NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 342

TOXICOLOGY AND CARCINOGENESIS STUDIES OF DICHLORVOS

(CAS NO. 62-73-7)

IN F344/N RATS AND B6C3F$_1$ MICE

(GAVAGE STUDIES)

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

NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS STUDIES OF DICHLORVOS

(CAS NO. 62-73-7)

IN F344/N RATS AND B6C3F$_1$ MICE

(GAVAGE STUDIES)

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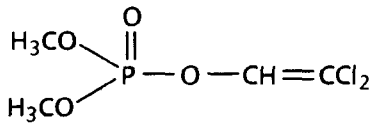

DICHLORVOS

CAS No. 62-73-7

$C_4H_7Cl_2PO_4$ Molecular weight 221

Synonyms: 2,2-dichloroethenyl dimethyl phosphate; 2,2-dichlorovinyl dimethyl phosphate; *O,O*-dimethyl-*O*-(2,2-dichlorovinyl)phosphate; DDVP

Trade names: BAY-19149; DDVF; ENT-20738; OMS-14; SD 1750; Canogard®; Crossman's Fly-Cake®; Dedevap®; De-Pester Insect Strip®; Estrosol®; Herkol®; Kill-fly Resin Strip®; Lethalaire®; Mafu®; Misect®; Nogos®; Nuvan®; No-Pest Strip®; Oko®; Phoracide®; Phosvit®; Vapona®; Vaponicide®; Vaporette Bar®

Anthelmintics: Atgard®; Dichlorman®; Equigard®; Task®

ABSTRACT

Toxicology and carcinogenesis studies of dichlorvos (99% pure), a contact and stomach poison for control of insects and parasites, were conducted by administering dichlorvos in corn oil by gavage to groups of F344/N rats and B6C3F$_1$ mice of each sex for 13 weeks or 2 years. Previous feed studies were done by the National Cancer Institute using Osborne-Mendel rats and B6C3F$_1$ mice (NCI TR 10, 1977).

Thirteen-Week Studies: Thirteen-week studies with groups of 10 rats of each sex were conducted at doses of 0, 2, 4, 8, 16, 32, or 64 mg/kg dichlorvos in corn oil. All rats that received 32 or 64 mg/kg dichlorvos and 4/10 females that received 16 mg/kg died before the end of the studies. Final mean body weights of dosed and vehicle control rats were similar. Thirteen-week studies with groups of 10 mice of each sex were conducted at doses of 0, 5, 10, 20, 40, 80, or 160 mg/kg. All 10 male mice and 9/10 female mice that received 160 mg/kg and 5/10 male mice that received 80 mg/kg dichlorvos died before the end of the studies. Final mean body weights of dosed and vehicle control mice were similar. No compound-related gross or microscopic pathologic effects were observed in rats or mice.

Two-year studies of dichlorvos were conducted by administering 0, 4, or 8 mg/kg dichlorvos, 5 days per week for 103 weeks, to groups of 50 F344/N rats of each sex. Groups of 50 male B6C3F$_1$ mice were administered 0, 10, or 20 mg/kg dichlorvos on the same schedule, and groups of 50 B6C3F$_1$ female mice were administered 0, 20, or 40 mg/kg dichlorvos.

Body Weight and Survival in the Two-Year Studies: Mean body weights of dosed and vehicle control rats and mice were similar. No significant differences in survival were observed between any groups of rats or mice of either sex (rats--male: vehicle control, 31/50; low dose, 25/50; high dose, 24/50; female: 31/50; 26/50; 26/50; mice--male: 35/50; 27/50; 29/50; female: 26/50; 29/50; 34/50).

Neoplastic Effects in the Two-Year Studies: Adenomas of the exocrine pancreas occurred at greater incidences in dosed rats than in vehicle controls (male: vehicle control, 25/50; low dose, 30/49; high dose, 33/50; female: 2/50; 3/47; 6/50). Mononuclear cell leukemia in both dosed groups of male rats occurred more frequently than in vehicle controls (11/50; 20/50; 21/50). Mammary gland fibroadenomas and fibroadenomas or adenomas (combined) in dosed female rats occurred at increased incidences

relative to vehicle controls (9/50, 19/50, 17/50) Multiple fibroadenomas occurred in dosed female rats but not in vehicle controls (0/50; 6/50; 3/50); carcinomas occurred in two vehicle control and two low dose female rats.

In mice, incidences of squamous cell papillomas of the forestomach were increased in the high dose groups compared with those in the vehicle controls (male: 1/50; 1/50; 5/50; female: 5/49; 6/49; 18/50). Two high dose female mice developed forestomach squamous cell carcinomas.

Genetic Toxicology: Dichlorvos was mutagenic in *Salmonella typhimurium* strain TA100 with and without metabolic activation but was not mutagenic in strain TA98. Dichlorvos was mutagenic in the mouse lymphoma L5178Y/TK$^{+/-}$ assay without metabolic activation. Dichlorvos induced sister chromatid exchanges and chromosomal aberrations in Chinese hamster ovary cells in the absence and presence of metabolic activation.

Conclusions: Under the conditions of these 2-year gavage studies, there was *some evidence of carcinogenic activity** of dichlorvos for male F344/N rats, as shown by increased incidences of adenomas of the exocrine pancreas and mononuclear cell leukemia. There was *equivocal evidence of carcinogenic activity* of dichlorvos for female F344/N rats, as shown by increased incidences of adenomas of the exocrine pancreas and mammary gland fibroadenomas. There was *some evidence of carcinogenic activity* of dichlorvos for male B6C3F$_1$ mice, as shown by increased incidences of forestomach squamous cell papillomas. There was *clear evidence of carcinogenic activity* of dichlorvos for female B6C3F$_1$ mice, as shown by increased incidences of forestomach squamous cell papillomas.

SUMMARY OF THE TWO-YEAR GAVAGE AND GENETIC TOXICOLOGY STUDIES OF DICHLORVOS

Male F344/N Rats	Female F344/N Rats	Male B6C3F$_1$ Mice	Female B6C3F$_1$ Mice
Doses			
4 or 8 mg/kg dichlorvos in corn oil, 5 d/wk	4 or 8 mg/kg dichlorvos in corn oil, 5 d/wk	10 or 20 mg/kg dichlorvos in corn oil, 5 d/wk	20 or 40 mg/kg dichlorvos in corn oil, 5 d/wk
Body weights in the 2-year study			
Dosed and vehicle control similar	Dosed and vehicle control similar	Dosed and vehicle control similar	Dosed and vehicle control similar
Survival rates in the 2-year study			
31/50; 25/50; 24/50	31/50; 26/50; 26/50	35/50; 27/50; 29/50	26/50; 29/50; 34/50
Nonneoplastic effects			
Cytoplasmic vacuolization in liver and adrenal glands	Atrophy of pancreatic cells; cytoplasmic vacuolization in adrenal glands	None	None
Neoplastic effects			
Pancreatic adenomas; mononuclear cell leukemia	Pancreatic adenomas, mammary gland fibroadenomas	Forestomach squamous cell papillomas	Forestomach squamous cell papillomas
Level of evidence of carcinogenic activity			
Some evidence	Equivocal evidence	Some evidence	Clear evidence
Genetic toxicology			
Mutagenic in *S. typhimurium* strain TA100 with and without Aroclor 1254-induced liver S9 from male Sprague Dawley rats and male Syrian hamsters but was not mutagenic in strain TA98. Induced trifluorothymidine resistance in mouse lymphoma L5178Y/TK$^{+/-}$ assay without metabolic activation. Induced sister chromatid exchanges and chromosomal aberrations in Chinese hamster ovary cells in the absence and presence of metabolic activation.			

*Explanation of Levels of Evidence of Carcinogenic Activity is on page 5.
A summary of the Peer Review comments and the public discussion on this Technical Report appears on pages 8-9 and 11.

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

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

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

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

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

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

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

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

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

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

CONTRIBUTORS

The NTP Technical Report on the Toxicology and Carcinogenesis Studies of Dichlorvos is based on the 13-week studies that began in April 1980 and ended in July 1980 and on the 2-year studies that began in January 1981 and ended in February 1983 at Southern Research Institute (Birmingham, Alabama).

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PEER REVIEW PANEL (July 14, 1987)

The members of the Peer Review Panel who evaluated the draft Technical Report on dichlorvos on July 14, 1987, 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 DICHLORVOS (July 14, 1987)

On July 14, 1987, the draft Technical Report on the toxicology and carcinogenesis studies of dichlorvos received public review by the National Toxicology Program (NTP) Board of Scientific Counselors' Technical Reports Review Subcommittee and associated Panel of Experts. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina.

Dr. P.C. Chan, NIEHS, began the discussion by reviewing the experimental design, results, and proposed conclusions (clear evidence of carcinogenic activity for male rats, some evidence of carcinogenic activity for female rats, some evidence of carcinogenic activity for male or female mice).

Dr. Hooper, a principal reviewer, agreed with the conclusions for male and female rats and male mice but proposed that the conclusions in female mice be changed to clear evidence of carcinogenic activity, based on a dose-related increase in a combination of benign and malignant neoplasms (forestomach squamous cell papillomas and carcinomas). No squamous cell carcinomas have been observed in corn oil vehicle control female $B6C3F_1$ mice in NTP studies. He suggested that male mice likely could have tolerated the same dose as that given to female mice, or twice that given to males. Dr. Chan agreed and speculated that if the doses in males had been the same as those in females, the incidences of forestomach papillomas likely would have been increased.

As a second principal reviewer, Dr. Ashby stated that with the possible exception of female mice, the conclusions in this Report more appropriately might be equivocal evidence of carcinogenic activity. He reasoned that since the chemical is an alkylating agent and direct-acting mutagen, one might expect tumors at the site of exposure (i.e., stomach) but not at further sites. The reverse was found in rats, no increased incidences of stomach tumors but increased incidences of pancreatic acinar cell adenomas in males and females, of mononuclear cell leukemia in males, and of mammary gland tumors in females. Confounding the biologic significance in rats were the high concurrent vehicle control incidences for the tumors in male rats (compared with the historical corn oil vehicle control incidence for the laboratory), and conversely, the low concurrent vehicle control incidence of mammary gland tumors in females. Dr. S. Eustis, NIEHS, and Dr. J. Haseman, NIEHS, said that the incidence of mononuclear cell leukemia in rats has been increasing over the last several years, so the incidence in concurrent vehicle control male rats was probably not unusual. Dr. J. Huff, NIEHS, explained that the level of evidence in male rats was based largely on the high incidence of pancreatic neoplasia and that the mononuclear cell leukemia was contributory. Dr. Ashby said that points supporting a conclusion of equivocal evidence of carcinogenic activity for male mice were no increases in forestomach hyperplasia, equal incidences of squamous cell papillomas in vehicle control and low dose mice, and an absence of malignant tumors.

As a third reviewer, Dr. Gallo agreed with the conclusion for male rats, noting the possible effects of corn oil interaction, and with the conclusion for male mice, noting that the increased incidences of forestomach lesions in high dose animals were not statistically significant. He also agreed with the conclusion for female mice. He thought that the conclusion for female rats should be changed to equivocal evidence of carcinogenic activity because the incidence of mammary gland fibroadenomas was within the historical corn oil vehicle control incidence for both the laboratory and the NTP. Dr. Chan noted that when the most appropriate comparisons are made with concurrent controls, there are significantly increased incidences for fibroadenomas in both low and high dose groups. Further, there were increased incidences of multiple fibroadenomas in the dosed groups which were not seen in

the vehicle controls. Dr. Huff pointed out that the increase in pancreatic tumors in the high dose female rats was supported by the same effect in male rats.

Dr. Mirer and other Panel members said that there was insufficient information on the methodology used for measuring cholinesterase inhibition as well as lack of adequate interpretation and discussion of the results. Dr. Gallo also questioned the rationale for the choice of route of administration; either the inhalation or the dermal route would have been more appropriate.

Professor Paul Grasso, Robens Institute, United Kingdom, representing Shell Internationale Petroleum, suggested that the data did not support association of chemical exposure with increased incidences of mammary gland tumors and mononuclear cell leukemia in female rats and the high incidence of pancreatic tumors in vehicle control male rats did not allow a conclusion to be drawn as to causation in dosed animals. He suggested that the cluster of forestomach tumors in female vehicle control mice obscured any association of the chemical with increased incidences of these tumors in exposed mice.

Dr. Hooper moved that the conclusion for male rats, clear evidence of carcinogenic activity, be accepted as written, with mention made of the high concurrent vehicle control incidences of pancreatic tumors and mononuclear cell leukemia. Dr. Gallo seconded the motion, which was approved by six affirmative votes to two negative votes (Dr. Ashby and Dr. Popp). Dr. Hooper moved that the conclusion for female rats, some evidence of carcinogenic activity, be accepted as written. The motion failed for lack of a second. Dr. Ashby moved that the conclusion be changed to equivocal evidence of carcinogenic activity. Dr. Sivak seconded the motion, which was approved by six affirmative votes to two negative votes (Dr. Hooper and Dr. Mirer). Dr. Hooper moved that the conclusion for male mice, some evidence of carcinogenic activity, be accepted as written. Dr. Gallo seconded the motion, which was approved by seven affirmative votes to one negative vote (Dr. Sivak). Dr. Hooper moved that the conclusion for female mice be changed to clear evidence of carcinogenic activity. Dr. Ashby seconded the motion, which was approved by seven affirmative votes to one negative vote (Dr. Gallo).

PEER REVIEW PANEL (April 18, 1988)

The members of the Peer Review Panel who evaluated the draft Technical Report on dichlorvos on April 18, 1988, are listed below. Panel members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, Panel members have five major responsibilities: (a) to ascertain that all relevant literature data have been adequately cited and interpreted, (b) to determine if the design and conditions of the NTP studies were appropriate, (c) to ensure that the Technical Report presents the experimental results and conclusions fully and clearly, (d) to judge the significance of the experimental results by scientific criteria, and (e) to assess the evaluation of the evidence of carcinogenicity and other observed toxic responses.

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SUMMARY OF PEER REVIEW COMMENTS ON THE TOXICOLOGY AND CARCINOGENESIS STUDIES OF DICHLORVOS (April 18, 1988)

The 2-year toxicology and carcinogenesis studies of dichlorvos in rats and mice first underwent peer review on July 14, 1987, and the conclusions were approved by the Peer Review Panel. At that time, the Panel questioned the data presented on plasma and erythrocyte cholinesterase activity. Subsequently, the NTP performed an additional examination of all remaining pancreata of male and female rats in the studies. Since the level of evidence in male rats was supported by an increased incidence of mononuclear cell leukemia, data were presented to the Panel meeting on April 18, 1988, on the effects of dichlorvos administration on the growth of transplantable mononuclear cell leukemia in male F344/N rats; new data on cholinesterase activity measurements and findings from recut pancreas sections were also presented.

Dr. M.P. Dieter, NIEHS, described the biologic features of leukemia in F344 rats, the development of a leukemia transplant model, and validation of the model with chemicals from the NTP data base. He described the findings with dichlorvos, noting that the transplant model showed the same type of positive response as was observed in the 2-year studies. He concluded by pointing out the structure-activity relationships among dichlorvos and other phosphoric acid esters as leukemogens. These data would be added to the Technical Report.

Dr. P.C. Chan, NIEHS, presented data from short-term studies of plasma and erythrocyte cholinesterase activity in rats and mice of each sex administered dichlorvos by gavage in corn oil five times per week for 5 weeks over a range of doses. The studies showed that dichlorvos suppressed plasma cholinesterase activity in a dose-related manner at all time points when given to rats and mice of each sex. Enzyme activity returned to normal levels within 3-4 days after cessation of exposure. In contrast, dichlorvos had no effect on erythrocyte cholinesterase activity in any of the sex/species groups. These results have been added to the Technical Report.

Dr. Chan discussed the findings from an additional longitudinal section of the pancreas of male and female rats in the 2-year studies. He reviewed the original findings from the Technical Report for pancreatic acinar cell hyperplasia and adenomas in male and female rats, the findings from the additional sampling, and the incidences resulting when the original and new data were combined. Although the incidences of pancreatic adenomas in dosed male rats were still increased, the new data weaken the statistical significance of this response. The conclusion approved by the Panel for male rats was clear evidence of carcinogenic activity, as shown by increased incidences of adenomas of the exocrine pancreas and mononuclear cell leukemia; the conclusion was based primarily on the strength of the pancreas response. Dr. Chan said that the data presented from the leukemia transplant model supported the mononuclear cell leukemia results in the 2-year studies, but in light of the new data on pancreatic lesions, the NTP staff requested that the Panel consider a change in the conclusion for male rats to some evidence of carcinogenic activity. In reply to discussion as to why the leukemia findings were supportive only of some evidence of carcinogenic activity, Dr. J. Huff, NIEHS, said that it was because these tumors are quite variable in historical controls, the findings in both dosed groups in the 2-year studies were only marginally statistically significant, and there was a lack of dose response.

Dr. Popp moved that the Panel support the recommendation of the staff that the conclusion for male rats in the Technical Report on dichlorvos be changed to some evidence of carcinogenic activity. Dr. Hughes seconded the motion, which was approved by nine affirmative votes to one negative vote (Dr. Perera).

I. INTRODUCTION

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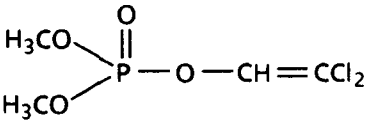

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Anthelmintics: Atgard®; Dichlorman®; Equigard®; Task®

Properties

Dichlorvos, an organophosphorus pesticide, is a vinyl triester of phosphoric acid. It is a colorless to amber liquid with a mild aromatic odor and has a density of 1.415 g/ml at 25° C, a boiling point of 35° C at 0.05 mm mercury, a vapor pressure of 0.012 mm mercury at 20° C, and a refractive index of 1.452° at 25° C (Hayes, 1982; Pesticide Manual, 1983).

Dichlorvos is miscible with alcohols, most nonpolar solvents, and aerosol propellants. The solubility of dichlorvos is 1% in water at 20° C and 3% in kerosene and mineral oils (Hayes, 1982; Pesticide Manual, 1983).

Dichlorvos is stable to heat. It hydrolyzes to dimethyl hydrogen phosphate and dichloroacetaldehyde at room temperature in the presence of moisture. The rate of decomposition is rapid at increased temperatures and in strong acids and bases. It is corrosive to iron and mild steel but noncorrosive to stainless steel, aluminum, nickel, Hastelloy B, and Teflon® (IARC, 1979; Shell Chemical Co., 1979). Technical-grade dichlorvos may be stabilized by the use of 2%-4% epichlorohydrin (Melnikov, 1971), but improved production and storage technologies have eliminated the need for the use of stabilizers.

Production Volume, Uses, and Environmental Effects

Dichlorvos has been commercially manufactured since 1961 by reacting chloral with trimethyl phosphite. The product is 93% pure (Melnikov, 1971). Current production figures in the United States are not available, but two companies produced dichlorvos in the United States in 1985 (USITC, 1986). Production in 1974 was about 10 million kg in Western Europe, 0.1 million kg in Eastern European countries, and 0.9 million kg in the United States and in 1976 1.1 million kg in Japan (IARC, 1979). Dichlorvos is available in emulsifiable and oil-soluble concentrates, aerosols, granules, baits, and impregnated resin strips. The amount used in the United States in 1974 was estimated to be greater than 1.4 million kg. Dichlorvos also occurs in the environment as a degradation product of trichlorfon and butonate.

Dichlorvos, which has the characteristic anticholinesterase activity of organophosphate insecticides, is used as a contact and stomach poison for control of internal and external parasites of livestock and insects in houses, buildings, restaurants, storage, and outdoor areas. Because of its high vapor pressure, it is very effective in closed areas. It is not directly applied

to soil or water because of its volatility and rapid degradation by hydrolysis. It also is used in polyvinyl chloride resin strips worn by cats and dogs as collars for flea control. Dichlorvos is administered to humans (12 mg/kg) and domestic animals as an anthelmintic (Pena Chavarri et al., 1969; Hayes, 1982).

In the presence of water, dichlorvos decomposes to dichloroethanol, dichloroacetaldehyde, dichloroacetic acid, dimethylphosphate, dimethylphosphoric acid, and other water soluble compounds. The rate of dichlorvos degradation depends on environmental conditions such as humidity, pH, and temperature. The half-life of dichlorvos in water at pH 7.0 is about 8 hours. Degradation occurs rapidly in alkaline solutions and slowly in acidic solutions. Dichlorvos is not toxic to micro-organisms that degrade organic matter in sewage. Micro-organisms, such as *Bacillus cereus*, can utilize dichlorvos as a sole carbon source, but not as a sole phosphorus source, and are partially responsible for the rapid loss of dichlorvos in soil (Lamoreaux and Newland, 1978). Other micro-organisms known to degrade dichlorvos include *Pseudomonas melophthora* (Boush and Matsumura, 1967) and *Trichoderma viride* (Matsumura and Boush, 1968). There is no evidence that dichlorvos bioaccumulates, and the long-term effect of dichlorvos on the environment is believed to be minimal because of its rapid degradation. Dichlorvos has been detected in a number of agricultural products at concentrations up to 7 mg/kg (IARC, 1979).

Human Exposure

Occupational exposure to dichlorvos may occur during manufacture, formulation, or use or in accidental spills. The National Institute for Occupational Safety and Health estimates that approximately 190,000 workers are exposed to dichlorvos (OSHA, 1977). The general public is exposed to dichlorvos mainly through household and public health use. Although dichlorvos has been detected in food and water soon after application, there is no evidence of human exposure to dichlorvos via water or food because it degrades rapidly. Furthermore, dichlorvos residues are readily destroyed during food processing, e.g., washing and cooking (Abbott et al., 1970). Inhalation and dermal absorption are the main routes of human exposure to dichlorvos.

Absorption

Dichlorvos administered orally to rats is absorbed from the gastrointestinal tract and is rapidly metabolized by the liver (Gaines et al., 1966; Laws, 1966). After administration of an oral dose of [^{32}P]dichlorvos (10 mg/kg) to rats, maximum concentrations of radioactivity in kidney, liver, stomach, and intestines were reached in 1 hour. There was a gradual increase in radioactivity in bones because of the presence in the phosphate pool of inorganic phosphate derived from dichlorvos (Casida et al., 1962). Unchanged dichlorvos was not found in muscle or fat of rabbits administered dichlorvos orally at 5 mg/kg per day for 2 weeks and killed 48 hours after the last dose (Majewski et al., 1979).

When pregnant sows were fed [vinyl-1-^{14}C]dichlorvos or [^{36}Cl]dichlorvos in polyvinyl chloride pellets at 4 mg/kg per day during the last third of the gestation period, the tissues of the sows and piglets contained carbon-14 or chlorine-36 residues ranging from 0.3 to 18 ppm equivalents (Potter et al., 1973a,b). No dichlorvos, dichloroacetaldehyde, desmethyldichlorvos, dichloroacetic acid, or dichloroethanol was found in the tissues. Radioactivity was detected in the tissues of male pigs fed [vinyl-1-^{14}C]dichlorvos (42 mg/kg) in polyvinyl chloride pellets, but no unchanged dichlorvos, dichloroacetaldehyde, desmethyldichlorvos, dichloroacetic acid, or dichloroethanol was found. It was concluded that the radioactivity present in the tissues was due to incorporation of one- and two-carbon fragments derived from the vinyl moiety of dichlorvos into normal tissue constituents.

Inhaled dichlorvos is also absorbed and degraded rapidly. Dichlorvos at low concentrations was detected in the blood, liver, testes, lung, brain, kidney, and fat of rats exposed by inhalation at 90 mg/m^3 for 4 hours, with the highest concentrations found in kidney and fat (Blair et al., 1975). In rats exposed to dichlorvos at 10 mg/m^3 for 4 hours, the parent compound was detected only in the kidney. Unchanged dichlorvos was not detected in the blood, liver, kidney, renal fat, or lung tissues of rats exposed at 0.5 mg/m^3 for 14 days. In young swine exposed to [vinyl-1-^{14}C]dichlorvos at 0.15 mg/m^3 for 24 hours, radioactivity was detected in various tissues, but

unchanged dichlorvos was not found (Loeffler et al., 1976).

In humans, dichlorvos (concentration unknown) was detected in the blood of professional dichlorvos sprayers within 24 hours of exposure but not at 48 hours (Fournier et al., 1978). Dichlorvos was not detected in the blood of two men immediately after inhalation exposure to dichlorvos at 0.25 mg/m^3 for 10 hours or 0.7 mg/m^3 for 20 hours (Blair et al., 1975).

Metabolism

Figure 1 depicts the two metabolic pathways of dichlorvos in the liver:

(1) A glutathione-dependent pathway. This pathway produces primarily desmethyldichlorvos. In addition, *S*-methylglutathione is formed and degraded to methyl mercapturic acid and excreted in the urine (Hutson and Hoadley, 1972a). Further degradation of desmethyldichlorvos to dichloroacetaldehyde and monomethylphosphate is glutathione-independent (Dicowsky and Morello, 1971).

(2) A hydrolytic pathway catalyzed by aryl esterases. The hydrolytic pathway is the predominant pathway in dichlorvos metabolism. The oxygen-vinyl bond is split by a glutathione-independent process, producing dimethyl phosphate and dichloroacetaldehyde. Dimethyl phosphate is not metabolized further (Casida et al., 1962). Dichloroacetaldehyde can be reduced to dichloroethanol or possibly converted to dichloroacetic acid (Hodgson and Casida, 1962) and eventually to dichloroethanol glucuronide, hippuric acid, urea, carbon dioxide, or other endogenous chemicals such as glycine and serine. The final metabolites, such as two-carbon fragments, phosphate ions, and chloride ions, are utilized in the body in the same manner as those coming from other sources. Thus, most of the observed radioactivity in carcasses and tissues of animals administered dichlorvos is present as glycine, serine, and other normal body components (Hutson et al., 1971; Page et al., 1971; Hutson and Hoadley, 1972a,b; Potter et al., 1973a,b; Loeffler et al., 1976).

Dichlorvos is also metabolized in the blood, adrenal gland, kidney, lung, and spleen to dimethyl phosphate, desmethyldichlorvos, monomethylphosphate, and inorganic phosphate (Loeffler et al., 1976).

The half-life of dichlorvos in blood is difficult to determine because its metabolism is rapid. In one inhalation study in which rats were exposed at 50 mg/m^3 for 4 hours, a half-life of 13.5 minutes in the kidney was reported (Blair et al., 1975).

None of the metabolites of dichlorvos is more toxic than the parent compound; however, dichloroacetaldehyde reportedly induced base-pair substitutions in Salmonella (Lofroth, 1978) and dominant lethal mutations in mice (Fischer et al., 1977).

Metabolism studies of dichlorvos in mice, rats, Syrian hamsters, pigs, goats, cows, and humans have shown that dichlorvos is metabolized by these species at different rates but that the metabolites are similar (Hutson and Hoadley, 1972a; Page et al., 1971).

Excretion

The mode of excretion of dichlorvos metabolites is similar in different species. In general, urine is the major route of elimination of the phosphorus-containing moiety; a secondary route is expired air. The vinyl moiety is excreted primarily in expired air and secondarily in urine.

In rats dosed orally with [^{32}P]dichlorvos at 0.1-80 mg/kg, 60%-70% of the radioactivity was recovered in urine and 10% in feces in 7 days (Casida et al., 1962). A glucuronic acid conjugate of dichloroethanol was excreted in urine. Metabolites excreted in the feces were not identified. Goats also excreted about 80% of the [^{32}P]dichlorvos metabolites in urine and about 15% in feces. In cows, 70%-80% of radioactivity of intravenously or subcutaneously injected [^{32}P]dichlorvos was excreted in urine and 15% in feces. A trace of organosoluble phosphorus was

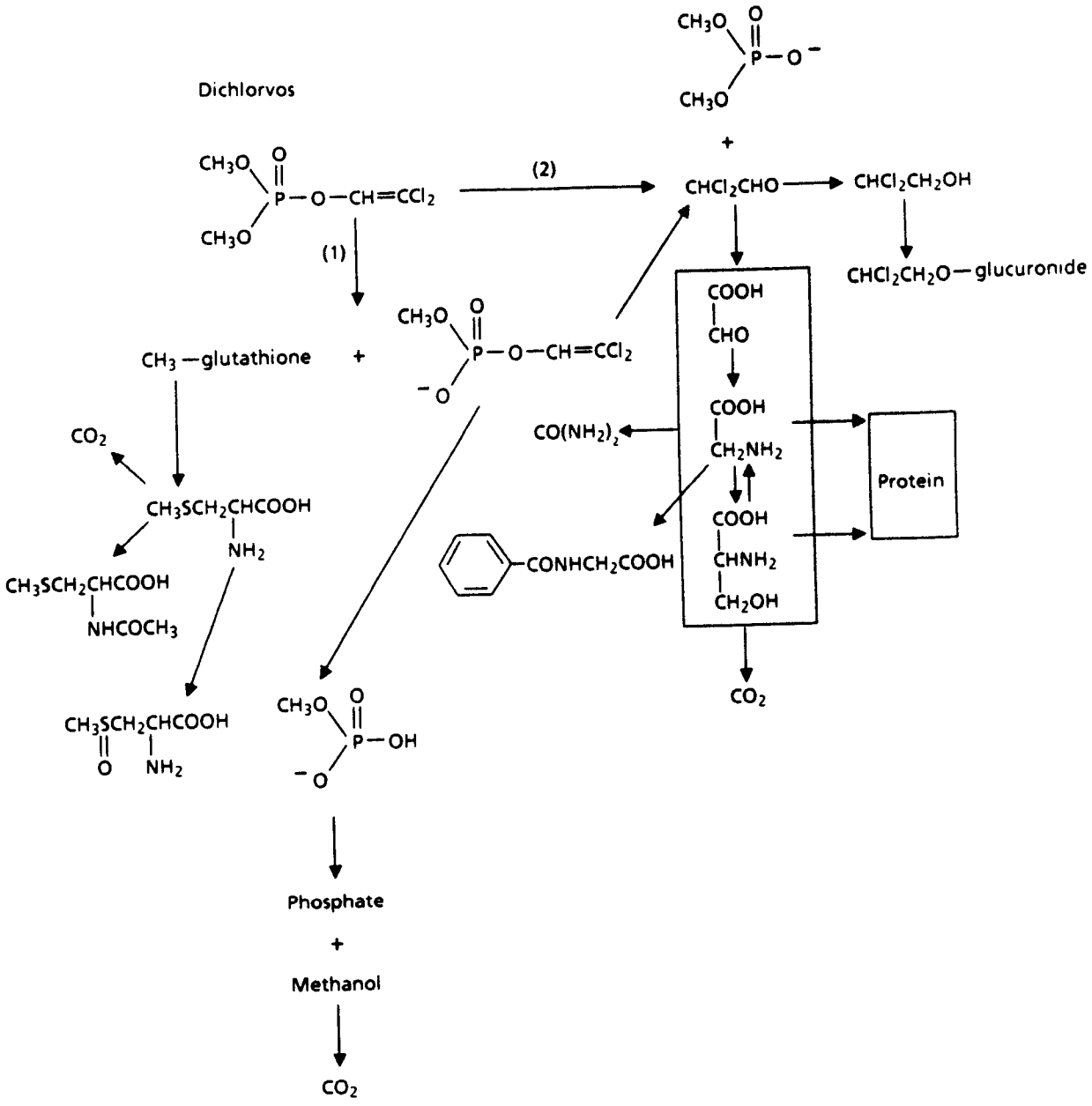

FIGURE 1. METABOLIC PATHWAYS OF DICHLORVOS
(Wright et al., 1979)

detected in milk during the first 2 hours after intravenous or oral administration of [^{32}P]dichlorvos. In the following 4-48 hours, a substantial amount of unextractable phosphorus-32 radioactivity was found in milk.

After administration of an oral dose of [methyl-^{14}C]dichlorvos to rats and mice, about 60% of the radioactivity was excreted in urine, primarily as dimethyl phosphate, and 15% was exhaled as carbon dioxide in 4 days, primarily during the first 24 hours (Hutson and Hoadley, 1972b).

After rats received an oral dose of [vinyl-1-^{14}C]dichlorvos, 10%-20% of the carbon-14 was excreted in urine, 3%-5% in feces, and 40% as carbon dioxide in expired air over a 4-day period (Hutson et al., 1971). In a man, 27% of orally administered [vinyl-1-^{14}C]dichlorvos (5 mg in orange juice) was exhaled as [^{14}C]carbon dioxide in 8 hours, and 8% was excreted in urine in 24 hours. No radioactivity was detected in urine by day 9 (Hutson and Hoadley, 1972a).

Biochemical Effects

The mode of action of dichlorvos is inhibition of cholinesterase. The pI_{50} of dichlorvos is 5.66 (Durham et al., 1957). Death due to respiratory failure occurs when a high percentage of brain cholinesterase activity is inhibited.

Rats fed diets containing 5 ppm dichlorvos for 4 days showed a detectable reduction of blood cholinesterase. Administration of dichlorvos to dogs in capsules at 0.65 or 1.30 mg/kg per day lowered brain cholinesterase activity by 22% and 67%, respectively (FAO/WHO, 1967). Monkeys exposed to dichlorvos at 7 mg/m^3 for 2 hours per day for 4 days had lower blood cholinesterase activity than did controls (Durham et al., 1957). Men showed a dose-related reduction in erythrocyte cholinesterase activity after receiving a single oral dose (up to 32 mg/kg) of dichlorvos in a polyvinyl chloride formulation (Slomka and Hine, 1981). In the same persons, plasma cholinesterase activity was lowered 50% at 1 mg/kg and 80% at 6 mg/kg.

Inhalation exposure to dichlorvos at low concentrations inhibits cholinesterase activity at the site of direct contact without exerting any systemic effect (Schmidt et al., 1979). For example, acetylcholinesterase activity of bronchial homogenates was reduced to 63% and 51% when rats were exposed to dichlorvos at 0.8 or 1.8 mg/m^3, respectively. Blood acetylcholinesterase activity of these rats was not affected. At 4.3 mg/m^3, the activities in both bronchial homogenate and blood dropped to 40% of control values.

Dichlorvos has a greater affinity for insect than for mammalian cholinesterase. The I_{50} of mouse brain cholinesterase is 10^{-7} M, whereas that of fly head cholinesterase is 10^{-9} M (Hayes, 1982).

Rath and Misra (1981) reported that inhibition of brain and liver cholinesterase of the fresh water fish *Tilapia mossambica* by dichlorvos (0.25-1.25 mg/liter) was dose and time dependent. Dichlorvos also inhibits growth of certain algae, plankton, and fungi species but has no effect on bacteria (Cain and Cain, 1984).

In vitro studies have demonstrated that dichlorvos alkylates isolated bacterial and mammalian nucleic acids and produces 3-methylguanine, 7-methylguanine, 3-methyladenine, and O^6-methylguanine. Dichlorvos also methylates nucleic acids and proteins of intact *Escherichia coli* and HeLa cells (Lawley et al., 1974).

Methylation of guanine moieties by dichlorvos also has been detected from urine samples of mice exposed to [^{14}C- or ^{3}H-methyl]dichlorvos by inhalation or intraperitoneal injection (Wennerberg and Lofroth, 1974). Methylation of N^7-guanine in DNA isolated from testis, spleen, liver, kidney, brain, heart, and lung has also been reported after intraperitoneal administration of [methyl-^{14}C]dichlorvos to mice (Segerback and Ehrenberg, 1981).

Acute Toxicity and Exposure Limits

The LD_{50} values are 80 and 55 mg/kg for dichlorvos administered orally and 107 and 75 mg/kg for dichlorvos applied dermally for male and female rats, respectively (Hayes, 1982). The oral LD_{50} values for male and female mice are 135-148 mg/kg, and the subcutaneous LD_{50} values are 22-24 mg/kg. The signs of intoxication are typical of organophosphorus poisoning (i.e., salivation, lacrimation, diarrhea, tremors, and terminal convulsions), with death occurring from

respiratory failure. The signs of intoxication are usually apparent shortly after dosing. Survivors usually recover completely within 24 hours. Dichlorvos is less toxic when administered via the dermal and oral routes than via the respiratory route.

A man reportedly died after ingesting about 400 mg/kg dichlorvos, and two workers died after their skin was splashed with a concentrated dichlorvos formulation and they failed to wash it off (Hayes, 1982). A woman who ingested about 100 mg/kg dichlorvos survived after intensive care.

The permissible exposure level for dichlorvos set by the Occupational Safety and Health Administration is 0.1 ppm or 1.2 mg/m^3 (OSHA, 1977), and the short-term exposure level is 0.3 ppm or 3.6 mg/m^3. The acceptable daily intake for humans established by the Joint FAO/WHO Expert Committee on Pesticide Residues is 0-0.004 mg/kg (FAO/WHO, 1978).

Birds are more sensitive to dichlorvos than are mammals. The acute oral LD_{50} values for redwing blackbirds, common pigeons, quail, house sparrows, and common grackles range from 13 to 24 mg/kg; for starlings, the LD_{50} value is 42 mg/kg (Schafer and Brunton, 1979). The dietary LD_{50} values (5 days of formulated diet followed by 3 days of untreated diet) for Japanese quail and ring-neck pheasants are 300 and 570 mg/kg, respectively (Hill et al., 1975).

The 96-hour LC_{50} values for estuarine fish species are less than 3 mg/liter (Eisler, 1970).

Genotoxic Effects

Dichlorvos has been extensively studied for mutagenicity and has been demonstrated to be mutagenic in a wide variety of in vitro and in vivo systems (see reviews by Wild, 1975, and Ramel, 1981). Dichlorvos is only weakly effective in methylating isolated DNA in vitro, primarily at the N^7 atom of guanine (Lofroth, 1970; Lawley et al., 1974). It has been shown to alkylate DNA from intact bacterial and mammalian cells via a mechanism similar to, but much slower than, that of methyl methanesulfonate alklation (Lawley et al., 1974). Exposure to dichlorvos also produces strand breakage in isolated DNA (Rosenkranz and Rosenkranz, 1972; Olinski et al., 1980), as well as in DNA of viral (Shooter, 1975) and bacterial systems (Green et al., 1974; Griffin and Hill, 1978).

Dichlorvos is clearly mutagenic in bacterial and fungal test systems both with and without metabolic activation. This activity is attributed mainly to the methylating ability of the chemical. Early work with *E. coli* in the absence of exogenous metabolic activation (S9) indicated that the mutagenicity of dichlorvos was dependent on error-prone DNA repair pathways (Bridges et al., 1973; Mohn, 1973; Wild, 1973; Nagy et al., 1975; Green et al., 1976). Subsequent tests demonstrated that the mutagenic activity of dichlorvos in *E. coli* is unaffected by the addition of S9 (Shirasu et al., 1977; Moriya et al., 1978). Induction of gene mutations by dichlorvos in the absence of S9 has been reported for several other bacterial species (Dean, 1972; Voogd et al., 1972; Dyer and Hanna, 1973; Carere and Morpurgo, 1981). Dichlorvos was reported to induce gene mutations in *Salmonella typhimurium* base substitution strains TA1535 and TA100 (Byeon et al., 1976; Shirasu et al., 1976, 1977; Carere et al., 1978a,b; Bartsch et al., 1980; Braun et al., 1982). Because only strain TA100 employs error-prone DNA repair, the observations of gene mutation in TA1535 indicate that mutation induction by dichlorvos is not dependent on particular DNA repair pathways. The differential sensitivity of *E. coli* WP2 try$^-$ derivatives hcr$^+$ (excision-repair competent) and hcr$^-$ (excision-repair deficient) to the mutagenic action of dichlorvos supports this contention (Nagy et al., 1975). A National Toxicology Program (NTP) Salmonella assay demonstrated significant mutagenic activity in strain TA100 following preincubation with dichlorvos in both the presence and absence of S9 from Aroclor 1254-induced Sprague Dawley rat or Syrian hamster liver; no increase in histidine-revertant colonies was observed in strain TA98 (frameshift mutant with error-prone DNA repair) (Table E1).

The mutagenicity of dichlorvos to fungi includes studies with both Saccharomyces and Aspergillus. Gene mutation (Bignami et al., 1977; Morpurgo et al., 1977), somatic crossing-over

(Bignami et al., 1977; Morpurgo et al., 1977), and nondisjunction (Bignami et al., 1977; Morpurgo et al., 1979) were demonstrated in *Aspergillus nidulans* following exposure to dichlorvos. Morpurgo et al. (1977) concluded that dichlorvos exerts its genotoxic effect only in metabolically active cells or in cells undergoing division, since no mutational events were detected after treatment of quiescent conidia with dichlorvos. Mitotic gene conversion in *Saccharomyces cerevisiae* was reported by Dean et al. (1972) and Fahrig (1974) when the cells were exposed directly to dichlorvos in vitro; however, no increases in mitotic gene conversion were measured at either of two loci when yeast cells were exposed within the peritoneal cavity of male mice receiving 100 mg/kg orally or up to 99 µg/liter by inhalation for 5 hours. This single dose is equivalent to that accumulated over a 1- to 2-week period in the 2-year rodent studies. The failure to induce mutations in yeast exposed in an in vivo mammalian host-mediated assay is presumably due to the rapid metabolic breakdown of dichlorvos by the animal (Dean et al., 1972).

Dichlorvos is both a gene mutagen and a clastogen for mammalian cells exposed in vitro. A significant increase in forward mutations at the $TK^{+/-}$ locus in mouse lymphoma L5178Y cells was induced with dichlorvos in the absence of exogenous metabolic activation; this assay was not performed with S9 (Table E2). In NTP cytogenetic studies with Chinese hamster ovary (CHO) cells, dichlorvos induced both sister chromatid exchanges (SCEs) and chromosomal aberrations in the absence and presence of Aroclor 1254-induced Sprague Dawley rat liver S9 (Tables E3 and E4). These results are similar to those from other studies with CHO cells (Tezuka et al., 1980; Ishidate and Yoshikawa, 1980; Sasaki et al., 1980; Nishio and Uyeki, 1981). Unscheduled DNA synthesis in EUE cells and human lymphocytes has also been reported (Perocco and Fini, 1980; Benigni and Dogliotti, 1980).

Gupta and Singh (1974) reported induction of aberrations in salivary gland chromosomes of *Drosophila melanogaster* third instar larvae after administration of 1 ppm dichlorvos in feed; however, a similar procedure that also would have been expected to yield a high incidence of sex-linked recessive lethal mutations was negative to that endpoint (Kramers and Knapp, 1978). Although results of assays for sex-linked recessive lethal mutations with dichlorvos were negative (Jayasuriya and Ratnayake, 1973; Sobels and Todd, 1979), feeding the chemical at a gradually increasing dose of 0.1-0.75 ppm to 30 continuous generations of larvae of a pesticide-resistant strain of Oregon-R flies was reported to produce significant numbers of autosomal recessive lethal mutations (Hanna and Dyer, 1975).

In vivo mammalian tests with rodents exposed to dichlorvos via various routes of administration, including inhalation, oral gavage, and intraperitoneal injection, were generally negative with the exception of chromosomal aberrations induced in Syrian hamsters given intraperitoneal injections of 3, 6, 15, or 30 mg/kg dichlorvos (Dzwonkowska and Hubner, 1986). Chromatid breaks were observed at the two highest doses, but the rates were not proportional to the dose. Assays for induction of SCEs in mouse peripheral blood cells (Kligerman et al., 1985), for chromosomal aberrations in bone marrow of mice (Dean and Thorpe, 1972a; Kurinnyi, 1975) and Chinese hamsters (Dean and Thorpe, 1972a) as well as in testes of mice and Chinese hamsters (Dean and Thorpe, 1972a), and for dominant lethal mutations in mice (Dean and Thorpe, 1972b; Epstein et al., 1972; Dean and Blair, 1976; Moutschen-Dahmen et al., 1981) were uniformly negative.

Segerback (1981) concluded that dichlorvos exposure in vivo presents a relatively low genetic risk, based on the very small amounts of methylated guanine-N^7 detected in pooled soft organs of male mice given a high dose of dichlorvos by intraperitoneal injection. In that study, the clearance time of dichlorvos was estimated to be about 2 minutes, a much longer time than was found in previous studies; this may possibly indicate that the arylesterase metabolic systems normally used in the breakdown of dichlorvos were saturated. The primary nucleophilic reaction by dichlorvos in vivo is not methylation but phosphorylation. A slower degradation of dichlorvos due to saturation of arylesterases, however, could lead to an increased rate of methylation.

Degradation of dichlorvos by nucleophilic attack at the phosphorus moiety generates a mutagenic intermediate, dichloroacetaldehyde, which is in turn converted to dichloroethanol. The action of these compounds may present a greater genetic risk to the organism than alkylation, particularly since it is this pathway by which dichlorvos is metabolized in higher organisms. Dichloroacetaldehyde induced reverse mutations in Salmonella strain TA100 both with and without S9, but the strength of the mutagenic response was reduced in the presence of S9 (Lofroth, 1978; Bignami et al., 1980). Lofroth (1978) also reported a similar pattern of mutagenic activity in TA1535. Gene mutation after exposure to dichloroacetaldehyde in the absence of S9 was also observed in *Streptomyces coelicolor* and *A. nidulans* (Bignami et al., 1980). Fischer et al. (1977) reported induction of dominant lethal mutations in Jena-Halle mice after a single intraperitoneal injection of 176 mg/kg dichloroacetaldehyde. Treatment with dichloroethanol in the absence of exogenous metabolic activation induced gene mutations in *S. coelicolor*, *A. nidulans*, and *Klebsiella pneumoniae* (Voogd et al., 1972; Bignami et al., 1980).

Carcinogenesis

Increased tumor incidences have not been observed in previous studies in rats and mice exposed to dichlorvos for 2 years. Negative results were reported for rats exposed at 280 mg/liter in drinking water (M. Enomoto, personal communication) or at 4.7 mg/m^3 by inhalation (Blair et al., 1976). In a study reported in an abstract, no tumors attributable to dichlorvos administration were observed in rats receiving dichlorvos in feed at up to 25 mg/kg per day for 2 years and dogs receiving up to 10 mg/kg per day for 2 years (Witherup et al., 1971). Details of the study were not available.

Male and female Osborne-Mendel rats given feed containing dichlorovos at time-weighted-average concentrations of 7 or 16 mg/kg per day (150 and 326 ppm) and male and female B6C3F$_1$ mice given feed containing dichlorovos at concentrations of 41 or 81 mg/kg per day (318 and 635 ppm) for 78 weeks and killed at 110-111 weeks (rats) or 92-94 weeks (mice) did not have significant increases in tumor incidences (NCI, 1977). However, in mice, one low dose male and one high dose female had squamous cell carcinomas of the esophagus; one high dose female had a papilloma of the esophagus, and two low dose males and one high dose female had focal hyperplasia of the esophageal epithelium. These neoplasms were considered to be unusual.

In in vitro assays with Syrian hamster embryo cells, a low transformation frequency was recorded when the cells were incubated with dichlorvos (Tu et al., 1986). Dichlorvos was also reported to enhance SA7 transformation of hamster embryo cells (Hatch et al., 1986).

No epidemiologic studies or case reports examining the relationship between exposure to dichlorvos and human cancer incidences were found in the literature. Based on existing data, the International Agency for Research on Cancer was unable to evaluate the carcinogenicity of dichlorvos (IARC, 1979).

Effects on Reproduction

In a three-generation study, rats were exposed to dichlorvos at dietary concentrations of 0, 0.1, 1, 10, 100, or 500 ppm (Witherup et al., 1971). No harmful effects on reproduction, survival, or growth were observed.

Reproductive activity of male and female swine given dichlorvos at 500 ppm in feed was normal (Collins et al., 1971). Development of offspring was normal in pigs fed dichlorvos at 800 mg per animal through gestation (Batte et al., 1969) and in a pregnant cow fed 6.2 mg/kg per day for 134 days before parturition (Macklin and Ribelin, 1971). Inhalation studies in which 15 rats were exposed to dichlorvos from day 1 through day 20 of pregnancy at doses up to 6.25 mg/m^3 (0.027-0.69 ppm), 23 hours per day, revealed no effects on pregnancies, number of fetal resorptions, late fetal deaths, litter size, or fetal weights (Thorpe et al., 1972).

Embryotoxicity was not observed in gavage and inhalation studies of CF-1 mice and New Zealand rabbits at doses that did not cause maternal toxicity (Schwetz et al., 1979). When pregnant New Zealand rabbits were given dichlorvos in corn oil by gavage at 5 mg/kg from day 6 through

day 18 of gestation, the number of resorptions was increased. Reversible disturbances in spermatogenesis were observed in mice given toxic doses of dichlorvos (Wyrobek and Bruce, 1975).

Dichlorvos is not teratogenic in rats (Witherup et al., 1971) or rabbits (Vogin et al., 1971; Thorpe et al., 1972), but Kimbrough and Gaines (1968) reported that 3/41 fetuses of rats receiving a single intraperitoneal injection of 15 mg/kg on day 11 of pregnancy developed omphaloceles.

Immunotoxicity

In studies of effects of pesticides on immunologic reactivity, Desi et al. (1978) reported that dichlorvos orally administered to rabbits caused a dose-related decrease in antibody titer against *S. typhimurium*. Dichlorvos compromised both the humoral immune response to *S. typhimurium* and cell-mediated immunity measured by the tuberculin skin test (Desi et al., 1980). Immunosuppression occurred only at doses producing severe anticholinesterase suppression and was thought to be associated with cholinergic poisoning (Casale et al., 1983).

Study Rationale

Dichlorvos was selected for toxicity and carcinogenesis studies because of its widespread human exposure, reported mutagenicity, and chemical structure and the appearance of a small number of rare tumors of the esophagus in mice in a previous National Cancer Institute study (NCI, 1977). In a carcinogenesis study submitted by one manufacturer to the U.S. Environmental Protection Agency (EPA), a few tumors were found. The EPA was interested in further carcinogenesis study of dichlorvos to evaluate the significance of these tumors. The major routes of human exposure are dermal and inhalation. Because dichlorvos is unstable in feed and drinking water, the gavage route of administration was selected. Further, previous studies have shown that metabolic pathways of dichlorvos administered to rats orally or by inhalation are similar (Hutson et al., 1971).

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF DICHLORVOS

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Study Design

Source and Specifications of Animals

Animal Maintenance

Clinical Examinations and Pathology

Statistical Methods

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF DICHLORVOS

Dichlorvos (technical-grade Vapona®) was obtained in one lot (lot no. SDC 092179) from Shell Development Company (Houston, Texas) as a clear, pale yellow liquid with a boiling point of 242.8° C at 730.4 mm mercury and a density of 1.4161 ± 0.0001(δ) g/ml at 22° C. Chemical identity and purity analyses were conducted at Midwest Research Institute (MRI) (Kansas City, Missouri). MRI reports on analyses performed in support of the dichlorvos studies are on file at the National Institute of Environmental Health Sciences.

The chemical identity of the study material was confirmed by spectroscopy. The infrared (Figure 2), ultraviolet/visible, and nuclear magnetic resonance (Figure 3) spectra were consistent with the literature spectra (Sadtler Agricultural Spectra; Keith et al., 1968; Core et al., 1971).

Purity was found to be approximately 99% as determined by elemental analysis, water analysis, thin-layer chromatography, and gas chromatography. Results of elemental analyses agreed with the theoretical values for carbon, hydrogen, chlorine, and phosphorus. The water content by Karl Fischer titration was 0.023%. A major spot and two minor impurities were detected by thin-layer chromatography on silica gel plates with a hexanes:acetone (80:20) solvent system and a spray of 0.5% silver nitrate in ethanol for visualization (Touchstone and Dobbins, 1978). Gas chromatography with a 5% NPGSB/1% phosphoric acid column, a nitrogen carrier at a flow rate of 30 ml/minute, and flame ionization detection indicated 10 impurities that had a combined area 0.62% of the major peak area; dichloroacetaldehyde, quantitated against a standard, was present at a concentration of 0.1% by this gas chromatographic system. Eight impurities, which had a combined area 1.12% of the major peak area, were detected by gas chromatography with a 3% SP2100 column, a nitrogen carrier at a flow rate of 70 ml/minute, and flame ionization detection.

Stability studies performed by gas chromatography with a 5% NPGSB/1% phosphoric acid column, a nitrogen carrier at 30 ml/minute, and flame ionization detection indicated that dichlorvos was stable as a bulk chemical when stored for 2 weeks at temperatures up to 60° C. Further confirmation of the bulk chemical stability during the toxicity studies (storage at −20° C to 5° C) was obtained by the same gas chromatographic system and a second system with a 3% OV-1 column. No degradation was seen over the course of the studies. Identity of the chemical at the study laboratory was confirmed by infrared spectroscopy.

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES

Dose mixtures were prepared by mixing the appropriate amounts of dichlorvos with corn oil (Table 1). Studies to determine the stability of dichlorvos in rodent feed were conducted. Feed mixes containing 600 ppm dichlorvos were stored, sealed, and protected from light at temperatures of −20° C, 5° C, 25° C, and 45° C. Feed samples were also stored under simulated study conditions of room temperature in a rat cage, open to air and light for up to 48 hours. Samples from the stability studies were extracted with methanol:acetic acid solutions (99:1), and the extracts were analyzed by gas chromatography with a 5% NPGSB/1% phosphoric acid column and an electron-capture detector. The analysis indicated that dichlorvos was not stable in feed when stored for 2 weeks at temperatures from −20° C to 45° C and underwent a 13% reduction in concentration after 24 hours under simulated cage conditions and a 24% reduction after 48 hours.

