gland: Carcinoma			
Overall Rates (a)	3/49 (6%)	1/49 (2%)	0/49 (0%)
Adjusted Rates (b)	7.4%	3.2%	0.0%
Terminal Rates (c)	1/33 (3%)	0/24 (0%)	0/28 (0%)
Week of First Observation	87	98	
Life Table Tests (d)	P=0.090N	P=0.412N	P=0.155N
Incidental Tumor Tests (d)	P=0.059N	P=0.295N	P=0.122N
Cochran-Armitage Trend Test (d)	P=0.060N		
Fisher Exact Test (d)		P=0.309N	P=0.121N
Pituitary Gland: Adenoma or Carcinoma			
Overall Rates (a)	30/49 (61%)	20/49 (41%)	26/49 (53%)
Adjusted Rates (b)	72.6%	61.5%	67.2%
Terminal Rates (c)	22/33 (67%)	12/24 (50%)	16/28 (57%)
Week of First Observation	87	90	76
Life Table Tests (d)	P=0.490	P=0.402N	P=0.520
Incidental Tumor Tests (d)	P=0.380N	P=0.154N	P=0.394N
Cochran-Armitage Trend Test (d)	P=0.240N		
Fisher Exact Test (d)		P=0.034N	P=0.270N
Adrenal Gland: Cortical Adenoma			
Overall Rates (a)	3/50 (6%)	1/50 (2%)	1/50 (2%)
Adjusted Rates (b)	8.8%	4.2%	3.4%
Terminal Rates (c)	3/34 (9%)	1/24 (4%)	1/29 (3%)
Week of First Observation	105	105	105
Life Table Tests (d)	P=0.257N	P=0.436N	P=0.363N
Incidental Tumor Tests (d)	P=0.257N	P=0.436N	P=0.363N
Cochran-Armitage Trend Test (d)	P=0.202N		
Fisher Exact Test (d)		P=0.309N	P=0.309N
Adrenal Gland: Pheochromocytoma			
Overall Rates (a)	1/50 (2%)	3/50 (6%)	3/50 (6%)
Adjusted Rates (b)	2.9%	10.4%	10.3%
Terminal Rates (c)	1/34 (3%)	2/24 (8%)	3/29 (10%)
Week of First Observation	105	84	105
Life Table Tests (d)	P=0.195	P=0.212	P=0.249
Incidental Tumor Tests (d)	P=0.215	P=0.321	P=0.249
Cochran-Armitage Trend Test (d)	P=0.239		
Fisher Exact Test (d)		P=0.309	P=0.309
Adrenal Gland: Pheochromocytoma or Pheochromocytoma, Malignant			
Overall Rates (a)	2/50 (4%)	3/50 (6%)	4/50 (8%)
Adjusted Rates (b)	5.9%	10.4%	13.8%
Terminal Rates (c)	2/34 (6%)	2/24 (8%)	4/29 (14%)
Week of First Observation	105	84	105
Life Table Tests (d)	P=0.208	P=0.367	P=0.264
Incidental Tumor Tests (d)	P=0.227	P=0.496	P=0.264
Cochran-Armitage Trend Test (d)	P=0.264		
Fisher Exact Test (d)		P=0.500	P=0.339
Thyroid Gland: Follicular Cell Adenoma			
Overall Rates (a)	0/50 (0%)	6/50 (12%)	3/50 (6%)
Adjusted Rates (b)	0.0%	18.9%	8.7%
Terminal Rates (c)	0/34 (0%)	3/24 (13%)	0/29 (0%)
Week of First Observation		83	88
Life Table Tests (d)	P=0.118	P=0.009	P=0.094
Incidental Tumor Tests (d)	P=0.153	P=0.020	P=0.128
Cochran-Armitage Trend Test (d)	P=0.147		
Fisher Exact Test (d)		P=0.013	P=0.121

TABLE E2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) (Continued)

	Vehicle Control	312 mg/kg	625 mg/kg
Thyroid Gland: Follicular Cell Carcinoma			
Overall Rates (a)	0/50 (0%)	0/50 (0%)	3/50 (6%)
Adjusted Rates (b)	0.0%	0.0%	10.3%
Terminal Rates (c)	0/34 (0%)	0/24 (0%)	3/29 (10%)
Week of First Observation			105
Life Table Tests (d)	P=0.033	(e)	P=0.094
Incidental Tumor Tests (d)	P=0.033	(e)	P=0.094
Cochran-Armitage Trend Test (d)	P=0.037		
Fisher Exact Test (d)		(e)	P=0.121
Thyroid Gland: Follicular Cell Adenoma or Carcinoma			
Overall Rates (a)	0/50 (0%)	6/50 (12%)	6/50 (12%)
Adjusted Rates (b)	0.0%	18.9%	18.1%
Terminal Rates (c)	0/34 (0%)	3/24 (13%)	3/29 (10%)
Week of First Observation		83	88
Life Table Tests (d)	P=0.016	P=0.009	P=0.011
Incidental Tumor Tests (d)	P=0.020	P=0.020	P=0.016
Cochran-Armitage Trend Test (d)	P=0.021		
Fisher Exact Test (d)		P=0.013	P=0.013
Thyroid Gland: C-Cell Adenoma			
Overall Rates (a)	15/50 (30%)	5/50 (10%)	5/50 (10%)
Adjusted Rates (b)	41.3%	20.8%	16.6%
Terminal Rates (c)	13/34 (38%)	5/24 (21%)	4/29 (14%)
Week of First Observation	97	105	101
Life Table Tests (d)	P=0.017N	P=0.069N	P=0.032N
Incidental Tumor Tests (d)	P=0.013N	P=0.055N	P=0.024N
Cochran-Armitage Trend Test (d)	P=0.005N		
Fisher Exact Test (d)		P=0.011N	P=0.011N
Thyroid Gland: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	15/50 (30%)	5/50 (10%)	7/50 (14%)
Adjusted Rates (b)	41.3%	20.8%	22.0%
Terminal Rates (c)	13/34 (38%)	5/24 (21%)	5/29 (17%)
Week of First Observation	97	105	94
Life Table Tests (d)	P=0.066N	P=0.069N	P=0.106N
Incidental Tumor Tests (d)	P=0.051N	P=0.055N	P=0.080N
Cochran-Armitage Trend Test (d)	P=0.026N		
Fisher Exact Test (d)		P=0.011N	P=0.045N
Mammary Gland: Fibroadenoma			
Overall Rates (a)	19/50 (38%)	18/50 (36%)	9/50 (18%)
Adjusted Rates (b)	49.1%	54.6%	28.8%
Terminal Rates (c)	15/34 (44%)	10/24 (42%)	7/29 (24%)
Week of First Observation	81	81	98
Life Table Tests (d)	P=0.086N	P=0.233	P=0.070N
Incidental Tumor Tests (d)	P=0.033N	P=0.525	P=0.038N
Cochran-Armitage Trend Test (d)	P=0.020N		
Fisher Exact Test (d)		P=0.500N	P=0.022N
Mammary Gland: Adenoma or Fibroadenoma			
Overall Rates (a)	19/50 (38%)	18/50 (36%)	10/50 (20%)
Adjusted Rates (b)	49.1%	54.6%	32.1%
Terminal Rates (c)	15/34 (44%)	10/24 (42%)	8/29 (28%)
Week of First Observation	81	81	98
Life Table Tests (d)	P=0.126N	P=0.233	P=0.110N
Incidental Tumor Tests (d)	P=0.055N	P=0.525	P=0.064N
Cochran-Armitage Trend Test (d)	P=0.033N		
Fisher Exact Test (d)		P=0.500N	P=0.038N

TABLE E2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) (Continued)

	Vehicle Control	312 mg/kg	625 mg/kg
Mammary Gland: Adenoma, Fibroadenoma, or Adenocarcinoma			
Overall Rates (a)	21/50 (42%)	18/50 (36%)	10/50 (20%)
Adjusted Rates (b)	54.5%	54.6%	32.1%
Terminal Rates (c)	17/34 (50%)	10/24 (42%)	8/29 (28%)
Week of First Observation	81	81	98
Life Table Tests (d)	P=0.065N	P=0.344	P=0.054N
Incidental Tumor Tests (d)	P=0.023N	P=0.505N	P=0.028N
Cochran-Armitage Trend Test (d)	P=0.013N		
Fisher Exact Test (d)		P=0.341N	P=0.015N
Clitoral Gland: Adenoma			
Overall Rates (a)	1/50 (2%)	3/50 (6%)	0/50 (0%)
Adjusted Rates (b)	2.9%	10.3%	0.0%
Terminal Rates (c)	1/34 (3%)	2/24 (8%)	0/29 (0%)
Week of First Observation	105	83	
Life Table Tests (d)	P=0.428N	P=0.215	P=0.532N
Incidental Tumor Tests (d)	P=0.374N	P=0.321	P=0.532N
Cochran-Armitage Trend Test (d)	P=0.378N		
Fisher Exact Test (d)		P=0.309	P=0.500N
Clitoral Gland: Adenoma or Carcinoma			
Overall Rates (a)	1/50 (2%)	4/50 (8%)	2/50 (4%)
Adjusted Rates (b)	2.9%	12.4%	6.4%
Terminal Rates (c)	1/34 (3%)	2/24 (8%)	1/29 (3%)
Week of First Observation	105	83	100
Life Table Tests (d)	P=0.348	P=0.119	P=0.438
Incidental Tumor Tests (d)	P=0.431	P=0.272	P=0.471
Cochran-Armitage Trend Test (d)	P=0.407		
Fisher Exact Test (d)		P=0.181	P=0.500
Uterus: Endometrial Stromal Polyp			
Overall Rates (a)	5/50 (10%)	13/50 (26%)	11/50 (22%)
Adjusted Rates (b)	13.1%	41.7%	32.8%
Terminal Rates (c)	3/34 (9%)	7/24 (29%)	8/29 (28%)
Week of First Observation	95	90	66
Life Table Tests (d)	P=0.045	P=0.007	P=0.048
Incidental Tumor Tests (d)	P=0.067	P=0.015	P=0.089
Cochran-Armitage Trend Test (d)	P=0.082		
Fisher Exact Test (d)		P=0.033	P=0.086
Uterus: Endometrial Stromal Polyp or Sarcoma			
Overall Rates (a)	6/50 (12%)	14/50 (28%)	11/50 (22%)
Adjusted Rates (b)	15.1%	45.1%	32.8%
Terminal Rates (c)	3/34 (9%)	8/24 (33%)	8/29 (28%)
Week of First Observation	95	90	66
Life Table Tests (d)	P=0.074	P=0.008	P=0.083
Incidental Tumor Tests (d)	P=0.110	P=0.017	P=0.151
Cochran-Armitage Trend Test (d)	P=0.134		
Fisher Exact Test (d)		P=0.039	P=0.143

