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TOXICOLOGY AND CARCINOGENESIS STUDIES OF HEXACHLOROETHANE

(CAS NO. 67-72-1)

IN F344/N RATS

(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 HEXACHLOROETHANE

(CAS NO. 67-72-1)

IN F344/N RATS

(GAVAGE STUDIES)

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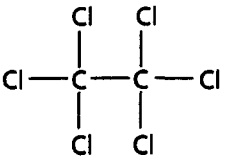

HEXACHLOROETHANE

CAS No. 67-72-1

C_2Cl_6 Molecular weight 236.7

Synonyms: carbon hexachloride; ethane hexachloride; hexachlorethane; hexachloroethylene; 1,1,1,2,2,2-hexachloroethane; perchloroethane

Trade names: Avlothane; Distokal; Distopan; Distopin; Egitol; Falkitol; Fasciolin; Mottenhexe; Phenohep

ABSTRACT

Hexachloroethane is used in organic synthesis as a retarding agent in fermentation, as a camphor substitute in nitrocellulose, in pyrotechnics and smoke devices, in explosives, and as a solvent. In previous long-term gavage studies with B6C3F$_1$ mice and Osborne-Mendel rats (78 weeks of exposure followed by 12-34 weeks of observation), hexachloroethane caused increased incidences of hepatocellular carcinomas in mice (NCI TR 68). However, survival of low and high dose rats was reduced compared with that of vehicle controls, and the effects on rats were inconclusive. Therefore, additional toxicology and carcinogenesis studies were conducted in F344/N rats by administering hexachloroethane (approximately 99% pure) in corn oil by gavage to groups of males and females for 16 days, 13 weeks, or 2 years. Genetic toxicology studies were conducted in *Salmonella typhimurium* and in Chinese hamster ovary (CHO) cells. Urinalysis was performed in conjunction with the 13-week studies.

Sixteen-Day Studies: In the 16-day studies (dose range, 187-3,000 mg/kg), all rats that received 1,500 or 3,000 mg/kg and 1/5 males and 2/5 females that received 750 mg/kg died before the end of the studies. Final mean body weights of rats that received 750 mg/kg were 25% lower than that of vehicle controls for males and 37% lower for females. Compound-related clinical signs seen at 750 mg/kg or more included dyspnea, ataxia, prostration, and excessive lacrimation. Other compound-related effects included hyaline droplet formation in the tubular epithelial cells in all dosed males and tubular cell regeneration and granular casts in the tubules at the corticomedullary junction in the kidney in males receiving 187 and 375 mg/kg.

Thirteen-Week Studies: In the 13-week studies (dose range, 47-750 mg/kg), 5/10 male rats and 2/10 female rats that received 750 mg/kg died before the end of the studies. The final mean body weight of male rats that received 750 mg/kg was 19% lower than that of vehicle controls. Compound-related clinical signs for both sexes included hyperactivity at doses of 94 mg/kg or higher and convulsions at doses of 375 or 750 mg/kg. The relative weights of liver, heart, and kidney were increased for exposed males and females. Kidney lesions were seen in all dosed male groups, and the severity increased with dose. Papillary necrosis and tubular cell necrosis and degeneration in the kidney and hemorrhagic necrosis in the urinary bladder were observed in the five male rats that received 750 mg/kg and died before the end of the studies; at all lower doses, hyaline droplets, tubular regeneration, and granular casts were present in the kidney. No chemical-related kidney lesions were observed in females. Foci of hepatocellular necrosis were observed in several male and female rats at doses of 188 mg/kg or higher.

Dose selection for the 2-year studies was based primarily on the lesions of the kidney in males and of the liver in females. Studies were conducted by administering hexachloroethane in corn oil by gavage at 0, 10, or 20 mg/kg body weight, 5 days per week, to groups of 50 male rats. Groups of 50 female rats were administered 0, 80, or 160 mg/kg on the same schedule.

Body Weight and Survival in the Two-Year Studies: Mean body weights of high dose rats were slightly (5%-9%) lower than those of vehicle controls toward the end of the studies. No significant differences in survival were observed between any groups of rats (male: vehicle control, 31/50; 10 mg/kg, 29/50; 20 mg/kg, 26/50; female: vehicle control, 32/50; 80 mg/kg, 27/50; 160 mg/kg, 32/50).

Nonneoplastic and Neoplastic Effects in the Two-Year Studies: Incidences of kidney mineralization (vehicle control, 2/50; low dose, 15/50; high dose, 32/50) and hyperplasia of the pelvic transitional epithelium (0/50; 7/50; 7/50) were increased in dosed male rats. Renal tubule hyperplasia was observed at an increased incidence in high dose male rats (2/50; 4/50; 11/50). These lesions have been described as characteristic of the hyaline droplet nephropathy that is associated with an accumulation of liver-generated $\alpha_{2\mu}$-globulin in the cytoplasm of tubular epithelial cells. The severity of nephropathy was increased in high dose male rats (moderate vs. mild), and the incidences and severity of nephropathy were increased in dosed females (22/50; 42/50; 45/50). The incidences of adenomas (1/50; 2/50; 4/50), carcinomas (0/50; 0/50; 3/50), and adenomas or carcinomas (combined) (1/50; 2/50; 7/50) of the renal tubule were also increased in the high dose male group. One of the carcinomas in the high dose group metastasized to the lung. No compound-related neoplasms were observed in females.

The incidence of pheochromocytomas of the adrenal gland in low dose male rats was significantly greater than that in vehicle controls (15/50; 28/45; 21/49), and the incidences for both dosed groups were greater than the mean historical control incidence (28% ± 11%).

Genetic Toxicology: Hexachloroethane was not mutagenic in *S. typhimurium* strains TA98, TA100, TA1535, or TA1537 when tested with and without exogenous metabolic activation. In CHO cells, hexachloroethane did not induce chromosomal aberrations with or without metabolic activation but did produce sister chromatid exchanges in the presence of exogenous metabolic activation.

Audit: The data, documents, and pathology materials from the 2-year studies of hexachloroethane have been audited. The audit findings show that the conduct of the studies is documented adequately and support the data and results given in this Technical Report.

Conclusions: Under the conditions of these 2-year gavage studies, there was *clear evidence of carcinogenic activity** of hexachloroethane for male F344/N rats, based on the increased incidences of renal neoplasms. The marginally increased incidences of pheochromocytomas of the adrenal gland may have been related to hexachloroethane administration to male rats. There was *no evidence of carcinogenic activity* of hexachloroethane for female F344/N rats administered 80 or 160 mg/kg by gavage for 103 weeks.

The severity of nephropathy and incidences of linear mineralization of the renal papillae and hyperplasia of the transitional epithelium of the renal pelvis were increased in dosed male rats. The incidences and severity of nephropathy were increased in dosed female rats.

*Explanation of Levels of Evidence of Carcinogenic Activity is on page 6.
A summary of the Peer Review comments and the public discussion on this Technical Report appears on page 9.

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

Male F344/N Rats	Female F344/N Rats
Doses 0, 10, or 20 mg/kg hexachloroethane in corn oil, 5 d/wk	0, 80, or 160 mg/kg hexachloroethane in corn oil, 5 d/wk
Body weights in the 2-year study High dose slightly less than vehicle controls	High dose slightly less than vehicle controls
Survival rates in the 2-year study 31/50; 29/50; 26/50	32/50; 27/50; 32/50
Nonneoplastic effects Kidney mineralization, hyperplasia of the pelvis, tubule hyperplasia; increased severity of nephropathy at the high dose	Increased incidence and severity of nephropathy
Neoplastic effects Renal neoplasms (1/50; 2/50; 7/50)	None
Level of evidence of carcinogenic activity Clear evidence	No evidence
Other considerations *Adrenal gland pheochromocytomas* (15/50; 28/45; 21/49)	

Genetic toxicology

Salmonella	CHO Cells in Vitro	
(gene mutation)	SCE	Aberration
Negative with and without S9	Negative without S9; positive with S9	Negative with and without S9

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

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

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

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

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

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

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

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

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

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

CONTRIBUTORS

The NTP Technical Report on the Toxicology and Carcinogenesis Studies of Hexachloroethane is based on 13-week studies that began in April 1981 and ended in July 1981 and on 2-year studies that began in April 1982 and ended in April 1984 at EG&G Mason Research Institute (Worcester, MA).

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PEER REVIEW PANEL

The members of the Peer Review Panel who evaluated the draft Technical Report on hexachloroethane on October 3, 1988, are listed below. Panel members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, Panel members have five major responsibilities: (a) to ascertain that all relevant literature data have been adequately cited and interpreted, (b) to determine if the design and conditions of the NTP studies were appropriate, (c) to ensure that the Technical Report presents the experimental results and conclusions fully and clearly, (d) to judge the significance of the experimental results by scientific criteria, and (e) to assess the evaluation of the evidence of carcinogenicity and other observed toxic responses.

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SUMMARY OF PEER REVIEW COMMENTS ON THE TOXICOLOGY AND CARCINOGENESIS STUDIES OF HEXACHLOROETHANE

On October 3, 1988, the draft Technical Report on the toxicology and carcinogenesis studies of hexachloroethane received public review by the National Toxicology Program Board of Scientific Counselors' Technical Reports Review Subcommittee and associated Panel of Experts. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Dr. W.C. Eastin, NIEHS, began the discussion by reviewing the experimental design, results, and proposed conclusions (clear evidence of carcinogenic activity for male rats, no evidence of carcinogenic activity for female rats).

Dr. Popp, a principal reviewer, agreed with the conclusion for female rats but thought that the conclusion for male rats should be reduced to some evidence of carcinogenic activity, based on the incidences of renal neoplasms (one in the vehicle controls vs. two in the low dose group and seven in the high dose group) and on hyaline droplet nephropathy and its likely relationship to the renal tubular cell neoplasms. In his opinion, the high dose for male rats was too low, being below the lowest dose evaluated in the 13-week study. Dr. Eastin replied that the choice of the high dose for male rats reflected the fact that there was toxicity even at the lowest dose used in the 13-week studies. Dr. J. Huff, NIEHS, commented that when all dosed groups have significant lesions in the 13-week studies, the Program considers doing another short-term study; for this chemical, the decision was not to repeat the 13-week studies. Dr. Popp stated that the portion of the Discussion that dealt with hyaline droplet nephropathy could have been better organized; further, he believed that the $\alpha_{2\mu}$-globulin concept is more widely supported than is indicated in the Discussion. He recommended that a final vote on the Report be deferred pending revision of the discussion.

Dr. Mirer, the second principal reviewer, agreed with the conclusions and thought that the increased incidences of pheochromocytomas in male rats were more supportive than was indicated. He opined that the treatment of the $\alpha_{2\mu}$-globulin hypothesis in the Discussion was appropriate but that reference to the hypothesis should be deleted from the Abstract. He felt that the appearance of renal toxicity in female rats should receive more discussion, especially since such toxicity was not seen in an earlier study with *d*-limonene.

Dr. McKnight, the third principal reviewer, agreed with the conclusions. She asked for more specific descriptions in the text of how certain pathology evaluations and statistical analyses were performed.

In ensuing discussion, Dr. Garman and Dr. Gallo said that the statement associating renal nephropathy with $\alpha_{2\mu}$-globulin should remain in the Abstract. Dr. Perera pointed out analogies with issues concerning the role of the protein as discussed by the Panel in the review of the Technical Report on *d*-limonene (NTP TR 347), April 18, 1988, and she read from relevant sections of the minutes of that review. She noted that there was a consensus by the Panel that the statement about $\alpha_{2\mu}$-globulin be retained in the Abstract but no mention be made of the uniqueness to male rats of the $\alpha_{2\mu}$-globulin-associated nephropathy. Dr. Perera felt that the Panel had concluded that the relationship between the protein and nephropathy was fairly well established but that the correlation with tumorigenicity was not established. Dr. Ashby suggested that the current Report on hexachloroethane include a statement that the induction of hyaline droplets in the kidney in male rats may or may not provide insight into a possible nonmutagenic mechanism.

In response to the proposal by Dr. Popp that the Report be deferred to allow major revision in the Discussion on hyaline droplet nephropathy, Dr. Huff asked that action on the Report not be delayed but

suggested that a revised Discussion be mailed to Panel members for their comments and approval. Dr. Eastin stated that the revision would consider the major points made by the Panel. This course of action was acceptable to Dr. Popp.

Dr. Mirer moved that the Technical Report on hexachloroethane be accepted with the revisions as discussed, with retention of the statement on $\alpha_{2\mu}$-globulin in the Abstract, and with the conclusions as written for male rats, clear evidence of carcinogenic activity, and for female rats, no evidence of carcinogenic activity. Dr. McKnight seconded the motion, which was approved by five members (Drs. Gallo, Garman, Klaassen, McKnight, and Mirer) with two dissenting members (Drs. Newberne and Popp) and two abstaining (Drs. Ashby and Gold).

I. INTRODUCTION

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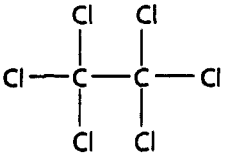

HEXACHLOROETHANE

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Synonyms: carbon hexachloride; ethane hexachloride; hexachlorethane; hexachloroethylene; 1,1,1,2,2,2-hexachloroethane; perchloroethane

Trade names: Avlothane; Distokal; Distopan; Distopin; Egitol; Falkitol; Fasciolin; Mottenhexe; Phenohep

Physical and Chemical Properties

Hexachloroethane is a colorless, crystalline substance with a camphoraceous odor, a low vapor pressure (0.21 mm mercury at 32.7° C), and a sublimation temperature of 186° C. It is soluble in alcohol, benzene, chloroform, ether, and oils but is relatively insoluble in water (5 mg/100 ml water at 22° C) (Archer, 1979; Torkelson and Rowe, 1981; CRC, 1982-83; Merck, 1983).

Production

Chlorination of tetrachloroethylene in the presence of ferric chloride at 100°-140°C is the commercial process used to produce hexachloroethane (Hardie, 1964). Photochemical chlorination of tetrachloroethylene under pressure and below 60° C is a patented method for producing hexachloroethane (Archer, 1979). Hexachloroethane is apparently not manufactured as an end-use product in the United States (NIOSH, 1978; Santodonato et al., 1985). However, it does occur as a minor by-product in the chlorination processes of saturated and unsaturated two-carbon hydrocarbons (Archer, 1979). Current estimates on the production of hexachloroethane were not found. In 1977, an estimated 1-10 million kilograms was produced (USEPA, 1977), and U.S. imports in 1976 were 730,000 kg (U.S. Department of Commerce, 1977).

Use and Exposure

Hexachloroethane has been used as a moth repellent, a plasticizer for cellulose esters, a degassing agent for magnesium, a component of extreme pressure lubricants, an ignition suppressant in combustible liquids, a retardant in fermentation processes, a component of submarine paints, an additive to fire-extinguishing fluids, and a rubber vulcanizing accelerator (Hardie, 1964). This compound has been used in veterinary practice as an anthelmintic in livestock (Merck, 1983); it is an effective treatment for *Fasciola hepatica* in dairy cows (Randell and Bradley, 1980). A National Institute for Occupational Safety and Health (NIOSH) survey lists the real estate, paper and allied products, lumber and wood products, and amusement and recreation services industries as those that use hexachloroethane (NIOSH, 1978). Workers who use this chemical include cleaning people, millwrights, machine operators, plumbers and pipefitters, and electricians. The U.S. Army reportedly uses relatively large amounts in pyrotechnics and smoke devices (Weeks et al., 1979). In an occupational hazard survey conducted from 1972 to 1974, it was estimated that about 1,500 workers were potentially exposed to hexachloroethane (NIOSH, 1974). Occupational health standards for exposure to atmospheric hexachloroethane require that exposure not exceed an 8-hour time-weighted average of 10 mg/m^3 (1 ppm) (OSHA, 1976).

Occurrence

Hexachloroethane has been found in river water, drinking water, industrial effluent water, and effluent from sewage treatment plants that use chlorination (Kleopfer, 1976; Shackelford and Keith, 1976; Suffet et al., 1976; Kraybill,

1983; Rivera et al., 1987). Hexachloroethane also was detected in waste streams and stack emissions of incinerators burning pesticide-related wastes (Travis et al., 1986). However, only one sample of surface water from 204 sites in the vicinity of heavily industrialized areas contained hexachloroethane at detectable levels (Ewing et al., 1977). In 1981, the findings of a collaborative study undertaken by the National Cancer Institute, U.S. Department of Energy, Mitre Corporation, and SRI International identified hexachloroethane as a contaminant in drinking water (Kraybill, 1983). Chemical analysis of the organic phase of Love Canal chemical dump site leachate showed a small amount of hexachloroethane (0.66% of total of organic phase) (Silkworth et al., 1986).

In 1976, an initial list of 671 potential airborne pollutants was developed (Fuller et al., 1976). From this list, only 77, including hexachloroethane, have actually been measured in ambient air (Helmes et al., 1982; Kraybill, 1983). Class and Ballschmiter (1987) analyzed several atmospheric halocarbons in air samples from sampling sites distant from inhabited areas in the region of the North and South Atlantic and the Indian Oceans and estimated that the emissions of hexachloroethane into the northern hemisphere were less than 1 kiloton per year and that the tropospheric lifetime was very long.

Absorption, Distribution, and Metabolism

Hexachloroethane administered orally (500, 750, or 1,000 mg/kg, 15% w/v in olive oil and emulsified in water) to Scottish Blackface and Cheviot cross or castrated male sheep (15-23 kg) was readily absorbed, reaching a maximum concentration in the systemic circulation at 24 hours (Fowler, 1969). At 24 hours, the concentration of hexachloroethane was 2.3-2.6 times greater in plasma than in erythrocytes. The compound was distributed widely throughout the body, with the highest concentrations found in fat and the lowest in muscle. By 15 minutes after administration, hexachloroethane was found in the bile, and in venous blood 27 minutes after dosing; the concentrations in bile were 8-10 times greater than those in blood. More than 80% of the total fecal hexachloroethane (1-2 mg) was excreted in the 24 hours after administration, and little was detected in urine. Increases in blood activities of sorbitol dehydrogenase, glutamate dehydrogenase, and ornithine carbamoyl transferase were observed. Tetrachloroethylene and pentachloroethane were detected in the hexane extracts of venous blood after oral hexachloroethane administration, and both were also detected in feces and urine. The water-soluble fractions were not assayed. These metabolites were also produced in vitro after addition of hexachloroethane to fresh liver slices prepared from sheep.

When 500 mg/kg [^{14}C]hexachloroethane was given orally to rabbits, only 5% of the radioactivity was excreted in the urine within 3 days; metabolites included di- and trichloroethanol, mono-, di- and trichloroacetic acid, and oxalic acid (Jondorf et al., 1957). Between 14% and 24% of the dose was expired unchanged or as carbon dioxide, tetrachloroethylene, or 1,1,2,2-tetrachloroethane; the rest was retained in the carcass. Bray et al. (1952) reported that there was no spontaneous liberation of chloride ions from hexachloroethane in an in vitro sodium chloride phosphate buffer solution but that a considerable percentage of the chlorine was released after rabbit liver extract was added. Gorzinski et al. (1985) fed diets containing hexachloroethane at doses of 0, 1, 15, or 62 mg/kg body weight per day to groups of 10 F344 rats of each sex for 16 weeks. The kidney was identified as a target organ, based on dose-related increased kidney weights, on tubular atrophy and degeneration in males and females, and on hypertrophy and/or dilation observed in males. Male rats were more sensitive than females to the nephrotoxic effects of hexachloroethane. Clearance of hexachloroethane followed first-order kinetics, suggesting to the authors that metabolic pathways and excretory functions were not saturated at 62 mg/kg.

Short-Term Toxicity

Several reviews have been published which discuss the toxicity of chloroethanes in general or hexachloroethane in particular (IARC, 1979; Parker et al., 1979; Canada Safety Council, 1981). The intraperitoneal LD_{50} of hexachloroethane is 4.5 g/kg body weight for mice (Baganz et al., 1961) and 2.9 g/kg for male Sprague Dawley rats (Weeks et al., 1979). For rats, the oral

LD_{50} was reported to be 5.9-6.0 g/kg (Thorpe, 1965; Broome and Jones, 1966). Weeks et al. (1979) reported LD_{50} values of 5.2 g/kg (males) and 4.5 g/kg (females) in corn oil and 7.7 g/kg (males) and 7.1 g/kg (females) in methylcellulose for Sprague Dawley rats and 5.0 g/kg for male Hartley guinea pigs. The oral LD_{50} for rabbits was greater than 1,000 mg/kg, and the dermal LD_{50} determined on shaved rabbits wrapped with a water paste of hexachloroethane for 24 hours was greater than 32,000 mg/kg. Barsoum and Saad (1934) reported that 4,000 mg/kg hexachloroethane given by subcutaneous injection to rabbits and 325 mg/kg given by intravenous injection to dogs was lethal, but dogs survived an oral dose of 6 g/kg. However, a dose of 6 g/kg was lethal to cats over a 2-day period (Plotnikov and Sokolov, 1947, in ACGIH, 1980). Male rats were reported to survive 2.6 g/kg for 24 hours (Reynolds and Yee, 1968).

Rats exposed by inhalation at a concentration of 5,900 ppm for 8 hours showed severe toxic signs, including staggering gait and reduced body weight gain over the 14-day observation period, and two of six died (Weeks et al., 1979). No toxic effects were observed when the exposure concentration was reduced to 260 ppm. No effects on body weights or organ weights or gross pathologic effects related to hexachloroethane were observed in rats, quail, pigs, or dogs exposed by inhalation at 15 or 48 ppm, and no behavioral effects were noted. Liver degeneration and necrosis occurred in rabbits administered hexachloroethane in 5% aqueous methylcellulose by gavage at 320 or 1,000 mg/kg for 12 days, but these effects were not seen at 100 mg/kg. Blood potassium and glucose concentrations were significantly reduced at the higher doses. Results of other blood analyses, including serum glutamic-oxaloacetic transaminase, serum glutamic-pyruvic transaminase, blood urea nitrogen, alkaline phosphatase, and bilirubin, were not affected at any of the doses tested. Binz (1894, cited in ACGIH, 1980) found that administration of oral doses of 1-1.4 g/kg caused weakness, staggering gait, and twitching muscles in dogs. Dogs developed tremors, ataxia, hypersalivation, severe head bobbing, and facial muscular fasciculations when exposed by inhalation at 260 ppm, 6 hours per day, 5 days per week for 6 weeks (Weeks et al., 1979).

Hexachloroethane caused central nervous system effects in cattle treated for fluke infestations (Bywater, 1955) and affected the nervous system and caused hepatic dysfunction and damage in sheep (Fowler, 1969). Vainio et al. (1976) reported that a single dose of 2.5 g/kg body weight reduced hepatic microsomal mono-oxygenase activities in rats by 50%. Gorzinski et al. (1985) fed diets containing hexachloroethane to CDF F344 rats for 110 days at concentrations that resulted in doses of 0, 1, 15, or 62 mg/kg body weight per day. In females, pathologic changes included slight renal tubular atrophy and degeneration at the highest dose. Male rats had increased kidney weights at 62 mg/kg and tubular atrophy, degeneration, and/or dilatation at 15 and 62 mg/kg. In addition, males had an increased urinary excretion of uroporphyrins at the two highest doses and of creatinine and δ-aminolevulinic acid at all doses. In male New Zealand white rabbits given oral doses of 0, 100, 320, or 1,000 mg/kg in methylcellulose for 12 days, dose-related liver degeneration and necrosis and toxic tubular nephrosis of the convoluted tubules were observed in the 320 and 1,000 mg/kg groups (Weeks et al., 1979). These changes were not observed in rabbits receiving 100 mg/kg or in the vehicle controls.

Crystalline hexachloroethane (0.1 g) caused moderate corneal opacity, iritis, and severe swelling and discharge in 5/6 of male New Zealand white rabbits when applied to the cornea and allowed to remain overnight (Weeks et al., 1979). No adverse signs were seen 72 hours later. Application of crystalline hexachloroethane (0.5 g) to intact and abraded rabbit skin did not cause skin irritation; a water paste of hexachloroethane caused slight redness that was absent 72 hours after exposure. No potential for sensitization was apparent when hexachloroethane was applied to the skin of male Hartley guinea pigs.

Screening smokes are used to obscure vision and hide targets from view in military operations. Separate groups of 42 female Sprague Dawley rats (60-80 days old) were exposed to white smoke generated from mixtures of either 7 g titanium dioxide-hexachloroethane for up to 10 minutes or 0.5 g zinc-hexachloroethane for 2.5 minutes in an inhalation chamber operated in

the static mode (Karlsson et al., 1986). No deaths occurred in 42 rats exposed to titanium dioxide-hexachloroethane compared with 7/42 in the group exposed to zinc-hexachloroethane. It is not clear if hexachloroethane contributed to the deaths of study animals.

Weeks et al. (1979) exposed groups of 25 male and 25 female Sprague Dawley rats, 4 male beagle dogs, 10 male Hartley guinea pigs, and 20 male and female *Coturnix japonica* quail to hexachloroethane vapor at concentrations of 15, 48, or 260 ppm or to control air for 6 hours per day, 5 days per week for 6 weeks. At the highest concentration, one dog, two guinea pigs, and two rats died, and clinical signs of effects on neurobehavior were observed in dogs and rats. Quail showed no clinical signs of toxicity or body weight changes. No gross pathologic changes were seen in any animals killed 12 weeks after termination of exposure.

Long-Term Toxicity and Carcinogenicity

Osborne-Mendel rats and B6C3F$_1$ mice of each sex were exposed to technical-grade hexachloroethane by gavage in corn oil in long-term studies (NCI, 1978a). The chemical was administered to groups of 50 male and 50 female animals of each species 5 days per week intermittently for 44 of 78 weeks in rats and continuously for 78 weeks in mice, followed by an observation period of 33 or 34 weeks for rats and 12 or 13 weeks for mice. The time-weighted-average doses were 212 and 423 mg/kg per day for male and female rats and 590 and 1,179 mg/kg per day for male and female mice. There were 20 male and 20 female vehicle controls (corn oil only) and 20 male and 20 female untreated controls for each species. Mortality was significantly increased in the dosed rat groups compared with vehicle controls (male: vehicle control, 9/20; low dose, 42/50; high dose, 40/50; female: 6/20; 23/50; 26/50) but not in mice. Toxic tubular nephropathy was observed in all groups of dosed animals, characterized by degeneration, necrosis, and regenerative epithelial cells in rats and degeneration of convoluted tubule epithelium in mice. Hexachloroethane caused increased incidences of hepatocellular carcinomas in dosed mice of each sex (male: untreated control, 1/18; vehicle control, 3/20; low dose, 15/50; high dose, 31/49; female: 0/18; 2/20; 20/50; 15/49). No evidence for carcinogenicity was provided for rats of either sex; however, early deaths may have reduced the sensitivity of these studies and could have obscured carcinogenic effects. Because of the early deaths in rats, a dosing regimen was established after 23 weeks of dosing whereby 1 week without dosing was followed by 4 weeks of dosing for the remainder of the 78-week dosing period. With the exception of renal lesions, the inflammatory, degenerative, and proliferative lesions seen in control and dosed rats were similar in number and kind. A toxic tubular cell nephropathy was associated with compound administration. This lesion was not observed in control rats of either sex, but it occurred in 22/49 low dose males, 33/50 high dose males, 9/50 low dose females, and 29/49 high dose females.