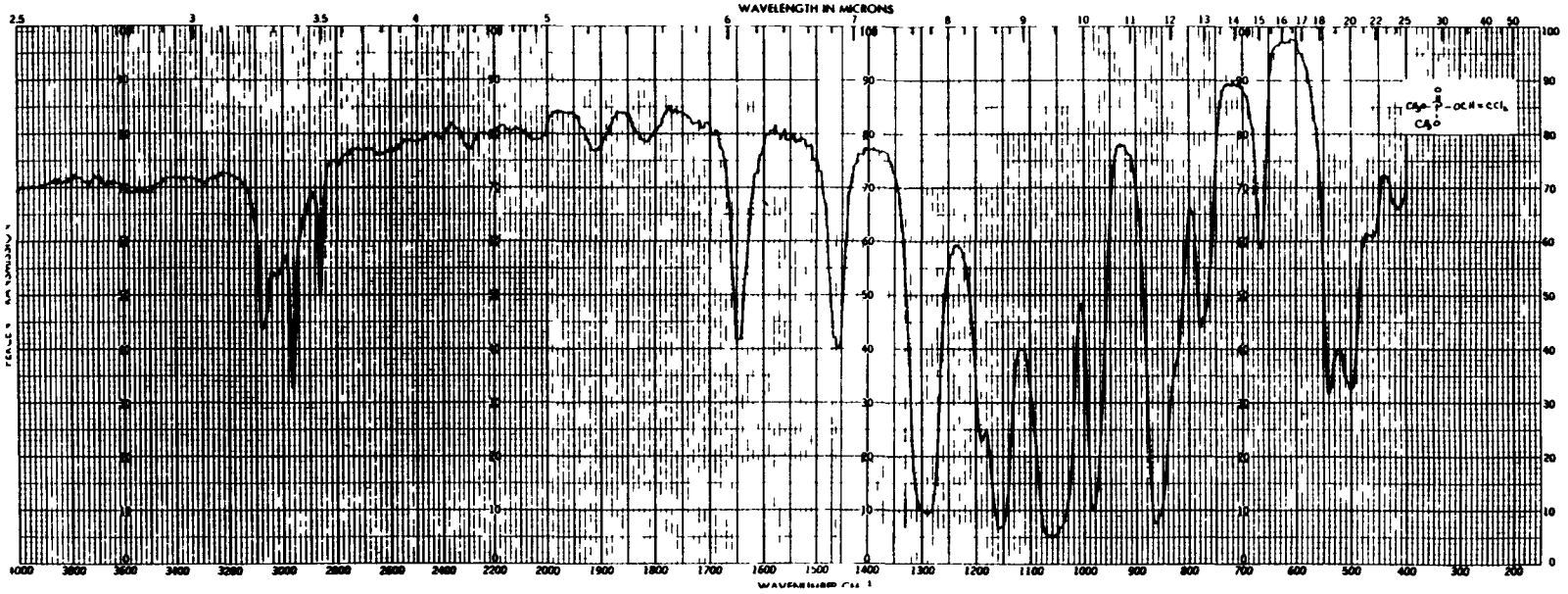

FIGURE 2. INFRARED ABSORPTION SPECTRUM OF DICHLORVOS (LOT NO. SDC 092179)

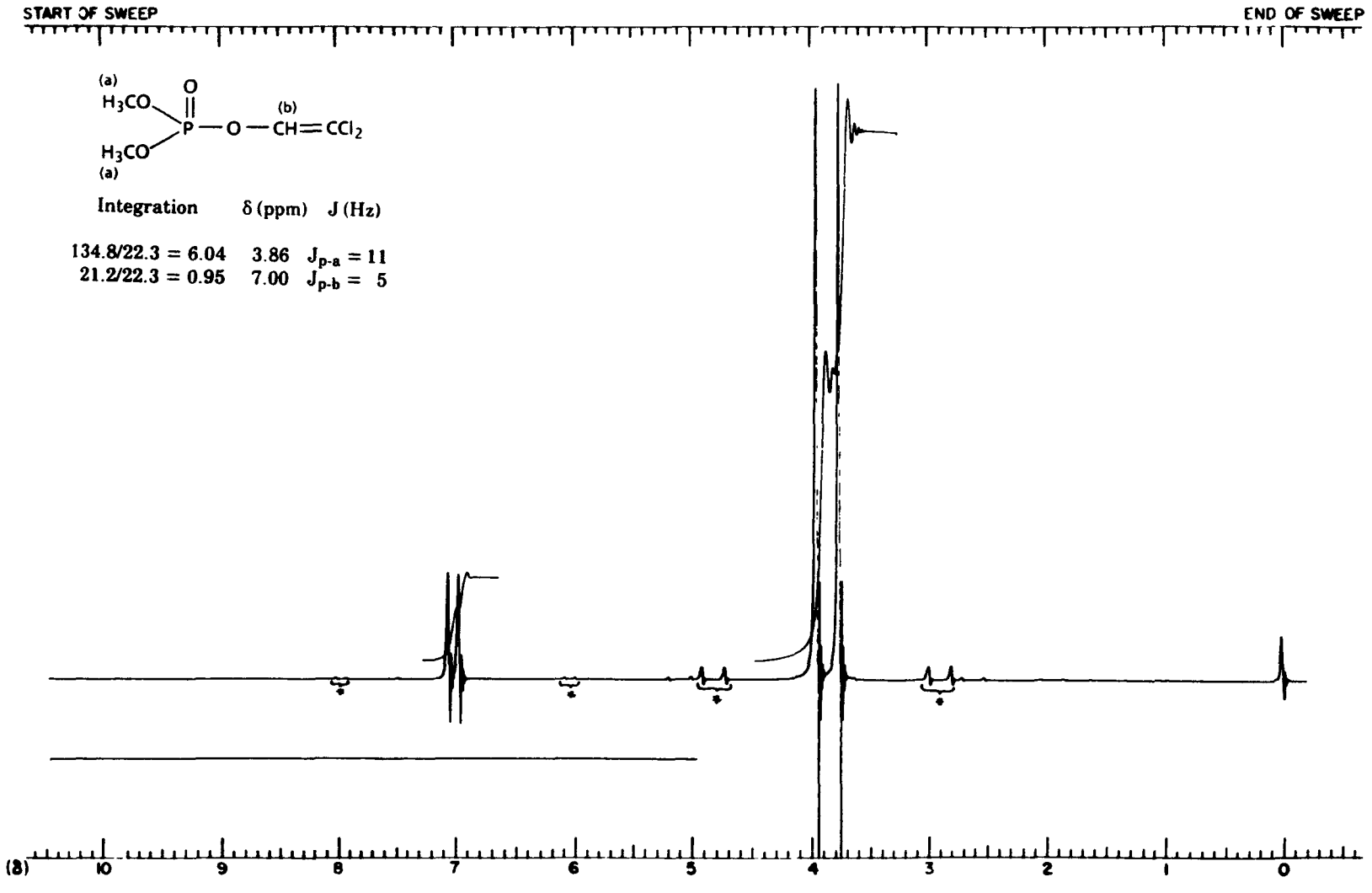

FIGURE 3. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF DICHLORVOS (LOT NO. SDC 092179)

TABLE 1. PREPARATION AND STORAGE OF DOSE MIXTURES IN THE GAVAGE STUDIES OF DICHLORVOS

Thirteen-Week Studies	Two-Year Studies
Preparation	
Weighed amount of chemical added by syringe and 23-gauge needle into tared beaker. Corn oil added to specified volume and mixture stirred with stir bar until homogeneous in appearance (at least 5 min). Mixture protected from light	Before 3/13/81: weighed amount of chemical at room temperature added to tared beaker. Corn oil added to specified volume and mixture stirred with stir bar for 30 min. Beginning 3/13/81: volume of chemical at room temperature added by pipette to weight of corn oil at vortex and stirred with stir bar for approximately 5 min
Maximum Storage Time	
2 wk	2 wk
Storage Conditions	
5° C in the dark	5° C in the dark

Stability studies of corn oil solutions of dichlorvos were conducted. Solutions of dichlorvos in corn oil at a concentration of approximately 6 mg/ml showed no loss of study chemical after 14 days in the dark at room temperature and at 5° C. No loss was found for solutions exposed to air and light for 3 hours. The stability was monitored by dilutions of the corn oil solutions with hexane and gas chromatographic analysis with the conditions described above for the feed stability study. Dose formulations were stored in amber glass serum bottles at 5° C.

Periodic analysis for dichlorvos in dose mixtures with the same gas chromatographic quantitation step (carrier gas at a flow rate of 25-35 ml/minute) was performed by the study and analytical chemistry laboratories to determine if the dose mixtures contained the correct concentrations of dichlorvos. Dose mixtures were analyzed three times during the 13-week studies (Table 2). The results ranged from 89% to 308% of the target concentrations; the second highest concentration was 131%. During the 2-year studies, the dose mixtures were analyzed approximately every 8 weeks; concentrations varied from 85% to 113% of the target concentrations (Table 3). Because 63/68 dose mixtures analyzed were within 10% of the target concentrations, the dose mixtures were estimated to have been within specifications 93% of the time throughout the entire studies. Referee analysis was performed periodically by the analytical chemistry laboratory (Table 4). Good agreement was generally found between laboratories.

TABLE 2. RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE THIRTEEN-WEEK GAVAGE STUDIES OF DICHLORVOS

Date Mixed	Concentration of Dichlorvos in Corn Oil (percent, w/v) (a)		Determined as a Percent of Target
	Target	Determined	
04/15/80	0.04	(b) 0.046	115
	0.05	(b) 0.058	116
	0.08	0.082	103
	0.10	0.110	110
	0.16	0.160	100
	0.20	(b) 0.262	131
	0.32	0.332	104
	0.40	0.402	101
	0.64	0.653	102
	0.80	0.845	106
	1.28	1.27	99
	1.60	1.47	92
05/13/80	0.04	(b) 0.047	118
	0.05	(b) 0.058	116
	0.08	0.082	103
	0.10	(b) 0.126	126
	0.16	0.166	104
	0.20	(b) 0.230	115
	0.32	0.348	109
	0.40	(b) 1.23	308
	0.64	0.572	89
	0.80	0.823	103
	1.28	(b) 1.45	113
	1.60	1.68	105
06/17/80	0.04	(b) 0.046	115
	0.05	0.050	100
	0.08	0.082	103
	0.10	0.096	96
	0.16	0.176	110
	0.20	0.190	95
	0.32	0.286	89
	0.40	0.397	99
	0.80	0.729	91
	1.60	1.44	90

(a) Results of duplicate analysis
(b) Out of specifications; not remixed.

TABLE 3. RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR GAVAGE STUDIES OF DICHLORVOS (a)

Date Mixed	Concentration of Dichlorvos in Corn Oil for Target Concentration (percent, w/w) (b) 0.09	0.11	0.17	0.22	0.44
01/23/81	(c) 0.0757		0.155		
01/27/81	(d) 0.0811		(d) 0.184		
01/30/81		0.120		0.216	0.456
02/27/81	(c) 0.0781	0.110			0.434
03/02/81	(d) 0.0905				
03/27/81			0.154	0.198	
04/24/81	0.089	0.106			0.421
05/22/81			0.180	0.243	
06/19/81	0.0822	0.110			0.420
07/17/81			0.185	0.232	
08/14/81	0.0927	0.118			0.441
09/11/81			0.172	0.212	
10/09/81	0.0854	0.110			0.405
11/06/81			0.168	0.213	
12/04/81	0.093	(c) 0.124			0.457
12/10/81		(d) 0.114			
01/08/82	0.0908	0.120	0.178	0.217	0.440
04/16/82	0.0810	0.109	0.156	0.216	0.442
04/30/82	0.0918	0.107	0.176	0.223	0.449
06/25/82	0.0947	0.120	0.182	0.226	0.456
08/27/82	0.0906	(c) 0.124	0.168	0.214	0.449
09/01/82		(d) 0.103			
10/15/82	0.0942	0.116	0.182	0.230	0.466
12/10/82	0.0937	(c) 0.122	0.178	0.220	0.448
12/15/82		(d) 0.106			
Mean (percent)	0.0881	0.115	0.172	0.220	0.442
Standard deviation	0.0064	0.0065	0.0109	0.0112	0.0168
Coefficient of variation (percent)	7.3	5.7	6.3	5.1	3.8
Range (percent)	0.0757-0.0947	0.106-0.124	0.154-0.185	0.198-0.243	0.405-0.466
Number of samples	14	14	13	13	14

(a) Results of duplicate analysis
(b) Values for mix dates 1/23/81, 1/27/81, and 1/30/81 have been converted from percent, w/v, to percent, w/w.
(c) Out of specifications; not used in the study.
(d) Remix; not included in the mean.

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

Date Mixed	Target Concentration (percent, w/w)	Determined Concentration (percent, w/w) (a) Study Laboratory (b)	Referee Laboratory (c)
02/27/81	0.44	0.434	0.472
07/17/81	0.22	0.232	0.235
01/08/82	0.09	0.0908	0.0974
08/27/82	0.17	0.168	0.167

(a) Referee values for mix dates 2/27/81, 7/17/81, and 1/8/82 have been converted from percent, w/v, to percent, w/w.
(b) Results of duplicate analysis
(c) Results of triplicate analysis

II. MATERIALS AND METHODS

THIRTEEN-WEEK STUDIES

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

Four-week-old male and female F344/N rats and $B6C3F_1$ mice were obtained from Charles River Breeding Laboratories, observed for 3 weeks, distributed to weight classes, and assigned to cages and groups according to tables of random numbers. Groups of 10 rats of each sex were administered 0, 2, 4, 8, 16, 32, or 64 mg/kg dichlorvos in corn oil by gavage, 5 days per week for 13 weeks. Groups of 10 mice of each sex were administered 0, 5, 10, 20, 40, 80, or 160 mg/kg dichlorvos on the same schedule. Further experimental details are summarized in Table 5.

Animals were observed two times per day; moribund animals were killed. At the end of the studies, survivors were killed. A necropsy was performed on all animals except those excessively autolyzed or cannibalized. Tissues and groups examined are listed in Table 5.

TWO-YEAR STUDIES

Study Design

Groups of 50 rats of each sex were administered nominal doses of 0, 4, or 8 mg/kg dichlorvos in corn oil by gavage, 5 days per week for 103 weeks (actual doses, 0, 4.14, or 7.82 mg/kg). Groups of 50 male mice were administered 0, 10, or 20 mg/kg dichlorvos and groups of 50 female mice were administered 0, 20, or 40 mg/kg dichlorvos on the same schedule.

Source and Specifications of Animals

The male and female F344/N rats and $B6C3F_1$ (C57BL/6N, female × C3H/HeN MTV^-, male) mice used in these studies were produced under strict barrier conditions at Charles River Breeding Laboratories. Breeding stock for the foundation colonies at the production facility originated at the National Institutes of Health Repository. Animals shipped for study were progeny of defined microflora-associated parents that were transferred from isolators to barrier-maintained rooms. Rats were shipped to the study laboratory at 4 weeks of age and mice at 6 weeks. The rats were quarantined at the study laboratory for 14 days and the mice for 19 days. Thereafter, a complete necropsy was performed on five animals of each sex and species to assess their health status. The rats were placed on study at 7 weeks of age and the mice at 8 weeks. The health of the animals was monitored during the course of the studies according to the protocols of the NTP Sentinel Animal Program (Appendix F).

A quality control skin grafting program has been in effect since early 1978 to monitor the genetic integrity of the inbred mice used to produce the hybrid $B6C3F_1$ study animal. In mid-1981, data were obtained that showed incompatibility between the NIH C3H reference colony and the C3H colony from a Program supplier. In August 1981, inbred parental lines of mice were further tested for genetic integrity via isozyme and protein electrophoresis profiles that demonstrate phenotype expressions of known genetic loci.

The C57BL/6N mice were homogeneous at all loci tested. Eighty-five percent of the C3H mice monitored were variant at one to three loci, indicating some heterogeneity in the C3H line from this supplier. Nevertheless, the genome of this line is more homogeneous than that of randomly bred stocks. Male mice from the C3H colony and female mice from the C57BL/6N colony were used as parents for the hybrid $B6C3F_1$ mice used in these studies. The influence of the potential genetic nonuniformity in the hybrid mice on these results is not known, but results of the studies are not affected because concurrent controls were included in each study.

Animal Maintenance

Animals were housed five per cage. Feed and water were available ad libitum. Further details of animal maintenance are given in Table 5.

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

Thirteen-Week Studies	Two-Year Studies
EXPERIMENTAL DESIGN	
Size of Study Groups	
10 males and 10 females of each species	50 males and 50 females of each species for histologic examination
Doses	
Rats--0, 2, 4, 8, 16, 32, or 64 mg/kg dichlorvos in corn oil by gavage; dose vol--5 ml/kg; mice--0, 5, 10, 20, 40, 80, or 160 mg/kg; dose vol--10 ml/kg	Rats--0, 4, or 8 mg/kg (a) dichlorvos in corn oil by gavage; dose vol--5 ml/kg; male mice--0, 10, or 20 mg/kg, female mice- 0, 20, or 40 mg/kg; dose vol--10 ml/kg
Date of First Dose	
4/15/80	Rats--1/29/81; mice--2/10/81
Date of Last Dose	
7/14/80	Rats--1/19/83; mice--1/31/83
Duration of Dosing	
5 d/wk for 13 wk	5 d/wk for 103 wk
Type and Frequency of Observation	
Observed 2 × d; weighed initially and 1 × wk thereafter	Observed 2 × d; weighed initially, 1 × wk for 14 wk (rats) or 12 wk (mice), and once per month thereafter
Necropsy and Histologic Examinations	
Necropsy performed on all animals; esophagus and gastrointestinal tract of all animals dying after d 46 examined histologically. All vehicle controls and all animals in the highest dose group with survivors at the end of the studies were examined histologically. Tissues examined include: adrenal glands, brain, colon, esophagus, femur including marrow, heart, kidneys, liver, lungs and bronchi, mammary gland, mandibular and mesenteric lymph nodes, ovaries/uterus or prostate/seminal vesicles/testes, pancreas, parathyroid glands, pituitary gland, rectum, salivary glands, skin, small intestine, spleen, stomach, thigh muscle, thymus, thyroid gland, trachea, and urinary bladder	Necropsy and histologic examination performed on all animals. The following tissues were examined: adrenal glands, brain, cecum, colon, duodenum, esophagus, femur including marrow, gallbladder (mice), gross lesions, heart, ileum, jejunum, kidneys, liver, lungs and mainstem bronchi, mammary gland, mandibular or mesenteric lymph nodes, nasal cavity and turbinates, pancreas, parathyroid glands, pituitary gland, preputial or clitoral gland, prostate/testes/epididymis or ovaries/uterus, rectum, salivary glands, sciatic nerve, skin, spleen, stomach, thymus, thyroid gland, tissue masses, trachea, and urinary bladder
ANIMALS AND ANIMAL MAINTENANCE	
Strain and Species	
F344/N rats; B6C3F$_1$ mice	F344/N rats; B6C3F$_1$ mice
Animal Source	
Charles River Breeding Laboratories (Portage, MI)	Rats -Charles River Breeding Laboratories (Kingston, NY); mice--Charles River Breeding Laboratories (Portage, MI)
Study Laboratory	
Southern Research Institute	Southern Research Institute
Method of Animal Identification	
Ear mark	Ear mark
Time Held Before Study	
21 d	Rats--14 d; mice--19 d
Age When Placed on Study	
7 wk	Rats--7 wk; mice--8 wk
Age When Killed	
20 wk	Rats--111-112 wk; mice--112-113 wk

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

Thirteen-Week Studies	Two-Year Studies
ANIMALS AND ANIMAL MAINTENANCE (Continued)	
Necropsy Dates 7/15/80-7/19/80	Rats--1/27/83-2/2/83; mice--2/8/83-2/14/83
Method of Animal Distribution Animals grouped in weight classes and assigned to cages and groups according to tables of random numbers	Same as 13-wk studies
Feed NIH 07 Rat and Mouse Ration (Zeigler Bros., Inc., Gardners, PA); available ad libitum	Same as 13-wk studies
Bedding Beta Chips®--heat-treated hardwood chips (Northeastern Products Corp., Warrensburg, NY)	Same as 13-wk studies
Water Automatic watering system (Edstrom Industries, Waterford, WI); available ad libitum	Same as 13-wk studies
Cages Polycarbonate (Lab Products, Garfield, NJ)	Same as 13-wk studies
Cage Filters Reemay® spun-bonded polyester filters (Snow Filtration, Cincinnati, OH)	Same as 13-wk studies
Animals per Cage 5	5
Other Chemicals on Study in the Same Room None	None
Animal Room Environment Temp--21°-24° C; hum--37%-75%; fluorescent light 12 h/d; 15 room air changes/h	Temp--23° ± 2° C; hum--19%-76%; fluorescent light 12 h/d; 15 room air changes/h

(a) The nominal doses are used in the text; the actual doses of 4.14 and 7.82 mg/kg were used for most of the statistical calculations of tumor incidence.

Clinical Examinations and Pathology

All animals were observed two times per day, and clinical signs were recorded when the animals were weighed. Body weights were recorded once per week for the first 14 weeks (rats) or 12 weeks (mice) of the studies and once per month thereafter. Mean body weights were calculated for each group. Animals found moribund and those surviving to the end of the studies were humanely killed. A necropsy was performed on all animals, except for tissues that were excessively autolyzed or missing. Thus, the number of animals from which particular organs or tissues were examined microscopically varies and is not necessarily equal to the number of animals that were placed on study.

During necropsy, all organs and tissues were examined for grossly visible lesions. Tissues were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Tissues examined are listed in Table 5. The pancreas of rats was microscopically examined twice. The first time, a routine cross-section of the pancreas of each rat was examined. The second time, the remaining pancreatic tissues were laid flat, and horizontal sections were made and examined.

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

Representative slides selected by the Chairperson were reviewed by the PWG, which included the laboratory pathologist, without knowledge of previously rendered diagnoses. When the consensus diagnosis of the PWG differed from that of the laboratory pathologist, the laboratory pathologist was asked to reconsider the original diagnosis. This procedure has been described, in part, by Maronpot and Boorman (1982) and Boorman et al. (1985). The final diagnoses represent a consensus of contractor pathologists and the NTP Pathology Working Group. For subsequent analysis of pathology data, the diagnosed lesions for each tissue type are combined according to the guidelines of McConnell et al. (1986).

Slides/tissues are generally not evaluated in a blind fashion (i.e., without knowledge of dose group) unless the lesions in question are subtle or unless there is an inconsistent diagnosis of lesions by the laboratory pathologist. Nonneoplastic lesions are not examined routinely by the quality assessment pathologist or PWG unless they are considered part of the toxic effect of the chemical.

Statistical Methods

Data Recording: Body weight data for this experiment were recorded in the Carcinogenesis Bioassay Data System (Linhart et al., 1974). Other data elements were recorded in the Toxicology Data Management System. The data elements include descriptive information on the animals, experimental design, survival, 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: life table tests, logistic regression, and Fisher exact/Cochran-Armitage trend analyses. Tests of significance include pairwise comparisons of high dose and low dose groups with vehicle controls and tests for overall dose-response trends, calculated using actual rather than nominal doses. For studies in which administration of the study compound has little effect on survival, the results of the three alternative analyses

will generally be similar. When differing results are obtained by the three methods, the final interpretation of the data will depend on the extent to which the tumor under consideration is regarded as being the cause of death. Continuity-corrected tests are used in the analysis of tumor incidence, and reported P values are one-sided. The procedures described below also were used to evaluate selected nonneoplastic lesions.

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

Logistic Regression Analyses--This method of analysis assumes that all tumors of a given type observed in animals that died before the end of the study were "incidental"; i.e., they did not alter the risk of death and were discovered merely as the result of death from an unrelated cause. According to this approach, tumor prevalence was modeled as a logistic function of dose and time. Both linear and quadratic terms in time were incorporated initially, and the quadratic term was eliminated if it did not significantly enhance the fit of the model. The dosed and vehicle control groups were compared on the basis of the likelihood score test for the regression coefficient of dose. This method of adjusting for intercurrent mortality is the prevalence analysis of Dinse and Lagakos (1983), further described and illustrated by Dinse and Haseman (1986). If the tumor type is nonlethal, prevalence analyses and incidence analyses are equivalent.

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

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

III. RESULTS

RATS

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

MICE

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

THIRTEEN-WEEK STUDIES

All the rats that received 32 or 64 mg/kg dichlorvos and 1/10 males and 4/10 females that received 16 mg/kg died before the end of the studies (Table 6). The death of the male in the 16 mg/kg group was gavage related.

The final mean body weights of dosed and vehicle control male rats were similar. The final mean body weights of females that received 8 or 16 mg/kg were 5% lower than that of vehicle controls. No compound-related clinical signs were observed in animals that lived to the end of the studies. Some animals that died were trembling and inactive immediately before death. No compound-related gross or microscopic pathologic effects were observed.

Dose Selection Rationale: Because of deaths at higher doses, doses selected for rats for the 2-year studies were 4 and 8 mg/kg dichlorvos, administered in corn oil by gavage 5 days per week.

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of dosed and vehicle control rats were similar throughout the studies (Table 7 and Figure 4). Mild diarrhea was considered to be compound related.

TABLE 6. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF DICHLORVOS

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	142 ± 4	351 ± 10	+209 ± 10	
2	10/10	145 ± 4	362 ± 5	+217 ± 5	103
4	10/10	148 ± 4	360 ± 4	+212 ± 4	103
8	10/10	152 ± 5	365 ± 7	+213 ± 8	104
16	9/10	156 ± 4	352 ± 9	+196 ± 7	100
32	(d) 0/10	141 ± 3	(e)	(e)	(e)
64	(f) 0/10	149 ± 3	(e)	(e)	(e)
FEMALE					
0	10/10	124 ± 2	210 ± 2	+86 ± 2	
2	10/10	120 ± 3	208 ± 4	+88 ± 4	99
4	10/10	118 ± 3	204 ± 3	+86 ± 3	97
8	10/10	116 ± 2	200 ± 3	+84 ± 3	95
16	(g) 6/10	119 ± 2	199 ± 3	+78 ± 5	95
32	(h) 0/10	121 ± 3	(e)	(e)	(e)
64	(h) 0/10	117 ± 3	(e)	(e)	(e)

(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 ± standard error of the mean
(d) Week of death: 1,7,7,7,7,7,7,7,7,7
(e) No data are reported due to 100% mortality in this group
(f) Week of death: 1,1,1,1,1,1,1,1,1,4
(g) Week of death: all 7
(h) Week of death: all 1

TABLE 7. MEAN BODY WEIGHTS AND SURVIVAL OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF DICHLORVOS

Weeks on Study	Vehicle Control Av. Wt. (grams)	Vehicle Control No. of Survivors	4 mg/kg Av. Wt. (grams)	4 mg/kg Wt. (percent of veh. controls)	4 mg/kg No. of Survivors	8 mg/kg Av. Wt. (grams)	8 mg/kg Wt. (percent of veh. controls)	8 mg/kg No. of Survivors
MALE								
0	130	50	132	102	50	127	98	50
1	170	50	170	100	50	169	99	50
2	209	50	209	100	50	209	100	50
3	240	50	241	100	50	241	100	50
4	262	50	263	100	50	264	101	50
5	283	50	285	101	50	286	101	50
6	301	50	300	100	50	302	100	50
7	312	50	313	100	50	312	100	50
8	320	50	314	98	50	319	100	50
9	321	50	320	100	50	322	100	50
10	333	50	331	99	50	333	100	50
11	343	50	339	99	50	343	100	50
12	353	50	349	99	50	353	100	50
13	366	50	357	98	50	363	99	50
14	364	50	358	98	50	361	99	50
18	399	50	390	98	50	394	99	50
22	424	50	414	98	50	413	97	50
27	449	50	440	98	50	436	97	50
31	458	50	449	98	50	448	98	50
36	481	50	469	98	50	467	97	50
40	491	50	480	98	50	477	97	50
44	500	50	490	98	50	487	97	50
49	512	50	499	97	50	498	97	50
53	516	50	502	97	50	501	97	50
57	522	49	509	98	50	507	97	50
62	524	49	511	98	48	514	98	50
66	525	49	516	98	48	519	99	49
70	529	49	519	98	46	525	99	47
76	525	48	512	98	45	518	99	47
81	515	48	506	98	43	511	99	46
85	515	45	499	97	42	502	97	44
89	505	42	493	98	40	490	97	42
93	486	41	485	100	36	481	99	38
97	489	37	481	98	32	480	98	33
101	446	36	479	107	25	472	106	28
104	462	32	457	99	25	446	97	24
FEMALE								
0	104	50	105	101	50	105	101	50
1	130	50	127	98	50	129	99	50
2	146	50	146	100	50	146	100	50
3	158	50	159	101	50	159	101	50
4	165	50	168	102	50	167	101	50
5	175	50	178	102	50	177	101	50
6	184	50	187	102	50	184	100	50
7	188	50	191	102	50	189	101	50
8	189	50	193	102	50	193	102	50
9	193	50	197	102	50	194	101	50
10	195	50	200	103	50	198	102	50
11	198	50	204	103	50	200	101	50
12	202	50	209	103	50	205	101	50
13	207	50	214	103	50	211	102	50
14	209	50	217	104	50	214	102	50
18	219	50	226	103	49	223	102	50
22	229	50	237	103	49	232	101	50
27	233	50	246	106	49	240	103	50
31	243	50	253	104	49	246	101	50
36	248	50	262	106	49	255	103	50
40	254	50	268	106	49	261	103	50
44	261	50	273	105	49	269	103	50
49	272	50	286	105	49	278	102	50
53	278	50	291	105	48	282	101	50
57	286	50	300	105	48	291	102	49
62	299	49	311	104	48	301	101	48
66	308	49	323	105	47	313	102	48
70	317	49	332	105	47	323	102	47
76	323	48	337	104	46	330	102	47
81	325	47	341	105	43	330	102	45
85	328	46	343	105	43	333	102	42
89	333	43	348	105	41	332	100	40
93	331	41	347	105	40	333	101	36
97	329	40	350	106	38	337	102	31
101	306	36	315	103	32	339	111	31
104	327	31	349	107	27	335	102	26

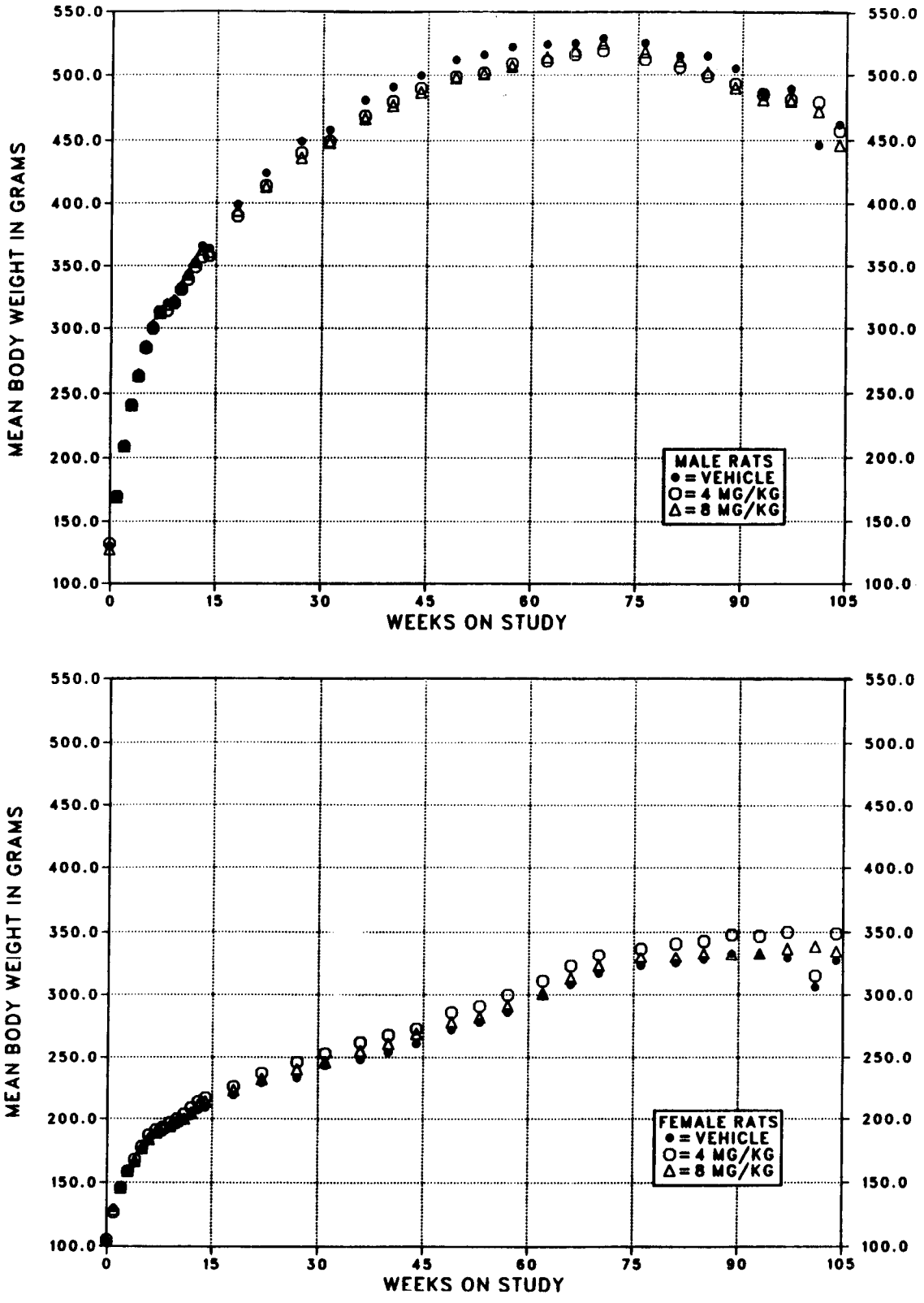

FIGURE 4. GROWTH CURVES FOR RATS ADMINISTERED DICHLORVOS IN CORN OIL BY GAVAGE FOR TWO YEARS

Survival

Estimates of the probabilities of survival for male and female rats administered dichlorvos at the doses used in these studies and for vehicle controls are shown in Table 8 and in the Kaplan and Meier curves in Figure 5. No significant differences in survival were observed between any groups of either sex.

Pathology and Statistical Analyses of Results

This section describes statistically significant or biologically noteworthy changes in the incidences of rats with neoplastic or nonneoplastic lesions of the pancreas, hematopoietic system, mammary gland, lung, liver, and adrenal glands.

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

TABLE 8. SURVIVAL OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF DICHLORVOS

	Vehicle Control	4 mg/kg	8 mg/kg
MALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	18	20	22
Accidentally killed	1	5	4
Killed at termination	31	25	24
Survival P values (c)	0.368	0.524	0.401
FEMALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	18	24	24
Accidentally killed	1	0	0
Killed at termination	31	26	26
Survival P values (c)	0.239	0.309	0.276

(a) First day of termination period: 729
(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.

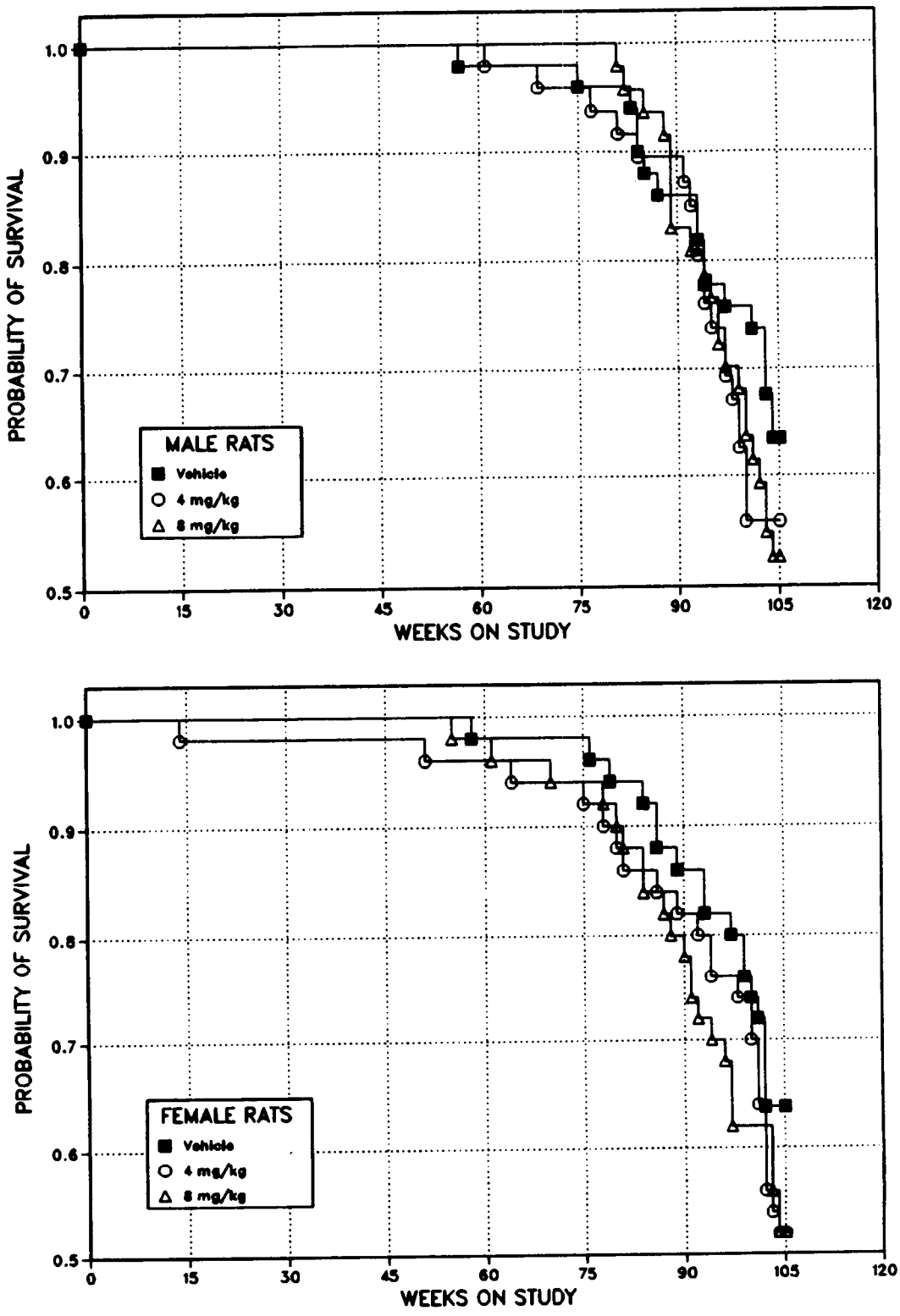

FIGURE 5. KAPLAN-MEIER SURVIVAL CURVES FOR RATS ADMINISTERED DICHLORVOS IN CORN OIL BY GAVAGE FOR TWO YEARS

Pancreas: The pancreas was examined in two ways: first, by the routine method employing examination of cross-sections, and second by a supplemental method employing examination of horizontal sections. In the routine sampling method, atrophy was observed at an increased incidence in high dose female rats (male: vehicle control, 17/50; low dose, 14/49; high dose, 18/50; female: 5/50; 6/47; 15/50). These lesions were focal and generally minimal in severity. Adenomas of the exocrine pancreas in male rats occurred with a significant positive trend, and the incidences in the dosed groups were significantly greater than that in the vehicle controls (Table 9). Incidences of multiple adenomas also were greater in dosed males than in vehicle controls (2/50; 7/49; 13/50). Adenomas were seen in 1/50 vehicle control, 1/47 low dose, and 4/50 high dose female rats. Hyperplasia and adenomas of the exocrine pancreas are part of a morphologic continuum. Adenomas are distinguished from hyperplasia by a greater heterogeneity in growth pattern, loss of normal acinar structure, and a larger size. When the horizontal sections of the pancreas were examined, additional acinar cell hyperplasia and adenomas were observed (Table 10). When the original and new data were combined, the incidences of pancreatic adenomas were 25/50, 30/50, and 33/50 in male rats and 2/50, 3/50, and 6/50 in female rats.

TABLE 9. PANCREATIC LESIONS OBSERVED IN A TISSUE CROSS-SECTION IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF DICHLORVOS (a)

	Vehicle Control	4 mg/kg	8 mg/kg
MALE			
Hyperplasia			
Overall Rates	9/50 (18%)	9/49 (18%)	9/50 (18%)
Adenoma (b)			
Overall Rates	16/50 (32%)	25/49 (51%)	30/50 (60%)
Adjusted Rates	45.2%	80.0%	82.5%
Terminal Rates	12/31 (39%)	19/25 (76%)	18/24 (75%)
Day of First Observation	653	533	564
Life Table Tests	P<0.001	P=0.006	P<0.001
Logistic Regression Tests	P<0.001	P=0.007	P=0.001
FEMALE			
Hyperplasia			
Overall Rates	2/50 (4%)	3/47 (6%)	0/50 (0%)
Adenoma (c)			
Overall Rates	1/50 (2%)	1/47 (2%)	4/50 (8%)
Adjusted Rates	3.2%	4.0%	12.5%
Terminal Rates	1/31 (3%)	1/25 (4%)	2/26 (8%)
Day of First Observation	729	729	631
Life Table Tests	P=0.079	P=0.714	P=0.140
Logistic Regression Tests	P=0.102	P=0.714	P=0.171

(a) The statistical analyses used are discussed in Section II (Statistical Methods) and Table A3 (footnotes).
(b) Includes multiple adenomas; historical incidence of adenomas or carcinomas (combined) at study laboratory (mean ± SD): 31/347 (9% ± 11%); historical incidence in NTP studies: 93/1,624 (6% ± 7%)
(c) Historical incidence of adenomas or carcinomas (combined) at study laboratory (mean ± SD): 1/397 (0.3% ± 0.7%); historical incidence in NTP studies: 7/1,679 (0.4% ± 1%)

TABLE 10. NUMBERS OF RATS WITH PANCREATIC LESIONS IN THE TWO-YEAR GAVAGE STUDIES OF DICHLORVOS

	Vehicle Control	4 mg/kg	8 mg/kg
MALE			
Horizontal sections			
Acinar cell hyperplasia	33	44	39
Acinar cell adenoma (single)	12	13	7
Acinar cell adenoma (multiple)	3	10	10
Acinar cell adenoma (total)	15	23	17
Cross-sections and horizontal sections (composite)			
Acinar cell hyperplasia	37	45	39
Acinar cell adenoma (single)	16	8	13
Acinar cell adenoma (multiple)	9	*22	*20
Acinar cell adenoma (total)	25	*30	*33
FEMALE			
Horizontal sections			
Acinar cell hyperplasia	21	22	30
Acinar cell adenoma (single)	1	2	1
Acinar cell adenoma (multiple)	0	0	1
Acinar cell adenoma (total)	1	2	2
Cross-sections and horizontal sections (composite)			
Acinar cell hyperplasia	21	23	30
Acinar cell adenoma (single)	2	3	5
Acinar cell adenoma (multiple)	0	0	1
Acinar cell adenoma (total)	2	3	6

*P<0.05 vs. vehicle controls by logistic regression test

Hematopoietic System: Mononuclear cell leukemia in male rats occurred with a significant positive trend; the incidences in the dosed groups were significantly greater than that in the vehicle controls (Table 11). Incidences of mononuclear cell leukemia in female rats were not significantly different between the vehicle controls and the dosed groups (vehicle control, 17/50; low dose, 21/50; high dose, 23/50).

Mammary Gland: Fibroadenomas and fibroadenomas or adenomas (combined) in female rats occurred with significant positive trends; the incidences of fibroadenomas or adenomas (combined) in dosed female rats were significantly greater than that in vehicle controls (Table 12). The incidence of fibroadenomas, adenomas, or carcinomas (combined) was greater in low dose females than that in vehicle controls. The incidences of multiple fibroadenomas were greater in the dosed female groups than that in the vehicle controls (vehicle control, 0/50; low dose, 6/50; high dose, 3/50).

Lung: In male rats, three alveolar/bronchiolar adenomas occurred in the high dose group, but none occurred in the low dose group or in the vehicle controls. Although the trend was significant (P = 0.037), the difference between the vehicle control and high dose group was not. Alveolar/bronchiolar carcinomas were not diagnosed. A slight decrease was observed in the incidences of adenomatosis in dosed male rats compared with that in vehicle controls (5/50; 4/50; 3/49).

Liver: Cytoplasmic vacuolization was observed at increased incidences in dosed male rats (male: vehicle control, 7/50; low dose, 13/50; high dose, 19/50; female: 6/50; 7/50; 5/50).

Adrenal Glands: Cortical cytoplasmic vacuolization was observed at increased incidences in dosed male and low dose female rats (male: vehicle control, 3/50; low dose, 8/50; high dose, 13/50; female: 9/50; 17/50; 12/50).

TABLE 11. MONONUCLEAR CELL LEUKEMIA IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DICHLORVOS (a)

	Vehicle Control	4 mg/kg	8 mg/kg
Overall Rates	11/50 (22%)	20/50 (40%)	21/50 (42%)
Adjusted Rates	31.7%	59.0%	57.1%
Terminal Rates	8/31 (26%)	12/25 (48%)	9/24 (38%)
Day of First Observation	595	607	610
Life Table Tests	P=0.006	P=0.012	P=0.008
Logistic Regression Tests	P=0.011	P=0.016	P=0.015

(a) Historical incidence of leukemia at study laboratory (mean ± SD): 35/400 (9% ± 7%); historical incidence in NTP studies: 259/1,699 (15% ± 9%)

TABLE 12. MAMMARY GLAND TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DICHLORVOS

	Vehicle Control	4 mg/kg	8 mg/kg
Fibroadenoma (a)			
Overall Rates	9/50 (18%)	19/50 (38%)	16/50 (32%)
Adjusted Rates	24.5%	62.4%	45.6%
Terminal Rates	6/31 (19%)	15/26 (58%)	8/26 (31%)
Day of First Observation	547	545	582
Life Table Tests	P=0.030	P=0.007	P=0.047
Logistic Regression Tests	P=0.045	P=0.015	P=0.070
Adenoma			
Overall Rates	0/50 (0%)	0/50 (0%)	1/50 (2%)
Fibroadenoma or Adenoma			
Overall Rates	9/50 (18%)	19/50 (38%)	17/50 (34%)
Adjusted Rates	24.5%	62.4%	48.6%
Terminal Rates	6/31 (19%)	15/26 (58%)	9/26 (35%)
Day of First Observation	547	545	582
Life Table Tests	P=0.019	P=0.007	P=0.030
Logistic Regression Tests	P=0.028	P=0.015	P=0.044
Carcinoma			
Overall Rates	2/50 (4%)	2/50 (4%)	0/50 (0%)
Fibroadenoma, Adenoma, or Carcinoma (b)			
Overall Rates	11/50 (22%)	20/50 (40%)	17/50 (34%)
Adjusted Rates	28.2%	65.8%	48.6%
Terminal Rates	6/31 (19%)	16/26 (62%)	9/26 (35%)
Day of First Observation	547	545	582
Life Table Tests	P=0.049	P=0.015	P=0.074
Logistic Regression Tests	P=0.072	P=0.028	P=0.113

(a) Includes multiple fibroadenomas; historical incidence of fibroadenomas at study laboratory (mean ± SD): 113/400 (28% ± 7%); historical incidence in NTP studies: 436/1,700 (26% ± 7%)
(b) Historical incidence of benign or malignant mammary gland neoplasms (all types combined) at study laboratory (mean ± SD): 124/400 (31% ± 8%); historical incidence in NTP studies: 474/1,700 (28% ± 8%)

THIRTEEN-WEEK STUDIES

All 10 male mice and 9/10 female mice that received 160 mg/kg and 5/10 male mice that received 80 mg/kg dichlorvos died before the end of the studies (Table 13). Other deaths that occurred were probably due to improper gavage technique. Final mean body weights of dosed and vehicle control mice were similar. No compound-related clinical signs were observed in mice that lived to the end of the studies. No compound-related gross or microscopic pathologic effects were observed.

Dose Selection Rationale: Because of deaths observed at higher doses, doses selected for mice for the 2-year studies were 10 and 20 mg/kg dichlorvos for males and 20 and 40 mg/kg for females, administered in corn oil by gavage 5 days per week.

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of dosed and vehicle control male and low dose and vehicle control female mice were generally similar throughout the studies. Mean body weights of high dose female mice were 99%-110% those of the vehicle controls (Table 14 and Figure 6). No compound-related clinical signs were observed.

TABLE 13. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE THIRTEEN-WEEK GAVAGE STUDIES OF DICHLORVOS

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	22.5 ± 0.6	35.9 ± 1.2	+13.4 ± 0.7	
5	10/10	23.7 ± 0.6	33.9 ± 1.3	+10.2 ± 1.0	94.4
10	10/10	24.4 ± 0.6	37.1 ± 1.0	+12.7 ± 0.9	103.3
20	10/10	24.6 ± 0.5	37.9 ± 1.0	+13.3 ± 0.8	105.6
40	10/10	24.7 ± 0.7	39.9 ± 1.6	+15.2 ± 1.1	111.1
80	(d) 5/10	23.2 ± 0.8	37.4 ± 2.6	+13.6 ± 1.7	104.2
160	(e) 0/10	24.0 ± 0.6	(f)	(f)	(f)
FEMALE					
0	9/10	18.3 ± 0.4	27.3 ± 0.5	+8.9 ± 0.5	
5	10/10	19.1 ± 0.3	28.5 ± 0.7	+9.4 ± 0.5	104.4
10	9/10	19.0 ± 0.4	29.0 ± 1.0	+9.9 ± 0.9	106.2
20	(g) 9/10	19.2 ± 0.3	27.4 ± 0.6	+8.4 ± 0.6	100.4
40	10/10	18.7 ± 0.3	28.2 ± 0.6	+9.5 ± 0.5	103.3
80	9/10	18.3 ± 0.3	27.0 ± 0.6	+8.8 ± 0.5	98.9
160	(h) 1/10	19.6 ± 0.4	28.0	+7.0	102.6

(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 ± standard error of the mean
(d) Week of death: 2,3,3,3,11
(e) Week of death: 1,1,1,1,1,1,1,1,2,3
(f) No data are reported due to 100% mortality in this group.
(g) Week of death: 3
(h) Week of death: 1,1,1,3,4,5,7,7,12

TABLE 14. MEAN BODY WEIGHTS AND SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF DICHLORVOS

Weeks on Study	Vehicle Control Av. Wt. (grams)	Vehicle Control No. of Survivors	Low Dose Av. Wt. (grams)	Low Dose Wt. (percent of veh. controls)	Low Dose No. of Survivors	High Dose Av. Wt. (grams)	High Dose Wt. (percent of veh. controls)	High Dose No. of Survivors
MALE				**10 mg/kg**			**20 mg/kg**	
0	25 0	50	24 7	99	50	24 3	97	50
1	27 3	49	27 3	100	50	26 6	97	49
2	29 2	49	27 8	95	50	28 4	97	49
3	30 5	49	29 5	97	50	29 6	97	49
4	31 7	49	31 0	98	50	30 2	95	49
5	32 9	49	32 2	98	50	31 6	96	49
6	33 7	49	32 9	98	50	32 8	97	49
7	34 5	49	33 2	96	50	33 4	97	49
8	35 1	49	33 8	96	50	33 7	96	49
9	35 6	49	33 6	94	50	34 5	97	49
10	36 5	48	34 0	93	50	36 1	99	49
11	36 5	48	35 4	97	50	36 0	99	49
12	37 2	48	36 8	99	50	37 2	100	49
16	39 7	47	38 3	96	50	38 1	96	49
20	42 0	47	41 0	98	50	40 4	96	49
25	43 1	47	41 9	97	50	42 5	99	49
29	44 0	47	42 7	97	50	43 3	98	49
34	44 8	46	43 9	98	50	44 6	100	48
38	46 0	46	45 6	99	50	46 0	100	48
42	46 4	46	45 1	97	50	45 9	99	48
47	47 2	46	46 7	99	50	48 0	102	48
51	47 5	46	46 6	98	50	47 6	100	48
55	47 0	46	46 3	99	50	47 7	101	48
60	47 6	45	46 5	98	50	47 9	101	47
64	47 1	45	46 8	99	50	47 3	100	47
68	47 9	45	47 2	99	50	47 8	100	46
74	47 1	45	48 0	102	48	47 2	100	45
79	45 5	41	45 3	100	46	45 9	101	44
82	46 0	41	46 0	100	44	45 8	100	42
86	46 4	38	46 9	101	42	46 9	101	36
90	45 8	38	46 5	102	39	45 7	100	35
94	46 3	37	46 3	100	36	47 2	102	31
99	45 9	35	46 7	102	31	46 8	102	30
104	44 2	35	44 3	100	28	44 4	100	29
FEMALE				**20 mg/kg**			**40 mg/kg**	
0	18 2	50	18 5	102	50	18 9	104	50
1	20 2	44	20 2	100	45	20 0	99	48
2	21 2	44	20 6	97	45	21 7	102	48
3	22 4	44	22 1	99	45	22 5	100	48
4	23 3	44	23 1	99	45	23 0	99	48
5	24 0	44	22 8	95	45	24 0	100	48
6	24 3	44	24 6	101	45	24 4	100	48
7	25 0	44	24 4	98	45	24 9	100	48
8	25 5	44	25 2	99	45	25 7	101	48
9	24 9	44	25 5	102	45	25 1	101	48
10	26 0	44	24 4	94	45	26 0	100	48
11	25 5	44	25 6	100	45	25 8	101	48
12	26 1	44	25 9	99	45	26 5	102	48
16	28 5	44	28 1	99	45	28 1	99	48
20	29 9	44	29 5	99	45	29 5	99	48
25	30 0	44	30 8	103	45	30 5	102	48
29	30 8	44	31 1	101	45	31 9	104	48
34	32 4	44	32 0	99	45	32 9	102	48
38	33 3	44	33 8	102	45	34 2	103	48
42	34 3	44	34 5	101	45	36 0	105	48
47	35 7	44	36 0	101	45	37 9	106	48
51	36 7	44	35 7	97	45	38 2	104	48
55	37 1	44	35 8	96	45	38 3	103	47
60	38 3	44	35 0	91	45	39 2	102	47
64	39 0	43	37 5	96	44	40 8	105	47
68	40 7	42	38 2	94	44	42 2	104	47
74	40 3	42	38 3	95	43	41 6	103	46
79	39 3	42	38 9	99	42	41 0	104	45
82	38 9	41	38 8	100	39	41 4	106	45
86	40 2	37	40 6	101	37	42 2	105	45
90	40 6	34	39 8	98	36	42 4	104	43
94	40 7	33	39 9	98	34	43 6	107	39
99	40 3	30	41 1	102	31	43 3	107	37
104	39 4	26	40 7	103	29	43 4	110	34

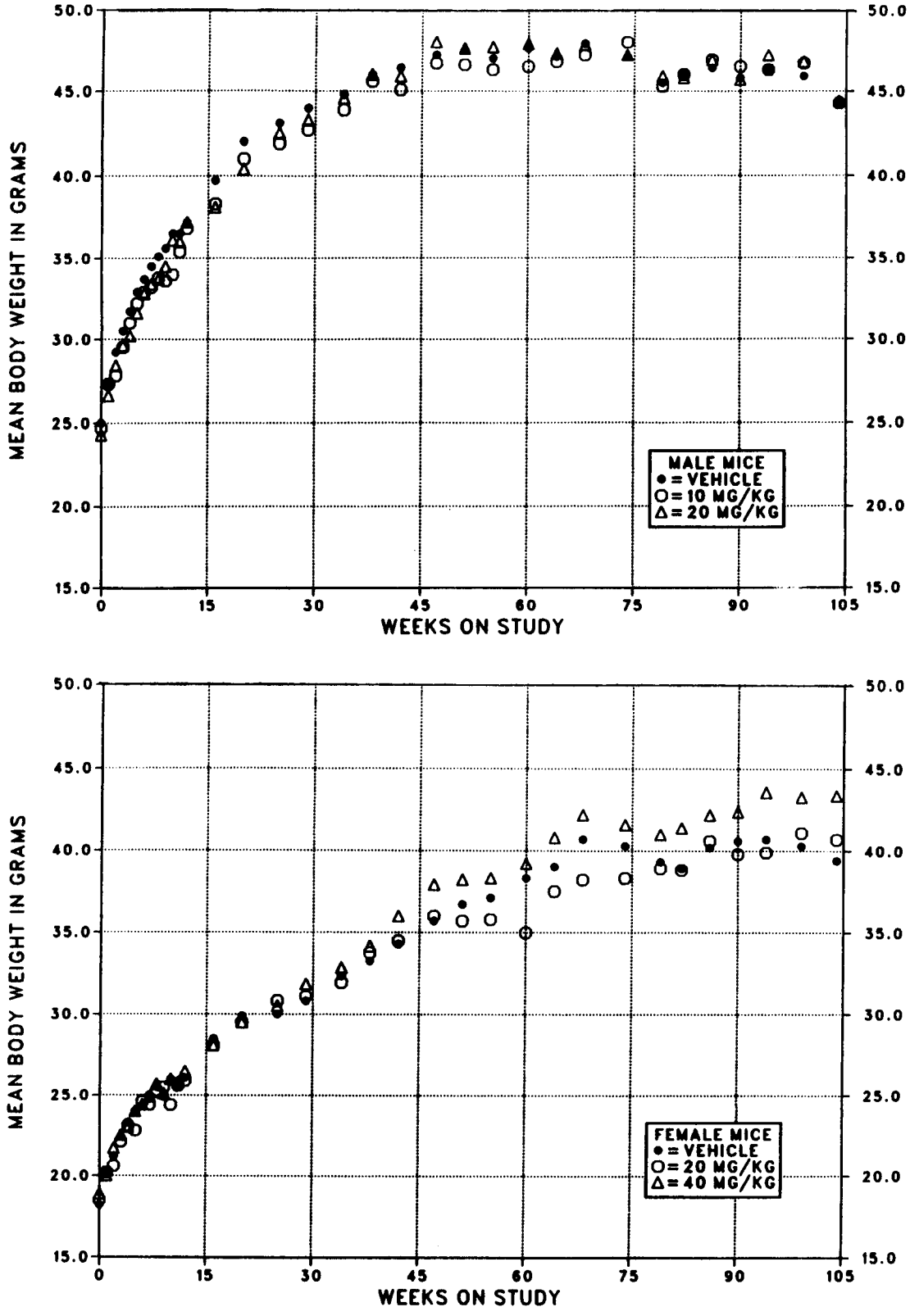

FIGURE 6. GROWTH CURVES FOR MICE ADMINISTERED DICHLORVOS IN CORN OIL BY GAVAGE FOR TWO YEARS

Survival

Estimates of the probabilities of survival for male and female mice administered dichlorvos at the doses used in these studies and for vehicle controls are shown in Table 15 and in the Kaplan and Meier curves in Figure 7 No significant differences in survival were observed between any groups of either sex

Pathology and Statistical Analyses of Results

This section describes statistically significant or biologically noteworthy changes in the incidences of mice with neoplastic or nonneoplastic lesions of the forestomach, pituitary gland, and hematopoietic system

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

TABLE 15. SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF DICHLORVOS

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg
MALE (a)				
Animals initially in study	50	50	50	
Nonaccidental deaths before termination (b)	14	23	21	
Accidentally killed	1	0	0	
Killed at termination	35	27	29	
Survival P values (c)	0 218	0 206	0 266	
FEMALE (a)				
Animals initially in study	50		50	50
Nonaccidental deaths before termination (b)	18		16	14
Accidentally killed	6		5	2
Killed at termination	25		29	34
Died during termination period	1		0	0
Survival P values (c)	0 271		0 840	0 296

(a) First day of termination period 729
(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

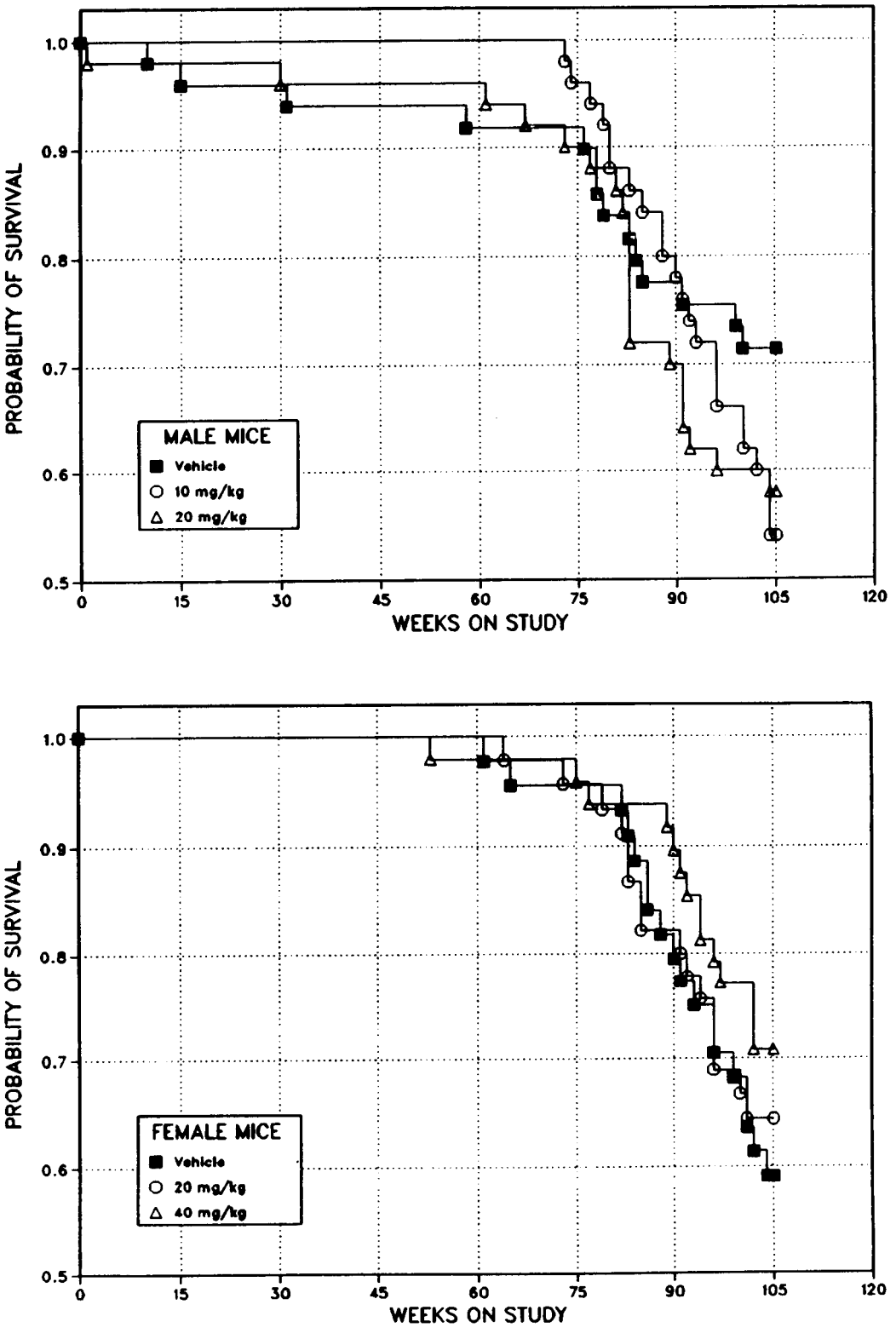

FIGURE 7. KAPLAN-MEIER SURVIVAL CURVES FOR MICE ADMINISTERED DICHLORVOS IN CORN OIL BY GAVAGE FOR TWO YEARS

Forestomach: Squamous cell papillomas in male and female mice occurred with significant positive trends; two carcinomas also occurred in high dose female mice (Table 16). No increases in the incidences of hyperplasia were seen in the dosed mice compared with vehicle controls.