(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 312 mg/kg and vehicle control groups

TABLE E3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{12}, 60% Cl)

	Vehicle Control	125 mg/kg	250 mg/kg
Subcutaneous Tissue: Sarcoma			
Overall Rates (a)	1/50 (2%)	3/50 (6%)	2/50 (4%)
Adjusted Rates (b)	2.6%	8.1%	4.5%
Terminal Rates (c)	0/34 (0%)	1/31 (3%)	0/31 (0%)
Week of First Observation	103	89	67
Life Table Tests (d)	P=0.362	P=0.278	P=0.462
Incidental Tumor Tests (d)	P=0.382	P=0.294	P=0.553
Cochran-Armitage Trend Test (d)	P=0.399		
Fisher Exact Test (d)		P=0.309	P=0.500
Subcutaneous Tissue: Sarcoma or Fibrosarcoma			
Overall Rates (a)	1/50 (2%)	4/50 (8%)	3/50 (6%)
Adjusted Rates (b)	2.6%	10.6%	7.6%
Terminal Rates (c)	0/34 (0%)	1/31 (3%)	1/31 (3%)
Week of First Observation	103	89	67
Life Table Tests (d)	P=0.221	P=0.160	P=0.272
Incidental Tumor Tests (d)	P=0.217	P=0.167	P=0.331
Cochran-Armitage Trend Test (d)	P=0.252		
Fisher Exact Test (d)		P=0.181	P=0.309
Subcutaneous Tissue: Fibroma, Sarcoma or Fibrosarcoma			
Overall Rates (a)	1/50 (2%)	5/50 (10%)	3/50 (6%)
Adjusted Rates (b)	2.6%	13.2%	7.6%
Terminal Rates (c)	0/34 (0%)	1/31 (3%)	1/31 (3%)
Week of First Observation	103	89	67
Life Table Tests (d)	P=0.228	P=0.090	P=0.272
Incidental Tumor Tests (d)	P=0.215	P=0.089	P=0.331
Cochran-Armitage Trend Test (d)	P=0.264		
Fisher Exact Test (d)		P=0.102	P=0.309
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	5/50 (10%)	3/50 (6%)	3/50 (6%)
Adjusted Rates (b)	13.5%	9.7%	8.2%
Terminal Rates (c)	3/34 (9%)	3/31 (10%)	1/31 (3%)
Week of First Observation	103	104	80
Life Table Tests (d)	P=0.341N	P=0.415N	P=0.424N
Incidental Tumor Tests (d)	P=0.303N	P=0.395N	P=0.371N
Cochran-Armitage Trend Test (d)	P=0.283N		
Fisher Exact Test (d)		P=0.357N	P=0.357N
Lung: Alveolar/Bronchiolar Carcinoma			
Overall Rates (a)	0/50 (0%)	3/50 (6%)	6/50 (12%)
Adjusted Rates (b)	0.0%	9.7%	17.9%
Terminal Rates (c)	0/34 (0%)	3/31 (10%)	5/31 (16%)
Week of First Observation		104	71
Life Table Tests (d)	P=0.008	P=0.105	P=0.014
Incidental Tumor Tests (d)	P=0.011	P=0.105	P=0.021
Cochran-Armitage Trend Test (d)	P=0.010		
Fisher Exact Test (d)		P=0.121	P=0.013
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	5/50 (10%)	6/50 (12%)	9/50 (18%)
Adjusted Rates (b)	13.5%	19.4%	25.1%
Terminal Rates (c)	3/34 (9%)	6/31 (19%)	6/31 (19%)
Week of First Observation	103	104	71
Life Table Tests (d)	P=0.114	P=0.430	P=0.149
Incidental Tumor Tests (d)	P=0.145	P=0.447	P=0.205
Cochran-Armitage Trend Test (d)	P=0.152		
Fisher Exact Test (d)		P=0.500	P=0.194

TABLE E3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) (Continued)

	Vehicle Control	125 mg/kg	250 mg/kg
Hematopoietic System: Malignant Lymphoma, Histiocytic Type			
Overall Rates (a)	3/50 (6%)	1/50 (2%)	0/50 (0%)
Adjusted Rates (b)	8.2%	2.0%	0.0%
Terminal Rates (c)	2/34 (6%)	0/31 (0%)	0/31 (0%)
Week of First Observation	101	55	
Life Table Tests (d)	P=0.074N	P=0.339N	P=0.146N
Incidental Tumor Tests (d)	P=0.046N	P=0.264N	P=0.152N
Cochran-Armitage Trend Test (d)	P=0.060N		
Fisher Exact Test (d)		P=0.309N	P=0.122N
Hematopoietic System: Malignant Lymphoma, Mixed Type			
Overall Rates (a)	2/50 (4%)	4/50 (8%)	3/50 (6%)
Adjusted Rates (b)	5.9%	12.0%	8.2%
Terminal Rates (c)	2/34 (6%)	3/31 (10%)	1/31 (3%)
Week of First Observation	105	91	81
Life Table Tests (d)	P=0.371	P=0.299	P=0.452
Incidental Tumor Tests (d)	P=0.411	P=0.303	P=0.540
Cochran-Armitage Trend Test (d)	P=0.417		
Fisher Exact Test (d)		P=0.339	P=0.500
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	6/50 (12%)	6/50 (12%)	5/50 (10%)
Adjusted Rates (b)	15.8%	16.2%	13.6%
Terminal Rates (c)	4/34 (12%)	3/31 (10%)	2/31 (6%)
Week of First Observation	87	55	81
Life Table Tests (d)	P=0.510N	P=0.556	P=0.574N
Incidental Tumor Tests (d)	P=0.457N	P=0.619N	P=0.545N
Cochran-Armitage Trend Test (d)	P=0.437N		
Fisher Exact Test (d)		P=0.620N	P=0.500N
Circulatory System: Hemangiosarcoma			
Overall Rates (a)	2/50 (4%)	6/50 (12%)	4/50 (8%)
Adjusted Rates (b)	5.3%	17.4%	11.5%
Terminal Rates (c)	1/34 (3%)	4/31 (13%)	2/31 (6%)
Week of First Observation	101	87	87
Life Table Tests (d)	P=0.237	P=0.110	P=0.282
Incidental Tumor Tests (d)	P=0.209	P=0.118	P=0.253
Cochran-Armitage Trend Test (d)	P=0.290		
Fisher Exact Test (d)		P=0.134	P=0.339
Liver: Hepatocellular Adenoma			
Overall Rates (a)	11/50 (22%)	20/50 (40%)	29/50 (58%)
Adjusted Rates (b)	30.9%	52.9%	76.1%
Terminal Rates (c)	10/34 (29%)	14/31 (45%)	22/31 (71%)
Week of First Observation	86	47	86
Life Table Tests (d)	P<0.001	P=0.024	P<0.001
Incidental Tumor Tests (d)	P<0.001	P=0.034	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P=0.041	P<0.001
Liver: Hepatocellular Carcinoma			
Overall Rates (a)	11/50 (22%)	15/50 (30%)	17/50 (34%)
Adjusted Rates (b)	24.4%	35.1%	39.8%
Terminal Rates (c)	3/34 (9%)	6/31 (19%)	7/31 (23%)
Week of First Observation	86	47	71
Life Table Tests (d)	P=0.084	P=0.198	P=0.095
Incidental Tumor Tests (d)	P=0.245	P=0.394	P=0.285
Cochran-Armitage Trend Test (d)	P=0.112		
Fisher Exact Test (d)		P=0.247	P=0.133

TABLE E3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) (Continued)