Aquatic Toxicity

The 48-hour LC_{50} for hexachloroethane was determined to be 2.9 mg/liter for the freshwater daphnid or water flea (*Daphnia magna*) (Richter et al., 1983). Hexachloroethane added to seawater bathing sea urchin (*Arbacia punctulata*) embryos was found to inhibit the incorporation of tritiated thymidine. Incorporation of exogenously administered radiolabeled thymidine was considered to be a measure of DNA synthesis and therefore cell division (Jackim and Nacci, 1984). The median effective toxicity value of hexachloroethane on sea urchin embryos (EC_{50} = 8.31 mg/liter) is similar to median lethal values (LC_{50}) in standard short-term toxicity studies with freshwater species, i.e., fathead minnow (*Pimephales promelas*) and water flea (*D. magna*) (Nacci and Jackim, 1985).

Reproductive Effects and Teratogenicity

Hexachloroethane (260 and 500 mg/kg) administered orally from day 6 through day 16 of gestation caused tremors and body weight gain depressions in Sprague Dawley rat dams (Weeks et al., 1979). Although development was slowed in fetuses from dosed dams, no teratogenic effect was observed.

Genetic Toxicology

Hexachloroethane was not mutagenic with or without exogenous metabolic activation at doses

up to 10 mg/plate (Simmon and Kauhanen, 1978; Kinae et al., 1981; Haworth et al., 1983) (see Table 14). Hexachloroethane did not induce mitotic recombination in *Saccharomyces cerevisiae* (Simmon and Kauhanen, 1978) or chromosomal aberrations in cultured Chinese hamster ovary (CHO) cells in either the presence or absence of S9 (Galloway et al., 1987) (see Table 16).

The only reported genetic effect from hexachloroethane treatment was induction of sister chromatid exchanges (SCEs) in CHO cells at concentrations of 330 µg/ml in the presence of Aroclor 1254-induced male Sprague Dawley rat liver S9 (Galloway et al., 1987) (see Table 15).

Tetrachloroethylene and pentachloroethane, two metabolites of hexachloroethane, have been tested in bacterial mutagenicity tests, again with negative results (Greim et al., 1975; Henschler, 1977; Bartsch et al., 1979; Haworth et al., 1983). Callen et al. (1980) reported gene conversion and mitotic recombination in *S. cerevisiae* D7 after treatment with tetrachloroethylene at concentrations up to 8.2 mM, but subsequent studies by Bronzetti et al. (1983) with the same and higher doses did not confirm these results. Also, tetrachloroethylene did not induce unscheduled DNA synthesis in human lymphocytes (Perocco et al., 1983), sex-linked recessive lethal mutations in Drosophila (Valencia et al., 1985), or chromosomal aberrations and SCEs in CHO cells (Galloway et al., 1987). A positive response was reported for SCEs in the CHO cell test for pentachloroethane in the absence of S9 only. Some cell cycle delay was observed at the doses that elicited the positive response, indicating a toxic effect of the chemical on the cells; no induction of chromosomal aberrations occurred in CHO cells exposed to pentachloroethane (Galloway et al., 1987). Both pentachloroethane and tetrachloroethylene were positive without exogenous metabolic activation in the mouse L5178Y lymphoma test for induction of trifluorothymidine resistance (NTP unpublished results).

Study Rationale

Hexachloroethane was nominated to the NTP by the National Institute for Occupational Safety and Health for evaluation of carcinogenicity and mutagenicity because of worker exposure.

In the studies of the long-term effects of hexachloroethane in B6C3F$_1$ mice and Osborne-Mendel rats (NCI, 1978a), hexachloroethane caused increased incidences of hepatocellular carcinomas in mice; the results in rats were not definitive because hexachloroethane adversely affected survival, and early deaths could have obscured a carcinogenic effect. Further, the exposure duration was only 78 weeks for this negative rat study, and control groups contained only 20 animals. Therefore, to better evaluate the effects of hexachloroethane exposure in a second species, toxicology and carcinogenesis studies were conducted in F344/N rats of each sex. The gavage route of exposure was selected so that a precise dose could be delivered and to allow for a comparison with the previous long-term studies in Osborne-Mendel rats and B6C3F$_1$ mice (NCI, 1978a).

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF HEXACHLOROETHANE

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES

SIXTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

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

GENETIC TOXICOLOGY

PROCUREMENT AND CHARACTERIZATION OF HEXACHLOROETHANE

Hexachloroethane was obtained in one lot (lot no. H013080) from Hummel Chemical Co. (South Plainfield, NJ). Purity and identity analyses were conducted at Midwest Research Institute (MRI) (Kansas City, MO). MRI reports on the analyses performed in support of the hexachloroethane studies are on file at the National Institute of Environmental Health Sciences.

The study chemical was identified as hexachloroethane by infrared (Figure 1), ultraviolet/visible, and nuclear magnetic resonance spectroscopy. The infrared spectrum was consistent with that expected for the structure and with the literature spectra (Sadtler Standard Spectra), except for a small peak in the sample spectrum at about 1,380 cm^{-1} which was not present in the literature spectrum. The ultraviolet/visible spectrum was consistent with that expected for the structure of hexachloroethane; there were no maxima, but an increase in absorbance was observed toward the solvent cutoff. No peaks were observed in the nuclear magnetic resonance spectrum, a finding consistent with the structure.

The purity of the lot studied was determined by elemental analysis, Karl Fischer water analysis, and gas chromatography. Cumulative data indicated that lot no. H013080 was greater than 99% pure. Gas chromatographic analysis was performed with flame ionization detection and either a 20% SP2100/0.1% Carbowax 1500 column (system 1) or a 10% Carbowax 20M-TPA column (system 2). The water content was 0.017%. The results of elemental analysis for carbon and chlorine were in agreement with theoretical values. No impurities with areas 0.1% or greater than the major peak area were detected by gas chromatographic system 1; system 2 detected a group of unresolved impurities with a combined area 0.18% that of the major peak.

Stability studies, performed by gas chromatography with the same column as that described above for system 1 and with 0.16% dodecane as the internal standard, indicated that hexachloroethane was stable as a bulk chemical when kept for 2 weeks at temperatures of up to 60° C, although extensive sublimation occurred at that temperature. The bulk chemical was reanalyzed every 4 months over the course of the studies by gas chromatographic analysis with the same column as described in system 2. No deterioration of the study material was seen by the study laboratory over the course of the studies. Therefore, it is concluded that the hexachloroethane study material remained stable during the studies.

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES

The appropriate amounts of hexachloroethane and corn oil were homogenized for 3 minutes at medium speed with a Brinkman Polytron® (w/v for the 13-week and w/w for the 2-year studies) to give the desired concentrations (Table 1).

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

Thirteen-Week Studies	Two-Year Studies
Preparation Appropriate amounts of hexachloroethane and corn oil homogenized with a Brinkman Polytron® at medium speed for 3 min	Same as 13-wk studies
Maximum Storage Time 2 wk	2 wk
Storage Conditions 4° C in serum vials	0° ± 5° C in serum vials

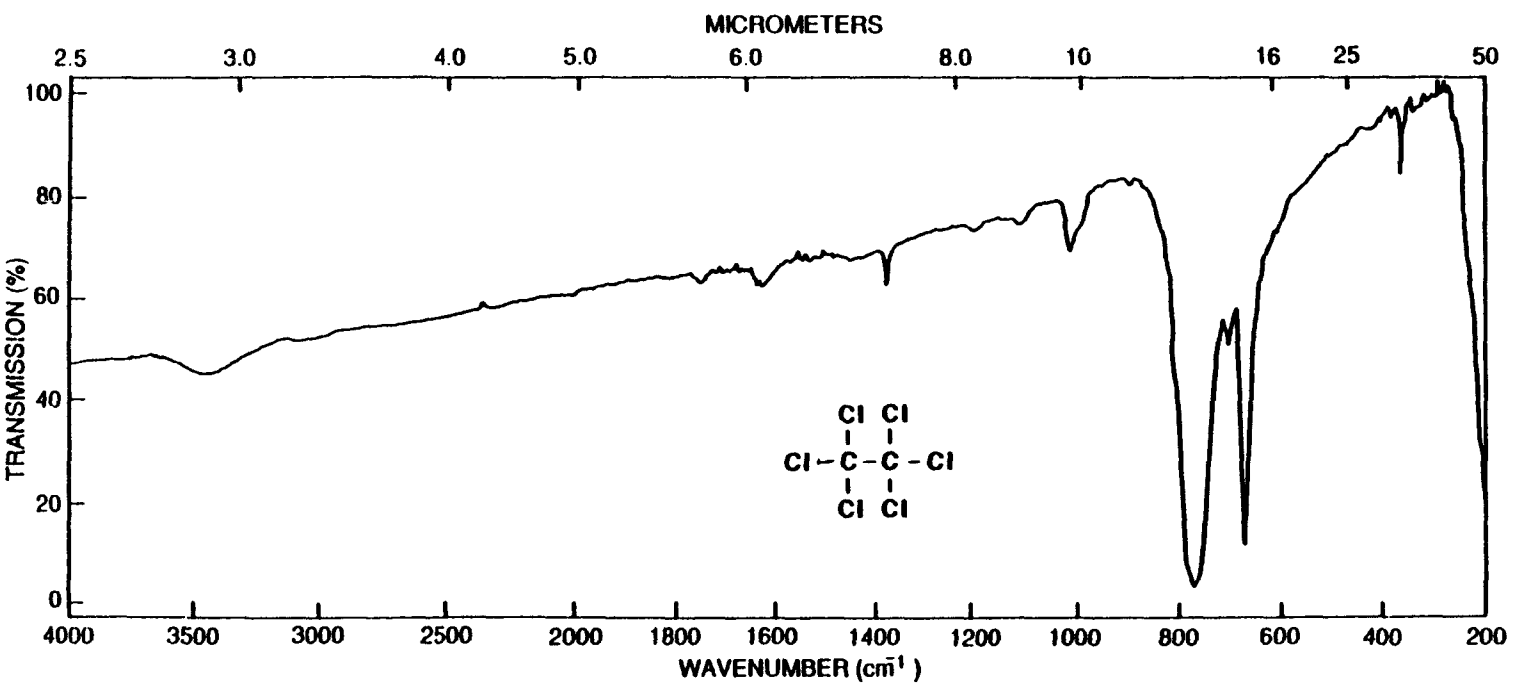

FIGURE 1. INFRARED ABSORPTION SPECTRUM OF HEXACHLOROETHANE (LOT NO. H013080)

Each lot of corn oil used in these studies was analyzed for peroxide content before its first use and at 1-month intervals thereafter by the Official Method of the American Oil Chemists' Society (Mehlenbacher et al., 1972). The maximum allowable level of peroxide in NTP studies is 3 meq/kg. The lots of corn oil used for the dimethoxane study were determined to contain less than 3 meq/kg peroxide. The stability of hexachloroethane in corn oil (100 mg/ml) was determined by gas chromatography performed with flame ionization detection on a 1% SP1000 column after dilution with hexane containing trichloroethane as an internal standard. The chemical was found to be stable in corn oil for at least 14 days in the dark at room temperature or for 3 hours when exposed to light and air. During the 13-week studies, hexachloroethane/corn oil mixtures were stored at 4° C for up to 2 weeks. During the 2-year studies, the dose mixtures were stored at 0° ± 5° C for up to 2 weeks.

Periodic analysis of hexachloroethane/corn oil dose mixtures was conducted at the study and analytical chemistry laboratories by diluting the dose mixtures with hexane containing 1,1,2-trichloroethane as an internal standard followed by gas chromatographic analysis. The study laboratory analyzed dose mixtures two times during the 13-week studies (Table 2) and at approximately 8-week intervals during the 2-year studies (Table 3). The hexachloroethane mixtures were formulated within ±10% of the target concentrations approximately 98% (51/52) of the time throughout the 2-year studies. Results of referee analysis performed periodically at the analytical chemistry laboratory were generally in good agreement with those from the study laboratory (Table 4).

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

Date Mixed	Concentration of Hexachloroethane in Corn Oil for Target Concentration (mg/ml)		Determined as a Percent of Target
	Target	Determined (a)	
04/06/81	9	9.0	100
	19	17.9	94
	36	35.3	98
04/08/81	38	38.1	100
04/07/81	75	75.4	102
04/06/81	150	148.9	99
06/01/81	9	8.7	97
	19	17.95	95
	38	37.05	97
	75	75.7	101
	150	149.8	100

(a) Results of duplicate analysis

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

Date Mixed	Concentration of Hexachloroethane in Corn Oil for Target Concentration (mg/ml) (a)			
	2	4	16	32
03/29/82	2.07	4.05	15.40	31.54
05/18/82	2.11	3.86	14.94	30.58
09/08/82	1.89	4.11	--	--
09/01/82	--	--	14.96	29.96
10/13/82	2.00	3.92	15.28	30.54
12/29/82	1.89	3.78	15.26	31.46
01/19/83	2.02	3.92	15.54	31.67
03/16/83	(b) 1.69	4.00	15.54	32.08
03/18/83	(c) 1.93	--	--	--
06/15/83	1.99	3.82	15.24	29.54
06/29/83	1.90	3.78	15.83	32.02
(d) 10/12/83	1.87	3.77	16.04	30.62
11/02/83	2.04	4.03	16.03	31.43
01/11/84	2.04	4.09	15.22	30.61
03/05/84	2.07	4.12	15.72	32.47
Mean (mg/ml)	1.97	3.94	15.46	31.12
Standard deviation	0.115	0.132	0.363	0.877
Coefficient of variation (percent)	5.8	3.4	2.3	2.8
Range (mg/ml)	1.69-2.10	3.77-4.12	14.94-16.04	29.54-32.47
Number of samples	13	13	13	13

(a) Results of duplicate analysis
(b) Out of specifications; not used in the studies.
(c) Remix; not included in the mean.
(d) Beginning on 10/12/83, dose mixtures were prepared on a milligram per gram basis. Reported concentrations have been divided by 1.09 or 1.10 (32 mg/ml mixtures only) to compensate for the different method of reporting.

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

Date Mixed	Target Concentration (mg/ml)	Determined Concentration (mg/ml)	
		Study Laboratory (a)	Referee Laboratory (b)
03/29/82	2	2.07	2.08
10/13/82	4	3.92	4.18
06/15/83	32	29.54	31.4
11/02/83	(c) 17.29	(c) 17.47	(c) 17.0

(a) Results of duplicate analysis
(b) Results of triplicate analysis
(c) Reported in milligrams per gram

SIXTEEN-DAY STUDIES

F344/N rats were obtained from Harlan Industries, Inc. (males) or Charles River Breeding Laboratories (females) and held for 20 days (males) or 21 days (females) before the studies began. The rats were approximately 7-8 weeks old when placed on study.

Groups of five rats of each sex were administered 0, 187, 375, 750, 1,500, or 3,000 mg/kg hexachloroethane in corn oil by gavage for 12 doses over 16 days. Animals were housed five per cage. Water and feed were available ad libitum. The rats were observed two times per day and weighed on days 0, 7, and 14 and at the end of the studies. A necropsy was performed on all animals. Further experimental details are summarized in Table 5.

THIRTEEN-WEEK STUDIES

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

Four- to five-week-old male and female F344/N rats were obtained from Charles River Breeding Laboratories, observed for 14 days, and then assigned to dose groups so that the average cage weights were approximately equal for all animals of the same sex. Rats were approximately 6-7 weeks old when placed on study.

Groups of 10 rats of each sex were administered 0, 47, 94, 188, 375, or 750 mg/kg hexachloroethane in corn oil by gavage, 5 days per week for 13 weeks. Rats were housed five per cage. Feed and water were available ad libitum. Further experimental details are summarized in Table 5.

Animals were observed two times per day; moribund animals were killed. Individual animal weights were recorded one time per week. At the end of the 13-week studies, survivors were killed. A necropsy was performed on all animals except those excessively autolyzed or cannibalized. Tissues and groups examined are listed in Table 5. At the end of the 13-week studies, urine from each animal was collected over a cold pack (1°-3° C) for 18-24 hours.

TWO-YEAR STUDIES

Study Design

Groups of 50 male rats were administered 0, 10, or 20 mg/kg hexachloroethane in corn oil by gavage, 5 days per week for 103 weeks. Groups of 50 female rats were administered 0, 80, or 160 mg/kg on the same schedule.

Source and Specifications of Animals

The male and female F344/N rats used in these studies were produced under strict barrier conditions at Charles River Breeding Laboratories under a contract to the Carcinogenesis Program. Breeding stock for the foundation colony at the production facility originated at the National Institutes of Health Repository. The rats shipped for study were progeny of defined microflora-associated parents that were transferred from isolators to barrier-maintained rooms. Animals were shipped to the study laboratory at 5 weeks of age. Male rats were quarantined at the study laboratory for 15 days and females for 14 days. Thereafter, a complete necropsy was performed on five animals of each sex to assess their health status. The rodents were placed on study at 7 weeks of age. The health of the animals was monitored during the course of the studies according to the protocols of the NTP Sentinel Animal Program (Appendix C).

Animal Maintenance

Animals were housed five per cage. Cages were rotated during the studies. Feed and water were available ad libitum.

Clinical Examinations and Pathology

All animals were observed two times per day, and clinical signs were recorded at least one time per month. Body weights were recorded one time per week for the first 14 weeks of the studies and one time every 4 weeks thereafter. Mean body weights were calculated for each group. Animals found moribund and those surviving to the end of the studies were humanely killed. A necropsy was performed on all animals including those found dead. Some tissues were

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

Sixteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
EXPERIMENTAL DESIGN		
Size of Study Groups		
5 males and 5 females	10 males and 10 females	50 males and 50 females
Doses		
0, 187, 375, 750, 1,500, or 3,000 mg/kg hexachloroethane in corn oil by gavage; dose vol--5 ml/kg	0, 47, 94, 188, 375, or 750 mg/kg hexachloroethane in corn oil by gavage; dose vol--5 ml/kg	Male--0, 10, or 20 mg/kg hexachloroethane in corn oil by gavage; female--0, 80, or 160 mg/kg; dose vol--5 ml/kg
Date of First Dose		
Male--12/30/80; female--1/13/81	Male--4/8/81; female--4/22/81	Male--4/1/82; female--4/7/82
Date of Last Dose		
Male--1/14/81; female--1/28/81	Male--7/7/81 or 7/9/81; female--7/20/81 or 7/22/81	Male--3/22/84; female--3/28/84
Duration of Dosing		
12 doses over 16 d	5 d/wk for 13 wk	5 d/wk for 103 wk
Type and Frequency of Observation		
Observed 2 × d; weighed 1 × wk	Observed 2 × d; weighed 1 × wk, 3-4 d before scheduled kill, and at necropsy	Observed 2 × d; weighed initially, 1 × wk for 14 wk, and then 1 × mo
Necropsy, Histologic Examinations, and Supplemental Studies		
Necropsy performed on all animals	Necropsy performed on all animals; the following tissues examined histologically for all vehicle controls and high dose females, 5 high dose males, and all males receiving 375 mg/kg: adrenal glands, brain, cecum, colon, duodenum, esophagus, eyes (if grossly abnormal), gross lesions and tissue masses with regional lymph nodes, heart, ileum, jejunum, kidney, liver, lungs and mainstem bronchi, mammary gland, mandibular and mesenteric lymph nodes, nasal cavity and turbinates, pancreas, parathyroid glands, pharynx (if grossly abnormal), pituitary gland, preputial or clitoral gland, prostate/testes/seminal vesicles or ovaries/uterus, rectum, salivary glands, skin, spleen, sternebrae including marrow, stomach, thymus, thyroid gland, trachea, and urinary bladder. Kidney examined in the 47, 94, and 188 mg/kg male groups, liver in the 94 and 188 mg/kg male groups, and liver and kidney in the 47, 94, 188, and 375 mg/kg female groups. Urinalysis performed; organ weights recorded at necropsy	Necropsy performed on all animals; the following tissues examined histologically for vehicle control and high dose groups: abnormal regional lymph nodes, adrenal glands, bone marrow, brain, colon, costochondral junction, duodenum, esophagus, heart, ileum, jejunum, kidney, larynx, liver, lungs and bronchi, mammary gland, mandibular and mesenteric lymph nodes, pancreas, parathyroid glands, pituitary gland, prostate/testes/seminal vesicles or ovaries/uterus, salivary glands, skin, spleen, stomach, thymus, thyroid gland, tissue masses, trachea, and urinary bladder. Additional tissues examined in the vehicle control and high dose female groups include anterior cervical spinal cord, sciatic nerve, and thoracolumbar spinal cord. Tissues examined in the low dose groups include adrenal glands (males), gross lesions, kidney, pituitary gland, and thyroid gland
ANIMALS AND ANIMAL MAINTENANCE		
Strain and Species		
F344/N rats	F344/N rats	F344/N rats

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

Sixteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
ANIMALS AND ANIMAL MAINTENANCE (Continued)		
Animal Source Male--Harlan Industries (Indianapolis, IN); female--Charles River Breeding Laboratories (Kingston, NY)	Charles River Breeding Laboratories (Kingston, NY)	Charles River Breeding Laboratories (Portage, MI)
Study Laboratory EG&G Mason Research Institute	EG&G Mason Research Institute	EG&G Mason Research Institute
Method of Animal Identification Ear punch	Ear punch	Ear punch
Time Held Before Study Male--20 d; female--21 d	14 d	Male--15 d; female--14 d
Age When Placed on Study 7-8 wk	Male--6-7 wk; female--7 wk	7 wk
Age When Killed 9-10 wk	Male--20 wk; female--20 wk	Male--112 wk; female--111-112 wk
Necropsy Dates Male--1/15/81; female--1/29/81	Male--7/8/81-7/10/81; female--7/21/81-7/23/81	Male--4/2/84-4/5/84; female--4/6/84-4/18/84
Method of Animal Distribution Assigned to groups such that for a given sex and species all cage weights were approximately equal	Same as 16-d studies	Assigned to cages according to one table of random numbers and then to groups according to another table of random numbers
Feed NIH 07 Rat and Mouse Ration (Zeigler Bros., Inc., Gardners, PA); available ad libitum	Same as 16-d studies	Same as 16-d studies
Bedding Aspen Bed (American Excelsior, Baltimore, MD)	Same as 16-d studies	Same as 16-d studies
Water Automatic watering system (Edstrom Industries, Waterford, WI); available ad libitum	Same as 16-d studies; city water filtered through a 5-μ filter	Same as 13-wk studies
Cages Polycarbonate (Lab Products, Inc., Rochelle Park, NJ)	Same as 16-d studies	Same as 16-d studies
Cage Filters Nonwoven fiber (Snow Filtration, Cincinnati, OH)	Nonwoven fiber sheet (Lab Products, Rochelle Park, NJ, or Snow Filtration, Cincinnati, OH)	Same as 13-wk studies
Animals per Cage 5	5	5
Other Chemicals on Study in the Same Room None	None	None

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

Sixteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
ANIMALS AND ANIMAL MAINTENANCE (Continued)		
Animal Room Environment		
Temp--22.2°-25.6° C; hum--37%-61%; fluorescent light 12 h/d; 12-15 room air changes/h	Temp--mean, 21.5° C; range, 17.2°-23.8° C; hum--mean, 57%; range, 42%-77%; fluorescent light 12 h/d; >12 room air changes/h	Temp--mean, 23.3° C; range, 18°-27° C; hum--mean, 43%; range, 3%-68%; fluorescent light 12 h/d; 14.9 room air changes/h

excessively autolyzed or missing, and thus, the number of animals from which particular organs or tissues were examined microscopically varies and is not necessarily equal to the number of animals that were placed on study.

During necropsy, all organs and tissues were examined for grossly visible lesions. Tissues were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Histopathologic examination of tissues was performed according to an "inverse pyramid" design (McConnell, 1983a,b). That is, complete histopathologic examinations (Table 5) were performed on all high dose and vehicle control animals and on low dose animals dying through month 21 of the study. In addition, histopathologic examinations were performed on all grossly visible lesions in all dose groups. Potential target organs for chemically related neoplastic and nonneoplastic effects were identified as adrenal glands (male), kidney, pituitary gland, and thyroid gland from the short-term studies or the literature and were determined by examination of the pathology data; these target organs/tissues in the lower dose group were examined histopathologically.

When the pathology evaluation was completed by the laboratory pathologist and the pathology data entered into the Toxicology Data Management System, 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).

Nonneoplastic lesions in the adrenal glands and kidneys were examined by the quality assessment pathologist and PWG because they were considered part of the toxic effect of the chemical.

Statistical Methods

Survival Analyses: The probability of survival was estimated by the product-limit procedure of Kaplan and Meier (1958) and is presented in the form of graphs. Animals were censored from the

survival analyses at the time they were found to be dead from other than natural causes; animals dying from natural causes were not censored. Statistical analyses for a possible dose-related effect on survival used the method of Cox (1972) for testing two groups for equality and Tarone's (1975) life table test for a dose-related trend. When significant survival differences were detected, additional analyses using these procedures were carried out to determine the time point at which significant differences in the survival curves were first detected. All reported P values for the survival analysis are two-sided.

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

Analysis of Tumor Incidence: The majority of tumors in this study were considered to be incidental to the cause of death or not rapidly lethal. Thus, the primary statistical method used was a logistic regression analysis, which assumed that the diagnosed tumors were discovered as the result of death from an unrelated cause and thus did not affect the risk of death. In this approach, tumor prevalence was modeled as a logistic function of chemical exposure 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). When tumors are incidental, this comparison of the time-specific tumor prevalences also provides a comparison of the time-specific tumor incidences (McKnight and Crowley, 1984).