Hyperplasia and squamous cell papillomas are part of a morphologic continuum Hyperplasia was characterized by focal thickening of the stratified squamous epithelium with limited extension of the lamina propria into the epithelial folds. Squamous cell papillomas were distinguished from hyperplasia by their pedunculated branching structure consisting of a central core of connective tissue covered by thick stratified squamous epithelium. Some papillomas were sessile with elongated rete pegs rather than the typical branching pattern

TABLE 16. FORESTOMACH SQUAMOUS LESIONS IN MICE IN THE TWO-YEAR GAVAGE STUDIES OF DICHLORVOS (a)

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg
MALE				
Hyperplasia				
Overall Rates	11/50 (22%)	5/50 (10%)	9/50 (18%)	
Papilloma (b)				
Overall Rates	1/50 (2%)	1/50 (2%)	5/50 (10%)	
Adjusted Rates	2 9%	3.2%	17 2%	
Terminal Rates	1/35 (3%)	0/27 (0%)	5/29 (17%)	
Day of First Observation	729	714	729	
Life Table Tests	P=0 033	P=0.718	P=0.064	
Logistic Regression Tests	P=0.032	P=0.753	P=0.067	
FEMALE				
Hyperplasia				
Overall Rates	6/49 (12%)		7/49 (14%)	5/50 (10%)
Papilloma				
Overall Rates	5/49 (10%)		6/49 (12%)	18/50 (36%)
Adjusted Rates	17.4%		18.1%	44.9%
Terminal Rates	3/26 (12%)		4/29 (14%)	13/34 (38%)
Day of First Observation	669		442	520
Life Table Tests	P=0.006		P=0.556	P=0.016
Logistic Regression Tests	P=0.002		P=0.505	P=0.004
Carcinoma				
Overall Rates	0/49 (0%)		0/49 (0%)	2/50 (4%)
Papilloma or Carcinoma (c)				
Overall Rates	5/49 (10%)		6/49 (12%)	19/50 (38%)
Adjusted Rates	17.4%		18.1%	47.5%
Terminal Rates	3/26 (12%)		4/29 (14%)	14/34 (41%)
Day of First Observation	669		442	520
Life Table Tests	P=0.004		P=0 556	P=0.011
Logistic Regression Tests	P<0 001		P=0 505	P=0.003

(a) The statistical analyses used are discussed in Section II (Statistical Methods) and Table C3 (footnotes)
(b) Historical incidence of papillomas or carcinomas (combined) at study laboratory (mean ± SD): 4/396 (1% ± 3%); historical incidence in NTP studies. 23/1,703 (1% ± 2%)
(c) Historical incidence of papillomas at study laboratory (mean ± SD): 4/396 (1% ± 2%); historical incidence in NTP studies: 16/1,709 (0.9% ± 2%) No squamous cell carcinomas have been observed in corn oil vehicle control female B6C3F_1 mice in NTP studies.

Pituitary Gland: Adenomas and adenomas or carcinomas (combined) of the pars distalis in female mice occurred with significant negative trends ($P<0.05$); the incidences of adenomas or carcinomas (combined) in dosed female mice were not significantly lower than that in the vehicle controls (vehicle control, 12/45; low dose, 6/45; high dose, 6/44).

Hematopoietic System: Lymphomas in female mice occurred with a significant negative trend ($P<0.04$); the incidence in the high dose group was significantly lower than that in the vehicle controls (vehicle control, 16/50, low dose, 11/50; high dose, 9/50; $P\leq0.05$).

IV. DISCUSSION AND CONCLUSIONS

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In the 13-week studies, male and female F344/N rats received dichlorvos in corn oil by gavage at 0, 2, 4, 8, 16, 32, or 64 mg/kg. All rats in the 32 and 64 mg/kg groups died, and 4/10 female rats in the 16 mg/kg group died. Body weight gains of male and female rats receiving dichlorvos at 16 mg/kg or lower were not notably different from those of vehicle controls. No compound-related gross or microscopic lesions were found. Male and female B6C3F$_1$ mice received dichlorvos at 0, 5, 10, 20, 40, 80, or 160 mg/kg. All 10 male mice and 9/10 female mice in the 160 mg/kg group and 5/10 male mice in the 80 mg/kg group died. Mean body weights of surviving mice in all dose groups were similar to those of vehicle controls. No compound-related gross or microscopic pathologic effects were observed.

In the 2-year studies, male and female F344/N rats were administered dichlorvos by gavage at 0, 4, or 8 mg/kg. Body weights and survival of dosed rats were similar to those of their respective vehicle controls.

Increased incidences of pancreatic adenomas (see Tables 9 and 10) and mononuclear cell leukemia (see Table 11) were associated with dichlorvos administration in male rats. The incidence of exocrine pancreatic adenomas was also marginally increased in high dose female rats (vehicle control, 2/50; low dose, 3/47; high dose, 6/50). The incidences of mammary gland fibroadenomas and fibroadenomas or adenomas (combined) in dosed female rats were increased (see Table 12). However, when mammary gland fibromas, fibroadenomas, adenomas, or carcinomas were evaluated together, only the incidence in the low dose group was significantly greater than that in the vehicle controls. Increased incidences of multiple mammary gland fibroadenomas were also observed (0/50; 6/50; 3/50).

Dichlorvos administration also was associated with increases in hepatic cytoplasmic vacuolization in male rats and adrenal cortical cytoplasmic vacuolization in male and female rats. Each of these organs is active in the metabolism of lipids, and cytoplasmic vacuolization is characteristic of lipid accumulation within the cells. These changes were minor in extent and may be related to other primary processes rather than to a direct effect of dichlorvos.

In the 2-year studies, male B6C3F$_1$ mice received dichlorvos at 0, 10, or 20 mg/kg and female B6C3F$_1$ mice at 0, 20, or 40 mg/kg. No notable differences were seen in body weight gain or survival between the dosed mice and the vehicle controls.

Forestomach squamous cell papillomas occurred in both dosed male and female mice with a positive trend (see Table 16). The incidence in high dose (20 mg/kg) male mice was greater than that in vehicle controls, but the increase was not significant; the incidence in high dose (40 mg/kg) female mice was significantly greater than that in vehicle controls. Squamous cell carcinomas were observed in two high dose female mice. These increased incidences were probably related to dichlorvos administration. According to the results of the 2-year study, male mice might have been able to tolerate a dose of 40 mg/kg without an effect on body weight or survival; female mice tolerated 40 mg/kg. Administration of dichlorvos also was associated with significant negative trends in the incidences of pituitary gland adenomas and adenomas or carcinomas (combined) and lymphomas in female mice.

Although dichlorvos administration inhibited acetylcholinesterase activity in male and female rats and mice by more than 50%, no effects on body weight or survival or signs of neurotoxicity were evident at similar doses in the 2-year studies. In a separate study conducted after the end of the 2-year studies, dichlorvos administration in the dose range used in the 2-year studies was shown to depress plasma cholinesterase activity in male and female rats and mice through day 32, the last time it was measured (Tables H1 and H2); erythrocyte cholinesterase activity was not affected.

Male F344/N rats receiving corn oil by gavage are known to have an increased incidence of pancreatic acinar cell adenomas compared with that in untreated controls (Haseman et al., 1985). The overall historical incidence of acinar cell adenomas is 5.5% in corn oil vehicle control male F344/N rats (Table A4a) compared with 0.3% in untreated controls. The mechanism of action of corn oil in pancreatic carcinogenesis in male rats remains to be elucidated. In the current study, the incidence of pancreatic adenomas in male vehicle controls was 32% in tissue cross-sections

and 50% in tissue cross-sections and horizontal sections (composite); this incidence is greater than the historical incidence of 9% at the laboratory and the overall National Toxicology Program (NTP) historical incidence of 6% in tissue cross-sections (Table A4a). The reason for the high vehicle control incidence is unknown. The incidence of 50% was based on examinations of cross-sections and additional horizontal sections; thus, the amount of pancreatic tissue examined was greater than usual. Eustis and Boorman (1985) reported that the laboratory, the animal source, the brand or lot of corn oil, or the peroxide level in corn oil had no bearing on the incidence of pancreatic adenomas in male F344/N rats. High mean body weights reportedly are related to the occurrence of pancreatic acinar cell hyperplasia and adenomas (Haseman et al., 1985; Eustis and Boorman, 1985). In male rats given 8 mg/kg dichlorvos in corn oil by gavage, the incidence of pancreatic adenomas in tissue cross-sections and horizontal sections (composite) of 66% was significantly greater than the incidence of 50% observed in vehicle controls and was considered to be related to dichlorvos administration. Multiple adenomas also occurred at a higher incidence in the dosed than in the vehicle control male rats (vehicle control, 9/50; low dose, 22/49; high dose, 19/50; see Tables 9 and 10). Corn oil may act synergistically with dichlorvos and perhaps exacerbates the effects of dichlorvos on pancreatic adenoma induction in male F344/N rats. Exocrine pancreatic adenomas occur rarely in female F344/N rats. In the NTP carcinogenesis studies, the incidence in tissue cross-sections is 3/1,936 (0.2%) in untreated control female F344/N rats and 7/1,679 (0.4%) in corn oil control female F344/N rats. Corn oil gavage has no enhancing effect on the exocrine pancreatic adenoma incidence in female F344/N rats. In the current study, the incidence of exocrine pancreatic adenomas observed in tissue cross-sections and horizontal sections (composite) in the vehicle control female F344/N rats (2/50, 4%) and the incidence of adenomas (6/50, 12%) in the high dose female rats may have been related to dichlorvos administration. The increased incidence, although not statistically significant, is believed to be biologically important in view of the carcinogenic effects of dichlorvos on the pancreas of male rats. Interestingly, pancreatic acinar cell atrophy also was observed in both vehicle control and dosed male and female rats, and the incidence was significantly greater in high dose female rats than in vehicle controls. The atrophy in dosed female rats was typical of that occurring naturally in untreated rats, and it is uncertain how the increased incidence is related to dichlorvos.

Mononuclear cell leukemia develops spontaneously in F344/N rats (Stromberg and Vogtsberger, 1983). The historical incidence of mononuclear cell leukemia in corn oil vehicle control male rats at the laboratory is 9%, and that in the overall NTP studies is 15%. The incidence of 22% for mononuclear cell leukemia observed in vehicle control male F344/N rats in the current study is high compared with historical incidences at the laboratory and in the overall NTP studies. Haseman et al. (1985) reported that corn oil administration by gavage depressed the incidence of mononuclear cell leukemia in male F344/N rats. In the current study, dichlorvos in corn oil appeared to stimulate development of mononuclear cell leukemia in male F344/N rats. This was confirmed in a study of the effects of dichlorvos in a transplantable mononuclear cell leukemia model (Dieter et al., 1989)

Dichlorvos administration was associated with marginal increases in the incidences of mammary gland fibroadenomas and fibroadenomas or adenomas (combined) in dosed female rats (fibroadenomas or adenomas, combined: vehicle control, 9/50; low dose, 19/50; high dose, 17/50). The incidences of multiple fibroadenomas were also increased (0/50; 6/50; 3/49). Although mammary gland fibroadenomas are common neoplasms in older female rats, the incidences in the dosed females in the current study were greater than the study laboratory mean historical incidence of 113/400 (28%) and the overall NTP mean historical incidence of 436/1,700 (26%) in corn oil vehicle control female rats (Table B2). The increases may have been related to dichlorvos administration.

In mice, dichlorvos appears to act at the site of contact, since positive trends in forestomach squamous cell papillomas and papillomas or carcinomas (combined) were observed in both males (papillomas only) and females. The direct-acting carcinogenic effect of dichlorvos is supported by the mutagenic effects of dichlorvos on bacterial

and mammalian cells in vitro, since the addition of liver S9 to the cultures diminished the mutagenic effect.

In carcinogenesis studies conducted by the National Cancer Institute (NCI), male and female B6C3F$_1$ mice fed dichlorvos at 318 or 635 ppm in the diet (41 or 81 mg/kg per day) for 78 weeks did not develop greater incidences of neoplasms than did the controls (NCI, 1977). However, uncommon esophageal neoplasms were observed in the dosed mice. Although the NCI studies differed from the current studies in that esophageal neoplasms instead of forestomach neoplasms were found, the tumor types observed in the two studies are considered similar.

Dichlorvos is clearly mutagenic in in vitro studies. It induces gene mutations in bacteria and cultured mammalian cells, as well as cytogenetic effects in cultured mammalian cells, both with and without metabolic activation. In vivo studies showed that dichlorvos induced dominant lethal mutations (Fischer et al., 1977), sperm abnormalities (Wyrobek and Bruce, 1975), and depletion of testicular germinal epithelium in mice at 40 mg/kg (Krause and Homola, 1972). Chromosomal aberrations were detected in human blood cells (Trinh et al., 1975) and in bone marrow cells of Syrian hamsters (Dzwonkowska and Hubner, 1986) after in vivo exposure. Two potentially reactive moieties of dichlorvos are thought to be involved in its mutagenicity: the methyl groups and the dichlorovinyl moiety. Direct mutagenicity is possible through alkylation of DNA or proteins by a methyl group. Enzymatically mediated cleavage of the P-O bond may lead to subsequent phosphorylation of the hydrolyzing enzyme as well as various reactions of the dichlorovinyl moiety with nucleophilic sites on both protein and DNA.

When dichlorvos was tested by the NTP in in vivo mouse bone marrow studies with intraperitoneal doses up to 25 mg/kg at one laboratory and up to 40 mg/kg at a second laboratory, both laboratories failed to observe an increase in either chromosomal aberrations or sister chromatid exchanges.

Methylation of biologic macromolecules has been demonstrated in in vitro and in vivo studies with dichlorvos (Lofroth, 1970; Page et al., 1972; Lawley et al., 1974; Wennerberg and Lofroth, 1974; Loeffler et al., 1976; Segerback, 1981; Segerback and Ehrenberg, 1981).

Both dichloroacetaldehyde and dichloroethanol are mutagenic in bacteria and lower eukaryotes. Dichloroacetaldehyde was also found to induce dominant lethal mutations in mice (Fischer et al., 1977), indicating that it is clastogenic in germ cells in vivo. The potential for dichlorvos to induce mutations in vivo, either by direct methylation or by reactions involving its metabolites, is undoubtedly dependent on the pharmacokinetics of its distribution and perhaps its metabolism within target tissues. The current studies indicate for the first time that dichlorvos or its metabolite can effect carcinogenesis in rats and mice.

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

Under the conditions of these 2-year gavage studies, there was *some evidence of carcinogenic activity** of dichlorvos for male F344/N rats, as shown by increased incidences of adenomas of the exocrine pancreas and mononuclear cell leukemia. There was *equivocal evidence of carcinogenic activity* of dichlorvos for female F344/N rats, as shown by increased incidences of adenomas of the exocrine pancreas and mammary gland fibroadenomas. There was *some evidence of carcinogenic activity* of dichlorvos for male B6C3F$_1$ mice, as shown by increased incidences of forestomach squamous cell papillomas. There was *clear evidence of carcinogenic activity* of dichlorvos for female B6C3F$_1$ mice, as shown by increased incidences of forestomach squamous cell papillomas.

*Explanation of Levels of Evidence of Carcinogenic Activity is on page 5.
A summary of the Peer Review comments and the public discussion on this Technical Report appears on pages 8-9 and 11.

V. REFERENCES

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1. Abbott, D.C.; Crisp, S.; Tarrant, K.R.; Tatton, J.O.G. (1970) Pesticide residues in the total diet in England and Wales, III. Organophosphorus pesticide residues in the total diet, 1966-1967. Pestic. Sci. 1:10-13.

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

3. Bartsch, H.; Malaveille, C.; Camus, A.-M.; Martel-Planche, G.; Brun, G.; Hautefeuille, A.; Sabadie, N.; Barbin, A.; Kuroki, T.; Drevon, C.; Piccoli, C.; Montesano, R. (1980) Validation and comparative studies on 180 chemicals with *S. typhimurium* strains and V79 Chinese hamster cells in the presence of various metabolizing systems. Mutat. Res. 76:1-50.

4. Batte, E.G.; Robison, O.W.; Moncol, D.J. (1969) Influence of dichlorvos on swine reproduction and performance of offspring to weaning. J. Am. Vet. Med. Assoc. 154:1397.

5. Benigni, R.; Dogliotti, E. (1980) UDS studies on selected environmental chemicals. Mutat. Res. 74:248-249.

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

7. Bignami, M.; Aulicino, F.; Velcich, A.; Carere, A.; Morpurgo, G. (1977) Mutagenic and recombinogenic action of pesticides in *Aspergillus nidulans*. Mutat. Res. 46:395-402.

8. Bignami, M.; Conti, G.; Conti, L.; Crebelli, F.; Misuraca, F.; Puglia, A.M.; Randazzo, R.; Sciandrello, G.; Carere, A. (1980) Mutagenicity of halogenated aliphatic hydrocarbons in *Salmonella typhimurium, Streptomyces coelicolor* and *Aspergillus nidulans*. Chem. Biol. Interact. 30:9-23.

9. Blair, D.; Hoadley, E.C.; Hutson, D.H. (1975) The distribution of dichlorvos in the tissues of mammals after its inhalation or intravenous administration. Toxicol. Appl. Pharmacol. 31:243-253.

10. Blair, D.; Dix, K.M.; Hunt, P.F.; Thorpe, E.; Stevenson, D.E.; Walker, A.I.T. (1976) Dichlorvos--A 2-year inhalation carcinogenesis study in rats. Arch. Toxicol. 35:281-294.

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

12. Boush, G.M.; Matsumura, F. (1967) Insecticidal degradation by *Pseudomonas melophthora*, the bacterial symbiote of the apple maggot. J. Econ. Entomol. 60:918-920.

13. Braun, R.; Schoeneich, J.; Weissflog, L.; Dedek, W. (1982) Activity of organophosphorus insecticides in bacterial tests for mutagenicity and DNA repair: Direct alkylation vs. metabolic activation and breakdown. 1. Butonate, vinylbutonate, trichlorfon, dichlorvos, demethyl dichlorvos and demethyl vinylbutonate. Chem. Biol. Interact. 39:339-350.

14. Bridges, B.A.; Mottershead, R.P.; Green, M.H.L.; Gray, W.J.H. (1973) Mutagenicity of dichlorvos and methyl methanesulfonate for *Escherichia coli* WP2 and some derivatives deficient in DNA repair. Mutat. Res. 19:295-303.

15. Byeon, W.H.; Hyun, H.H.; Lee, S.Y. (1976) Mutagenicity of pesticides in the *Salmonella/* microsome system. Misaengmul Hakhoe Chi (Korean J. Microbiol.) 14:128-134.

16. Cain, J.R.; Cain, R.K. (1984) Effects of five insecticides on zygospore germination and growth of the green alga *Chlamydomonas moewasii*. Bull. Environ. Contam. Toxicol. 33:572-574.

17. Carere, A.; Morpurgo, G. (1981) Comparison of the mutagenic activity of pesticides *in vitro* in various short-term assays. Prog. Mutat. Res. 2:87-104.

18. Carere, A.; Ortali, V.A.; Cardamone, G.; Torracca, A.M.; Raschetti, R. (1978a) Microbiological mutagenicity studies of pesticides in vitro. Mutat. Res. 57:277-286.

19. Carere, A.; Ortali, V.A.; Cardamone, G.; Morpurgo, G. (1978b) Mutagenicity of dichlorvos and other structurally related pesticides in *Salmonella* and *Streptomyces*. Chem. Biol. Interact. 22:297-308.

20. Casale, G.P.; Cohen, S.D.; DiCapua, R.A. (1983) The effects of organophosphate-induced cholinergic stimulation on the antibody response to sheep erthyrocytes in inbred mice. Toxicol. Appl. Pharmacol. 68:198-205.

21. Casida, J.E.; McBride, L.; Niedermeier, R.P. (1962) Metabolism of 2,2-dichlorovinyl dimethyl phosphate in relation to residues in milk and mammalian tissues. J. Agric. Food Chem. 10:370-377.

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

23. Collins, J.A.; Schooley, M.A.; Singh, V.K. (1971) The effect of dietary dichlorvos on swine reproduction and viability of their offspring. Toxicol. Appl. Pharmacol. 19:377.

24. Core, R.C.; et al. (1971) Infrared and ultraviolet spectra of seventy-six pesticides. I. Organophosphorous pesticides, spectrum no. 74. J. Assoc. Off. Anal. Chem. 54:1081.

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

26. Dean, B.J. (1972) The effect of dichlorvos on cultured human lymphocytes. Arch. Toxicol. 30:75-85.

27. Dean, B.J.; Blair, D. (1976) Dominant lethal assay in female mice after oral dosing with dichlorvos or exposure to atmospheres containing dichlorvos. Mutat. Res. 40:67-72.

28. Dean, B.J.; Thorpe, E. (1972a) Cytogenetic studies with dichlorvos in mice and Chinese hamsters. Arch. Toxicol. 30:39-49.

29. Dean, B.J.; Thorpe, E. (1972b) Studies with dichlorvos vapour in dominant lethal mutation tests on mice. Arch. Toxicol. 30:51-59.

30. Dean, B.J.; Doak, S.M.A.; Funnell, J. (1972) Genetic studies with dichlorvos in the host-mediated assay and in liquid medium using *Saccharomyces cerevisiae*. Arch. Toxicol. 30:61-66.

31. Desi, I.; Varge, L.; Farkas, I. (1978) Studies on the immunosuppressive effect of organochlorine and organophosphoric pesticides in subacute experiments. J. Hyg. Epidemiol. Microbiol. Immunol. 22:115-122.

32. Desi, I.; Varge, L.; Farkas, I. (1980) The effect of DDVP, an organophosphate pesticide on the humoral and cell-mediated immunity of rabbits. Arch. Toxicol. 4(Suppl.):171-174.

33. Dicowsky, L.; Morello, A. (1971) Glutathione-dependent degradation of 2,2 dichlorovinyl dimethyl phosphate (DDVP) by the rat. Life Sci. 10:1031-1037.

34. Dieter, M.P.; Jameson, C.W.; French, J.E.; Gangjee, S.; Stefanski, S.A.; Chhabra, R.S.; Chan, P.C. (1989) Development and validation of a cellular transplant model for leukemia in Fischer rats: A short-term assay for potential anti-leukemic chemicals. Leuk. Res. (in press).

35. Dinse, G.E.; Haseman, J.K. (1986) Logistic regression analysis of incidental-tumor data from animal carcinogenicity experiments. Fundam. Appl. Toxicol. 6:44-52.

36. Dinse, G.E.; Lagakos, S.W. (1983) Regression analysis of tumour prevalence data. J. R. Stat. Soc. Ser. C (Applied Statistics) 32:236-248.

37. Dunnett, C.W. (1955) A multiple comparison procedure for comparing several treatments with a control. J. Am. Stat. Assoc. 50:1096-1122.

38. Durham, W.F.; Gaines, T.B.; McCauley, R.H., Jr.; Sedlak, V.A.; Mattson, A.M.; Hayes, W.J., Jr. (1957) Studies on the toxicity of *O,O*-dimethyl-2,2-dichlorovinyl phosphate (DDVP). Arch. Ind. Health 15:340-349.

39. Dyer, K.F.; Hanna, P.J. (1973) Comparative mutagenic activity and toxicity of triethylphosphate and dichlorvos in bacteria and *Drosophila*. Mutat. Res. 21:175-177.

V. REFERENCES

40. Dzwonkowska, A.; Hubner, H. (1986) Induction of chromosomal aberrations in the Syrian hamster by insecticides tested in vivo. Arch. Toxicol. 58:152-156.

41. Eisler, R. (1970) Acute Toxicities of Organochlorine and Organophosphorus Insecticides to Estuarine Fish. Technical Paper No. 46. Washington, D.C.: U.S. Department of the Interior, Fish and Wildlife Service, Bureau of Sport Fisheries and Wildlife.

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

43. Eustis, S.L.; Boorman, G.A. (1985) Proliferative lesions of the exocrine pancreas: Relationship to corn oil gavage in the National Toxicology Program. J. Natl. Cancer Inst. 75:1067-1073.

44. Fahrig, R. (1974) Comparative mutagenicity studies with pesticides. Montesano, R.; Tomatis, L., Eds.: Chemical Carcinogenesis Essays. IARC Scientific Publication No. 10. Lyon, France: International Agency for Research on Cancer, pp. 161-181.

45. Fischer, G.W.; Schneider, P.; Scheufler, H. (1977) Zur Mutagenitat von Dichloroacetaldehyde und 2,2-Dichlor-1,1-dihydroxyathanphosphonsauremethylester, moglichen Metaboliten des phosphoroorganischen Pesticides Trichlorphon. Chem. Biol. Interact. 19:205-213.

46. Food and Agriculture Organization/World Health Organization (FAO/WHO) (1967) Pesticide Residues in Food. Report of the Joint Meeting on Pesticide Residues. FAO Agricultural Studies No. 73; WHO Technical Report No. 370. Rome: Food and Agriculture Organization of the United Nations.

47. Food and Agriculture Organization/World Health Organization (FAO/WHO) (1978) Pesticide Residues in Food--1977. FAO Plant Production and Protection Paper, 10 rev., p. 24.

48. Fournier, E.; Sonnier, M.; Dally, S. (1978) Detection and assay of organophosphate pesticides in human blood by gas chromatography. Clin. Toxicol. 12:457-462.

49. Gaines, T.B.; Hayes, W.J., Jr.; Linder, R.E. (1966) Liver metabolism of anticholinesterase compounds in live rats: Relation to toxicity. Nature 209:88-89.

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

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

52. Green, M.H.L.; Medcalf, A.S.C.; Arlett, C.F.; Harcourt, S.A.; Lehmann, A.R. (1974) DNA strand breakage caused by dichlorvos, methyl methanesulfonate and iodoacetamide in *Escherichia coli* and cultured Chinese hamster cells. Mutat. Res. 24:365-378.

53. Green, M.H.L.; Muriel, W.J.; Bridges, B.A. (1976) Use of a simplified fluctuation test to detect low levels of mutagens. Mutat. Res. 38:33-42.

54. Griffin, D.E., III; Hill, W.E. (1978) In vitro breakage of plasmid DNA by mutagens and pesticides. Mutat. Res. 52:161-169.

55. Gupta, A.K.; Singh, J. (1974) Dichlorvos (DDVP) induced breaks in the salivary gland chromosomes of Drosophila melanogaster. Curr. Sci. 43:661-662.

56. Hanna, P.J.; Dyer, K.F. (1975) Mutagenicity of organophosphorus compounds in bacteria and Drosophila. Mutat. Res. 28:405-420.

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

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

59. Hatch, G.G.; Anderson, T.M.; Luber, R.A.; et al. (1986) Chemical enhancement of SA7 virus transformation of hamster embryo cells: Evaluation by interlaboratory testing of diverse chemicals. Environ. Mutagen. 8:515-531.

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

61. Hayes, W.J., Jr. (1982) Pesticide Studies in Man. Baltimore: Williams and Wilkins, pp. 343-351.

62. Hill, E.F.; Heath, R.G.; Spann, J.W.; Williams, J.D. (1975) Lethal Dietary Toxicities of Environmental Pollutants to Birds. Fish Wildl. Serv., Spec. Sci. Rep.: Wildl. No. 191. Washington, D.C.: U.S. Department of the Interior, pp. 1-51.

63. Hodgson, E.; Casida, J.E. (1962) Mammalian enzymes involved in the degradation of 2,2-dichlorovinyl dimethyl phosphate. J. Agric. Food Chem. 10:208-214.

64. Hutson, D.H.; Hoadley, E.C. (1972a) The comparative metabolism of [^{14}C-vinyl]dichlorvos in animals and man. Arch. Toxicol. 30:9-18.

65. Hutson, D.H.; Hoadley, E.C. (1972b) The metabolism of [^{14}C-methyl]dichlorvos in the rat and mouse. Xenobiotica 2:107-116.

66. Hutson, D.H.; Hoadley, E.C.; Pickering, B.A. (1971) The metabolic fate of [vinyl-1-^{14}C]dichlorvos in the rat after oral and inhalation exposure. Xenobiotica 1:593-611.

67. International Agency for Research on Cancer (IARC) (1979) Some Halogenated Hydrocarbons. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Vol. 20. Lyon: IARC, pp. 97-127.

68. International Programme on Chemical Safety (IPCS) (1986) Environmental Health Criteria 63. Organophosphorus Insecticides: A General Introduction. Geneva: World Health Organization, p. 15.

69. Ishidate, M., Jr.; Yoshikawa, K. (1980) Chromosome aberration tests with Chinese hamster cells *in vitro* with and without metabolic activation: A comparative study on mutagens and carcinogens. Further Studies in the Assessment of Toxic Actions. Arch. Toxicol. Suppl. 4:41-44.

70. Jayasuriya, V.U. de S.; Ratnayake, W.E. (1973) Screening of some pesticides on *Drosophila melanogaster* for toxic and genetic effects. Dros. Info. Serv. 50:184-186.

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

72. Keith, L.H.; et al. (1968) The high resolution NMR spectra of pesticides. I. Organophosphorous pesticides. J. Assoc. Off. Anal. Chem. 51:1065.

73. Kimbrough, R.D.; Gaines, T.B. (1968) Effect of organic phosphorus compounds and alkylating agents on the rat fetus. Arch. Environ. Health 16:805-808.

74. Kligerman, A.D.; Erexson, G.L.; Wilmer, J.L. (1985) Induction of sister-chromatid exchange (SCE) and cell cycle inhibition in mouse peripheral blood B lymphocytes exposed to mutagenic carcinogens in vivo. Mutat. Res. 157:181-187.

75. Kramers, P.G.N.; Knaap, A.G.A.C. (1978) Absence of a mutagenic effect after feeding dichlorvos to larvae of *Drosophila melanogaster*. Mutat. Res. 57:103-105.

76. Krause, W.; Homola, S. (1972) Beeinflussung der Spermiogenese durch DDVP (Dichlorvos). Arch. Dermatol. Forsch. 244:439-441.

V. REFERENCES

77. Kurinnyi, A.I. (1975) Comparative study of the cytogenetic effect of certain organophosphorus pesticides. Sov. Genet. 11:1534-1538.

78. Lamoreaux, R.J.; Newland, L.W. (1978) The fate of dichlorvos in soil. Chemosphere 7:807-814.

79. Lawley, P.D.; Shah, S.A.; Orr, D.J. (1974) Methylation of nucleic acids by 2,2-dichlorovinyl dimethyl phosphate (dichlorvos, DDVP). Chem. Biol. Interact. 8:171-182.

80. Laws, E.R., Jr. (1966) Route of absorption of DDVP after oral administration to rats. Toxicol. Appl. Pharmacol. 8:193-196.

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

82. Loeffler, J.E.; Potter, J.C.; Scordelis, S.L.; Hendrickson, H.R.; Huston, C.K.; Page, A.C. (1976) Long-term exposure of swine to a ^{14}C-dichlorvos atmosphere. J. Agric. Food Chem. 24:367-371.

83. Lofroth, G. (1970) Alkylation of DNA by dichlorvos. Naturwissenschaften 57:393-394.

84. Lofroth, G. (1978) The mutagenicity of dichloroacetaldehyde. Z. Naturforsch. 33c:783-785.

85. Macklin, A.W.; Ribelin, W.E. (1971) The relation of pesticides to abortion in dairy cattle. J. Am. Vet. Med. Assoc. 159:1743-1748.

86. Majewski, T.; Podgorski, W.; Michalowska, R. (1979) Retention of dichlorvos (DDVP) in rabbits. Pol. Arch. Weter. 21:249-255.

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

88. Margolin, B.H.; Resnick, M.A.; Rimo, J.Y.; Archer, P.; Galloway, S.M.; Bloom, A.D.; Zeiger, E. (1986) Statistical analysis for in vitro cytogenetic assays using Chinese Hamster ovary cells. Environ. Mutagen. 8:183-204.

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

90. Matsumura, F.; Boush, G.M. (1968) Degradation of insecticides by a soil fungus *Trichoderma viride*. J. Econ. Entomol. 61:610-612.

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

92. McFee, A.F.; Lowe, K.W.; San Sebastian, J.R. (1983) Improved sister-chromatid differentiation using paraffin-coated bromodeoxyuridine tablets in mice. Mutat. Res. 119:83-88.

93. Melnikov, N.N. (1971) Chemistry of pesticides. Residue Rev. 36:310-311.

94. Mohn, G. (1973) 5-Methyltryptophan resistance mutations in *Escherichia coli* K-12: Mutagenic activity of monofunctional alkylating agents including organophosphorus insecticides. Mutat. Res. 20:7-15.

95. Moriya, M.; Kato, K.; Shirasu, Y. (1978) Effects of cysteine and a liver metabolic activation system on the activities of mutagenic pesticides. Mutat. Res. 57:259-263.

96. Morpurgo, G.; Aulicino, F.; Bignami, M.; Conti, L.; Velcich, A. (1977) Relationship between structure and mutagenicity of dichlorvos and other pesticides. Atti. Accad. Naz. Lincei, Cl. Sci. Fis. Mat. Natl. Rend. 62:692-701.

97. Morpurgo, G.; Bellincampi, D.; Gualandi, G., Baldinelli, L.; Crescenzi, O.S. (1979) Analysis of mitotic nondisjunction with Aspergillus nidulans. Environ. Health Perspect. 31:81-95.

98. Moutschen-Dahmen, J.; Moutschen-Dahmen, M.; Degraeve, N. (1981) Metrifonate and dichlorvos: Cytogenetic investigations. Acta Pharmacol. Toxicol. 49(Suppl. V):29-39.

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

100. Nagy, Z.; Mile, I.; Antoni, F. (1975) Mutagenic effect of pesticides on *Escherichia coli* WP2 try$^-$. Acta Microbiol. Acad. Sci. Hung. 22:309-314.

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

102. National Cancer Institute (NCI) (1977) Bioassay of Dichlorvos for Possible Carcinogenicity. NCI Technical Report No. 10. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health. 40 p.

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

104. Nishio, A.; Uyeki, E.M. (1981) Induction of sister chromatid exchanges in Chinese hamster ovary cells by organophosphate insecticides and their oxygen analogs. J. Toxicol. Environ. Health 8:939-946.

105. Occupational Safety and Health Administration (OSHA) (1977) Occupational Safety and Health Standards, Subpart Z - Toxic and Hazardous Substances. U.S. Code Fed. Regul., Title 29, part 1910.93, p. 60.

106. Olinski, R.; Walter, Z.; Wiaderkiewicz, R.; Lukasova, E.; Palecek, E. (1980) Changes in DNA properties due to treatment with the pesticides malathion and DDVP. Radiat. Environ. Biophys. 18:65-72.

107. Page, A.C.; DeVries, D.M.; Young, R.; Loeffler, J.E. (1971) Metabolic fate of ingested dichlorvos in swine. Toxicol. Appl. Pharmacol. 19:378.

108. Page, A.C.; Loeffler, J.E.; Hendrickson, H.R.; Huston, C.K.; DeVries, D.M. (1972) Metabolic fate of dichlorvos in swine. Arch. Toxicol. 30:19-27.

109. Pena Chavarri, A.; Swartzwelder, J.C.; Villarejos, V.M.; Kotcher, E.; Arguedas, J. (1969) Dichlorvos: An effective broad spectrum anthelmintic. Am. J. Trop. Med. Hyg. 18:907-911.

110. Perocco, P.; Fini, A. (1980) Damage by dichlorvos of human lymphocyte DNA. Tumori 66:425-430.

111. Pesticide Manual (1983) 7th ed. Dichlorvos. British Crop Protection Council, p. 152.

112. Potter, J.C.; Loeffler, J.E.; Collins, R.D.; Young, R.; Page, A.C. (1973a) Carbon-14 balance and residues of dichlorvos and its metabolites in pigs dosed with dichlorvos-^{14}C. J. Agric. Food Chem. 21:163-166.

113. Potter, J.C.; Boyer, A.C.; Marxmiller, R.E.; Young, R.; Loeffler, J.E. (1973b) Radioisotope residues and residues of dichlorvos and its metabolites in pregnant sows and their progeny dosed with dichlorvos-*^{14}C* or dichlorvos-*^{36}Cl* formulated as PVC pellets. J. Agric. Food Chem. 21:734-738.

114. Ramel, C. (1981) Does dichlorvos constitute a genotoxic hazard? Prog. Mutat. Res. 2:69-78.

115. Rath, S.; Misra, B.N. (1981) Toxicological effects of dichlorvos (DDVP) on brain and liver acetylcholinesterase (AChe) activity of *Tilapia mossambica*, Peters. Toxicology 19:239-245.

116. Rosenkranz, H.S.; Rosenkranz, S. (1972) Reaction of DNA with phosphoric acid esters: Gasoline additive and insecticides. Experientia 28:386-387.

117. Sadtler Agricultural Spectra. IR No. A4282. Philadelphia: Sadtler Research Laboratories.

118. Sasaki, M.; Sugimura, K.; Yoshida, M.; Mitsuaki, A.; Abe, S. (1980) Cytogenetic effects of 60 chemicals on cultured human and Chinese hamster cells. Senshokutai (Kromosoma) 20:574-584.

119. Schafer, E.W., Jr.; Brunton, R.B. (1979) Indicator bird species for toxicity determinations: Is the technique usable in test method development? Beck, J.R., Ed.: Vertebrae Pest Control and Management Materials. ASTM STP 680. Philadelphia: American Society for Testing and Materials, pp. 157-168.

120. Schmidt, G.; Schmidt, M.; Nenner, M.; Vetterlein, F. (1979) Effects of dichlorvos (DDVP) inhalation on the activity of acetylcholinesterase in the bronchial tissue of rats. Arch. Toxicol. 42:191-198.

121. Schwetz, B.A.; Ioset, H.D.; Leong, B.K.J.; Staples, R.E. (1979) Teratogenic potential of dichlorvos given by inhalation and gavage to mice and rabbits. Teratology 20:383-388.

122. Segerback, D. (1981) Estimation of genetic risks of alkylating agents, V. Methylation of DNA in the mouse by DDVP (2,2-dichlorovinyldimethyl phosphate). Hereditas 94:73-76.

123. Segerback, D.; Ehrenberg, L. (1981) Alkylating properties of dichlorvos (DDVP). Acta Pharmacol. Toxicol. 49(Suppl. V):56-66.

124. Shell Chemical Company (1979) Summary of Basic Data for Technical Vapona® Insecticide. Technical Data Bulletin, ACD: 67-110A, rev. 5-79. Shell Chemical Company/Agricultural Chemicals, Houston, TX.

125. Shirasu, Y.; Moriya, M.; Kato, K.; Furuhashi, A.; Kada, T. (1976) Mutagenicity screening of pesticides in the microbial system. Mutat. Res. 40:19-30.

126. Shirasu, Y.; Moriya, M.; Kato, K.; Lienard, F.; Tezuka, H.; Teramoto, S.; Kada, T. (1977) Mutagenicity screening on pesticides and modification products: A basis of carcinogenicity evaluation. Cold Spring Harbor Conference on Cell Proliferation 4:267-285.

127. Shooter, K.V. (1975) Assays for phosphotriester formation in the reaction of bacteriophage R17 with a group of alkylating agents. Chem. Biol. Interact. 11:575-588.

128. Slomka, M.B.; Hine, C.H. (1981) Clinical pharmacology of dichlorvos. Acta Pharmacol. Toxicol. 49(Suppl. 5):105-108.

129. Sobels, F.H.; Todd, N.K. (1979) Absence of a mutagenic effect of dichlorvos on Drosophila melanogaster. Mutat. Res. 67:89-92.

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

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

132. Tezuka, H.; Ando, N.; Suzuki, R.; Terahata, M.; Moriya, M.; Shirasu, Y. (1980) Sister-chromatid exchanges and chromosomal aberrations in cultured Chinese hamster cells treated with pesticides positive in microbial reversion assays. Mutat. Res. 78:177-191.

133. Thorpe, E.; Wilson, A.B.; Dix, K.M.; Blair, D. (1972) Teratological studies with dichlorvos vapour in rabbits and rats. Arch. Toxicol. 30:29-38.

134. Touchstone, J.C.; Dobbins, M.F. (1978) Spray Reagent No. 146a. Practice of Thin-Layer Chromatography. New York: Wiley-Interscience, p.201.

135. Trinh, B.V.; Szabo, I.; Ruzicska, P.; Czeizel, A. (1975) Chromosome aberrations in patients suffering acute organic phosphate insecticide intoxication. Humangenetik 24:33-57.

136. Tu, A.; Hallowell, W.; Pallotta, S.; et al. (1986) An interlaboratory comparison of transformation in Syrian hamster embryo cells with model and coded chemicals. Environ. Mutagen. 8:77-98.

137. U.S. International Trade Commission (USITC) (1986) Synthetic Organic Chemicals, United States Production and Sales, 1985. USITC Publication No. 1892. Washington, DC: Government Printing Office, p. 238.

138. Vogin, E.E.; Carson, S.; Slomka, M.B. (1971) Teratology studies with dichlorvos in rabbits. Toxicol. Appl. Pharmacol. 19:377-378.

139. Voogd, C.E.; Jacobs, J.J.; Van Der Stel, J.J. (1972) On the mutagenic action of dichlorvos. Mutat. Res. 16:413-416.

140. Wennerberg, R.; Lofroth, G. (1974) Formation of 7-methylguanine by dichlorvos in bacteria and mice. Chem. Biol. Interact. 8:339-348.

141. Wild, D. (1973) Chemical induction of streptomycin-resistant mutations in *Escherichia coli*: Dose and mutagenic effects of dichlorvos and methyl methanesulfonate. Mutat. Res. 19:33-41.

142. Wild, D. (1975) Mutagenicity studies on organophosphorus insecticides. Mutat. Res. 32:133-150.

143. Witherup, S.; Jolley, W.J.; Stemmer, K.; Pfitzer, E.A. (1971) Chronic toxicity studies with 2,2-dichlorovinyl dimethyl phosphate (DDVP) in dogs and rats including observations on rat reproduction. Toxicol. Appl. Pharmacol. 19:377.

144. Wright, A.S.; Hutson, D.H.; Wooder, M.F. (1979) The chemical and biochemical reactivity of dichlorvos. Arch. Toxicol. 42:1-18.

145. Wyrobek, A.J.; Bruce, W.R. (1975) Chemical induction of sperm abnormalities in mice. Proc. Natl. Acad. Sci. USA 72:4425-4429.