	Vehicle Control	125 mg/kg	250 mg/kg
Liver: Hepatocellular Carcinoma or Hepatoblastoma			
Overall Rates (a)	11/50 (22%)	16/50 (32%)	17/50 (34%)
Adjusted Rates (b)	24.4%	37.7%	39.8%
Terminal Rates (c)	3/34 (9%)	7/31 (23%)	7/31 (23%)
Week of First Observation	86	47	71
Life Table Tests (d)	P=0.084	P=0.148	P=0.095
Incidental Tumor Tests (d)	P=0.245	P=0.303	P=0.285
Cochran-Armitage Trend Test (d)	P=0.114		
Fisher Exact Test (d)		P=0.184	P=0.133
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	20/50 (40%)	34/50 (68%)	38/50 (76%)
Adjusted Rates (b)	46.4%	75.0%	86.2%
Terminal Rates (c)	12/34 (35%)	20/31 (65%)	25/31 (81%)
Week of First Observation	86	47	71
Life Table Tests (d)	P<0.001	P=0.006	P<0.001
Incidental Tumor Tests (d)	P<0.001	P=0.009	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P=0.004	P<0.001
Adrenal: Adenoma			
Overall Rates (a)	3/50 (6%)	3/48 (6%)	3/49 (6%)
Adjusted Rates (b)	8.8%	9.1%	9.7%
Terminal Rates (c)	3/34 (9%)	2/30 (7%)	3/31 (10%)
Week of First Observation	104	95	104
Life Table Tests (d)	P=0.535	P=0.608	P=0.621
Incidental Tumor Tests (d)	P=0.520	P=0.607	P=0.621
Cochran-Armitage Trend Test (d)	P=0.573		
Fisher Exact Test (d)		P=0.641	P=0.651
Adrenal: Adenoma or Cortical Adenoma			
Overall Rates (a)	3/50 (6%)	3/48 (6%)	4/49 (8%)
Adjusted Rates (b)	8.8%	9.1%	12.9%
Terminal Rates (c)	3/34 (9%)	2/30 (7%)	4/31 (13%)
Week of First Observation	104	95	104
Life Table Tests (d)	P=0.372	P=0.608	P=0.449
Incidental Tumor Tests (d)	P=0.357	P=0.607	P=0.449
Cochran-Armitage Trend Test (d)	P=0.410		
Fisher Exact Test (d)		P=0.641	P=0.489
Thyroid: Follicular Cell Adenoma			
Overall Rates (a)	2/49 (4%)	3/50 (6%)	2/49 (4%)
Adjusted Rates (b)	6.1%	9.7%	6.5%
Terminal Rates (c)	2/33 (6%)	3/31 (10%)	2/31 (6%)
Week of First Observation	104	104	104
Life Table Tests (d)	P=0.567	P=0.471	P=0.673
Incidental Tumor Tests (d)	P=0.567	P=0.471	P=0.673
Cochran-Armitage Trend Test (d)	P=0.594		
Fisher Exact Test (d)		P=0.510	P=0.691
Thyroid: Follicular Cell Adenoma or Carcinoma			
Overall Rates (a)	3/49 (6%)	4/50 (8%)	3/49 (6%)
Adjusted Rates (b)	9.1%	12.9%	8.4%
Terminal Rates (c)	3/33 (9%)	4/31 (13%)	2/31 (6%)
Week of First Observation	104	104	71
Life Table Tests (d)	P=0.547	P=0.465	P=0.635
Incidental Tumor Tests (d)	P=0.557N	P=0.465	P=0.611N
Cochran-Armitage Trend Test (d)	P=0.580		
Fisher Exact Test (d)		P=0.511	P=0.661

TABLE E3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) (Continued)

	Vehicle Control	125 mg/kg	250 mg/kg
Harderian Gland: Adenoma			
Overall Rates (a)	3/50 (6%)	2/50 (4%)	4/50 (8%)
Adjusted Rates (b)	7.9%	6.5%	12.9%
Terminal Rates (c)	2/34 (6%)	2/31 (6%)	4/31 (13%)
Week of First Observation	87	104	104
Life Table Tests (d)	P=0.369	P=0.540N	P=0.446
Incidental Tumor Tests (d)	P=0.362	P=0.534N	P=0.435
Cochran-Armitage Trend Test (d)	P=0.417		
Fisher Exact Test (d)		P=0.500N	P=0.500
Harderian Gland: Adenoma or Carcinoma			
Overall Rates (a)	4/50 (8%)	2/50 (4%)	4/50 (8%)
Adjusted Rates (b)	10.1%	6.5%	12.9%
Terminal Rates (c)	2/34 (6%)	2/31 (6%)	4/31 (13%)
Week of First Observation	87	104	104
Life Table Tests (d)	P=0.527	P=0.377N	P=0.587
Incidental Tumor Tests (d)	P=0.511	P=0.367N	P=0.564
Cochran-Armitage Trend Test (d)	P=0.579		
Fisher Exact Test (d)		P=0.339N	P=0.643

(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 E4. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{12}, 60% Cl)

	Vehicle Control	125 mg/kg	250 mg/kg
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	1/50 (2%)	4/49 (8%)	1/50 (2%)
Adjusted Rates (b)	2.8%	12.3%	4.0%
Terminal Rates (c)	1/36 (3%)	3/30 (10%)	1/25 (4%)
Week of First Observation	104	96	104
Life Table Tests (d)	P=0.462	P=0.136	P=0.678
Incidental Tumor Tests (d)	P=0.506	P=0.149	P=0.678
Cochran-Armitage Trend Test (d)	P=0.600		
Fisher Exact Test (d)		P=0.175	P=0.753
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	3/50 (6%)	4/49 (8%)	1/50 (2%)
Adjusted Rates (b)	8.3%	12.3%	4.0%
Terminal Rates (c)	3/36 (8%)	3/30 (10%)	1/25 (4%)
Week of First Observation	104	96	104
Life Table Tests (d)	P=0.398N	P=0.410	P=0.442N
Incidental Tumor Tests (d)	P=0.361N	P=0.429	P=0.442N
Cochran-Armitage Trend Test (d)	P=0.253N		
Fisher Exact Test (d)		P=0.489	P=0.309N
Hematopoietic System: Malignant Lymphoma, Lymphocytic Type			
Overall Rates (a)	0/50 (0%)	3/50 (6%)	6/50 (12%)
Adjusted Rates (b)	0.0%	8.8%	19.0%
Terminal Rates (c)	0/36 (0%)	2/31 (6%)	3/25 (12%)
Week of First Observation		95	85
Life Table Tests (d)	P=0.004	P=0.099	P=0.008
Incidental Tumor Tests (d)	P=0.012	P=0.115	P=0.024
Cochran-Armitage Trend Test (d)	P=0.010		
Fisher Exact Test (d)		P=0.121	P=0.013
Hematopoietic System: Malignant Lymphoma, Histiocytic Type			
Overall Rates (a)	3/50 (6%)	0/50 (0%)	1/50 (2%)
Adjusted Rates (b)	6.9%	0.0%	4.0%
Terminal Rates (c)	0/36 (0%)	0/31 (0%)	1/25 (4%)
Week of First Observation	94		104
Life Table Tests (d)	P=0.251N	P=0.151N	P=0.423N
Incidental Tumor Tests (d)	P=0.130N	P=0.083N	P=0.227N
Cochran-Armitage Trend Test (d)	P=0.176N		
Fisher Exact Test (d)		P=0.122N	P=0.309N
Hematopoietic System: Malignant Lymphoma, Mixed Type			
Overall Rates (a)	9/50 (18%)	9/50 (18%)	8/50 (16%)
Adjusted Rates (b)	22.2%	25.5%	27.6%
Terminal Rates (c)	6/36 (17%)	6/31 (19%)	5/25 (20%)
Week of First Observation	82	87	95
Life Table Tests (d)	P=0.374	P=0.487	P=0.429
Incidental Tumor Tests (d)	P=0.502N	P=0.592	P=0.542N
Cochran-Armitage Trend Test (d)	P=0.447N		
Fisher Exact Test (d)		P=0.603N	P=0.500N
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	12/50 (24%)	12/50 (24%)	15/50 (30%)
Adjusted Rates (b)	27.7%	33.2%	46.7%
Terminal Rates (c)	6/36 (17%)	8/31 (26%)	9/25 (36%)
Week of First Observation	82	87	85
Life Table Tests (d)	P=0.081	P=0.452	P=0.101
Incidental Tumor Tests (d)	P=0.279	P=0.584N	P=0.362
Cochran-Armitage Trend Test (d)	P=0.284		
Fisher Exact Test (d)		P=0.592N	P=0.326

TABLE E4. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) (Continued)

	Vehicle Control	125 mg/kg	250 mg/kg
Hematopoietic System: Lymphoma or Leukemia			
Overall Rates (a)	12/50 (24%)	12/50 (24%)	16/50 (32%)
Adjusted Rates (b)	27.7%	33.2%	47.9%
Terminal Rates (c)	6/36 (17%)	8/31 (26%)	9/25 (36%)
Week of First Observation	82	87	79
Life Table Tests (d)	P=0.056	P=0.452	P=0.072
Incidental Tumor Tests (d)	P=0.238	P=0.584N	P=0.329
Cochran-Armitage Trend Test (d)	P=0.214		
Fisher Exact Test (d)		P=0.592N	P=0.252
Circulatory System: Hemangiosarcoma			
Overall Rates (a)	3/50 (6%)	1/50 (2%)	2/50 (4%)
Adjusted Rates (b)	8.3%	3.2%	6.4%
Terminal Rates (c)	3/36 (8%)	1/31 (3%)	1/25 (4%)
Week of First Observation	105	105	87
Life Table Tests (d)	P=0.530N	P=0.359N	P=0.643N
Incidental Tumor Tests (d)	P=0.492N	P=0.359N	P=0.596N
Cochran-Armitage Trend Test (d)	P=0.399N		
Fisher Exact Test (d)		P=0.309N	P=0.500N
Circulatory System: Hemangioma or Hemangiosarcoma			
Overall Rates (a)	3/50 (6%)	1/50 (2%)	3/50 (6%)
Adjusted Rates (b)	8.3%	3.2%	10.3%
Terminal Rates (c)	3/36 (8%)	1/31 (3%)	2/25 (8%)
Week of First Observation	105	105	87
Life Table Tests (d)	P=0.450	P=0.359N	P=0.505
Incidental Tumor Tests (d)	P=0.484	P=0.359N	P=0.551
Cochran-Armitage Trend Test (d)	P=0.594		
Fisher Exact Test (d)		P=0.309N	P=0.661N
Liver: Hepatocellular Adenoma			
Overall Rates (a)	0/50 (0%)	18/50 (36%)	22/50 (44%)
Adjusted Rates (b)	0.0%	49.4%	65.4%
Terminal Rates (c)	0/36 (0%)	13/31 (42%)	14/25 (56%)
Week of First Observation		87	84
Life Table Tests (d)	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests (d)	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P<0.001	P<0.001
Liver: Hepatocellular Carcinoma			
Overall Rates (a)	3/50 (6%)	4/50 (8%)	9/50 (18%)
Adjusted Rates (b)	8.3%	11.0%	26.9%
Terminal Rates (c)	3/36 (8%)	2/31 (6%)	4/25 (16%)
Week of First Observation	105	68	75
Life Table Tests (d)	P=0.014	P=0.435	P=0.022
Incidental Tumor Tests (d)	P=0.067	P=0.508	P=0.093
Cochran-Armitage Trend Test (d)	P=0.037		
Fisher Exact Test (d)		P=0.500	P=0.061
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	3/50 (6%)	22/50 (44%)	28/50 (56%)
Adjusted Rates (b)	8.3%	57.3%	74.8%
Terminal Rates (c)	3/36 (8%)	15/31 (48%)	16/25 (64%)
Week of First Observation	105	68	75
Life Table Tests (d)	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests (d)	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P<0.001	P<0.001