In addition to logistic regression, alternative methods of statistical analysis were used, and the results of these tests are summarized in the appendixes. These include the life table test (Cox, 1972; Tarone, 1975), appropriate for rapidly lethal tumors, and the Fisher exact test and the Cochran-Armitage trend test (Armitage, 1971; Gart et al., 1979), procedures based on the overall proportion of tumor-bearing animals.

Tests of significance include pairwise comparisons of each dosed group with vehicle controls and a test for an overall dose-response trend. Continuity-corrected tests were used in the analysis of tumor incidence, and reported P values are one-sided. The procedures described above also were used to evaluate selected nonneoplastic lesions. (For further discussion of these statistical methods, see Haseman, 1984.)

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

Analysis of Continuous Variables: For the hematologic, serum chemical, and relative organ weight data, the nonparametric multiple comparison procedures of Dunnett (1980) and Williams (1971, 1972) were used to assess the significance of pairwise differences between dosed and vehicle control groups. Jonckheere's test (Jonckheere, 1954) was used to evaluate the significance of dose-response trends.

GENETIC TOXICOLOGY

Salmonella Protocol: Testing was performed as reported by Ames et al. (1975) with modifications listed below and described in greater detail by Haworth et al. (1983). Hexachloroethane was sent to two testing laboratories as coded aliquots from Radian Corporation (Austin, TX). The

study chemical was incubated with the *Salmonella typhimurium* tester strains (TA98, TA100, TA1535, and TA1537) either in buffer or S9 mix (metabolic activation enzymes and cofactors from Aroclor 1254-induced male Sprague Dawley rat or Syrian hamster liver) for 20 minutes at 37° C before the addition of soft agar supplemented with L-histidine and D-biotin and subsequent plating on minimal glucose agar plates. Incubation was continued for an additional 48 hours.

Hexachloroethane was tested in duplicate in all four strains at each laboratory. Each test consisted of triplicate plates of concurrent positive and negative controls and of at least five doses of the study chemical. The high dose was limited by toxicity or solubility but did not exceed 10 mg/plate.

A positive response was defined as a reproducible, dose-related increase in histidine-independent (revertant) colonies in any one strain/activation combination. An equivocal response was defined as an increase in revertants which was not dose related, not reproducible, or of insufficient magnitude to support a determination of mutagenicity. A response was considered negative when no increase in revertant colonies was observed after chemical treatment.

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

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

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

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

Cells were selected for scoring on the basis of good morphology and completeness of karyotype (21 ± 2 chromosomes). All slides were scored blind, and those from a single test were read by the same person. For the SCE test, 50 second-division metaphase cells were usually scored for frequency of SCEs per cell from each dose; 100 first-division metaphase cells were scored at each dose for the chromosomal aberration test.

Classes of aberrations included simple (breaks and terminal deletions), complex (rearrangements and translocations), and other (pulverized cells, despiralized chromosomes, and cells containing 10 or more aberrations).

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

III. RESULTS

RATS

SIXTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

GENETIC TOXICOLOGY

SIXTEEN-DAY STUDIES

All rats that received 1,500 or 3,000 mg/kg and 1/5 males and 2/5 females that received 750 mg/kg died before the end of the studies (Table 6). The final mean body weights of rats that received 750 mg/kg were 25% lower than that of vehicle controls for males and 37% lower for females. Compound-related clinical signs seen at 750 mg/kg or more included dyspnea, ataxia, prostration, and excessive lacrimation. Compound-related effects observed microscopically included hyaline droplet formation in the cytoplasm of the renal tubular epithelium in all dosed males and tubular cell regeneration and eosinophilic granular casts of cell debris in the tubule lumina at the corticomedullary junction in the kidney at 187 and 375 mg/kg.

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

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	5/5	130 ± 7	188 ± 7	+58 ± 2	
187	5/5	130 ± 5	193 ± 5	+63 ± 1	103
375	5/5	130 ± 7	182 ± 5	+52 ± 3	97
750	(d) 4/5	130 ± 4	141 ± 5	+14 ± 2	75
1,500	(e) 0/5	130 ± 5	(f)	(f)	(f)
3,000	(g) 0/5	130 ± 6	(f)	(f)	(f)
FEMALE					
0	5/5	136 ± 2	164 ± 4	+28 ± 2	
187	5/5	135 ± 2	162 ± 4	+27 ± 3	99
375	5/5	135 ± 3	154 ± 4	+19 ± 1	94
750	(h) 3/5	136 ± 3	(i) 104 ± 4	−35 ± 3	63
1,500	(j) 0/5	135 ± 2	(f)	(f)	(f)
3,000	(k) 0/5	135 ± 3	(f)	(f)	(f)

(a) Number surviving/number initially in the group
(b) Initial group mean body weight ± standard error of the mean. Subsequent calculations are based on animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean
(d) Day of death: 6
(e) Day of death: 4,5,6,6,8
(f) No data are reported due to 100% mortality in this group.
(g) Day of death: 2,3,3,3,4
(h) Day of death: 5,15
(i) Data for three animals; a fourth animal was alive at day 14 when the rest were weighed, but its weight was not reported.
(j) Day of death: 3,3,5,5,5
(k) Day of death: 3,4,5,5,5

THIRTEEN-WEEK STUDIES

Five of 10 male rats and 2/10 female rats that received 750 mg/kg died before the end of the studies (Table 7). The final mean body weights of rats that received 750 mg/kg were 19% lower than that of vehicle controls for males and 4% lower for females. Compound-related clinical signs included postgavage hyperactivity for both sexes at doses of 94 mg/kg or more and convulsions at 375 or 750 mg/kg; the week of first appearance decreased with increased dose. Increased relative organ weights at 750 mg/kg included liver, heart, kidney, and brain for males and females (Table 8). Kidney changes were seen in all dosed male groups (9/10 at the lowest dose), and the severity increased with dose. At the highest dose, only the five male rats that died before the end of the study were examined microscopically. All five had renal papillary necrosis and degeneration and necrosis of the renal tubular epithelium. Other changes seen in the kidney in male rats at this dose and all lower doses were identical to those observed in the 16-day study and consisted of hyaline droplet formation, tubular regeneration, and tubular casts. The rounded to crystalloid-shaped hyaline droplets were present in tubular cells throughout the cortex of the kidney and were characterized by epithelial cells with an increased basophilic staining of the cytoplasm. Tubule lumina at the corticomedullary junction were slightly distended by the eosinophilic granular casts. Hepatocellular necrosis was observed in 2/5 males and 8/10 females at 750 mg/kg, 1/10 males and 4/10 females at 375 mg/kg, and 2/10 females at 188 mg/kg. These focal areas of necrosis were centrilobular and contained a minimal inflammatory cell infiltrate. Hemorrhagic necrosis of the urinary bladder was seen in 5/5 males that received 750 mg/kg. Urinalysis indicated findings consistent with the histopathologic changes in the kidney of dosed male rats (fine and coarse granular casts accompanied by cellular casts and epithelial cells). These same changes were not seen in female rats.

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

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	120 ± 2	344 ± 7	+224 ± 7	
47	10/10	120 ± 2	354 ± 8	+234 ± 7	103
94	10/10	119 ± 2	352 ± 4	+233 ± 5	102
188	10/10	120 ± 2	356 ± 6	+236 ± 6	103
375	10/10	119 ± 2	330 ± 5	+211 ± 4	96
750	(d) 5/10	119 ± 2	279 ± 14	+160 ± 14	81
FEMALE					
0	10/10	110 ± 1	214 ± 4	+104 ± 3	
47	10/10	110 ± 1	219 ± 3	+109 ± 2	102
94	10/10	111 ± 1	220 ± 2	+109 ± 3	103
188	10/10	110 ± 1	210 ± 3	+100 ± 2	98
375	10/10	110 ± 1	213 ± 4	+103 ± 3	100
750	(e) 8/10	111 ± 2	206 ± 3	+95 ± 2	96

(a) Number surviving/number initially in group
(b) Initial group mean body weight ± standard error of the mean. Subsequent calculations are based on animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean
(d) Week of death: 7,7,8,12,12
(e) Two animals died during week 13 after the final body weights had been taken.

TABLE 8. ORGAN WEIGHT TO BODY WEIGHT RATIOS FOR RATS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF HEXACHLOROETHANE (a)

Organ	Vehicle Control	47 mg/kg	94 mg/kg	188 mg/kg	375 mg/kg	750 mg/kg
MALE						
Number weighed (b)	10	10	10	10	9	5
Body weight (c)	340 ± 7.6	349 ± 8.8	343 ± 5.9	348 ± 5.9	319 ± 4.00	(d) 262 ± 13.5
Liver	35.8 ± 0.61	37.3 ± 0.37	36.0 ± 0.71	(d) 39.1 ± 0.62	(d) 42.5 ± 0.74	(d) 46.3 ± 0.95
Brain	6.0 ± 0.30	5.7 ± 0.17	5.7 ± 0.10	5.8 ± 0.23	6.3 ± 0.21	(d) 7.2 ± 0.31
Heart	2.8 ± 0.04	2.8 ± 0.04	2.9 ± 0.07	(e) 3.2 ± 0.17	(d) 3.3 ± 0.18	(e) 3.2 ± 0.10
Kidney	3.0 ± 0.05	3.8 ± 0.37	(e) 4.1 ± 0.27	(d) 4.7 ± 0.44	(d) 5.2 ± 0.35	(d) 4.7 ± 0.28
Lung	4.2 ± 0.21	4.6 ± 0.40	4.4 ± 0.48	3.9 ± 0.22	3.9 ± 0.15	4.9 ± 0.50
Right testis	4.2 ± 0.05	4.8 ± 0.38	4.3 ± 0.10	4.4 ± 0.17	4.7 ± 0.05	(d) 5.3 ± 0.21
Thymus	0.8 ± 0.04	(f) 0.8 ± 0.06	0.6 ± 0.02	(g) 0.8 ± 0.10	0.7 ± 0.04	(h) 0.6 ± 0.06
FEMALE						
Number weighed (b)	10	10	10	10	10	8
Body weight (c)	206 ± 3.7	210 ± 3.9	208 ± 2.6	200 ± 2.9	203 ± 4.3	(c) 189 ± 3.8
Liver	32.2 ± 0.56	33.4 ± 0.63	(e) 34.3 ± 0.39	(d) 36.3 ± 0.44	(d) 42.0 ± 0.60	(d) 52.4 ± 0.88
Brain	8.7 ± 0.17	8.6 ± 0.14	8.6 ± 0.10	9.0 ± 0.14	9.0 ± 0.15	(d,i) 9.5 ± 0.17
Heart	2.9 ± 0.04	3.0 ± 0.05	3.0 ± 0.03	3.0 ± 0.04	3.1 ± 0.07	(d) 3.4 ± 0.07
Kidney	3.1 ± 0.04	3.2 ± 0.05	3.2 ± 0.07	3.2 ± 0.06	(d) 3.6 ± 0.05	(d) 4.1 ± 0.10
Lung	4.2 ± 0.09	4.1 ± 0.09	4.2 ± 0.10	4.1 ± 0.06	4.2 ± 0.08	4.5 ± 0.13
Thymus	1.1 ± 0.05	1.1 ± 0.05	(f) 1.1 ± 0.04	1.0 ± 0.06	1.1 ± 0.07	(d) 0.8 ± 0.05

(a) Mean ± standard error (in milligrams per gram except as noted); P values vs. the vehicle controls by Williams' test or Dunnett's test (Williams, 1971, 1972; Dunnett, 1980).
(b) Except as noted
(c) Absolute body weight (in grams) ± standard error
(d) $P<0.01$
(e) $P<0.05$
(f) Nine animals were weighed.
(g) Eight animals were weighed.
(h) Three animals were weighed.
(i) Ten animals were weighed.

Dose Selection Rationale: Doses for the 2-year studies were based on observations in the 13-week studies of dose-related kidney changes in males at all doses (lowest dose, 47 mg/kg) and hepatocellular necrosis in females (188 mg/kg and higher). Hexachloroethane doses selected for rats for the 2-year studies were 10 or 20 mg/kg for males and 80 or 160 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 high dose male rats were 5%-6% lower than those of vehicle controls after week 81; mean body weights of high dose female rats were 5%-9% lower than those of vehicle controls between week 41 and week 101 (Table 9 and Figure 2). Dosed female rats were hyperexcitable.

TABLE 9. MEAN BODY WEIGHTS OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF HEXACHLOROETHANE (a)

Weeks on Study	Vehicle Control Av. Wt. (grams)	Vehicle Control No. Weighed	Low Dose Av. Wt. (grams)	Low Dose Wt. (percent of vehicle controls)	Low Dose No. Weighed	High Dose Av. Wt. (grams)	High Dose Wt. (percent of vehicle controls)	High Dose No. Weighed
MALE				**10 mg/kg**			**20 mg/kg**	
1	183	50	174	95	50	178	97	50
2	212	50	204	96	50	208	98	50
3	237	50	230	97	50	235	99	50
4	264	50	256	97	50	259	98	50
5	281	50	275	98	50	276	98	50
6	298	50	291	98	50	293	98	50
7	313	50	307	98	50	305	97	50
8	330	50	322	98	50	324	98	50
9	339	50	331	98	50	331	98	50
10	348	50	341	98	50	341	98	50
11	357	50	349	98	50	352	99	50
12	365	50	356	98	50	356	98	50
13	374	50	367	98	50	366	98	50
14	382	50	374	98	50	373	98	50
17	401	50	392	98	50	389	97	50
21	422	50	413	98	50	412	98	50
25	441	49	433	98	50	434	98	50
29	453	49	445	98	50	443	98	50
33	472	(a) 48	462	98	50	459	97	50
37	487	49	479	98	50	475	98	50
41	500	49	492	98	50	489	98	50
45	513	49	506	99	50	502	98	50
49	516	49	509	99	50	502	97	49
53	524	48	512	98	49	511	98	48
57	534	48	524	98	48	520	97	48
61	540	47	531	98	48	525	97	48
65	547	47	535	98	48	526	96	48
69	547	47	532	97	48	528	97	46
73	542	47	527	97	47	522	96	45
77	542	46	527	97	47	523	96	45
81	541	46	522	96	46	515	95	42
85	543	43	523	96	45	515	95	39
89	540	43	518	96	40	507	94	38
93	532	40	513	96	37	499	94	34
97	518	36	503	97	36	492	95	32
101	510	35	492	96	33	480	94	29
104	499	32	483	97	31	471	94	27
FEMALE				**80 mg/kg**			**160 mg/kg**	
1	125	50	128	102	50	125	100	50
2	149	50	149	100	50	146	98	50
3	161	50	161	100	50	159	99	50
4	171	50	171	100	50	168	98	50
5	179	50	178	99	50	175	98	50
6	184	50	185	101	50	182	99	50
7	190	50	190	100	50	187	98	50
8	196	50	195	99	50	194	99	50
9	200	50	200	100	50	197	99	50
10	203	50	206	101	50	203	100	50
11	209	50	209	100	50	207	99	50
12	213	50	211	99	50	210	99	50
13	215	50	214	100	50	213	99	50
14	218	50	219	100	50	217	100	50
17	225	50	225	100	50	223	99	50
21	233	50	234	100	50	229	98	50
25	240	50	240	100	50	234	98	50
29	246	50	246	100	50	238	97	50
33	256	50	258	101	50	248	97	50
37	264	50	265	100	50	253	96	50
41	274	50	273	100	50	259	95	50
45	282	50	281	100	50	267	95	50
49	297	50	294	99	50	282	95	50
53	303	50	301	99	50	287	95	50
57	317	50	313	99	50	298	94	50
61	327	50	321	98	49	304	93	49
65	336	50	328	98	49	310	92	49
69	340	50	331	97	49	310	91	46
73	344	49	329	96	48	314	91	46
77	353	49	338	96	48	322	91	46
81	357	48	341	96	47	324	91	46
85	358	47	344	96	45	326	91	42
89	360	44	348	97	42	326	91	42
93	362	40	346	96	40	335	93	36
97	364	36	346	95	31	333	91	36
101	363	34	345	95	29	336	93	35
104	358	32	343	96	27	346	97	33

(a) One animal was not weighed.

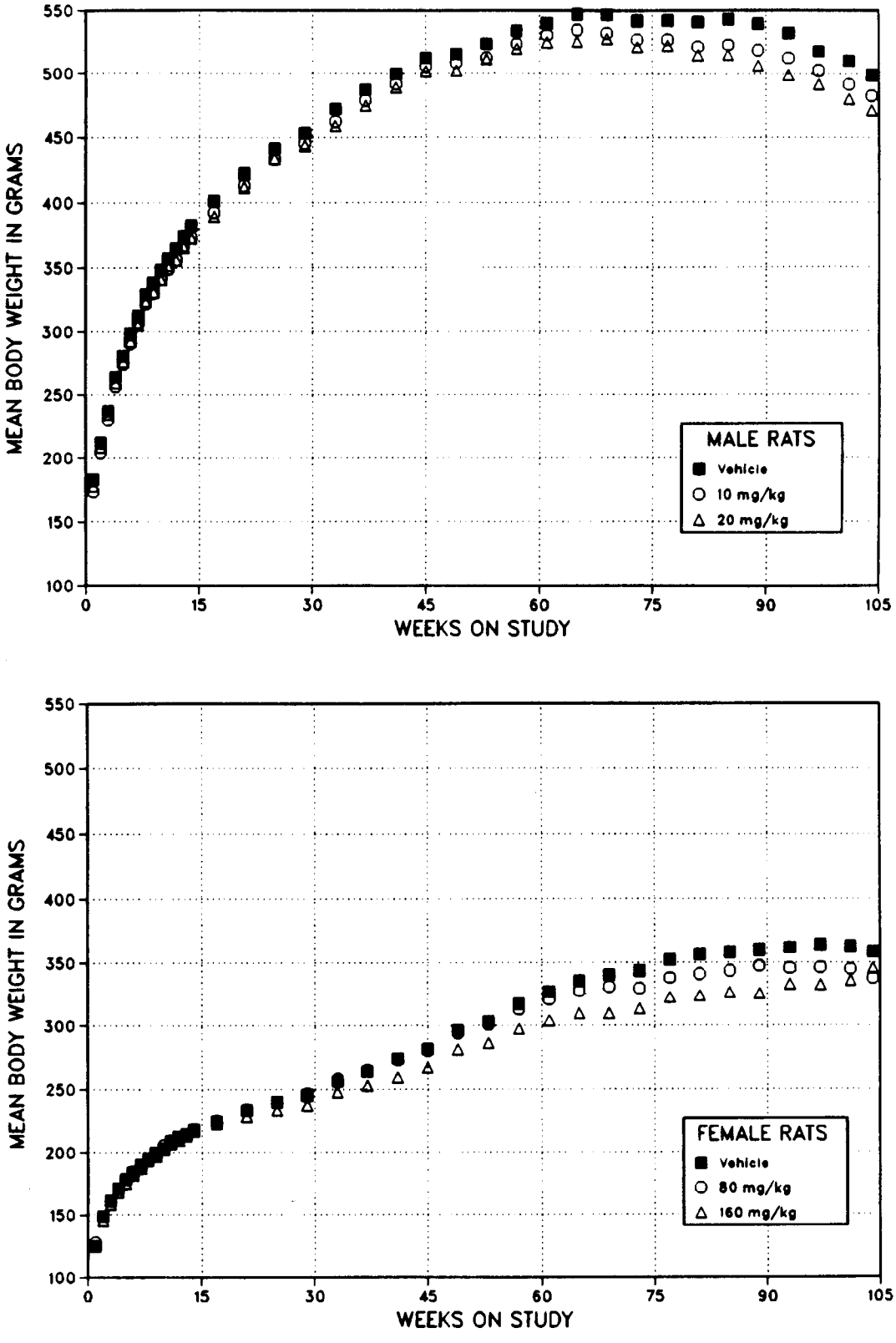

FIGURE 2. GROWTH CURVES FOR RATS ADMINISTERED HEXACHLOROETHANE IN CORN OIL BY GAVAGE FOR TWO YEARS

Survival

Estimates of the probabilities of survival for male and female rats administered hexachloroethane at the doses used in these studies and for vehicle controls are shown in Table 10 and in the Kaplan and Meier curves in Figure 3. No significant differences in survival were observed between any groups of either sex.

Pathology and Statistical Analyses of Results

This section describes the significant or noteworthy changes in the incidences of rats with neoplastic or nonneoplastic lesions of the kidney and adrenal gland.

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

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

	Vehicle Control	10 mg/kg	20 mg/kg	80 mg/kg	160 mg/kg
MALE (a)					
Animals initially in study	50	50	50		
Natural deaths	2	6	4		
Moribund kills	16	14	19		
Accidentally killed	1	1	1		
Animals surviving until study termination	31	29	26		
Survival P values (b)	0.290	0.806	0.332		
FEMALE (a)					
Animals initially in study	50			50	50
Natural deaths	4			2	3
Moribund kills	14			20	15
Accidentally killed	0			1	0
Animals surviving until study termination	32			27	32
Survival P values (b)	0.955			0.498	0.959

(a) First day of termination period: male--733; female--731
(b) The result of the life table trend test is in the vehicle control column, and the results of the life table pairwise comparisons with the vehicle controls are in the dosed columns.

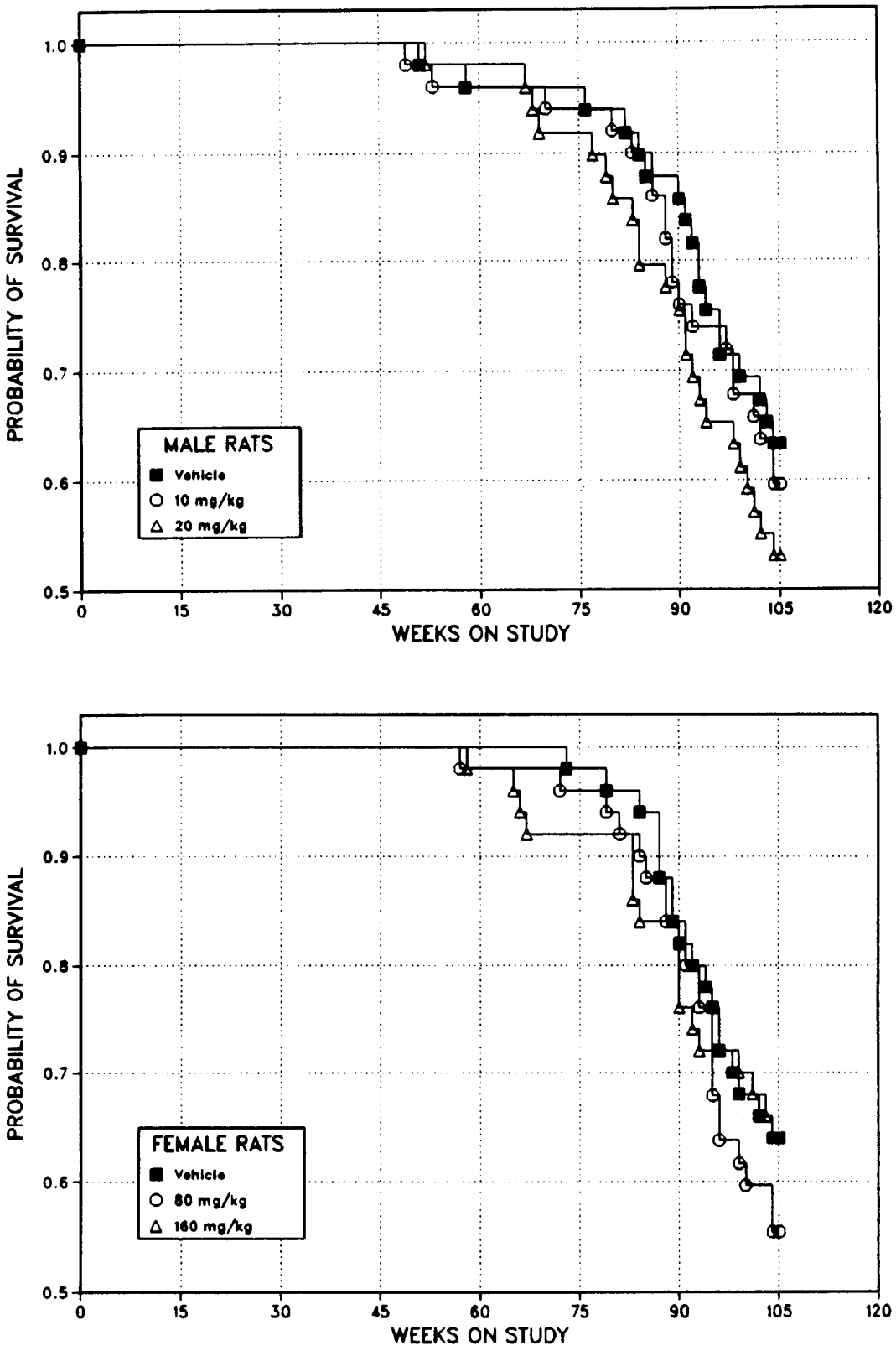

FIGURE 3. KAPLAN-MEIER SURVIVAL CURVES FOR RATS ADMINISTERED HEXACHLOROETHANE IN CORN OIL BY GAVAGE FOR TWO YEARS

Kidney: Renal tubule hyperplasia and neoplasia were observed at greater incidences in dosed male rats (Table 11). The combined incidence of adenomas or carcinomas in the high dose males was significantly greater than that in the vehicle controls. All the carcinomas and one of the adenomas, also in a high dose male, were seen grossly; one of the carcinomas metastasized. Microscopically, tubular hyperplasia and neoplasia represented a morphologic continuum. Hyperplasia consisted of tubules that were slightly enlarged (up to approximately twice the normal diameter) and contained increased numbers of tubular epithelial cells that were stratified and filled the tubular lumens. Adenomas were larger than the hyperplasia and ranged in size from less than 1 mm up to approximately 4 mm. Adenomas were discrete masses consisting of variably sized, solid nests of cells and occasional tubular structures separated by a sparse fibrovascular stroma. The adenomas were composed of moderately large, somewhat pleomorphic epithelial cells with round-to-ovoid nuclei with a prominent nucleolus and eosinophilic granular to clear vacuolated cytoplasm. One adenoma consisted of enlarged cells with prominent eosinophilic cytoplasmic granules characteristic of renal "oncocytoma." The histogenesis of the oncocytoma is uncertain but may be derived either from the proximal tubule or collecting ducts of the kidney. Carcinomas were larger masses, up to 1 cm or more in diameter, and consisted of sheets of pleomorphic epithelial cells that, in some tumors, surrounded a central cystic area. Nephropathy was observed in nearly all males, but the severity was slightly increased in dosed males relative to vehicle controls; the overall average severity was mild in vehicle controls and mild to moderate in dosed males (Table 12). The incidences of nephropathy were also increased in dosed females (vehicle control, 22/50; low dose, 42/50; high dose, 45/50), and the severity of nephropathy was significantly ($P<0.01$) increased in dosed females relative to vehicle controls; the overall average severity was minimal in vehicle controls and minimal to mild in dosed females. Nephropathy in each sex consisted of tubular cell degeneration and regeneration, tubular dilatation and atrophy, glomerulosclerosis, interstitial fibrosis, and chronic inflammation. Linear mineralization of the renal papillae (2/50; 15/50; 32/50) and hyperplasia of the pelvic transitional epithelium (0/50; 7/50; 7/50) were increased in dosed males. The incidences of these lesions were not increased in females by chemical administration.