APPENDIX A

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

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

	Vehicle Control	Low Dose	High Dose
Animals initially in study	50	50	50
Animals removed	50	50	50
Animals examined histopathologically	50	50	50
ALIMENTARY SYSTEM			
Intestine large	(50)	(49)	(50)
Cecum, lipoma		1 (2%)	
Colon, polyp adenomatous			1 (2%)
Intestine small	(50)	(50)	(50)
Sarcoma, metastatic, mesentery	1 (2%)		
Ileum, leukemia mononuclear		2 (4%)	1 (2%)
Liver	(50)	(50)	(50)
Hepatocellular carcinoma	1 (2%)	1 (2%)	1 (2%)
Leukemia mononuclear	11 (22%)	20 (40%)	21 (42%)
Neoplastic nodule		2 (4%)	1 (2%)
Sarcoma, metastatic, mesentery	1 (2%)		
Mesentery	*(50)	*(50)	*(50)
Leukemia mononuclear		3 (6%)	
Mesothelioma malignant	3 (6%)	1 (2%)	1 (2%)
Sarcoma	1 (2%)		
Pancreas	(50)	(49)	(50)
Adenoma	14 (28%)	18 (37%)	17 (34%)
Adenoma, multiple	2 (4%)	7 (14%)	13 (26%)
Leukemia mononuclear		2 (4%)	1 (2%)
Pharynx	*(50)	*(50)	*(50)
Palate, fibrosarcoma			1 (2%)
Salivary glands	(48)	(48)	(49)
Fibrosarcoma, metastatic, skin			1 (2%)
Leukemia mononuclear			1 (2%)
Stomach	(50)	(49)	(50)
Leukemia mononuclear	1 (2%)	1 (2%)	
Forestomach, fibrosarcoma	1 (2%)		
Forestomach, papilloma squamous	2 (4%)	1 (2%)	
Glandular, adenoma			1 (2%)
Tongue	*(50)	*(50)	*(50)
Papilloma squamous			1 (2%)
CARDIOVASCULAR SYSTEM			
Heart	(50)	(50)	(49)
Leukemia mononuclear	2 (4%)	2 (4%)	5 (10%)
ENDOCRINE SYSTEM			
Adrenal gland	(50)	(50)	(50)
Leukemia mononuclear	4 (8%)	8 (16%)	8 (16%)
Cortex, adenoma	1 (2%)	1 (2%)	
Medulla, pheochromocytoma malignant	2 (4%)	5 (10%)	4 (8%)
Medulla, pheochromocytoma malignant, multiple		1 (2%)	
Medulla, pheochromocytoma benign	13 (26%)	12 (24%)	12 (24%)
Medulla, pheochromocytoma benign, multiple	8 (16%)	4 (8%)	2 (4%)
Islets, pancreatic	(50)	(48)	(50)
Adenoma	6 (12%)	5 (10%)	3 (6%)
Adenoma, multiple		1 (2%)	2 (4%)
Parathyroid gland	(45)	(46)	(47)
Adenoma	1 (2%)	1 (2%)	

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

	Vehicle Control	Low Dose	High Dose
ENDOCRINE SYSTEM (Continued)			
Pituitary gland	(50)	(48)	(49)
Leukemia mononuclear	3 (6%)		1 (2%)
Pars distalis, adenoma	9 (18%)	11 (23%)	7 (14%)
Pars distalis, carcinoma	1 (2%)		2 (4%)
Pars intermedia, adenoma	2 (4%)		
Thyroid gland	(49)	(49)	(49)
C-cell, adenoma	6 (12%)	9 (18%)	7 (14%)
C-cell, adenoma, multiple			1 (2%)
C-cell, carcinoma, multiple		1 (2%)	
Follicular cell, adenoma	1 (2%)		
GENERAL BODY SYSTEM			
None			
GENITAL SYSTEM			
Preputial gland	(48)	(46)	(45)
Adenoma	2 (4%)	4 (9%)	3 (7%)
Carcinoma	1 (2%)		3 (7%)
Leukemia mononuclear	2 (4%)		1 (2%)
Prostate	(50)	(50)	(49)
Adenoma	1 (2%)	1 (2%)	
Carcinoma	1 (2%)		
Leukemia mononuclear		2 (4%)	
Seminal vesicle	*(50)	*(50)	*(50)
Leukemia mononuclear		1 (2%)	1 (2%)
Lymphoma malignant lymphocytic			1 (2%)
Testes	(50)	(50)	(50)
Interstitial cell, adenoma	29 (58%)	18 (36%)	19 (38%)
Interstitial cell, adenoma, multiple	16 (32%)	28 (56%)	27 (54%)
HEMATOPOIETIC SYSTEM			
Bone marrow	(50)	(50)	(50)
Leukemia mononuclear	5 (10%)	10 (20%)	10 (20%)
Lymph node	(50)	(50)	(50)
Fibrosarcoma, metastatic, skin			1 (2%)
Bronchial, leukemia mononuclear			1 (2%)
Iliac, leukemia mononuclear			1 (2%)
Inguinal, leukemia mononuclear			1 (2%)
Mandibular, leukemia mononuclear	2 (4%)	6 (12%)	5 (10%)
Mandibular, lymphoma malignant lymphocytic			1 (2%)
Mediastinal, leukemia mononuclear	2 (4%)	8 (16%)	4 (8%)
Mediastinal, lymphoma malignant lymphocytic			1 (2%)
Mesenteric, leukemia mononuclear	4 (8%)	6 (12%)	3 (6%)
Pancreatic, leukemia mononuclear	2 (4%)	3 (6%)	5 (10%)
Renal, leukemia mononuclear			1 (2%)
Spleen	(49)	(50)	(50)
Fibrosarcoma			1 (2%)
Leukemia mononuclear	10 (20%)	18 (36%)	21 (42%)
Lymphoma malignant histiocytic			1 (2%)
Lymphoma malignant lymphocytic			1 (2%)
Thymus	(34)	(29)	(34)
Leukemia mononuclear	1 (3%)	2 (7%)	2 (6%)

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

	Vehicle Control	Low Dose	High Dose
INTEGUMENTARY SYSTEM			
Mammary gland	(46)	(44)	(46)
Fibroadenoma	6 (13%)	1 (2%)	2 (4%)
Skin	(49)	(49)	(49)
Basal cell adenoma			1 (2%)
Basal cell carcinoma		1 (2%)	2 (4%)
Carcinosarcoma		1 (2%)	
Keratoacanthoma	3 (6%)	4 (8%)	1 (2%)
Leukemia mononuclear		1 (2%)	
Lymphoma malignant lymphocytic			1 (2%)
Papilloma squamous	3 (6%)	3 (6%)	2 (4%)
Trichoepithelioma	1 (2%)		
Subcutaneous tissue, fibroma	7 (14%)	6 (12%)	4 (8%)
Subcutaneous tissue, fibrosarcoma	2 (4%)		2 (4%)
Subcutaneous tissue, hemangioma	1 (2%)		
Subcutaneous tissue, schwannoma malignant	2 (4%)	1 (2%)	
MUSCULOSKELETAL SYSTEM			
Bone	(50)	(50)	(50)
Osteosarcoma			1 (2%)
NERVOUS SYSTEM			
Brain	(50)	(50)	(48)
Astrocytoma malignant	1 (2%)		1 (2%)
Granular cell tumor benign		1 (2%)	
Oligodendroglioma malignant	1 (2%)		
RESPIRATORY SYSTEM			
Lung	(50)	(50)	(49)
Alveolar/bronchiolar adenoma			3 (6%)
Fibrosarcoma, metastatic, skin			1 (2%)
Leukemia mononuclear	5 (10%)	14 (28%)	16 (33%)
Lymphoma malignant lymphocytic			1 (2%)
Neoplasm, NOS, metastatic	1 (2%)		
Pheochromocytoma malignant, metastatic, adrenal gland		1 (2%)	
Mediastinum, mesothelioma malignant		1 (2%)	
Nose	(49)	(49)	(47)
Leukemia mononuclear			1 (2%)
Schwannoma malignant		1 (2%)	
SPECIAL SENSES SYSTEM			
Eye	*(50)	*(50)	*(50)
Leukemia mononuclear			1 (2%)
Zymbal gland	*(50)	*(50)	*(50)
Carcinoma			1 (2%)
URINARY SYSTEM			
Kidney	(50)	(50)	(50)
Hamartoma	1 (2%)		
Leukemia mononuclear	5 (10%)	6 (12%)	4 (8%)
Renal tubule, adenoma		1 (2%)	
Urinary bladder	(50)	(50)	(50)
Leukemia mononuclear		2 (4%)	1 (2%)

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

	Vehicle Control	Low Dose	High Dose
SYSTEMIC LESIONS			
Multiple organs	*(50)	*(50)	*(50)
Hemangioma	1 (2%)		
Leukemia mononuclear	11 (22%)	20 (40%)	21 (42%)
Mesothelioma malignant	3 (6%)	2 (4%)	1 (2%)
Lymphoma malignant lymphocytic			1 (2%)
Lymphoma malignant histiocytic			1 (2%)
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Moribund	14	17	18
Terminal sacrifice	31	25	24
Dead	4	3	4
Accident	1	5	4
TUMOR SUMMARY			
Total animals with primary neoplasms **	50	49	50
Total primary neoplasms	163	174	173
Total animals with benign neoplasms	49	49	49
Total benign neoplasms	135	140	130
Total animals with malignant neoplasms	25	29	32
Total malignant neoplasms	28	34	43
Total animals with secondary neoplasms ***	2	1	1
Total secondary neoplasms	3	1	3

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

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

WEEKS ON STUDY	057	075	083	084	084	085	087	089	093	093	094	094	097	101	103	103	103	104	104	105	105	105	105	105	105
CARCASS ID	081	021	111	041	061	022	071	091	101	051	042	043	102	062	082	023	072	103	084	085	052	053	054	064	073
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, mesentery																									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																		X							
Leukemia mononuclear						X									X				X		X				X
Sarcoma, metastatic, mesentery																									
Mesentery	+									+										+	+		+	+	+
Mesothelioma malignant										X										X			X		
Sarcoma																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma											X			X		X		X				X		X	
Adenoma, multiple																									
Pharynx																									
Salivary glands	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																			X						
Forestomach, fibrosarcoma													X												
Forestomach, papilloma squamous																									
Tooth																+									
CARDIOVASCULAR SYSTEM																									
Blood vessel																	+								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																			X						
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear						X									X				X						
Cortex, adenoma																		X							
Medulla, pheochromocytoma malignant												X		X											
Medulla, pheochromocytoma benign						X			X			X									X		X	X	
Medulla, pheochromocytoma benign, multiple															X				X						X
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma									X															X	
Parathyroid gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Adenoma																									
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear						X									X										
Pars distalis, adenoma													X				X	X					X	X	X
Pars distalis, carcinoma	X																								
Pars intermedia, adenoma			X						X																
Thyroid gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma													X												
Follicular cell, adenoma																									
GENERAL BODY SYSTEM																									
Tissue, NOS																									
GENITAL SYSTEM																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma					X																				
Carcinoma																									
Leukemia mononuclear															X										
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma																	X								
Seminal vesicle																									
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma		X			X		X		X	X		X	X	X	X	X	X			X			X	X	X
Interstitial cell, adenoma, multiple				X				X			X								X		X	X			

+: Tissue examined microscopically
: Not examined
−. Present but not examined microscopically
I: Insufficient tissue

M: Missing
A. Autolysis precludes examination
X. Incidence of listed morphology

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

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	TOTAL
CARCASS ID	0074	0075	0083	0112	0113	0114	0115	0124	0125	0131	0132	0133	0134	0135	0144	0145	0155	0163	0165	0192	0193	0194	0195	0104	0105	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, metastatic, mesentery							X																			1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma																										1
Leukemia mononuclear						X		X			X						X		X	X						11
Sarcoma, metastatic, mesentery							X																			1
Mesentery						+	+																			9
Mesothelioma malignant																										3
Sarcoma							X																			1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma			X	X	X					X		X	X				X					X				14
Adenoma, multiple	X																		X							2
Pharynx												+														1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Forestomach, fibrosarcoma																										1
Forestomach, papilloma squamous					X							X														2
Tooth																					+					2
CARDIOVASCULAR SYSTEM																										
Blood vessel															+	+		+								4
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																	X									2
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																	X									4
Cortex, adenoma																										1
Medulla, pheochromocytoma malignant																										2
Medulla, pheochromocytoma benign													X	X	X	X	X	X						X		13
Medulla, pheochromocytoma benign, multiple	X			X				X	X		X															8
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma		X	X	X									X													6
Parathyroid gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	45
Adenoma												X														1
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																	X									3
Pars distalis, adenoma					X	X																		X		9
Pars distalis, carcinoma																										1
Pars intermedia, adenoma																										2
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C cell, adenoma			X						X				X		X	X										6
Follicular cell, adenoma																								X		1
GENERAL BODY SYSTEM																										
Tissue, NOS												+														1
GENITAL SYSTEM																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma									X																	2
Carcinoma	X																									1
Leukemia mononuclear																	X									2
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma						X																				1
Carcinoma																										1
Seminal vesicle																							+	+	+	3
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell, adenoma				X	X	X	X	X	X	X	X	X			X	X	X		X						X	29
Interstitial cell, adenoma, multiple	X	X	X										X	X				X		X	X	X	X			16

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

WEEKS ON STUDY	057	075	083	084	084	085	087	089	093	093	094	094	097	101	103	103	103	104	104	105	105	105	105	105	105
CARCASS ID	081	021	011	041	061	022	071	091	101	051	042	043	102	062	082	023	072	103	084	085	052	053	054	064	073
HEMATOPOIETIC SYSTEM																									
Blood																			+						
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear						X									X				X						
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mandibular, leukemia mononuclear						X									X										
Mediastinal, leukemia mononuclear						X									X										
Mesenteric, leukemia mononuclear						X									X						X				
Pancreatic, leukemia mononuclear															X										
Spleen	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear						X									X				X		X				X
Thymus	+	+	+	+	M	+	+	M	+	+	+	M	M	+	M	+	+	+	+	+	M	+	M	+	+
Leukemia mononuclear						X																			
INTEGUMENTARY SYSTEM																									
Mammary gland	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Fibroadenoma									X								X						X	X	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																									
Papilloma squamous			X																						
Trichoepithelioma		X																							
Subcutaneous tissue, fibroma			X	X					X															X	
Subcutaneous tissue, fibrosarcoma																									
Subcutaneous tissue, hemangioma																									
Subcutaneous tissue, schwannoma malignant																									
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																				+					
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant																									
Oligodendroglioma malignant							X																		
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear						X									X				X		X				
Neoplasm, NOS, metastatic		X																							
Nose	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Eye																		+			+				
Harderian gland																									
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hamartoma											X														
Leukemia mononuclear						X									X										
Ureter																	+								
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

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

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	TOTAL TISSUES TUMORS
CARCASS ID	074	075	083	012	013	014	015	024	025	031	032	033	034	035	044	045	055	063	065	092	093	094	095	104	105	
HEMATOPOIETIC SYSTEM																										
Blood																										1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																	X			X						5
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mandibular, leukemia mononuclear																										2
Mediastinal, leukemia mononuclear																										2
Mesenteric, leukemia mononuclear																			X							4
Pancreatic, leukemia mononuclear																	X									2
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear						X		X			X						X		X							10
Thymus	+	+	+	+	M	+	+	+	+	M	+	+	+	M	+	+	M	M	M	M	M	M	+	+	+	34
Leukemia mononuclear																										1
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	46
Fibroadenoma						X									X											6
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Keratoacanthoma																			X	X					X	3
Papilloma squamous																						X	X			3
Trichoepithelioma																										1
Subcutaneous tissue, fibroma							X	X															X			7
Subcutaneous tissue, fibrosarcoma												X						X								2
Subcutaneous tissue, hemangioma						X																				1
Subcutaneous tissue, schwannoma malignant						X		X																		2
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma malignant												X														1
Oligodendroglioma malignant																										1
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																	X									5
Neoplasm, NOS, metastatic																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPECIAL SENSES SYSTEM																										
Eye																										2
Harderian gland					+																					1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hamartoma																										1
Leukemia mononuclear																	X		X	X						5
Ureter																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

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

WEEKS ON STUDY	058	061	067	069	074	077	081	084	087	089	091	092	093	093	094	094	095	097	097	098	099	099	100	100	100
CARCASS ID	291	271	321	292	293	301	331	302	251	272	322	311	252	332	303	281	253	261	341	254	273	342	312	323	324
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cecum, lipoma																									
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ileum, leukemia mononuclear																									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																									
Leukemia mononuclear									X			X	X	X				X		X	X			X	
Neoplastic nodule													X												
Mesentery													+					+	+			+			
Leukemia mononuclear													X					X							
Mesothelioma malignant																						X			
Pancreas	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma						X													X			X	X		
Adenoma, multiple																X	X								
Leukemia mononuclear												X						X							
Pharynx																						+			
Salivary glands	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																		X							
Forestomach, papilloma squamous																									
Tongue																									
Tooth																									
CARDIOVASCULAR SYSTEM																									
Blood vessel															+										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																		X							
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear									X				X					X			X				
Cortex, adenoma																									
Medulla, pheochromocytoma malignant																									
Medulla, pheochromocytoma malignant, multiple																								X	
Medulla, pheochromocytoma benign							X								X	X	X	X			X		X		
Medulla, pheochromocytoma benign, multiple																									
Islets, pancreatic	+	+	+	+	A	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma													X						X		X				X
Adenoma, multiple																									
Parathyroid gland	M	+	+	+	M	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Pituitary gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma		X	X	X													X		X	X					X
Thyroid gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C cell, adenoma															X			X	X	X			X		
C cell, carcinoma, multiple																									
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma		X																					X		
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Leukemia mononuclear													X					X							
Seminal vesicle																		+				+			+
Leukemia mononuclear																		X							
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma			X										X	X	X				X	X	X	X	X	X	
Interstitial cell, adenoma, multiple					X	X	X	X	X	X	X	X				X		X							X

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

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	TOTAL:
CARCASS ID	255	262	263	264	265	274	275	282	283	284	285	294	295	304	305	313	314	315	325	333	334	335	343	344	345	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cecum, lipoma																			X							1
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Ileum, leukemia mononuclear			X																X							2
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma	X																									1
Leukemia mononuclear	X	X	X		X				X		X	X	X			X	X		X						X	20
Neoplastic nodule					X																					2
Mesentery	+	+		+																						7
Leukemia mononuclear		X																								3
Mesothelioma malignant																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma	X	X		X	X	X	X		X	X	X		X		X	X				X				X		18
Adenoma, multiple												X		X							X	X	X			7
Leukemia mononuclear																										2
Pharynx											+															2
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear																										1
Forestomach, papilloma squamous																					X					1
Tongue																			+							1
Tooth																							+			1
CARDIOVASCULAR SYSTEM																										
Blood vessel				+		+									+											4
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																			X							2
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X	X								X														X	8
Cortex, adenoma	X																									1
Medulla, pheochromocytoma malignant									X	X			X	X			X									5
Medulla, pheochromocytoma malignant, multiple																										1
Medulla, pheochromocytoma benign							X		X			X									X			X		12
Medulla, pheochromocytoma benign, multiple		X		X															X			X				4
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma																									X	5
Adenoma, multiple												X														1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Adenoma																						X				1
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	48
Pars distalis, adenoma	X						X									X			X							11
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C cell, adenoma			X		X								X					X								9
C-cell, carcinoma, multiple																				X						1
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Adenoma					X							X														4
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																					X					1
Leukemia mononuclear																										2
Seminal vesicle									+																	4
Leukemia mononuclear																										1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell, adenoma		X						X	X							X	X		X		X				X	18
Interstitial cell, adenoma, multiple	X		X	X	X	X	X			X	X	X	X	X	X			X		X		X	X	X		28

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

WEEKS ON STUDY	058	061	067	069	074	077	081	084	087	089	091	092	093	093	093	094	094	095	097	097	098	099	099	100	100	100
CARCASS ID	291	271	321	292	293	301	331	302	251	272	322	311	252	332	303	281	253	261	341	254	273	342	312	323	324
HEMATOPOIETIC SYSTEM																										
Blood																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear												X	X	X				X			X			X		
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mandibular, leukemia mononuclear												X	X							X	X			X		
Mediastinal, leukemia mononuclear												X	X					X			X			X		
Mesenteric, leukemia mononuclear													X					X								
Pancreatic, leukemia mononuclear													X													
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear									X			X	X	X						X	X			X		
Thymus	+	I	+	+	M	M	M	M	M	M	+	M	+	M	M	M	+	+	+	+	+	+	M	+	I	
Leukemia mononuclear													X					X								
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	
Fibroadenoma																				X						
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Basal cell carcinoma																										
Carcinosarcoma																X										
Keratoacanthoma									X			X														
Leukemia mononuclear																		X								
Papilloma squamous																										
Subcutaneous tissue, fibroma												X					X									
Subcutaneous tissue, schwannoma malignant				X																						
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Skeletal muscle											+															
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Granular cell tumor benign																										
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Leukemia mononuclear												X	X	X				X		X	X			X		
Pheochromocytoma malignant, metastatic, adrenal gland																								X		
Mediastinum, mesothelioma malignant																										
Nose	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Schwannoma malignant																										
Trachea	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
SPECIAL SENSES SYSTEM																										
Ear																										
Eye				M			M																	+		
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Leukemia mononuclear													X					X			X					
Renal tubule, adenoma																								X		
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Leukemia mononuclear																		X								

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

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	
CARCASS ID	255	262	263	264	265	274	275	282	283	284	285	294	295	304	305	313	314	315	325	333	334	335	343	344	345	TOTAL: TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Blood													+													1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X	X									X							X							10
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mandibular, leukemia mononuclear											X															6
Mediastinal, leukemia mononuclear			X								X								X							8
Mesenteric, leukemia mononuclear		X	X																X						X	6
Pancreatic, leukemia mononuclear											X														X	3
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X	X	X		X				X		X	X	X			X			X						X	18
Thymus	+	+	M	M	+	+	+	+	+	M	+	+	+	+	M	M	+	M	M	M	+	+	+	+	+	29
Leukemia mononuclear																										2
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	+	+	M	+	+	+	+	M	M	+	+	+	M	+	+	+	+	+	+	M	+	44
Fibroadenoma																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Basal cell carcinoma	X																									1
Carcinosarcoma																										1
Keratoacanthoma					X														X							4
Leukemia mononuclear																										1
Papilloma squamous		X													X		X									3
Subcutaneous tissue, fibroma							X	X	X															X		6
Subcutaneous tissue, schwannoma malignant																										1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granular cell tumor benign	X																									1
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	48
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X	X						X		X	X							X						X	14
Pheochromocytoma malignant, metastatic, adrenal gland																										1
Mediastinum, mesothelioma malignant				X																						1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Schwannoma malignant											X															1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPECIAL SENSES SYSTEM																										
Ear																									M	
Eye								+																		2
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X	X																X							6
Renal tubule, adenoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																			X							2

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

WEEKS ON STUDY	066	066	068	081	082	085	088	089	089	089	089	092	094	095	096	096	097	099	099	100	100	101	102	103	103
CARCASS ID	161	141	142	211	162	201	191	202	181	212	221	182	151	192	131	171	222	193	203	163	132	172	133	213	164
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Colon, polyp adenomatous																									
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ileum, leukemia mononuclear																									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																									
Leukemia mononuclear							X		X	X		X						X	X	X	X	X	X	X	X
Neoplastic nodule																									
Mesentery		+		+							+		+								+				
Mesothelioma malignant											X														
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma				X					X		X	X		X	X		X								
Adenoma, multiple													X							X	X				X
Leukemia mononuclear																									
Pharynx																									
Palate, fibrosarcoma																									
Salivary glands	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin																									
Leukemia mononuclear																								X	
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Glandular, adenoma																			X						
Tongue																		+							
Papilloma squamous																									
CARDIOVASCULAR SYSTEM																									
Blood vessel																+									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear												X									X		X	X	
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X			X											X	X	X	X	X
Medulla, pheochromocytoma malignant																			X	X					
Medulla, pheochromocytoma benign				X								X		X	X		X							X	
Medulla, pheochromocytoma benign, multiple																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma									X																
Adenoma, multiple																	X								
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																					X				
Pars distalis, adenoma						X				X							X								
Pars distalis, carcinoma								X																	
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C cell, adenoma									X	X	X											X			
C cell, adenoma, multiple																							X		
GENERAL BODY SYSTEM																									
Tissue, NOS																							+		
GENITAL SYSTEM																									
Epididymis	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	M	M	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma														X											
Carcinoma													X		X										
Leukemia mononuclear																								X	
Prostate	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle																								+	
Leukemia mononuclear																								X	
Lymphoma malignant lymphocytic																									
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma		X	X	X		X			X			X		X				X	X		X		X	X	
Interstitial cell, adenoma, multiple	X				X		X				X		X		X	X		X		X		X			X

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

WEEKS ON STUDY	104	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	
CARCASS ID	143	134	135	144	145	152	153	154	155	165	173	174	175	183	184	185	194	195	204	205	214	215	223	224	225	TOTAL TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	M	M	+	+	+	+	+	+	+	+	44
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Colon, polyp adenomatous														X												1
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Ileum, leukemia mononuclear																									X	1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma							X																			1
Leukemia mononuclear		X	X	X		X			X			X										X	X		X	21
Neoplastic nodule																									X	1
Mesentery				+																				+		8
Mesothelioma malignant																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma	X			X	X		X						X			X	X		X		X			X		17
Adenoma, multiple		X				X		X			X				X			X		X		X	X			13
Leukemia mononuclear			X																							1
Pharynx									+																	1
Palate, fibrosarcoma									X																	1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibrosarcoma, metastatic, skin																			X							1
Leukemia mononuclear																										1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Glandular, adenoma																										1
Tongue															+											2
Papilloma squamous															X											1
CARDIOVASCULAR SYSTEM																										
Blood vessel						+								+												3
Heart	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear			X																							5
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear												X														8
Medulla, pheochromocytoma malignant		X					X																			4
Medulla, pheochromocytoma benign								X				X				X			X				X		X	12
Medulla, pheochromocytoma benign, multiple														X										X		2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																							X		X	3
Adenoma, multiple															X											2
Parathyroid gland	+	+	+	+	+	+	+	M	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear																										1
Pars distalis, adenoma								X							X								X		X	7
Pars distalis, carcinoma						X																				2
Thyroid gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C cell, adenoma						X													X						X	7
C cell, adenoma, multiple																										1
GENERAL BODY SYSTEM																										
Tissue, NOS																										1
GENITAL SYSTEM																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Preputial gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Adenoma												X												X		3
Carcinoma																									X	3
Leukemia mononuclear																										1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Seminal vesicle																	+									2
Leukemia mononuclear																										1
Lymphoma malignant lymphocytic																	X									1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell, adenoma			X		X			X		X		X		X				X			X					19
Interstitial cell, adenoma, multiple	X	X		X		X	X		X		X		X			X	X		X	X		X	X	X	X	27

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

WEEKS ON STUDY	066	066	068	081	082	085	088	089	089	089	089	092	094	095	096	096	097	099	099	100	100	101	102	103	103
CARCASS ID	161	141	142	211	162	201	191	202	181	212	221	182	151	192	131	171	222	193	203	163	132	172	133	213	164
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X			X		X									X	X	X	X	X
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin																									
Bronchial, leukemia mononuclear																								X	
Iliac, leukemia mononuclear																								X	
Inguinal, leukemia mononuclear																								X	
Mandibular, leukemia mononuclear							X			X												X		X	
Mandibular, lymphoma malignant lymphocytic																									
Mediastinal, leukemia mononuclear							X			X											X			X	
Mediastinal, lymphoma malignant lymphocytic																									
Mesenteric, leukemia mononuclear							X																X	X	
Pancreatic, leukemia mononuclear										X		X									X				
Renal, leukemia mononuclear							X																		
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																									
Leukemia mononuclear							X		X	X		X						X	X	X	X	X	X	X	X
Lymphoma malignant histiocytic				X																					
Lymphoma malignant lymphocytic																									
Thymus	+	+	M	+	+	+	M	+	+	I	+	+	M	M	+	+	+	M	+	+	M	+	+	+	+
Leukemia mononuclear																								X	
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	+	+	+	M	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma														X									X		
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma																									
Basal cell carcinoma																									X
Keratoacanthoma															X										
Lymphoma malignant lymphocytic																									
Papilloma squamous				X																					
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, fibrosarcoma																									
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma					X																				
NERVOUS SYSTEM																									
Brain	+			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant																									
Peripheral nerve	+	+	+	+	+	I	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma														X											
Fibrosarcoma, metastatic, skin																									
Leukemia mononuclear							X		X	X		X						X		X	X	X	X	X	X
Lymphoma malignant lymphocytic																									
Nose	M	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																								X	
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Ear																								+	
Eye					+		+			+	+		+		+		+				+	+	+	+		+
Leukemia mononuclear																									
Zymbal gland																									
Carcinoma																									
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X															X	X		
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																								X	

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

WEEKS ON STUDY	104	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	
CARCASS ID	143	134	135	144	145	152	153	154	155	165	173	174	175	183	184	185	194	195	204	205	214	215	223	224	225	TOTAL TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear			X									X														10
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, skin																			X							1
Bronchial, leukemia mononuclear																										1
Iliac, leukemia mononuclear																										1
Inguinal, leukemia mononuclear																										1
Mandibular, leukemia mononuclear												X														5
Mandibular, lymphoma malignant lymphocytic																	X									1
Mediastinal, leukemia mononuclear																										4
Mediastinal, lymphoma malignant lymphocytic																	X									1
Mesenteric, leukemia mononuclear																										3
Pancreatic, leukemia mononuclear												X									X					5
Renal, leukemia mononuclear																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma					X																					1
Leukemia mononuclear		X	X	X		X			X			X									X	X			X	21
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic																	X									1
Thymus	M	+	+	+	+	M	M	M	M	+	+	+	+	I	M	M	M	+	+	+	+	+	+	+	+	34
Leukemia mononuclear			X																							2
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	46
Fibroadenoma																										2
Skin	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Basal cell adenoma			X																							1
Basal cell carcinoma									X																	2
Keratoacanthoma																										1
Lymphoma malignant lymphocytic																	X									1
Papilloma squamous															X											2
Subcutaneous tissue, fibroma		X			X						X				X											4
Subcutaneous tissue, fibrosarcoma			X																X							2
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Astrocytoma malignant																X										1
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma						X													X							3
Fibrosarcoma, metastatic, skin																			X							1
Leukemia mononuclear			X									X									X	X			X	16
Lymphoma malignant lymphocytic																	X									1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Leukemia mononuclear																										1
Trachea	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPECIAL SENSES SYSTEM																										
Ear																										1
Eye		+	+	+	+	+	+	+	+	+		+	+	+					+				+	+	+	28
Leukemia mononuclear			X																							1
Zymbal gland																					+					1
Carcinoma																					X					1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear			X																							4
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1

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

	Vehicle Control	4 mg/kg	8 mg/kg
Adrenal Gland: Pheochromocytoma			
Overall Rates (a)	21/50 (42%)	16/50 (32%)	14/50 (28%)
Adjusted Rates (b)	57.6%	48.2%	43.8%
Terminal Rates (c)	16/31 (52%)	9/25 (36%)	8/24 (33%)
Day of First Observation	595	561	564
Life Table Tests (d)	P=0.283N	P=0.472N	P=0.321N
Logistic Regression Tests (d)	P=0.121N	P=0.332N	P=0.145N
Cochran-Armitage Trend Test (d)	P=0.084N		
Fisher Exact Test (d)		P=0.204N	P=0.104N
Adrenal Gland: Malignant Pheochromocytoma			
Overall Rates (a)	2/50 (4%)	6/50 (12%)	4/50 (8%)
Adjusted Rates (b)	5.2%	22.9%	14.0%
Terminal Rates (c)	0/31 (0%)	5/25 (20%)	2/24 (8%)
Day of First Observation	657	695	692
Life Table Tests (d)	P=0.187	P=0.076	P=0.260
Logistic Regression Tests (d)	P=0.231	P=0.090	P=0.317
Cochran-Armitage Trend Test (d)	P=0.279		
Fisher Exact Test (d)		P=0.134	P=0.339
Adrenal Gland: Pheochromocytoma or Malignant Pheochromocytoma			
Overall Rates (a)	22/50 (44%)	21/50 (42%)	18/50 (36%)
Adjusted Rates (b)	58.8%	62.6%	53.8%
Terminal Rates (c)	16/31 (52%)	13/25 (52%)	10/24 (42%)
Day of First Observation	595	561	564
Life Table Tests (d)	P=0.505	P=0.325	P=0.558
Logistic Regression Tests (d)	P=0.336N	P=0.461	P=0.356N
Cochran-Armitage Trend Test (d)	P=0.243N		
Fisher Exact Test (d)		P=0.500N	P=0.270N
Preputial Gland: Adenoma			
Overall Rates (a)	2/48 (4%)	4/46 (9%)	3/45 (7%)
Adjusted Rates (b)	5.4%	13.8%	11.2%
Terminal Rates (c)	1/30 (3%)	2/23 (9%)	2/23 (9%)
Day of First Observation	587	426	660
Life Table Tests (d)	P=0.330	P=0.255	P=0.422
Logistic Regression Tests (d)	P=0.367	P=0.358	P=0.466
Cochran-Armitage Trend Test (d)	P=0.380		
Fisher Exact Test (d)		P=0.318	P=0.469
Preputial Gland: Carcinoma			
Overall Rates (a)	1/48 (2%)	0/46 (0%)	3/45 (7%)
Adjusted Rates (b)	3.3%	0.0%	9.5%
Terminal Rates (c)	1/30 (3%)	0/23 (0%)	1/23 (4%)
Day of First Observation	729		652
Life Table Tests (d)	P=0.164	P=0.553N	P=0.253
Logistic Regression Tests (d)	P=0.180	P=0.560N	P=0.282
Cochran-Armitage Trend Test (d)	P=0.180		
Fisher Exact Test (d)		P=0.511N	P=0.284
Preputial Gland: Adenoma or Carcinoma			
Overall Rates (a)	3/48 (6%)	4/46 (9%)	6/45 (13%)
Adjusted Rates (b)	8.7%	13.8%	19.9%
Terminal Rates (c)	2/30 (7%)	2/23 (9%)	3/23 (13%)
Day of First Observation	587	426	652
Life Table Tests (d)	P=0.135	P=0.390	P=0.173
Logistic Regression Tests (d)	P=0.159	P=0.514	P=0.209
Cochran-Armitage Trend Test (d)	P=0.165		
Fisher Exact Test (d)		P=0.476	P=0.211

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

	Vehicle Control	4 mg/kg	8 mg/kg
Pancreatic Islets: Adenoma			
Overall Rates (a)	6/50 (12%)	6/48 (13%)	5/50 (10%)
Adjusted Rates (b)	18.1%	19.3%	17.1%
Terminal Rates (c)	5/31 (16%)	2/25 (8%)	3/24 (13%)
Day of First Observation	646	645	623
Life Table Tests (d)	P=0.544	P=0.473	P=0.610
Logistic Regression Tests (d)	P=0.485N	P=0.539	P=0.545N
Cochran-Armitage Trend Test (d)	P=0.438N		
Fisher Exact Test (d)		P=0.591	P=0.500N
Liver: Neoplastic Nodule or Hepatocellular Carcinoma			
Overall Rates (a)	1/50 (2%)	3/50 (6%)	2/50 (4%)
Adjusted Rates (b)	3.0%	10.4%	8.3%
Terminal Rates (c)	0/31 (0%)	2/25 (8%)	2/24 (8%)
Day of First Observation	727	645	729
Life Table Tests (d)	P=0.306	P=0.239	P=0.409
Logistic Regression Tests (d)	P=0.349	P=0.263	P=0.407
Cochran-Armitage Trend Test (d)	P=0.394		
Fisher Exact Test (d)		P=0.309	P=0.500
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	0/50 (0%)	0/50 (0%)	3/49 (6%)
Adjusted Rates (b)	0.0%	0.0%	11.2%
Terminal Rates (c)	0/31 (0%)	0/25 (0%)	2/23 (9%)
Day of First Observation			660
Life Table Tests (d)	P=0.028	(e)	P=0.088
Logistic Regression Tests (d)	P=0.037	(e)	P=0.104
Cochran-Armitage Trend Test (d)	P=0.036		
Fisher Exact Test (d)		(e)	P=0.117
Mammary Gland: Fibroadenoma			
Overall Rates (a)	6/50 (12%)	1/50 (2%)	2/50 (4%)
Adjusted Rates (b)	17.4%	3.2%	6.2%
Terminal Rates (c)	4/31 (13%)	0/25 (0%)	0/24 (0%)
Day of First Observation	646	684	660
Life Table Tests (d)	P=0.117N	P=0.105N	P=0.218N
Logistic Regression Tests (d)	P=0.078N	P=0.078N	P=0.154N
Cochran-Armitage Trend Test (d)	P=0.066N		
Fisher Exact Test (d)		P=0.056N	P=0.134N
Pancreas: Adenoma			
Overall Rates (a)	16/50 (32%)	25/49 (51%)	30/50 (60%)
Adjusted Rates (b)	45.2%	80.0%	82.5%
Terminal Rates (c)	12/31 (39%)	19/25 (76%)	18/24 (75%)
Day of First Observation	653	533	564
Life Table Tests (d)	P<0.001	P=0.006	P<0.001
Logistic Regression Tests (d)	P<0.001	P=0.007	P=0.001
Cochran-Armitage Trend Test (d)	P=0.003		
Fisher Exact Test (d)		P=0.043	P=0.004
Pituitary Gland/Pars Distalis: Adenoma			
Overall Rates (a)	9/50 (18%)	11/48 (23%)	7/49 (14%)
Adjusted Rates (b)	26.0%	31.6%	22.8%
Terminal Rates (c)	6/31 (19%)	4/24 (17%)	4/24 (17%)
Day of First Observation	674	426	592
Life Table Tests (d)	P=0.521N	P=0.235	P=0.572N
Logistic Regression Tests (d)	P=0.373N	P=0.386	P=0.454N
Cochran-Armitage Trend Test (d)	P=0.366N		
Fisher Exact Test (d)		P=0.362	P=0.410N

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

	Vehicle Control	4 mg/kg	8 mg/kg
Pituitary Gland/Pars Distalis: Adenoma or Carcinoma			
Overall Rates (a)	10/50 (20%)	11/48 (23%)	9/49 (18%)
Adjusted Rates (b)	27.5%	31.6%	28.4%
Terminal Rates (c)	6/31 (19%)	4/24 (17%)	5/24 (21%)
Day of First Observation	393	426	592
Life Table Tests (d)	P=0.473	P=0.318	P=0.520
Logistic Regression Tests (d)	P=0.452N	P=0.535	P=0.517N
Cochran-Armitage Trend Test (d)	P=0.471N		
Fisher Exact Test (d)		P=0.458	P=0.520N
Skin: Keratoacanthoma			
Overall Rates (a)	3/50 (6%)	4/50 (8%)	1/50 (2%)
Adjusted Rates (b)	9.7%	12.5%	2.8%
Terminal Rates (c)	3/31 (10%)	2/25 (8%)	0/24 (0%)
Day of First Observation	729	607	667
Life Table Tests (d)	P=0.347N	P=0.410	P=0.381N
Logistic Regression Tests (d)	P=0.283N	P=0.458	P=0.338N
Cochran-Armitage Trend Test (d)	P=0.268N		
Fisher Exact Test (d)		P=0.500	P=0.309N
Skin: Squamous Papilloma			
Overall Rates (a)	3/50 (6%)	3/50 (6%)	2/50 (4%)
Adjusted Rates (b)	8.4%	12.0%	6.2%
Terminal Rates (c)	2/31 (6%)	3/25 (12%)	1/24 (4%)
Day of First Observation	576	729	
Life Table Tests (d)	P=0.520N	P=0.569	P=0.577N
Logistic Regression Tests (d)	P=0.430N	P=0.620	P=0.478N
Cochran-Armitage Trend Test (d)	P=0.421N		
Fisher Exact Test (d)		P=0.661N	P=0.500N
Skin: Trichoepithelioma, Basal Cell Adenoma, or Basal Cell Carcinoma			
Overall Rates (a)	1/50 (2%)	1/50 (2%)	3/50 (6%)
Adjusted Rates (b)	2.0%	4.0%	11.9%
Terminal Rates (c)	0/31 (0%)	1/25 (4%)	2/24 (8%)
Day of First Observation	522	729	719
Life Table Tests (d)	P=0.161	P=0.727	P=0.236
Logistic Regression Tests (d)	P=0.210	P=0.722N	P=0.315
Cochran-Armitage Trend Test (d)	P=0.213		
Fisher Exact Test (d)		P=0.753N	P=0.309
Subcutaneous Tissue: Fibroma			
Overall Rates (a)	7/50 (14%)	6/50 (12%)	4/50 (8%)
Adjusted Rates (b)	18.5%	20.6%	16.7%
Terminal Rates (c)	4/31 (13%)	4/25 (16%)	4/24 (17%)
Day of First Observation	576	644	729
Life Table Tests (d)	P=0.349N	P=0.599	P=0.390N
Logistic Regression Tests (d)	P=0.245N	P=0.522N	P=0.272N
Cochran-Armitage Trend Test (d)	P=0.220N		
Fisher Exact Test (d)		P=0.500N	P=0.262N
Subcutaneous Tissue: Fibroma or Fibrosarcoma			
Overall Rates (a)	9/50 (18%)	6/50 (12%)	6/50 (12%)
Adjusted Rates (b)	24.6%	20.6%	25.0%
Terminal Rates (c)	6/31 (19%)	4/25 (16%)	6/24 (25%)
Day of First Observation	576	644	729
Life Table Tests (d)	P=0.390N	P=0.429N	P=0.458N
Logistic Regression Tests (d)	P=0.276N	P=0.323N	P=0.324N
Cochran-Armitage Trend Test (d)	P=0.233N		
Fisher Exact Test (d)		P=0.288N	P=0.288N

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

	Vehicle Control	4 mg/kg	8 mg/kg
Testes: Adenoma			
Overall Rates (a)	45/50 (90%)	46/50 (92%)	46/50 (92%)
Adjusted Rates (b)	97.8%	100.0%	97.8%
Terminal Rates (c)	30/31 (97%)	25/25 (100%)	23/24 (96%)
Day of First Observation	522	468	461
Life Table Tests (d)	P=0.069	P=0.078	P=0.079
Logistic Regression Tests (d)	P=0.323	P=0.185	P=0.427
Cochran-Armitage Trend Test (d)	P=0.431		
Fisher Exact Test (d)		P=0.500	P=0.500
Thyroid Gland: C-Cell Adenoma			
Overall Rates (a)	6/49 (12%)	9/49 (18%)	8/49 (16%)
Adjusted Rates (b)	18.3%	28.4%	24.8%
Terminal Rates (c)	5/31 (16%)	4/25 (16%)	3/23 (13%)
Day of First Observation	674	653	623
Life Table Tests (d)	P=0.205	P=0.175	P=0.243
Logistic Regression Tests (d)	P=0.290	P=0.212	P=0.353
Cochran-Armitage Trend Test (d)	P=0.338		
Fisher Exact Test (d)		P=0.288	P=0.387
Thyroid Gland: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	6/49 (12%)	10/49 (20%)	8/49 (16%)
Adjusted Rates (b)	18.3%	31.8%	24.8%
Terminal Rates (c)	5/31 (16%)	5/25 (20%)	3/23 (13%)
Day of First Observation	674	653	623
Life Table Tests (d)	P=0.201	P=0.114	P=0.243
Logistic Regression Tests (d)	P=0.284	P=0.138	P=0.353
Cochran-Armitage Trend Test (d)	P=0.341		
Fisher Exact Test (d)		P=0.207	P=0.387
Hematopoietic System: Mononuclear Leukemia			
Overall Rates (a)	11/50 (22%)	20/50 (40%)	21/50 (42%)
Adjusted Rates (b)	31.7%	59.0%	57.1%
Terminal Rates (c)	8/31 (26%)	12/25 (48%)	9/24 (38%)
Day of First Observation	595	607	610
Life Table Tests (d)	P=0.006	P=0.012	P=0.008
Logistic Regression Tests (d)	P=0.011	P=0.016	P=0.015
Cochran-Armitage Trend Test (d)	P=0.022		
Fisher Exact Test (d)		P=0.041	P=0.026
All Sites: Mesothelioma			
Overall Rates (a)	3/50 (6%)	2/50 (4%)	1/50 (2%)
Adjusted Rates (b)	8.7%	7.3%	2.4%
Terminal Rates (c)	2/31 (6%)	1/25 (4%)	0/24 (0%)
Day of First Observation	651	691	623
Life Table Tests (d)	P=0.287N	P=0.591N	P=0.361N
Logistic Regression Tests (d)	P=0.236N	P=0.549N	P=0.301N
Cochran-Armitage Trend Test (d)	P=0.227N		
Fisher Exact Test (d)		P=0.500N	P=0.309N

(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 calculated using doses actually administered to the animals (4.14 and 7.82 mg/kg). 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 logistic regression 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 4 mg/kg and vehicle control groups.

TABLE A4a. HISTORICAL INCIDENCE OF PANCREATIC TUMORS IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls	
	Adenoma	Adenoma or Carcinoma
Historical Incidence at Southern Research Institute		
Ethyl acrylate	0/49	0/49
Allyl isovalerate	1/50	1/50
HC Red No. 3	11/50	(b) 11/50
Chlorinated paraffins (43% chlorine)	6/49	6/49
Chlorinated paraffins (60% chlorine)	11/50	12/50
Allyl isothiocyanate	(c) 1/50	1/50
Geranyl acetate	0/49	0/49
TOTAL	30/347 (8.6%)	31/347 (8.9%)
SD (d)	10.06%	10.52%
Range (e)		
High	11/50	11/50
Low	0/49	0/49
Overall Historical Incidence		
TOTAL	(f) 90/1,624 (5.5%)	(f,g) 93/1,624 (5.7%)
SD (d)	7.29%	7.41%
Range (e)		
High	14/50	14/50
Low	0/50	0/50

(a) Data as of August 7, 1986, for studies of at least 104 weeks (data from the benzyl acetate study--22/50--have been deleted); tumors were diagnosed as acinar cell unless otherwise specified.
(b) An acinar cell carcinoma was observed in an animal bearing an acinar cell adenoma.
(c) Adenoma, NOS
(d) Standard deviation
(e) Range and SD are presented for groups of 35 or more animals.
(f) Includes one adenoma, NOS
(g) Includes one adenocarcinoma, NOS, and one carcinoma, NOS; a total of four malignant tumors were diagnosed, one in an animal bearing a benign tumor.

TABLE A4b. 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
Chlorinated paraffins (43% chlorine)	9/50
Chlorinated paraffins (60% chlorine)	7/50
Allyl isothiocyanate	2/50
Geranyl acetate	1/50
TOTAL	35/400 (8.8%)
SD (b)	7.17%
Range (c)	
High	9/50
Low	1/50
Overall Historical Incidence	
TOTAL	259/1,699 (15.2%)
SD (b)	8.81%
Range (c)	
High	22/50
Low	1/50

(a) Data as of August 7, 1986, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE A4c. HISTORICAL INCIDENCE OF ALVEOLAR/BRONCHIOLAR 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	3/50	1/50	4/50
Benzyl acetate	0/50	0/50	0/50
Allyl isovalerate	2/50	1/50	3/50
HC Red No. 3	2/50	0/50	2/50
Chlorinated paraffins (43% chlorine)	0/50	0/50	0/50
Chlorinated paraffins (60% chlorine)	1/50	0/50	1/50
Allyl isothiocyanate	2/49	1/49	3/49
Geranyl acetate	1/50	0/50	1/50
TOTAL	11/399 (2.8%)	3/399 (0.8%)	14/399 (3.5%)
SD (b)	2.13%	1.04%	2.99%
Range (c)			
High	3/50	1/49	4/50
Low	0/50	0/50	0/50
Overall Historical Incidence			
TOTAL	37/1,697 (2.2%)	20/1,697 (1.2%)	57/1,697 (3.4%)
SD (b)	2.23%	1.64%	2.82%
Range (c)			
High	4/50	3/50	4/50
Low	0/50	0/50	0/50

(a) Data as of August 7, 1986, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

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

	Vehicle Control	Low Dose	High Dose
Animals initially in study	50	50	50
Animals removed	50	50	50
Animals examined histopathologically	50	50	50
ALIMENTARY SYSTEM			
Intestine large	(50)	(49)	(50)
Cecum, erosion		1 (2%)	
Cecum, fibrosis			1 (2%)
Cecum, mineralization			1 (2%)
Cecum, parasite metazoan	4 (8%)		1 (2%)
Colon, edema			1 (2%)
Colon, inflammation, chronic active			1 (2%)
Colon, mineralization	1 (2%)		
Colon, parasite metazoan	9 (18%)	6 (12%)	
Rectum, parasite metazoan	3 (6%)	4 (8%)	4 (8%)
Intestine small	(50)	(50)	(50)
Duodenum, erosion			1 (2%)
Duodenum, inflammation, chronic			1 (2%)
Duodenum, inflammation, suppurative			1 (2%)
Duodenum, mucosa, hyperplasia		1 (2%)	
Ileum, mineralization		1 (2%)	
Ileum, ulcer		1 (2%)	
Jejunum, inflammation, chronic	2 (4%)		
Muscularis, jejunum, hyperplasia			1 (2%)
Liver	(50)	(50)	(50)
Angiectasis	4 (8%)	3 (6%)	2 (4%)
Basophilic focus	16 (32%)	12 (24%)	10 (20%)
Clear cell focus	4 (8%)	7 (14%)	6 (12%)
Cyst multilocular		6 (12%)	5 (10%)
Eosinophilic focus	1 (2%)		
Hematopoietic cell proliferation	2 (4%)	1 (2%)	2 (4%)
Hemorrhage			2 (4%)
Inflammation, chronic	8 (16%)	6 (12%)	4 (8%)
Inflammation, chronic active			1 (2%)
Inflammation, granulomatous		1 (2%)	2 (4%)
Mixed cell focus			1 (2%)
Bile duct, hyperplasia	47 (94%)	39 (78%)	43 (86%)
Hepatocyte, atrophy, multifocal	6 (12%)	8 (16%)	9 (18%)
Hepatocyte, hyperplasia, nodular	1 (2%)	6 (12%)	3 (6%)
Hepatocyte, necrosis, multifocal	3 (6%)	1 (2%)	1 (2%)
Hepatocyte, vacuolization cytoplasmic	7 (14%)	13 (26%)	19 (38%)
Hepatocyte, centrilobular, necrosis	3 (6%)		1 (2%)
Portal, fibrosis	24 (48%)	14 (28%)	15 (30%)
Mesentery	(9)	(7)	(8)
Ectopic tissue		1 (14%)	
Inflammation, chronic active	1 (11%)		
Mineralization			1 (13%)
Pigmentation	1 (11%)		
Fat, fibrosis		1 (14%)	
Fat, inflammation, granulomatous		1 (14%)	1 (13%)
Fat, inflammation, suppurative		2 (29%)	
Fat, necrosis	1 (11%)		
Fat, necrosis, focal	3 (33%)	2 (29%)	6 (75%)
Pancreas	(50)	(49)	(50)
Atrophy	17 (34%)	14 (29%)	18 (36%)
Cyst	1 (2%)		
Hyperplasia	9 (18%)	9 (18%)	9 (18%)
Infiltration cellular, lymphocytic	1 (2%)		
Pharynx	(1)	(2)	(1)
Palate, hyperplasia	1 (100%)		
Palate, inflammation, suppurative	1 (100%)		
Palate, ulcer		2 (100%)	

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

	Vehicle Control	Low Dose	High Dose
ALIMENTARY SYSTEM (Continued)			
Salivary glands	(48)	(48)	(49)
Atrophy		1 (2%)	
Stomach	(50)	(49)	(50)
Forestomach, diverticulum		1 (2%)	
Forestomach, edema		1 (2%)	1 (2%)
Forestomach, erosion			2 (4%)
Forestomach, fibrosis			1 (2%)
Forestomach, inflammation, chronic	1 (2%)	1 (2%)	2 (4%)
Forestomach, inflammation, chronic active	1 (2%)		1 (2%)
Forestomach, inflammation, suppurative		1 (2%)	
Forestomach, mineralization	2 (4%)	2 (4%)	1 (2%)
Forestomach, necrosis		1 (2%)	
Forestomach, perforation		2 (4%)	1 (2%)
Forestomach, ulcer	2 (4%)	3 (6%)	2 (4%)
Forestomach, mucosa, dysplasia		1 (2%)	
Forestomach, mucosa, hyperplasia	9 (18%)	8 (16%)	6 (12%)
Glandular, cyst	1 (2%)		
Glandular, erosion	4 (8%)	3 (6%)	1 (2%)
Glandular, hemorrhage		1 (2%)	
Glandular, inflammation, chronic active			1 (2%)
Glandular, mineralization	10 (20%)	9 (18%)	4 (8%)
Glandular, necrosis		1 (2%)	
Glandular, ulcer		1 (2%)	2 (4%)
Tongue		(1)	(2)
Epithelium, hyperplasia		1 (100%)	1 (50%)
Tooth	(2)	(1)	
Inflammation, chronic	1 (50%)		
CARDIOVASCULAR SYSTEM			
Blood vessel	(4)	(4)	(3)
Hypertrophy	2 (50%)	2 (50%)	
Inflammation, chronic active	2 (50%)	3 (75%)	3 (100%)
Mineralization	1 (25%)	1 (25%)	1 (33%)
Thrombus		1 (25%)	
Heart	(50)	(50)	(49)
Thrombus	2 (4%)		3 (6%)
Artery, mineralization	1 (2%)		
Myocardium, fibrosis	36 (72%)	38 (76%)	36 (73%)
Myocardium, inflammation, chronic	9 (18%)	9 (18%)	3 (6%)
Myocardium, inflammation, chronic active	1 (2%)	2 (4%)	
Myocardium, metaplasia, osseous	1 (2%)	1 (2%)	
Myocardium, mineralization	2 (4%)	1 (2%)	1 (2%)
ENDOCRINE SYSTEM			
Adrenal gland	(50)	(50)	(50)
Fibrosis		1 (2%)	
Hematopoietic cell proliferation	1 (2%)		
Pigmentation		1 (2%)	
Cortex, cyst	2 (4%)	1 (2%)	
Cortex, fibrosis	1 (2%)		
Cortex, hematocyst	3 (6%)	1 (2%)	
Cortex, hyperplasia	3 (6%)	3 (6%)	1 (2%)
Cortex, inflammation, suppurative	1 (2%)		
Cortex, necrosis		1 (2%)	
Cortex, vacuolization cytoplasmic	3 (6%)	8 (16%)	13 (26%)
Extra adrenal tissue, developmental malformation	3 (6%)	2 (4%)	2 (4%)
Medulla, hyperplasia	3 (6%)	5 (10%)	4 (8%)
Islets, pancreatic	(50)	(48)	(50)
Hyperplasia		1 (2%)	1 (2%)

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

	Vehicle Control	Low Dose	High Dose
ENDOCRINE SYSTEM (Continued)			
Pituitary gland	(50)	(48)	(49)
Angiectasis			1 (2%)
Pars distalis, angiectasis	1 (2%)	2 (4%)	1 (2%)
Pars distalis, cyst	4 (8%)	5 (10%)	2 (4%)
Pars distalis, hemorrhage			1 (2%)
Pars distalis, hyperplasia	5 (10%)	4 (8%)	3 (6%)
Pars distalis, necrosis			1 (2%)
Pars intermedia, angiectasis		1 (2%)	
Pars intermedia, cyst	2 (4%)		3 (6%)
Thyroid gland	(49)	(49)	(49)
Ultimobranchial cyst		2 (4%)	2 (4%)
C-cell, hyperplasia	7 (14%)	4 (8%)	11 (22%)
Follicle, dilatation	1 (2%)		4 (8%)
Follicle, pigmentation	2 (4%)	2 (4%)	
Follicular cell, hyperplasia		2 (4%)	1 (2%)
GENERAL BODY SYSTEM			
Tissue, NOS	(1)		(1)
Ectasia			1 (100%)
GENITAL SYSTEM			
Epididymis	(50)	(50)	(49)
Edema	1 (2%)		
Preputial gland	(48)	(46)	(45)
Cyst	1 (2%)		
Ectasia		6 (13%)	1 (2%)
Hyperplasia	9 (19%)	3 (7%)	5 (11%)
Inflammation, chronic	16 (33%)	16 (35%)	12 (27%)
Inflammation, suppurative	16 (33%)	13 (28%)	10 (22%)
Metaplasia, squamous		1 (2%)	
Prostate	(50)	(50)	(49)
Corpora amylacea	6 (12%)	4 (8%)	3 (6%)
Edema			1 (2%)
Fibrosis	2 (4%)		
Foreign body		1 (2%)	
Inflammation, chronic	1 (2%)		2 (4%)
Inflammation, granulomatous		1 (2%)	
Inflammation, suppurative	17 (34%)	18 (36%)	17 (35%)
Epithelium, hyperplasia	1 (2%)	2 (4%)	2 (4%)
Seminal vesicle	(3)	(4)	(2)
Fibrosis		1 (25%)	
Testes	(50)	(50)	(50)
Fibrosis			1 (2%)
Hemorrhage			1 (2%)
Necrosis			1 (2%)
Interstitial cell, hyperplasia	2 (4%)		1 (2%)
Seminiferous tubule, atrophy	6 (12%)	6 (12%)	3 (6%)
Seminiferous tubule, mineralization	17 (34%)	20 (40%)	14 (28%)
HEMATOPOIETIC SYSTEM			
Bone marrow	(50)	(50)	(50)
Angiectasis		1 (2%)	
Hemorrhage	1 (2%)		
Hyperplasia	2 (4%)	2 (4%)	2 (4%)
Hyperplasia, reticulum cell	1 (2%)	1 (2%)	1 (2%)
Myelofibrosis		1 (2%)	

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

	Vehicle Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM (Continued)			
Lymph node	(50)	(50)	(50)
Axillary, hyperplasia, plasma cell			1 (2%)
Bronchial, pigmentation			1 (2%)
Inguinal, hemorrhage	1 (2%)		
Inguinal, hyperplasia, plasma cell			1 (2%)
Inguinal, lymphatic, ectasia	1 (2%)		1 (2%)
Lumbar, lymphatic, ectasia			1 (2%)
Lymphatic, mandibular, ectasia	4 (8%)	4 (8%)	7 (14%)
Mandibular, hyperplasia, lymphoid		2 (4%)	
Mandibular, hyperplasia, plasma cell	8 (16%)	7 (14%)	6 (12%)
Mandibular, metaplasia, osseous	1 (2%)		
Mediastinal, atrophy	1 (2%)		1 (2%)
Mediastinal, erythrophagocytosis	2 (4%)	3 (6%)	1 (2%)
Mediastinal, hemorrhage	6 (12%)	4 (8%)	3 (6%)
Mediastinal, hyperplasia, histiocyte		1 (2%)	
Mediastinal, hyperplasia, lymphoid		1 (2%)	1 (2%)
Mediastinal, hyperplasia, plasma cell	1 (2%)	1 (2%)	
Mediastinal, infiltration cellular, histiocytic		1 (2%)	
Mediastinal, pigmentation	3 (6%)	3 (6%)	3 (6%)
Mediastinal, lymphatic, ectasia	1 (2%)	2 (4%)	1 (2%)
Mesenteric, atrophy	3 (6%)	2 (4%)	5 (10%)
Mesenteric, hematopoietic cell proliferation	1 (2%)		
Mesenteric, hemorrhage		1 (2%)	1 (2%)
Mesenteric, hyperplasia, histiocyte	1 (2%)		
Mesenteric, hyperplasia, lymphoid			1 (2%)
Mesenteric, hyperplasia, plasma cell	1 (2%)		
Mesenteric, necrosis	1 (2%)		
Mesenteric, lymphatic, ectasia	2 (4%)		1 (2%)
Pancreatic, hyperplasia, lymphoid	1 (2%)		
Pancreatic, pigmentation	1 (2%)		
Pancreatic, lymphatic, ectasia	1 (2%)		
Renal, pigmentation			1 (2%)
Spleen	(49)	(50)	(50)
Atrophy	4 (8%)	3 (6%)	
Congestion	1 (2%)		
Degeneration, fatty	1 (2%)		
Fibrosis	4 (8%)	6 (12%)	1 (2%)
Hematopoietic cell proliferation granulocytic	1 (2%)	2 (4%)	3 (6%)
Hematopoietic cell proliferation erythrocytic	9 (18%)	8 (16%)	8 (16%)
Hyperplasia, histiocyte	1 (2%)		
Necrosis		2 (4%)	
Pigmentation, hemosiderin	2 (4%)	1 (2%)	1 (2%)
Lymphatic, ectasia	1 (2%)	1 (2%)	
Thymus	(34)	(29)	(34)
Cyst	5 (15%)	1 (3%)	1 (3%)
Ectopic parathyroid gland	1 (3%)		
INTEGUMENTARY SYSTEM			
Mammary gland	(46)	(44)	(46)
Angiectasis		1 (2%)	
Hyperplasia, cystic	16 (35%)	13 (30%)	12 (26%)
Hyperplasia, lobular	1 (2%)	1 (2%)	
Inflammation, granulomatous		1 (2%)	
Inflammation, suppurative	1 (2%)		

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

	Vehicle Control	Low Dose	High Dose
INTEGUMENTARY SYSTEM (Continued)			
Skin	(49)	(49)	(49)
Acanthosis		4 (8%)	3 (6%)
Cyst epithelial inclusion	2 (4%)	1 (2%)	1 (2%)
Edema		1 (2%)	
Exudate			3 (6%)
Foreign body	1 (2%)		
Hyperkeratosis		3 (6%)	1 (2%)
Inflammation, chronic		3 (6%)	
Inflammation, chronic active	1 (2%)		1 (2%)
Inflammation, granulomatous	1 (2%)		
Inflammation, suppurative	2 (4%)	2 (4%)	2 (4%)
Necrosis		1 (2%)	
MUSCULOSKELETAL SYSTEM			
Bone	(50)	(50)	(50)
Fibrous osteodystrophy	2 (4%)		
Hyperostosis	2 (4%)		
Hyperplasia		1 (2%)	
Necrosis		1 (2%)	
Skeletal muscle	(1)	(1)	
Inflammation, suppurative		1 (100%)	
NERVOUS SYSTEM			
Brain	(50)	(50)	(48)
Compression	2 (4%)	1 (2%)	
Degeneration, multiple	3 (6%)	8 (16%)	4 (8%)
Necrosis			1 (2%)
Cerebellum, mineralization			1 (2%)
Cerebrum, degeneration	1 (2%)	1 (2%)	1 (2%)
Cerebrum, hemorrhage			1 (2%)
Cerebrum, necrosis			1 (2%)
Thalamus, degeneration			1 (2%)
Thalamus, hemorrhage	1 (2%)		
Peripheral nerve	(50)	(48)	(48)
Infiltration cellular, mast cell	1 (2%)		
Infiltration cellular, lymphocytic, polymorphonuclear	1 (2%)		
RESPIRATORY SYSTEM			
Lung	(50)	(50)	(49)
Adenomatosis	5 (10%)	4 (8%)	3 (6%)
Edema, diffuse	1 (2%)	2 (4%)	1 (2%)
Foreign body		6 (12%)	2 (4%)
Hemorrhage	1 (2%)	1 (2%)	2 (4%)
Infiltration cellular, histiocytic	28 (56%)	27 (54%)	29 (59%)
Inflammation, chronic	1 (2%)	2 (4%)	
Inflammation, granulomatous	4 (8%)	2 (4%)	3 (6%)
Inflammation, suppurative	2 (4%)		
Metaplasia, osseous		1 (2%)	
Pigmentation		1 (2%)	
Artery, mineralization	2 (4%)		
Artery, media, hypertrophy		2 (4%)	
Parenchyma, mineralization	1 (2%)		