TABLE E4. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) (Continued)

	Vehicle Control	125 mg/kg	250 mg/kg
Forestomach: Squamous Cell Papilloma			
Overall Rates (a)	2/50 (4%)	5/50 (10%)	0/50 (0%)
Adjusted Rates (b)	5.6%	13.8%	0.0%
Terminal Rates (c)	2/36 (6%)	3/31 (10%)	0/25 (0%)
Week of First Observation	104	86	
Life Table Tests (d)	P=0.350N	P=0.173	P=0.322N
Incidental Tumor Tests (d)	P=0.240N	P=0.223	P=0.322N
Cochran-Armitage Trend Test (d)	P=0.238N		
Fisher Exact Test (d)		P=0.218	P=0.247N
Pituitary: Adenoma			
Overall Rates (a)	18/49 (37%)	14/47 (30%)	9/46 (20%)
Adjusted Rates (b)	44.8%	42.5%	30.5%
Terminal Rates (c)	14/36 (39%)	10/28 (36%)	6/25 (24%)
Week of First Observation	95	98	67
Life Table Tests (d)	P=0.203N	P=0.534N	P=0.221N
Incidental Tumor Tests (d)	P=0.072N	P=0.399N	P=0.081N
Cochran-Armitage Trend Test (d)	P=0.042N		
Fisher Exact Test (d)		P=0.307N	P=0.051N
Pituitary: Adenoma or Carcinoma			
Overall Rates (a)	18/49 (37%)	14/47 (30%)	10/46 (22%)
Adjusted Rates (b)	44.8%	42.5%	32.4%
Terminal Rates (c)	14/36 (39%)	10/28 (36%)	6/25 (24%)
Week of First Observation	95	98	67
Life Table Tests (d)	P=0.279N	P=0.534N	P=0.306N
Incidental Tumor Tests (d)	P=0.106N	P=0.399N	P=0.117N
Cochran-Armitage Trend Test (d)	P=0.069N		
Fisher Exact Test (d)		P=0.307N	P=0.084N
Thyroid: Follicular Cell Adenoma			
Overall Rates (a)	8/50 (16%)	12/49 (24%)	13/49 (27%)
Adjusted Rates (b)	20.7%	35.5%	44.2%
Terminal Rates (c)	6/36 (17%)	9/30 (30%)	9/25 (36%)
Week of First Observation	95	95	95
Life Table Tests (d)	P=0.024	P=0.128	P=0.033
Incidental Tumor Tests (d)	P=0.063	P=0.162	P=0.082
Cochran-Armitage Trend Test (d)	P=0.127		
Fisher Exact Test (d)		P=0.212	P=0.150
Thyroid: Follicular Cell Adenoma or Carcinoma			
Overall Rates (a)	8/50 (16%)	12/49 (24%)	15/49 (31%)
Adjusted Rates (b)	20.7%	35.5%	49.1%
Terminal Rates (c)	6/36 (17%)	9/30 (30%)	10/25 (40%)
Week of First Observation	95	95	90
Life Table Tests (d)	P=0.007	P=0.128	P=0.011
Incidental Tumor Tests (d)	P=0.024	P=0.162	P=0.033
Cochran-Armitage Trend Test (d)	P=0.056		
Fisher Exact Test (d)		P=0.212	P=0.069
Mammary Gland: Adenocarcinoma			
Overall Rates (a)	5/50 (10%)	0/50 (0%)	4/50 (8%)
Adjusted Rates (b)	13.0%	0.0%	11.5%
Terminal Rates (c)	4/36 (11%)	0/31 (0%)	0/25 (0%)
Week of First Observation	81		84
Life Table Tests (d)	P=0.550N	P=0.047N	P=0.607
Incidental Tumor Tests (d)	P=0.289N	P=0.031N	P=0.346N
Cochran-Armitage Trend Test (d)	P=0.417N		
Fisher Exact Test (d)		P=0.028N	P=0.500N

TABLE E4. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) (Continued)

	Vehicle Control	125 mg/kg	250 mg/kg
Uterus: Endometrial Stromal Polyp			
Overall Rates (a)	4/50 (8%)	2/50 (4%)	3/50 (6%)
Adjusted Rates (b)	11.1%	5.9%	9.8%
Terminal Rates (c)	4/36 (11%)	1/31 (3%)	1/25 (4%)
Week of First Observation	104	101	84
Life Table Tests (d)	P=0.578N	P=0.401N	P=0.637
Incidental Tumor Tests (d)	P=0.419N	P=0.381N	P=0.516N
Cochran-Armitage Trend Test (d)	P=0.417N		
Fisher Exact Test (d)		P=0.339N	P=0.500N
Uterus: Endometrial Stromal Polyp or Sarcoma			
Overall Rates (a)	4/50 (8%)	2/50 (4%)	5/50 (10%)
Adjusted Rates (b)	11.1%	5.9%	15.7%
Terminal Rates (c)	4/36 (11%)	1/31 (3%)	2/25 (8%)
Week of First Observation	104	101	84
Life Table Tests (d)	P=0.270	P=0.401N	P=0.323
Incidental Tumor Tests (d)	P=0.467	P=0.381N	P=0.546
Cochran-Armitage Trend Test (d)	P=0.424		
Fisher Exact Test (d)		P=0.339N	P=0.500
Harderian Gland: Adenoma			
Overall Rates (a)	1/50 (2%)	(e) 6/50 (12%)	2/50 (4%)
Adjusted Rates (b)	2.8%	18.5%	8.0%
Terminal Rates (c)	1/36 (3%)	5/31 (16%)	2/25 (8%)
Week of First Observation	104	101	104
Life Table Tests (d)	P=0.251	P=0.040	P=0.373
Incidental Tumor Tests (d)	P=0.286	P=0.044	P=0.373
Cochran-Armitage Trend Test (d)	P=0.417		
Fisher Exact Test (d)		P=0.056	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) A carcinoma was also observed in one of these animals.

APPENDIX F

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

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

Study	Incidence in Vehicle Controls
Historical Incidence at Southern Research Institute	
Ethyl acrylate	1/50
Benzyl acetate	5/50
Allyl isovalerate	1/50
HC Red No. 3	9/50
Allyl isothiocyanate	2/50
Geranyl acetate	1/50
TOTAL	19/300 (6.3%)
SD (b)	6.50%
Range (c)	
High	9/50
Low	1/50
Overall Historical Incidence	
TOTAL	152/1,100 (13.8%)
SD (b)	8.12%
Range (c)	
High	14/50
Low	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 F2. HISTORICAL INCIDENCE OF HEPATOCELLULAR TUMORS IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls		
	Neoplastic Nodule	Carcinoma	Neoplastic Nodule or Carcinoma
Historical Incidence at Southern Research Institute			
Ethyl acrylate	0/50	0/50	0/50
Benzyl acetate	1/49	0/49	1/49
Allyl isovalerate	1/50	0/50	1/50
HC Red No. 3	3/50	1/50	4/50
Allyl isothiocyanate	2/50	0/50	2/50
Geranyl acetate	0/50	0/50	0/50
TOTAL	7/299 (2.3%)	1/299 (0.3%)	8/299 (2.7%)
SD (b)	2.34%	0.82%	3.01%
Range (c)			
High	3/50	1/50	4/50
Low	0/50	0/50	0/50
Overall Historical Incidence			
TOTAL	35/1,098 (3.2%)	8/1,098 (0.7%)	43/1,098 (3.9%)
SD (b)	3.36%	1.32%	3.68%
Range (c)			
High	7/50	2/50	7/50
Low	0/50	0/50	0/50

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

Study	No. of Animals Examined	No. of Tumors	Diagnosis
Historical Incidence at Southern Research Institute			
Benzyl acetate	50	1	Adenocarcinoma, NOS
All others	250	0	
TOTAL	300	1 (0.3%)	
Overall Historical Incidence			
	1,098	1	Tubular cell adenoma
		2	Adenocarcinoma, NOS
		2	Tubular cell adenocarcinoma
TOTAL		5 (0.5%)	

(a) Data as of August 3, 1984. No more than one tumor was observed in any vehicle control group.

TABLE F4. 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	(b) 1/50
Geranyl acetate	0/49	0/49	0/49
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%)	(e) 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 F5. HISTORICAL INCIDENCE OF LEUKEMIA IN FEMALE F344/NRATS ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls
Historical Incidence at Southern Research Institute	
Ethyl acrylate	5/50
Benzyl acetate	2/50
Allyl isovalerate	4/50
HC Red No. 3	10/50
Allyl isothiocyanate	7/50
Geranyl acetate	8/50
TOTAL	36/300 (12.0%)
SD (b)	5.80%
Range (c)	
High	10/50
Low	2/50
Overall Historical Incidence	
TOTAL	196/1,100 (17.8%)
SD (b)	8.94%
Range (c)	
High	(d) 21/50
Low	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 F6. HISTORICAL INCIDENCE OF HEPATOCELLULAR NEOPLASTIC NODULES IN FEMALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls
Historical Incidence at Southern Research Institute	
Ethyl acrylate	0/50
Benzyl acetate	1/50
Allyl isovalerate	1/50
HC Red No. 3	0/50
Allyl isothiocyanate	0/50
Geranyl acetate	0/50
TOTAL	2/300 (0.7%)
SD (b)	1.03%
Range (c)	
High	1/50
Low	0/50
Overall Historical Incidence	
TOTAL	(d) 21/1,098 (1.9%)
SD (b)	2.58%
Range (c)	
High	5/50
Low	0/50

(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) No hepatocellular carcinomas were observed in 1,098 vehicle controls.