TABLE 11. RENAL OR RENAL TUBULE LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF HEXACHLOROETHANE (a)

	Vehicle Control	10 mg/kg	20 mg/kg
Hyperplasia			
Overall Rates	2/50 (4%)	4/50 (8%)	(b) 11/50 (22%)
Adenoma			
Overall Rates	1/50 (2%)	2/50 (4%)	4/50 (8%)
Carcinoma			
Overall Rates	0/50 (0%)	0/50 (0%)	3/50 (6%)
Adenoma or Carcinoma (c)			
Overall Rates	1/50 (2%)	2/50 (4%)	7/50 (14%)
Adjusted Rates	2.6%	5.9%	23.7%
Terminal Rates	0/31 (0%)	0/29 (0%)	5/26 (19%)
Day of First Observation	654	677	636
Life Table Tests	P=0.009	P=0.497	P=0.020
Logistic Regression Tests	P=0.011	P=0.500	P=0.026

(a) The statistical analyses used are discussed in Section II (Statistical Methods) and Table A3 (footnotes).
(b) $P<0.01$ vs. vehicle controls
(c)Historical incidence of renal tubular cell neoplasms (combined) at study laboratory (mean ± SD): 1/300 (0.3% ± 0.8%); historical incidence in NTP studies: 10/1,943 (0.5% ± 0.9%)

TABLE 12. NUMBER OF RATS WITH VARIOUS DEGREES OF SEVERITY OF NEPHROPATHY IN THE TWO-YEAR GAVAGE STUDIES OF HEXACHLOROETHANE (a)

Severity of Nephropathy	Male			Female		
	Vehicle Control	10 mg/kg	20 mg/kg	Vehicle Control	80 mg/kg	160 mg/kg (b)
None (0)	2	2	3	28	8	5
Minimal (1)	4	3	4	10	17	12
Mild (2)	26	21	13	10	23	25
Moderate (3)	11	10	16	2	2	7
Marked (4)	7	14	14	0	0	0
Overall severity (c)	2.34 ± 0.14	2.62 ± 0.15	(d) 2.68 ± 0.16	0.72 ± 0.13	(e) 1.38 ± 0.11	(e) 1.69 ± 0.12

(a) Fifty animals were examined in each group.
(b) One female with nephropathy was not graded.
(c) Mean ± standard error
(d) $P<0.05$ vs. vehicle controls
(e) $P<0.01$ vs. vehicle controls

Adrenal Gland: Pheochromocytomas occurred at an increased incidence in low dose male rats and, to a lesser extent, in high dose male rats, relative to vehicle controls. Malignant pheochromocytomas occurred in one vehicle control, two low dose, and one high dose male rats, and two complex pheochromocytomas occurred in high dose male rats. Pheochromocytomas were circumscribed masses of altered adrenal medullary cells that lacked the normal orderly arrangement in small packets separated by a sparse fibrovascular stroma. The cells were arranged in large solid clusters or irregular branching cords. The cells had small hyperchromatic nuclei or slightly enlarged vesicular nuclei with prominent nucleoli. The cytoplasm of the cells was often more basophilic than that of normal cells. The malignant pheochromocytomas consisted of anaplastic pleomorphic cells that obliterated the adrenal gland. Since complex pheochromocytomas are simply variants of the usual pheochromocytomas which contain nervous tissue in addition to adrenal medullary cells, these neoplasms were combined with the others for purposes of analysis. The incidence of pheochromocytomas in low dose male rats was significantly greater than that in the vehicle control group (Table 13).

TABLE 13. ADRENAL MEDULLARY LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF HEXACHLOROETHANE

	Vehicle Control	10 mg/kg	20 mg/kg
Focal Hyperplasia			
Overall Rates	6/50 (12%)	4/45 (9%)	10/49 (20%)
Pheochromocytoma			
Overall Rates	14/50 (28%)	26/45 (58%)	19/49 (39%)
Adjusted Rates	37.8%	76.1%	56.3%
Terminal Rates	9/31 (29%)	20/28 (71%)	12/26 (46%)
Day of First Observation	637	578	577
Life Table Tests	P=0.064	P=0.006	P=0.091
Logistic Regression Tests	P=0.089	P=0.002	P=0.133
Complex Pheochromocytoma			
Overall Rates	0/50 (0%)	0/45 (0%)	2/49 (4%)
Malignant Pheochromocytoma			
Overall Rates	1/50 (2%)	2/45 (4%)	1/49 (2%)
Pheochromocytoma or Complex or Malignant Pheochromocytoma (a)			
Overall Rates	15/50 (30%)	28/45 (62%)	21/49 (43%)
Adjusted Rates	40.7%	82.1%	62.5%
Terminal Rates	10/31 (32%)	22/28 (79%)	14/26 (54%)
Day of First Observation	637	578	577
Life Table Tests	P=0.038	P=0.003	P=0.058
Logistic Regression Tests	P=0.051	P<0.001	P=0.086

(a) Historical incidence at study laboratory (mean ± SD): 75/300 (25% ± 7%); historical incidence in NTP studies: 543/1,937 (28% ± 11%)

Hexachloroethane, tested with a preincubation protocol at concentrations up to 10 mg/plate, was not mutagenic in *Salmonella typhimurium* strains TA98, TA100, TA1535, or TA1537; all strains were tested with or without Aroclor 1254-induced male Sprague Dawley rat or Syrian hamster liver S9 (Table 14; Haworth et al., 1983). In cytogenetic tests with cultured Chinese hamster ovary (CHO) cells, no induction of chromosomal aberrations was observed after treatment with up to 500 µg/ml hexachloroethane in the absence of S9 or 1,000 µg/ml in the presence of Aroclor 1254-induced male Sprague Dawley rat liver S9 (Table 15; Galloway et al., 1987). In these tests, treatment with hexachloroethane caused a considerable delay in cell cycle time, indicating toxicity. Also, precipitation of the study chemical occurred at several concentrations. Hexachloroethane did not induce sister chromatid exchanges (SCEs) in CHO cells in the absence of S9; with S9, doses of 330 µg/ml hexachloroethane and above resulted in a significant increase in SCEs as well as toxicity, as evidenced by cell cycle delay; precipitation of hexachloroethane occurred at all doses of 330 µg/ml and above (Table 16; Galloway et al., 1987).

TABLE 14. MUTAGENICITY OF HEXACHLOROETHANE IN *SALMONELLA TYPHIMURIUM* (a)

Strain	Dose (µg/plate)	Revertants/Plate (b) −S9 Trial 1	−S9 Trial 2	+S9 (hamster) Trial 1	+S9 (hamster) Trial 2	+S9 (rat) Trial 1	+S9 (rat) Trial 2
Study performed at Case Western Reserve University							
TA100	0	122 ± 2.3	153 ± 4.7	156 ± 4.5	191 ± 5.6	199 ± 13.5	170 ± 18.5
	10	141 ± 3.8	147 ± 9.9	165 ± 2.9	203 ± 5.5	194 ± 2.0	169 ± 3.5
	33	142 ± 1.5	143 ± 11.5	154 ± 3.2	195 ± 7.4	192 ± 0.6	175 ± 6.7
	100	131 ± 10.2	138 ± 6.9	170 ± 3.1	215 ± 6.8	210 ± 6.7	182 ± 9.6
	333	134 ± 4.0	156 ± 6.9	176 ± 12.2	222 ± 4.4	201 ± 11.9	190 ± 13.7
	1,000	135 ± 11.5	146 ± 5.9	170 ± 9.2	213 ± 3.5	217 ± 12.1	192 ± 9.3
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control (c)		381 ± 7	470 ± 16.8	745 ± 19.9	545 ±113.1	572 ± 88.8	362 ± 20.0
TA1535	0	7 ± 0.5	10 ± 1.2	7 ± 0.0	12 ± 1.9	7 ± 1.0	11 ± 1.2
	10	4 ± 0.7	11 ± 2.6	8 ± 1.5	18 ± 3.2	5 ± 0.6	13 ± 2.5
	33	4 ± 0.3	11 ± 3.2	8 ± 1.8	14 ± 3.2	3 ± 0.9	9 ± 3.5
	100	4 ± 0.3	8 ± 1.2	9 ± 0.7	16 ± 2.9	5 ± 1.5	11 ± 1.5
	333	4 ± 0.9	5 ± 0.6	5 ± 1.2	10 ± 1.9	7 ± 1.9	13 ± 2.2
	1,000	3 ± 0.6	7 ± 2.5	8 ± 1.5	12 ± 2.3	4 ± 1.9	9 ± 2.5
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control (c)		121 ± 3.8	157 ± 6.1	110 ± 17.0	98 ± 14.1	61 ± 3.0	91 ± 8.1
TA1537	0	3 ± 0.0	5 ± 1.5	6 ± 0.6	8 ± 1.2	6 ± 0.7	7 ± 0.7
	1	2 ± 0.7	4 ± 0.6	4 ± 1.2	9 ± 2.1	6 ± 0.6	8 ± 0.7
	33	2 ± 1.3	5 ± 2.5	5 ± 1.5	7 ± 0.0	3 ± 0.6	9 ± 2.7
	100	2 ± 0.6	4 ± 0.7	5 ± 1.2	6 ± 0.6	4 ± 1.5	6 ± 1.5
	333	2 ± 0.3	5 ± 0.9	3 ± 1.5	8 ± 3.4	2 ± 0.9	6 ± 2.2
	1,000	2 ± 1.0	5 ± 0.9	2 ± 1.2	6 ± 2.2	2 ± 0.3	10 ± 1.9
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control (c)		323 ± 24.4	185 ± 52.1	55 ± 16.5	89 ± 23.8	20 ± 4.2	55 ± 28.3
TA98	0	20 ± 1.2	15 ± 2.3	24 ± 3.0	15 ± 1.2	28 ± 6.4	14 ± 0.9
	10	23 ± 6.4	12 ± 3.2	27 ± 4.7	15 ± 2.0	24 ± 2.2	13 ± 0.7
	33	21 ± 0.6	17 ± 1.0	23 ± 3.2	13 ± 0.9	23 ± 3.1	15 ± 2.5
	100	37 ± 5.1	12 ± 2.8	23 ± 1.8	13 ± 0.6	20 ± 1.5	16 ± 3.5
	333	29 ± 7.0	17 ± 3.2	30 ± 0.9	11 ± 4.3	23 ± 0.0	14 ± 1.5
	1,000	21 ± 3.6	12 ± 2.1	28 ± 6.7	15 ± 1.8	19 ± 2.4	16 ± 3.8
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control (c)		102 ± 6.7	83 ± 10.7	757 ± 35.8	519 ± 57.2	322 ± 22.7	339 ± 10.4
Study performed at SRI International							
TA100	0	91 ± 3.5	97 ± 3.2	102 ± 5.1	133 ± 2.2	110 ± 1.2	104 ± 5.3
	100	79 ± 8.7	93 ± 7.2	95 ± 6.8	104 ± 4.8	99 ± 1.0	114 ± 4.6
	333.3	76 ± 6.7	100 ± 4.6	92 ± 4.6	116 ± 5.3	84 ± 2.7	97 ± 12.2
	1,000	75 ± 3.5	104 ± 4.6	88 ± 4.4	104 ± 5.7	95 ± 8.5	82 ± 2.3
	3,333.3	82 ± 9.8	101 ± 2.0	87 ± 2.8	101 ± 5.3	92 ± 3.2	94 ± 11.6
	10,000	80 ± 5.0	108 ± 1.8	96 ± 8.3	111 ± 1.7	99 ± 2.1	95 ± 11.0
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control (c)		375 ± 8	263 ± 22.9	1,503 ± 33.8	1,563 ± 23.4	884 ± 38.2	867 ± 37.5
TA1535	0	24 ± 2.1	25 ± 2.6	11 ± 0.7	10 ± 1.2	14 ± 1.2	12 ± 2.6
	100	17 ± 2.6	23 ± 3.4	8 ± 0.3	10 ± 2.4	10 ± 1.5	11 ± 2.2
	333.3	21 ± 2.2	23 ± 3.1	11 ± 2.5	10 ± 3.2	8 ± 0.7	7 ± 1.2
	1,000	13 ± 2.4	22 ± 1.9	7 ± 0.9	10 ± 2.5	9 ± 1.5	7 ± 0.9
	3,333.3	12 ± 2.0	21 ± 2.3	14 ± 4.4	12 ± 2.1	9 ± 2.0	9 ± 2.3
	10,000	10 ± 2.3	20 ± 1.9	9 ± 2.1	9 ± 2.5	8 ± 0.3	9 ± 1.5
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control (c)		381 ± 11.9	334 ± 52.4	364 ± 13.8	424 ± 16.7	213 ± 9.6	288 ± 3.7

TABLE 14. MUTAGENICITY OF HEXACHLOROETHANE IN *SALMONELLA TYPHIMURIUM* (Continued)

Strain	Dose (µg/plate)	Revertants/Plate (b) −S9 Trial 1	−S9 Trial 2	+S9 (hamster) Trial 1	+S9 (hamster) Trial 2	+S9 (rat) Trial 1	+S9 (rat) Trial 2
TA1537	0	19 ± 2.6	12 ± 2.5	25 ± 2.2	34 ± 1.5	21 ± 4.3	26 ± 1.7
	100	7 ± 0.3	12 ± 1.7	7 ± 0.6	24 ± 1.7	10 ± 1.7	17 ± 2.2
	333.3	9 ± 1.2	12 ± 2.5	10 ± 2.3	31 ± 2.6	10 ± 2.5	15 ± 0.3
	1,000	10 ± 2.4	12 ± 1.9	10 ± 3.5	27 ± 5.3	10 ± 1.2	17 ± 0.3
	3,333.3	9 ± 1.7	18 ± 1.8	10 ± 4.1	23 ± 3.4	8 ± 1.3	12 ± 2.0
	10,000	11 ± 0.9	10 ± 1.8	11 ± 2.1	19 ± 1.3	11 ± 1.0	12 ± 1.7
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control (c)		154 ± 41.5	729 ±105.3	510 ± 40.2	462 ± 13.5	231 ± 41.9	293 ± 9.6
TA98	0	37 ± 3.5	21 ± 3.5	49 ± 2.6	43 ± 1.7	42 ± 5.5	35 ± 4.0
	100	28 ± 1.2	20 ± 1.0	45 ± 4.1	37 ± 1.0	58 ± 6.8	20 ± 3.5
	333.3	23 ± 5.2	21 ± 1.3	33 ± 5.9	35 ± 1.5	43 ± 9.4	21 ± 5.3
	1,000	28 ± 1.2	20 ± 0.3	33 ± 3.8	39 ± 0.3	47 ± 2.2	22 ± 6.1
	3,333.3	26 ± 4.8	22 ± 3.5	32 ± 6.3	37 ± 3.5	39 ± 3.8	19 ± 2.4
	10,000	28 ± 2.5	33 ± 2.3	48 ± 9.3	48 ± 6.6	37 ± 3.3	32 ± 3.5
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control (c)		420 ± 8.4	373 ± 9.1	1,210 ± 11.8	1,528 ± 6.1	517 ± 27.4	698 ± 37.4

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

TABLE 15. INDUCTION OF SISTER CHROMATID EXCHANGES IN CHINESE HAMSTER OVARY CELLS BY HEXACHLOROETHANE (a)

Compound	Dose (µg/ml)	Total Cells	No. of Chromo-somes	No. of SCEs	SCEs/ Chromo-some	SCEs/ Cell	Hours in BrdU	Relative SCEs/Cell (percent) (b)
-S9 (c)--Summary: Negative								
Dimethyl sulfoxide		50	1,044	432	0.41	8.6	25.7	--
Hexachloroethane	10	50	1,046	446	0.43	8.9	25.7	103.5
	33	50	1,042	471	0.45	9.4	25.7	109.3
	100	50	1,042	482	0.46	9.6	25.7	111.6
	(d) 330	0	--	--	--	--	(e) 33.0	--
Mitomycin C	0.005	25	520	675	1.30	27.0	25.7	314.0
+S9 (f)								
Trial 1--Summary: Positive								
Dimethyl sulfoxide		50	1,043	481	0.46	9.6	25.7	--
Hexachloroethane	100	50	1,043	471	0.45	9.4	25.7	97.9
	(d) 330	50	1,048	622	0.59	12.4	(e) 33.2	129.2
	1,000	50	1,042	682	0.65	13.6	(e) 33.2	141.7
Cyclophosphamide	1.5	25	522	801	1.53	32.0	25.7	333.3
Trial 2--Summary: Positive								
Dimethyl sulfoxide		50	1,042	435	0.42	8.7	25.3	--
Hexachloroethane	(d) 400	50	1,032	585	0.57	11.7	(e) 35.8	134.5
	600	50	1,044	627	0.60	12.5	(e) 35.8	143.7
	800	0	--	--	--	--	(e) 35.8	--
	1,000	50	1,048	638	0.61	12.8	(e) 35.8	147.1
Cyclophosphamide	1.5	25	520	889	1.71	35.6	25.3	409.2

(a) Study performed at Litton Bionetics, Inc. SCE = sister chromatid exchange; BrdU = bromodeoxyuridine. A detailed description of the SCE protocol is presented by Galloway et al. (1987). Briefly, Chinese hamster ovary cells were incubated with study compound or solvent (dimethyl sulfoxide) as described in (c) and (f) below and cultured for sufficient time to reach second metaphase division. Cells were then collected by mitotic shake-off, fixed, air dried, and stained.
(b) SCEs/cell of culture exposed to study chemical relative to those of culture exposed to solvent
(c) In the absence of S9, Chinese hamster ovary cells were incubated with study compound or solvent for 2 hours at 37° C. Then BrdU was added, and incubation was continued for 24 hours. Cells were washed, fresh medium containing BrdU and colcemid was added, and incubation was continued for 2-3 hours.
(d) Precipitate observed at this and all higher concentrations
(e) 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.
(f) In the presence of S9, cells were incubated with study compound or solvent for 2 hours at 37° C. Cells were then washed, and medium containing BrdU was added. Cells were incubated for a further 26 hours, with colcemid present for the final 2-3 hours. S9 was from the liver of Aroclor 1254-induced male Sprague Dawley rats.

TABLE 16. INDUCTION OF CHROMOSOMAL ABERRATIONS IN CHINESE HAMSTER OVARY CELLS BY HEXACHLOROETHANE (a)

	−S9 (b)					+S9 (c)			
Dose (µg/ml)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells with Abs	Dose (µg/ml)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells with Abs
Trial 1--Harvest time: 20 hours (d)					**Trial 1--Harvest time: 20.3 hours (d)**				
Dimethyl sulfoxide					Dimethyl sulfoxide				
	50	0	0.00	0.0		100	6	0.06	6.0
Hexachloroethane					Hexachloroethane				
150	50	1	0.02	2.0	(e) 800	100	4	0.04	4.0
250	50	1	0.02	2.0	900	100	10	0.10	7.0
500	25	1	0.04	4.0	1,000	100	2	0.02	2.0
Summary: Negative					Summary: Negative				
Mitomycin C					Cyclophosphamide				
0.065	25	9	0.36	28.0	15	50	52	1.04	44.0
Trial 2--Harvest time: 20 hours (d)					**Trial 2--Harvest time: 20.0 hours (d)**				
Dimethyl sulfoxide					Dimethyl sulfoxide				
	100	6	0.06	5.0		100	3	0.03	3.0
Hexachloroethane					Hexachloroethane				
(e) 200	100	29	0.29	15.0	(e) 800	100	9	0.09	5.0
300	50	3	0.06	6.0	900	100	4	0.04	4.0
400	50	0	0.00	0.0	1,000	100	2	0.02	2.0
Summary: Equivocal					Summary: Negative				
Mitomycin C					Cyclophosphamide				
0.065	50	9	0.18	18.0	10	50	14	0.28	24.0
Trial 3--Harvest time: 21.5 hours (d)									
Dimethyl sulfoxide									
	100	2	0.02	2.0					
Hexachloroethane									
200	100	1	0.01	1.0					
250	100	6	0.06	6.0					
300	100	3	0.03	3.0					
Summary: Negative									
Mitomycin C									
0.062	50	25	0.50	36.0					

(a) Study performed at Litton Bionetics, Inc.; Abs = aberrations. A detailed presentation of the technique for detecting chromosomal aberrations is found in Galloway et al. (1987). Briefly, Chinese hamster ovary cells were incubated with study compound or solvent (dimethyl sulfoxide) as indicated in (b) and (c). Cells were arrested in first metaphase by addition of colcemid and harvested by mitotic shake-off, fixed, and stained in 6% Giemsa.
(b) In the absence of S9, cells were incubated with study compound or solvent for 8-10 hours at 37° C. Cells were then washed, and fresh medium containing colcemid was added for an additional 2-3 hours followed by harvest.
(c) In the presence of S9, cells were incubated with study compound or solvent for 2 hours at 37° C. Cells were then washed, medium was added, and incubation was continued for 8-10 hours. Colcemid was added for the last 2-3 hours of incubation before harvest. S9 was from the liver of Aroclor 1254-induced male Sprague Dawley rats.
(d) Because of significant chemically induced cell cycle delay, incubation time prior to addition of colcemid was lengthened to provide sufficient metaphases at harvest.
(e) Precipitate observed at this and all higher concentrations

IV. DISCUSSION AND CONCLUSIONS

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Doses of hexachloroethane selected for the 2-year studies were based primarily on the kidney lesions in male rats and the liver lesions in female rats which were observed in the 13-week studies. In the 2-year studies, mean body weights of chemically exposed males were never more than 6% lower than those of vehicle controls, survival of the dosed groups was similar to that of vehicle controls, and there were no clinical signs of hexachloroethane toxicity. There were no compound-related malignant neoplasms in low dose male rats. Survival of female rats was similar to that of vehicle controls. There were no chemical-related neoplasms in females, but there was a dose-related increase in the incidence and severity of nephropathy. In addition, some high dose female rats were observed to be hyperactive after dosing, and body weights of the high dose females remained about 9% lower than those of the vehicle controls after week 69. The presence of clinical signs of minimal toxicity in some high dose animals and lower body weight gain indicate that higher doses of hexachloroethane would not have been well tolerated by female rats. These data suggest that the doses selected for the 2-year studies were appropriate for evaluating the long-term effects of hexachloroethane exposure.

In the current study, hexachloroethane exposure in male rats caused a dose-related increased incidence in renal tubule hyperplasia (vehicle control, 2/50; low dose, 4/50; high dose, 11/50) and adenomas (1/50; 2/50; 4/50); there were three carcinomas in the high dose group, one of which metastasized. The historical incidence of renal tubular cell neoplasms in corn oil vehicle control male F344/N rats in National Toxicology Program (NTP) studies is 10/1,943 (0.5% ± 0.9%; Table A4a), and neoplasms with this frequency of background occurrence are considered rare. Taken together, these data were considered strong enough to provide clear, rather than some, evidence of carcinogenic activity of hexachloroethane in male rats.

Incidences of pheochromocytomas were also increased in dosed male rats (vehicle control, 15/50; low dose, 28/45; high dose, 21/49). Although there was a marginally significant positive trend, only the incidence of pheochromocytomas in the low dose males was statistically different from that in the vehicle controls. The incidence of pheochromocytomas in groups of historical control F344/N rats is highly variable, but the incidences in rats given 10 and 20 mg/kg hexachloroethane were greater than the mean historical control incidence (62% and 43% vs. 28% ± 11%). However, none of the other chlorinated ethanes studied by the National Cancer Institute (NCI) or the NTP caused increased incidences of pheochromocytomas (NCI, 1977a, 1978b,c,d,e; NTP, 1983, 1989a). Therefore, it was unclear whether the marginally increased incidences of pheochromocytomas in male rats were related to hexachloroethane administration.

Several chlorinated ethanes and chlorinated ethylenes have been found to produce cancer in laboratory animals. A review of more than 230 two-year studies by the NCI and NTP identified two chemical classes that commonly produced nonneoplastic chronic renal disease in rodents: aromatic amines and organohalides (Kluwe et al., 1984). Renal neoplasms were most often produced by the organohalides, especially the halogenated hydrocarbons. In studies reported by NCI (NCI, 1976a, 1977b, 1978a,b,c), the pattern of response to 78 weeks of exposure to chloroethanes and chloroethylenes was an increase in hepatocellular carcinomas in B6C3F$_1$ mice with little or no carcinogenicity apparent in Osborne-Mendel rats. The results of these earlier carcinogenicity studies have been summarized (Weisburger, 1977) and reviewed (IARC, 1979). However, the interpretation of carcinogenic effects in rats in those studies was complicated by the fact that the exposure regimens employed generally shortened the survival of the animals. For example, in the NCI hexachloroethane gavage study with Osborne-Mendel rats (time-weighted-average doses of 212 and 423 mg/kg per day for each sex), there was a significant association between increased dose and accelerated mortality (NCI, 1978a). Although these data clearly indicated that the rat kidney was the target organ of hexachloroethane exposure, i.e., dose-related nonneoplastic renal lesions in males and females, the absence of increased neoplasm incidences could have been a consequence of the animals' not having lived long enough for neoplasms to develop. This concept is supported by the current hexachloroethane studies in which

survival of exposed F344/N rats was similar to that of vehicle controls; both dose-related renal nephropathy in males and females and an increased incidence of renal neoplasms in males were observed.