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

	Vehicle Control	Low Dose	High Dose
RESPIRATORY SYSTEM (Continued)			
Nose	(49)	(49)	(47)
Lumen, foreign body	2 (4%)	1 (2%)	
Lumen, fungus	4 (8%)	1 (2%)	1 (2%)
Lumen, hemorrhage		1 (2%)	
Lumen, inflammation, suppurative	8 (16%)	3 (6%)	7 (15%)
Mucosa, hyperplasia	1 (2%)		1 (2%)
Mucosa, inflammation, chronic	1 (2%)		
Mucosa, metaplasia, squamous		1 (2%)	
Mucosa, necrosis	1 (2%)		
Nasolacrimal duct, inflammation, chronic			1 (2%)
Nasolacrimal duct, inflammation, suppurative	2 (4%)	2 (4%)	1 (2%)
Nasopharyngeal duct, foreign body		1 (2%)	
Nasopharyngeal duct, inflammation, suppurative		1 (2%)	
Submucosa, inflammation, chronic	1 (2%)	3 (6%)	2 (4%)
Trachea	(49)	(49)	(49)
Lumen, exudate			1 (2%)
SPECIAL SENSES SYSTEM			
Ear			(1)
Middle ear, inflammation, suppurative			1 (100%)
Eye	(2)	(2)	(28)
Angiectasis			1 (4%)
Cataract	1 (50%)	1 (50%)	25 (89%)
Retinal detachment			1 (4%)
Synechia			1 (4%)
Retina, atrophy	2 (100%)	2 (100%)	28 (100%)
Harderian gland	(1)		
Hyperplasia	1 (100%)		
URINARY SYSTEM			
Kidney	(50)	(50)	(50)
Cyst		1 (2%)	
Fibrosis			1 (2%)
Hydronephrosis	3 (6%)		
Inflammation, chronic	30 (60%)	30 (60%)	27 (54%)
Inflammation, suppurative	6 (12%)	6 (12%)	8 (16%)
Nephropathy	50 (100%)	49 (98%)	49 (98%)
Papilla, necrosis	1 (2%)		
Pelvis, mineralization	1 (2%)	1 (2%)	
Pelvis, epithelium, hyperplasia		1 (2%)	
Renal tubule, dilatation	1 (2%)		
Renal tubule, mineralization	8 (16%)	12 (24%)	6 (12%)
Renal tubule, pigmentation	3 (6%)	3 (6%)	2 (4%)
Ureter	(1)		
Dilatation	1 (100%)		

APPENDIX B

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

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

	Vehicle Control	Low Dose	High Dose
Animals initially in study	50	50	50
Animals removed	50	50	50
Animals examined histopathologically	50	50	50
ALIMENTARY SYSTEM			
Intestine large	(50)	(49)	(50)
Cecum, leukemia mononuclear		1 (2%)	
Rectum, leiomyosarcoma	1 (2%)		
Intestine small	(50)	(49)	(50)
Ileum, leukemia mononuclear	1 (2%)		
Jejunum, leiomyoma		1 (2%)	
Liver	(50)	(50)	(50)
Hepatocellular carcinoma		1 (2%)	
Leukemia mononuclear	17 (34%)	18 (36%)	23 (46%)
Neoplastic nodule			1 (2%)
Mesentery	*(50)	*(50)	*(50)
Leukemia mononuclear	1 (2%)	1 (2%)	
Pancreas	(50)	(47)	(50)
Adenoma	1 (2%)	1 (2%)	4 (8%)
Leukemia mononuclear	4 (8%)	1 (2%)	2 (4%)
Pharynx	*(50)	*(50)	*(50)
Squamous cell carcinoma			1 (2%)
Salivary glands	(49)	(50)	(49)
Fibrosarcoma, metastatic, skin		1 (2%)	
Leukemia mononuclear	2 (4%)		1 (2%)
Stomach	(50)	(49)	(50)
Leukemia mononuclear	3 (6%)	3 (6%)	2 (4%)
Forestomach, papilloma squamous		1 (2%)	
Tongue	*(50)	*(50)	*(50)
Leukemia mononuclear	1 (2%)		
Papilloma squamous			1 (2%)
CARDIOVASCULAR SYSTEM			
Heart	(50)	(50)	(50)
Leukemia mononuclear	4 (8%)	3 (6%)	3 (6%)
ENDOCRINE SYSTEM			
Adrenal gland	(50)	(50)	(50)
Leukemia mononuclear	2 (4%)	11 (22%)	7 (14%)
Pheochromocytoma benign		1 (2%)	
Cortex, adenoma	1 (2%)	4 (8%)	
Medulla, pheochromocytoma malignant			2 (4%)
Medulla, pheochromocytoma benign	4 (8%)	1 (2%)	2 (4%)
Medulla, pheochromocytoma benign, multiple			2 (4%)
Islets, pancreatic	(50)	(48)	(50)
Adenoma	1 (2%)	2 (4%)	1 (2%)
Leukemia mononuclear			2 (4%)
Parathyroid gland	(49)	(47)	(45)
Adenoma			1 (2%)
Leukemia mononuclear			1 (2%)

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

	Vehicle Control	Low Dose	High Dose
ENDOCRINE SYSTEM (Continued)			
Pituitary gland	(50)	(49)	(50)
Leukemia mononuclear	2 (4%)	2 (4%)	1 (2%)
Pars distalis, adenoma	27 (54%)	19 (39%)	19 (38%)
Pars distalis, carcinoma	1 (2%)	2 (4%)	4 (8%)
Pars intermedia, adenoma		1 (2%)	1 (2%)
Pars intermedia, carcinoma	1 (2%)		
Thyroid gland	(50)	(49)	(50)
Leukemia mononuclear			1 (2%)
C-cell, adenoma	4 (8%)	7 (14%)	5 (10%)
C-cell, adenoma, multiple	1 (2%)		
C-cell, carcinoma		1 (2%)	
Follicular cell, adenoma			1 (2%)
GENERAL BODY SYSTEM			
None			
GENITAL SYSTEM			
Clitoral gland	(44)	(43)	(41)
Adenoma	3 (7%)	1 (2%)	3 (7%)
Carcinoma			1 (2%)
Ovary	(50)	(50)	(50)
Granulosa cell tumor	2 (4%)		
Leiomyosarcoma		1 (2%)	
Leukemia mononuclear	4 (8%)		1 (2%)
Uterus	(50)	(50)	(50)
Adenoma		1 (2%)	
Carcinoma		1 (2%)	
Leiomyoma		1 (2%)	
Leiomyosarcoma			1 (2%)
Leukemia mononuclear	3 (6%)	1 (2%)	2 (4%)
Polyp stromal	15 (30%)	14 (28%)	13 (26%)
Sarcoma stromal			2 (4%)
HEMATOPOIETIC SYSTEM			
Blood	*(50)	*(50)	*(50)
Leukemia mononuclear	2 (4%)	1 (2%)	
Bone marrow	(50)	(49)	(50)
Leukemia mononuclear	5 (10%)	11 (22%)	9 (18%)
Lymph node	(50)	(50)	(50)
Bronchial, leukemia mononuclear		1 (2%)	1 (2%)
Iliac, leukemia mononuclear			1 (2%)
Inguinal, leukemia mononuclear		2 (4%)	1 (2%)
Mandibular, leukemia mononuclear	8 (16%)	10 (20%)	9 (18%)
Mediastinal, leukemia mononuclear	6 (12%)	6 (12%)	5 (10%)
Mesenteric, leukemia mononuclear	6 (12%)	12 (24%)	10 (20%)
Pancreatic, leukemia mononuclear	4 (8%)	6 (12%)	5 (10%)
Spleen	(50)	(50)	(50)
Leukemia mononuclear	15 (30%)	21 (42%)	23 (46%)
Thymus	(39)	(39)	(39)
Leukemia mononuclear	3 (8%)	4 (10%)	2 (5%)

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

	Vehicle Control	Low Dose	High Dose
INTEGUMENTARY SYSTEM			
Mammary gland	(50)	(50)	(49)
Adenoma			1 (2%)
Carcinoma	2 (4%)	2 (4%)	
Fibroadenoma	9 (18%)	13 (26%)	13 (27%)
Fibroadenoma, multiple		6 (12%)	3 (6%)
Skin	(50)	(48)	(48)
Basal cell carcinoma			1 (2%)
Keratoacanthoma	1 (2%)		
Papilloma squamous	1 (2%)	1 (2%)	1 (2%)
Sebaceous gland, carcinoma	2 (4%)		
Subcutaneous tissue, fibroma			2 (4%)
Subcutaneous tissue, fibrosarcoma		3 (6%)	1 (2%)
MUSCULOSKELETAL SYSTEM			
Skeletal muscle	*(50)	*(50)	*(50)
Leukemia mononuclear	1 (2%)		
Squamous cell carcinoma, metastatic, lung		1 (2%)	
NERVOUS SYSTEM			
Brain	(50)	(50)	(50)
Leukemia mononuclear	2 (4%)	2 (4%)	
Oligodendroglioma malignant	1 (2%)		
RESPIRATORY SYSTEM			
Lung	(50)	(50)	(50)
Carcinoma, metastatic, mammary gland	1 (2%)		
Leukemia mononuclear	10 (20%)	16 (32%)	15 (30%)
Squamous cell carcinoma		1 (2%)	
Nose	(50)	(49)	(47)
Leukemia mononuclear			1 (2%)
SPECIAL SENSES SYSTEM			
None			
URINARY SYSTEM			
Kidney	(50)	(50)	(50)
Adenoma	1 (2%)		
Leukemia mononuclear	4 (8%)	3 (6%)	3 (6%)
Urinary bladder	(50)	(49)	(50)
Leukemia mononuclear	3 (6%)	2 (4%)	1 (2%)
Papilloma	1 (2%)		1 (2%)
SYSTEMIC LESIONS			
Multiple organs	*(50)	*(50)	*(50)
Leukemia mononuclear	17 (34%)	21 (42%)	23 (46%)
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Dead	4	3	5
Accident	1		
Moribund	14	21	19
Terminal sacrifice	31	26	26

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

	Vehicle Control	Low Dose	High Dose
TUMOR SUMMARY			
Total animals with primary neoplasms **	47	46	46
Total primary neoplasms	97	108	111
Total animals with benign neoplasms	40	40	39
Total benign neoplasms	70	75	75
Total animals with malignant neoplasms	23	32	30
Total malignant neoplasms	25	33	36
Total animals with secondary neoplasms ***	1	2	
Total secondary neoplasms	1	2	
Total animals with neoplasms--uncertain benign or malignant	2		
Total uncertain neoplasms	2		

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

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

WEEKS ON STUDY	058	076	079	084	086	086	089	093	093	097	099	099	100	101	102	102	102	102	102	105	105	105	105	105	105
CARCASS ID	42 1	42 2	41 1	41 2	44 1	40 1	46 1	42 3	39 1	43 1	44 2	39 2	39 3	37 1	37 2	37 3	46 3	38 1	46 2	37 4	37 5	38 2	38 3	38 4	38 5
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Rectum, leiomyosarcoma																			X						
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ileum, leukemia mononuclear		X																							
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X		X	X	X	X	X	X				X	X			X								
Mesentery			+						+	+	+			+		+	+			+					
Leukemia mononuclear														X											
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Leukemia mononuclear		X		X					X				X												
Pharynx																		+							
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Leukemia mononuclear									X				X												
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X	X								X												
Tongue														+											
Leukemia mononuclear																									
Tooth															+										
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X	X			X				X												
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X									X												
Cortex, adenoma																									
Medulla, pheochromocytoma benign						X					X														
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma												X													
Parathyroid gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X				X																
Pars distalis, adenoma			X	X			X	X			X	X		X	X	X		X	X			Y	X		
Pars distalis, carcinoma																	X								
Pars intermedia, carcinoma	X																								
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C cell, adenoma					X																				
C cell, adenoma, multiple																									
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Clitoral gland	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	M	+	+	+	+	M	+	+	M
Adenoma								X						X											
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor								X																	
Leukemia mononuclear		X		X					X				X												
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X		X					X																
Polyp stromal				X		X		X			X	X									X		X	X	
Vagina						+			+									+							

+ Tissue examined microscopically
Not examined
– Present but not examined microscopically
I Insufficient tissue

M Missing
A. Autolysis precludes examination
X Incidence of listed morphology

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

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	
CARCASS ID	394	395	402	403	404	455	405	413	414	415	424	425	432	433	434	435	443	444	445	451	452	453	454	464	465	TOTAL TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Rectum, leiomyosarcoma																										1
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Ileum, leukemia mononuclear																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear					X	X				X		X		X				X						X		17
Mesentery									+														+			10
Leukemia mononuclear																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																	X									1
Leukemia mononuclear																										4
Pharynx																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear																										2
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										3
Tongue						+															+					3
Leukemia mononuclear						X																				1
Tooth													+													2
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										4
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										2
Cortex, adenoma																	X									1
Medulla, pheochromocytoma benign														X							X					4
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										2
Pars distalis, adenoma		X	X	X			X	X		X			X			X				X	X	X	X	X	X	27
Pars distalis, carcinoma																										1
Pars intermedia, carcinoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C cell, adenoma			X					X				X														4
C cell, adenoma, multiple	X																									1
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Adenoma																X										3
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa cell tumor																							X			2
Leukemia mononuclear																										4
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										3
Polyp stromal	X	X	X								X			X				X		X						15
Vagina																		+								4

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

WEEKS ON STUDY	058	076	079	084	086	086	089	093	093	097	099	099	100	101	102	102	102	102	102	105	105	105	105	105	105
CARCASS ID	421	422	411	412	441	401	461	423	391	431	442	392	393	371	372	373	463	381	462	374	375	382	383	384	385
HEMATOPOIETIC SYSTEM																									
Blood						+	+																		
Leukemia mononuclear						X	X																		
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X				X							X	X			X								
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mandibular, leukemia mononuclear		X		X	X	X			X				X	X											
Mediastinal, leukemia mononuclear		X		X	X				X				X	X											
Mesenteric, leukemia mononuclear		X		X	X								X												
Pancreatic, leukemia mononuclear		X					X							X			X								
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X		X	X		X		X				X	X			X								
Thymus	M	M	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X		X										X								
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma										X		X													
Fibroadenoma			X	X				X																	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																						X			
Papilloma squamous																									
Sebaceous gland, carcinoma											X														
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle		+																							
Leukemia mononuclear		X																							
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X				X																
Oligodendroglioma malignant																									
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, mammary gland										X															
Leukemia mononuclear		X		X	X	X			X				X	X											
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Eye				M			M									+									
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma													X												
Leukemia mononuclear		X		X					X					X											
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X					X				X												
Papilloma																									

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

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	TOTAL TISSUES TUMORS
CARCASS ID	394	395	402	403	404	455	405	413	414	415	424	425	432	433	434	435	443	444	445	451	452	453	454	464	465	
HEMATOPOIETIC SYSTEM																										
Blood																										2
Leukemia mononuclear																										2
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										5
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mandibular, leukemia mononuclear												X														8
Mediastinal, leukemia mononuclear																										6
Mesenteric, leukemia mononuclear						X												X								6
Pancreatic, leukemia mononuclear																										4
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear					X	X				X		X		X				X						X		15
Thymus	+	+	M	+	M	+	M	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	M	M	+	39
Leukemia mononuclear																										3
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										2
Fibroadenoma			X					X					X		X		X		X							9
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma																										1
Papilloma squamous																X										1
Sebaceous gland, carcinoma						X																				2
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Leukemia mononuclear																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										2
Oligodendroglioma malignant																			X							1
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, mammary gland																										1
Leukemia mononuclear										X		X						X								10
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Eye																							+			2
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Leukemia mononuclear																										4
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										3
Papilloma																				X						1

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

WEEKS ON STUDY	014	051	064	075	078	080	081	086	089	092	094	094	098	100	100	101	101	101	102	102	102	102	103	104	105
CARCASS ID	691	661	651	701	681	671	611	692	672	612	641	693	613	621	631	694	702	652	662	622	673	682	705	655	614
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cecum, leukemia mononuclear																							X		
Intestine small	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Jejunum, leiomyoma																			X						
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																	X								
Leukemia mononuclear				X			X		X	X	X	X	X		X	X			X				X	X	
Mesentery	+					+	+								+	+		+				+			
Leukemia mononuclear															X										
Pancreas	+	A	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Leukemia mononuclear																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin																					X				
Stomach	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X																			X		
Forestomach, papilloma squamous																									
Tongue																									
Tooth																						+			
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X																			X		
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X			X		X		X	X	X			X			X				X	X	
Pheochromocytoma benign														X											
Cortex, adenoma											X				X										
Medulla, pheochromocytoma benign																									
Islets, pancreatic	+	A	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																X									
Parathyroid gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Pituitary gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																							X	X	
Pars distalis, adenoma					X			X						X	X		X		X		X			X	X
Pars distalis, carcinoma																									
Pars intermedia, adenoma																									
Thyroid gland	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C cell, adenoma												X				X					X		X		
C cell, carcinoma																									
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Clitoral gland	M	M	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M
Adenoma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma															X										
Carcinoma																									
Leiomyoma																			X						
Leukemia mononuclear																							X		
Polyp stromal						X							X				X	X					X		
Vagina			+				+						+		+	+			+	+					

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

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	TOTAL:
CARCASS ID	615	623	624	625	632	633	634	635	642	643	644	645	653	654	663	664	665	674	675	683	684	685	695	703	704	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cecum, leukemia mononuclear																										1
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Jejunum, leiomyoma																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma																										1
Leukemia mononuclear		X				X					X		X			X						X				18
Mesentery	+			+		+					+						+									12
Leukemia mononuclear																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma					X																					1
Leukemia mononuclear											X															1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, skin																										1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear											X															3
Forestomach, papilloma squamous											X															1
Tongue					+																					1
Tooth																										1
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear											X															3
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																						X				11
Pheochromocytoma benign																										1
Cortex, adenoma																					X			X		4
Medulla, pheochromocytoma benign				X																						1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma																X										2
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	47
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear																										2
Pars distalis, adenoma		X		X		X					X			X		X		X	X				X		X	19
Pars distalis, carcinoma			X																		X					2
Pars intermedia, adenoma																								X		1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell, adenoma			X						X			X														7
C-cell, carcinoma							X																			1
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Clitoral gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	43
Adenoma														X												1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma																								X		1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Carcinoma																				X						1
Leiomyoma																										1
Leukemia mononuclear																										1
Polyp stromal			X	X	X	X							X	X	X						X			X		14
Vagina					+																					8

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

WEEKS ON STUDY	014	051	064	075	078	080	081	086	089	092	094	094	098	100	100	101	101	101	102	102	102	102	103	104	105
CARCASS ID	691	861	851	701	881	711	611	692	672	612	641	693	613	621	631	694	702	652	662	622	673	682	705	655	614
HEMATOPOIETIC SYSTEM																									
Blood															+										
Leukemia mononuclear															X										
Bone marrow	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X			X				X	X	X		X				X				X	X	
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bronchial, leukemia mononuclear																									
Inguinal, leukemia mononuclear																			X					X	
Mandibular, leukemia mononuclear				X			X		X		X	X	X		X								X	X	
Mediastinal, leukemia mononuclear				X					X			X			X				X					X	
Mesenteric, leukemia mononuclear				X			X				X	X	X		X				X				X	X	
Pancreatic, leukemia mononuclear											X				X	X			X				X		
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X			X		X	X	X	X	X		X	X			X				X	X	
Thymus	+	M	+	+	+	+	+	M	+	+	+	M	+	+	+	M	+	+	M	+	+	+	+	+	+
Leukemia mononuclear				X																			X	X	
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Fibroadenoma					X													X	X			X			
Fibroadenoma, multiple																									
Skin	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Papilloma squamous																									
Subcutaneous tissue, fibrosarcoma														X						X	X				
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle			+																						
Squamous cell carcinoma, metastatic, lung			X																						
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear													X										X		
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X			X		X		X	X	X		X				X				X	X	
Squamous cell carcinoma			X																						
Nose	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Eye				M			+		M	+	+		+	+	+			+		+			+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear											X								X				X		
Urinary bladder	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X																					

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

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	
CARCASS ID	615	623	624	625	632	633	634	635	642	643	644	645	653	654	663	664	665	674	675	683	684	685	695	703	704	TOTAL: TISSUES / TUMORS
HEMATOPOIETIC SYSTEM																										
Blood		+																								2
Leukemia mononuclear																										1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear						X					X															11
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bronchial, leukemia mononuclear											X															1
Inguinal, leukemia mononuclear																										2
Mandibular, leukemia mononuclear											X															10
Mediastinal, leukemia mononuclear																										6
Mesenteric, leukemia mononuclear											X		X									X				12
Pancreatic, leukemia mononuclear																						X				6
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X	X			X			X	X	X		X			X						X				21
Thymus	+	+	M	+	M	+	+	+	M	M	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	39
Leukemia mononuclear											X															4
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma													X												X	2
Fibroadenoma	X		X		X					X	X	X				X				X			X			13
Fibroadenoma, multiple				X		X							X	X							X	X				6
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Papilloma squamous																									X	1
Subcutaneous tissue, fibrosarcoma																										3
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Squamous cell carcinoma, metastatic, lung																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										2
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	48
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X				X					X		X			X						X				16
Squamous cell carcinoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPECIAL SENSES SYSTEM																										
Eye	+	+		+		+			+		+	+	+	+			+		+				+			23
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										3
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear											X															2

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

WEEKS ON STUDY	055	061	070	078	080	081	084	084	087	088	090	091	091	092	094	096	097	097	097	103	103	103	104	104	105
CARCASS ID	491	541	511	551	492	493	501	531	581	561	552	571	582	494	562	521	532	572	583	535	575	584	512	513	495
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X		X			X			X	X	X		X		X	X	X	X	X	X	X	
Neoplastic nodule																									
Mesentery										+									+	+				+	
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma													X	X											
Leukemia mononuclear									X					X											
Pharynx	+																								
Squamous cell carcinoma	X																								
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear									X																
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear									X																
Tongue																									
Papilloma squamous																									
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear									X											X					
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear									X			X		X				X				X	X		
Medulla, pheochromocytoma malignant																									
Medulla, pheochromocytoma benign																							X		
Medulla, pheochromocytoma benign, multiple																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Leukemia mononuclear									X					X											
Parathyroid gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Adenoma																									
Leukemia mononuclear									X																
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear									X																
Pars distalis, adenoma			X	X															X			X	X	X	X
Pars distalis, carcinoma					X										X						X				
Pars intermedia, adenoma											X														
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear									X																
C cell, adenoma												X					X	X							X
Follicular cell, adenoma																									
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Clitoral gland	M	M	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	M	+
Adenoma																						X			
Carcinoma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear									X																
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma																									
Leukemia mononuclear									X																
Polyp stromal							X				X	X	X	X	X					X	X		X		
Sarcoma stromal								X							X										
Vagina	+				+			M						+	+			+		M		+			

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

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	TOTAL:
CARCASS ID	502	503	504	505	514	515	522	523	524	525	533	534	542	543	544	545	553	554	555	563	564	565	573	574	585	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X			X							X		X		X		X					X		X	X	23
Neoplastic nodule					X																					1
Mesentery		+								+					+											7
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma										X						X										4
Leukemia mononuclear																										2
Pharynx																+										2
Squamous cell carcinoma																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear																										1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																						X				2
Tongue				+																						1
Papilloma squamous				X																						1
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																						X				3
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																						X				7
Medulla, pheochromocytoma malignant							X			X																2
Medulla, pheochromocytoma benign											X															2
Medulla, pheochromocytoma benign, multiple								X															X			2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma														X												1
Leukemia mononuclear																										2
Parathyroid gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	45
Adenoma	X																									1
Leukemia mononuclear																										1
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Pars distalis, adenoma	X		X		X	X	X	X	X				X				X		X			X	X			19
Pars distalis, carcinoma																									X	4
Pars intermedia, adenoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
C-cell, adenoma						X																				5
Follicular cell, adenoma								X																		1
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Clitoral gland	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	41
Adenoma												X	X													3
Carcinoma				X																						1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma														X												1
Leukemia mononuclear																						X				2
Polyp stromal															X		X	X				X				13
Sarcoma stromal																										2
Vagina							+			M																7

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

WEEKS ON STUDY	055	061	070	078	080	081	084	084	087	088	090	091	091	092	094	096	097	097	097	103	103	103	104	104	105
CARCASS ID	491	541	511	551	492	493	501	531	581	561	552	571	582	494	562	521	532	572	583	535	575	584	512	513	495
HEMATOPOIETIC SYSTEM																									
Blood																							+		
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear									X			X		X				X		X		X			
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bronchial, leukemia mononuclear												X													
Iliac, leukemia mononuclear									X																
Inguinal, leukemia mononuclear																									
Mandibular, leukemia mononuclear						X			X			X								X		X			
Mediastinal, leukemia mononuclear									X			X		X						X					
Mesenteric, leukemia mononuclear						X			X			X		X				X		X		X			
Pancreatic, leukemia mononuclear												X						X		X					
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X		X			X			X	X	X		X		X	X	X	X	X			
Thymus	+	+	M	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+
Leukemia mononuclear												X													
INTEGUMENTARY SYSTEM																									
Mammary gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Fibroadenoma							X			X			X				X	X				X	X	X	
Fibroadenoma, multiple																									
Skin	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma																									
Papilloma squamous																									
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, fibrosarcoma																									
MUSCULOSKELETAL SYSTEM																									
Bone	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear						X			X			X	X	X		X		X		X		X	X		
Nose	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear									X																
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Eye		+						M	+																
Harderian gland														+											
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear									X			X		X											
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear									X																
Papilloma																									

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

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	TOTAL:
CARCASS ID	502	503	504	505	514	515	522	523	524	525	533	534	542	543	544	545	553	554	555	563	564	565	573	574	585	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Blood					+																	+				3
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear													X				X					X				9
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bronchial, leukemia mononuclear																										1
Iliac, leukemia mononuclear																										1
Inguinal, leukemia mononuclear													X													1
Mandibular, leukemia mononuclear											X		X				X					X				9
Mediastinal, leukemia mononuclear																						X				5
Mesenteric, leukemia mononuclear											X						X					X				10
Pancreatic, leukemia mononuclear											X						X									5
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X			X							X		X		X		X					X		X	X	23
Thymus	+	+	+	+	+	M	M	+	+	+	M	M	+	+	+	+	+	+	+	M	+	M	+	+	+	39
Leukemia mononuclear													X													2
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma											X															1
Fibroadenoma				X		X							X	X										X		13
Fibroadenoma, multiple								X		X									X							3
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	48
Basal cell carcinoma	X																									1
Papilloma squamous								X																		1
Subcutaneous tissue, fibroma															X				X							2
Subcutaneous tissue, fibrosarcoma																									X	1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear											X		X		X							X			X	15
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	47
Leukemia mononuclear																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Eye										+																3
Harderian gland																										1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										3
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Papilloma															X											1

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

	Vehicle Control	4 mg/kg	8 mg/kg
Adrenal Gland: Cortical Adenoma			
Overall Rates (a)	1/50 (2%)	4/50 (8%)	0/50 (0%)
Adjusted Rates (b)	3.2%	12.5%	0.0%
Terminal Rates (c)	1/31 (3%)	2/26 (8%)	0/26 (0%)
Day of First Observation	729	656	
Life Table Tests (d)	P=0.491N	P=0.150	P=0.535N
Logistic Regression Tests (d)	P=0.456N	P=0.163	P=0.535N
Cochran-Armitage Trend Test (d)	P=0.426N		
Fisher Exact Test (d)		P=0.181	P=0.500N
Adrenal Gland: Pheochromocytoma			
Overall Rates (a)	4/50 (8%)	1/50 (2%)	4/50 (8%)
Adjusted Rates (b)	10.8%	3.8%	14.7%
Terminal Rates (c)	2/31 (6%)	1/26 (4%)	3/26 (12%)
Day of First Observation	602	729	727
Life Table Tests (d)	P=0.522	P=0.225N	P=0.550
Logistic Regression Tests (d)	P=0.563	P=0.187N	P=0.600
Cochran-Armitage Trend Test (d)	P=0.569N		
Fisher Exact Test (d)		P=0.181N	P=0.643N
Adrenal Gland: Pheochromocytoma or Malignant Pheochromocytoma			
Overall Rates (a)	4/50 (8%)	1/50 (2%)	6/50 (12%)
Adjusted Rates (b)	10.8%	3.8%	22.1%
Terminal Rates (c)	2/31 (6%)	1/26 (4%)	5/26 (19%)
Day of First Observation	602	729	727
Life Table Tests (d)	P=0.231	P=0.225N	P=0.273
Logistic Regression Tests (d)	P=0.257	P=0.187N	P=0.309
Cochran-Armitage Trend Test (d)	P=0.307		
Fisher Exact Test (d)		P=0.181N	P=0.370
Clitoral Gland: Adenoma			
Overall Rates (a)	3/44 (7%)	1/43 (2%)	3/41 (7%)
Adjusted Rates (b)	8.2%	4.3%	11.6%
Terminal Rates (c)	1/29 (3%)	1/23 (4%)	2/23 (9%)
Day of First Observation	646	729	721
Life Table Tests (d)	P=0.530	P=0.364N	P=0.578
Logistic Regression Tests (d)	P=0.552	P=0.315N	P=0.601
Cochran-Armitage Trend Test (d)	P=0.584		
Fisher Exact Test (d)		P=0.317N	P=0.628
Clitoral Gland: Adenoma or Carcinoma			
Overall Rates (a)	3/44 (7%)	1/43 (2%)	4/41 (10%)
Adjusted Rates (b)	8.2%	4.3%	15.8%
Terminal Rates (c)	1/29 (3%)	1/23 (4%)	3/23 (13%)
Day of First Observation	646	729	721
Life Table Tests (d)	P=0.348	P=0.364N	P=0.403
Logistic Regression Tests (d)	P=0.362	P=0.315N	P=0.420
Cochran-Armitage Trend Test (d)	P=0.401		
Fisher Exact Test (d)		P=0.317N	P=0.460
Mammary Gland: Fibroadenoma			
Overall Rates (a)	9/50 (18%)	19/50 (38%)	16/50 (32%)
Adjusted Rates (b)	24.5%	62.4%	45.6%
Terminal Rates (c)	6/31 (19%)	15/26 (58%)	8/26 (31%)
Day of First Observation	547	545	582
Life Table Tests (d)	P=0.030	P=0.007	P=0.047
Logistic Regression Tests (d)	P=0.045	P=0.015	P=0.070
Cochran-Armitage Trend Test (d)	P=0.070		
Fisher Exact Test (d)		P=0.022	P=0.083

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

	Vehicle Control	4 mg/kg	8 mg/kg
Mammary Gland: Adenoma or Fibroadenoma			
Overall Rates (a)	9/50 (18%)	19/50 (38%)	17/50 (34%)
Adjusted Rates (b)	24.5%	62.4%	48.6%
Terminal Rates (c)	6/31 (19%)	15/26 (58%)	9/26 (35%)
Day of First Observation	547	545	582
Life Table Tests (d)	P=0.019	P=0.007	P=0.030
Logistic Regression Tests (d)	P=0.028	P=0.015	P=0.044
Cochran-Armitage Trend Test (d)	P=0.046		
Fisher Exact Test (d)		P=0.022	P=0.055
Mammary Gland: Fibroadenoma, Adenoma, or Carcinoma			
Overall Rates (a)	11/50 (22%)	20/50 (40%)	17/50 (34%)
Adjusted Rates (b)	28.2%	65.8%	48.6%
Terminal Rates (c)	6/31 (19%)	6/26 (62%)	9/26 (35%)
Day of First Observation	547	545	582
Life Table Tests (d)	P=0.049	P=0.015	P=0.074
Logistic Regression Tests (d)	P=0.072	P=0.028	P=0.113
Cochran-Armitage Trend Test (d)	P=0.111		
Fisher Exact Test (d)		P=0.041	P=0.133
Pancreas: Adenoma			
Overall Rates (a)	1/50 (2%)	1/47 (2%)	4/50 (8%)
Adjusted Rates (b)	3.2%	4.0%	12.5%
Terminal Rates (c)	1/31 (3%)	1/25 (4%)	2/26 (8%)
Day of First Observation	729	729	631
Life Table Tests (d)	P=0.079	P=0.714	P=0.140
Logistic Regression Tests (d)	P=0.102	P=0.714	P=0.171
Cochran-Armitage Trend Test (d)	P=0.103		
Fisher Exact Test (d)		P=0.737	P=0.181
Pituitary Gland/Pars Distalis: Adenoma			
Overall Rates (a)	27/50 (54%)	19/49 (39%)	19/50 (38%)
Adjusted Rates (b)	63.7%	54.3%	58.3%
Terminal Rates (c)	16/31 (52%)	11/26 (42%)	13/26 (50%)
Day of First Observation	547	545	486
Life Table Tests (d)	P=0.232N	P=0.258N	P=0.265N
Logistic Regression Tests (d)	P=0.098N	P=0.115N	P=0.124N
Cochran-Armitage Trend Test (d)	P=0.065N		
Fisher Exact Test (d)		P=0.094N	P=0.080N
Pituitary Gland/Pars Distalis: Carcinoma			
Overall Rates (a)	1/50 (2%)	2/49 (4%)	4/50 (8%)
Adjusted Rates (b)	2.9%	7.7%	11.5%
Terminal Rates (c)	0/31 (0%)	2/26 (8%)	1/26 (4%)
Day of First Observation	711	729	557
Life Table Tests (d)	P=0.101	P=0.434	P=0.160
Logistic Regression Tests (d)	P=0.119	P=0.470	P=0.189
Cochran-Armitage Trend Test (d)	P=0.119		
Fisher Exact Test (d)		P=0.492	P=0.181
Pituitary Gland/Pars Distalis: Adenoma or Carcinoma			
Overall Rates (a)	28/50 (56%)	21/49 (43%)	23/50 (46%)
Adjusted Rates (b)	64.8%	60.4%	64.6%
Terminal Rates (c)	16/31 (52%)	13/26 (50%)	14/26 (54%)
Day of First Observation	547	545	486
Life Table Tests (d)	P=0.444N	P=0.337N	P=0.481N
Logistic Regression Tests (d)	P=0.252N	P=0.165N	P=0.289N
Cochran-Armitage Trend Test (d)	P=0.184N		
Fisher Exact Test (d)		P=0.134N	P=0.212N

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

	Vehicle Control	4 mg/kg	8 mg/kg
Subcutaneous Tissue: Fibrosarcoma			
Overall Rates (a)	0/50 (0%)	3/50 (6%)	1/50 (2%)
Adjusted Rates (b)	0.0%	9.0%	3.8%
Terminal Rates (c)	0/31 (0%)	0/26 (0%)	1/26 (4%)
Day of First Observation		695	729
Life Table Tests (d)	P=0.317	P=0.107	P=0.465
Logistic Regression Tests (d)	P=0.334	P=0.112	P=0.469
Cochran-Armitage Trend Test (d)	P=0.362		
Fisher Exact Test (d)		P=0.121	P=0.500
Subcutaneous Tissue: Fibroma or Fibrosarcoma			
Overall Rates (a)	0/50 (0%)	3/50 (6%)	3/50 (6%)
Adjusted Rates (b)	0.0%	9.0%	11.5%
Terminal Rates (c)	0/31 (0%)	0/26 (0%)	3/26 (12%)
Day of First Observation		695	729
Life Table Tests (d)	P=0.076	P=0.107	P=0.091
Logistic Regression Tests (d)	P=0.079	P=0.112	P=0.091
Cochran-Armitage Trend Test (d)	P=0.099		
Fisher Exact Test (d)		P=0.121	P=0.121
Thyroid Gland: C-Cell Adenoma			
Overall Rates (a)	5/50 (10%)	7/49 (14%)	5/50 (10%)
Adjusted Rates (b)	14.8%	21.8%	15.3%
Terminal Rates (c)	4/31 (13%)	3/26 (12%)	2/26 (8%)
Day of First Observation	596	656	631
Life Table Tests (d)	P=0.454	P=0.295	P=0.525
Logistic Regression Tests (d)	P=0.517	P=0.341	P=0.610
Cochran-Armitage Trend Test (d)	P=0.562		
Fisher Exact Test (d)		P=0.365	P=0.630
Thyroid Gland: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	5/50 (10%)	8/49 (16%)	5/50 (10%)
Adjusted Rates (b)	14.8%	25.2%	15.3%
Terminal Rates (c)	4/31 (13%)	4/26 (15%)	2/26 (8%)
Day of First Observation	596	656	631
Life Table Tests (d)	P=0.448	P=0.202	P=0.525
Logistic Regression Tests (d)	P=0.505	P=0.239	P=0.610
Cochran-Armitage Trend Test (d)	P=0.561		
Fisher Exact Test (d)		P=0.264	P=0.630
Uterus: Stromal Polyp			
Overall Rates (a)	15/50 (30%)	14/50 (28%)	13/50 (26%)
Adjusted Rates (b)	39.8%	43.5%	34.7%
Terminal Rates (c)	10/31 (32%)	9/26 (35%)	4/26 (15%)
Day of First Observation	582	556	582
Life Table Tests (d)	P=0.534	P=0.499	P=0.579N
Logistic Regression Tests (d)	P=0.423N	P=0.560N	P=0.434N
Cochran-Armitage Trend Test (d)	P=0.372N		
Fisher Exact Test (d)		P=0.500N	P=0.412N
Hematopoietic System: Mononuclear Cell Leukemia			
Overall Rates (a)	17/50 (34%)	21/50 (42%)	23/50 (46%)
Adjusted Rates (b)	39.1%	53.2%	56.8%
Terminal Rates (c)	7/31 (23%)	9/26 (35%)	9/26 (35%)
Day of First Observation	532	519	546
Life Table Tests (d)	P=0.082	P=0.186	P=0.100
Logistic Regression Tests (d)	P=0.125	P=0.278	P=0.166
Cochran-Armitage Trend Test (d)	P=0.131		
Fisher Exact Test (d)		P=0.268	P=0.154

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DICHLORVOS (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 calculated using doses actually administered to the animals (4.14 and 7.82 mg/kg). 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 logistic regression 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 B4a. HISTORICAL INCIDENCE OF PANCREATIC ACINAR CELL TUMORS 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	0/49
Allyl isovalerate	0/49
HC Red No. 3	0/50
Chlorinated paraffins (43% chlorine)	0/50
Chlorinated paraffins (60% chlorine)	1/50
Allyl isothiocyanate	0/49
Geranyl acetate	0/50
TOTAL	1/397 (0.3%)
SD (b)	0.71%
Range (c)	
High	1/50
Low	0/50
Overall Historical Incidence	
TOTAL	7/1,679 (0.4%)
SD (b)	0.97%
Range (c)	
High	2/49
Low	0/50

(a) Data as of August 7, 1986, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE B4b. HISTORICAL INCIDENCE OF MAMMARY GLAND TUMORS IN FEMALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls		
	Fibroadenomas	Adenocarcinomas	All Tumors
Historical Incidence at Southern Research Institute			
Ethyl acrylate	13/50	1/50	(b) 14/50
Benzyl acetate	16/50	1/50	(c) 18/50
Allyl isovalerate	17/50	2/50	19/50
HC Red No. 3	14/50	0/50	14/50
Chlorinated paraffins (43% chlorine)	14/50	3/50	(b) 16/50
Chlorinated paraffins (60% chlorine)	19/50	2/50	21/50
Allyl isothiocyanate	8/50	1/50	9/50
Geranyl acetate	12/50	0/50	(b) 13/50
TOTAL	113/400 (28.3%)	10/400 (2.5%)	124/400 (31.0%)
SD (d)	6.71%	2.07%	7.63%
Range (e)			
High	19/50	3/50	21/50
Low	8/50	0/50	9/50
Overall Historical Incidence			
TOTAL	436/1,700 (25.6%)	33/1,700 (1.9%)	(f) 474/1,700 (27.9%)
SD (d)	7.49%	1.59%	7.97%
Range (e)			
High	20/50	3/50	21/50
Low	6/50	0/50	8/50

(a) Data as of August 7, 1986, for studies of at least 104 weeks
(b) Includes one adenoma, NOS
(c) Includes one cystadenoma, NOS
(d) Standard deviation
(e) Range and SD are presented for groups of 35 or more animals.
(f) Includes 10 adenomas, NOS, 1 papillary adenoma, 4 cystadenomas, NOS, 1 papillary cystadenoma, NOS, and 1 papillary cystadenocarcinoma, NOS

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

	Vehicle Control	Low Dose	High Dose
Animals initially in study	50	50	50
Animals removed	50	50	50
Animals examined histopathologically	50	50	50
ALIMENTARY SYSTEM			
Esophagus	(49)	(50)	(50)
Ulcer	1 (2%)		
Intestine large	(50)	(49)	(50)
Cecum, parasite metazoan	2 (4%)		1 (2%)
Colon, mineralization		1 (2%)	
Colon, parasite metazoan	5 (10%)	1 (2%)	8 (16%)
Colon, serosa, cyst			1 (2%)
Rectum, parasite metazoan	2 (4%)	3 (6%)	3 (6%)
Intestine small	(50)	(49)	(50)
Duodenum, ectopic tissue		1 (2%)	
Duodenum, ulcer		1 (2%)	
Jejunum, developmental malformation			1 (2%)
Jejunum, hemorrhage			1 (2%)
Jejunum, hyperplasia, re cell			1 (2%)
Liver	(50)	(50)	(50)
Angiectasis	3 (6%)		1 (2%)
Basophilic focus	32 (64%)	27 (54%)	24 (48%)
Clear cell focus	1 (2%)	6 (12%)	2 (4%)
Developmental malformation		2 (4%)	2 (4%)
Hematopoietic cell proliferation	3 (6%)	1 (2%)	
Hyperplasia, lymphoid	1 (2%)		
Inflammation, chronic	8 (16%)	7 (14%)	6 (12%)
Inflammation, chronic active	1 (2%)	1 (2%)	
Inflammation, granulomatous	11 (22%)	10 (20%)	13 (26%)
Mixed cell focus	1 (2%)		1 (2%)
Bile duct, hyperplasia	27 (54%)	29 (58%)	17 (34%)
Capsule, fibrosis			1 (2%)
Hepatocyte, atrophy, multifocal	5 (10%)	12 (24%)	11 (22%)
Hepatocyte, cytoplasmic alteration	1 (2%)	1 (2%)	
Hepatocyte, hyperplasia, nodular	2 (4%)	5 (10%)	3 (6%)
Hepatocyte, necrosis, multifocal	2 (4%)	3 (6%)	2 (4%)
Hepatocyte, vacuolization cytoplasmic	6 (12%)	7 (14%)	5 (10%)
Hepatocyte, centrilobular, necrosis			1 (2%)
Kupffer cell, hyperplasia	1 (2%)		
Kupffer cell, pigmentation	4 (8%)	1 (2%)	2 (4%)
Portal, fibrosis	13 (26%)	13 (26%)	3 (6%)
Vein, thrombus		1 (2%)	
Mesentery	(10)	(12)	(7)
Ectopic tissue			1 (14%)
Inflammation, granulomatous		2 (17%)	
Inflammation, suppurative		1 (8%)	
Fat, fibrosis			1 (14%)
Fat, hemorrhage		1 (8%)	
Fat, mineralization	4 (40%)	1 (8%)	3 (43%)
Fat, necrosis, focal	9 (90%)	12 (100%)	6 (86%)
Pancreas	(50)	(47)	(50)
Atrophy	5 (10%)	6 (13%)	15 (30%)
Cyst	1 (2%)		
Cytoplasmic alteration	1 (2%)		
Hyperplasia	2 (4%)	3 (6%)	
Pharynx	(1)		(2)
Palate, inflammation, suppurative	1 (100%)		1 (50%)
Palate, necrosis	1 (100%)		1 (50%)

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

	Vehicle Control	Low Dose	High Dose
ALIMENTARY SYSTEM (Continued)			
Salivary glands	(49)	(50)	(49)
Ectopic tissue	2 (4%)		1 (2%)
Parotid gland, hyperplasia, focal		1 (2%)	
Parotid gland, vacuolization cytoplasmic		1 (2%)	
Stomach	(50)	(49)	(50)
Forestomach, diverticulum	1 (2%)		
Forestomach, edema	1 (2%)	4 (8%)	
Forestomach, foreign body		1 (2%)	
Forestomach, granuloma		1 (2%)	
Forestomach, inflammation, chronic active	1 (2%)		
Forestomach, inflammation, suppurative		1 (2%)	1 (2%)
Forestomach, ulcer	5 (10%)	6 (12%)	3 (6%)
Forestomach, mucosa, dysplasia	1 (2%)		2 (4%)
Forestomach, mucosa, hyperplasia	5 (10%)	6 (12%)	6 (12%)
Glandular, dysplasia	1 (2%)	1 (2%)	
Glandular, edema	1 (2%)		
Glandular, erosion	3 (6%)	4 (8%)	2 (4%)
Glandular, inflammation, suppurative		1 (2%)	
Glandular, mineralization	5 (10%)	11 (22%)	3 (6%)
Glandular, ulcer	1 (2%)	3 (6%)	
Tongue	(3)	(1)	(1)
Inflammation, suppurative	1 (33%)		
Epithelium, hyperplasia	2 (67%)	1 (100%)	
CARDIOVASCULAR SYSTEM			
Heart	(50)	(50)	(50)
Thrombus		1 (2%)	
Myocardium, fibrosis	19 (38%)	18 (36%)	9 (18%)
Myocardium, hemorrhage		1 (2%)	
Myocardium, inflammation, chronic	8 (16%)	9 (18%)	3 (6%)
Myocardium, mineralization	1 (2%)		
Myocardium, pigmentation		1 (2%)	1 (2%)
ENDOCRINE SYSTEM			
Adrenal gland	(50)	(50)	(50)
Angiectasis	1 (2%)		
Hematopoietic cell proliferation		1 (2%)	
Infiltration cellular, eosinophilic	1 (2%)		
Infiltration cellular, mononuclear cell			1 (2%)
Inflammation, chronic	2 (4%)	1 (2%)	
Cortex, congestion	1 (2%)		1 (2%)
Cortex, cyst	2 (4%)		
Cortex, cytoplasmic alteration, diffuse			1 (2%)
Cortex, hematocyst			1 (2%)
Cortex, hyperplasia	5 (10%)	1 (2%)	7 (14%)
Cortex, necrosis	1 (2%)		1 (2%)
Cortex, pigmentation	1 (2%)		
Cortex, vacuolization cytoplasmic	9 (18%)	17 (34%)	12 (24%)
Extra adrenal tissue, developmental malformation		2 (4%)	1 (2%)
Medulla, hyperplasia, focal	3 (6%)	2 (4%)	1 (2%)
Islets, pancreatic	(50)	(48)	(50)
Hyperplasia		1 (2%)	
Parathyroid gland	(49)	(47)	(45)
Hyperplasia	1 (2%)		
Pigmentation		1 (2%)	

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

	Vehicle Control	Low Dose	High Dose
ENDOCRINE SYSTEM (Continued)			
Pituitary gland	(50)	(49)	(50)
Pars distalis, angiectasis	2 (4%)	4 (8%)	6 (12%)
Pars distalis, cyst	17 (34%)	19 (39%)	16 (32%)
Pars distalis, hyperplasia	4 (8%)	5 (10%)	6 (12%)
Pars distalis, pigmentation		1 (2%)	
Pars intermedia, cyst	1 (2%)		
Pars intermedia, infiltration cellular		1 (2%)	
Pars nervosa, hemorrhage		1 (2%)	
Pars nervosa, infiltration cellular		1 (2%)	
Thyroid gland	(50)	(49)	(50)
Inflammation, chronic	1 (2%)		
Ultimobranchial cyst	2 (4%)		
C-cell, hyperplasia	15 (30%)	9 (18%)	10 (20%)
GENERAL BODY SYSTEM			
None			
GENITAL SYSTEM			
Clitoral gland	(44)	(43)	(41)
Dysplasia			1 (2%)
Ectasia	4 (9%)	5 (12%)	3 (7%)
Hyperplasia	3 (7%)	3 (7%)	5 (12%)
Inflammation, chronic		2 (5%)	1 (2%)
Inflammation, suppurative	8 (18%)	6 (14%)	7 (17%)
Metaplasia, squamous	1 (2%)		
Ovary	(50)	(50)	(50)
Cyst	6 (12%)	4 (8%)	6 (12%)
Uterus	(50)	(50)	(50)
Abscess	2 (4%)	4 (8%)	6 (12%)
Atrophy		1 (2%)	
Cyst		5 (10%)	1 (2%)
Hydrometria	3 (6%)	1 (2%)	3 (6%)
Hyperplasia, cystic		6 (12%)	2 (4%)
Hyperplasia, glandular			1 (2%)
Inflammation, chronic active			1 (2%)
Inflammation, suppurative	2 (4%)		1 (2%)
Prolapse			1 (2%)
Endometrium, dysplasia			1 (2%)
Mucosa, hyperplasia	1 (2%)	1 (2%)	1 (2%)
Vagina	(4)	(8)	(7)
Abscess			1 (14%)
Cyst			1 (14%)
Inflammation, suppurative	1 (25%)		
HEMATOPOIETIC SYSTEM			
Bone marrow	(50)	(49)	(50)
Hemorrhage		1 (2%)	
Hyperplasia	3 (6%)	1 (2%)	2 (4%)
Hyperplasia, reticulum cell	8 (16%)	5 (10%)	5 (10%)
Myelofibrosis	1 (2%)	2 (4%)	5 (10%)
Lymph node	(50)	(50)	(50)
Axillary, hyperplasia, lymphoid	1 (2%)		
Axillary, inflammation, suppurative	1 (2%)		
Axillary, lymphatic, ectasia	1 (2%)		
Bronchial, hemorrhage	2 (4%)		
Bronchial, infiltration cellular, mast cell	1 (2%)		
Inguinal, hyperplasia, plasma cell			1 (2%)
Lymphatic, mandibular, ectasia	1 (2%)		2 (4%)

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

	Vehicle Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM			
Lymph node (Continued)	(50)	(50)	(50)
Mandibular, hyperplasia, histiocyte			1 (2%)
Mandibular, hyperplasia, lymphoid		1 (2%)	
Mandibular, hyperplasia, plasma cell	4 (8%)	5 (10%)	7 (14%)
Mandibular, infiltration cellular, mast cell			1 (2%)
Mediastinal, erythrophagocytosis	3 (6%)		1 (2%)
Mediastinal, hemorrhage	5 (10%)	5 (10%)	6 (12%)
Mediastinal, hyperplasia, histiocyte			1 (2%)
Mediastinal, hyperplasia, plasma cell	1 (2%)		
Mediastinal, infiltration cellular, mast cell	1 (2%)		
Mediastinal, pigmentation	10 (20%)	8 (16%)	10 (20%)
Mesenteric, atrophy	3 (6%)	4 (8%)	5 (10%)
Mesenteric, erythrophagocytosis	1 (2%)		
Mesenteric, hemorrhage	2 (4%)	2 (4%)	2 (4%)
Mesenteric, hyperplasia, histiocyte	1 (2%)		
Mesenteric, hyperplasia, lymphoid			1 (2%)
Mesenteric, infiltration cellular, mast cell	2 (4%)		1 (2%)
Mesenteric, pigmentation	1 (2%)		
Mesenteric, lymphatic, ectasia			2 (4%)
Pancreatic, hemorrhage			1 (2%)
Pancreatic, hyperplasia, histiocyte	1 (2%)		
Pancreatic, hyperplasia, lymphoid	1 (2%)		
Spleen	(50)	(50)	(50)
Congestion	1 (2%)		
Developmental malformation		1 (2%)	
Erythrophagocytosis	1 (2%)		
Fibrosis	1 (2%)	5 (10%)	1 (2%)
Hematopoietic cell proliferation granulocytic	3 (6%)		2 (4%)
Hematopoietic cell proliferation erythrocytic	7 (14%)	7 (14%)	9 (18%)
Hemorrhage			1 (2%)
Necrosis		1 (2%)	2 (4%)
Pigmentation, hemosiderin	2 (4%)	5 (10%)	4 (8%)
Thymus	(39)	(39)	(39)
Atrophy		1 (3%)	
INTEGUMENTARY SYSTEM			
Mammary gland	(50)	(50)	(49)
Fibrosis			1 (2%)
Hyperplasia, cystic	41 (82%)	43 (86%)	35 (71%)
Hyperplasia, lobular	2 (4%)	5 (10%)	3 (6%)
Inflammation, suppurative	1 (2%)		
Skin	(50)	(48)	(48)
Acanthosis	2 (4%)	1 (2%)	2 (4%)
Cyst epithelial inclusion		1 (2%)	
Exudate		1 (2%)	
Hyperkeratosis	1 (2%)	1 (2%)	
Inflammation, chronic	1 (2%)	1 (2%)	1 (2%)
Inflammation, suppurative	1 (2%)		
Ulcer			1 (2%)
MUSCULOSKELETAL SYSTEM			
Bone	(50)	(50)	(49)
Developmental malformation		1 (2%)	
Hemorrhage		1 (2%)	
Hyperostosis		1 (2%)	2 (4%)
Hyperplasia		1 (2%)	
Necrosis		1 (2%)	
Skeletal muscle	(1)	(1)	
Hemorrhage	1 (100%)		