TABLE F7. HISTORICAL INCIDENCE OF PANCREATIC ACINAR CELL ADENOMAS IN FEMALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

	Incidence in Vehicle Controls
Historical Incidence at Southern Research Institute	
No tumors have been observed in 297 vehicle controls.	
Overall Historical Incidence	
TOTAL	4/1,084 (0.4%)
SD (b)	1.02%
Range (c)	
High	2/49
Low	0/50

(a) Data as of August 3, 1984, for studies of at least 104 weeks. No carcinomas have been observed in these studies.
(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 FEMALE 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	1/50	0/50	1/50
Benzyl acetate	0/50	0/50	0/50
Allyl isovalerate	0/48	0/48	0/48
HC Red No. 3	1/50	0/50	1/50
Allyl isothiocyanate	0/50	0/50	0/50
Geranyl acetate	0/49	1/49	1/49
TOTAL	2/297 (0.7%)	1/297 (0.3%)	3/297 (1.0%)
SD (b)	1.03%	0.83%	1.10%
Range (c)			
High	1/50	1/49	1/49
Low	0/50	0/50	0/50
Overall Historical Incidence			
TOTAL	(d) 10/1,076 (0.9%)	5/1,076 (0.5%)	(d) 15/1,076 (1.4%)
SD (b)	1.65%	0.88%	1.74%
Range (c)			
High	3/48	1/46	3/48
Low	0/50	0/50	0/50

(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) Includes two cystadenomas and two papillary cystadenomas

TABLE F9. HISTORICAL INCIDENCE OF UTERINE ENDOMETRIAL STROMAL TUMORS IN FEMALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls		
	Polyp	Sarcoma	Polyp or Sarcoma
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 (2.6%)	76/300 (25.3%)
SD (b)	6.32%	2.42%	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 F10. HISTORICAL INCIDENCE OF ALVEOLAR/BRONCHIOLAR TUMORS IN MALE 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	5/48	3/48	8/48
Benzyl acetate	7/50	5/50	12/50
Allyl isovalerate	10/50	3/50	13/50
HC Red No. 3	6/50	6/50	11/50
Allyl isothiocyanate	4/50	0/50	4/50
Geranyl acetate	6/50	0/50	6/50
TOTAL	38/298 (12.8%)	17/298 (5.7%)	54/298 (18.1%)
SD (b)	4.08%	4.97%	7.12%
Range (c)			
High	10/50	6/50	13/50
Low	4/50	0/50	4/50
Overall Historical Incidence			
TOTAL	111/1,093 (10.2%)	63/1,093 (5.8%)	169/1,093 (15.5%)
SD (b)	4.27%	3.82%	5.95%
Range (c)			
High	10/50	6/50	13/50
Low	1/50	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.

TABLE F11. HISTORICAL INCIDENCE OF HEPATOCELLULAR TUMORS IN MALE 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	6/49	12/49	17/49
Benzyl acetate	0/50	10/50	10/50
Allyl isovalerate	7/50	18/50	23/50
HC Red No. 3	11/50	17/50	25/50
Allyl isothiocyanate	9/49	13/49	21/49
Geranyl acetate	3/50	11/50	13/50
TOTAL	36/298 (12.1%)	81/298 (27.2%)	109/298 (36.6%)
SD (b)	8.06%	6.49%	11.82%
Range (c)			
High	11/50	18/50	25/50
Low	0/50	10/50	10/50
Overall Historical Incidence			
TOTAL	140/1,091 (12.8%)	238/1,091 (21.8%)	357/1,091 (32.7%)
SD (b)	6.82%	7.75%	9.63%
Range (c)			
High	14/50	19/50	25/50
Low	0/50	5/50	7/50

(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 F12. 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.

TABLE F13. HISTORICAL INCIDENCE OF THYROID GLAND FOLLICULAR CELL 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	4/48	1/48	4/48
Benzyl acetate	3/47	0/47	3/47
Allyl isovalerate	3/49	1/49	4/49
HC Red 3	2/49	0/49	2/49
Allyl isothiocyanate	1/48	0/48	1/48
Geranyl acetate	5/50	0/50	5/50
TOTAL	18/291 (6.2%)	2/291 (0.7%)	19/291 (6.5%)
SD (b)	2.84%	1.06%	2.96%
Range (c)			
High	5/50	1/48	5/50
Low	1/48	0/50	1/48
Overall Historical Incidence			
TOTAL	(d) 36/1,009 (3.6%)	5/1,009 (0.5%)	(d) 40/1,009 (4.0%)
SD (b)	3.01%	1.10%	3.04%
Range (c)			
High	5/50	2/49	5/50
Low	0/49	0/50	0/47

(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 one papillary adenoma, one cystadenoma, and two papillary cystadenomas

TABLE F14. HISTORICAL INCIDENCE OF HARDERIAN GLAND TUMORS IN FEMALE $B6C3F_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence of Adenoma or Carcinoma in Vehicle Controls
Historical Incidence at Southern Research Institute	
Ethyl acrylate	1/50
Benzyl acetate	0/50
Allyl isovalerate	1/50
HC Red 3	0/50
Allyl isothiocyanate	(b) 2/50
Geranyl acetate	1/50
TOTAL	5/300 (1.7%)
SD (c)	1.51%
Range (d)	
High	2/50
Low	0/50
Overall Historical Incidence	
TOTAL	(e) 21/1,096 (1.9%)
SD (c)	2.51%
Range (d)	
High	5/50
Low	0/50

(a) Data as of August 3, 1984, for studies of at least 104 weeks
(b) Includes one adenoma, NOS, and one cystadenoma
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.
(e) Includes 18 adenomas, NOS, 1 papillary adenoma, 1 cystadenoma, and 1 carcinoma, NOS

APPENDIX G

GENETIC TOXICOLOGY OF

CHLORINATED PARAFFINS (C_{12}, 60% Chlorine)

TABLE G1. MUTAGENICITY OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) IN *SALMONELLA TYPHIMURIUM*

Strain	Dose (µg/plate)	Revertants/plate (a,b) −S9	+S9 (rat)	+S9 (hamster)
TA100	0	174 ± 15.8	237 ± 16.8	272 ± 3.0
	33	152 ± 5.9	226 ± 6.7	245 ± 26.7
	100	141 ± 4.5	243 ± 14.2	233 ± 29.9
	333	143 ± 4.3	240 ± 12.5	275 ± 25.5
	1,000	158 ± 3.3	282 ± 26.9	305 ± 28.4
	3,333	171 ± 7.0	349 ± 16.0	302 ± 1.0
TA1535				
	0	7 ± 1.9	7 ± 1.2	5 ± 0.9
	33	5 ± 1.2	8 ± 2.0	5 ± 2.5
	100	5 ± 1.5	6 ± 2.6	7 ± 1.5
	333	6 ± 1.2	8 ± 1.7	4 ± 0.9
	1,000	5 ± 1.8	6 ± 1.2	7 ± 1.7
	3,333	8 ± 3.5	5 ± 0.6	4 ± 1.5
TA97	0	5 ± 1.5	10 ± 1.5	9 ± 3.0
	33	8 ± 1.9	12 ± 3.8	13 ± 1.0
	100	8 ± 1.0	9 ± 3.0	8 ± 3.4
	333	10 ± 2.7	10 ± 3.8	14 ± 2.7
	1,000	6 ± 2.3	11 ± 2.9	9 ± 2.3
	3,333	7 ± 2.6	8 ± 2.3	12 ± 3.5
TA98	0	19 ± 2.6	28 ± 4.2	26 ± 3.2
	33	24 ± 3.1	25 ± 0.3	30 ± 2.4
	100	24 ± 3.7	27 ± 2.3	25 ± 1.9
	333	23 ± 3.2	33 ± 2.2	26 ± 4.0
	1,000	23 ± 1.5	30 ± 2.7	23 ± 4.0
	3,333	22 ± 5.5	22 ± 3.8	26 ± 6.9

(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 (dimethyl sulfoxide) were incubated for 20 min 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 h (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_{12}, 60% Chlorine)

APPENDIX H. CHEMICAL CHARACTERIZATION

I. Identity and Purity Determinations of Lot No. R-201-198 Performed by the Analytical Chemistry Laboratory

A. Physical properties: Appearance--Very viscous, clear, colorless liquid

B. Spectral data	**Determined**	**Literature Values**
1. Infrared		
Instrument:	Beckman IR-12	
Cell:	Thin film between silver chloride plates	
Results:	See Figure 5	Consistent with literature spectrum (Sadtler Standard Spectra)
2. Ultraviolet/visible		
Instrument:	Cary 118	
Solvent:	Hexanes	
Results:	No maximum absorbance between 800 and 350 nm at 2% concentration, although there is a gradual increase in absorbance toward 350 nm. Between 350 and 215 nm there was one maximum, one shoulder, and an increase in absorbance toward the solvent cutoff which did not resolve into a maximum at 0.08% concentration.	No literature reference found. Spectrum consistent with structure.