Renal effects in rats have also been reported in long-term studies with other chlorinated hydrocarbons. In a long-term strain comparison study, male and female ACI, August, Marshall, and Osborne-Mendel rats were given 0, 500, or 1,000 mg/kg trichloroethylene in corn oil by gavage (NTP, 1988). Trichloroethylene administration caused renal tubular cell cytomegaly and toxic nephropathy in each sex of all four strains. Although the studies were considered to be inadequate studies of carcinogenicity because of chemically induced toxicity, increased incidences of renal tubular cell neoplasms were observed in three of the four strains of rats. In a 2-year gavage study of epichlorohydrin-free trichloroethylene, reduced survival caused the study to be judged inadequate in male F344/N rats (NTP, 1989a). Nevertheless, trichloroethylene-dosed male rats had renal tubular cell tumors (untreated control, 0/49; vehicle control, 0/49; low dose, 2/49; high dose, 3/49), and nephropathy was observed in rats of each sex. In 2-year inhalation studies in F344/N rats, tetrachloroethylene exposure (200 or 400 ppm, equivalent to 311 or 622 mg/kg per day) was associated with renal tubular cell karyomegaly in male and female rats and renal tubular cell hyperplasia and adenomas or adenocarcinomas in males (NTP, 1986).

The similar toxic effects of chlorinated hydrocarbons could be related to their metabolism. Mitoma et al. (1985) reported that 29% of a 500 mg/kg dose of [^{14}C]hexachloroethane orally administered to male Osborne-Mendel rats was metabolized. Tetrachloroethylene and pentachloroethane were two major metabolites found after in vitro hexachloroethane exposure to hepatic microsomal cytochrome P450 preparations from male Sprague Dawley rats (Nastainczyk et al., 1982). These same two metabolites were detected in the urine of mice (Mitoma et al., 1985) and in the blood, bile, and urine of sheep after an oral dose of hexachloroethane and also after in vitro exposure of hexachloroethane to fresh sheep liver slices (Fowler, 1969).

Although the kidney was the target organ in both sexes, there was a difference in the kidney response between male and female rats in the current hexachloroethane studies. In the 13-week studies, renal papillary necrosis and degeneration and necrosis of the renal tubular epithelium were observed in the highest dose males (750 mg/kg) that died before the end of the study. Hyaline droplet formation, tubular regeneration, and tubular casts were observed at all doses (lowest dose, 47 mg/kg). No renal lesions of similar severity were observed in females. In the 2-year study, males had increased severity of nephropathy at doses of 10 and 20 mg/kg and increased incidences of renal tubule neoplasms at 20 mg/kg, whereas females were observed to have increased incidences and severity of nephropathy, but no renal tubule neoplasms at 80 and 160 mg/kg. Differences in the kidney response to hexachloroethane between male and female F344 rats were reported by Gorzinski et al. (1985). After 16 weeks of dietary exposure at concentrations equivalent to 1, 15, or 62 mg/kg hexachloroethane per day, male rats had renal tubular atrophy, degeneration, hypertrophy, and/or dilatation at the highest two doses, whereas females had only very slight renal tubular atrophy and degeneration at the highest dose. The difference between male and female rats suggests that hexachloroethane toxicity may be, at least in part, mediated by a sex-specific physiologic component.

The renal lesions in male rats in the current 13-week hexachloroethane studies include an increased number of hyaline droplets (crystallized protein) in the epithelial cells of the proximal convoluted tubules, granular casts in the tubules at the junction of the inner and outer stripe of the outer medulla, and an increased incidence and severity of nephropathy (e.g., tubular degenerative and regenerative changes). These lesions were similar to those observed in male rats after 13 weeks of exposure to several other compounds studied by the NTP, including *d*-limonene (NTP, 1989b), dimethyl methylphosphonate (NTP, 1987a), and 1,4-dichlorobenzene (NTP, 1987b). Similar renal lesions have also been reported for a variety of other compounds, including decalin (Kanerva et al., 1987a,b,c; Stone et al., 1987a,b), unleaded gasoline (Kitchen, 1984), 2,2,4-trimethylpentane (Short et al.,

1986, 1987), and other hydrocarbon solvents and fuels (Halder et al., 1984).

In long-term studies, the organs affected by exposure to these compounds varied between species and sex and from chemical to chemical, but similar toxic kidney lesions were consistently produced in male rats in each case. In male rats given *d*-limonene, dimethyl methylphosphonate, 1,4-dichlorobenzene, or unleaded gasoline, there was an increased severity of chronic nephropathy (a spontaneous age-related disease of rats), linear deposits of mineral (calcium) in the renal medulla, and variable numbers of renal tubular cell tumors.

The underlying cause for the male rat-specific nature of the kidney lesions in animals exposed to some hydrocarbon compounds has been attributed to the accumulation of a low molecular weight protein, $\alpha_{2\mu}$-globulin (Alden et al., 1984; Short et al., 1986; Stonard et al., 1986; Goldsworthy et al., 1988). The comparative pathobiology of the $\alpha_{2\mu}$-globulin nephropathy syndrome has recently been reviewed by Swenberg and coworkers (Swenberg et al., 1989). $\alpha_{2\mu}$-Globulin is synthesized in the liver under multihormonal control and secreted into the blood, where it is readily filtered through the glomeruli of the kidney (Roy and Neuhaus, 1967; Vandoren et al., 1978), and partially reabsorbed in the proximal tubule (Trump et al., 1984). Short-term exposure to decalin, unleaded gasoline, or trimethylpentane (Charbonneau et al., 1987) produced an accumulation of $\alpha_{2\mu}$-globulin in epithelial cell phagolysosomes, primarily in the P2 segment of the nephron, which appears microscopically as hyaline droplets. In short-term studies of *d*-limonene, the NTP observed similar dose-related increased hyaline droplet formation and $\alpha_{2\mu}$-globulin concentration in the kidney of male F344/N rats; moreover, $\alpha_{2\mu}$-globulin was shown to be present in the hyaline droplets (NTP, 1989b).

The mechanism of action giving rise to rat kidney tubular cell cytotoxicity may not be the same for all chemicals, but the similarity in the pattern of renal effects caused by several hydrocarbon solvents and fuels suggests a common chain of events leading to male rat-specific renal tubular cell necrosis and nephropathy. Therefore, information obtained from studies with other hydrocarbon solvents and fuels that produce these sequelae of events in the kidney is probably relevant to the current hexachloroethane studies and to the understanding of the association between protein accumulation and renal tumorigenesis. For example, the reversible binding of a chemical or its metabolite to $\alpha_{2\mu}$-globulin within the kidney, as reported by Lock et al. (1987) for trimethylpentane, may somehow affect urinary excretion or decrease lysosomal catabolism of this protein, leading to its accumulation in the tubular epithelium. Accumulation of $\alpha_{2\mu}$-globulin was accompanied by tubular cell degeneration and granular casts consisting of necrotic cell debris in the tubule lumina in the current 13-week hexachloroethane studies and in studies of other chemicals in this group cited earlier. Results of biochemical studies also support the histologic evidence that regeneration of the tubular epithelium occurs in response to cell necrosis. Trimethylpentane, tetrachloroethylene, and pentachloroethane exposure caused an increased rate of cell replication in the P2 segment of the nephron, and an increase in DNA synthesis in this segment was shown by an increased incorporation of [^{3}H]thymidine into the renal DNA of male rats exposed to these solvents or to 1,4-dichlorobenzene (Charbonneau et al., 1987, 1989; Goldsworthy et al., 1988).

The reason for the difference in the response of the kidney in male and female rats to hexachloroethane exposure is not clear but may be related to the sex differences in urinary proteins. Proteinuria has been shown to be under hormonal control. Roy and Neuhaus (1967) showed that in male Sprague Dawley rats, $\alpha_{2\mu}$-globulin was produced in the liver and was the major urinary protein, whereas in females, this protein appeared to be absent. Vandoren et al. (1983) reported that a protein similar to male $\alpha_{2\mu}$-globulin was found in the urine of female Wistar rats; however, the isoelectric point and mobility of this protein on sodium dodecyl sulfate/polyacrylamide gel electrophoresis differed from the isoelectric point and mobility of the urinary $\alpha_{2\mu}$-globulin from male rats, but there were no immunologic differences and only minor differences were found in amino acid composition. $\alpha_{2\mu}$-Globulin was also present in the kidney of

F344/N rats of each sex, but the concentration (per milligram total protein) was four times greater in males than in females (NTP, 1989b).

Roy and Neuhaus (1967) showed that ovariectomized Sprague Dawley female rats injected with testosterone propionate excreted a new protein that migrated electrophoretically in the same position as $\alpha_{2\mu}$-globulin; and when male rats were given injections of estradiol dipropionate, the excretion of $\alpha_{2\mu}$-globulin was abolished. In addition, Vandoren et al. (1983) reported estrogen treatment suppressed only the male form of the protein in Wistar rats. It has also been reported that other hormones influence synthesis of this protein and that androgens and glucocorticoids are the major inducers. Curiously, androgens stimulate $\alpha_{2\mu}$-globulin production in male and female rats, whereas glucocorticoids induce this protein in males only (Vandoren et al., 1978).

The function of these urinary proteins is not known; however, Caviaggioni et al. (1987) showed that a pyrazine-binding protein from bovine olfactory mucosa is markedly homologous to male rat urinary $\alpha_{2\mu}$-globulin. These investigators suggested that male rat urinary proteins act as carriers of volatile pheromones. Other species also have proteins belonging to the $\alpha_{2\mu}$-globulin superfamily. For example, human apolipoprotein D from plasma was recently sequenced and was shown to have a high degree of homology to retinol-binding protein and other members of the $\alpha_{2\mu}$-globulin protein superfamily. This protein was obtained from cloned adult human liver DNA, but it can apparently be produced in other organs, since apolipoprotein D mRNA has been detected in human liver, intestine, pancreas, kidney, placenta, adrenal gland, spleen, and fetal brain tissue (Drayna et al., 1986). In addition, rat androgen-dependent epididymal protein has been shown to have a significant homology to human serum retinol-binding protein and rat $\alpha_{2\mu}$-globulin (Brooks, 1987). Phagolysosomes containing crystallized proteins with associated renal tubule cell damage were also reported in humans and experimental animals with proteinuric conditions caused by increased glomerular filtration of the light-chain portion of the immunoglobulins (Clyne et al., 1974), lysozyme (Osserman and Azar, 1969), and lysine (Madsen et al., 1976; Males et al., 1984).

Although all of the above data point to some association between the accumulation of $\alpha_{2\mu}$-globulin, hyaline droplet formation, and renal tumorigenesis in male rats, the nature of this relationship is not clear. Other chlorinated hydrocarbons have produced chemical-related nephropathy and renal neoplasms without hyaline droplet formation, (NTP, 1986, 1988).

Whatever the mechanism, genetic toxicity does not appear to be a factor involved in the production of renal neoplasms by hexachloroethane. Hexachloroethane was not mutagenic in Salmonella (Simmon and Kauhanen, 1978; Kinae et al., 1981; Haworth et al., 1983; see Table 14) and did not induce chromosomal aberrations in Chinese hamster ovary cells, but it did produce a significant increase in sister chromatid exchanges (Galloway et al., 1987; see Table 15). The lack of mutagenic activity in Salmonella and the lack of a potentially DNA-reactive chemical structure (Ashby and Tennant, 1988) indicate that hexachloroethane is a chemical that increases neoplasm incidences through a process that probably does not involve mutation induction.

The experimental and tabulated data for the NTP Technical Report on hexachloroethane were examined for accuracy, consistency, completeness, and compliance with Good Laboratory Practice regulations. As summarized in Appendix E, 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.

IV. DISCUSSION AND CONCLUSIONS

Under the conditions of these 2-year gavage studies, there was *clear evidence of carcinogenic activity** of hexachloroethane for male F344/N rats, based on the increased incidences of renal neoplasms. The marginally increased incidences of pheochromocytomas of the adrenal gland may have been related to hexachloroethane administration to male rats. There was *no evidence of carcinogenic activity* of hexachloroethane for female F344/N rats administered 80 or 160 mg/kg by gavage for 103 weeks.

The severity of nephropathy and incidences of linear mineralization of the renal papillae and hyperplasia of the transitional epithelium of the renal pelvis were increased in dosed male rats. The incidences and severity of nephropathy were increased in dosed female rats.

*Explanation of Levels of Evidence of Carcinogenic Activity is on page 6.
A summary of the Peer Review comments and the public discussion on this Technical Report appears on page 9.

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APPENDIX A

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

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

	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, colon	(50)	*(50)	(46)
Mesothelioma, NOS		1 (2%)	1 (2%)
Intestine small, duodenum	(50)	*(50)	(50)
Adenocarcinoma			1 (2%)
Leiomyosarcoma	1 (2%)		
Mesothelioma, NOS			1 (2%)
Intestine small, ileum	(49)	*(50)	(47)
Leiomyosarcoma		1 (2%)	
Leukemia mononuclear	1 (2%)		
Mesothelioma, NOS			1 (2%)
Liver	(50)	*(50)	(50)
Fibrosarcoma, metastatic, skin		1 (2%)	
Hepatocellular carcinoma	1 (2%)		1 (2%)
Leukemia mononuclear	13 (26%)	13 (26%)	11 (22%)
Neoplastic nodule	1 (2%)	1 (2%)	1 (2%)
Mesentery	*(50)	*(50)	*(50)
Mesothelioma malignant		2 (4%)	
Mesothelioma, NOS	1 (2%)	1 (2%)	2 (4%)
Sarcoma			1 (2%)
Pancreas	(50)	*(50)	(50)
Adenoma		1 (2%)	
Mesothelioma malignant		1 (2%)	
Mesothelioma, NOS	1 (2%)	1 (2%)	1 (2%)
Acinus, adenoma		3 (6%)	
Pharynx	*(50)	*(50)	*(50)
Palate, papilloma squamous		1 (2%)	1 (2%)
Stomach, forestomach	(48)	*(50)	(49)
Papilloma squamous		1 (2%)	
Stomach, glandular	(50)	*(50)	(49)
Leukemia mononuclear	1 (2%)		
Tongue	*(50)	*(50)	*(50)
Papilloma squamous		1 (2%)	
CARDIOVASCULAR SYSTEM			
Heart	(50)	*(50)	(50)
Leukemia mononuclear	1 (2%)	2 (4%)	4 (8%)
Schwannoma malignant	1 (2%)		
ENDOCRINE SYSTEM			
Adrenal gland	(50)	(50)	(50)
Pheochromocytoma benign		1 (2%)	
Adrenal gland, cortex	(50)	(50)	(50)
Leukemia mononuclear	1 (2%)		
Adrenal gland, medulla	(50)	(45)	(49)
Leukemia mononuclear	1 (2%)		
Pheochromocytoma malignant	1 (2%)	2 (4%)	1 (2%)
Pheochromocytoma complex			2 (4%)
Pheochromocytoma benign	11 (22%)	18 (40%)	15 (31%)
Bilateral, pheochromocytoma benign	3 (6%)	7 (16%)	4 (8%)
Islets, pancreatic	(50)	*(50)	(50)
Adenoma	2 (4%)	2 (4%)	
Carcinoma			2 (4%)
Parathyroid gland	(41)	*(50)	(43)
Adenoma		1 (2%)	1 (2%)

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

	Vehicle Control	Low Dose	High Dose
ENDOCRINE SYSTEM (Continued)			
Pituitary gland	(49)	(50)	(48)
Leukemia mononuclear		1 (2%)	
Pars distalis, adenoma	24 (49%)	22 (44%)	16 (33%)
Thyroid gland	(49)	(50)	(50)
Leukemia mononuclear		1 (2%)	
C-cell, adenoma	6 (12%)	9 (18%)	5 (10%)
C-cell, carcinoma	3 (6%)	2 (4%)	
Follicular cell, adenoma		1 (2%)	
Follicular cell, carcinoma	1 (2%)		2 (4%)
GENERAL BODY SYSTEM			
None			
GENITAL SYSTEM			
Epididymis	(49)	*(50)	(50)
Mesothelioma malignant		1 (2%)	
Mesothelioma, NOS	1 (2%)	1 (2%)	4 (8%)
Preputial gland	(46)	*(50)	(49)
Adenoma	1 (2%)	2 (4%)	2 (4%)
Carcinoma		1 (2%)	1 (2%)
Bilateral, adenoma			1 (2%)
Prostate	(50)	*(50)	(48)
Mesothelioma, NOS			1 (2%)
Testes	(49)	*(50)	(50)
Mesothelioma malignant		2 (4%)	
Mesothelioma, NOS	1 (2%)	1 (2%)	5 (10%)
Bilateral, interstitial cell, adenoma	32 (65%)	36 (72%)	42 (84%)
Interstitial cell, adenoma	11 (22%)	5 (10%)	3 (6%)
HEMATOPOIETIC SYSTEM			
Bone marrow	(50)	*(50)	(49)
Leukemia mononuclear	4 (8%)		1 (2%)
Lymph node	(50)	*(50)	(50)
Mediastinal, leukemia mononuclear	2 (4%)	6 (12%)	3 (6%)
Pancreatic, leukemia mononuclear		1 (2%)	3 (6%)
Lymph node, mandibular	(45)	*(50)	(44)
Leukemia mononuclear	8 (18%)	3 (6%)	9 (20%)
Lymph node, mesenteric	(50)	*(50)	(48)
Leukemia mononuclear	11 (22%)	5 (10%)	11 (23%)
Spleen	(49)	*(50)	(50)
Leukemia mononuclear	13 (27%)	14 (28%)	11 (22%)
Mesothelioma, NOS	1 (2%)	1 (2%)	
Thymus	(47)	*(50)	(43)
Leukemia mononuclear	6 (13%)	1 (2%)	2 (5%)
Thymoma benign			2 (5%)
INTEGUMENTARY SYSTEM			
Mammary gland	(33)	*(50)	(23)
Adenocarcinoma	1 (3%)		1 (4%)
Fibroadenoma	6 (18%)	6 (12%)	1 (4%)
Fibroadenoma, multiple	1 (3%)		
Lipoma		1 (2%)	
Skin	(48)	*(50)	(50)
Basal cell adenoma		1 (2%)	
Basal cell carcinoma	1 (2%)		
Keratoacanthoma	6 (13%)	5 (10%)	5 (10%)
Papilloma squamous	1 (2%)	1 (2%)	
Squamous cell carcinoma	1 (2%)		1 (2%)

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

	Vehicle Control	Low Dose	High Dose
INTEGUMENTARY SYSTEM			
Skin (Continued)	(48)	*(50)	(50)
Trichoepithelioma		1 (2%)	
Subcutaneous tissue, fibroma	6 (13%)	3 (6%)	2 (4%)
Subcutaneous tissue, fibrosarcoma	2 (4%)	3 (6%)	2 (4%)
Subcutaneous tissue, lipoma	1 (2%)	1 (2%)	
MUSCULOSKELETAL SYSTEM			
Bone	(50)	*(50)	(50)
Osteosarcoma	1 (2%)		
Skeletal muscle	*(50)	*(50)	*(50)
Leukemia mononuclear		1 (2%)	
Lipoma	1 (2%)		
Mesothelioma malignant		1 (2%)	
Mesothelioma, NOS	1 (2%)		2 (4%)
NERVOUS SYSTEM			
Brain	(50)	*(50)	(50)
Astrocytoma malignant	1 (2%)		
Leukemia mononuclear		2 (4%)	
Cranial nerve, schwannoma malignant	1 (2%)		
Spinal cord	*(50)	*(50)	*(50)
Leukemia mononuclear		1 (2%)	
RESPIRATORY SYSTEM			
Lung	(50)	*(50)	(50)
Alveolar/bronchiolar adenoma	4 (8%)		2 (4%)
Carcinoma, metastatic, kidney			1 (2%)
Leukemia mononuclear	10 (20%)	7 (14%)	9 (18%)
Nose	(50)	*(50)	(50)
Leukemia mononuclear	1 (2%)	1 (2%)	
SPECIAL SENSES SYSTEM			
Harderian gland	*(50)	*(50)	*(50)
Adenoma		1 (2%)	
Zymbal gland	*(50)	*(50)	*(50)
Carcinoma	1 (2%)		
URINARY SYSTEM			
Kidney	(50)	(50)	(50)
Adenoma			1 (2%)
Leukemia mononuclear		3 (6%)	2 (4%)
Renal tubule, adenoma	1 (2%)	2 (4%)	3 (6%)
Renal tubule, carcinoma			3 (6%)
Urinary bladder	(47)	*(50)	(46)
Leukemia mononuclear	1 (2%)		1 (2%)
Mesothelioma, NOS			2 (4%)
SYSTEMIC LESIONS			
Multiple organs	*(50)	*(50)	*(50)
Leukemia mononuclear	13 (26%)	15 (30%)	11 (22%)
Mesothelioma, NOS	1 (2%)	1 (2%)	5 (10%)
Mesothelioma malignant		2 (4%)	

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

	Vehicle Control	Low Dose	High Dose
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Terminal sacrifice	31	29	26
Moribund	16	14	19
Accident	1	1	
Dead	2	6	4
Gavage death			1
TUMOR SUMMARY			
Total animals with primary neoplasms **	48	49	48
Total primary neoplasms	149	161	141
Total animals with benign neoplasms	48	49	48
Total benign neoplasms	118	134	107
Total animals with malignant neoplasms	24	22	22
Total malignant neoplasms	30	26	29
Total animals with secondary neoplasms ***		1	1
Total secondary neoplasms		1	1
Total animals with neoplasms-- uncertain benign or malignant	1	1	5
Total uncertain neoplasms	6	6	20

* Number of animals receiving complete necropsy examination; 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 HEXACHLOROETHANE: VEHICLE CONTROL

WEEKS ON STUDY	022	051	058	076	082	084	085	090	091	092	093	093	094	096	096	099	102	103	104	105	105	105	105	105
CARCASS ID	031	105	075	074	073	055	095	094	081	015	025	045	113	014	065	084	035	104	085	111	112	121	122	233	232
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma																									
Intestine small, ileum	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma								X																	
Leukemia mononuclear				X		X	X				X					X							X	
Neoplastic nodule																								X	
Mesentery																									
Mesothelioma, NOS																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma, NOS																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear						X																			
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear						X																			
Schwannoma malignant																									
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X																		
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X																		
Pheochromocytoma malignant																									
Pheochromocytoma benign										X		X							X			X			
Bilateral, pheochromocytoma benign									X				X												
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	M	M	M	M	M	M	+	+	+	M	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+
Pituitary gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma					X	X					X		X	X			X		X			X	X	X	
Thyroid gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C cell, adenoma															X		X								X
C cell, carcinoma								X											X						
Follicular cell, carcinoma																			X						
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Epididymis	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma, NOS																									
Preputial gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+
Adenoma																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma, NOS																									
Bilateral, interstitial cell, adenoma			X				X	X	X	X	X	X		X	X	X		X	X	X		X			X
Interstitial cell, adenoma				X	X	X															X		X	X	
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mediastinal, leukemia mononuclear				X			X																		
Lymph node, mandibular	+	M	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear						X										X									
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X		X	X									X								X	
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Leukemia mononuclear				X		X	X			X						X								X	
Mesothelioma, NOS																									
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+
Leukemia mononuclear				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	106	106	106	106	106	106	106	TOTAL TISSUES TUMORS
CARCASS ID	03 3	03 4	04 1	04 2	04 3	05 1	05 2	05 3	06 1	06 2	06 3	06 4	07 1	07 2	08 2	08 3	10 3	02 4	04 4	05 4	09 1	09 2	09 3	10 1	10 2	
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma																						X				1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear																								X		1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma																										1
Leukemia mononuclear			X				X				X	X				X			X					X		13
Neoplastic nodule																										1
Mesentery																								+		1
Mesothelioma, NOS																								X		1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma, NOS																								X		1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	48
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Schwannoma malignant																					X					1
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Pheochromocytoma malignant				X																						1
Pheochromocytoma benign		X	X					X	X					X					X	X						11
Bilateral, pheochromocytoma benign																X										3
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma								X											X							2
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma		X				X	X	X	X					X	X	X		X	X			X		X	X	24
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C cell, adenoma		X															X									6
C cell, carcinoma																X										3
Follicular cell, carcinoma																										1
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Mesothelioma, NOS																								X		1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	46
Adenoma				X																						1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Mesothelioma, NOS																								X		1
Bilateral, interstitial cell, adenoma	X		X	X	X			X	X	X		X	X		X	X	X		X	X	X			X	X	32
Interstitial cell, adenoma		X				X					X			X									X			11
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear			X								X								X					X		4
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mediastinal, leukemia mononuclear																										2
Lymph node, mandibular	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	45
Leukemia mononuclear			X				X				X	X							X					X		8
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear			X				X				X	X							X					X		11
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear			X				X				X	X				X			X					X		13
Mesothelioma, NOS																								X		1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	47
Leukemia mononuclear												X							X					X		6

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

WEEKS ON STUDY	02 2	05 1	05 8	07 6	08 2	08 4	08 5	09 0	09 1	09 2	09 3	09 3	09 4	09 6	09 6	09 9	10 2	10 3	10 4	10 5	10 5	10 5	10 5	10 5
CARCASS ID	03 1	10 5	07 5	07 4	07 3	5 5	09 5	09 4	08 1	01 5	02 5	04 5	01 3	01 4	06 5	08 4	03 5	10 4	08 5	01 1	01 2	02 1	02 2	02 3	03 2
INTEGUMENTARY SYSTEM																									
Mammary gland	M	M	M	M	+	M	M	+	+	M	+	M	+	+	+	+	M	+	+	+	+	+	M	+	
Adenocarcinoma																									
Fibroadenoma								X											X	X					
Fibroadenoma, multiple																						X			
Skin	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma																					X				
Keratoacanthoma													X												
Papilloma squamous												X													
Squamous cell carcinoma																									
Subcutaneous tissue, fibroma					X										X									
Subcutaneous tissue, fibrosarcoma												X													
Subcutaneous tissue, lipoma																		X							
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma																			X						
Skeletal muscle			+	+							+														
Lipoma											X														
Mesothelioma, NOS																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant																									
Cranial nerve, schwannoma malignant														X											
Spinal cord			I																						
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma											X						X								
Leukemia mononuclear				X		X	X									X									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear						X																			
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Ear																									+
Eye						+	+												+		+				
Zymbal gland											+														
Carcinoma											X														
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma													X												
Urinary bladder	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Leukemia mononuclear						X																			

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	106	106	106	106	106	106	106	106	TOTAL TISSUES TUMORS
CARCASS ID	033	034	041	042	043	051	052	053	061	062	063	064	071	072	082	083	103	024	044	054	091	092	093	101	102	
INTEGUMENTARY SYSTEM																										
Mammary gland	M	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	M	M	M	+	33
Adenocarcinoma															X											1
Fibroadenoma												X					X								X	6
Fibroadenoma, multiple																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Basal cell carcinoma																										1
Keratoacanthoma		X					X														X		X		X	6
Papilloma squamous																										1
Squamous cell carcinoma													X													1
Subcutaneous tissue, fibroma										X										X			X	X		6
Subcutaneous tissue, fibrosarcoma									X																	2
Subcutaneous tissue, lipoma																										1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma																										1
Skeletal muscle																								+		4
Lipoma																										1
Mesothelioma, NOS																								X		1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma malignant												X														1
Cranial nerve, schwannoma malignant																										1
Spinal cord																										
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma										X	X															4
Leukemia mononuclear			X				X				X	X							X					X		10
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Ear																										1
Eye														+												5
Zymbal gland																		+								2
Carcinoma																										1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Leukemia mononuclear																										1