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

	Vehicle Control	Low Dose	High Dose
NERVOUS SYSTEM			
Brain	(50)	(50)	(50)
Compression	2 (4%)	5 (10%)	4 (8%)
Degeneration, multiple	7 (14%)	7 (14%)	5 (10%)
Hydrocephalus	1 (2%)	1 (2%)	
Cerebrum, degeneration	2 (4%)	2 (4%)	4 (8%)
Thalamus, degeneration			2 (4%)
RESPIRATORY SYSTEM			
Lung	(50)	(50)	(50)
Adenomatosis	3 (6%)	1 (2%)	3 (6%)
Edema, diffuse	1 (2%)		
Fibrosis	1 (2%)		
Foreign body	1 (2%)		
Hemorrhage	3 (6%)		
Infiltration cellular, histiocytic	35 (70%)	39 (78%)	46 (92%)
Inflammation, chronic	1 (2%)		
Inflammation, suppurative	1 (2%)		2 (4%)
Mineralization			1 (2%)
Nose	(50)	(49)	(47)
Lumen, foreign body		1 (2%)	2 (4%)
Lumen, fungus	2 (4%)	1 (2%)	3 (6%)
Lumen, inflammation, suppurative	3 (6%)	4 (8%)	4 (9%)
Mucosa, metaplasia, squamous	2 (4%)	1 (2%)	
Nasolacrimal duct, inflammation, suppurative	3 (6%)	1 (2%)	
Nasopharyngeal duct, inflammation, suppurative			1 (2%)
Submucosa, inflammation, chronic	1 (2%)	3 (6%)	1 (2%)
SPECIAL SENSES SYSTEM			
Eye	(2)	(23)	(3)
Angiectasis		2 (9%)	
Cataract	2 (100%)	23 (100%)	1 (33%)
Hemorrhage		2 (9%)	
Retinal detachment			1 (33%)
Cornea, inflammation, chronic		1 (4%)	
Cornea, mineralization		1 (4%)	
Retina, atrophy	1 (50%)	23 (100%)	1 (33%)
Harderian gland			(1)
Hemorrhage			1 (100%)
Inflammation, suppurative			1 (100%)
URINARY SYSTEM			
Kidney	(50)	(50)	(50)
Cyst			1 (2%)
Infarct		1 (2%)	
Inflammation, chronic	4 (8%)	2 (4%)	3 (6%)
Inflammation, suppurative	1 (2%)		
Nephropathy	34 (68%)	38 (76%)	35 (70%)
Pelvis, mineralization	13 (26%)	19 (38%)	18 (36%)
Pelvis, epithelium, hyperplasia		1 (2%)	1 (2%)
Renal tubule, mineralization	4 (8%)	12 (24%)	3 (6%)
Renal tubule, necrosis	1 (2%)		
Renal tubule, pigmentation	8 (16%)	6 (12%)	5 (10%)
Urinary bladder	(50)	(49)	(50)
Edema	1 (2%)		
Inflammation, chronic	1 (2%)		
Mucosa, hyperplasia	1 (2%)	1 (2%)	

APPENDIX C

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

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

	Vehicle Control	Low Dose	High Dose
Animals initially in study	50	50	50
Animals removed	50	50	50
Animals examined histopathologically	50	50	50
ALIMENTARY SYSTEM			
Intestine large	(49)	(50)	(49)
Cecum, carcinoma	1 (2%)		
Cecum, lymphoma malignant lymphocytic		1 (2%)	
Cecum, lymphoma malignant mixed	1 (2%)		1 (2%)
Intestine small	(48)	(50)	(49)
Duodenum, adenocarcinoma	1 (2%)	1 (2%)	1 (2%)
Duodenum, lymphoma malignant lymphocytic		1 (2%)	
Duodenum, lymphoma malignant mixed, multiple	1 (2%)		
Duodenum, polyp adenomatous			1 (2%)
Ileum, lymphoma malignant lymphocytic			1 (2%)
Ileum, lymphoma malignant mixed	3 (6%)		2 (4%)
Jejunum, adenocarcinoma		1 (2%)	
Jejunum, lymphoma malignant mixed	1 (2%)		
Liver	(50)	(50)	(50)
Hemangiosarcoma	1 (2%)		
Hemangiosarcoma, multiple		2 (4%)	
Hepatocellular carcinoma	7 (14%)	13 (26%)	8 (16%)
Hepatocellular carcinoma, multiple	3 (6%)	3 (6%)	2 (4%)
Hepatocellular adenoma	5 (10%)	3 (6%)	8 (16%)
Hepatocellular adenoma, multiple	2 (4%)		3 (6%)
Lymphoma malignant histiocytic		1 (2%)	
Lymphoma malignant lymphocytic	1 (2%)	1 (2%)	1 (2%)
Lymphoma malignant mixed	1 (2%)		2 (4%)
Pheochromocytoma malignant, metastatic, adrenal gland			1 (2%)
Mesentery	*(50)	*(50)	*(50)
Hemangioma	1 (2%)		
Hemangiosarcoma		1 (2%)	
Lymphoma malignant lymphocytic			1 (2%)
Lymphoma malignant mixed	2 (4%)		2 (4%)
Pancreas	(50)	(48)	(48)
Lymphoma malignant lymphocytic			1 (2%)
Lymphoma malignant mixed			2 (4%)
Salivary glands	(50)	(50)	(50)
Lymphoma malignant mixed			1 (2%)
Stomach	(50)	(50)	(50)
Forestomach, papilloma squamous		1 (2%)	5 (10%)
Forestomach, papilloma squamous, multiple	1 (2%)		
Glandular, carcinoid tumor malignant			1 (2%)
Tooth	*(50)	*(50)	*(50)
Neoplasm, NOS			1 (2%)
CARDIOVASCULAR SYSTEM			
Heart	(50)	(50)	(50)
Lymphoma malignant lymphocytic	1 (2%)		
Sarcoma		1 (2%)	
ENDOCRINE SYSTEM			
Adrenal gland	(48)	(50)	(49)
Lymphoma malignant mixed			1 (2%)
Cortex, adenoma		1 (2%)	
Medulla, pheochromocytoma malignant			1 (2%)
Medulla, pheochromocytoma benign	2 (4%)	5 (10%)	1 (2%)

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

	Vehicle Control	Low Dose	High Dose
ENDOCRINE SYSTEM (Continued)			
Islets, pancreatic	(50)	(47)	(48)
Lymphoma malignant mixed			1 (2%)
Pituitary gland	(40)	(44)	(40)
Pars distalis, adenoma		1 (2%)	1 (3%)
Thyroid gland	(45)	(50)	(49)
Lymphoma malignant mixed			1 (2%)
Follicular cell, adenoma		3 (6%)	
GENERAL BODY SYSTEM			
None			
GENITAL SYSTEM			
Epididymis	(50)	(49)	(49)
Lymphoma malignant mixed			1 (2%)
Preputial gland	*(50)	*(50)	*(50)
Hemangiosarcoma	1 (2%)		
Testes	(50)	(50)	(49)
Interstitial cell, adenoma		1 (2%)	
HEMATOPOIETIC SYSTEM			
Bone marrow	(50)	(50)	(50)
Hemangiosarcoma		2 (4%)	
Lymphoma malignant histiocytic		1 (2%)	
Lymphoma malignant lymphocytic	1 (2%)		
Lymph node	(47)	(48)	(50)
Bronchial, lymphoma malignant lymphocytic			1 (2%)
Bronchial, lymphoma malignant mixed			1 (2%)
Inguinal, lymphoma malignant lymphocytic			1 (2%)
Inguinal, lymphoma malignant mixed	1 (2%)		2 (4%)
Mandibular, lymphoma malignant lymphocytic	1 (2%)		1 (2%)
Mandibular, lymphoma malignant mixed	1 (2%)		3 (6%)
Mandibular, sarcoma		1 (2%)	1 (2%)
Mediastinal, lymphoma malignant lymphocytic	1 (2%)		
Mediastinal, lymphoma malignant mixed	2 (4%)		3 (6%)
Mesenteric, lymphoma malignant lymphocytic	1 (2%)		
Mesenteric, lymphoma malignant lymphocytic, multiple			1 (2%)
Mesenteric, lymphoma malignant mixed	3 (6%)		2 (4%)
Mesenteric, lymphoma malignant mixed, multiple	1 (2%)		1 (2%)
Pancreatic, lymphoma malignant lymphocytic	1 (2%)		
Pancreatic, lymphoma malignant mixed	2 (4%)		1 (2%)
Spleen	(49)	(49)	(49)
Hemangiosarcoma		1 (2%)	
Lymphoma malignant lymphocytic	1 (2%)		1 (2%)
Lymphoma malignant mixed	4 (8%)		2 (4%)
Lymphoma malignant mixed, multiple			1 (2%)
Thymus	(35)	(32)	(36)
Lymphoma malignant lymphocytic	1 (3%)		

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

	Vehicle Control	Low Dose	High Dose
INTEGUMENTARY SYSTEM			
Skin	(50)	(49)	(50)
Basal cell carcinoma		1 (2%)	
Keratoacanthoma, multiple			1 (2%)
Papilloma			1 (2%)
Plasma cell tumor malignant	1 (2%)		
Subcutaneous tissue, fibroma	4 (8%)		2 (4%)
Subcutaneous tissue, fibroma, multiple	1 (2%)		1 (2%)
Subcutaneous tissue, fibrosarcoma	2 (4%)	4 (8%)	4 (8%)
Subcutaneous tissue, fibrosarcoma, multiple	4 (8%)	4 (8%)	3 (6%)
Subcutaneous tissue, hemangiosarcoma		1 (2%)	
Subcutaneous tissue, sarcoma	1 (2%)	2 (4%)	
Subcutaneous tissue, sarcoma, multiple			1 (2%)
Subcutaneous tissue, schwannoma malignant		1 (2%)	
Subcutaneous tissue, schwannoma malignant, multiple			1 (2%)
MUSCULOSKELETAL SYSTEM			
None			
NERVOUS SYSTEM			
None			
RESPIRATORY SYSTEM			
Lung	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	9 (18%)	13 (26%)	8 (16%)
Alveolar/bronchiolar adenoma, multiple		1 (2%)	1 (2%)
Alveolar/bronchiolar carcinoma	1 (2%)	1 (2%)	2 (4%)
Alveolar/bronchiolar carcinoma, multiple		1 (2%)	
Hepatocellular carcinoma, metastatic	1 (2%)		
Hepatocellular carcinoma, metastatic, liver	3 (6%)	1 (2%)	3 (6%)
Lymphoma malignant histiocytic		1 (2%)	
Lymphoma malignant lymphocytic	1 (2%)		
Lymphoma malignant mixed	1 (2%)		2 (4%)
Pheochromocytoma malignant, metastatic, adrenal gland			1 (2%)
Sarcoma		1 (2%)	
Nose	(46)	(50)	(48)
Lymphoma malignant mixed			1 (2%)
SPECIAL SENSES SYSTEM			
Harderian gland	*(50)	*(50)	*(50)
Adenoma	5 (10%)	3 (6%)	5 (10%)
Lymphoma malignant mixed			2 (4%)
URINARY SYSTEM			
Kidney	(50)	(50)	(50)
Lymphoma malignant lymphocytic	1 (2%)		
Lymphoma malignant mixed			2 (4%)
Sarcoma		1 (2%)	
Urinary bladder	(50)	(48)	(49)
Lymphoma malignant mixed			2 (4%)

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

	Vehicle Control	Low Dose	High Dose
SYSTEMIC LESIONS			
Multiple organs	*(50)	*(50)	*(50)
Hemangiosarcoma	2 (4%)	3 (6%)	
Lymphoma malignant mixed	6 (12%)		3 (6%)
Lymphoma malignant lymphocytic	1 (2%)	1 (2%)	1 (2%)
Hemangioma	1 (2%)		
Lymphoma malignant histiocytic		1 (2%)	
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Dead	9	6	8
Terminal sacrifice	35	27	29
Moribund	5	17	13
Accident	1		
TUMOR SUMMARY			
Total animals with primary neoplasms **	37	41	37
Total primary neoplasms	60	73	68
Total animals with benign neoplasms	24	26	28
Total benign neoplasms	30	32	38
Total animals with malignant neoplasms	24	31	23
Total malignant neoplasms	30	41	29
Total animals with secondary neoplasms ***	4	1	4
Total secondary neoplasms	4	1	5
Total animals with neoplasms-- uncertain benign or malignant			1
Total uncertain neoplasms			1

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

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

WEEKS ON STUDY	002	010	015	031	058	076	078	078	079	083	084	085	091	099	100	105	105	105	105	105	105	105	105	105	105
CARCASS ID	10 01	02 11	03 11	02 22	04 41	04 42	04 43	06 61	08 81	02 23	09 91	01 11	03 32	03 33	05 51	01 12	01 13	01 14	01 15	02 24	02 25	03 34	03 35	04 44	04 45
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	M	+	+	+	A	+	+	A	M	+	+	+	+	+	+	+	+	+	+	M	+	I	+	M
Intestine large	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cecum, carcinoma																									
Cecum, lymphoma malignant mixed											X														
Intestine small	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Duodenum, adenocarcinoma																								X	
Duodenum, lymphoma malignant mixed, multiple													X												
Ileum, lymphoma malignant mixed													X						X						
Jejunum, lymphoma malignant mixed													X												
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									X
Hepatocellular carcinoma								X							X										
Hepatocellular carcinoma, multiple										X															
Hepatocellular adenoma																				X					
Hepatocellular adenoma, multiple																	X								
Lymphoma malignant lymphocytic						X																			
Lymphoma malignant mixed											X														
Mesentery			+									+	+						+						
Hemangioma																									
Lymphoma malignant mixed													X						X						
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Forestomach, papilloma squamous, multiple																									
Tooth						+																	+		+
CARDIOVASCULAR SYSTEM																									
Blood vessel					+				+		+														
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic						X																			
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Medulla, pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	M	+	+	+	+	+	+	+	+	+	M	M	M	M	+	M	I	M	M	M	+	+	M
Pituitary gland	M	M	+	+	+	M	M	+	+	M	+	+	+	+	+	+	+	M	+	+	+	M	M	+	+
Thyroid gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+
GENERAL BODY SYSTEM																									
Tissue, NOS	+				+																				
GENITAL SYSTEM																									
Coagulating gland																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland		+				+						+				+	+	+	+						
Hemangiosarcoma																			X						
Prostate	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Seminal vesicle		A		+			+													+					+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

+: Tissue examined microscopically
Not examined
–: Present but not examined microscopically
I: Insufficient tissue

M: Missing
A: Autolysis precludes examination
X: Incidence of listed morphology

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

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	
CARCASS ID	052	053	054	055	062	063	064	065	071	072	073	074	075	082	083	084	085	092	093	094	095	102	103	104	105	TOTAL TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	M	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cecum, carcinoma													X													1
Cecum, lymphoma malignant mixed																										1
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Duodenum, adenocarcinoma																										1
Duodenum, lymphoma malignant mixed, multiple																										1
Ileum, lymphoma malignant mixed				X																						3
Jejunum, lymphoma malignant mixed																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Hepatocellular carcinoma							X						X				X							X	X	7
Hepatocellular carcinoma, multiple		X																X								3
Hepatocellular adenoma						X							X		X					X						5
Hepatocellular adenoma, multiple														X												2
Lymphoma malignant lymphocytic																										1
Lymphoma malignant mixed																										1
Mesentery																					+					5
Hemangioma																					X					1
Lymphoma malignant mixed																										2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Forestomach, papilloma squamous, multiple		X																								1
Tooth	+												+		+				+							7
CARDIOVASCULAR SYSTEM																										
Blood vessel																										3
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																										1
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	48
Medulla, pheochromocytoma benign					X																				X	2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	M	M	M	M	+	+	+	+	+	+	M	+	M	M	M	I	+	+	+	+	+	+	M	M	28
Pituitary gland	I	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Thyroid gland	+	+	+	+	+	*I*	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*I*	45
GENERAL BODY SYSTEM																										
Tissue, NOS																										2
GENITAL SYSTEM																										
Coagulating gland			+	M															+							2
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+						+	+		+				+	+			+	+	+	M	+	+	+	+	20
Hemangiosarcoma																										1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	47
Seminal vesicle	+																									5
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

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

WEEKS ON STUDY	002	010	015	031	058	076	078	078	079	083	084	085	091	099	100	105	105	105	105	105	105	105	105	105
CARCASS ID	101	021	031	022	041	042	043	061	081	023	091	011	032	033	051	012	013	014	015	024	025	034	035	044	045
HEMATOPOIETIC SYSTEM																									
Blood																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic						X																			
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	M
Inguinal, lymphoma malignant mixed											X														
Mandibular, lymphoma malignant lymphocytic						X																			
Mandibular, lymphoma malignant mixed													X												
Mediastinal, lymphoma malignant lymphocytic						X																			
Mediastinal, lymphoma malignant mixed													X												
Mesenteric, lymphoma malignant lymphocytic						X																			
Mesenteric, lymphoma malignant mixed											X		X												
Mesenteric, lymphoma malignant mixed, multiple																									
Pancreatic, lymphoma malignant lymphocytic						X																			
Pancreatic, lymphoma malignant mixed													X												
Spleen	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic						X																			
Lymphoma malignant mixed											X		X												
Thymus	+	M	M	+	+	+	M	+	+	+	M	+	M	+	+	+	M	M	+	+	+	M	+	+	M
Lymphoma malignant lymphocytic						X																			
INTEGUMENTARY SYSTEM																									
Mammary gland	M	M	M	+	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Plasma cell tumor malignant											X														
Subcutaneous tissue, fibroma														X					X						
Subcutaneous tissue, fibroma, multiple																									
Subcutaneous tissue, fibrosarcoma																									
Subcutaneous tissue, fibrosarcoma, multiple														X											
Subcutaneous tissue, sarcoma																	X								
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle															+	+									+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve	+	M	M	M	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	I	I	+	+	M	M
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma								X																	X
Alveolar/bronchiolar carcinoma												X													
Hepatocellular carcinoma, metastatic								X																	
Hepatocellular carcinoma, metastatic, liver																									
Lymphoma malignant lymphocytic						X																			
Lymphoma malignant mixed											X														
Nose	M	M	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Harderian gland							+																		
Adenoma							X																		
Lacrimal gland				M																					
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic						X																			
Urethra		+	+																						
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

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

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	TOTAL
CARCASS ID	052	053	054	055	062	063	064	065	071	072	073	074	075	082	083	084	085	092	093	094	095	102	103	104	105	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Blood																+										1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																										1
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Inguinal, lymphoma malignant mixed																										1
Mandibular, lymphoma malignant lymphocytic																										1
Mandibular, lymphoma malig mixed																										1
Mediastinal, lymphoma malignant lymphocytic																										1
Mediastinal, lymphoma malig mixed																	X									2
Mesenteric, lymphoma malignant lymphocytic																										1
Mesenteric, lymphoma malignant mixed																								X		3
Mesenteric, lymphoma malignant mixed, multiple																	X									1
Pancreatic, lymphoma malignant lymphocytic																										1
Pancreatic, lymphoma malignant mixed																								X		2
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant lymphocytic																										1
Lymphoma malignant mixed																	X							X		4
Thymus	+	M	+	M	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	M	+	+	M	35
Lymphoma malignant lymphocytic																										1
INTEGUMENTARY SYSTEM																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Plasma cell tumor malignant																										1
Subcutaneous tissue, fibroma										X												X				4
Subcutaneous tissue, fibroma, multiple																X										1
Subcutaneous tissue, fibrosarcoma									X		X															2
Subcutaneous tissue, fibrosarcoma, multiple										X						X	X									4
Subcutaneous tissue, sarcoma																										1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle						+														+						5
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma			X	X		X								X	X						X		X			9
Alveolar/bronchiolar carcinoma																										1
Hepatocellular carcinoma, metastatic																										1
Hepatocellular carcinoma, metastatic, liver							X										X	X								3
Lymphoma malignant lymphocytic																										1
Lymphoma malignant mixed																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Trachea	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPECIAL SENSES SYSTEM																										
Harderian gland	+						+			+	+						+									6
Adenoma	X									X	X						X									5
Lacrimal gland																					+					1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																										1
Urethra																										2
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

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

WEEKS ON STUDY	073	074	077	079	080	080	083	085	088	088	090	091	092	093	096	096	096	100	100	102	104	104	104	105	105
CARCASS ID	2811	2711	2611	2511	3011	2822	3111	2833	3022	3311	3411	3211	2622	3122	2844	3422	2911	3133	3332	3033	3455	2992	2755	2552	2553
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	A	+	M	M	+	+	M	M	+	M	M	+	+	M	I	+	+	+	+	+	M	+	M	M
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cecum, lymphoma malignant lymphocytic																									
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Duodenum, adenocarcinoma																									
Duodenum, lymphoma malignant lymphocytic																									
Jejunum, adenocarcinoma																									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, multiple		X									X														
Hepatocellular carcinoma			X			X	X	X	X			X	X		X									X	
Hepatocellular carcinoma, multiple																X							X		
Hepatocellular adenoma																									
Lymphoma malignant histiocytic																									
Lymphoma malignant lymphocytic																									
Mesentery											+							+			+				
Hemangiosarcoma											X														
Pancreas	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Forestomach, papilloma squamous																				X					
Tooth																					+			+	+
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma	X																								
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortex, adenoma																			X						
Medulla, pheochromocytoma benign						X	X		X							X									
Islets, pancreatic	+	M	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	+	+	+	+	+	I	+	+	M	+	M	M	M	+	+	+	+	+	+	M	+	+	+	+
Pituitary gland	+	+	+	I	+	+	M	+	+	+	+	+	+	I	M	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma										X															
GENERAL BODY SYSTEM																									
Tissue, NOS														+											
GENITAL SYSTEM																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland		+			+								+					+			+				+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle															+		+	+	+				+		
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma																									

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

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	TOTAL
CARCASS ID	254	255	263	264	265	272	273	274	285	293	294	295	304	305	314	315	322	323	324	325	333	334	335	343	344	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	M	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	35
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cecum, lymphoma malig lymphocytic							X																			1
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Duodenum, adenocarcinoma							X																			1
Duodenum, lymphoma malignant lymphocytic							X																			1
Jejunum, adenocarcinoma	X																									1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma, multiple																										2
Hepatocellular carcinoma					X	X		X			X															13
Hepatocellular carcinoma, multiple		X																								3
Hepatocellular adenoma								X										X					X			3
Lymphoma malignant histiocytic																			X							1
Lymphoma malignant lymphocytic							X																			1
Mesentery										+						+			+							6
Hemangiosarcoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Forestomach, papilloma squamous																										1
Tooth	+						+	+			+	+				+									+	10
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma																										1
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortex, adenoma																										1
Medulla, pheochromocytoma benign																				X						5
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Parathyroid gland	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	40
Pituitary gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	44
Pars distalis, adenoma					X																					1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma																								X	X	3
GENERAL BODY SYSTEM																										
Tissue, NOS																								+		2
GENITAL SYSTEM																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Preputial gland	+							+			+	+	+			+	+								+	14
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	49
Seminal vesicle																										5
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell, adenoma														X												1

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

WEEKS ON STUDY	07 73	07 74	07 77	07 79	08 80	08 80	08 83	08 85	08 88	08 88	09 90	09 91	09 92	09 93	09 96	09 96	09 96	10 00	10 00	10 02	10 44	10 44	10 44	10 45	10 55
CARCASS ID	28 11	27 11	26 11	25 11	30 11	28 22	31 11	28 33	30 22	33 11	34 11	32 11	26 22	31 12	28 44	34 22	29 11	31 13	33 22	30 33	34 45	29 22	27 75	25 22	25 53
HEMATOPOIETIC SYSTEM																									
Blood																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma											X						X								
Lymphoma malignant histiocytic																									
Lymph node	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Mandibular, sarcoma	X																								
Spleen	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma											X														
Thymus	M	+	+	M	M	M	+	M	M	+	M	M	+	+	+	M	+	M	+	+	+	+	+	+	+
INTEGUMENTARY SYSTEM																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma																									
Subcutaneous tissue, fibrosarcoma													X										X		
Subcutaneous tissue, fibrosarcoma, multiple										X		X													
Subcutaneous tissue, hemangiosarcoma											X														
Subcutaneous tissue, sarcoma	X																								
Subcutaneous tissue, schwannoma malignant				X																					
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma												X			X	X							X	X	
Alveolar/bronchiolar adenoma, multiple																									
Alveolar/bronchiolar carcinoma																				X					
Alveolar/bronchiolar carcinoma, multiple																									
Hepatocellular carcinoma, metastatic, liver																							X		
Lymphoma malignant histiocytic																									
Sarcoma	X																								
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Harderian gland																			+			+			+
Adenoma																			X			X			X
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma	X																								
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+

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

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	TOTAL:
CARCASS ID	254	255	263	264	265	272	273	274	285	293	294	295	304	305	311	315	322	323	324	325	333	334	335	343	344	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Blood							+																			1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										2
Lymphoma malignant histiocytic																			X							1
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Mandibular, sarcoma																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																										1
Thymus	+	+	+	+	M	M	+	M	M	+	+	+	+	M	+	+	+	+	+	+	M	M	+	+	M	32
INTEGUMENTARY SYSTEM																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	
Skin	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Basal cell carcinoma																						X				1
Subcutaneous tissue, fibrosarcoma	X																			X						4
Subcutaneous tissue, fibrosarcoma, multiple				X																	X					4
Subcutaneous tissue, hemangiosarcoma																										1
Subcutaneous tissue, sarcoma			X																							2
Subcutaneous tissue, schwannoma malignant																										1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle		+																								1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma			X		X		X						X		X					X	X				X	13
Alveolar/bronchiolar adenoma, multiple																		X								1
Alveolar/bronchiolar carcinoma																										1
Alveolar/bronchiolar carcinoma, multiple							X																			1
Hepatocellular carcinoma, metastatic, liver																										1
Lymphoma malignant histiocytic																			X							1
Sarcoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Harderian gland																										3
Adenoma																										3
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	48

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

WEEKS ON STUDY	0 0 1	0 3 0	0 6 1	0 6 7	0 7 3	0 7 7	0 8 1	0 8 2	0 8 3	0 8 3	0 8 3	0 8 3	0 8 3	0 8 3	0 8 9	0 9 1	0 9 1	0 9 2	0 9 6	1 0 4	1 0 5	1 0 5	1 0 5	1 0 5
CARCASS ID	1 6 1	1 7 1	2 1 1	2 2 1	1 4 1	2 1 2	1 5 1	2 0 1	1 7 2	1 8 1	1 9 1	1 9 2	2 1 3	1 4 2	2 0 2	1 3 1	2 2 2	1 4 3	2 2 3	1 4 4	1 8 5	1 3 2	1 3 3	1 3 4	1 3 5
ALIMENTARY SYSTEM																								
Esophagus	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	A	+	M	+	+	M	M	+	+	+	+	+	+	M	M	M	+	M	+	M	+	+	+	+
Intestine large	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cecum, lymphoma malignant mixed																			X					
Intestine small	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Duodenum, adenocarcinoma																								
Duodenum, polyp adenomatous																								
Ileum, lymphoma malignant lymphocytic										X														
Ileum, lymphoma malignant mixed													X						X					
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma					X		X		X			X	X			X								X
Hepatocellular carcinoma, multiple																			X					
Hepatocellular adenoma										X												X		
Hepatocellular adenoma, multiple																								X
Lymphoma malignant lymphocytic										X														
Lymphoma malignant mixed														X					X					
Pheochromocytoma malignant, metastatic, adrenal gland																								
Mesentery										+			+	+										
Lymphoma malignant lymphocytic										X														
Lymphoma malignant mixed													X	X										
Pancreas	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic										X														
Lymphoma malignant mixed														X					X					
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed														X										
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Forestomach, papilloma squamous																							X	
Glandular, carcinoid tumor malignant																								
Tooth																				+	+			
Neoplasm, NOS																								
CARDIOVASCULAR SYSTEM																								
Blood vessel																								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																								
Adrenal gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																			X					
Medulla, pheochromocytoma malignant									X															
Medulla, pheochromocytoma benign																								
Islets, pancreatic	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Lymphoma malignant mixed														X										
Parathyroid gland	I	+	M	M	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	M	+	+	+	+
Pituitary gland	+	+	+	+	M	+	I	+	+	+	M	M	M	+	+	+	M	+	+	I	+	+	+	+
Pars distalis, adenoma																								
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Lymphoma malignant mixed														X										
GENERAL BODY SYSTEM																								
Tissue, NOS											+													
GENITAL SYSTEM																								
Coagulating gland																				+				
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Lymphoma malignant mixed														X										
Preputial gland												+		+			+						+	+
Prostate	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle												+								+			+	
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+

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

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	
CARCASS ID	145	152	153	154	155	162	163	164	165	173	174	175	182	183	184	193	194	195	203	204	205	214	215	224	225	TOTAL: TISSUES / TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+		48
Gallbladder	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	M	37
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Cecum, lymphoma malignant mixed																										1
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Duodenum, adenocarcinoma							X																			1
Duodenum, polyp adenomatous															X											1
Ileum, lymphoma malig. lymphocytic																										1
Ileum, lymphoma malignant mixed																										2
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Hepatocellular carcinoma					X																					8
Hepatocellular carcinoma, multiple				X																						2
Hepatocellular adenoma						X	X		X	X							X				X					8
Hepatocellular adenoma, multiple	X															X										3
Lymphoma malignant lymphocytic																										1
Lymphoma malignant mixed																										2
Pheochromocytoma malignant, metastatic, adrenal gland																X										1
Mesentery	+						+					+									+			+		8
Lymphoma malignant lymphocytic																										1
Lymphoma malignant mixed																										2
Pancreas	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Lymphoma malignant lymphocytic																										1
Lymphoma malignant mixed																										2
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Lymphoma malignant mixed																										1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Forestomach, papilloma squamous			X				X				X	X														5
Glandular, carcinoid tumor malignant																									X	1
Tooth									+	+																4
Neoplasm, NOS										X																1
CARDIOVASCULAR SYSTEM																										
Blood vessel							+																			1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Lymphoma malignant mixed																										1
Medulla, pheochromocytoma malignant																X										1
Medulla, pheochromocytoma benign																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Lymphoma malignant mixed																										1
Parathyroid gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		43
Pituitary gland	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	40
Pars distalis, adenoma				X																						1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Lymphoma malignant mixed																										1
GENERAL BODY SYSTEM																										
Tissue, NOS																										1
GENITAL SYSTEM																										
Coagulating gland																										1
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Lymphoma malignant mixed																										1
Preputial gland		+	+						+					+		+				M	+					11
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Seminal vesicle						+						+														5
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49

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

WEEKS ON STUDY	001	030	061	067	073	077	081	082	083	083	083	083	083	083	089	091	091	091	092	096	104	105	105	105	105
CARCASS ID	161	171	211	221	141	212	151	201	172	181	191	192	213	142	202	131	222	143	223	144	185	132	133	134	135
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bronchial, lymphoma malignant lymphocytic									X																
Bronchial, lymphoma malignant mixed													X												
Inguinal, lymphoma malignant lymphocytic									X																
Inguinal, lymphoma malignant mixed													X							X					
Mandibular, lymphoma malignant lymphocytic									X																
Mandibular, lymphoma malignant mixed												X	X							X					
Mandibular, sarcoma				X																					
Mediastinal, lymphoma malignant mixed												X	X							X					
Mesenteric, lymphoma malignant lymphocytic, multiple									X																
Mesenteric, lymphoma malignant mixed													X							X					
Mesenteric, lymphoma malignant mixed, multiple												X													
Pancreatic, lymphoma malignant mixed																				X					
Spleen	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic									X																
Lymphoma malignant mixed													X							X					
Lymphoma malignant mixed, multiple												X													
Thymus	+	+	+	+	M	+	+	+	M	M	M	+	M	M	+	+	M	+	M	+	M	+	+	I	+
INTEGUMENTARY SYSTEM																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma, multiple													X												
Papilloma																X									
Subcutaneous tissue, fibroma																						X			X
Subcutaneous tissue, fibroma, multiple																									
Subcutaneous tissue, fibrosarcoma								X																	
Subcutaneous tissue, fibrosarcoma, multiple			X																						X
Subcutaneous tissue, sarcoma, multiple				X																					
Subcutaneous tissue, schwannoma malignant, multiple																									
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle			+	+																					
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve	+	+	M	+	+	+	+	+	M	+	+	+	+	+	M	M	+	M	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma								X								X	X					X		X
Alveolar/bronchiolar adenoma, multiple																									
Alveolar/bronchiolar carcinoma																						X			
Hepatocellular carcinoma, metastatic, liver					X				X			X													
Lymphoma malignant mixed													X							X					
Pheochromocytoma malignant, metastatic, adrenal gland																									
Nose	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																				X					
Trachea	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Eye										M														+	
Harderian gland								+			+	+	+							+			+	+	
Adenoma											X	X											X	X	
Lymphoma malignant mixed													X							X					
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed													X							X					
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Lymphoma malignant mixed													X							X					

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

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	
CARCASS ID	145	152	153	154	155	162	163	164	165	173	174	175	182	183	184	193	194	195	203	204	205	214	215	224	225	TOTAL TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bronchial, lymphoma malignant lymphocytic																										1
Bronchial, lymphoma malignant mixed																										1
Inguinal, lymphoma malignant lymphocytic																										1
Inguinal, lymphoma malignant mixed																										2
Mandibular, lymphoma malignant lymphocytic																										1
Mandibular, lymphoma malig mixed																										3
Mandibular, sarcoma																										1
Mediastinal, lymphoma malig mixed																										3
Mesenteric, lymphoma malignant lymphocytic, multiple																										1
Mesenteric, lymphoma malignant mixed																										2
Mesenteric, lymphoma malignant mixed, multiple																										1
Pancreatic, lymphoma malignant mixed																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant lymphocytic																										1
Lymphoma malignant mixed																										2
Lymphoma malignant mixed, multiple																										1
Thymus	M	+	+	+	+	M	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	36
INTEGUMENTARY SYSTEM																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma, multiple																										1
Papilloma																										1
Subcutaneous tissue, fibroma																										2
Subcutaneous tissue, fibroma, multiple															X											1
Subcutaneous tissue, fibrosarcoma																X				X					X	4
Subcutaneous tissue, fibrosarcoma, multiple						X																				3
Subcutaneous tissue, sarcoma, multiple																										1
Subcutaneous tissue, schwannoma malignant, multiple	X																									1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	–	–	+	+	+	+	47
Skeletal muscle									+																+	4
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	M	+	+	42
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma													X	X			X									8
Alveolar/bronchiolar adenoma, multiple				X																						1
Alveolar/bronchiolar carcinoma																									X	2
Hepatocellular carcinoma, metastatic, liver																										3
Lymphoma malignant mixed																										2
Pheochromocytoma malignant, metastatic, adrenal gland																X										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymphoma malignant mixed																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPECIAL SENSES SYSTEM																										
Eye																										1
Harderian gland		+																								8
Adenoma		X																								5
Lymphoma malignant mixed																										2
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed																										2
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant mixed																										2

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

	Vehicle Control	10 mg/kg	20 mg/kg
Adrenal Gland: Pheochromocytoma			
Overall Rates (a)	2/48 (4%)	5/50 (10%)	1/49 (2%)
Adjusted Rates (b)	6.1%	12.7%	2.4%
Terminal Rates (c)	2/33 (6%)	1/27 (4%)	0/29 (0%)
Day of First Observation	729	559	578
Life Table Tests (d)	P=0.445N	P=0.201	P=0.527N
Logistic Regression Tests (d)	P=0.405N	P=0.226	P=0.492N
Cochran-Armitage Trend Test (d)	P=0.402N		
Fisher Exact Test (d)		P=0.235	P=0.492N
Adrenal Gland: Pheochromocytoma or Malignant Pheochromocytoma			
Overall Rates (a)	2/48 (4%)	5/50 (10%)	2/49 (4%)
Adjusted Rates (b)	6.1%	12.7%	5.7%
Terminal Rates (c)	2/33 (6%)	1/27 (4%)	1/29 (3%)
Day of First Observation	729	559	578
Life Table Tests (d)	P=0.545	P=0.201	P=0.661
Logistic Regression Tests (d)	P=0.574N	P=0.226	P=0.691N
Cochran-Armitage Trend Test (d)	P=0.574N		
Fisher Exact Test (d)		P=0.235	P=0.684N
Harderian Gland: Adenoma			
Overall Rates (a)	5/50 (10%)	3/50 (6%)	5/50 (10%)
Adjusted Rates (b)	13.4%	9.8%	14.6%
Terminal Rates (c)	4/35 (11%)	1/27 (4%)	3/29 (10%)
Day of First Observation	541	694	578
Life Table Tests (d)	P=0.483	P=0.464N	P=0.548
Logistic Regression Tests (d)	P=0.564	P=0.336N	P=0.627
Cochran-Armitage Trend Test (d)	P=0.571		
Fisher Exact Test (d)		P=0.357N	P=0.630N
Liver: Hepatocellular Adenoma			
Overall Rates (a)	7/50 (14%)	3/50 (6%)	11/50 (22%)
Adjusted Rates (b)	20.0%	11.1%	36.0%
Terminal Rates (c)	7/35 (20%)	3/27 (11%)	10/29 (34%)
Day of First Observation	729	729	578
Life Table Tests (d)	P=0.080	P=0.277N	P=0.107
Logistic Regression Tests (d)	P=0.093	P=0.277N	P=0.134
Cochran-Armitage Trend Test (d)	P=0.157		
Fisher Exact Test (d)		P=0.159N	P=0.218
Liver: Hepatocellular Carcinoma			
Overall Rates (a)	10/50 (20%)	16/50 (32%)	10/50 (20%)
Adjusted Rates (b)	25.9%	40.0%	25.1%
Terminal Rates (c)	7/35 (20%)	6/27 (22%)	3/29 (10%)
Day of First Observation	543	534	505
Life Table Tests (d)	P=0.420	P=0.087	P=0.491
Logistic Regression Tests (d)	P=0.546N	P=0.137	P=0.598N
Cochran-Armitage Trend Test (d)	P=0.547N		
Fisher Exact Test (d)		P=0.127	P=0.598N
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	16/50 (32%)	18/50 (36%)	20/50 (40%)
Adjusted Rates (b)	41.8%	45.8%	52.3%
Terminal Rates (c)	13/35 (37%)	8/27 (30%)	12/29 (41%)
Day of First Observation	543	534	505
Life Table Tests (d)	P=0.128	P=0.245	P=0.141
Logistic Regression Tests (d)	P=0.229	P=0.471	P=0.253
Cochran-Armitage Trend Test (d)	P=0.233		
Fisher Exact Test (d)		P=0.417	P=0.266

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

	Vehicle Control	10 mg/kg	20 mg/kg
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	9/50 (18%)	14/50 (28%)	9/50 (18%)
Adjusted Rates (b)	24.7%	44 1%	27.0%
Terminal Rates (c)	8/35 (23%)	10/27 (37%)	6/29 (21%)
Day of First Observation	543	637	573
Life Table Tests (d)	P=0 375	P=0 064	P=0.463
Logistic Regression Tests (d)	P=0.492	P=0.171	P=0.573
Cochran-Armitage Trend Test (d)	P=0.549		
Fisher Exact Test (d)		P=0.171	P=0 602N
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	10/50 (20%)	15/50 (30%)	10/50 (20%)
Adjusted Rates (b)	26.6%	45.9%	30 1%
Terminal Rates (c)	8/35 (23%)	10/27 (37%)	7/29 (24%)
Day of First Observation	543	637	573
Life Table Tests (d)	P=0 368	P=0.074	P=0 452
Logistic Regression Tests (d)	P=0.498	P=0.193	P=0 576
Cochran-Armitage Trend Test (d)	P=0.547		
Fisher Exact Test (d)		P=0.178	P=0 598N
Subcutaneous Tissue: Fibroma			
Overall Rates (a)	5/50 (10%)	0/50 (0%)	3/50 (6%)
Adjusted Rates (b)	13.8%	0.0%	10.3%
Terminal Rates (c)	4/35 (11%)	0/27 (0%)	3/29 (10%)
Day of First Observation	690		729
Life Table Tests (d)	P=0.336N	P=0.058N	P=0.465N
Logistic Regression Tests (d)	P=0.308N	P=0.035N	P=0.433N
Cochran-Armitage Trend Test (d)	P=0 252N		
Fisher Exact Test (d)		P=0.028N	P=0.357N
Subcutaneous Tissue: Fibrosarcoma			
Overall Rates (a)	6/50 (12%)	8/50 (16%)	7/50 (14%)
Adjusted Rates (b)	16.6%	23.9%	20.9%
Terminal Rates (c)	5/35 (14%)	4/27 (15%)	5/29 (17%)
Day of First Observation	690	616	422
Life Table Tests (d)	P=0.326	P=0.265	P=0.386
Logistic Regression Tests (d)	P=0.429	P=0.408	P=0 486
Cochran-Armitage Trend Test (d)	P=0.443		
Fisher Exact Test (d)		P=0.387	P=0.500
Subcutaneous Tissue: Sarcoma or Fibrosarcoma			
Overall Rates (a)	7/50 (14%)	10/50 (20%)	8/50 (16%)
Adjusted Rates (b)	19.4%	28.7%	22.5%
Terminal Rates (c)	6/35 (17%)	5/27 (19%)	5/29 (17%)
Day of First Observation	690	511	422
Life Table Tests (d)	P=0 328	P=0.187	P=0 385
Logistic Regression Tests (d)	P=0.445	P=0.328	P=0.496
Cochran-Armitage Trend Test (d)	P=0.447		
Fisher Exact Test (d)		P=0.298	P=0.500
Subcutaneous Tissue: Fibroma or Fibrosarcoma			
Overall Rates (a)	8/50 (16%)	8/50 (16%)	9/50 (18%)
Adjusted Rates (b)	22.2%	23.9%	27.4%
Terminal Rates (c)	7/35 (20%)	4/27 (15%)	7/29 (24%)
Day of First Observation	690	616	422
Life Table Tests (d)	P=0.312	P=0.447	P=0.358
Logistic Regression Tests (d)	P=0 421	P=0.591	P=0.469
Cochran-Armitage Trend Test (d)	P=0.447		
Fisher Exact Test (d)		P=0.607	P=0.500

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

	Vehicle Control	10 mg/kg	20 mg/kg
Subcutaneous Tissue: Fibroma, Sarcoma, or Fibrosarcoma			
Overall Rates (a)	9/50 (18%)	10/50 (20%)	10/50 (20%)
Adjusted Rates (b)	24.9%	28.7%	29.0%
Terminal Rates (c)	8/35 (23%)	5/27 (19%)	7/29 (24%)
Day of First Observation	690	511	422
Life Table Tests (d)	P=0.313	P=0.336	P=0.358
Logistic Regression Tests (d)	P=0.442	P=0.538	P=0.486
Cochran-Armitage Trend Test (d)	P=0.450		
Fisher Exact Test (d)		P=0.500	P=0.500
Forestomach: Squamous Papilloma			
Overall Rates (a)	1/50 (2%)	1/50 (2%)	5/50 (10%)
Adjusted Rates (b)	2.9%	3.2%	17.2%
Terminal Rates (c)	1/35 (3%)	0/27 (0%)	5/29 (17%)
Day of First Observation	729	714	729
Life Table Tests (d)	P=0.033	P=0.718	P=0.064
Logistic Regression Tests (d)	P=0.032	P=0.753	P=0.067
Cochran-Armitage Trend Test (d)	P=0.049		
Fisher Exact Test (d)		P=0.753N	P=0.102
Thyroid Gland: Follicular Cell Adenoma			
Overall Rates (a)	0/45 (0%)	3/50 (6%)	0/49 (0%)
Adjusted Rates (b)	0.0%	9.6%	0.0%
Terminal Rates (c)	0/31 (0%)	2/27 (7%)	0/29 (0%)
Day of First Observation		616	
Life Table Tests (d)	P=0.621	P=0.112	(e)
Logistic Regression Tests (d)	P=0.625N	P=0.146	(e)
Cochran-Armitage Trend Test (d)	P=0.618N		
Fisher Exact Test (d)		P=0.142	(e)
All Sites: Hemangiosarcoma			
Overall Rates (a)	2/50 (4%)	3/50 (6%)	0/50 (0%)
Adjusted Rates (b)	5.7%	7.3%	0.0%
Terminal Rates (c)	2/35 (6%)	0/27 (0%)	0/29 (0%)
Day of First Observation	729	514	
Life Table Tests (d)	P=0.243N	P=0.458	P=0.280N
Logistic Regression Tests (d)	P=0.202N	P=0.490	P=0.272N
Cochran-Armitage Trend Test (d)	P=0.202N		
Fisher Exact Test (d)		P=0.500	P=0.247N
All Sites: Hemangioma or Hemangiosarcoma			
Overall Rates (a)	3/50 (6%)	3/50 (6%)	0/50 (0%)
Adjusted Rates (b)	8.6%	7.3%	0.0%
Terminal Rates (c)	3/35 (9%)	0/27 (0%)	0/29 (0%)
Day of First Observation	729	514	
Life Table Tests (d)	P=0.135N	P=0.604	P=0.156N
Logistic Regression Tests (d)	P=0.100N	P=0.662N	P=0.148N
Cochran-Armitage Trend Test (d)	P=0.101N		
Fisher Exact Test (d)		P=0.661N	P=0.121N
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	7/50 (14%)	2/50 (4%)	4/50 (8%)
Adjusted Rates (b)	17.8%	7.4%	10.3%
Terminal Rates (c)	4/35 (11%)	2/27 (7%)	0/29 (0%)
Day of First Observation	527	729	578
Life Table Tests (d)	P=0.250N	P=0.127N	P=0.333N
Logistic Regression Tests (d)	P=0.188N	P=0.074N	P=0.262N
Cochran-Armitage Trend Test (d)	P=0.187N		
Fisher Exact Test (d)		P=0.080N	P=0.262N

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DICHLORVOS (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 logistic regression 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 20 mg/kg and vehicle control groups.

TABLE C4. HISTORICAL INCIDENCE OF STOMACH SQUAMOUS CELL TUMORS IN MALE B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls		
	Papilloma	Carcinoma	Papilloma or Carcinoma
Historical Incidence at Southern Research Institute			
Ethyl acrylate	0/48	0/48	0/48
Benzyl acetate	3/49	1/49	4/49
Allyl isovalerate	0/50	0/50	0/50
HC Red No. 3	0/50	0/50	0/50
Chlorinated paraffins (43% chlorine)	0/50	0/50	0/50
Chlorinated paraffins (60% chlorine)	0/50	0/50	0/50
Allyl isothiocyanate	0/49	0/49	0/49
Geranyl acetate	0/50	0/50	0/50
TOTAL	3/396 (0.8%)	1/396 (0.3%)	4/396 (1.0%)
SD (b)	2.16%	0.72%	2.89%
Range (c)			
High	3/49	1/49	4/49
Low	0/50	0/50	0/50
Overall Historical Incidence			
TOTAL	17/1,703 (1.0%)	(d) 6/1,703 (0.4%)	23/1,703 (1.4%)
SD (b)	1.85%	0.79%	2.08%
Range (c)			
High	3/49	1/46	4/49
Low	0/50	0/50	0/50

(a) Data as of August 7, 1986, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.
(d) One squamous cell carcinoma, in situ, was also observed; the inclusion of this tumor would not affect the reported range.

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

	Vehicle Control	Low Dose	High Dose
Animals initially in study	50	50	50
Animals removed	50	50	50
Animals examined histopathologically	50	50	50
ALIMENTARY SYSTEM			
Gallbladder	(40)	(35)	(37)
Amyloid deposition		1 (3%)	
Concretion	2 (5%)		
Hemorrhage	1 (3%)		
Inflammation, suppurative	1 (3%)	1 (3%)	
Intestine large	(49)	(50)	(49)
Cecum, hyperplasia, lymphoid	2 (4%)		
Cecum, mucosa, fibrosis	1 (2%)		
Cecum, serosa, ectopic tissue			1 (2%)
Intestine small	(48)	(50)	(49)
Duodenum, ulcer		1 (2%)	
Ileum, Peyer's patch, hyperplasia, lymphoid	3 (6%)	2 (4%)	3 (6%)
Mucosa, ileum, dysplasia	1 (2%)		
Serosa, jejunum, cyst		1 (2%)	
Serosa, jejunum, inflammation, granulomatous		1 (2%)	
Liver	(50)	(50)	(50)
Amyloid deposition	1 (2%)		
Angiectasis			1 (2%)
Clear cell focus	2 (4%)	1 (2%)	2 (4%)
Eosinophilic focus			1 (2%)
Hematopoietic cell proliferation	3 (6%)	3 (6%)	4 (8%)
Hyperplasia, focal			1 (2%)
Inflammation, chronic	2 (4%)	3 (6%)	5 (10%)
Inflammation, chronic active		1 (2%)	
Mineralization			1 (2%)
Bile duct, cyst		1 (2%)	
Hepatocyte, anisokaryosis	1 (2%)		
Hepatocyte, cytomegaly	2 (4%)		
Hepatocyte, cytoplasmic alteration		2 (4%)	
Hepatocyte, karyomegaly	3 (6%)	2 (4%)	2 (4%)
Hepatocyte, necrosis	3 (6%)	4 (8%)	3 (6%)
Hepatocyte, vacuolization cytoplasmic	7 (14%)	6 (12%)	10 (20%)
Kupffer cell, hyperplasia	3 (6%)	2 (4%)	1 (2%)
Kupffer cell, pigmentation	3 (6%)		1 (2%)
Vein, thrombus			1 (2%)
Vein, adventitia, fibrosis			1 (2%)
Mesentery	(5)	(6)	(8)
Fibrosis			1 (13%)
Hemorrhage		1 (17%)	
Inflammation, suppurative	1 (20%)		
Mineralization		1 (17%)	1 (13%)
Artery, inflammation, chronic			1 (13%)
Artery, necrosis		1 (17%)	
Artery, thrombus		1 (17%)	
Fat, necrosis, focal	1 (20%)	3 (50%)	3 (38%)
Pancreas	(50)	(48)	(48)
Atrophy	1 (2%)	1 (2%)	
Atypical cells, focal	1 (2%)		
Cyst		2 (4%)	
Hyperplasia, focal		1 (2%)	
Inflammation, chronic	1 (2%)	2 (4%)	2 (4%)
Inflammation, suppurative		1 (2%)	
Artery, inflammation, chronic		1 (2%)	
Salivary glands	(50)	(50)	(50)
Inflammation, chronic	13 (26%)	8 (16%)	8 (16%)

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

	Vehicle Control	Low Dose	High Dose
ALIMENTARY SYSTEM (Continued)			
Stomach	(50)	(50)	(50)
Forestomach, cyst	1 (2%)		
Forestomach, hyperplasia	10 (20%)	5 (10%)	9 (18%)
Forestomach, inflammation, chronic	3 (6%)	1 (2%)	1 (2%)
Forestomach, inflammation, chronic active	4 (8%)	2 (4%)	2 (4%)
Forestomach, inflammation, suppurative		1 (2%)	
Forestomach, mineralization	1 (2%)	1 (2%)	
Forestomach, ulcer	2 (4%)		
Forestomach, mucosa, hyperplasia	1 (2%)		
Glandular, cyst	1 (2%)		1 (2%)
Glandular, dysplasia	2 (4%)		
Glandular, erosion		2 (4%)	
Glandular, inflammation, chronic active	1 (2%)		
Glandular, inflammation, suppurative	3 (6%)	2 (4%)	
Glandular, metaplasia, squamous	1 (2%)		
Glandular, mineralization	2 (4%)	3 (6%)	3 (6%)
Tooth	(7)	(10)	(4)
Developmental malformation	4 (57%)	10 (100%)	3 (75%)
Foreign body		1 (10%)	
Peridontal tissue, fibrosis	1 (14%)		
Peridontal tissue, inflammation, chronic active	2 (29%)	1 (10%)	
Peridontal tissue, inflammation, suppurative	1 (14%)	2 (20%)	
Pulp, inflammation, suppurative		2 (20%)	
CARDIOVASCULAR SYSTEM			
Blood vessel	(3)		(1)
Inflammation, chronic active	1 (33%)		1 (100%)
Aorta, embolus bacterial	2 (67%)		
Aorta, inflammation, chronic active	1 (33%)		
Heart	(50)	(50)	(50)
Embolus bacterial	1 (2%)		
Thrombus	1 (2%)		
Coronary artery, inflammation, chronic		2 (4%)	1 (2%)
Coronary artery, inflammation, chronic active			1 (2%)
Coronary artery, inflammation, suppurative	1 (2%)		
Coronary artery, necrosis, fibrinoid	1 (2%)		
Endocardium, inflammation, chronic	1 (2%)		
Epicardium, fibrosis	1 (2%)		
Epicardium, inflammation, chronic	1 (2%)		
Myocardium, fibrosis	1 (2%)		
Myocardium, inflammation, chronic	1 (2%)	2 (4%)	
Myocardium, inflammation, suppurative	1 (2%)		
ENDOCRINE SYSTEM			
Adrenal gland	(48)	(50)	(49)
Developmental malformation	1 (2%)	1 (2%)	2 (4%)
Cortex, atrophy			1 (2%)
Cortex, hyperplasia	1 (2%)		
Cortex, hyperplasia, focal	2 (4%)	4 (8%)	1 (2%)
Cortex, infiltration cellular, lymphocytic	1 (2%)		
Cortex, vacuolization cytoplasmic		2 (4%)	
Medulla, hyperplasia	2 (4%)	1 (2%)	2 (4%)
Spindle cell, hyperplasia	27 (56%)	27 (54%)	21 (43%)

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

	Vehicle Control	Low Dose	High Dose
ENDOCRINE SYSTEM (Continued)			
Islets, pancreatic	(50)	(47)	(48)
Dysplasia	1 (2%)		
Hyperplasia	15 (30%)	13 (28%)	7 (15%)
Infiltration cellular, lymphocytic		1 (2%)	
Parathyroid gland	(28)	(40)	(43)
Crystals			1 (2%)
Cyst		1 (3%)	2 (5%)
Infiltration cellular, lymphocytic	1 (4%)		1 (2%)
Pituitary gland	(40)	(44)	(40)
Pars distalis, cyst	3 (8%)	4 (9%)	
Pars distalis, hyperplasia		2 (5%)	1 (3%)
Thyroid gland	(45)	(50)	(49)
Infiltration cellular, lymphocytic	1 (2%)		
Mineralization			1 (2%)
Follicle, crystals	1 (2%)		
Follicle, dilatation	5 (11%)	3 (6%)	3 (6%)
Follicular cell, hyperplasia	4 (9%)	3 (6%)	2 (4%)
GENERAL BODY SYSTEM			
Tissue, NOS	(2)	(2)	(1)
Foreign body	1 (50%)		
Hemorrhage	1 (50%)	1 (50%)	
Inflammation, suppurative	1 (50%)		
GENITAL SYSTEM			
Coagulating gland	(2)		(1)
Dilatation	1 (50%)		1 (100%)
Epididymis	(50)	(49)	(49)
Fibrosis		1 (2%)	
Inflammation, chronic	1 (2%)		1 (2%)
Inflammation, granulomatous		1 (2%)	
Preputial gland	(20)	(14)	(11)
Ectasia	14 (70%)	12 (86%)	5 (45%)
Inflammation, chronic	10 (50%)	6 (43%)	7 (64%)
Inflammation, chronic active	1 (5%)		
Inflammation, suppurative	9 (45%)	3 (21%)	5 (45%)
Prostate	(47)	(49)	(49)
Dilatation		1 (2%)	
Inflammation, chronic	7 (15%)	4 (8%)	2 (4%)
Inflammation, suppurative	4 (9%)	3 (6%)	1 (2%)
Seminal vesicle	(5)	(5)	(5)
Amyloid deposition	1 (20%)		
Dilatation	1 (20%)		1 (20%)
Fibrosis	2 (40%)	1 (20%)	2 (40%)
Inflammation, chronic	1 (20%)		1 (20%)
Inflammation, chronic active			1 (20%)
Inflammation, suppurative	2 (40%)	3 (60%)	
Pigmentation		1 (20%)	
Testes	(50)	(50)	(49)
Artery, mineralization	1 (2%)		
Seminiferous tubule, atrophy	3 (6%)	7 (14%)	2 (4%)
Seminiferous tubule, mineralization	4 (8%)	4 (8%)	3 (6%)