λ_{max} (nm)	ε_{max}
283	6.25 ± 0.05(δ)
215 (shoulder)	342 ± 3(δ)

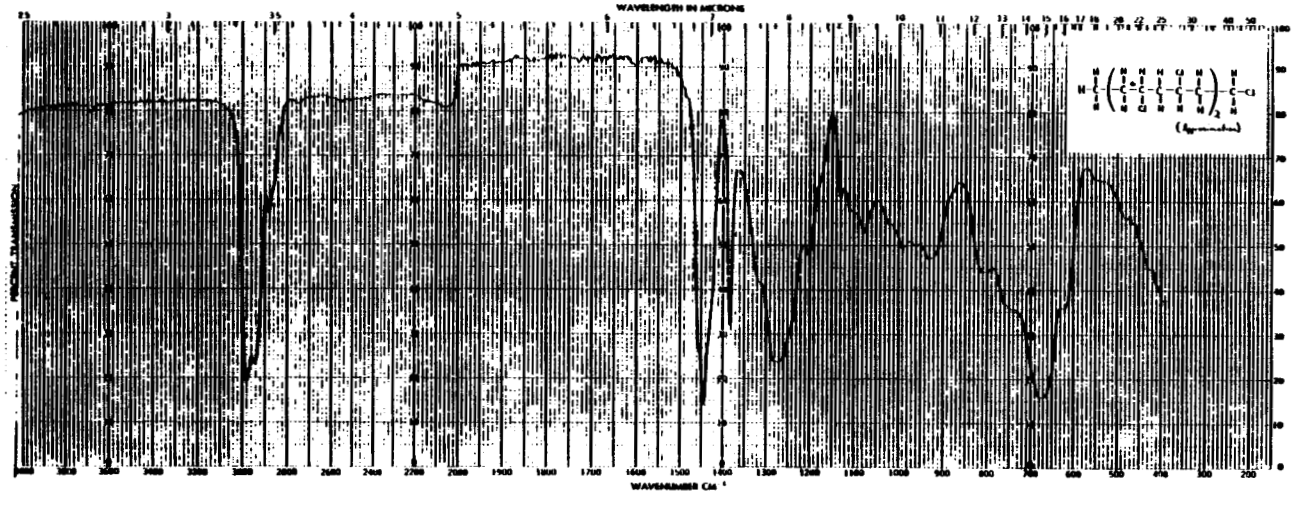


FIGURE 5. INFRARED ABSORPTION SPECTRUM OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) (LOT NO. R-201-198)

3. **Nuclear magnetic resonance**

	Determined	Literature Values
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 0.93-1.28 ppm b 1.28-2.93 ppm c 3.37-4.68 ppm	
Integration ratios:	a 1.40 b 12.62 c 5.98	

C. **Water analysis (Karl Fischer):** 0.035% ± 0.002(δ)%

D. **Elemental analyses:** Theoretical values are based on the average empirical formula $C_{12}H_{19}Cl_7$.

Element	C	H	Cl
Theory (T)	35.03	4.65	60.32
Determined (D)	34.85 35.08	4.49 4.45	60.33 60.41
Percent D/T	99.81	96.13	100.08

E. **Titration for acidic components:** Titration with sodium hydroxide of an aqueous extract of a solution of chlorinated paraffins (C_{12}, 60% chlorine) in carbon tetrachloride

6.0 ± 1.0 ppm (assumed to be hydrochloric acid)

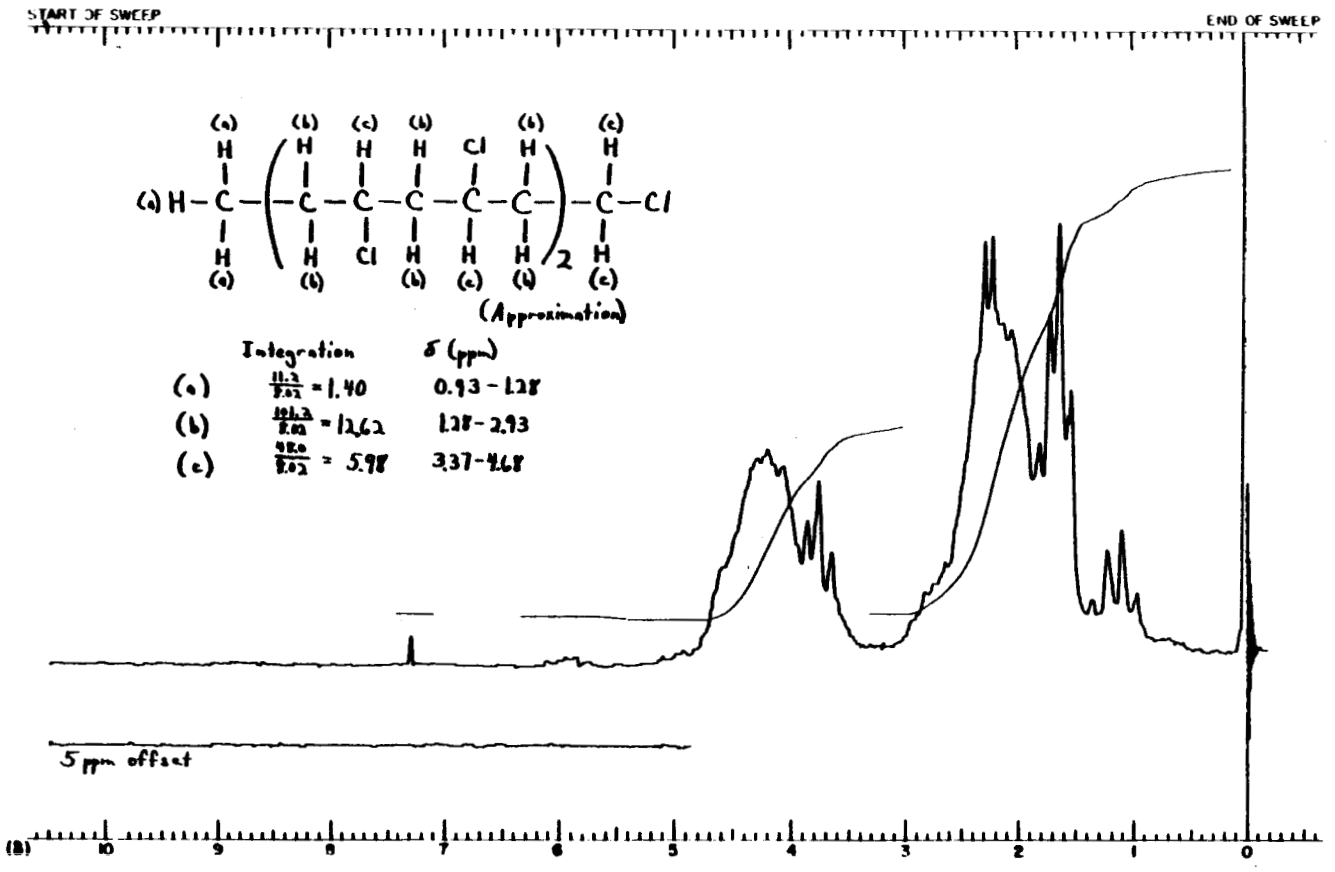


FIGURE 6. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) (LOT NO. R-201-198)

F. 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 15-20 minutes at 110° C, for sample. Reference visualized with ultraviolet light before spraying.

System 1

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

Results: R_f: 0.79
R_{st}: 0.95

System 2

Solvent: Methanol
Plates: Whatman KC_{18} reverse-phase, F-254

Results: R_f: 0.66
R_{st}: 1.12

G. Conclusions: The results of the elemental analyses for carbon, hydrogen, and chlorine agreed with the theoretical values for an empirical formula of $C_{12}H_{19}Cl_7$, which best fits 60% chlorine content and average approximate molecular weight of 411. Water content was 0.035% ± 0.002(δ)% by Karl Fischer analysis. Titration for acidic components indicated 6.0 ± 1.0 ppm (assumed to be hydrochloric acid) as compared with 7.0 ppm listed on the manufacturer's label. Thin-layer chromatography with two systems each indicated a single major spot. The infrared, ultraviolet/visible, and nuclear magnetic resonance spectra were consistent with the structure.

II. Chemical Stability Study of Lot No. R-201-198 Performed by the Analytical Chemistry Laboratory

A. Sample storage: Chlorinated paraffins (C_{12}, 60% chlorine) samples were stored (protected from light) for 2 weeks at −20°, 5°, 25°, or 60° C in amber bottles with polyseal lids.

B. Analytical method: Samples (aqueous extracts of a solution of chlorinated paraffins [C_{12}, 60% chlorine] in carbon tetrachloride) from each storage temperature were analyzed by titration with sodium hydroxide. Hydrochloric acid is an expected decomposition product of chlorinated paraffins (C_{12}, 60% 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	6.0 ± 1.0
5° C	7.0 ± 1.0
25° C	8.0 ± 1.0
60° C	(a) 18.1 ± 1.0

(a) The 60° C sample had a brownish tint.

D. Conclusion: Chlorinated paraffins (C_{12}, 60% chlorine) showed evidence of instability after storage for 2 weeks at 60° C. No notable decomposition was observed after storage at 25° C for 2 weeks.

III. Chemical Stability Study of Lot No. R-201-198 Performed by the Study Laboratory

A. Analytical methods

1. Thin-layer chromatography

Amount spotted: 100 and 300 µg (10 mg/ml in diethyl ether)
Reference standard: Hexachlorocyclopentadiene (10 mg/ml in diethyl ether)
Visualization: Ultraviolet light before spraying with potassium dichromate spray (5% in water), then heated. Plates were developed 10 cm in each system used.

System 1

Solvent: *o*-Xylene
Plates: Brinkman aluminum oxide, Type T, F-254, 0.25 mm, 5 × 20 cm (heated to 115° C for 30 minutes before use)

System 2:

Solvent: Acetone:water (85:15)
Plates: Whatman KC_{18} reverse-phase, fluorescent indicator, 0.20 mm, 5 × 20 cm

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

B. Results

1. Thin-layer chromatography

	System 1				System 2			
	R_f		R_{st}		R_f		R_{st}	
Date	100 µg	300 µg	100 µg	300 µg	100 µg	300 µg	100 µg	300 µg
01/25/80	0.70	0.65	0.96	0.87	0.58	0.58	1.02	1.02
	0.70	0.67	0.95	0.91	0.60	0.57	1.05	1.04
05/27/80	0.72	0.71	0.97	0.95	0.54	0.55	1.02	1.02
	0.72	0.72	0.97	0.95	0.56	0.57	1.02	1.04
09/16/80	0.67	0.66	0.94	0.93	0.61	0.65	1.03	1.08
01/29/81	0.89	0.92	(a)	(a)	0.60	0.60	(a)	(a)
05/19/81	0.76	0.77	0.95	0.95	0.64	0.63	1.00	1.00
09/17/81	0.79	0.80	0.96	0.94	0.49	0.49	0.96	0.94
01/28/80	0.70	0.69	0.95	0.97	0.58	0.58	1.05	1.04
05/29/82	0.46	0.45	0.98	0.94	0.74	0.76	0.99	1.02

(a) Data missing

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

C. Conclusion: No noticeable degradation occurred during the 2-year studies.

APPENDIX I

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES

APPENDIX I. PREPARATION AND CHARACTERIZATION

I. Temperature Stability Studies in Corn Oil Conducted at the Analytical Chemistry Laboratory

A. Spectrophotometric method

1. **Sample preparation and storage:** Chlorinated paraffins (C_{12}, 60% chlorine) (200.0 g) was dissolved in corn oil in a 2-liter volumetric flask and diluted to volume. After a thorough mixing, the solution was allowed to stand to permit bubbles to rise to the surface; then the volume was adjusted exactly with corn oil, and the contents were thoroughly remixed. The target concentration of the chemical in the solution was 100 mg/ml (10% weight/volume). The preparation and subsequent handling procedures were all conducted in subdued room light or in light-protected vessels (aluminum foil or tape wrapped).