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

WEEKS ON STUDY	049	053	070	080	083	086	088	088	088	089	090	092	095	097	098	098	101	102	104	104	105	105	105	105
CARCASS ID	145	115	165	135	114	195	113	112	155	205	194	134	125	193	204	185	192	124	203	123	164	121	122	131	132
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	M	+	+											
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+		+										
Intestine large, cecum	+	+	+	+	+	+	A	+	+	+	+	A	+		+										
Intestine large, colon	+	M	+	+	+	+	+	+	+	+	+	+	+		+										
Mesothelioma, NOS									X																
Intestine large, rectum	+	+	+	+	+	+	+	M	+	+	+	+	+												
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+			+		+							
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+					+							
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	A	A	+			+		+							
Leiomyosarcoma										X															
Intestine small, jejunum	+	+	M	+	+	+	+	+	+	+	+	+	+					+							
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+		+		+	+	+	
Fibrosarcoma, metastatic, skin																									
Leukemia mononuclear			X			X				X	X				X	X				X				X	
Neoplastic nodule																						X			
Mesentery									+											+	+				+
Mesothelioma malignant																				X	X				
Mesothelioma, NOS									X																
Pancreas	+	+	+	+	+	A	+	+	+	+	+	+	+							+	+	+			+
Adenoma																									X
Mesothelioma malignant																				X					
Mesothelioma, NOS									X																
Acinus, adenoma										X												X			
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+												
Pharynx																									
Palate, papilloma squamous																									
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+		+			+							
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+		+			+						+	
Papilloma squamous																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+		+			+						+	
Tongue									+																
Papilloma squamous																									
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+												
Leukemia mononuclear						X				X															
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign					X																				
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	I	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	M	+	+	+	+	+	+
Pheochromocytoma malignant																									X
Pheochromocytoma benign																	X			X	X	X	X	X	
Bilateral, pheochromocytoma benign															X			X							
Islets, pancreatic	+	+	+	+	+	A	+	+	+	+	+	+	+							+	+	+			+
Adenoma		X																							
Parathyroid gland	M	M	M	M	M	M	M	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear											X														
Pars distalis, adenoma				X			X	X			X	X			X	X		X	X	X		X			
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear											X														
C cell, adenoma													X	X						X					
C cell, carcinoma								X																	
Follicular cell, adenoma											X														
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+								+				
Mesothelioma malignant																					X				
Mesothelioma, NOS									X																
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+						+						+
Adenoma																			X						
Carcinoma																									
Prostate	+	+	+	+	+	+	+	+	+	+		+	+												
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+						+			+	+	+	
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			+	+	+	+	+	
Mesothelioma malignant																				X	X				
Mesothelioma, NOS									X																
Bilateral, interstitial cell, adenoma			X	X	X	X				X			X	X			X			X	X		X	X	X
Interstitial cell, adenoma								X	X		X					X									
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+												
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+			+		+	+
Mediastinal, leukemia mononuclear			X			X					X													X	X
Pancreatic, leukemia mononuclear																			X						
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+				+			
Leukemia mononuclear			X			X					X														
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+												+
Leukemia mononuclear			X			X				X	X														X
Spleen	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+			+	+			+	+	+
Leukemia mononuclear			x			x				x	x			x	x				x	x				x	x
Mesothelioma, NOS									X																
Thymus	+	+	M	+	+	+	+	+		+	M	+	M	+	+										
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	TOTAL
CARCASS ID	133	111	141	142	143	144	151	152	153	154	161	162	163	171	172	173	174	175	181	182	183	184	191	201	202	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus																										13
Intestine large																										14
Intestine large, cecum																										12
Intestine large, colon																										13
Mesothelioma, NOS																										1
Intestine large, rectum																										12
Intestine small																		+								16
Intestine small, duodenum																		+								15
Intestine small, ileum																		+								14
Leiomyosarcoma																										1
Intestine small, jejunum																		+								14
Liver	+			+	+			+		+		+		+	+	+				+						31
Fibrosarcoma, metastatic, skin														X												1
Leukemia mononuclear	X			X	X					X						X										13
Neoplastic nodule																										1
Mesentery	+																									5
Mesothelioma malignant																										2
Mesothelioma, NOS																										1
Pancreas										+		+														18
Adenoma																										1
Mesothelioma malignant																										1
Mesothelioma, NOS																										1
Acinus, adenoma										X																3
Pharynx						+																				1
Palate, papilloma squamous						X																				1
Salivary glands																										13
Stomach								+									+								+	19
Stomach, forestomach								+									+									18
Papilloma squamous								X																		1
Stomach, glandular								+									+								+	19
Tongue																					+					2
Papilloma squamous																					X					1
CARDIOVASCULAR SYSTEM																										
Heart	+							+																		15
Leukemia mononuclear																										2
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																										1
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	45
Pheochromocytoma malignant								X																		2
Pheochromocytoma benign		X			X	X	X		X	X	X		X				X						X	X	X	18
Bilateral, pheochromocytoma benign	X		X									X			X				X							7
Islets, pancreatic										+																17
Adenoma										X																2
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	40
Adenoma										X																1
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Pars distalis, adenoma		X	X				X		X				X			X		X		X			X	X	X	22
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
C cell, adenoma		X			X	X			X		X				X											9
C cell, carcinoma												X														2
Follicular cell, adenoma																										1
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Epididymis																										14
Mesothelioma malignant																										1
Mesothelioma, NOS																										1
Preputial gland					+															+						17
Adenoma																				X						2
Carcinoma					X																					1
Prostate																									+	13
Seminal vesicle						+											+	+		+	+	+				23
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	46
Mesothelioma malignant																										2
Mesothelioma NOS																										1
Bilateral, interstitial cell, adenoma	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X		X	36
Interstitial cell, adenoma											X															5
HEMATOPOIETIC SYSTEM																										
Bone marrow																										13
Lymph node	+				+		+			+						+	+	+		+	+	+				31
Mediastinal, leukemia mononuclear	X																									6
Pancreatic, leukemia mononuclear																										1
Lymph node, mandibular							+			+						+					+	+				23
Leukemia mononuclear																										3
Lymph node, mesenteric																	+									15
Leukemia mononuclear																										5
Spleen	+			+	+			+		+	+								+							28
Leukemia mononuclear	X			X	X			X																		14
Mesothelioma, NOS																										1
Thymus																	M									11
Leukemia mononuclear																										1

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

WEEKS ON STUDY	049	053	070	080	083	086	086	088	088	089	089	090	092	095	097	098	098	101	102	104	104	105	105	105
CARCASS ID	145	115	165	135	114	195	113	112	155	205	194	134	125	193	204	185	192	124	203	223	164	121	122	131	132
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	M	+	M	M	M	+	+	+	M	+	+		+		+			+		+			
Fibroadenoma																	X			X		X			
Lipoma																						X			
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+							+				+
Basal cell adenoma																									X
Keratoacanthoma				X																	X				
Papilloma squamous								X																	
Trichoepithelioma																									
Subcutaneous tissue, fibroma										X				X											
Subcutaneous tissue, fibrosarcoma		X		X																					
Subcutaneous tissue, lipoma									X																
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+												
Skeletal muscle			+	M																	+				
Leukemia mononuclear			X																						
Mesothelioma malignant																					X				
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+												
Leukemia mononuclear						X					X														
Spinal cord			+																						
Leukemia mononuclear			X																						
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+					+	
Leukemia mononuclear			X			X					X					X			X					X	
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+												
Leukemia mononuclear			X																						
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+												
SPECIAL SENSES SYSTEM																									
Eye										+				+											
Harderian gland										+															
Adenoma																									
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X			X					X														
Renal tubule, adenoma															X						X				
Urinary bladder	+	+	A	+	+	+	A	+	+	+	A	A	+				+								

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	133	111	141	142	143	144	151	152	153	154	161	162	163	171	172	173	174	175	181	182	183	184	191	201	202	TOTAL TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Mammary gland						+														+			+	+		16
Fibroadenoma						X														X			X			6
Lipoma																										1
Skin										+	+			+		+			+							21
Basal cell adenoma																										1
Keratoacanthoma										X	X			X												5
Papilloma squamous																										1
Trichoepithelioma																X										1
Subcutaneous tissue, fibroma																			X							3
Subcutaneous tissue, fibrosarcoma														X												3
Subcutaneous tissue, lipoma																										1
MUSCULOSKELETAL SYSTEM																										
Bone																										13
Skeletal muscle																										2
Leukemia mononuclear																										1
Mesothelioma malignant																										1
NERVOUS SYSTEM																										
Brain																										13
Leukemia mononuclear																										2
Spinal cord																										1
Leukemia mononuclear																										1
RESPIRATORY SYSTEM																										
Lung	+																+			+	+				+	24
Leukemia mononuclear	X																									7
Nose																										13
Leukemia mononuclear																										1
Trachea																										13
SPECIAL SENSES SYSTEM																										
Eye																					+					3
Harderian gland								+																		2
Adenoma								X																		1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										3
Renal tubule, adenoma																										2
Urinary bladder																										10

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

WEEKS ON STUDY	047	052	067	068	069	077	079	080	083	084	084	088	090	091	091	092	093	094	098	099	100	101	102	104	105
CARCASS ID	305	245	244	304	215	235	295	255	285	234	303	233	284	232	265	275	254	283	294	274	264	293	225	224	211
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	M	+	+	+	+	+	M	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	A	+	+	+
Mesothelioma, NOS						X																			
Intestine large, rectum	+	+	+	+	+	+	M	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Mesothelioma, NOS						X																			
Intestine small, ileum	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+
Mesothelioma, NOS						X																			
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																						X			
Leukemia mononuclear					X		X	X						X				X	X						
Neoplastic nodule																									
Mesentery		+				+			M										+	+					
Mesothelioma, NOS						X													X						
Sarcoma																				X					
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma, NOS						X																			
Pharynx																	+								
Palate, papilloma squamous																	X								
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+
Tongue																	+								
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X		X											X							
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																									
Pheochromocytoma complex																						X			
Pheochromocytoma benign									X		X			X	X				X			X			
Bilateral, pheochromocytoma benign																							X		X
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma													X												
Parathyroid gland	M	+	M	+	M	+	+	+	+	M	M	+	M	M	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Pituitary gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma				X						X	X					X						X	X		
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C cell, adenoma				X											X										X
Follicular cell, carcinoma																								X	
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma, NOS			X			X														X					
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma								X																	
Bilateral, adenoma													X												
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma, NOS						X																			
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma, NOS			X			X														X					
Bilateral, interstitial cell, adenoma			X		X	X	X	X	X	X	X	X	X	X	X		X	X	X	X		X	X	X	X
Interstitial cell, adenoma																					X				
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																		X							
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mediastinal, leukemia mononuclear					X														X						
Pancreatic, leukemia mononuclear						X												X							
Lymph node, mandibular	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X		X	X						X				X	X						
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+
Leukemia mononuclear					X		X	X						X				X	X						
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X		X	X						X				X	X						
Thymus	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	A	+	+	+
Leukemia mononuclear					X		X																		
Thymoma benign																									

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE 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	2122	2113	2114	2221	2222	2223	2231	2243	2251	2252	2253	2241	2242	2261	2262	2263	2271	2272	2273	2281	2282	2291	2292	3012	3022	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	46
Mesothelioma, NOS																										1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma							X																			1
Mesothelioma, NOS																										1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	47
Mesothelioma, NOS																										1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma																										1
Leukemia mononuclear					X			X		X		X					X									11
Neoplastic nodule															X											1
Mesentery																					+					5
Mesothelioma, NOS																										2
Sarcoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma, NOS																										1
Pharynx																										1
Palate, papilloma squamous																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tongue																										1
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																	X									4
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma malignant							X																			1
Pheochromocytoma complex												X														2
Pheochromocytoma benign	X		X	X	X				X					X		X	X	X								15
Bilateral, pheochromocytoma benign																			X						X	4
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																						X				2
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Adenoma																						X				1
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	48
Pars distalis, adenoma		X		X	X			X	X	X	X			X			X								X	16
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma						X								X												5
Follicular cell, carcinoma										X																2
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma, NOS																X										4
Preputial gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma												X				X										2
Carcinoma																										1
Bilateral, adenoma																										1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	48
Mesothelioma, NOS																										1
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	48
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma, NOS																X				X						5
Bilateral, interstitial cell, adenoma	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X			42
Interstitial cell, adenoma										X														X		3
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear																										1
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mediastinal, leukemia mononuclear																		X								3
Pancreatic, leukemia mononuclear																		X								3
Lymph node, mandibular	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	M	44
Leukemia mononuclear					X			X										X								9
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	48
Leukemia mononuclear					X			X		X		X						X								11
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear					X			X		X		X						X								11
Thymus	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	43
Leukemia mononuclear																										2
Thymoma benign														X	X											2

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

WEEKS ON STUDY	047	052	067	068	069	077	079	080	083	084	084	088	090	091	091	092	093	094	098	099	100	101	102	104	105
CARCASS ID	305	245	244	304	215	235	295	255	285	234	303	233	284	232	265	275	254	283	294	274	264	293	225	244	211
INTEGUMENTARY SYSTEM																									
Mammary gland	+	M	+	M	M	M	M	+	+	M	+	+	M	+	M	M	+	M	+	M	+	+	+	+	+
Adenocarcinoma																									
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma											X														
Squamous cell carcinoma										X															
Subcutaneous tissue, fibroma																								X	
Subcutaneous tissue, *fibrosarcoma*																						X			
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle						+														+					
Mesothelioma, NOS						X														X					
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma															X										
Carcinoma, metastatic, kidney															X										
Leukemia mononuclear					X		X								X			X	X						
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Ear			+																	+					
Eye			M										+							+					
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Leukemia mononuclear							X											X							
Renal tubule, adenoma																									
Renal tubule, carcinoma															X	X									
Urinary bladder	+	+	+	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	A	+	+
Leukemia mononuclear																		X							
Mesothelioma, NOS						X														X					

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE 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	212	213	214	221	222	223	231	243	251	252	253	241	242	261	262	263	271	272	273	281	282	291	292	301	302	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Mammary gland	M	+	+	+	+	M	M	M	M	M	M	+	+	M	M	M	M	M	+	M	M	M	+	M	+	23
Adenocarcinoma																			X							1
Fibroadenoma																							X			1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma		X			X									X									X			5
Squamous cell carcinoma																										1
Subcutaneous tissue, fibroma																				X						2
Subcutaneous tissue, fibrosarcoma															X											2
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										2
Mesothelioma, NOS																										2
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma		X																								2
Carcinoma, metastatic, kidney																										1
Leukemia mononuclear					X			X		X								X								9
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Ear																										2
Eye																										2
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																X										1
Leukemia mononuclear																										2
Renal tubule, adenoma							X					X							X							3
Renal tubule, carcinoma									X																	3
Urinary bladder	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Leukemia mononuclear																										1
Mesothelioma, NOS																										2

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

	Vehicle Control	10 mg/kg	20 mg/kg
Adrenal Medulla: Pheochromocytoma			
Overall Rates (a)	14/50 (28%)	26/45 (58%)	19/49 (39%)
Adjusted Rates (b)	37.8%	76.1%	56.3%
Terminal Rates (c)	9/31 (29%)	20/28 (71%)	12/26 (46%)
Day of First Observation	637	578	577
Life Table Tests (d)	P=0.064	P=0.006	P=0.091
Logistic Regression Tests (d)	P=0.089	P=0.002	P=0.133
Cochran-Armitage Trend Test (d)	P=0.158		
Fisher Exact Test (d)		P=0.003	P=0.178
Adrenal Medulla: Pheochromocytoma, Benign, Complex, or Malignant			
Overall Rates (a)	15/50 (30%)	28/45 (62%)	21/49 (43%)
Adjusted Rates (b)	40.7%	82.1%	62.5%
Terminal Rates (c)	10/31 (32%)	22/28 (79%)	14/26 (54%)
Day of First Observation	637	578	577
Life Table Tests (d)	P=0.038	P=0.003	P=0.058
Logistic Regression Tests (d)	P=0.051	P<0.001	P=0.086
Cochran-Armitage Trend Test (d)	P=0.115		
Fisher Exact Test (d)		P=0.002	P=0.131
Preputial Gland: Adenoma			
Overall Rates (a)	1/46 (2%)	(e) 2/17 (12%)	3/49 (6%)
Adjusted Rates (b)	3.3%		10.4%
Terminal Rates (c)	1/30 (3%)		2/25 (8%)
Day of First Observation	733		630
Life Table Test (d)			P=0.249
Logistic Regression Test (d)			P=0.290
Fisher Exact Test (d)			P=0.333
Preputial Gland: Adenoma or Carcinoma			
Overall Rates (a)	1/46 (2%)	(e) 3/17 (18%)	4/49 (8%)
Adjusted Rates (b)	3.3%		12.5%
Terminal Rates (c)	1/30 (3%)		2/25 (8%)
Day of First Observation	733		558
Life Table Test (d)			P=0.141
Logistic Regression Test (d)			P=0.195
Fisher Exact Test (d)			P=0.201
Kidney: Adenoma or Renal Tubule Adenoma			
Overall Rates (a)	1/50 (2%)	2/50 (4%)	4/50 (8%)
Adjusted Rates (b)	2.6%	5.9%	15.4%
Terminal Rates (c)	0/31 (0%)	0/29 (0%)	4/26 (15%)
Day of First Observation	654	677	733
Life Table Tests (d)	P=0.088	P=0.497	P=0.132
Logistic Regression Tests (d)	P=0.096	P=0.500	P=0.146
Cochran-Armitage Trend Test (d)	P=0.118		
Fisher Exact Test (d)		P=0.500	P=0.181
Kidney: Renal Tubule Carcinoma			
Overall Rates (a)	0/50 (0%)	0/50 (0%)	3/50 (6%)
Adjusted Rates (b)	0.0%	0.0%	9.2%
Terminal Rates (c)	0/31 (0%)	0/29 (0%)	1/26 (4%)
Day of First Observation			636
Life Table Tests (d)	P=0.030	(f)	P=0.098
Logistic Regression Tests (d)	P=0.037	(f)	P=0.120
Cochran-Armitage Trend Test (d)	P=0.037		
Fisher Exact Test (d)		(f)	P=0.121

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

	Vehicle Control	10 mg/kg	20 mg/kg
Kidney: Adenoma, Renal Tubule Adenoma, or Renal Tubule Carcinoma			
Overall Rates (a)	1/50 (2%)	2/50 (4%)	7/50 (14%)
Adjusted Rates (b)	2.6%	5.9%	23.7%
Terminal Rates (c)	0/31 (0%)	0/29 (0%)	5/26 (19%)
Day of First Observation	654	677	636
Life Table Tests (d)	P=0.009	P=0.497	P=0.020
Logistic Regression Tests (d)	P=0.011	P=0.500	P=0.026
Cochran-Armitage Trend Test (d)	P=0.014		
Fisher Exact Test (d)		P=0.500	P=0.030
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	4/50 (8%)	(e) 0/24 (0%)	2/50 (4%)
Adjusted Rates (b)	11.5%		6.5%
Terminal Rates (c)	2/31 (6%)		1/26 (4%)
Day of First Observation	646		636
Life Table Test (d)			P=0.424N
Logistic Regression Test (d)			P=0.361N
Fisher Exact Test (d)			P=0.339N
Mammary Gland: Fibroadenoma			
Overall Rates (a)	7/50 (14%)	6/50 (12%)	1/50 (2%)
Adjusted Rates (b)	20.6%	19.0%	3.8%
Terminal Rates (c)	5/31 (16%)	4/29 (14%)	1/26 (4%)
Day of First Observation	630	684	733
Life Table Tests (d)	P=0.053N	P=0.550N	P=0.057N
Logistic Regression Tests (d)	P=0.042N	P=0.519N	P=0.045N
Cochran-Armitage Trend Test (d)	P=0.029N		
Fisher Exact Test (d)		P=0.500N	P=0.030N
Mammary Gland: Fibroadenoma or Adenocarcinoma			
Overall Rates (a)	8/50 (16%)	6/50 (12%)	2/50 (4%)
Adjusted Rates (b)	23.7%	19.0%	7.7%
Terminal Rates (c)	6/31 (19%)	4/29 (14%)	2/26 (8%)
Day of First Observation	630	684	733
Life Table Tests (d)	P=0.068N	P=0.439N	P=0.083N
Logistic Regression Tests (d)	P=0.055N	P=0.405N	P=0.069N
Cochran-Armitage Trend Test (d)	P=0.037N		
Fisher Exact Test (d)		P=0.387N	P=0.046N
Pancreas: Adenoma			
Overall Rates (a)	0/50 (0%)	(e,g) 4/18 (22%)	0/50 (0%)
Pituitary Gland/Pars Distalis: Adenoma			
Overall Rates (a)	24/49 (49%)	22/50 (44%)	16/48 (33%)
Adjusted Rates (b)	62.5%	55.3%	49.4%
Terminal Rates (c)	17/31 (55%)	12/29 (41%)	10/25 (40%)
Day of First Observation	568	559	472
Life Table Tests (d)	P=0.243N	P=0.517N	P=0.265N
Logistic Regression Tests (d)	P=0.099N	P=0.405N	P=0.121N
Cochran-Armitage Trend Test (d)	P=0.073N		
Fisher Exact Test (d)		P=0.384N	P=0.087N
Skin: Keratoacanthoma			
Overall Rates (a)	6/50 (12%)	5/50 (10%)	5/50 (10%)
Adjusted Rates (b)	18.3%	15.1%	17.5%
Terminal Rates (c)	5/31 (16%)	3/29 (10%)	4/26 (15%)
Day of First Observation	654	559	587
Life Table Tests (d)	P=0.548N	P=0.536N	P=0.617N
Logistic Regression Tests (d)	P=0.487N	P=0.506N	P=0.567N
Cochran-Armitage Trend Test (d)	P=0.436N		
Fisher Exact Test (d)		P=0.500N	P=0.500N

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

	Vehicle Control	10 mg/kg	20 mg/kg
Subcutaneous Tissue: Fibroma			
Overall Rates (a)	6/50 (12%)	3/50 (6%)	2/50 (4%)
Adjusted Rates (b)	17.2%	8.3%	7.4%
Terminal Rates (c)	4/31 (13%)	1/29 (3%)	1/26 (4%)
Day of First Observation	568	617	724
Life Table Tests (d)	P=0.134N	P=0.269N	P=0.195N
Logistic Regression Tests (d)	P=0.097N	P=0.242N	P=0.154N
Cochran-Armitage Trend Test (d)	P=0.090N		
Fisher Exact Test (d)		P=0.243N	P=0.134N
Subcutaneous Tissue: Fibrosarcoma			
Overall Rates (a)	2/50 (4%)	3/50 (6%)	2/50 (4%)
Adjusted Rates (b)	5.6%	7.4%	7.2%
Terminal Rates (c)	1/31 (3%)	1/29 (3%)	1/26 (4%)
Day of First Observation	646	370	703
Life Table Tests (d)	P=0.535	P=0.485	P=0.631
Logistic Regression Tests (d)	P=0.583N	P=0.466	P=0.672
Cochran-Armitage Trend Test (d)	P=0.594		
Fisher Exact Test (d)		P=0.500	P=0.691N
Subcutaneous Tissue: Fibroma or Fibrosarcoma			
Overall Rates (a)	8/50 (16%)	6/50 (12%)	4/50 (8%)
Adjusted Rates (b)	22.2%	15.3%	14.2%
Terminal Rates (c)	5/31 (16%)	2/29 (7%)	2/26 (8%)
Day of First Observation	568	370	703
Life Table Tests (d)	P=0.217N	P=0.421N	P=0.271N
Logistic Regression Tests (d)	P=0.139N	P=0.395N	P=0.208N
Cochran-Armitage Trend Test (d)	P=0.141N		
Fisher Exact Test (d)		P=0.387N	P=0.178N
Testis: Interstitial Cell Adenoma			
Overall Rates (a)	43/49 (88%)	41/46 (89%)	45/50 (90%)
Adjusted Rates (b)	93.4%	100.0%	97.8%
Terminal Rates (c)	28/31 (90%)	27/27 (100%)	25/26 (96%)
Day of First Observation	406	489	467
Life Table Tests (d)	P=0.086	P=0.320	P=0.111
Logistic Regression Tests (d)	P=0.250	P=0.505	P=0.362
Cochran-Armitage Trend Test (d)	P=0.422		
Fisher Exact Test (d)		P=0.545	P=0.486
Thyroid Gland: C-Cell Adenoma			
Overall Rates (a)	6/49 (12%)	9/50 (18%)	5/50 (10%)
Adjusted Rates (b)	17.8%	27.3%	15.8%
Terminal Rates (c)	4/31 (13%)	6/29 (21%)	3/26 (12%)
Day of First Observation	667	644	472
Life Table Tests (d)	P=0.549	P=0.255	P=0.607N
Logistic Regression Tests (d)	P=0.485N	P=0.272	P=0.519N
Cochran-Armitage Trend Test (d)	P=0.426N		
Fisher Exact Test (d)		P=0.303	P=0.486N
Thyroid Gland: C-Cell Carcinoma			
Overall Rates (a)	3/49 (6%)	2/50 (4%)	0/50 (0%)
Adjusted Rates (b)	8.4%	5.7%	0.0%
Terminal Rates (c)	1/31 (3%)	1/29 (3%)	0/26 (0%)
Day of First Observation	630	614	
Life Table Tests (d)	P=0.109N	P=0.532N	P=0.156N
Logistic Regression Tests (d)	P=0.081N	P=0.491N	P=0.126N
Cochran-Armitage Trend Test (d)	P=0.079N		
Fisher Exact Test (d)		P=0.490N	P=0.117N

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

	Vehicle Control	10 mg/kg	20 mg/kg
Thyroid Gland: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	9/49 (18%)	11/50 (22%)	5/50 (10%)
Adjusted Rates (b)	25.1%	32.1%	15.8%
Terminal Rates (c)	5/31 (16%)	7/29 (24%)	3/26 (12%)
Day of First Observation	630	614	472
Life Table Tests (d)	P=0.288N	P=0.352	P=0.300N
Logistic Regression Tests (d)	P=0.198N	P=0.394	P=0.208N
Cochran-Armitage Trend Test (d)	P=0.162N		
Fisher Exact Test (d)		P=0.421	P=0.183N
Hematopoietic System: Mononuclear Leukemia			
Overall Rates (a)	13/50 (26%)	(h) 15/50 (30%)	11/50 (22%)
Adjusted Rates (b)	34.3%	38.8%	31.1%
Terminal Rates (c)	8/31 (26%)	7/29 (24%)	5/26 (19%)
Day of First Observation	530	489	483
Life Table Tests (d)	P=0.527N	P=0.372	P=0.558N
Logistic Regression Tests (d)	P=0.368N	P=0.413	P=0.408N
Cochran-Armitage Trend Test (d)	P=0.366N		
Fisher Exact Test (d)		P=0.412	P=0.408N
All Sites: All Mesothelioma			
Overall Rates (a)	1/50 (2%)	3/50 (6%)	5/50 (10%)
Adjusted Rates (b)	3.2%	8.6%	14.5%
Terminal Rates (c)	1/31 (3%)	0/29 (0%)	2/26 (8%)
Day of First Observation	733	614	467
Life Table Tests (d)	P=0.056	P=0.296	P=0.086
Logistic Regression Tests (d)	P=0.073	P=0.305	P=0.107
Cochran-Armitage Trend Test (d)	P=0.070		
Fisher Exact Test (d)		P=0.309	P=0.102

(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) Incomplete sampling of tissues
(f) No P value is reported because no tumors were observed in the 10 mg/kg and vehicle control groups.
(g) Includes three acinar adenomas and one adenoma
(h) Thirty-one livers and 28 spleens were examined microscopically.