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

	Vehicle Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM			
Bone marrow	(50)	(50)	(50)
Congestion	1 (2%)		
Hyperplasia	9 (18%)	7 (14%)	10 (20%)
Hyperplasia, histiocyte	1 (2%)		
Pigmentation	1 (2%)		
Lymph node	(47)	(48)	(50)
Iliac, hyperplasia, plasma cell	1 (2%)		
Inguinal, fibrosis	1 (2%)		
Inguinal, hyperplasia, histiocyte	2 (4%)	1 (2%)	2 (4%)
Inguinal, hyperplasia, plasma cell		1 (2%)	2 (4%)
Inguinal, infiltration cellular, polymorphonuclear		1 (2%)	
Inguinal, pigmentation		4 (8%)	4 (8%)
Lymphatic, mandibular, ectasia			1 (2%)
Mandibular, hyperplasia, lymphoid		1 (2%)	1 (2%)
Mandibular, hyperplasia, plasma cell	1 (2%)	2 (4%)	5 (10%)
Mandibular, pigmentation		2 (4%)	
Mesenteric, angiectasis		2 (4%)	1 (2%)
Mesenteric, atrophy	1 (2%)	1 (2%)	1 (2%)
Mesenteric, congestion			1 (2%)
Mesenteric, hematopoietic cell proliferation	4 (9%)	6 (13%)	4 (8%)
Mesenteric, hemorrhage	19 (40%)	14 (29%)	14 (28%)
Mesenteric, hyperplasia, histiocyte	1 (2%)		1 (2%)
Mesenteric, hyperplasia, lymphoid	1 (2%)		3 (6%)
Mesenteric, hyperplasia, plasma cell		1 (2%)	1 (2%)
Mesenteric, infiltration cellular, mast cell			1 (2%)
Mesenteric, infiltration cellular, megakaryocyte			1 (2%)
Mesenteric, infiltration cellular, polymorphonuclear		1 (2%)	
Mesenteric, lymphatic, ectasia		2 (4%)	
Renal, hemorrhage		1 (2%)	
Renal, hyperplasia, histiocyte			1 (2%)
Renal, hyperplasia, plasma cell		1 (2%)	
Renal, lymphatic, ectasia		1 (2%)	
Spleen	(49)	(49)	(49)
Hematopoietic cell proliferation granulocytic	2 (4%)	4 (8%)	5 (10%)
Hematopoietic cell proliferation erythrocytic	10 (20%)	10 (20%)	9 (18%)
Hyperplasia, lymphoid	2 (4%)	3 (6%)	1 (2%)
Hyperplasia, megakaryocyte		1 (2%)	
Hyperplasia, plasma cell			1 (2%)
Necrosis, focal			1 (2%)
Lymphoid follicle, atrophy		1 (2%)	
Thymus	(35)	(32)	(36)
Atrophy		1 (3%)	
Cyst	3 (9%)	7 (22%)	7 (19%)
INTEGUMENTARY SYSTEM			
Skin	(50)	(49)	(50)
Acanthosis	12 (24%)	16 (33%)	17 (34%)
Acanthosis, multiple		1 (2%)	
Edema		3 (6%)	1 (2%)
Erosion			2 (4%)
Exudate	1 (2%)	1 (2%)	2 (4%)
Fibrosis	3 (6%)	3 (6%)	1 (2%)
Foreign body			1 (2%)
Fungus		1 (2%)	1 (2%)

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

	Vehicle Control	Low Dose	High Dose
INTEGUMENTARY SYSTEM			
Skin (Continued)	(50)	(49)	(50)
Hyperkeratosis			1 (2%)
Inflammation, chronic	4 (8%)	7 (14%)	7 (14%)
Inflammation, chronic active	1 (2%)	1 (2%)	3 (6%)
Inflammation, chronic active, multiple	1 (2%)		
Inflammation, granulomatous		2 (4%)	2 (4%)
Inflammation, suppurative	1 (2%)	3 (6%)	1 (2%)
Ulcer	1 (2%)	2 (4%)	6 (12%)
Lymphatic, angiectasis		1 (2%)	
Sebaceous gland, hyperplasia			1 (2%)
Subcutaneous tissue, fibrosis			1 (2%)
MUSCULOSKELETAL SYSTEM			
Bone	(50)	(50)	(47)
Dysplasia		2 (4%)	
Necrosis	1 (2%)		1 (2%)
Proliferation	1 (2%)		
Skeletal muscle	(5)	(1)	(4)
Foreign body			1 (25%)
Hemorrhage			1 (25%)
Inflammation, chronic	2 (40%)	1 (100%)	1 (25%)
Inflammation, chronic active	1 (20%)		
Inflammation, granulomatous			1 (25%)
Inflammation, suppurative	2 (40%)		1 (25%)
NERVOUS SYSTEM			
Brain	(50)	(50)	(50)
Cerebrum, vacuolization cytoplasmic			1 (2%)
Hippocampus, infiltration cellular, lymphocytic			1 (2%)
Thalamus, mineralization	20 (40%)	26 (52%)	25 (50%)
Venule, infiltration cellular, lymphocytic	1 (2%)		
Peripheral nerve	(40)	(50)	(42)
Degeneration		1 (2%)	1 (2%)
Inflammation, chronic	1 (3%)		2 (5%)
Inflammation, subacute	4 (10%)		2 (5%)
RESPIRATORY SYSTEM			
Lung	(50)	(50)	(50)
Hemorrhage		1 (2%)	3 (6%)
Infiltration cellular, eosinophilic			1 (2%)
Infiltration cellular, histiocytic	3 (6%)	8 (16%)	5 (10%)
Inflammation, chronic	27 (54%)	10 (20%)	17 (34%)
Inflammation, suppurative	1 (2%)	2 (4%)	9 (18%)
Thrombus	1 (2%)		1 (2%)
Alveolar epithelium, hyperplasia	1 (2%)	4 (8%)	
Artery, mineralization	1 (2%)		
Bronchus, foreign body			1 (2%)
Capillary, infiltration cellular, polymorphonuclear			1 (2%)
Glands, ectasia		1 (2%)	
Interstitium, edema	4 (8%)	4 (8%)	3 (6%)
Pleura, inflammation, suppurative	1 (2%)		

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

	Vehicle Control	Low Dose	High Dose
RESPIRATORY SYSTEM (Continued)			
Nose	(46)	(50)	(48)
Fungus			2 (4%)
Inflammation, chronic	1 (2%)		
Inflammation, suppurative	16 (35%)	5 (10%)	16 (33%)
Glands, cyst		1 (2%)	
Mucosa, metaplasia, squamous			1 (2%)
Trachea	(49)	(50)	(49)
Hemorrhage			1 (2%)
Submucosa, cyst			1 (2%)
SPECIAL SENSES SYSTEM			
Eye			(1)
Cornea, hyperplasia			1 (100%)
Cornea, inflammation, chronic active			1 (100%)
Harderian gland	(6)	(3)	(8)
Cyst			1 (13%)
Inflammation, chronic	1 (17%)		1 (13%)
Lacrimal gland	(1)		
Inflammation, chronic	1 (100%)		
URINARY SYSTEM			
Kidney	(50)	(50)	(50)
Amyloid deposition	1 (2%)		
Bacterium	1 (2%)		1 (2%)
Calculus micro observation only	1 (2%)		
Casts	5 (10%)	11 (22%)	5 (10%)
Congestion		1 (2%)	
Cyst	3 (6%)	8 (16%)	2 (4%)
Glomerulosclerosis		4 (8%)	3 (6%)
Hydronephrosis		1 (2%)	1 (2%)
Infarct	1 (2%)		1 (2%)
Inflammation, chronic	29 (58%)	27 (54%)	26 (52%)
Inflammation, chronic active		1 (2%)	
Inflammation, suppurative	3 (6%)	2 (4%)	3 (6%)
Metaplasia, osseous	1 (2%)	2 (4%)	
Cortex, necrosis			1 (2%)
Renal tubule, atrophy	2 (4%)	4 (8%)	4 (8%)
Renal tubule, degeneration	1 (2%)		
Renal tubule, dilatation	2 (4%)		
Renal tubule, mineralization	2 (4%)	3 (6%)	1 (2%)
Renal tubule, regeneration	26 (52%)	24 (48%)	22 (44%)
Renal tubule, vacuolization cytoplasmic	1 (2%)		
Urethra	(2)		
Angiectasis	1 (50%)		
Inflammation, chronic active	1 (50%)		
Inflammation, suppurative	1 (50%)		
Urinary bladder	(50)	(48)	(49)
Angiectasis	1 (2%)		
Calculus gross observation	1 (2%)		
Calculus micro observation only			2 (4%)
Edema		1 (2%)	
Fibrosis			1 (2%)
Hemorrhage			1 (2%)
Inflammation, chronic	4 (8%)	4 (8%)	2 (4%)
Inflammation, chronic active	1 (2%)	1 (2%)	
Inflammation, suppurative	1 (2%)		1 (2%)
Mineralization		1 (2%)	
Mucosa, hyperplasia	2 (4%)	1 (2%)	

APPENDIX D

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

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

	Vehicle Control	Low Dose	High Dose
Animals initially in study	50	50	50
Animals removed	50	50	50
Animals examined histopathologically	50	50	50
ALIMENTARY SYSTEM			
Intestine large	(49)	(50)	(50)
Rectum, lymphoma malignant lymphocytic	1 (2%)		
Intestine small	(46)	(49)	(48)
Ileum, lymphoma malignant mixed	1 (2%)		
Jejunum, fibrous histiocytoma	1 (2%)		
Jejunum, lymphoma malignant lymphocytic	1 (2%)	1 (2%)	
Jejunum, lymphoma malignant mixed		2 (4%)	1 (2%)
Jejunum, lymphoma malignant undifferentiated cell type	1 (2%)		
Liver	(50)	(50)	(50)
Fibrous histiocytoma	1 (2%)		
Hemangiosarcoma, multiple	1 (2%)		
Hepatocellular carcinoma	4 (8%)	3 (6%)	3 (6%)
Hepatocellular adenoma	2 (4%)	1 (2%)	4 (8%)
Lymphoma malignant histiocytic	2 (4%)		1 (2%)
Lymphoma malignant lymphocytic	4 (8%)	1 (2%)	
Lymphoma malignant mixed	2 (4%)	4 (8%)	2 (4%)
Lymphoma malignant undifferentiated cell type	1 (2%)		
Osteosarcoma, metastatic, bone			1 (2%)
Mesentery	*(50)	*(50)	*(50)
Fibrous histiocytoma, multiple	1 (2%)		
Lymphoma malignant lymphocytic	2 (4%)	2 (4%)	
Lymphoma malignant mixed	1 (2%)	1 (2%)	1 (2%)
Lymphoma malignant mixed, multiple		1 (2%)	
Lymphoma malignant undifferentiated cell type	1 (2%)		
Pancreas	(47)	(49)	(49)
Adenoma			1 (2%)
Fibrous histiocytoma	1 (2%)		
Lymphoma malignant lymphocytic	2 (4%)	1 (2%)	
Lymphoma malignant mixed	3 (6%)	1 (2%)	
Lymphoma malignant undifferentiated cell type	1 (2%)		
Salivary glands	(49)	(50)	(50)
Lymphoma malignant lymphocytic	2 (4%)		
Lymphoma malignant mixed	2 (4%)	1 (2%)	
Stomach	(49)	(49)	(50)
Fibrous histiocytoma	1 (2%)		
Lymphoma malignant lymphocytic	2 (4%)	1 (2%)	
Forestomach, papilloma squamous	5 (10%)	6 (12%)	18 (36%)
Forestomach, squamous cell carcinoma			2 (4%)
CARDIOVASCULAR SYSTEM			
Heart	(50)	(50)	(50)
Lymphoma malignant histiocytic	2 (4%)		
Lymphoma malignant lymphocytic	1 (2%)		
Lymphoma malignant mixed		1 (2%)	1 (2%)
ENDOCRINE SYSTEM			
Adrenal gland	(50)	(49)	(50)
Lymphoma malignant lymphocytic	2 (4%)	1 (2%)	
Lymphoma malignant undifferentiated cell type	1 (2%)		
Medulla, pheochromocytoma benign	4 (8%)	1 (2%)	

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

	Vehicle Control	Low Dose	High Dose
ENDOCRINE SYSTEM (Continued)			
Islets, pancreatic	(46)	(49)	(49)
Adenoma	1 (2%)		
Lymphoma malignant mixed	2 (4%)		1 (2%)
Pituitary gland	(45)	(45)	(44)
Pars distalis, adenoma	11 (24%)	6 (13%)	6 (14%)
Pars distalis, carcinoma	1 (2%)		
Pars intermedia, adenoma	2 (4%)	1 (2%)	
Thyroid gland	(49)	(48)	(50)
Lymphoma malignant lymphocytic	2 (4%)	1 (2%)	
Lymphoma malignant mixed	1 (2%)	1 (2%)	
Follicular cell, adenocarcinoma	1 (2%)		
Follicular cell, adenoma	3 (6%)	4 (8%)	3 (6%)
GENERAL BODY SYSTEM			
Tissue, NOS	*(50)	*(50)	*(50)
Lymphoma malignant mixed	1 (2%)		
GENITAL SYSTEM			
Ovary	(46)	(47)	(49)
Cystadenoma	2 (4%)		
Lymphoma malignant histiocytic	1 (2%)		
Lymphoma malignant lymphocytic	2 (4%)	1 (2%)	
Oviduct	*(50)	*(50)	*(50)
Lymphoma malignant lymphocytic	1 (2%)		
Uterus	(50)	(50)	(50)
Carcinoma	1 (2%)		
Hemangiosarcoma			1 (2%)
Leiomyosarcoma			1 (2%)
Lymphoma malignant histiocytic	1 (2%)		2 (4%)
Lymphoma malignant lymphocytic	2 (4%)		
Lymphoma malignant mixed		1 (2%)	
Lymphoma malignant undifferentiated cell type	1 (2%)		
Polyp stromal	2 (4%)		
Sarcoma stromal	1 (2%)		1 (2%)
Vagina	*(50)	*(50)	*(50)
Lymphoma malignant histiocytic	1 (2%)		
HEMATOPOIETIC SYSTEM			
Bone marrow	(50)	(50)	(50)
Hemangiosarcoma	1 (2%)		1 (2%)
Lymphoma malignant histiocytic	1 (2%)		1 (2%)
Lymphoma malignant lymphocytic	1 (2%)	1 (2%)	
Lymphoma malignant mixed	1 (2%)	3 (6%)	
Lymph node	(48)	(49)	(49)
Adenocarcinoma, metastatic, thyroid gland	1 (2%)		
Bronchial, lymphoma malignant lymphocytic	1 (2%)	1 (2%)	
Iliac, lymphoma malignant undifferentiated cell type	1 (2%)		
Inguinal, lymphoma malignant histiocytic	1 (2%)		
Inguinal, lymphoma malignant lymphocytic	2 (4%)	1 (2%)	
Inguinal, lymphoma malignant mixed	3 (6%)		
Inguinal, lymphoma malignant undifferentiated cell type	1 (2%)		

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

	Vehicle Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM			
Lymph node (Continued)	(48)	(49)	(49)
Lumbar, lymphoma malignant lymphocytic	1 (2%)		
Mandibular, lymphoma malignant histiocytic			1 (2%)
Mandibular, lymphoma malignant lymphocytic	3 (6%)	1 (2%)	
Mandibular, lymphoma malignant mixed	5 (10%)	2 (4%)	5 (10%)
Mandibular, lymphoma malignant mixed, multiple		1 (2%)	
Mandibular, lymphoma malignant undifferentiated cell type	1 (2%)		
Mediastinal, lymphoma malignant histiocytic			1 (2%)
Mediastinal, lymphoma malignant lymphocytic	3 (6%)	1 (2%)	
Mediastinal, lymphoma malignant mixed	4 (8%)	4 (8%)	4 (8%)
Mediastinal, lymphoma malignant mixed, multiple		1 (2%)	
Mediastinal, lymphoma malignant undifferentiated cell type	1 (2%)		
Mesenteric, lymphoma malignant histiocytic	1 (2%)		1 (2%)
Mesenteric, lymphoma malignant lymphocytic	3 (6%)	1 (2%)	
Mesenteric, lymphoma malignant mixed	6 (13%)	3 (6%)	4 (8%)
Mesenteric, lymphoma malignant mixed, multiple		1 (2%)	
Mesenteric, lymphoma malignant undifferentiated cell type	1 (2%)		
Pancreatic, lymphoma malignant histiocytic			1 (2%)
Pancreatic, lymphoma malignant lymphocytic	2 (4%)		
Pancreatic, lymphoma malignant mixed	1 (2%)	2 (4%)	1 (2%)
Renal, lymphoma malignant mixed		1 (2%)	1 (2%)
Renal, lymphoma malignant undifferentiated cell type	1 (2%)		
Spleen	(48)	(49)	(50)
Hemangiosarcoma			1 (2%)
Lymphoma malignant histiocytic	1 (2%)		1 (2%)
Lymphoma malignant lymphocytic	4 (8%)	2 (4%)	
Lymphoma malignant mixed	7 (15%)	8 (16%)	5 (10%)
Lymphoma malignant undifferentiated cell type	1 (2%)		
Thymus	(41)	(43)	(45)
Fibrous histiocytoma	1 (2%)		
Lymphoma malignant lymphocytic	1 (2%)	1 (2%)	
Lymphoma malignant mixed	4 (10%)		
INTEGUMENTARY SYSTEM			
Mammary gland	(48)	(48)	(49)
Adenocarcinoma	2 (4%)		
Lymphoma malignant lymphocytic	2 (4%)		
Skin	(50)	(49)	(50)
Sebaceous gland, adenoma			2 (4%)
Subcutaneous tissue, fibrosarcoma			1 (2%)
Subcutaneous tissue, hemangiosarcoma			2 (4%)
MUSCULOSKELETAL SYSTEM			
Bone	(50)	(50)	(50)
Hemangiosarcoma			1 (2%)
Osteosarcoma		1 (2%)	1 (2%)
Skeletal muscle	*(50)	*(50)	*(50)
Fibrous histiocytoma	1 (2%)		
Hemangiosarcoma	1 (2%)		
Lymphoma malignant mixed	1 (2%)	1 (2%)	

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

	Vehicle Control	Low Dose	High Dose
NERVOUS SYSTEM			
Brain	(50)	(50)	(50)
Lymphoma malignant lymphocytic		1 (2%)	
Lymphoma malignant mixed		1 (2%)	
Meningioma benign			1 (2%)
RESPIRATORY SYSTEM			
Lung	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	1 (2%)	3 (6%)	5 (10%)
Alveolar/bronchiolar carcinoma	2 (4%)		1 (2%)
Lymphoma malignant histiocytic	2 (4%)		
Lymphoma malignant lymphocytic	3 (6%)	2 (4%)	
Lymphoma malignant mixed	3 (6%)	1 (2%)	2 (4%)
Osteosarcoma, metastatic, bone		1 (2%)	1 (2%)
Nose	(43)	(44)	(47)
Lymphoma malignant mixed	1 (2%)		
SPECIAL SENSES SYSTEM			
Harderian gland	*(50)	*(50)	*(50)
Adenoma	1 (2%)	3 (6%)	3 (6%)
Lymphoma malignant mixed	1 (2%)		
URINARY SYSTEM			
Kidney	(49)	(50)	(50)
Lymphoma malignant lymphocytic	1 (2%)	1 (2%)	
Lymphoma malignant mixed	2 (4%)	2 (4%)	5 (10%)
Ureter	*(50)	*(50)	*(50)
Lymphoma malignant mixed			1 (2%)
Urinary bladder	(44)	(45)	(49)
Lymphoma malignant lymphocytic	1 (2%)	1 (2%)	
Lymphoma malignant mixed		2 (4%)	
SYSTEMIC LESIONS			
Multiple organs	*(50)	*(50)	*(50)
Hemangiosarcoma	1 (2%)		2 (4%)
Lymphoma malignant mixed	8 (16%)	9 (18%)	7 (14%)
Lymphoma malignant lymphocytic	5 (10%)	2 (4%)	
Lymphoma malignant histiocytic	2 (4%)		2 (4%)
Lymphoma malignant undifferentiated cell	1 (2%)		
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Moribund	15	5	9
Terminal sacrifice	25	29	34
Accident	6	5	2
Dead	4	11	5

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

	Vehicle Control	Low Dose	High Dose
TUMOR SUMMARY			
Total animals with primary neoplasms **	37	26	37
Total primary neoplasms	71	40	64
Total animals with benign neoplasms	26	17	32
Total benign neoplasms	34	25	43
Total animals with malignant neoplasms	24	15	18
Total malignant neoplasms	37	15	21
Total animals with secondary neoplasms ***	1	1	1
Total secondary neoplasms	1	1	2

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

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

WEEKS ON STUDY	0 0 1	0 0 2	0 0 2	0 0 2	0 0 2	0 0 2	0 6 1	0 6 5	0 8 2	0 8 3	0 8 4	0 8 6	0 8 6	0 8 8	0 9 0	0 9 1	0 9 3	0 9 6	0 9 6	0 9 9	1 0 1	1 0 1	1 0 2	1 0 4	1 0 5
CARCASS ID	3 8 1	4 6 1	4 2 1	4 3 1	4 5 1	3 9 1	4 4 5	4 6 2	4 5 2	4 1 1	4 5 3	4 2 2	3 8 2	4 1 2	4 3 2	4 5 5	3 7 1	3 9 2	4 3 3	4 3 4	4 5 4	4 6 3	4 2 5	4 0 4	4 0 5
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	A	+	M	A	M	A	+	M	A	M	+	+	+	+	+	+	+	+	M	+	I	+	M	M	+
Intestine large	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Rectum, lymphoma malignant lymphocytic																									
Intestine small	A	M	+	+	M	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ileum, lymphoma malignant mixed																								X	
Jejunum, fibrous histiocytoma																		X							
Jejunum, lymphoma malignant lymphocytic																				X					
Jejunum, lymphoma malignant undifferentiated cell type											X														
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma																		X							
Hemangiosarcoma, multiple																									
Hepatocellular carcinoma								X											X						
Hepatocellular adenoma																						X			
Lymphoma malignant histiocytic									X												X				
Lymphoma malignant lymphocytic								X				X										X			
Lymphoma malignant mixed																X								X	
Lymphoma malignant undifferentiated cell type											X														
Mesentery								+			+			+	+	+	+	+		+			+		+
Fibrous histiocytoma, multiple																		X							
Lymphoma malignant lymphocytic								X																	
Lymphoma malignant mixed																X									
Lymphoma malignant undifferentiated cell type											X														
Pancreas	A	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma																		X							
Lymphoma malignant lymphocytic								X				X													
Lymphoma malignant mixed																								X	
Lymphoma malignant undifferentiated cell type											X														
Salivary glands	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic												X													
Lymphoma malignant mixed																								X	
Stomach	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma																		X							
Lymphoma malignant lymphocytic												X													
Forestomach, papilloma squamous																			X			X			
CARDIOVASCULAR SYSTEM																									
Blood vessel																									+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic									X												X				
Lymphoma malignant lymphocytic												X													
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic												X													
Lymphoma malignant undifferentiated cell type											X														
Medulla, pheochromocytoma benign																								X	
Islets, pancreatic	A	+	+	+	A	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma										X															
Lymphoma malignant mixed																									
Parathyroid gland	A	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	M	+	+	M	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma							X											X	X						
Pars distalis, carcinoma																									
Pars intermedia, adenoma																									X
Thyroid gland	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic												X													
Lymphoma malignant mixed																									
Follicular cell, adenocarcinoma																									
Follicular cell, adenoma											X	X													
GENERAL BODY SYSTEM																									
Tissue, NOS	+	+	+	+	+	+										+									
Lymphoma malignant mixed																X									

+ Tissue examined microscopically
Not examined
– Present but not examined microscopically
I Insufficient tissue

M Missing
A Autolysis precludes examination
X Incidence of listed morphology

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

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	TOTAL
CARCASS ID	372	373	374	375	383	384	385	393	394	395	401	402	403	413	414	415	423	424	435	441	442	443	444	464	465	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	M	I	33
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Rectum, lymphoma malig lymphocytic																				X						1
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Ileum, lymphoma malignant mixed																										1
Jejunum, fibrous histiocytoma																										1
Jejunum, lymphoma malignant lymphocytic																										1
Jejunum, lymphoma malignant undifferentiated cell type																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma																										1
Hemangiosarcoma, multiple				X																						1
Hepatocellular carcinoma							X					X														4
Hepatocellular adenoma																								X		2
Lymphoma malignant histiocytic																										2
Lymphoma malignant lymphocytic																				X						4
Lymphoma malignant mixed																										2
Lymphoma malignant undifferentiated cell type																										1
Mesentery												+			+					+						13
Fibrous histiocytoma, multiple																										1
Lymphoma malignant lymphocytic																				X						2
Lymphoma malignant mixed																										1
Lymphoma malignant undifferentiated cell type																										1
Pancreas	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Fibrous histiocytoma																										1
Lymphoma malignant lymphocytic																										2
Lymphoma malignant mixed													X							X						3
Lymphoma malignant undifferentiated cell type																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant lymphocytic																				X						2
Lymphoma malignant mixed																				X						2
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibrous histiocytoma																										1
Lymphoma malignant lymphocytic																				X						2
Forestomach, papilloma squamous								X											X	X						5
CARDIOVASCULAR SYSTEM																										
Blood vessel																										1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant histiocytic																										2
Lymphoma malignant lymphocytic																										1
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																				X						2
Lymphoma malignant undifferentiated cell type																										1
Medulla, pheochromocytoma benign									X	X															X	4
Islets, pancreatic	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Adenoma																										1
Lymphoma malignant mixed													X							X						2
Parathyroid gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	46
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	45
Pars distalis, adenoma						X	X		X	X						X				X		X		X		11
Pars distalis carcinoma																		X								1
Pars intermedia, adenoma		X																								2
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant lymphocytic																					X					2
Lymphoma malignant mixed																				X						1
Follicular cell, adenocarcinoma																				X						1
Follicular cell, adenoma		X																								3
GENERAL BODY SYSTEM																										
Tissue, NOS																										7
Lymphoma malignant mixed																										1

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

WEEKS ON STUDY	001	002	002	002	002	002	061	065	082	083	084	086	086	088	090	091	093	096	096	099	101	101	102	104	105
CARCASS ID	381	461	421	431	451	391	445	462	452	411	453	422	382	412	432	455	371	392	433	434	454	463	425	404	405
GENITAL SYSTEM																									
Ovary	A	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma																									
Lymphoma malignant histiocytic																					X				
Lymphoma malignant lymphocytic								X																	
Oviduct																									
Lymphoma malignant lymphocytic																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Lymphoma malignant histiocytic																					X				
Lymphoma malignant lymphocytic												X													
Lymphoma malignant undifferentiated cell type											X														
Polyp stromal																				X			X		
Sarcoma stromal																									
Vagina																					+				
Lymphoma malignant histiocytic																					X				
HEMATOPOIETIC SYSTEM																									
Blood	A																							+	
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Lymphoma malignant histiocytic									X																
Lymphoma malignant lymphocytic								X																	
Lymphoma malignant mixed																									
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, thyroid gland																									
Bronchial, lymphoma malignant lymphocytic								X																	
Iliac, lymphoma malignant undifferentiated cell type											X														
Inguinal, lymphoma malignant histiocytic																					X				
Inguinal, lymphoma malignant lymphocytic								X																	
Inguinal, lymphoma malignant mixed																X								X	
Inguinal, lymphoma malignant undifferentiated cell type											X														
Lumbar, lymphoma malignant lymphocytic																				X					
Mandibular, lymphoma malignant lymphocytic								X				X													
Mandibular, lymphoma malignant mixed										X						X								X	
Mandibular, lymphoma malignant undifferentiated cell type											X														
Mediastinal, lymphoma malignant lymphocytic								X				X													
Mediastinal, lymphoma malignant mixed										X						X								X	
Mediastinal, lymphoma malignant undifferentiated cell type											X														
Mesenteric, lymphoma malignant histiocytic																					X				
Mesenteric, lymphoma malignant lymphocytic												X								X					
Mesenteric, lymphoma malignant mixed										X						X								X	
Mesenteric, lymphoma malignant undifferentiated cell type											X														
Pancreatic, lymphoma malignant lymphocytic								X				X													
Pancreatic, lymphoma malignant mixed																								X	
Renal, lymphoma malignant undifferentiated cell type											X														
Spleen	M	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic																					X				
Lymphoma malignant lymphocytic								X				X										X			
Lymphoma malignant mixed										X						X								X	
Lymphoma malignant undifferentiated cell type											X														
Thymus	+	+	+	+	M	+	I	+	M	+	M	+	+	+	+	+	+	+	M	+	+	M	+	M	+
Fibrous histiocytoma																		X							
Lymphoma malignant lymphocytic																									
Lymphoma malignant mixed										X															

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

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	TOTAL
CARCASS ID	372	373	374	375	383	384	385	393	394	395	401	402	403	413	414	415	423	424	435	441	442	443	444	464	465	TISSUES TUMORS
GENITAL SYSTEM																										
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	46
Cystadenoma														X						X						2
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic																					X					2
Oviduct																					+					1
Lymphoma malignant lymphocytic																					X					1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma				X																						1
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic																					X					2
Lymphoma malignant undifferentiated cell type																										1
Polyp stromal																										2
Sarcoma stromal																	X									1
Vagina																										1
Lymphoma malignant histiocytic																										1
HEMATOPOIETIC SYSTEM																										
Blood																	+									2
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma				X																						1
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic																										1
Lymphoma malignant mixed																						X				1
Lymph node	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	48
Adenocarcinoma, metastatic, thyroid gland																				X						1
Bronchial, lymphoma malignant lymphocytic																										1
Iliac, lymphoma malignant undifferentiated cell type																										1
Inguinal, lymphoma malignant histiocytic																										1
Inguinal, lymphoma malignant lymphocytic																					X					2
Inguinal, lymphoma malignant mixed					X																					3
Inguinal, lymphoma malignant undifferentiated cell type																										1
Lumbar, lymphoma malig lymphocytic																										1
Mandibular, lymphoma malignant lymphocytic																					X					3
Mandibular, lymphoma malig mixed					X															X						5
Mandibular, lymphoma malignant undifferentiated cell type																										1
Mediastinal, lymphoma malignant lymphocytic																					X					3
Mediastinal, lymphoma malig mixed					X																					4
Mediastinal, lymphoma malignant undifferentiated cell type																										1
Mesenteric, lymphoma malignant histiocytic																										1
Mesenteric, lymphoma malignant lymphocytic																					X					3
Mesenteric, lymphoma malignant mixed					X															X		X				6
Mesenteric, lymphoma malignant undifferentiated cell type																										1
Pancreatic, lymphoma malignant lymphocytic																										2
Pancreatic, lymphoma malignant mixed																										1
Renal, lymphoma malignant undifferentiated cell type																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic																					X					4
Lymphoma malignant mixed							X						X							X		X				7
Lymphoma malignant undifferentiated cell type																										1
Thymus	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	41
Fibrous histiocytoma																										1
Lymphoma malignant lymphocytic																					X					1
Lymphoma malignant mixed					X								X							X						4

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

WEEKS ON STUDY	001	002	002	002	002	002	061	065	082	083	084	086	086	088	090	091	093	096	096	099	101	101	102	104	105
CARCASS ID	381	461	421	431	451	391	445	462	452	411	453	422	382	412	432	455	371	392	433	434	454	463	425	404	405
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Adenocarcinoma																						X			X
Lymphoma malignant lymphocytic												X													
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																		+							+
Fibrous histiocytoma																		X							
Hemangiosarcoma																									
Lymphoma malignant mixed																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve	+	M	M	M	M	+	+	M	+	M	+	M	+	+	M	+	+	+	I	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																								X	
Alveolar/bronchiolar carcinoma													X												
Lymphoma malignant histiocytic									X												X				
Lymphoma malignant lymphocytic												X										X			
Lymphoma malignant mixed																X								X	
Nose	M	M	M	M	M	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																									
Trachea	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Harderian gland										+															
Adenoma																									
Lymphoma malignant mixed																									
URINARY SYSTEM																									
Kidney	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																									
Lymphoma malignant mixed										X															
Urinary bladder	+	+	+	+	A	+	+	+	A	+	+	M	+	+	+	+	+	+	+	M	+	+	+	I	+
Lymphoma malignant lymphocytic																									

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

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	
CARCASS ID	372	373	374	375	383	384	385	393	394	395	401	402	403	413	414	415	423	424	435	441	442	443	444	464	465	TOTAL TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenocarcinoma																										2
Lymphoma malignant lymphocytic																				X						2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle				+																		+				4
Fibrous histiocytoma																										1
Hemangiosarcoma				X																						1
Lymphoma malignant mixed																						X				1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										1
Alveolar/bronchiolar carcinoma																	X									2
Lymphoma malignant histiocytic																										2
Lymphoma malignant lymphocytic																					X					3
Lymphoma malignant mixed																				X						3
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Lymphoma malignant mixed																						X				1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPECIAL SENSES SYSTEM																										
Harderian gland																						+	+			3
Adenoma																							X			1
Lymphoma malignant mixed																						X				1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant lymphocytic																					X					1
Lymphoma malignant mixed													X													2
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	44
Lymphoma malignant lymphocytic																					X					1

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

WEEKS ON STUDY	0 0 1	0 0 1	0 0 1	0 0 1	0 0 1	0 6 4	0 7 3	0 7 9	0 8 2	0 8 3	0 8 3	0 8 5	0 8 5	0 9 1	0 9 2	0 9 4	0 9 6	0 9 6	0 9 6	1 0 0	1 0 1	1 0 5	1 0 5	1 0 5	1 0 5
CARCASS ID	6 8 1	6 3 1	6 9 1	6 9 2	6 2 1	6 3 2	7 0 1	6 3 3	6 7 1	6 3 4	6 1 1	6 6 1	6 3 5	6 8 2	6 9 3	7 0 2	6 8 3	6 9 4	6 7 2	6 1 2	6 7 3	6 1 3	6 1 4	6 1 5	6 2 2
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	I	+	+	+	+	A	+	A	A	+	+	+	+	M	+	+	+	+	+	+	+	+	I
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Jejunum, lymphoma malignant lymphocytic											X														
Jejunum, lymphoma malignant mixed															X										
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma								X																	
Hepatocellular adenoma																X									
Lymphoma malignant lymphocytic																									
Lymphoma malignant mixed									X						X		X								
Mesentary							+		+		+				+	+		+		+					
Lymphoma malignant lymphocytic											X					X									
Lymphoma malignant mixed															X										
Lymphoma malignant mixed, multiple									X																
Pancreas	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																X									
Lymphoma malignant mixed									X																
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed									X																
Stomach	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																X									
Forestomach, papilloma squamous						X										X									X
CARDIOVASCULAR SYSTEM																									
Blood vessel																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed															X										
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																X									
Medulla, pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+
Pituitary gland	+	+	+	M	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	M	+	+
Pars distalis, adenoma																									X
Pars intermedia, adenoma																									
Thyroid gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Lymphoma malignant lymphocytic																X									
Lymphoma malignant mixed									X																
Follicular cell, adenoma																									
GENERAL BODY SYSTEM																									
Tissue, NOS		+			+																				
GENITAL SYSTEM																									
Ovary	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic											X														
Oviduct																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed									X																

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

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	TOTAL
CARCASS ID	623	624	625	641	642	643	644	645	651	652	653	654	655	662	663	664	665	674	675	684	685	695	703	704	705	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	48
Gallbladder	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	41
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Jejunum, lymphoma malignant lymphocytic																										1
Jejunum, lymphoma malignant mixed											X															2
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma		X														X										3
Hepatocellular adenoma																		X								1
Lymphoma malignant lymphocytic																										1
Lymphoma malignant mixed								X																		4
Mesentery									+									+	+							10
Lymphoma malignant lymphocytic																										2
Lymphoma malignant mixed																										1
Lymphoma malignant mixed, multiple																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant lymphocytic																										1
Lymphoma malignant mixed																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed																										1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant lymphocytic																										1
Forestomach, papilloma squamous	X																	X			X					6
CARDIOVASCULAR SYSTEM																										
Blood vessel																							+			1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed																										1
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant lymphocytic																										1
Medulla, pheochromocytoma benign																							X			1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	43
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	45
Pars distalis, adenoma		X			X				X							X		X								6
Pars intermedia, adenoma											X															1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymphoma malignant lymphocytic																										1
Lymphoma malignant mixed																										1
Follicular cell, adenoma		X												X		X			X							4
GENERAL BODY SYSTEM																										
Tissue, NOS																										2
GENITAL SYSTEM																										
Ovary	+	M	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymphoma malignant lymphocytic																										1
Oviduct																								+		1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed																										1

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

WEEKS ON STUDY	0 0 1	0 0 1	0 0 1	0 0 1	0 0 1	0 6 4	0 7 3	0 7 9	0 8 2	0 8 3	0 8 3	0 8 5	0 8 5	0 9 1	0 9 2	0 9 4	0 9 6	0 9 6	0 9 6	1 0 0	1 0 1	1 0 5	1 0 5	1 0 5	1 0 5
CARCASS ID	6 6 8 1	6 6 3 1	6 6 9 1	6 6 9 2	6 6 2 1	6 6 3 2	7 0 1	6 6 3 3	6 6 7 1	6 6 3 4	6 6 1 1	6 6 6 1	6 6 3 5	6 6 8 2	6 6 9 3	7 0 2	6 6 8 3	6 6 9 4	6 6 7 2	6 6 1 2	6 6 7 3	6 6 1 3	6 6 1 4	6 6 1 5	6 6 2 2
HEMATOPOIETIC SYSTEM																									
Blood																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																X									
Lymphoma malignant mixed																	X								
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Bronchial, lymphoma malignant lymphocytic																X									
Inguinal, lymphoma malignant lymphocytic																X									
Mandibular, lymphoma malignant lymphocytic																X									
Mandibular, lymphoma malignant mixed															X										
Mandibular, lymphoma malignant mixed, multiple									X																
Mediastinal, lymphoma malignant lymphocytic											X														
Mediastinal, lymphoma malignant mixed															X		X								
Mediastinal, lymphoma malignant mixed, multiple									X																
Mesenteric, lymphoma malignant lymphocytic																X									
Mesenteric, lymphoma malignant mixed																									
Mesenteric, lymphoma malignant mixed, multiple									X																
Pancreatic, lymphoma malignant mixed																									
Renal, lymphoma malignant mixed															X										
Spleen	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic											X					X									
Lymphoma malignant mixed									X								X								
Thymus	+	+	+	+	+	+	+	+	M	M	M	+	+	+	M	+	+	M	M	+	+	+	+	+	+
Lymphoma malignant lymphocytic																X									
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma												X													
Skeletal muscle					+																				
Lymphoma malignant mixed																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																X									
Lymphoma malignant mixed																	X								
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma														X											
Lymphoma malignant lymphocytic											X					X									
Lymphoma malignant mixed									X																
Osteosarcoma, metastatic, bone												X													
Nose	M	M	M	M	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Harderian gland																									+
Adenoma																									X
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																X									
Lymphoma malignant mixed									X																
Urinary bladder	+	+	+	+	+	+	+	+	+	A	A	+	M	+	+	+	+	+	+	+	+	+	M	+	+
Lymphoma malignant lymphocytic																X									
Lymphoma malignant mixed									X																

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

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	TOTAL.
CARCASS ID	623	624	625	641	642	643	644	645	651	652	653	654	655	662	663	664	665	674	675	684	685	695	703	704	705	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Blood	+																									1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																										1
Lymphoma malignant mixed								X	X																	3
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Bronchial, lymphoma malignant lymphocytic																										1
Inguinal, lymphoma malignant lymphocytic																										1
Mandibular, lymphoma malignant lymphocytic																										1
Mandibular, lymphoma malig. mixed									X																	2
Mandibular, lymphoma malig. mixed, multiple																										1
Mediastinal, lymphoma malignant lymphocytic																										1
Mediastinal, lymphoma malig. mixed									X						X											4
Mediastinal, lymphoma malig mixed, multiple																										1
Mesenteric, lymphoma malignant lymphocytic																										1
Mesenteric, lymphoma malignant mixed									X		X				X											3
Mesenteric, lymphoma malignant mixed, multiple																										1
Pancreatic, lymphoma malignant mixed									X						X											2
Renal, lymphoma malignant mixed																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant lymphocytic																										2
Lymphoma malignant mixed						X		X	X	X	X				X											8
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	43
Lymphoma malignant lymphocytic																										1
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	49
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma																										1
Skeletal muscle								+																		2
Lymphoma malignant mixed								X																		1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																										1
Lymphoma malignant mixed																										1
Peripheral nerve	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma											X									X						3
Lymphoma malignant lymphocytic																										2
Lymphoma malignant mixed																										1
Osteosarcoma, metastatic, bone																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPECIAL SENSES SYSTEM																										
Harderian gland		+													+											3
Adenoma		X													X											3
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																										1
Lymphoma malignant mixed								X																		2
Urinary bladder	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Lymphoma malignant lymphocytic																										1
Lymphoma malignant mixed									X																	2

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

WEEKS ON STUDY	0 0 1	0 0 2	0 5 3	0 7 5	0 7 7	0 8 9	0 9 0	0 9 1	0 9 2	0 9 4	0 9 4	0 9 6	0 9 7	1 0 2	1 0 2	1 0 2	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5
CARCASS ID	5 0 1	5 2 1	5 6 1	5 7 1	5 4 1	5 1 1	5 3 1	5 0 2	5 4 2	4 9 1	5 7 2	5 1 2	5 0 3	5 1 3	4 9 4	4 9 5	4 9 2	4 9 3	5 0 4	5 0 5	5 1 4	5 1 5	5 2 2	5 2 3	5 2 4
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	M	+	M	+	+	+	+	+	+	M	+	+	A	+	+	+	M	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	–	+	+	+	+	+
Jejunum, lymphoma malignant mixed																									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma											X	X	X										X		
Hepatocellular adenoma							X																		
Lymphoma malignant histiocytic														X											
Lymphoma malignant mixed										X															X
Osteosarcoma, metastatic, bone															X										
Mesentery																+	+	+							
Lymphoma malignant mixed																		X							
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma												X													
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Forestomach, papilloma squamous				X	X	X		X	X										X	X	X	X	X	X	X
Forestomach, squamous cell carcinoma																		X		X					
CARDIOVASCULAR SYSTEM																									
Blood vessel																			+						
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed										X															
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																									
Parathyroid gland	+	+	+	+	M	M	M	M	+	+	+	+	+	+	+	+	M	M	+	+	+	+	M	+	+
Pituitary gland	+	M	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Pars distalis, adenoma																	X								
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma											X														
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma				X																					
Leiomyosarcoma									X																
Lymphoma malignant histiocytic														X						X					
Sarcoma stromal																									
Vagina						+																			

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

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	TOTAL TISSUES TUMORS
CARCASS ID	525	532	533	534	535	543	544	545	551	552	553	554	555	562	563	564	565	573	574	575	581	582	583	584	585	
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Jejunum, lymphoma malignant mixed																				X						1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma																										3
Hepatocellular adenoma		X			X																					4
Lymphoma malignant histiocytic																										1
Lymphoma malignant mixed																										2
Osteosarcoma, metastatic, bone																										1
Mesentery		+		+					+									+								7
Lymphoma malignant mixed																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Forestomach, papilloma squamous				X	X				X		X			X										X		18
Forestomach, squamous cell carcinoma																										2
CARDIOVASCULAR SYSTEM																										
Blood vessel																										1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed																										1
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant mixed									X																	1
Parathyroid gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	41
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	44
Pars distalis, adenoma	X							X			X						X	X								6
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma																			X					X		3
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Ovary	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Leiomyosarcoma																										1
Lymphoma malignant histiocytic																										2
Sarcoma stromal	X																									1
Vagina																										1

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

WEEKS ON STUDY	001	002	053	075	077	089	090	091	092	094	094	096	097	102	102	102	105	105	105	105	105	105	105	105	105
CARCASS ID	501	521	561	571	541	511	531	502	542	491	572	512	503	513	494	495	492	493	504	505	514	515	522	523	524
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma				X																					
Lymphoma malignant histiocytic														X											
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mandibular, lymphoma malignant histiocytic														X											
Mandibular, lymphoma malignant mixed										X								X							X
Mediastinal, lymphoma malignant histiocytic														X											
Mediastinal, lymphoma malignant mixed										X								X							X
Mesenteric, lymphoma malignant histiocytic														X											
Mesenteric, lymphoma malignant mixed										X															X
Pancreatic, lymphoma malignant histiocytic														X											
Pancreatic, lymphoma malignant mixed																									
Renal, lymphoma malignant mixed																									X
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma				X																					
Lymphoma malignant histiocytic														X											
Lymphoma malignant mixed										X								X							X
Thymus	+	+	+	M	+	+	+	M	+	+	+	+	+	–	+	+	+	+	+	+	+	+	M	+	+
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sebaceous gland, adenoma														X											
Subcutaneous tissue, fibrosarcoma							X																		
Subcutaneous tissue, hemangiosarcoma				X																	X				
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma				X																					
Osteosarcoma															X										
Skeletal muscle													+												
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Meningioma benign													X												
Peripheral nerve	+	+	+	+	+	+	M	M	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																	X								
Alveolar/bronchiolar carcinoma																									
Lymphoma malignant mixed										X								X							
Osteosarcoma, metastatic, bone															X										
Nose	M	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Ear			+																						
Harderian gland				+	+																				
Adenoma				X	X																				
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																		X							X
Ureter																									
Lymphoma malignant mixed																									
Urinary bladder	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

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

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	TOTAL:
CARCASS ID	525	532	533	534	535	543	544	545	551	552	553	554	555	562	563	564	565	573	574	575	581	582	583	584	585	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Lymphoma malignant histiocytic																										1
Lymph node	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Mandibular, lymphoma malignant histiocytic																										1
Mandibular, lymphoma malig. mixed		X								X																5
Mediastinal, lymphoma malignant histiocytic																										1
Mediastinal, lymphoma malig. mixed										X																4
Mesenteric, lymphoma malignant histiocytic																										1
Mesenteric, lymphoma malig. mixed	X									X																4
Pancreatic, lymphoma malignant histiocytic																										1
Pancreatic, lymphoma malignant mixed		X																								1
Renal, lymphoma malignant mixed																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Lymphoma malignant histiocytic																										1
Lymphoma malignant mixed		X								X																5
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	45
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sebaceous gland, adenoma																X										2
Subcutaneous tissue, fibrosarcoma																										1
Subcutaneous tissue, hemangiosarcoma																										2
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Osteosarcoma																										1
Skeletal muscle																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Meningioma benign																										1
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	45
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma		X			X			X			X															5
Alveolar/bronchiolar carcinoma																		X								1
Lymphoma malignant mixed																										2
Osteosarcoma, metastatic, bone																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPECIAL SENSES SYSTEM																										
Ear																					+					2
Harderian gland		+																								3
Adenoma		X																								3
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed	X	X								X																5
Ureter	+																									1
Lymphoma malignant mixed	X																									1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49

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

	Vehicle Control	20 mg/kg	40 mg/kg
Adrenal Gland: Pheochromocytoma			
Overall Rates (a)	4/50 (8%)	1/49 (2%)	0/50 (0%)
Adjusted Rates (b)	14.8%	3.4%	0.0%
Terminal Rates (c)	3/26 (12%)	1/29 (3%)	0/34 (0%)
Day of First Observation	724	729	
Life Table Tests (d)	P=0.014N	P=0.151N	P=0.036N
Logistic Regression Tests (d)	P=0.015N	P=0.158N	P=0.036N
Cochran-Armitage Trend Test (d)	P=0.026N		
Fisher Exact Test (d)		P=0.187N	P=0.059N
Harderian Gland: Adenoma			
Overall Rates (a)	1/50 (2%)	3/50 (6%)	3/50 (6%)
Adjusted Rates (b)	3.8%	10.3%	7.2%
Terminal Rates (c)	1/26 (4%)	3/29 (10%)	1/34 (3%)
Day of First Observation	729	729	534
Life Table Tests (d)	P=0.329	P=0.344	P=0.385
Logistic Regression Tests (d)	P=0.272	P=0.344	P=0.313
Cochran-Armitage Trend Test (d)	P=0.238		
Fisher Exact Test (d)		P=0.309	P=0.309
Liver: Hepatocellular Adenoma			
Overall Rates (a)	2/50 (4%)	1/50 (2%)	4/50 (8%)
Adjusted Rates (b)	7.2%	3.4%	10.9%
Terminal Rates (c)	1/26 (4%)	1/29 (3%)	3/34 (9%)
Day of First Observation	707	729	624
Life Table Tests (d)	P=0.337	P=0.475N	P=0.459
Logistic Regression Tests (d)	P=0.295	P=0.489N	P=0.402
Cochran-Armitage Trend Test (d)	P=0.238		
Fisher Exact Test (d)		P=0.500N	P=0.339
Liver: Hepatocellular Carcinoma			
Overall Rates (a)	4/50 (8%)	3/50 (6%)	3/50 (6%)
Adjusted Rates (b)	12.7%	9.1%	7.5%
Terminal Rates (c)	2/26 (8%)	2/29 (7%)	0/34 (0%)
Day of First Observation	452	551	656
Life Table Tests (d)	P=0.322N	P=0.463N	P=0.392N
Logistic Regression Tests (d)	P=0.396N	P=0.493N	P=0.483N
Cochran-Armitage Trend Test (d)	P=0.421N		
Fisher Exact Test (d)		P=0.500N	P=0.500N
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	6/50 (12%)	4/50 (8%)	7/50 (14%)
Adjusted Rates (b)	19.2%	12.4%	17.6%
Terminal Rates (c)	3/26 (12%)	3/29 (10%)	3/34 (9%)
Day of First Observation	452	551	624
Life Table Tests (d)	P=0.525N	P=0.330N	P=0.559N
Logistic Regression Tests (d)	P=0.496	P=0.358N	P=0.558
Cochran-Armitage Trend Test (d)	P=0.437		
Fisher Exact Test (d)		P=0.370N	P=0.500
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	1/50 (2%)	3/50 (6%)	5/50 (10%)
Adjusted Rates (b)	3.7%	9.4%	14.7%
Terminal Rates (c)	0/26 (0%)	2/29 (7%)	5/34 (15%)
Day of First Observation	724	632	729
Life Table Tests (d)	P=0.127	P=0.339	P=0.173
Logistic Regression Tests (d)	P=0.106	P=0.313	P=0.160
Cochran-Armitage Trend Test (d)	P=0.070		
Fisher Exact Test (d)		P=0.309	P=0.102

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

	Vehicle Control	20 mg/kg	40 mg/kg
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	3/50 (6%)	3/50 (6%)	6/50 (12%)
Adjusted Rates (b)	9.8%	9.4%	17.6%
Terminal Rates (c)	1/26 (4%)	2/29 (7%)	6/34 (18%)
Day of First Observation	602	632	729
Life Table Tests (d)	P=0.294	P=0.627N	P=0.381
Logistic Regression Tests (d)	P=0.242	P=0.654N	P=0.325
Cochran-Armitage Trend Test (d)	P=0.178		
Fisher Exact Test (d)		P=0.661N	P=0.243
Pituitary Gland/Pars Distalis: Adenoma			
Overall Rates (a)	11/45 (24%)	6/45 (13%)	6/44 (14%)
Adjusted Rates (b)	37.6%	22.2%	19.4%
Terminal Rates (c)	8/25 (32%)	6/27 (22%)	6/31 (19%)
Day of First Observation	427	729	729
Life Table Tests (d)	P=0.041N	P=0.108N	P=0.060N
Logistic Regression Tests (d)	P=0.072N	P=0.152N	P=0.111N
Cochran-Armitage Trend Test (d)	P=0.112N		
Fisher Exact Test (d)		P=0.141N	P=0.152N
Pituitary Gland/Pars Distalis: Adenoma or Carcinoma			
Overall Rates (a)	12/45 (27%)	6/45 (13%)	6/44 (14%)
Adjusted Rates (b)	41.2%	22.2%	19.4%
Terminal Rates (c)	9/25 (36%)	6/27 (22%)	6/31 (19%)
Day of First Observation	427	729	729
Life Table Tests (d)	P=0.022N	P=0.067N	P=0.034N
Logistic Regression Tests (d)	P=0.042N	P=0.101N	P=0.069N
Cochran-Armitage Trend Test (d)	P=0.071N		
Fisher Exact Test (d)		P=0.093N	P=0.102N
Forestomach: Squamous Papilloma			
Overall Rates (a)	5/49 (10%)	6/49 (12%)	18/50 (36%)
Adjusted Rates (b)	17.4%	18.1%	44.9%
Terminal Rates (c)	3/26 (12%)	4/29 (14%)	13/34 (38%)
Day of First Observation	669	442	520
Life Table Tests (d)	P=0.006	P=0.556	P=0.016
Logistic Regression Tests (d)	P=0.002	P=0.505	P=0.004
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P=0.500	P=0.002
Forestomach: Squamous Cell Papilloma or Carcinoma			
Overall Rates (a)	5/49 (10%)	6/49 (12%)	19/50 (38%)
Adjusted Rates (b)	17.4%	18.1%	47.5%
Terminal Rates (c)	3/26 (12%)	4/29 (14%)	14/34 (41%)
Day of First Observation	669	442	520
Life Table Tests (d)	P=0.004	P=0.556	P=0.011
Logistic Regression Tests (d)	P<0.001	P=0.505	P=0.003
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P=0.500	P=0.001
Thyroid Gland: Follicular Cell Adenoma			
Overall Rates (a)	3/49 (6%)	4/48 (8%)	3/50 (6%)
Adjusted Rates (b)	8.7%	14.3%	8.2%
Terminal Rates (c)	1/26 (4%)	4/28 (14%)	2/34 (6%)
Day of First Observation	582	729	656
Life Table Tests (d)	P=0.454N	P=0.523	P=0.562N
Logistic Regression Tests (d)	P=0.520N	P=0.498	P=0.635N
Cochran-Armitage Trend Test (d)	P=0.568N		
Fisher Exact Test (d)		P=0.488	P=0.651N

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

	Vehicle Control	20 mg/kg	40 mg/kg
Thyroid Gland: Follicular Cell Adenoma or Adenocarcinoma			
Overall Rates (a)	4/49 (8%)	4/48 (8%)	3/50 (6%)
Adjusted Rates (b)	12.3%	14.3%	8.2%
Terminal Rates (c)	2/26 (8%)	4/28 (14%)	2/34 (6%)
Day of First Observation	582	729	656
Life Table Tests (d)	P=0.301N	P=0.618N	P=0.385N
Logistic Regression Tests (d)	P=0.360N	P=0.643	P=0.457N
Cochran-Armitage Trend Test (d)	P=0.413N		
Fisher Exact Test (d)		P=0.631	P=0.489N
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	16/50 (32%)	11/50 (22%)	9/50 (18%)
Adjusted Rates (b)	42.6%	30.8%	24.6%
Terminal Rates (c)	6/26 (23%)	6/29 (21%)	7/34 (21%)
Day of First Observation	452	568	654
Life Table Tests (d)	P=0.024N	P=0.171N	P=0.031N
Logistic Regression Tests (d)	P=0.037N	P=0.168N	P=0.050N
Cochran-Armitage Trend Test (d)	P=0.064N		
Fisher Exact Test (d)		P=0.184N	P=0.083N

(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 logistic regression 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 D4a. HISTORICAL INCIDENCE OF FORESTOMACH SQUAMOUS CELL PAPILLOMAS IN FEMALE B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls
Historical Incidence at Southern Research Institute	
Ethyl acrylate	1/50
Benzyl acetate	0/50
Allyl isovalerate	1/50
HC Red No. 3	0/50
Chlorinated paraffins (43% chlorine)	0/49
Chlorinated paraffins (60% chlorine)	2/50
Allyl isothiocyanate	0/47
Geranyl acetate	0/50
TOTAL	4/396 (1.0%)
SD (b)	1.51%
Range (c)	
High	2/50
Low	0/50
Overall Historical Incidence	
TOTAL	16/1,709 (0.9%)
SD (b)	1.92%
Range (c)	
High	4/47
Low	0/50

(a) Data as of August 7, 1986, for studies of at least 104 weeks; no malignant squamous cell tumors have been observed.
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE D4b. HISTORICAL INCIDENCE OF ANTERIOR PITUITARY GLAND 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	8/46	2/46	10/46
Benzyl acetate	3/48	0/48	3/48
Allyl isovalerate	11/43	0/43	11/43
HC Red No. 3	4/47	0/47	4/47
Chlorinated paraffins (43% chlorine)	(b) 13/46	0/46	13/46
Chlorinated paraffins (60% chlorine)	18/49	0/49	18/49
Allyl isothiocyanate	3/47	(c) 3/47	6/47
Geranyl acetate	2/44	0/44	2/44
TOTAL	62/370 (16.8%)	5/370 (1.4%)	67/370 (18.1%)
SD (d)	12.22%	2.54%	11.74%
Range (e)			
High	18/49	3/47	18/49
Low	2/44	0/49	2/44
Overall Historical Incidence			
TOTAL	(f) 308/1,562 (19.7%)	(g) 21/1,562 (1.3%)	(f,g) 329/1,562 (21.1%)
SD (d)	9.47%	2.46%	9.84%
Range (e)			
High	20/49	5/47	21/49
Low	2/44	0/49	2/44

(a) Data as of August 7, 1986, for studies of at least 104 weeks
(b) Includes one acidophil adenoma
(c) One acidophil carcinoma was also observed.
(d) Standard deviation
(e) Range and SD are presented for groups of 35 or more animals.
(f) Includes 38 chromophobe adenomas and 1 acidophil adenoma
(g) Includes five adenocarcinomas, NOS; one acidophil carcinoma was also observed.