   The chlorinated paraffins (C_{12}, 60% chlorine) blend was stored in the dark at room temperature and was sampled in triplicate (94.0 g) for the analysis of water extractable chlorides after 0, 1, 3, 6, or 7 days of storage.

2. **Sample extraction and analysis**

   All glassware was rinsed with warm 5% nitric acid followed by five rinses with distilled water before use to remove chloride ion. Cleaned glassware was handled only with gloves.

   Samples (94.0 g) in 200-ml centrifuge bottles were mixed by being swirled with 75 ml of hexane; then 20.0 ml water was added and shaken for 2 minutes. Duplicate corn oil blanks (84.0 g), prepared from the same corn oil used for the blend, were analyzed along with the samples.

   When the layers had separated, the upper oily layer was removed by aspiration into a vacuum flask and discarded. The water layer was washed by being shaken for 30 seconds with 75 ml of hexane. The hexane layer was aspirated and discarded. A 15-ml centrifuge tube was filled with the water extract and centrifuged at 2,000 rpm for 3 minutes.

   For the determination of chlorides, a series of 50-ml septum vials containing 25 ml of 95% ethanol, 5 ml of 0.5 N nitric acid, and 1 ml of 0.5 N silver nitrate was prepared. Ten milliliters of water was added to one vial for a reagent blank, and 10.0 ml of each standard solution (concentration range, 2.5-20 µg/ml) and sample extract were added to the other vials.

   Immediately after the 10-ml aliquot was added, each vial was sealed, mixed, and stored in the dark. (From this point on, solutions were protected from light as much as possible.)

   One hour after the samples were sealed and mixed, the absorbance of the solutions was read on a spectrophotometer at 400 nm in 5-cm cells vs reagent blank. Results were calculated from a standard curve of the absorbance readings of the standards vs micrograms of chloride ion per 10 ml. The absorbance readings of the chlorinated paraffins (C_{12}, 60% chlorine)/corn oil blends were corrected for the absorbance of the corn oil blank.

3. **Quality control measures:** All sample analyses were run in triplicate and were corrected for the corn oil blank absorbance (0.010 absorbance units). Results were corrected for a mean spiked recovery yield of 73.3% ± 2.3% determined at a concentration of 8.8 ppm. The spiked samples were prepared by injecting 10 µl of a freshly prepared 2% solution of hydrochloric acid in acetone into 94.0 g (100 ml) of the blend and mixing thoroughly. Results were calculated from a standard curve prepared by adding 10-ml aliquots of standard sodium chloride solutions as concentrations of 2.5, 5.0, 7.5, 10.0, or 12.5 µg/ml into the same reaction mixture as was used for the chloride determination on the samples.

4. **Results**

Days Storage at Room Temperature	Water Extractable Chloride (µg/g) Found (a) (calculated as hydrochloric acid)	Percent Chloride Found Relative to Zero-Time Samples (b)
0	9.9	--
1	7.4	74.7 ± 5.1
3	3.4	34.3 ± 4.1
6	2.8	28.3 ± 1.0
7	2.3	23.2 ± 1.0

(a) Mean of three determinations. Results were corrected for a mean zero-time recovery yield, 73.3% ± 2.3%.
(b) The error values are expressed as the maximum deviation of an assay value from the mean.

5. **Conclusion:** The use of the chloride analysis to evaluate the stability of chlorinated paraffins (C_{12}, 60% chlorine) in gavage solution was based on the fact that the hydrochloric acid is liberated as chlorinated paraffins (C_{12}, 60% chlorine) degrades. In a simple mechanism, stability would be indicated by stable hydrochloric acid concentrations and instability, by increase in hydrochloric acid content. However, the results showing a rapid decline in extractable chloride content complicate the interpretation. Some loss reaction, either outgassing from the insoluble media or reaction with some media component, is also taking place. Because of this complicating reaction, the results can only be interpreted as indicative of the loss reaction being faster than the decomposition.

The loss reaction was studied by spiking hydrochloric acid at an 8.8-ppm level into the corn oil media. No hydrochloric acid was found after 4 days, supporting the interpretation of a slow chlorinated paraffins (C_{12}, 60% chlorine) decomposition reaction and slightly faster hydrochloric acid loss. Further supporting evidence for chlorinated paraffins (C_{12}, 60% chlorine) stability in corn oil was obtained by the viscosity measurements that exhibited no notable change during storage for 7 days in the dark at room temperature.

Viscosity and free hydrochloric acid measurements suggest that chlorinated paraffins (C12, 60% chlorine) is stable in corn oil solution when stored for 7 days in the dark at room temperature. The results are only suggestive because hydrochloric acid is lost during storage in the undosed corn oil vehicle, which complicates the interpretation of the data.

II. Studies Conducted at the Analytical Chemistry Laboratory

A. Sample preparation and storage: Chlorinated paraffins (C_{12}, 60% chlorine) (10.00 g) was 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. The volume was then adjusted with corn oil and the contents were remixed thoroughly. The target concentration of the chemical in the corn oil solution was 10% (weight/volume). The corn oil solution was maintained at room temperature (approximately 24° C) in the dark and was sampled at weekly intervals over 4 weeks.

B. Viscosity determination

1. Special equipment

a. 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 filled with water and 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.
b. Uncalibrated Kinematic Viscometer, Cannon-Fenske type, ASTM No. 300, 50-250 Centistokes range, available from Fisher Scientific Company.
c. Thermometer, graduated in 0.2° C divisions. A titer test thermometer, ASTM No. 36C, range −2° to 68° C, available from Fisher Scientific Company.
d. Timer, either mechanical or electric, capable of measuring to 0.1 second. A Precision Scientific Company Time It® electric stopwatch was used.

2. 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_{12}, 60% 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_{12}, 60% 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 with a rubber bulb, the corn oil solution was drawn 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)	Chlorinated Paraffins (C_{12}, 60% Cl) Stability Relative to Zero Time (percent)
0	290.8	290.7	290.5	290.7	100.0
7	290.4	290.4	290.5	290.4	99.9
14	288.9	289.3	288.9	289.0	99.4
21	290.7	290.5	290.7	290.6	100.0
28	289.3	289.5	289.7	289.5	99.6

D. **Conclusion:** A 10% (weight/volume) chlorinated paraffins (C_{12}, 60% 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

A. Gravimetric procedure: Samples were shaken for 20-30 minutes and then placed in a room temperature water bath on a stirring plate. After being stirred for 30 minutes, the samples were placed in a room temperature water bath without stirring and allowed to equilibrate for at least 1 hour. The sample bottle was then dried, and the sample was poured through a specially drawn funnel into a preweighed clean, dry 25-ml volumetric flask. The volumetric flask was then weighed, and the density was calculated.

Standards of the chlorinated paraffins (C_{12}, 60% chlorine) in corn oil were prepared over the concentration range of 0%-100% (weight/volume). These standards were also heated to approximately 45° C in a water bath before the density was determined. A standard curve of density vs concentration was then prepared. The sample concentrations were then determined from the measured density of the sample as compared with the standard curve.

B. Hydrometer procedure: Standards were prepared by weighing an amount of chlorinated paraffins (C_{12}, 60% chlorine) into a 200-ml volumetric flask. Corn oil was added with stirring over several hours until the standard was diluted to volume.

The standards and samples were shaken for 30 minutes in a constant-temperature water bath. The samples and standards were then allowed to equilibrate for 1 hour in an ambient constant-temperature water bath. Approximately 150 ml of the sample or standard was then poured into a 32 × 305 mm glass-stoppered tube. An appropriate hydrometer was immersed in the corn oil solution, so that it floated freely without touching the sides of the tube. Density measurements were made by a hydrometer after 10 minutes of equilibration. 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 determined from the measured density of the sample as compared with the standard curve.

II. Analytical Chemistry Laboratory

A. Viscosity method

1. **Preparation of standard spiked corn oil:** Six standards were prepared by weighing quantities of chlorinated paraffins (C_{12}, 60% chlorine) into individual 10-ml volumetric flasks and diluting to volume with undosed corn oil. The flasks were wrapped with foil and shaken thoroughly. A 10-ml volumetric flask containing only undosed corn oil was used for a blank. The standards bracketed the specified concentration range of the dosed sample and were used immediately in the analysis procedure described below.

2. **Preparation of dosed sample:** Two portions (10 ml) of the dosed corn oil sample were transferred to individual 10-ml volumetric flasks that were wrapped in foil to protect the solutions from light. The samples were analyzed immediately by the procedure described below.

3. **Analysis:** The contents of a 10-ml volumetric flask with dosed sample was poured carefully into the large-bore filling tube of the viscometer, and the flask 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 27.0° ± 0.1° C.

   When the solution had equilibrated, the vertical alignment of the tube was checked; then, with a rubber bulb, the corn oil solution was drawn up 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.

   Since the relationship of viscometer readings, in seconds, to chlorinated paraffins (C_{12}, 60% chlorine), concentration in the corn oil is not a linear function, the concentration of chlorinated paraffins (C_{12}, 60% chlorine) in the dosed sample was read from a standard curve obtained by plotting the average observed times (in seconds) for each spiked corn oil standard versus the total milligrams of chemical in the respective corn oil standard and drawing the best fitting line through the data points.

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

B. **Density method:** The original recommended analysis protocol for dosed corn oil solutions employed viscosity measurements. Although that method was satisfactory to determine concentrations above 5%, it was not well adapted for the analysis of samples in the dose range of 1%-5%. The analysis method below is based on the principle that corn oil solutions of chlorinated paraffins (C_{12}, 60% chlorine) increase in density as concentration is increased.