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

Study	Incidence of Adenomas or Adenocarcinomas in Vehicle Controls
Historical Incidence at EG&G Mason Research Institute	
Diglycidyl resorcinol ether	(b) 1/50
Diglycidyl resorcinol ether	0/50
1,2-Dichloropropane	0/50
Chlorodibromomethane	0/50
n-Butyl chloride	0/50
Bromodichloromethane	0/50
TOTAL	1/300 (0.3%)
SD (c)	0.82%
Range (d)	
High	1/50
Low	0/50
Overall Historical Incidence	
TOTAL	(e) 10/1,943 (0.5%)
SD (c)	0.89%
Range (d)	
High	1/48
Low	0/50

(a) Data as of April 29, 1987, for studies of at least 104 weeks
(b) Tubular cell adenocarcinoma
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.
(e) Includes three tubular cell adenomas, five tubular cell adenocarcinomas, and two adenocarcinomas, NOS

TABLE A4b. HISTORICAL INCIDENCE OF ADRENAL GLAND MEDULLARY TUMORS IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls		
	Pheochromocytoma	Malignant Pheochromocytoma	Pheochromocytoma or Malignant Pheochromocytoma
Historical Incidence at EG&G Mason Research Institute			
Diglycidyl resorcinol ether	11/50	1/50	12/50
Diglycidyl resorcinol ether	11/50	1/50	11/50
1,2-Dichloropropane	11/50	0/50	11/50
Chlorodibromomethane	7/50	1/50	8/50
n-Butyl chloride	14/50	1/50	15/50
Bromodichloromethane	17/50	1/50	18/50
TOTAL	71/300 (23.7%)	5/300 (1.7%)	75/300 (25.0%)
SD (b)	6.74%	0.82%	7.01%
Range (c)			
High	17/50	1/50	18/50
Low	7/50	0/50	8/50
Overall Historical Incidence			
TOTAL	521/1,937 (26.9%)	28/1,937 (1.4%)	543/1,937 (28.0%)
SD (b)	10.56%	1.90%	11.28%
Range (c)			
High	30/50	4/50	33/50
Low	2/50	0/50	2/50

(a) Data as of April 29, 1987, 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 HEXACHLOROETHANE

	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	(50)	(13)	(49)
Foreign body		1 (8%)	
Perforation		1 (8%)	
Periesophageal tissue, inflammation, acute		1 (8%)	
Periesophageal tissue, inflammation, chronic active	1 (2%)		
Intestine large, cecum	(49)	(12)	(45)
Parasite metazoan	4 (8%)	1 (8%)	2 (4%)
Intestine large, colon	(50)	(13)	(46)
Parasite metazoan	10 (20%)	1 (8%)	4 (9%)
Intestine large, rectum	(50)	(12)	(47)
Parasite metazoan	10 (20%)	1 (8%)	8 (17%)
Intestine small, ileum	(49)	(14)	(47)
Hyperplasia, lymphoid	1 (2%)		
Parasite metazoan	1 (2%)		1 (2%)
Liver	(50)	(31)	(50)
Angiectasis	1 (2%)		
Basophilic focus	11 (22%)	10 (32%)	26 (52%)
Congestion	1 (2%)	2 (6%)	
Cytoplasmic alteration, focal	2 (4%)	2 (6%)	2 (4%)
Fatty change	27 (54%)	14 (45%)	22 (44%)
Fibrosis, focal			1 (2%)
Hepatodiaphragmatic nodule	1 (2%)	3 (10%)	2 (4%)
Hyperplasia	1 (2%)		
Hyperplasia, focal		1 (3%)	
Mineralization, focal			1 (2%)
Necrosis, focal	20 (40%)	3 (10%)	23 (46%)
Bile duct, hyperplasia	40 (80%)	24 (77%)	42 (84%)
Centrilobular, necrosis, focal		1 (3%)	
Serosa, proliferation		1 (3%)	
Mesentery	(1)	(5)	(5)
Fat, necrosis		2 (40%)	2 (40%)
Pancreas	(50)	(18)	(50)
Inflammation, chronic	1 (2%)		
Acinus, atrophy	23 (46%)	3 (17%)	11 (22%)
Acinus, hyperplasia	5 (10%)		5 (10%)
Artery, inflammation			1 (2%)
Duct, hyperplasia, focal		1 (6%)	
Salivary glands	(50)	(13)	(50)
Inflammation, chronic	1 (2%)		
Karyomegaly, focal			2 (4%)
Stomach	(50)	(19)	(49)
Serosa, fibrosis			1 (2%)
Serosa, inflammation, chronic active			1 (2%)
Stomach, forestomach	(48)	(18)	(49)
Acanthosis	1 (2%)	3 (17%)	3 (6%)
Cyst epithelial inclusion			1 (2%)
Hyperkeratosis	4 (8%)	3 (17%)	2 (4%)
Hyperplasia, basal cell	1 (2%)	1 (6%)	1 (2%)
Inflammation, focal	2 (4%)		
Ulcer	2 (4%)	3 (17%)	3 (6%)
Epithelium, hyperplasia			1 (2%)
Stomach, glandular	(50)	(19)	(49)
Erosion			1 (2%)
Infiltration cellular, lymphocytic		2 (11%)	1 (2%)
Inflammation, chronic	1 (2%)		1 (2%)

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

	Vehicle Control	Low Dose	High Dose
CARDIOVASCULAR SYSTEM			
Heart	(50)	(15)	(50)
Cardiomyopathy	37 (74%)	14 (93%)	43 (86%)
Hemorrhage, focal		1 (7%)	
Inflammation, chronic	1 (2%)	1 (7%)	1 (2%)
Mineralization	1 (2%)		
Pigmentation, hemosiderin	1 (2%)	1 (7%)	
Atrium, dilatation		2 (13%)	3 (6%)
Atrium, thrombus	1 (2%)		5 (10%)
ENDOCRINE SYSTEM			
Adrenal gland, cortex	(50)	(50)	(50)
Accessory adrenal cortical nodule	1 (2%)		
Cytoplasmic alteration, focal	6 (12%)	1 (2%)	2 (4%)
Hyperplasia, focal	3 (6%)	5 (10%)	2 (4%)
Hypertrophy			1 (2%)
Vacuolization cytoplasmic	2 (4%)	8 (16%)	2 (4%)
Adrenal gland, medulla	(50)	(45)	(49)
Hyperplasia, focal	6 (12%)	4 (9%)	10 (20%)
Thrombus		1 (2%)	
Islets, pancreatic	(50)	(17)	(50)
Hyperplasia	4 (8%)		
Parathyroid gland	(41)	(40)	(43)
Cyst	1 (2%)		
Hyperplasia			1 (2%)
Pituitary gland	(49)	(50)	(48)
Pars distalis, angiectasis	2 (4%)		
Pars distalis, cyst	1 (2%)	1 (2%)	2 (4%)
Pars distalis, hemorrhage	1 (2%)	1 (2%)	
Pars distalis, hyperplasia, focal	11 (22%)	13 (26%)	13 (27%)
Pars distalis, pigmentation, hemosiderin		1 (2%)	1 (2%)
Pars distalis, vacuolization cytoplasmic			1 (2%)
Pars intermedia, cyst		1 (2%)	1 (2%)
Pars nervosa, cyst			1 (2%)
Thyroid gland	(49)	(50)	(50)
C-cell, hyperplasia	10 (20%)	10 (20%)	11 (22%)
Follicle, cyst	2 (4%)	3 (6%)	4 (8%)
GENERAL BODY SYSTEM			
None			
GENITAL SYSTEM			
Epididymis	(49)	(14)	(50)
Atrophy	1 (2%)		2 (4%)
Dilatation, focal			1 (2%)
Inflammation, chronic			1 (2%)
Preputial gland	(46)	(17)	(49)
Abscess		1 (6%)	3 (6%)
Atrophy	1 (2%)		
Ectasia	2 (4%)		2 (4%)
Hyperplasia	1 (2%)		
Inflammation, acute	1 (2%)		4 (8%)
Inflammation, chronic	29 (63%)	6 (35%)	18 (37%)
Inflammation, chronic active	1 (2%)		1 (2%)
Inflammation, granulomatous			1 (2%)

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

	Vehicle Control	Low Dose	High Dose
GENITAL SYSTEM (Continued)			
Prostate	(50)	(13)	(48)
Abscess		1 (8%)	
Atrophy			2 (4%)
Hyperplasia, focal	2 (4%)		6 (13%)
Inflammation, acute	3 (6%)	2 (15%)	1 (2%)
Inflammation, chronic	8 (16%)	5 (38%)	5 (10%)
Inflammation, chronic active			1 (2%)
Metaplasia, squamous			1 (2%)
Seminal vesicle	(50)	(23)	(48)
Atrophy	27 (54%)	12 (52%)	29 (60%)
Dilatation		2 (9%)	
Testes	(49)	(46)	(50)
Edema		1 (2%)	
Necrosis		1 (2%)	
Interstitial cell, hyperplasia		2 (4%)	
Seminiferous tubule, atrophy	8 (16%)	4 (9%)	3 (6%)
HEMATOPOIETIC SYSTEM			
Bone marrow	(50)	(13)	(49)
Hyperplasia	2 (4%)	2 (15%)	7 (14%)
Lymph node	(50)	(31)	(50)
Axillary, congestion		1 (3%)	
Inguinal, angiectasis	1 (2%)		
Lumbar, congestion		1 (3%)	
Lumbar, hyperplasia			1 (2%)
Lumbar, infiltration cellular, plasma cell	1 (2%)		
Lumbar, infiltration cellular, histiocytic	1 (2%)		
Mediastinal, congestion	3 (6%)	4 (13%)	3 (6%)
Mediastinal, infiltration cellular, plasma cell		2 (6%)	
Mediastinal, pigmentation, hemosiderin			1 (2%)
Pancreatic, congestion	1 (2%)	1 (3%)	
Pancreatic, pigmentation, hemosiderin			1 (2%)
Renal, congestion	1 (2%)	2 (6%)	
Renal, hyperplasia, lymphoid		1 (3%)	
Renal, infiltration cellular, histiocytic	2 (4%)		
Renal, pigmentation, hemosiderin			1 (2%)
Lymph node, mandibular	(45)	(23)	(44)
Angiectasis	3 (7%)		2 (5%)
Congestion	2 (4%)	5 (22%)	1 (2%)
Infiltration cellular, plasma cell	26 (58%)	16 (70%)	29 (66%)
Lymphatic, angiectasis		4 (17%)	
Lymph node, mesenteric	(50)	(15)	(48)
Congestion	2 (4%)	2 (13%)	2 (4%)
Cyst			1 (2%)
Hyperplasia, lymphoid			2 (4%)
Infiltration cellular, plasma cell		1 (7%)	
Infiltration cellular, histiocytic	1 (2%)		
Necrosis		1 (7%)	
Pigmentation, hemosiderin	1 (2%)		
Spleen	(49)	(28)	(50)
Congestion	1 (2%)	1 (4%)	1 (2%)
Depletion lymphoid			1 (2%)
Fibrosis		3 (11%)	
Fibrosis, focal	3 (6%)	1 (4%)	1 (2%)
Hematopoietic cell proliferation	6 (12%)	4 (14%)	8 (16%)
Necrosis	1 (2%)		
Pigmentation, hemosiderin	4 (8%)	5 (18%)	11 (22%)
Thymus	(47)	(11)	(43)
Congestion		2 (18%)	
Hyperplasia, lymphoid			1 (2%)

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

	Vehicle Control	Low Dose	High Dose
INTEGUMENTARY SYSTEM			
Mammary gland	(33)	(16)	(23)
Ectasia	1 (3%)		
Galactocele	1 (3%)	4 (25%)	
Hemorrhage			1 (4%)
Hyperplasia, glandular	1 (3%)		
Skin	(48)	(21)	(50)
Cyst epithelial inclusion	1 (2%)		3 (6%)
Hyperkeratosis			1 (2%)
Subcutaneous tissue, fibrosis			1 (2%)
Subcutaneous tissue, necrosis		1 (5%)	
MUSCULOSKELETAL SYSTEM			
Bone	(50)	(13)	(50)
Tarsal, hyperostosis	1 (2%)		
Skeletal muscle	(4)	(2)	(2)
Back, hemorrhage, focal	1 (25%)		
NERVOUS SYSTEM			
Brain	(50)	(13)	(50)
Hemorrhage, focal	4 (8%)	4 (31%)	3 (6%)
Hydrocephalus	5 (10%)		5 (10%)
RESPIRATORY SYSTEM			
Lung	(50)	(24)	(50)
Congestion	2 (4%)	7 (29%)	2 (4%)
Edema		1 (4%)	
Embolus	1 (2%)		
Foreign body		1 (4%)	1 (2%)
Fungus	1 (2%		
Granuloma	1 (2%)	1 (4%)	4 (8%)
Hemorrhage, focal		4 (17%)	
Infiltration cellular, histiocytic		1 (4%)	
Alveolar epithelium, hyperplasia, adenomatous	1 (2%)		2 (4%)
Alveolar epithelium, metaplasia, focal		1 (4%)	2 (4%)
Artery, ectasia			1 (2%)
Peribronchial, inflammation, chronic	34 (68%)	5 (21%)	32 (64%)
Pleura, inflammation, acute		1 (4%)	
Nose	(50)	(13)	(50)
Foreign body	1 (2%)		
Fungus	3 (6%)	1 (8%)	2 (4%)
Hemorrhage, focal		1 (8%)	
Inflammation, acute		1 (8%)	1 (2%)
Inflammation, chronic	36 (72%)	7 (54%)	30 (60%)
Inflammation, chronic active	1 (2%)		
Metaplasia, squamous	34 (68%)	1 (8%)	33 (66%)
Lymphatic, angiectasis			1 (2%)
SPECIAL SENSES SYSTEM			
Ear	(1)		(2)
Inflammation, chronic, focal	1 (100%)		
Eye	(5)	(3)	(2)
Cataract	3 (60%)	1 (33%)	
Retina, degeneration	1 (20%)	1 (33%)	1 (50%)
Sclera, mineralization, focal	1 (20%)		
Vitreous, hemorrhage			1 (50%)
Harderian gland		(2)	
Inflammation, chronic		1 (50%)	

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

	Vehicle Control	Low Dose	High Dose
URINARY SYSTEM			
Kidney	(50)	(50)	(50)
Casts			2 (4%)
Congestion	2 (4%)		
Cytomegaly			2 (4%)
Hemorrhage, focal		1 (2%)	
Hyperplasia		1 (2%)	1 (2%)
Inflammation, chronic			2 (4%)
Mineralization	2 (4%)	15 (30%)	32 (64%)
Nephropathy	48 (96%)	48 (96%)	47 (94%)
Artery, inflammation, chronic		1 (2%)	
Pelvis, inflammation, acute		2 (4%)	
Pelvis, transitional epithelium, hyperplasia		7 (14%)	7 (14%)
Renal tubule, cyst	2 (4%)	3 (6%)	1 (2%)
Renal tubule, hyperplasia	2 (4%)	4 (8%)	11 (22%)
Renal tubule, necrosis, focal			1 (2%)
Renal tubule, pigmentation	1 (2%)	4 (8%)	5 (10%)
Renal tubule, regeneration	1 (2%)		3 (6%)
Urinary bladder	(47)	(10)	(46)
Concretion	4 (9%)	1 (10%)	2 (4%)
Lumen, thrombus		1 (10%)	
Transitional epithelium, hyperplasia		1 (10%)	1 (2%)
Wall, inflammation, acute		1 (10%)	
Wall, inflammation, chronic active			1 (2%)

APPENDIX B

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

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

	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 small, ileum	(48)	*(50)	(47)
Leukemia mononuclear	2 (4%)		
Intestine small, jejunum	(50)	*(50)	(48)
Leukemia mononuclear	1 (2%)		
Liver	(50)	*(50)	(50)
Carcinoma, metastatic, adrenal gland		1 (2%)	
Hepatocellular carcinoma		1 (2%)	
Leukemia mononuclear	19 (38%)	11 (22%)	14 (28%)
Neoplastic nodule	1 (2%)	2 (4%)	1 (2%)
Mesentery	*(50)	*(50)	*(50)
Leukemia mononuclear	1 (2%)	1 (2%)	
Pancreas	(48)	*(50)	(49)
Leukemia mononuclear		1 (2%)	
Pharynx	*(50)	*(50)	*(50)
Palate, papilloma squamous			1 (2%)
Stomach, forestomach	(50)	*(50)	(50)
Leukemia mononuclear	1 (2%)		
Stomach, glandular	(49)	*(50)	(50)
Leukemia mononuclear		1 (2%)	
Sarcoma			1 (2%)
Tongue	*(50)	*(50)	*(50)
Papilloma squamous		1 (2%)	
CARDIOVASCULAR SYSTEM			
Heart	(50)	*(50)	(50)
Leukemia mononuclear	1 (2%)	2 (4%)	
Schwannoma malignant	1 (2%)		
Ventricle left, schwannoma malignant	1 (2%)		
ENDOCRINE SYSTEM			
Adrenal gland, cortex	(50)	*(50)	(50)
Adenoma	1 (2%)		1 (2%)
Carcinoma		1 (2%)	
Leukemia mononuclear	3 (6%)	2 (4%)	
Adrenal gland, medulla	(50)	*(50)	(46)
Leukemia mononuclear		2 (4%)	
Pheochromocytoma malignant		1 (2%)	
Pheochromocytoma benign	1 (2%)		1 (2%)
Bilateral, pheochromocytoma benign		1 (2%)	1 (2%)
Islets, pancreatic	(49)	*(50)	(49)
Carcinoma		1 (2%)	
Parathyroid gland	(38)	*(50)	(38)
Adenoma	1 (3%)		
Pituitary gland	(50)	(49)	(49)
Leukemia mononuclear		1 (2%)	
Pars distalis, adenoma	26 (52%)	20 (41%)	16 (33%)
Pars distalis, carcinoma			1 (2%)
Thyroid gland	(50)	(50)	(50)
C-cell, adenoma	9 (18%)	7 (14%)	6 (12%)
C-cell, carcinoma	1 (2%)		
Follicular cell, adenoma		1 (2%)	
Follicular cell, carcinoma			2 (4%)

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

	Vehicle Control	Low Dose	High Dose
GENERAL BODY SYSTEM			
None			
GENITAL SYSTEM			
Clitoral gland	(46)	*(50)	(39)
Adenoma	3 (7%)		2 (5%)
Carcinoma	1 (2%)	1 (2%)	
Leukemia mononuclear	1 (2%)		
Ovary	(50)	*(50)	(50)
Cystadenoma	1 (2%)		
Leukemia mononuclear	1 (2%)	1 (2%)	
Uterus	(48)	*(50)	(50)
Leiomyoma			1 (2%)
Leukemia mononuclear		1 (2%)	
Polyp stromal	10 (21%)	7 (14%)	5 (10%)
Cervix, leukemia mononuclear	1 (2%)		
Cervix, endometrium, sarcoma stromal	1 (2%)		
Endometrium, adenocarcinoma	1 (2%)		1 (2%)
HEMATOPOIETIC SYSTEM			
Bone marrow	(50)	*(50)	(49)
Leukemia mononuclear	3 (6%)		1 (2%)
Lymph node	(49)	*(50)	(50)
Carcinosarcoma, metastatic, Zymbal gland	1 (2%)		
Mediastinal, leukemia mononuclear	6 (12%)	3 (6%)	1 (2%)
Pancreatic, leukemia mononuclear	3 (6%)	2 (4%)	2 (4%)
Renal, leukemia mononuclear	2 (4%)		
Lymph node, mandibular	(46)	*(50)	(43)
Leukemia mononuclear	14 (30%)	3 (6%)	10 (23%)
Lymphoma malignant lymphocytic			1 (2%)
Lymph node, mesenteric	(48)	*(50)	(49)
Leukemia mononuclear	19 (40%)	3 (6%)	11 (22%)
Lymphoma malignant lymphocytic			1 (2%)
Spleen	(50)	*(50)	(50)
Leukemia monocytic		1 (2%)	
Leukemia mononuclear	19 (38%)	11 (22%)	14 (28%)
Lymphoma malignant lymphocytic			1 (2%)
Thymus	(41)	*(50)	(45)
Leukemia mononuclear	5 (12%)	2 (4%)	4 (9%)
INTEGUMENTARY SYSTEM			
Mammary gland	(48)	*(50)	(46)
Adenocarcinoma		1 (2%)	
Fibroadenoma	17 (35%)	17 (34%)	20 (43%)
Fibroadenoma, multiple	11 (23%)	4 (8%)	4 (9%)
Skin	(49)	*(50)	(48)
Keratoacanthoma		1 (2%)	
Papilloma squamous	1 (2%)		
Subcutaneous tissue, fibroma	1 (2%)	2 (4%)	1 (2%)
Subcutaneous tissue, fibrosarcoma			1 (2%)
Subcutaneous tissue, leukemia mononuclear	1 (2%)		
MUSCULOSKELETAL SYSTEM			
None			

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

	Vehicle Control	Low Dose	High Dose
NERVOUS SYSTEM			
Brain	(50)	*(50)	(50)
Astrocytoma malignant			1 (2%)
Meninges, leukemia mononuclear	1 (2%)		
RESPIRATORY SYSTEM			
Lung	(50)	*(50)	(50)
Alveolar/bronchiolar adenoma	2 (4%)		1 (2%)
Alveolar/bronchiolar carcinoma			1 (2%)
Carcinoma, metastatic, adrenal gland		1 (2%)	
Fibrosarcoma, metastatic, skin			1 (2%)
Leukemia mononuclear	14 (28%)	6 (12%)	10 (20%)
Nose	(49)	*(50)	(50)
Leukemia mononuclear	1 (2%)		
SPECIAL SENSES SYSTEM			
Eye	*(50)	*(50)	*(50)
Conjunctiva, squamous cell carcinoma	1 (2%)		
Harderian gland	*(50)	*(50)	*(50)
Adenocarcinoma			1 (2%)
Zymbal gland	*(50)	*(50)	*(50)
Carcinoma	2 (4%)		
URINARY SYSTEM			
Kidney	(50)	(50)	(50)
Leukemia mononuclear	3 (6%)	4 (8%)	
Urinary bladder	(46)	*(50)	(47)
Leukemia mononuclear			1 (2%)
Transitional epithelium, papilloma	1 (2%)		
SYSTEMIC LESIONS			
Multiple organs	*(50)	*(50)	*(50)
Leukemia mononuclear	19 (38%)	12 (24%)	15 (30%)
Leukemia monocytic		1 (2%)	
Lymphoma malignant lymphocytic			2 (4%)
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Terminal sacrifice	32	27	32
Dead	4	2	3
Moribund	14	20	15
Accident		1	
TUMOR SUMMARY			
Total animals with primary neoplasms **	50	44	43
Total primary neoplasms	114	82	87
Total animals with benign neoplasms	44	36	40
Total benign neoplasms	86	63	61
Total animals with malignant neoplasms	22	16	20
Total malignant neoplasms	28	19	26
Total animals with secondary neoplasms ***	1	1	1
Total secondary neoplasms	1	2	1

* Number of animals receiving complete necropsy examination; 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 HEXACHLOROETHANE: VEHICLE CONTROL

WEEKS ON STUDY	073	079	084	087	087	087	089	089	090	092	094	095	096	096	098	099	102	104	106	106	106	106	106	106	106
CARCASS ID	395	385	394	393	335	455	255	444	384	375	315	383	365	374	433	373	392	364	313	314	422	371	372	324	341
ALIMENTARY SYSTEM																									
Esophagus	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	A	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X					X																	
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X																						
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X	X	X		X	X	X					X		X							X	X	X
Neoplastic nodule																									
Mesentery			+				+											+		+					
Leukemia mononuclear			X																						
Pancreas	+	+	M	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X																		
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Schwannoma malignant																									
Ventricle left, schwannoma malignant																X									
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Leukemia mononuclear								X						X											
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	M	+	M	+	+	+	M	M	+	+	+	+	+	+	+	M	+	M	+	+	M	+	+	+
Adenoma	X																								
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma	X							X		X		X	X	X	X	X	X		X		X				X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma							X			X					X			X				X		
C-cell, carcinoma																									
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Clitoral gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																			X						
Carcinoma																							X		
Leukemia mononuclear			X																						
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma																									
Leukemia mononuclear								X																	
Uterus	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Polyp stromal			X													X									
Cervix, leukemia mononuclear								X																	
Cervix, endometrium, sarcoma stromal											X														
Endometrium, adenocarcinoma																									
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X					X																	
Lymph node	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinosarcoma, metastatic, Zymbal gland						X																			
Mediastinal, leukemia mononuclear			X	X	X		X	X																	
Pancreatic, leukemia mononuclear			X					X																	
Renal, leukemia mononuclear								X																	
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	A	M	+	+	+	M	+	+	+	+	+	+	M	+	+
Leukemia mononuclear			X	X	X		X	X	X					X										X	
Lymph node, mesenteric	M	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X	X	X		X	X	X					X		X							X	X	X
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X	X	X		X	X	X					X		X							X	X	X
Thymus	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M
Leukemia mononuclear			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 B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: VEHICLE CONTROL (Continued)