TABLE D4c. HISTORICAL INCIDENCE OF HEMATOPOIETIC SYSTEM TUMORS IN FEMALE B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls	
	Lymphoma	Lymphoma or Leukemia
Historical Incidence at Southern Research Institute		
Ethyl acrylate	11/50	11/50
Benzyl acetate	5/50	6/50
Allyl isovalerate	11/50	11/50
HC Red No. 3	4/50	4/50
Chlorinated paraffins (43% chlorine)	15/50	15/50
Chlorinated paraffins (60% chlorine)	12/50	12/50
Allyl isothiocyanate	5/50	5/50
Geranyl acetate	6/50	6/50
TOTAL	69/400 (17.3%)	70/400 (17.5%)
SD (b)	8.21%	7.98%
Range (c)		
High	15/50	15/50
Low	4/50	4/50
Overall Historical Incidence		
TOTAL	468/1,744 (26.8%)	483/1,744 (27.7%)
SD (b)	9.65%	9.71%
Range (c)		
High	22/50	23/50
Low	4/50	4/50

(a) Data as of August 7, 1986, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

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

	Vehicle Control	Low Dose	High Dose
Animals initially in study	50	50	50
Animals removed	50	50	50
Animals examined histopathologically	50	50	50
ALIMENTARY SYSTEM			
Esophagus	(49)	(48)	(50)
Diverticulum	1 (2%)		
Necrosis	1 (2%)		
Muscularis, inflammation, chronic		1 (2%)	
Gallbladder	(33)	(41)	(45)
Cyst			1 (2%)
Infiltration cellular, lymphocytic		1 (2%)	1 (2%)
Intestine large	(49)	(50)	(50)
Cecum, hyperplasia, lymphoid	2 (4%)		
Cecum, mucosa, necrosis			1 (2%)
Intestine small	(46)	(49)	(48)
Duodenum, amyloid deposition			1 (2%)
Duodenum, hyperplasia, re cell	1 (2%)		
Ileum, amyloid deposition			3 (6%)
Jejunum, amyloid deposition			2 (4%)
Jejunum, fibrosis		1 (2%)	
Jejunum, inflammation, suppurative		1 (2%)	
Jejunum, necrosis		1 (2%)	
Jejunum, Peyer's patch, hyperplasia, lymphoid		1 (2%)	3 (6%)
Jejunum, Peyer's patch, hyperplasia, mononuclear cell	1 (2%)		
Mucosa, ileum, dysplasia	1 (2%)		
Submucosa, ileum, infiltration cellular, plasma cell	1 (2%)		
Liver	(50)	(50)	(50)
Angiectasis			1 (2%)
Clear cell focus			1 (2%)
Fibrosis			1 (2%)
Hematopoietic cell proliferation	8 (16%)	5 (10%)	3 (6%)
Infiltration cellular, mononuclear cell			1 (2%)
Inflammation, chronic	15 (30%)	5 (10%)	13 (26%)
Inflammation, chronic active	2 (4%)	3 (6%)	1 (2%)
Inflammation, suppurative		1 (2%)	
Bile duct, cyst	1 (2%)		1 (2%)
Hepatocyte, cytoplasmic alteration	1 (2%)		1 (2%)
Hepatocyte, karyomegaly	1 (2%)	1 (2%)	1 (2%)
Hepatocyte, necrosis	5 (10%)	8 (16%)	5 (10%)
Hepatocyte, vacuolization cytoplasmic	4 (8%)	2 (4%)	4 (8%)
Kupffer cell, hyperplasia	3 (6%)	5 (10%)	4 (8%)
Kupffer cell, pigmentation	3 (6%)		
Mesentery	(13)	(10)	(7)
Inflammation, chronic	1 (8%)	2 (20%)	
Inflammation, chronic active		1 (10%)	
Inflammation, suppurative	5 (38%)	2 (20%)	1 (14%)
Artery, hypertrophy	1 (8%)		
Artery, inflammation, chronic	2 (15%)		
Fat, inflammation, chronic active			1 (14%)
Fat, mineralization			3 (43%)
Fat, necrosis, focal	1 (8%)	1 (10%)	4 (57%)

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

	Vehicle Control	Low Dose	High Dose
ALIMENTARY SYSTEM (Continued)			
Pancreas	(47)	(49)	(49)
Atrophy	2 (4%)		1 (2%)
Cytoplasmic alteration	1 (2%)		1 (2%)
Hyperplasia, focal	1 (2%)		
Infarct	1 (2%)		
Inflammation, chronic	4 (9%)	3 (6%)	1 (2%)
Acinus, vacuolization cytoplasmic			1 (2%)
Salivary glands	(49)	(50)	(50)
Inflammation, chronic	5 (10%)	6 (12%)	7 (14%)
Inflammation, suppurative			1 (2%)
Stomach	(49)	(49)	(50)
Forestomach, cyst	1 (2%)		
Forestomach, diverticulum	1 (2%)		1 (2%)
Forestomach, erosion	1 (2%)		
Forestomach, foreign body			1 (2%)
Forestomach, hyperplasia, focal	6 (12%)	6 (12%)	5 (10%)
Forestomach, inflammation, acute	1 (2%)		
Forestomach, inflammation, chronic	1 (2%)		
Forestomach, inflammation, chronic active		2 (4%)	2 (4%)
Forestomach, inflammation, suppurative			2 (4%)
Forestomach, mineralization		1 (2%)	
Forestomach, mucosa, hyperplasia, focal		1 (2%)	
Glandular, atrophy			1 (2%)
Glandular, cyst		2 (4%)	
Glandular, edema	1 (2%)		
Glandular, erosion	1 (2%)		
Glandular, hemorrhage		1 (2%)	
Glandular, inflammation, chronic	1 (2%)		
Glandular, inflammation, suppurative	3 (6%)		1 (2%)
Glandular, metaplasia, squamous		1 (2%)	1 (2%)
Glandular, mineralization	5 (10%)	1 (2%)	
Glandular, necrosis		1 (2%)	
CARDIOVASCULAR SYSTEM			
Blood vessel	(1)	(1)	(1)
Inflammation, chronic, multiple	1 (100%)		
Inflammation, chronic active, multiple		1 (100%)	
Aorta, mineralization			1 (100%)
Heart	(50)	(50)	(50)
Thrombus		2 (4%)	
Artery, mineralization		1 (2%)	
Coronary artery, inflammation, chronic	2 (4%)		
Coronary artery, media, hypertrophy	1 (2%)		
Endocardium, inflammation, chronic active			1 (2%)
Endocardium, inflammation, suppurative		1 (2%)	
Myocardium, angiectasis	1 (2%)		
Myocardium, fibrosis	3 (6%)		
Myocardium, inflammation, chronic	2 (4%)		1 (2%)
Myocardium, inflammation, chronic active		2 (4%)	1 (2%)
Myocardium, inflammation, suppurative	3 (6%)		
Myocardium, mineralization			1 (2%)
Pericardium, inflammation, chronic active		1 (2%)	
Pericardium, inflammation, suppurative	1 (2%)		
Valve, inflammation, suppurative		1 (2%)	
Ventricle, embolus bacterial			1 (2%)

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

	Vehicle Control	Low Dose	High Dose
ENDOCRINE SYSTEM			
Adrenal gland	(50)	(49)	(50)
Hematopoietic cell proliferation	2 (4%)	2 (4%)	
Cortex, cyst	1 (2%)		
Cortex, degeneration, fatty	4 (8%)	2 (4%)	2 (4%)
Cortex, developmental malformation	1 (2%)	3 (6%)	
Cortex, hyperplasia, focal	1 (2%)	1 (2%)	
Cortex, necrosis		1 (2%)	1 (2%)
Cortex, vacuolization cytoplasmic		1 (2%)	
Medulla, angiectasis			1 (2%)
Medulla, vacuolization cytoplasmic	1 (2%)		
Spindle cell, hyperplasia	40 (80%)	43 (88%)	48 (96%)
Islets, pancreatic	(46)	(49)	(49)
Hyperplasia			7 (14%)
Parathyroid gland	(46)	(43)	(41)
Cyst	3 (7%)	3 (7%)	
Ectopic thymus	1 (2%)		
Pituitary gland	(45)	(45)	(44)
Angiectasis	1 (2%)	2 (4%)	6 (14%)
Pars distalis, angiectasis	2 (4%)		2 (5%)
Pars distalis, cyst	1 (2%)		1 (2%)
Pars distalis, hyperplasia	13 (29%)	11 (24%)	13 (30%)
Pars intermedia, hyperplasia			1 (2%)
Thyroid gland	(49)	(48)	(50)
Infiltration cellular, lymphocytic	2 (4%)	4 (8%)	2 (4%)
Inflammation, chronic active		1 (2%)	
Inflammation, suppurative	1 (2%)	1 (2%)	
Ultimobranchial cyst		1 (2%)	
Follicle, dilatation	6 (12%)	8 (17%)	8 (16%)
Follicle, hyperplasia			1 (2%)
Follicular cell, hyperplasia	5 (10%)	6 (13%)	6 (12%)
GENERAL BODY SYSTEM			
Tissue, NOS	(7)	(2)	
Foreign body	6 (86%)	2 (100%)	
Hemorrhage		1 (50%)	
Inflammation, chronic active		1 (50%)	
Inflammation, suppurative	6 (86%)	1 (50%)	
GENITAL SYSTEM			
Ovary	(46)	(47)	(49)
Amyloid deposition			1 (2%)
Angiectasis			2 (4%)
Cyst	18 (39%)	16 (34%)	19 (39%)
Hemorrhage	3 (7%)	1 (2%)	7 (14%)
Inflammation, chronic	1 (2%)		
Inflammation, chronic active		1 (2%)	
Inflammation, suppurative	7 (15%)	5 (11%)	2 (4%)
Mineralization		1 (2%)	
Oviduct	(1)	(1)	
Inflammation, chronic		1 (100%)	
Uterus	(50)	(50)	(50)
Angiectasis	1 (2%)		1 (2%)
Hemorrhage		1 (2%)	
Hydrometria	1 (2%)	1 (2%)	1 (2%)
Hyperplasia, cystic	40 (80%)	41 (82%)	45 (90%)

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

	Vehicle Control	Low Dose	High Dose
GENITAL SYSTEM			
Uterus (Continued)	(50)	(50)	(50)
Hyperplasia, cystic, multiple	1 (2%)		
Hyperplasia, glandular	1 (2%)		2 (4%)
Inflammation, chronic	2 (4%)		1 (2%)
Inflammation, suppurative	8 (16%)	13 (26%)	7 (14%)
Endometrium, edema		1 (2%)	
Endometrium, vacuolization cytoplasmic			1 (2%)
Mucosa, metaplasia, squamous		1 (2%)	2 (4%)
Vagina	(1)		(1)
Hyperplasia, squamous			1 (100%)
HEMATOPOIETIC SYSTEM			
Bone marrow	(50)	(50)	(50)
Hyperplasia	14 (28%)	10 (20%)	2 (4%)
Hyperplasia, reticulum cell	1 (2%)		1 (2%)
Infiltration cellular, mononuclear cell		1 (2%)	
Myelofibrosis	1 (2%)		
Lymph node	(48)	(49)	(49)
Bronchial, inflammation, suppurative		1 (2%)	
Iliac, hematopoietic cell proliferation	1 (2%)		
Iliac, hyperplasia, lymphoid	1 (2%)		
Iliac, hyperplasia, plasma cell	1 (2%)	3 (6%)	
Inguinal, hyperplasia, lymphoid	1 (2%)		
Lymphatic, mandibular, ectasia	1 (2%)		
Mandibular, hyperplasia, histiocyte		1 (2%)	
Mandibular, hyperplasia, lymphoid	1 (2%)	2 (4%)	4 (8%)
Mandibular, hyperplasia, plasma cell	3 (6%)	1 (2%)	1 (2%)
Mandibular, necrosis, diffuse			1 (2%)
Mandibular, pigmentation		2 (4%)	3 (6%)
Mediastinal, angiectasis	1 (2%)		
Mediastinal, hematopoietic cell proliferation	1 (2%)	1 (2%)	
Mediastinal, hemorrhage		1 (2%)	
Mediastinal, hyperplasia, histiocyte	1 (2%)	1 (2%)	1 (2%)
Mediastinal, hyperplasia, plasma cell		2 (4%)	
Mediastinal, inflammation, suppurative		1 (2%)	
Mesenteric, angiectasis	1 (2%)		1 (2%)
Mesenteric, atrophy	1 (2%)		
Mesenteric, hematopoietic cell proliferation	3 (6%)	2 (4%)	1 (2%)
Mesenteric, hemorrhage	7 (15%)	5 (10%)	4 (8%)
Mesenteric, hyperplasia, histiocyte	1 (2%)	1 (2%)	2 (4%)
Mesenteric, hyperplasia, lymphoid	2 (4%)	3 (6%)	
Mesenteric, hyperplasia, plasma cell	1 (2%)	1 (2%)	
Mesenteric, infiltration cellular, polymorphonuclear	1 (2%)		
Mesenteric, inflammation, granulomatous	1 (2%)		
Mesenteric, lymphatic, ectasia	1 (2%)		
Pancreatic, hyperplasia, lymphoid			2 (4%)
Pancreatic, necrosis			1 (2%)
Renal, hematopoietic cell proliferation	1 (2%)		
Renal, hyperplasia, lymphoid	1 (2%)		2 (4%)
Renal, hyperplasia, plasma cell	4 (8%)	1 (2%)	1 (2%)
Renal, inflammation, suppurative	1 (2%)		
Spleen	(48)	(49)	(50)
Fibrosis		1 (2%)	
Hematopoietic cell proliferation granulocytic	8 (17%)	8 (16%)	2 (4%)
Hematopoietic cell proliferation erythrocytic	9 (19%)	8 (16%)	7 (14%)
Hemorrhage		1 (2%)	
Hyperplasia, lymphoid	4 (8%)	4 (8%)	7 (14%)
Hyperplasia, megakaryocyte		1 (2%)	
Necrosis		1 (2%)	
Red pulp, pigmentation			1 (2%)

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

	Vehicle Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM (Continued)			
Thymus	(41)	(43)	(45)
Atrophy	2 (5%)	4 (9%)	2 (4%)
Cyst	2 (5%)		3 (7%)
Hyperplasia, lymphoid	1 (2%)	1 (2%)	
Mineralization		1 (2%)	
Necrosis, diffuse	2 (5%)		
Medulla, hyperplasia, mononuclear cell	1 (2%)		
INTEGUMENTARY SYSTEM			
Mammary gland	(48)	(48)	(49)
Hyperplasia, cystic	12 (25%)	7 (15%)	9 (18%)
Hyperplasia, lobular	1 (2%)		
Skin	(50)	(49)	(50)
Acanthosis	1 (2%)	2 (4%)	3 (6%)
Exudate			1 (2%)
Inflammation, chronic active	1 (2%)		
Inflammation, granulomatous		1 (2%)	
Inflammation, suppurative			1 (2%)
Ulcer	1 (2%)		
MUSCULOSKELETAL SYSTEM			
Bone	(50)	(50)	(50)
Hyperostosis	15 (30%)	15 (30%)	14 (28%)
Necrosis	1 (2%)		
Cranium, hyperostosis	1 (2%)		
Skeletal muscle	(4)	(2)	(1)
Inflammation, chronic	1 (25%)		
Inflammation, chronic active		1 (50%)	
Mineralization			1 (100%)
NERVOUS SYSTEM			
Brain	(50)	(50)	(50)
Cerebellum, degeneration, multifocal			1 (2%)
Cerebellum, hemorrhage	1 (2%)	1 (2%)	1 (2%)
Cerebellum, infiltration cellular, lymphocytic	2 (4%)		
Cerebrum, hemorrhage	1 (2%)	1 (2%)	
Cerebrum, infiltration cellular, lymphocytic	1 (2%)		
Hippocampus, necrosis			1 (2%)
Meninges, infiltration cellular, lymphocytic			2 (4%)
Meninges, infiltration cellular, polymorphonuclear			1 (2%)
Thalamus, degeneration			1 (2%)
Thalamus, hemorrhage	1 (2%)		1 (2%)
Thalamus, infiltration cellular, lymphocytic	1 (2%)		
Thalamus, mineralization	24 (48%)	25 (50%)	18 (36%)
Vein, adventitia, infiltration cellular, lymphocytic	1 (2%)	1 (2%)	
Ventricle, hydrocephalus			1 (2%)
Ventricle, mineralization		1 (2%)	
Peripheral nerve	(41)	(49)	(45)
Degeneration		1 (2%)	1 (2%)
Infiltration cellular, plasma cell		1 (2%)	
Infiltration cellular, lymphocytic	1 (2%)	1 (2%)	2 (4%)

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

	Vehicle Control	Low Dose	High Dose
RESPIRATORY SYSTEM			
Lung	(50)	(50)	(50)
Adenomatosis			1 (2%)
Bacterium		1 (2%)	
Hemorrhage	1 (2%)		
Infiltration cellular, histiocytic	2 (4%)	2 (4%)	2 (4%)
Inflammation, chronic	24 (48%)	17 (34%)	19 (38%)
Inflammation, suppurative	2 (4%)	1 (2%)	1 (2%)
Alveolar epithelium, hyperplasia		1 (2%)	
Artery, inflammation, chronic active		1 (2%)	
Artery, inflammation, suppurative		1 (2%)	
Artery, mineralization			1 (2%)
Interstitium, edema	3 (6%)		2 (4%)
Pleura, inflammation, chronic		1 (2%)	
Pleura, inflammation, chronic active		1 (2%)	
Pleura, inflammation, suppurative	8 (16%)	2 (4%)	
Nose	(43)	(44)	(47)
Foreign body	1 (2%)	4 (9%)	2 (4%)
Fungus		1 (2%)	1 (2%)
Hemorrhage			3 (6%)
Inflammation, chronic	4 (9%)	1 (2%)	
Inflammation, chronic active	3 (7%)		
Inflammation, suppurative	26 (60%)	29 (66%)	33 (70%)
Mucosa, atrophy		1 (2%)	
Mucosa, necrosis		1 (2%)	
Submucosa, hyperplasia, lymphoid			2 (4%)
Trachea	(49)	(49)	(49)
Foreign body	2 (4%)		
Glands, inflammation, suppurative	1 (2%)		
SPECIAL SENSES SYSTEM			
Ear			(2)
Middle ear, inflammation, suppurative			2 (100%)
Harderian gland	(3)	(3)	(3)
Infiltration cellular, lymphocytic	1 (33%)		
URINARY SYSTEM			
Kidney	(49)	(50)	(50)
Casts	12 (24%)	10 (20%)	7 (14%)
Cyst	1 (2%)	2 (4%)	
Glomerulosclerosis	1 (2%)	2 (4%)	
Hydronephrosis		1 (2%)	
Infarct	1 (2%)	2 (4%)	
Inflammation, chronic	30 (61%)	24 (48%)	26 (52%)
Inflammation, suppurative	1 (2%)	2 (4%)	1 (2%)
Metaplasia, osseous	2 (4%)	3 (6%)	1 (2%)
Pigmentation		1 (2%)	
Artery, inflammation, chronic	1 (2%)		
Artery, media, hypertrophy	1 (2%)		
Glomerulus, inflammation, chronic active		1 (2%)	
Renal tubule, atrophy	3 (6%)	1 (2%)	5 (10%)
Renal tubule, degeneration	1 (2%)		
Renal tubule, dilatation	1 (2%)		
Renal tubule, mineralization		2 (4%)	
Renal tubule, regeneration	8 (16%)	5 (10%)	6 (12%)
Urinary bladder	(44)	(45)	(49)
Edema	1 (2%)		
Inflammation, chronic	19 (43%)	13 (29%)	13 (27%)
Inflammation, suppurative	1 (2%)		

APPENDIX E

GENETIC TOXICOLOGY OF DICHLORVOS

TABLE E1. MUTAGENICITY OF DICHLORVOS IN *SALMONELLA TYPHIMURIUM* (a)

Strain	Dose (µg/plate)	Revertants/Plate (b)					
		-S9		+30% S9 (hamster)		+30% S9 (rat)	
		Trial 1	Trial 2	Trial 1	Trial 2	Trial 1	Trial 2
TA100	0	86 ± 4.8	78 ± 7.9	79 ± 4.6	92 ± 2.4	78 ± 4 5	92 ± 5.5
	100	101 ± 1.0	93 ± 4.7	70 ± 11.3	97 ± 9 7	105 ± 1 7	95 ± 3.6
	333	134 ± 8 4	167 ± 9.6	102 ± 12.9	132 ± 3 8	112 ± 1 3	139 ± 9.0
	1,000	299 ± 3.7	471 ± 10.4	193 ± 9.9	190 ± 11.3	181 ± 4 4	170 ± 8 0
	3,333	(c) 390 ± 21.4	(c) 326 ± 36.8	391 ± 20.7	315 ± 5.6	339 ± 6 7	279 ± 3.9
	5,000		(c) 71 ± 36.2	-	(c) 291 ± 14.5	-	(c) 183 ± 3 0
	6,666	Toxic	--	(c) 0 ± 0.0	-	(c) 223 ± 27.6	-
	Trial summary	Positive	Positive	Positive	Positive	Positive	Positive
	Positive control (d)	279 ± 12.1	363 ± 14.0	511 ± 9.4	390 ± 9 9	297 ± 11.0	318 ± 7 9
TA98	0	17 ± 1 8	17 ± 2.0	27 ± 5.3	--	22 ± 4 4	-
	100	19 ± 4.7	19 ± 0.9	21 ± 2.2	--	23 ± 0.0	--
	333	14 ± 1.5	18 ± 1.5	24 ± 2.3	--	23 ± 3 8	--
	1,000	25 ± 4.3	19 ± 1.5	21 ± 0.9	--	28 ± 4 6	--
	3,333	(c) 32 ± 4.3	(c) 27 ± 2.2	32 ± 3.5	--	25 ± 0.9	--
	5,000	--	(c) 10 ± 3 2	--	--	--	--
	6,666	Toxic	--	(c) 9 ± 2.5	--	Toxic	-
	Trial summary	Equivocal	Negative	Negative	--	Negative	--
	Positive control (d)	225 ± 24.8	171 ± 9.4	113 ± 5.3	--	108 ± 5.9	--

(a) Study performed at Microbiological Associates. The detailed protocol is presented in Haworth et al (1983). Cells and study compound or solvent (dimethyl sulfoxide) were incubated in the absence of exogenous metabolic activation (-S9) or with Aroclor 1254-induced S9 from male Syrian hamster liver or male Sprague Dawley rat liver. High dose was limited by toxicity or solubility but did not exceed 10 mg/plate; 0 µg/plate dose is the solvent control.
(b) Revertants are presented as mean ± standard error from three plates.
(c) Slight toxicity
(d) Positive control; 2-aminoanthracene was used on all strains in the presence of S9. In the absence of metabolic activation, 4-nitro-*o*-phenylenediamine was used with TA98 and sodium azide was used with TA100.

TABLE E2. INDUCTION OF TRIFLUOROTHYMIDINE RESISTANCE IN MOUSE L5178Y LYMPHOMA CELLS BY DICHLORVOS (a,b)

Compound	Concentration (nl/ml)	Cloning Efficiency (percent)	Relative Total Growth (percent)	Tft-Resistant Cells	Mutant Fraction (c)
Trial 1					
Ethanol		70.7 ± 4 5	99.7 ± 13.9	100.3 ± 22 0	46.3 ± 7.9
Dichlorvos	(d) 12 5	51.0 ± 2.0	98.5 ± 10.5	73 5 ± 3.5	48 0 ± 4.0
	25	59.0 ± 9.2	98.0 ± 3.5	80.3 ± 8.1	47 3 ± 6.4
	100	50.0 ± 10.5	19 0 ± 7.2	488.0 ± 2.1	(e) 350 7 ± 61 6
	200	Lethal	--	--	--
Methyl methanesulfonate	(f) 5	57	61	537	313
Trial 2					
Ethanol		106 7 ± 5 9	100.0 ± 8.0	138 7 ± 18 5	44 0 ± 7 6
Dichlorvos	6.25	89.3 ± 7 9	79.3 ± 5.7	119.7 ± 12.0	45.0 ± 3.5
	12.5	94.3 ± 7.4	50.7 ± 4.3	213 7 ± 47.3	(e) 73.3 ± 11.3
	25	69 7 ± 2.4	14.0 ± 5 5	634 0 ± 76.4	(e) 305.3 ± 45.4
	50	Lethal	--	--	--
Methyl methanesulfonate	5	71.7 ± 4 7	59.7 ± 7.0	513.7 ± 49.3	(e) 237.7 ± 8.2

(a) Study performed at Litton Bionetics, Inc. The experimental protocol is presented in detail by Myhr et al. (1985) and follows the basic format of Clive et al. (1979). The highest dose of study compound is determined by solubility or toxicity and may not exceed 5 mg/ml. All doses are tested in triplicate; the average for the three tests (Unless otherwise indicated) is presented in the table. Cells (6×10^5/ml) were treated for 4 hours at 37° C in medium, washed, resuspended in medium, and incubated for 48 hours at 37° C. After expression, 3×10^6 cells were plated in medium and soft agar supplemented with trifluorothymidine (Tft) for selection of Tft-resistant cells, and 600 cells were plated in nonselective medium and soft agar to determine the cloning efficiency. All trials were conducted without metabolic activation.

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

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

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

(e) Significant positive response, occurs when the relative mutant fraction (average MF of treated culture/average MF of solvent control) is greater than or equal to 1 6

(f) Results of one test

TABLE E3. INDUCTION OF SISTER CHROMATID EXCHANGES IN CHINESE HAMSTER OVARY CELLS BY DICHLORVOS (a)

Compound	Dose (µg/ml)	Total Cells	Number of Chromosomes	Number of SCEs	SCEs/ Chromo-some	SCEs/ Cell	Hours in BrdU	Relative SCEs/Cell (percent) (b)
−S9 (c)								
Trial 1--Summary: Equivocal								
Dimethyl sulfoxide		50	1,042	456	0.44	9.1	26.0	--
Dichlorvos	1.6	50	1,050	357	0.34	7.1	26.0	78.0
	5	50	1,028	449	0.44	9.0	26.0	98.9
	16	50	1,040	587	0.56	11.7	26.0	128.6
Mitomycin C	0.003	50	1,036	1,537	1.48	30.7	26.0	337.4
Trial 2--Summary: Positive								
Dimethyl sulfoxide		50	1,031	435	0.42	8.7	26.0	--
Dichlorvos	1	50	1,027	422	0.41	8.4	26.0	96.6
	5	50	1,025	497	0.48	9.9	26.0	113.8
	10	50	1,034	656	0.63	13.1	26.0	150.6
	25	50	1,028	855	0.83	17.1	(d) 41.0	196.6
	50	50	1,044	1,162	1.11	23.2	(d) 41.0	266.7
Mitomycin C	0.005	50	1,039	1,385	1.33	27.7	26.0	318.4
+S9 (e)								
Trial 1--Summary: Positive								
Dimethyl sulfoxide		50	1,029	455	0.44	9.1	26.0	--
Dichlorvos	50	50	1,033	488	0.47	9.8	26.0	107.7
	160	50	1,043	601	0.58	12.0	26.0	131.9
	500	45	921	1,187	1.29	26.4	26.0	290.1
Cyclophosphamide	2	50	1,035	3,489	3.37	69.8	26.0	767.0
Trial 2--Summary: Positive								
Dimethyl sulfoxide		50	1,040	449	0.43	9.0	26.0	--
Dichlorvos								
	100	50	1,038	527	0.51	10.5	26.0	116.7
	200	50	1,039	742	0.71	14.8	26.0	164.4
	300	50	1,033	834	0.81	16.7	26.0	185.6
	400	50	1,028	949	0.92	19.0	26.0	211.1
	500	50	1,034	1,197	1.16	23.9	26.0	265.6
Cyclophosphamide	1.5	50	1,043	1,441	1.38	28.8	26.0	320.0

TABLE E3. INDUCTION OF SISTER CHROMATID EXCHANGES IN CHINESE HAMSTER OVARY CELLS BY DICHLORVOS (a)

(a) Study performed at Environmental Health Research and Testing Laboratory. SCE = sister chromatid exchange; BrdU = bromodeoxyuridine. A detailed description of the SCE protocol is presented by Galloway et al. (1985). Briefly, Chinese hamster ovary cells were incubated with study compound or solvent (dimethyl sulfoxide) as described in (c) or (e) below and cultured for sufficient time to reach second metaphase division. Cells were then collected by mitotic shake-off, fixed, air-dried, and stained.
(b) SCEs/cell in treated culture expressed as a percent of the SCEs/cell in the control culture
(c) In the absence of S9, Chinese hamster ovary cells were incubated with study compound or solvent for 2 hours at 37° C. Then BrdU was added, and incubation was continued for 24 hours. Cells were washed, fresh medium containing BrdU and colcemid was added, and incubation was continued for 2-3 hours.
(d) Because some chemicals induce a delay in the cell division cycle, harvest times are occasionally extended to maximize the proportion of second division cells available for analysis.
(e) In the presence of S9, cells were incubated with study compound or solvent for 2 hours at 37° C. Then cells were washed, and medium containing BrdU was added. Cells were incubated for a further 26 hours, with colcemid present for the final 2-3 hours. S9 was from the liver of Aroclor 1254-induced male Sprague Dawley rats.

TABLE E4. INDUCTION OF CHROMOSOMAL ABERRATIONS IN CHINESE HAMSTER OVARY CELLS BY DICHLORVOS (a)

Trial 1					Trial 2				
Dose (µg/ml)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells with Abs	Dose (µg/ml)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells with Abs
−S9 (b)--Harvest time 12.5 h					−S9 (b)--Harvest time 12.5 h				
Dimethyl sulfoxide					Dimethyl sulfoxide				
	100	2	0.02	2		100	1	0.01	1
Dichlorvos					Dichlorvos				
16	100	4	0.04	4	50	100	4	0.04	4
50	100	5	0.05	5	100	100	5	0.05	5
160	100	22	0.22	21	160	100	16	0.16	16
(d) 160	100	55	0.55	41					
Summary: Positive					Summary: Positive				
Mitomycin C					Mitomycin C				
0.250	100	58	0.58	40	0.250	100	57	0.57	42
+S9 (c)--Harvest time 12.0 h					+S9 (c)--Harvest time 12.5 h				
Dimethyl sulfoxide					Dimethyl sulfoxide				
	100	3	0.03	3		100	3	0.03	3
Dichlorvos					Dichlorvos				
50	100	7	0.07	5	500	100	8	0.08	7
50	100	4	0.04	3	750	100	33	0.33	23
160	100	8	0.08	8	1,000	100	70	0.70	46
(d) 160	100	65	0.65	44					
500	100	19	0.19	19					
(d) 500	100	55	0.55	42					
Summary: Positive					Summary: Positive				
Cyclophosphamide					Cyclophosphamide				
50	100	46	0.46	37	50	100	59	0.59	40

(a) Study performed at Environmental Health Research and Testing Laboratory. Abs = aberrations. A detailed presentation of the technique for detecting chromosomal aberrations is found in Galloway et al. (1985). Briefly, Chinese hamster ovary cells were incubated with study compound or solvent (dimethyl sulfoxide) as indicated in (b) or (c). Cells were arrested in first metaphase by addition of colcemid and harvested by mitotic shake-off, fixed, and stained in 6% Giemsa.
(b) In the absence of S9, Chinese hamster ovary cells were incubated with study compound or solvent (dimethyl sulfoxide) for 8-10 hours at 37° C. Cells were then washed, and fresh medium containing colcemid was added for an additional 2-3 hours followed by harvest.
(c) In the presence of S9, cells were incubated with study compound or solvent (dimethyl sulfoxide) for 2 hours at 37° C. Cells were then washed, medium was added, and incubation was continued for 8-10 hours. Colcemid was added for the last 2-3 hours of incubation before harvest. S9 was from the liver of Aroclor 1254-induced male Sprague Dawley rats.
(d) Culture harvested at 17.5 h

TABLE E5. INDUCTION OF SISTER CHROMATID EXCHANGES IN MOUSE BONE MARROW CELLS BY DICHLORVOS (a)

Compound	Dose (mg/kg) (b)	Mean SCEs/Cell (c)
Study Performed at Brookhaven National Laboratory		
Phosphate-buffered saline		4.2 ± 0.52
Dichlorvos	6.25 (0.03)	4.3 ± 0.73
	12.5 (0.06)	5.1 ± 0.67
	25 (0.11)	3.7 ± 0.36
Trend P value (d) = 0.2878		
Ethylmethane sulfonate (e)	100	15.0 ± 2.36
Phosphate-buffered saline (f)		4.9 ± 0.39
Pairwise P value (g) = 0.0112		
Study Performed at Oak Ridge Associated Universities		
Corn oil		4.6 ± 0.54
Dichlorvos	10 (0.05)	4.8 ± 0.23
	20 (0.09)	4.9 ± 0.21
	40 (0.18)	4.5 ± 0.14
Trend P value (d) = 0.4022		
Ethylmethane sulfonate (e)	93.75	9.67 ± 0.67
Phosphate-buffered saline (f)		4.41 ± 0.34
Pairwise P value (g) = 0.0007		

(a) SCE = sister chromatid exchange; doses are determined by the solubility of the chemical, its lethality in the animals, and/or cell cycle delay induced by chemical exposure. A range-finding study was performed to determine the appropriate dosing regimen. Based on animal mortality, the maximum dose was set at 25 mg/kg at Brookhaven National Laboratory and 40 mg/kg at Oak Ridge Associated Universities. Male B6C3F$_1$ mice (four animals per dose group) were subcutaneously implanted with a 50-mg bromodeoxyuridine tablet (McFee et al., 1983), 1 hour before an intraperitoneal injection of dichlorvos dissolved in solvent (saline or corn oil (injection volume: 0.2 ml). Solvent control mice received an equivalent injection of saline (Brookhaven or corn oil (Oak Ridge). Two hours before being killed, the mice received an intraperitoneal injection of 2 mg/kg colchicine (in saline). Seventeen hours after chemical administration, the animals were killed by cervical dislocation. One or both femurs were removed, and the marrow was flushed out with 5 ml phosphate-buffered saline (pH 7.0). The cells were treated with a hypotonic salt solution, fixed, and dropped onto chilled slides. After a 24-hour drying period, the slides were stained by the fluorescence plus-Giemsa method and scored. Twenty-five second-division metaphase cells were scored from each of four animals per treatment.
(b) Millimole equivalents are in parentheses.
(c) Mean ± standard error of the mean
(d) One-tailed trend test (Margolin et al., 1986)
(e) Positive control
(f) Solvent control for the ethylmethane sulfonate test
(g) Pairwise comparison between dosed group and solvent control group conducted with Student's one-tailed *t*-test

TABLE E6. INDUCTION OF CHROMOSOMAL ABERRATIONS IN MOUSE BONE MARROW CELLS BY DICHLORVOS (a)

Compound	Dose (mg/kg)	Aberrations/Cell (b)	Damaged Cells (b) (percent)
Study Performed at Brookhaven National Laboratory (c)			
Phosphate-buffered saline		0.03 ± 0.01	2.5 ± 0.63
Dichlorvos	6.25	0.02 ± 0.01	0.8 ± 0.53
	12.5	0.02 ± 0.01	1.8 ± 0.45
	25	0.02 ± 0.01	1.8 ± 0.70
Trend P value (d)		0.2571	0.3782
Ethylmethane sulfonate (e)	300	0.11 ± 0.02	10.3 ± 1.44
Phosphate-buffered saline (f)		0.04 ± 0.18	3.0 ± 1.00
Pairwise P value (g)		0.0122	0.0006
Study Performed at Oak Ridge Associated Universities (h)			
Corn oil		0.03 ± 0.01	3.3 ± 0.50
Dichlorvos	10	0.07 ± 0.04	3.8 ± 1.25
	20	0.03 ± 0.01	2.5 ± 0.65
	40	0.04 ± 0.01	3.5 ± 0.96
Trend P value (d)		0.2571	0.3782
Ethylmethane sulfonate (e)	375	0.09 ± 0.01	4.8 ± 0.75
Phosphate-buffered saline (f)		0.03 ± 0.02	2.0 ± 1.03
Pairwise P value (g)		0.0650	0.0186

(a) Doses are determined by the solubility of the chemical, its lethality in the animals, and/or cell cycle delay induced by chemical exposure. A range-finding study was performed first to determine the appropriate dosing regimen. Based on excessive animal mortality, the maximum dose was set at 25 mg/kg at Brookhaven National Laboratory and 40 mg/kg at Oak Ridge Associated Universities. Male B6C3F$_1$ mice were then subcutaneously implanted with a 50-mg bromodeoxyuridine (BrdU) tablet (McFee et al., 1983), 1 hour before an intraperitoneal injection of dichlorvos dissolved in solvent (saline or corn oil (injection volume: 0.2 ml). BrdU was used to allow selection of the appropriate cell population for scoring. (Chemically induced chromosomal aberrations are present in maximum number at the first metaphase after administration; they decline in number during subsequent nuclear divisions due to cell death.) Solvent control mice received an equivalent injection of saline (Brookhaven) or corn oil (Oak Ridge). Two hours before being killed, the mice received an intraperitoneal injection of 2 mg/kg colchicine (in saline). Seventeen hours after chemical administration, the animals were killed by cervical dislocation. One or both femurs were removed, and the marrow was flushed out with 5 ml phosphate-buffered saline (pH 7.0). The cells were treated with a hypotonic salt solution, fixed, and dropped onto chilled slides. After a 24-hour drying period, the slides were stained and scored. Responses were evaluated as the percentage of aberrant metaphase cells, excluding gaps. The number of aberrations per cell (excluding gaps) was also analyzed to provide information on the extent of individual cell damage. The data were analyzed by trend test and Student's *t*-test.
(b) Mean ± standard error of the mean
(c) Eight animals per exposure group were scored.
(d) One-tailed trend test (Margolin et al., 1986)
(e) Positive control
(f) Solvent control for the ethylmethane sulfonate test
(g) Pairwise comparison between dose group and solvent control group conducted with Student's one-tailed *t*-test
(h) Four animals per exposure group; 100 cells per animal were scored.

APPENDIX F

SENTINEL ANIMAL PROGRAM

APPENDIX F. SENTINEL ANIMAL PROGRAM

Methods

Rodents used in the Carcinogenesis Program of the National Toxicology Program are produced in optimally clean facilities to eliminate potential pathogens that may affect study results. The Sentinel Animal Program is part of the periodic monitoring of animal health that occurs during the toxicologic evaluation of chemical compounds. Under this program, the disease state of the rodents is monitored via viral serology on sera from extra (sentinel) animals in the study rooms. These animals are untreated, and these animals and the study animals are both subject to identical environmental conditions. The sentinel animals come from the same production source and weanling groups as the animals used for the studies of chemical compounds.

Fifteen B6C3F$_1$ mice and 15 F344/N rats of each sex were selected at the time of randomization and allocation of the animals to the various study groups. Five animals of each designated sentinel group were killed at 6, 12, and 18 months on study. Data from animals surviving 24 months were collected from 5/50 randomly selected vehicle control animals of each sex and species. The blood from each animal was collected and clotted, and the serum was separated. The serum was cooled on ice and shipped to Microbiological Associates' Comprehensive Animal Diagnostic Service for determination of the viral antibody titers. The following tests were performed:

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

Results

Results are presented in Table F1.

TABLE F1. MURINE VIRUS ANTIBODY DETERMINATIONS FOR RATS AND MICE IN THE TWO-YEAR GAVAGE STUDIES OF DICHLORVOS (a)

Interval (months)	Number of Animals	Positive Serologic Reaction for
RATS		
6	10/10	RCV
12	--	None positive
18	1/10	RCV
24	--	None positive
MICE		
6	--	None positive
12	--	None positive
18	--	None positive
24	--	None positive

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

APPENDIX G

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

Pelleted Diet: December 1980 to January 1983

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

TABLE G1. INGREDIENTS OF NIH 07 RAT AND MOUSE RATION (a)

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

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

TABLE G2. VITAMINS AND MINERALS IN NIH 07 RAT AND MOUSE RATION (a)

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

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

TABLE G3. NUTRIENT COMPOSITION OF NIH 07 RAT AND MOUSE RATION (a)

Nutrients	Mean ± Standard Deviation	Range	Number of Samples
Crude protein (percent by weight)	23.85 ± 0.78	22.7-25.3	24
Crude fat (percent by weight)	5.02 ± 0.44	4.2-5.7	24
Crude fiber (percent by weight)	3.31 ± 0.23	2.9-3.8	24
Ash (percent by weight)	6.44 ± 0.44	5.7-7.43	24
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)	10,917 ± 1,876	8,210-15,000	24
Vitamin D (IU/kg)	6,300		1
α-Tocopherol (ppm)	37.6	31.1-44.0	2
Thiamine (ppm) (b)	16.8 ± 2.0	14.0-21.0	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)	1.25 ± 0.15	1.08-1.69	24
Phosphorus (percent)	0.98 ± 0.06	0.88-1.10	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 (7/22/81) not analyzed for thiamine

TABLE G4. CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION

Contaminants	Mean ± Standard Deviation	Range	Number of Samples
Arsenic (ppm)	0.48 ± 0.17	<0.29-1.06	24
Cadmium (ppm) (a)	<0.10		24
Lead (ppm)	1.00 ± 0.74	0.42-3.37	24
Mercury (ppm) (b)	< 0.05		24
Selenium (ppm)	0.29 ± 0.07	0.13-0.40	24
Aflatoxins (ppb) (a,b)	<10	<5.0-<10.0	24
Nitrate nitrogen (ppm) (c)	9.22 ± 3.62	3.8-17.0	24
Nitrite nitrogen (ppm) (c)	2.16 ± 1.53	0.4-6.9	24
BHA (ppm) (d)	6.68 ± 4.95	<0.4-17.0	24
BHT (ppm) (d)	3.45 ± 2.56	0.9-12.0	24
Aerobic plate count (CFU/g) (e)	40,557 ± 29,431	4,900-88,000	23
Aerobic plate count (CFU/g) (f)	77,617 ± 183,824	4,900-930,000	24
Coliform (MPN/g) (g)	16.6 ± 22.9	<3-93	22
Coliform (MPN/g) (h)	80.2 ± 236.3	<3-1,100	24
E. coli (MPN/g) (i)	<3		24
Total nitrosamines (ppb) (j,k)	4.63 ± 4.19	0.8-18.5	21
Total nitrosamines (ppb) (j,l)	27.15 ± 64.35	0.8-273.2	24
N-Nitrosodimethylamine (ppb) (j,k)	3.43 ± 3.96	0.8-16.5	21
N-Nitrosodimethylamine (ppb) (j,l)	25.71 ± 64.90	0.8-272	24
N-Nitrosopyrrolidine (ppb)	1.05 ± 0.49	0.3-2.9	24
Pesticides (ppm)			
α-BHC (a,m)	<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 (n)	<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 PCBs (a)	<0.2		24
Ronnel (a)	<0.01		24
Ethion (a)	<0.02		24
Trithion (a)	<0.05		24
Diazinon (n)	<0.1	0.2 (4/27/81)	24
Methyl parathion (a)	<0.02		24
Ethyl parathion (a)	<0.02		24
Malathion (o)	0.10 ± 0.07	<0.05-0.27	24
Endosulfan I (a)	<0.01		24
Endosulfan II (a)	<0.01		24
Endosulfan sulfate (a)	<0.03		24

TABLE G4. CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION (Continued)

(a) All values were less than the detection limit, given in the table as the mean.
(b) The detection limit was reduced from 10 ppb to 5 ppb after 7/81.
(c) Source of contamination: alfalfa, grains, and fish meal
(d) Source of contamination: soy oil and fish meal
(e) Mean, standard deviation, and range exclude one very high value of 930,000 obtained for the batch produced on 12/22/82; CFU = colony-forming unit.
(f) Mean, standard deviation, and range include the high value listed in footnote (e).
(g) Mean, standard deviation, and range exclude one very high value of 1,100 obtained for the batch produced on 12/16/80 and one high value of 460 obtained in the batch produced on 9/23/82; MPN = most probable number.
(h) Mean, standard deviation, and range include the high values listed in footnote (g).
(i) All values were less than 3 MPN/g.
(j) All values were corrected for percent recovery.
(k) Mean, standard deviation, and range exclude three very high values in the range of 115-273.2 ppb obtained for batches produced on 1/26/81, 2/23/81, and 4/27/81.
(l) Mean, standard deviation, and range include the very high values given in footnote (k).
(m) BHC = hexachlorocyclohexane or benzene hexachloride.
(n) There was one observation above the detection limit; the value and date it was obtained are given under the range.
(o) Thirteen batches contained more than 0.05 ppm.

APPENDIX H

EFFECT OF DICHLORVOS ON

CHOLINESTERASE ACTIVITY

APPENDIX H. CHOLINESTERASE ACTIVITY

Materials and Methods

Groups of 10 male and female 8-week-old F344/N rats and 10 male and female 8-week-old B6C3F$_1$ mice were administered dichlorvos (lot no. SDC092179) in corn oil by gavage at doses of 2, 4, 8, or 16 mg/kg (rats) and 5, 10, 20, or 40 mg/kg (mice) five times per week for plasma and erythrocyte cholinesterase activity measurements on days 10 or 11, 25 or 26, 32 or 33, and 36 or 37. At each time interval, blood was collected for cholinesterase analysis approximately 3 hours after dichlorvos administration (0.5 ml from rats and 0.2 from mice, anesthetized with carbon dioxide) by retro-ocular sinus puncture with a heparinized tube. Activity was measured with an IL Monarch 2000 Chemistry Analyzer with kits from Boehringer Mannheim.

Results

Plasma cholinesterase activity in dosed rats was significantly lower than that in vehicle controls on days 10, 26, and 32 (Table H1). Erythrocyte cholinesterase activity in dosed and vehicle control rats was similar during this period.

Plasma cholinesterase activity was significantly lower in dosed male and female mice on days 11, 25, and 33 (Table H2). Erythrocyte cholinesterase activity in dosed and vehicle control mice was similar during this period.

TABLE H1. CHOLINESTERASE ACTIVITY IN RATS GIVEN DICHLORVOS BY GAVAGE FOR ONE MONTH (a)

	Dose				
	0 mg/kg	2 mg/kg	4 mg/kg	8 mg/kg	16 mg/kg
MALE					
Number examined (b)	10	10	10	8	9
Plasma (U/liter)					
Day 10	635 ± 25	**484 ± 21	**(c) 391 ± 15	**(d) 322 ± 32	**(d) 248 ± 22
Day 24	710 ± 22	**497 ± 25	**297 ± 18	**235 ± 26	**174 ± 20
Day 32	676 ± 22	**434 ± 20	**336 ± 15	**(c) 216 ± 14	**154 ± 17
Erythrocyte (U/liter)					
Day 10	(c) 5,300 ± 498	(c) 6,048 ± 372	(e) 5,540 ± 553	5,585 ± 526	(d) 5,023 ± 576
Day 24	(c) 7,043 ± 244	(e) 6,380 ± 198	*6,040 ± 334	*5,831 ± 347	**5,507 ± 254
Day 32	8,305 ± 149	7,686 ± 205	**6,823 ± 285	**(c) 7,278 ± 218	**6,966 ± 143
FEMALE					
Number examined (b)	9	10	9	9	3
Plasma (U/liter)					
Day 10	(d) 2,305 ± 82	**984 ± 103	**(e) 562 ± 36	**380 ± 13	**(f) 306 ± 29
Day 24	2,669 ± 108	**1,057 ± 58	**535 ± 19	**475 ± 63	**227 ± 37
Day 32	2,671 ± 85	**(e) 889 ± 19	**496 ± 28	**(e) 306 ± 19	**176 ± 24
Erythrocyte (U/liter)					
Day 10	5,280 ± 370	(c) 4,168 ± 411	(e) 4,896 ± 345	(e) 3,921 ± 313	(f) 4,312 ± 889
Day 24	6,836 ± 418	6,926 ± 310	6,311 ± 379	6,494 ± 290	5,536 ± 289
Day 32	8,021 ± 102	(e) 7,587 ± 329	*7,215 ± 209	(e) 7,383 ± 199	**6,595 ± 525

(a) Mean ± standard error, P values vs. the vehicle controls by Dunnett's test (Dunnett, 1955), U = units
(b) Unless otherwise specified
(c) Nine animals were examined
(d) Ten animals were examined
(e) Eight animals were examined
(f) Five animals were examined
*P<0 05
**P<0 01

TABLE H2. CHOLINESTERASE ACTIVITY IN MICE GIVEN DICHLORVOS BY GAVAGE FOR ONE MONTH (a)

	Dose				
	0 mg/kg	5 mg/kg	10 mg/kg	20 mg/kg	40 mg/kg
MALE					
Number examined (b)	8	8	8	9	8
Plasma (U/liter)					
Day 11	4,158 ± 175	**2,151 ± 100	**(c) 1,780 ± 96	**1,115 ± 26	**781 ± 34
Day 25	4,375 ± 135	**(c) 2,133 ± 85	**1,877 ± 142	**965 ± 48	**695 ± 23
Day 33	4,052 ± 175	**2,169 ± 96	**(d) 1,490 ± 65	**(e) 913 ± 56	**560 ± 41
Erythrocyte (U/liter)					
Day 11	(f) 5,859 ± 796	5,833 ± 508	6,536 ± 279	(e) 5,969 ± 462	(f) 5,744 ± 342
Day 25	7,067 ± 295	(c) 7,175 ± 334	6,199 ± 218	6,266 ± 188	6,135 ± 260
Day 33	6,749 ± 417	7,210 ± 305	(d) 5,787 ± 283	*(f) 5,399 ± 248	5,872 ± 322
FEMALE					
Number examined (b)	7	10	9	8	9
Plasma (U/liter)					
Day 11	(g) 6,911 ± 153	**4,247 ± 174	**(g) 2,987 ± 145	**(c) 1,743 ± 104	**(g) 1,033 ± 39
Day 25	7,417 ± 185	**3,588 ± 172	**2,709 ± 177	**1,277 ± 79	**928 ± 69
Day 33	7,066 ± 110	**(e) 3,566 ± 105	**2,684 ± 253	**1,071 ± 58	**(f) 759 ± 64
Erythrocyte (U/liter)					
Day 11	(g) 5,928 ± 426	(c) 5,753 ± 387	(g) 5,994 ± 208	(c) 5,316 ± 328	5,786 ± 160
Day 25	5,499 ± 295	6,371 ± 271	(e) 6,145 ± 285	6,285 ± 366	5,435 ± 264
Day 33	6,167 ± 245	(e) 5,667 ± 424	6,202 ± 374	6,037 ± 352	(f) 5,647 ± 271

(a) Mean ± standard error, P values vs the vehicle controls by Dunnett's test (Dunnett, 1955), U = units
(b) Unless otherwise specified
(c) Nine animals were examined
(d) Six animals were examined
(e) Eight animals were examined
(f) Seven animals were examined
(g) Ten animals were examined
*P<0 05
**P<0 01

APPENDIX I

AUDIT SUMMARY

APPENDIX I. AUDIT SUMMARY

The experimental data, documents, and pathology specimens for the 2-year toxicology and carcinogenesis studies of dichlorvos in rats and mice were audited for accuracy, consistency, completeness, and compliance with Good Laboratory Practice (GLP) regulations of the Food and Drug Administration (implemented by the National Toxicology Program [NTP] beginning on October 1, 1981). The studies were conducted for NTP by Southern Research Institute (Birmingham, Alabama) under a subcontract with Tracor Jitco, Inc., until May 31, 1982, and then under contract with the National Institute of Environmental Health Sciences (NIEHS). Dosing of animals with dichlorvos in corn oil began on January 29, 1981, for rats and on February 10, 1981, for mice. The retrospective audit was conducted at the NTP Archives (Research Triangle Park, North Carolina) in October 1986 and May 1987 by Program Resources, Inc. (P.K. Hill, Ph.D., Principal Investigator). Other individuals who conducted the audit are listed in the full audit report, which is on file at NIEHS. The audit included a review of:

(1) All records concerning animal receipt, quarantine, randomization, and disposition prior to study start.
(2) Body weight and clinical observation data for a random 10% sample of study animals.
(3) All inlife records involving protocol, correspondence, environmental conditions, masses, mortality, animal identification, and correlation of final inlife observation of masses, date of death, and disposition with necropsy records.
(4) All postmortem records for individual animals concerning identification, disposition codes, condition codes, correlations between gross observations and microscopic diagnoses, and tissue accountability.
(5) All chemistry records.
(6) All wet tissue bags for inventory and wet tissues from a random 10% sample of the study animals, plus other relevant cases, to verify animal identity and to examine for untrimmed potential lesions.
(7) Blocks and slides of tissues from all vehicle control and high dose animals to examine for proper match and inventory.
(8) Tabulated pathology diagnosis for a random 10% sample of study animals to verify computer data entry.

Audit of inlife toxicology documents and data revealed that procedures were implemented according to the Tracor Jitco, Inc., Basic Ordering Agreement during the conduct of the studies. There was no misdosing in rats, but mice (285 total) were underdosed on three occasions, which resulted from minor discrepancies in dose volume. Body weight fluctuations for two mice were greater than $\pm 15\%$, but neither instance was attributable to environmental or clinical conditions. Fifteen rats and 8 mice had final inlife masses that lacked corresponding necropsy observations Analytical chemistry records were present and documented study conduct and data adequately.

Audit of the pathology documents and specimens showed one unresolved gross to microscopic noncorrelation in a target organ and nine in nontarget organs in rats (out of thousands of observations reviewed). Seven unresolved gross to microscopic noncorrelations were found in target organs and 14 in nontarget organs in mice. Fifty-four of 58 rats were identified correctly by examination of their residual wet tissues; 1 could be read as 2 separate numbers, 2 were partially identifiable, and 1 had no identifiers. Sixty-two of 65 mice examined were identified correctly by examination of their residual wet tissues; the identifying tissues for the remaining 3 mice read as incorrect numbers but were not obviously mixed up with other animals; necropsy observations agreed with residual wet tissues. Full details about these and other audit findings are presented in the audit report.

In conclusion, the study records at the NTP Archives support the data and results presented in this NTP Technical Report.

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