1. **Preparation of the standard oil solutions:** Eight clean and dry 10-ml volumetric flasks were each weighed to the nearest 0.001 g; then chlorinated paraffins (C_{12}, 60% chlorine) was weighed into seven of the flasks, and the flasks were filled to the 10-ml mark with undosed corn oil to make solutions bracketing the concentration of the dosed sample. The remaining flask was filled to the 10-ml mark with undosed corn oil. The flasks were all thoroughly mixed and weighed to the nearest milligram.

2. **Preparation of the dosed sample:** Three clean and dry 10-ml volumetric flasks were each weighed to the nearest milligram; then they were filled to the 10-ml mark with dosed corn oil sample and again weighed to the nearest milligram.

3. **Analysis:** The analysis consisted of plotting the density (as grams per milliliter) of the undosed corn oil and spiked corn oil solutions versus the milligrams of chlorinated paraffins (C_{12}, 60% chlorine) added to each 10-ml flask and drawing the best fitting line through the data points. (The density curve was not linear in this concentration range.) The concentration of chlorinated paraffins (C_{12}, 60% chlorine) in the dosed samples was then determined from the standard curve.

4. **Quality assurance measures:** The dosed corn oil sample was analyzed in triplicate. Individually spiked portions of undosed corn oil (seven concentrations) prepared from seven independently weighed standards were treated like the sample to obtain standard curve data bracketing the concentration range of the dosed sample.

APPENDIX K

RESULTS OF ANALYSIS OF DOSE MIXTURES

TABLE K1. RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{12}, 60% Cl)

Date Mixed	Concentration (a) of Chlorinated Paraffins (C_{12}, 60% Cl) in Corn Oil for Target Concentration (percent)			
	1.25	2.50	6.24	12.50
9/9/80			(b) 8.10	13.20
9/11/80			(c) 6.63	
10/7/80	(b) 4.20	(b) 4.60		
10/10/80	(c) 1.20	(d) 3.00		
11/4/80	(e) 1.60		(b) 7.20	
11/7/80			(c) 7.00	
12/2/80		(e) 2.18		11.76
1/6/81	(b) 0.76		(b) 5.32	
1/8/81	(c) 1.18		(c) 6.25	
1/13/81	1.25	2.37	6.20	12.52
1/20/81	1.16	2.28	6.00	11.88
1/27/81	1.13	2.43	6.00	12.68
2/3/81	(b) 1.02	2.32	6.21	13.42
2/5/81	(f) 1.41			
2/9/81	(c) 1.20			
2/10/81	1.30	2.61	6.18	12.18
2/17/81	1.20	2.30	6.30	12.20
2/24/81	1.24	2.74	5.84	11.94
3/24/81	1.12	2.40	5.93	11.91
3/31/81	1.28	2.69	6.24	12.47
4/7/81	1.33	2.51	6.08	12.04
4/14/81	1.16	2.58	6.19	12.50
4/21/81	1.28	2.47	6.10	12.25
4/28/81	1.21	2.50	6.42	12.91
5/5/81	1.21	2.37	6.38	12.70
5/12/81	1.33	2.52	6.18	12.25
5/19/81	1.30	2.45	5.82	12.00
6/16/81 (g)	1.24		6.28	
8/11/81	1.37		6.42	
9/8/81		2.57		12.08
10/6/81	1.31		6.18	
11/3/81		2.33		12.48
12/1/81	(b) 1.10		6.27	
12/2/81	(c) 1.25			
12/29/81		2.33		12.32
2/2/82	1.18	2.37	6.45	12.50
3/30/82	(e) 1.12		6.04	12.50
5/25/82	1.20	2.56	6.17	12.41
Mean (percent)	1.33	2.54	6.25	12.38
Standard deviation	0.603	0.469	0.490	0.407
Coefficient of variation (percent)	45.3	18.5	7.8	3.3
Range (percent)	0.76-4.20	2.18-4.60	5.32-8.10	11.76-13.42
Number of samples	26	23	26	24
Number of samples > ±10% of target	6	2	3	0

(a) Results of duplicate analysis
(b) Out of specifications; not used in the study, included in the mean.
(c) Remix; used in the study, not included in the mean.
(d) Remix out of specifications; used in the study, not included in the mean.
(e) Out of specifications; used in the study.
(f) Remix out of specifications; not used in the study or included in the mean.
(g) All mixes beginning on 6/16/81 were prepared on a weight/weight rather than a weight/volume basis making the target concentrations 1.35%, 2.72%, 6.79%, and 13.60%, respectively. To allow comparison with the weight/volume percentages, all reported weight/weight values were divided by 1.088.

TABLE K2. RESULTS OF REFEREE ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{12}, 60% Cl)

Date Mixed	Target Concentration (percent)	Determined Concentration (percent)	
		Study Laboratory	Analytical Laboratory
10/7/80	2.5	(a) 4.6	5.69
3/24/81	12.5	11.91	12.55
7/14/81	2.5	2.34	1.57
2/2/82	6.24	6.45	6.59

(a) Dose mixture found to be out of specifications; not used in study.

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

Fifteen $B6C3F_1$ mice and 15 F344/N rats of each sex 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 (6, 12, 18 mo)	M. Ad. (mouse adenovirus) LCM (lymphocytic choriomeningitis virus) Sendai (24 mo) MHV (6, 12 mo)	MHV (mouse hepatitis virus) (18, 24 mo)
Rats	PVM KRV (Kilham rat virus) H-1 (Toolan's H-1 virus) Sendai (6, 12, 18 mo)	RCV (rat coronavirus) Sendai (24 mo)	

II. Results

Results are presented in Table L1.

TABLE L1. MURINE VIRUS ANTIBODY DETERMINATIONS FOR RATS AND MICE IN THE TWO-YEAR GAVAGE STUDIES OF CHLORINATED PARAFFINS (C_{12}, 60% Cl) (a)

	Interval (months)	No. of Animals	Positive Serologic Reaction for
RATS			
	6	10/10	RCV
	12	2/10	RCV
	18	--	None positive
	24	4/10	KRV
		2/10	RCV
MICE			
	6	--	None positive
	12	--	None positive
	18	2/5	MHV
	24	1/10	PVM
		2/10	MHV

(a) Blood samples were taken from sentinel animals at 6, 12, and 18 months after the start of dosing and from the vehicle control animals just before they were killed; samples were sent to Microbiological Associates, Inc. (Bethesda, MD) for the Animal Disease Screening Program.

APPENDIX M

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 M1. 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 M2. 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 M3. NUTRIENT COMPOSITION OF NIH 07 RAT AND MOUSE RATION (a)

Nutrient	Mean ± Standard Deviation	Range	No. of Samples
Crude protein (percent by weight)	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 M4. CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION

Contaminant	Mean ± Standard Deviation	Range	No. 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 M4. 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 N

ABSTRACT FROM THE NTP TECHNICAL REPORT ON CHLORINATED PARAFFINS (C_{23}, 43% CHLORINE)

NTP TR 305

NIH PUBLICATION NO. 86-2561

APPENDIX N. ABSTRACT FROM NTP TR 305

$CH_3CHCl(CHClCH_2CH_2CH_2)_5CH_2Cl$
(Approximation)

Chlorinated Paraffins
Average Chain Length: C_{23}
Approximately 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

APPENDIX O

DATA AUDIT SUMMARY

APPENDIX O. DATA AUDIT SUMMARY

The experimental data for the NTP Technical Report on the Toxicology and Carcinogenesis Studies of Chlorinated Paraffins (C_{12}, 60% chlorine) were examined for completeness, consistency, and accuracy and for procedures consistent with Good Laboratory Practice requirements. The audit was conducted during January 1985 at the National Toxicology Program Archives, Rockville, Maryland, by the following personnel of Argus Research Laboratories, Inc., and Pathology Associates, Inc.: J. Goeke, Ph.D.; J. Hills; A. Hoberman, Ph.D.; D. Willett; D. Copeland, D.V.M.; C. Veigle, HTL; and S. Corson, HT. The 2-year studies in F344/N rats and $B6C3F_1$ mice were conducted by Southern Research Institute, Birmingham, Alabama, from September 1980 to September 1982.

The full audit report has been reviewed and approved by NTP personnel and is on file at the NIEHS, Research Triangle Park, North Carolina. The audit involved a review of all prestudy data (i.e., receipt, quarantine, randomization, identification of animals) and a complete review of data (body weights, clinical observations, dosing) for 10% of the animals in each group. In addition, all records of study animal deaths, moribund or terminal kills, tumors, lesions, and masses were audited. All available chemistry data were audited, and 10% of the dose calculations were verified. For the pathology portion of the audit, 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, with subsequent followup identification of all mice, and the correlation of gross and microscopic diagnoses was audited for 10% of the rats and all of the mice.

The inlife data for the 2-year studies of chlorinated paraffins (C_{12}, 60% chlorine) were found to be in generally good order. There were seven occurrences of misdosing of study animals with resultant clinical effects in three cases (documented by the study laboratory), and several chemical vehicle mixtures that were outside ±10% of the target concentration were used for the dosing of animals. Periodic reanalysis of the bulk chemical by thin-layer chromatography and infrared spectral analysis indicated no significant degradation during the study, but the imprecise nature of these methods did not allow absolute confirmation that chemical purity was maintained.

Discrepancies between gross and microscopic diagnoses led to slide and/or wet tissue reexamination of 34 rats and 11 mice. Most discrepancies were followed to resolution, except untrimmed lesions in wet tissues of six rats and eight mice. The untrimmed mouse lesions were all stomach polyps or plaques, and the rat lesions were distributed between tissues and dose groups such that 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_{12}, 60% chlorine) revealed some uncertainties relating to bulk chemical analyses. This was largely due to difficulties encountered in the routine chemical analysis of chlorinated paraffins, and the impact (if any) on the studies cannot be determined from the available information. 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: 1986-491-292:41086