WEEKS ON STUDY	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	
CARCASS ID	354	355	363	405	323	322	331	332	333	334	351	352	353	361	381	382	391	401	402	404	411	412	421	462	403	TOTAL: TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia mononuclear																										2
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear				X			X	X	X				X							X			X	X		19
Neoplastic nodule									X																	1
Mesentery															+					+					+	7
Leukemia mononuclear																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																				X						1
Schwannoma malignant																								X		1
Ventricle left, schwannoma malignant																										1
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma								X																		1
Leukemia mononuclear																				X						3
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																			X							1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	M	+	+	M	M	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	38
Adenoma																										1
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma		X	X	X	X			X		X			X	X		X		X	X			X		X	X	26
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma								X				X							X	X						9
C-cell, carcinoma				X																						1
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Clitoral gland	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	46
Adenoma			X											X												3
Carcinoma																										1
Leukemia mononuclear																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cystadenoma	X																									1
Leukemia mononuclear																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Polyp stromal					X					X	X					X	X				X		X	X		10
Cervix, leukemia mononuclear																										1
Cervix, endometrium, sarcoma stromal																										1
Endometrium, adenocarcinoma																			X							1
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																				X						3
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinosarcoma, metastatic, Zymbal gland																										1
Mediastinal, leukemia mononuclear																				X						6
Pancreatic, leukemia mononuclear																				X						3
Renal, leukemia mononuclear																				X						2
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Leukemia mononuclear							X	X	X				X							X			X			14
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia mononuclear				X			X	X	X				X							X			X	X		19
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear				X			X	X	X				X							X			X	X		19
Thymus	+	+	+	+	+	+	I	M	M	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	41
Leukemia mononuclear																										5

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

WEEKS ON STUDY	073	079	084	087	087	089	089	090	092	094	095	096	098	098	099	102	104	106	106	106	106	106	106
CARCASS ID	395	385	394	393	335	345	325	344	384	375	315	383	365	374	343	373	392	364	313	314	342	371	372	324	341
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma		X				X		X				X	X	X			X			X					
Fibroadenoma, multiple									X									X							
Skin	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous																			X						
Subcutaneous tissue, fibroma								X																	
Subcutaneous tissue, leukemia mononuclear								X																	
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Meninges, leukemia mononuclear								X																	
Peripheral nerve											+		+	+	M	+	M	+	+	+	+	M	+	+	+
Spinal cord											+		+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Leukemia mononuclear			X	X	X		X	X	X					X		X								X	
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Leukemia mononuclear			X																						
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Eye	+			+												+									
Conjunctiva, squamous cell carcinoma																									
Zymbal gland						+																			
Carcinoma						X																			
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X					X																	
Urinary bladder	+	+	A	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional epithelium, papilloma																									

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

WEEKS ON STUDY	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	TOTAL
CARCASS ID	354	355	363	405	323	322	331	332	333	334	351	352	353	361	381	382	391	401	402	404	411	412	421	362	403	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Fibroadenoma	X	X		X				X				X		X		X				X					X	17
Fibroadenoma, multiple			X			X	X			X			X		X		X	X				X				11
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Papilloma squamous																										1
Subcutaneous tissue, fibroma																										1
Subcutaneous tissue, leukemia mononuclear																										1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Meninges, leukemia mononuclear																										1
Peripheral nerve	+	+	+	+	+	+	+	+		+	+		+	+	+	+	+	+	+	+	+	M	+	+	+	33
Spinal cord	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	38
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma								X																X		2
Leukemia mononuclear				X			X		X				X							X						14
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Eye												+		+					+							6
Conjunctiva, squamous cell carcinoma																			X							1
Zymbal gland							+																			2
Carcinoma							X																			2
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																				X						3
Urinary bladder	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Transitional epithelium, papilloma														X												1

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

WEEKS ON STUDY	057	072	079	081	084	085	088	088	091	091	093	093	095	095	095	095	095	096	096	099	100	104	104	105	105
CARCASS ID	41 5	49 5	43 5	49 4	49 3	50 5	50 4	46 5	41 4	45 5	46 4	50 3	44 5	47 4	47 5	45 4	46 3	42 5	48 5	43 4	50 2	42 4	45 3	41 1	41 2
ALIMENTARY SYSTEM																									
Esophagus	+	M	+	+	+	+	+	+	+	+															
Intestine large	+	+	+	+	+	+	+	+	+	+															
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+															
Intestine large, colon	+	+	+	+	+	+	+	+	+	+															
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+															
Intestine small	+	+	+	+	+	+	+	+	+	+															
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+															
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+															
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+															
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+		+	+	+	+
Carcinoma, metastatic, adrenal gland	X																								
Hepatocellular carcinoma																									
Leukemia mononuclear				X	X					X	X				X		X		X			X			X
Neoplastic nodule																									
Mesentery				+				+								+	+								
Leukemia mononuclear																	X								
Pancreas	+	+	+	+	+	+	+	+	+	+			+									+			
Leukemia mononuclear																						X			
Salivary glands	+	+	+	+	+	+	+	+	+	+															
Stomach	+	+	+	+	+	+	+	+	+	+	+													+	
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+													+	
Stomach, glandular	+	+	+	+	+	+	+	+	+	+															
Leukemia mononuclear					X																				
Tongue																									
Papilloma squamous																									
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+												+			
Leukemia mononuclear					X																	X			
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+			+				+								
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+			+				+								
Carcinoma	X																								
Leukemia mononuclear					X												X								
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+			+				+								
Leukemia mononuclear					X												X								
Pheochromocytoma malignant													X												
Bilateral, pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+			+												
Carcinoma													X												
Parathyroid gland	+	M	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+
Pituitary gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear															X										
Pars distalis, adenoma								X	X			X	X				X	X	X				X		X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma														X		X					X				X
Follicular cell, adenoma																									
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Clitoral gland	+	+	M	+	+	+	+		+	+															
Carcinoma																									
Ovary	+	+	+	+	+	+	+	+	+	+					+			+							
Leukemia mononuclear															X										
Uterus	+	+	+	+	+	+	+	+	+	+		+	+		+			+	+				+		
Leukemia mononuclear															X										
Polyp stromal		X											X						X				X		
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+									+						
Lymph node	+	+	+	+	+	+	+	+	+	+		+	+		+		+								
Mediastinal, leukemia mononuclear					X										X		X								
Pancreatic, leukemia mononuclear															X		X								
Lymph node, mandibular	+	M	+	+	+	+	+	+	+	+		+													
Leukemia mononuclear				X	X					X															
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+			+		+										
Leukemia mononuclear				X	X										X										
Spleen	+	+	+	+	+	+	+	+	+	+	+			+	+		+		+			+		+	+
Leukemia monocytic											X														
Leukemia mononuclear				X	X					X					X		X		X			X			X
Thymus	+	+	+	+	+	+	M	+	+	+					+							+			
Leukemia mononuclear															X							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	105	TOTAL
CARCASS ID	413	421	422	423	431	432	433	441	442	443	444	452	461	462	451	471	472	473	484	481	482	483	491	492	501		TISSUES TUMORS
ALIMENTARY SYSTEM																											
Esophagus																											9
Intestine large																											10
Intestine large, cecum																											10
Intestine large, colon																											10
Intestine large, rectum																											10
Intestine small																											10
Intestine small, duodenum																											10
Intestine small, ileum																											10
Intestine small, jejunum																											10
Liver			+							+		+	+						+	+		+	+	+			32
Carcinoma, metastatic, adrenal gland																											1
Hepatocellular carcinoma																								X			1
Leukemia mononuclear													X											X			11
Neoplastic nodule																			X			X					2
Mesentery																					+						5
Leukemia mononuclear																											1
Pancreas																											12
Leukemia mononuclear																											1
Salivary glands																											10
Stomach																											12
Stomach, forestomach																											12
Stomach, glandular																											10
Leukemia mononuclear																											1
Tongue		+																									1
Papilloma squamous		X																									1
CARDIOVASCULAR SYSTEM																											
Heart																											11
Leukemia mononuclear																											2
ENDOCRINE SYSTEM																											
Adrenal gland											+			+	+												15
Adrenal gland, cortex											+			+	+												15
Carcinoma																											1
Leukemia mononuclear																											2
Adrenal gland, medulla											+			+	+												15
Leukemia mononuclear																											2
Pheochromocytoma malignant																											1
Bilateral, pheochromocytoma benign											X																1
Islets, pancreatic																											11
Carcinoma																											1
Parathyroid gland	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	M	+	M	+	+	+		40
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Leukemia mononuclear																											1
Pars distalis, adenoma		X		X		X		X						X		X	X			X	X	X		X			20
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
C cell, adenoma										X			X							X							7
Follicular cell, adenoma													X														1
GENERAL BODY SYSTEM																											
None																											
GENITAL SYSTEM																											
Clitoral gland					+																				+		10
Carcinoma					X																						1
Ovary														+											+		14
Leukemia mononuclear																											1
Uterus						+	+	+	+				+			+					+			+	+		25
Leukemia mononuclear																											1
Polyp stromal																X					X				X		7
HEMATOPOIETIC SYSTEM																											
Bone marrow																											11
Lymph node				+						+											+						17
Mediastinal, leukemia mononuclear																											3
Pancreatic, leukemia mononuclear																											2
Lymph node, mandibular																											10
Leukemia mononuclear																											3
Lymph node, mesenteric																											12
Leukemia mononuclear																											3
Spleen								+					+								+		+	+			23
Leukemia monocytic																											1
Leukemia mononuclear								X					X											X			11
Thymus																											11
Leukemia mononuclear																											2

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

WEEKS ON STUDY	057	072	079	081	084	085	088	088	091	091	093	093	095	095	095	095	095	096	096	099	100	104	104	105	105
CARCASS ID	415	495	435	494	493	505	504	465	414	455	464	503	445	474	475	454	463	425	485	434	502	424	453	411	412
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	M	+	+		+						+	+	+	+		+		
Adenocarcinoma												X													
Fibroadenoma		X	X			X	X											X		X	X		X		
Fibroadenoma, multiple												X							X						
Skin	+	+	+	+	+	+	+	+	+	+								+							
Keratoacanthoma			X																						
Subcutaneous tissue, fibroma							X																		
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+															
Skeletal muscle													+												
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+															
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+			+	+	+		+	+				+			
Carcinoma, metastatic, adrenal gland	X																								
Leukemia mononuclear				X	X										X		X					X			
Nose	+	+	+		+	+	+	+	+	+															
Trachea	+	+	+	+	+	+	+	+	+	+															
SPECIAL SENSES SYSTEM																									
Eye			+	+																			+		
Harderian gland														+											
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X										X		X					X			
Urinary bladder	+	+	+	+	+	+	+	+	+	+				+											

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	105	TOTAL
CARCASS ID	413	421	422	423	431	432	433	441	442	443	444	452	461	462	451	471	472	473	484	481	482	483	491	492	501		TISSUES TUMORS
INTEGUMENTARY SYSTEM																											
Mammary gland	+	+	+	+		+			+	+			+			+	+		+		+	+				28
Adenocarcinoma																											1
Fibroadenoma	X		X	X		X			X	X			X			X	X										17
Fibroadenoma, multiple																					X	X					4
Skin																				+							12
Keratoacanthoma																											1
Subcutaneous tissue, fibroma																				X							2
MUSCULOSKELETAL SYSTEM																											
Bone																											10
Skeletal muscle																											1
NERVOUS SYSTEM																											
Brain																											10
RESPIRATORY SYSTEM																											
Lung	+			+		+		+	+	+	+			+	+		+			+	+			+			29
Carcinoma, metastatic, adrenal gland																											1
Leukemia mononuclear																								X			6
Nose																											9
Trachea																											10
SPECIAL SENSES SYSTEM																											
Eye						+							+											+			6
Harderian gland						+										+											3
URINARY SYSTEM																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Leukemia mononuclear																											4
Urinary bladder																											11

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

WEEKS ON STUDY	058	065	066	067	083	083	083	084	090	090	090	090	092	093	099	101	103	104	105	105	105	106	106	106
CARCASS ID	56 5	53 5	60 5	58 5	52 5	52 4	59 5	58 4	51 5	52 3	52 2	53 4	56 4	59 4	54 5	51 4	59 3	57 5	51 1	51 2	51 3	52 1	53 1	53 2	53 3
ALIMENTARY SYSTEM																								
Esophagus	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Intestine large	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	A	+	+	+	M	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X	X	X	X	X	X	X		X	X				X		X	
Neoplastic nodule															X									
Mesentery																		+						
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pharynx												+												
Palate, papilloma squamous												X												
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma																		X						
CARDIOVASCULAR SYSTEM																								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																								
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																						X		
Adrenal gland, medulla	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																								
Bilateral, pheochromocytoma benign																		X						
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	M	M	+	+	M	M	M	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Pituitary gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma					X		X		X									X	X	X			X	
Pars distalis, carcinoma															X									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma													X											
Follicular cell, carcinoma																					X			
GENERAL BODY SYSTEM																								
Tissue, NOS						+																		
GENITAL SYSTEM																								
Clitoral gland	+	M	+	+	M	+	M	M	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	M	+	+
Adenoma																	X							
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma																								
Polyp stromal								X							X	X								
Endometrium, adenocarcinoma																								
HEMATOPOIETIC SYSTEM																								
Bone marrow	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																	X							
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mediastinal, leukemia mononuclear										X														
Pancreatic, leukemia mononuclear										X														
Lymph node, mandibular	+	+	+	M	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X		X	X	X	X	X		X	X								
Lymphoma malignant lymphocytic																							X		
Lymph node, mesenteric	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear									X	X	X	X	X	X		X	X								
Lymphoma malignant lymphocytic																							X		
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X	X		X	X	X	X		X	X				X			X	
Lymphoma malignant lymphocytic										X															
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	I	M	M	I	+	+	+
Leukemia mononuclear									X	X			X												

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

WEEKS ON STUDY	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	
CARCASS ID	541	542	543	544	551	552	553	554	555	561	562	571	572	573	574	581	582	591	592	601	602	603	604	563	583	TOTAL TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear				X			X												X							14
Neoplastic nodule																										1
Mesentery									+						+		+						+			5
Pancreas	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pharynx																										1
Palate, papilloma squamous																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma																										1
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	I	46
Pheochromocytoma benign						X																				1
Bilateral, pheochromocytoma benign																										1
Islets, pancreatic	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	+	+	+	M	+	+	+	+	+	M	+	+	I	+	+	+	+	+	+	M	+	+	+	+	38
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma	X		X	X		X				X	X			X							X	X				16
Pars distalis, carcinoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C cell, adenoma		X		X						X		X								X						6
Follicular cell, carcinoma														X												2
GENERAL BODY SYSTEM																										
Tissue, NOS																										1
GENITAL SYSTEM																										
Clitoral gland	M	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	39
Adenoma																X										2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyoma										X																1
Polyp stromal		X								X																5
Endometrium, adenocarcinoma						X																				1
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear																										1
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mediastinal, leukemia mononuclear																										1
Pancreatic, leukemia mononuclear																			X							2
Lymph node, mandibular	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	I	+	+	+	43
Leukemia mononuclear							X												X							10
Lymphoma malignant lymphocytic																										1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear				X			X												X							11
Lymphoma malignant lymphocytic																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear				X			X					X							X							14
Lymphoma malignant lymphocytic																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Leukemia mononuclear																			X							4

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

WEEKS ON STUDY	058	065	066	067	083	083	083	084	090	090	090	090	092	093	099	101	103	104	105	105	105	105	106	106	106
CARCASS ID	56 5	53 5	60 5	58 5	52 5	52 4	59 5	58 4	51 5	52 3	52 2	53 4	56 4	59 4	54 5	51 4	59 3	57 5	51 1	51 2	51 3	52 1	53 1	53 2	53 3
INTEGUMENTARY SYSTEM																									
Mammary gland	M	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Fibroadenoma		X		X		X	X					X				X					X		X	X	
Fibroadenoma, multiple																		X		X		X			
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, fibrosarcoma												X													
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant																									
Peripheral nerve														M	+	+		+	+	+	+	+	+	+	+
Spinal cord			+											+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																		X							
Alveolar/bronchiolar carcinoma																									
Fibrosarcoma, metastatic, skin												X													
Leukemia mononuclear								X	X	X	X		X	X		X	X								
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Eye			+											+			+								
Harderian gland																									
Adenocarcinoma																									
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear									X																

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

WEEKS ON STUDY	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	
CARCASS ID	541	542	543	544	551	552	553	554	555	561	562	571	572	573	574	581	582	591	592	601	602	603	604	563	583	TOTAL TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Fibroadenoma	X			X			X		X			X			X		X	X	X		X			X		20
Fibroadenoma, multiple			X																							4
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	48
Subcutaneous tissue, fibroma		X																								1
Subcutaneous tissue, fibrosarcoma																										1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma malignant														X												1
Peripheral nerve	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	M	+	+	M	+	+	M	+	+	30
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	38
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										1
Alveolar/bronchiolar carcinoma												X														1
Fibrosarcoma, metastatic, skin																										1
Leukemia mononuclear							X												X							10
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Eye		+									+					+										6
Harderian gland																					+					1
Adenocarcinoma																					X					1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Leukemia mononuclear																										1

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

	Vehicle Control	80 mg/kg	160 mg/kg
Clitoral Gland: Adenoma			
Overall Rates (a)	3/46 (7%)	(b) 0/10 (0%)	2/39 (5%)
Adjusted Rates (c)	10.3%		6.7%
Terminal Rates (d)	3/29 (10%)		1/26 (4%)
Day of First Observation	731		715
Life Table Test (e)			P=0.537N
Logistic Regression Test (e)			P=0.548N
Fisher Exact Test (e)			P=0.579N
Clitoral Gland: Adenoma or Carcinoma			
Overall Rates (a)	4/46 (9%)	(b) 1/10 (10%)	2/39 (5%)
Adjusted Rates (c)	13.8%		6.7%
Terminal Rates (d)	4/29 (14%)		1/26 (4%)
Day of First Observation	731		715
Life Table Test (e)			P=0.377N
Logistic Regression Test (e)			P=0.381N
Fisher Exact Test (e)			P=0.420N
Liver: Neoplastic Nodule or Hepatocellular Carcinoma			
Overall Rates (a)	1/50 (2%)	(b) 3/32 (9%)	1/50 (2%)
Adjusted Rates (c)	3.1%		2.8%
Terminal Rates (d)	1/32 (3%)		0/32 (0%)
Day of First Observation	731		692
Life Table Test (e)			P=0.757N
Logistic Regression Test (e)			P=0.755
Fisher Exact Test (e)			P=0.753N
Mammary Gland: Fibroadenoma			
Overall Rates (a)	28/50 (56%)	(f) 21/50 (42%)	24/50 (48%)
Adjusted Rates (c)	67.8%	55.1%	60.6%
Terminal Rates (d)	19/32 (59%)	11/27 (41%)	17/32 (53%)
Day of First Observation	552	503	450
Life Table Tests (e)	P=0.293N	P=0.321N	P=0.316N
Logistic Regression Tests (e)	P=0.269N	P=0.133N	P=0.312N
Cochran-Armitage Trend Test (e)	P=0.242N		
Fisher Exact Test (e)		P=0.115N	P=0.274N
Pituitary Gland/Pars Distalis: Adenoma			
Overall Rates (a)	26/50 (52%)	20/49 (41%)	16/49 (33%)
Adjusted Rates (c)	63.0%	55.7%	43.4%
Terminal Rates (d)	17/32 (53%)	12/27 (44%)	12/32 (38%)
Day of First Observation	506	616	575
Life Table Tests (e)	P=0.047N	P=0.373N	P=0.051N
Logistic Regression Tests (e)	P=0.036N	P=0.214N	P=0.046N
Cochran-Armitage Trend Test (e)	P=0.032N		
Fisher Exact Test (e)		P=0.180N	P=0.040N
Pituitary Gland/Pars Distalis: Adenoma or Carcinoma			
Overall Rates (a)	26/50 (52%)	20/49 (41%)	17/49 (35%)
Adjusted Rates (c)	63.0%	55.7%	45.0%
Terminal Rates (d)	17/32 (53%)	12/27 (44%)	12/32 (38%)
Day of First Observation	506	616	575
Life Table Tests (e)	P=0.069N	P=0.373N	P=0.077N
Logistic Regression Tests (e)	P=0.057N	P=0.214N	P=0.070N
Cochran-Armitage Trend Test (e)	P=0.050N		
Fisher Exact Test (e)		P=0.180N	P=0.062N

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

	Vehicle Control	80 mg/kg	160 mg/kg
Thyroid Gland: C-Cell Adenoma			
Overall Rates (a)	9/50 (18%)	7/50 (14%)	6/50 (12%)
Adjusted Rates (c)	24.2%	22.1%	17.8%
Terminal Rates (d)	5/32 (16%)	4/27 (15%)	5/32 (16%)
Day of First Observation	618	660	643
Life Table Tests (e)	P=0.260N	P=0.507N	P=0.303N
Logistic Regression Tests (e)	P=0.262N	P=0.427N	P=0.311N
Cochran-Armitage Trend Test (e)	P=0.240N		
Fisher Exact Test (e)		P=0.393N	P=0.288N
Thyroid Gland: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	10/50 (20%)	7/50 (14%)	6/50 (12%)
Adjusted Rates (c)	27.0%	22.1%	17.8%
Terminal Rates (d)	6/32 (19%)	4/27 (15%)	5/32 (16%)
Day of First Observation	618	660	643
Life Table Tests (e)	P=0.185N	P=0.414N	P=0.221N
Logistic Regression Tests (e)	P=0.184N	P=0.333N	P=0.227N
Cochran-Armitage Trend Test (e)	P=0.166N		
Fisher Exact Test (e)		P=0.298N	P=0.207N
Uterus: Stromal Polyp			
Overall Rates (a)	10/48 (21%)	(g) 7/50 (14%)	5/50 (10%)
Adjusted Rates (c)	28.7%	20.7%	13.5%
Terminal Rates (d)	8/32 (25%)	3/27 (11%)	2/32 (6%)
Day of First Observation	585	503	588
Life Table Tests (e)	P=0.120N	P=0.415N	P=0.143N
Logistic Regression Tests (e)	P=0.094N	P=0.285N	P=0.129N
Cochran-Armitage Trend Test (e)	P=0.087N		
Fisher Exact Test (e)		P=0.266N	P=0.113N
Hematopoietic System: Mononuclear Leukemia			
Overall Rates (a)	19/50 (38%)	(h) 12/50 (24%)	15/50 (30%)
Adjusted Rates (c)	45.8%	31.4%	35.9%
Terminal Rates (d)	11/32 (34%)	4/27 (15%)	6/32 (19%)
Day of First Observation	585	566	588
Life Table Tests (e)	P=0.277N	P=0.207N	P=0.311N
Logistic Regression Tests (e)	P=0.205N	P=0.081N	P=0.245N
Cochran-Armitage Trend Test (e)	P=0.224N		
Fisher Exact Test (e)		P=0.097N	P=0.263N

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Incomplete sampling of tissues
(c) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(d) Observed tumor incidence at terminal kill
(e) Beneath the vehicle control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the vehicle controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The 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).
(f) An adenocarcinoma was also observed in an animal with a fibroadenoma.
(g) Twenty-five uteruses were examined microscopically.
(h) Thirty-two livers and 23 spleens were examined microscopically.

TABLE B4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF HEXACHLOROETHANE

	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, cecum	(48)	(10)	(48)
Parasite metazoan	2 (4%)	1 (10%)	5 (10%)
Intestine large, colon	(48)	(10)	(48)
Parasite metazoan	8 (17%)		7 (15%)
Intestine large, rectum	(50)	(10)	(47)
Parasite metazoan	4 (8%)	1 (10%)	12 (26%)
Liver	(50)	(32)	(50)
Angiectasis, focal	1 (2%)		
Basophilic focus	26 (52%)	17 (53%)	28 (56%)
Basophilic focus, multiple		1 (3%)	
Cytoplasmic alteration		1 (3%)	
Fatty change	19 (38%)	11 (34%)	20 (40%)
Granuloma	2 (4%)	4 (13%)	5 (10%)
Hemorrhage, focal		1 (3%)	
Hepatodiaphragmatic nodule	2 (4%)	7 (22%)	4 (8%)
Mixed cell focus	1 (2%)		
Necrosis, focal	16 (32%)	5 (16%)	14 (28%)
Bile duct, cyst		1 (3%)	
Bile duct, hyperplasia	21 (42%)	5 (16%)	21 (42%)
Periductular, inflammation, chronic	1 (2%)		1 (2%)
Perivascular, inflammation, chronic	3 (6%)		
Mesentery	(7)	(5)	(5)
Accessory spleen		1 (20%)	
Granuloma			1 (20%)
Hemorrhage		1 (20%)	
Fat, inflammation		1 (20%)	
Fat, necrosis	6 (86%)	3 (60%)	5 (100%)
Pancreas	(48)	(12)	(49)
Inflammation, chronic, focal	1 (2%)	1 (8%)	
Acinus, atrophy	9 (19%)	1 (8%)	5 (10%)
Acinus, hyperplasia, focal	2 (4%)		2 (4%)
Artery, inflammation			1 (2%)
Salivary glands	(50)	(10)	(50)
Inflammation, chronic		1 (10%)	1 (2%)
Acinus, atrophy, focal	1 (2%)		
Stomach	(50)	(12)	(50)
Lumen, thrombus			1 (2%)
Stomach, forestomach	(50)	(12)	(50)
Acanthosis		1 (8%)	3 (6%)
Hyperkeratosis			1 (2%)
Hyperplasia, basal cell, focal	1 (2%)		
Inflammation, chronic	1 (2%)	1 (8%)	
Inflammation, chronic active			2 (4%)
Mineralization, focal			1 (2%)
Stomach, glandular	(49)	(10)	(50)
Inflammation, acute			1 (2%)
Inflammation, chronic, focal			1 (2%)
Mineralization, focal	2 (4%)		2 (4%)
CARDIOVASCULAR SYSTEM			
Heart	(50)	(11)	(50)
Cardiomyopathy	28 (56%)	3 (27%)	27 (54%)
Artery, inflammation, chronic, focal			1 (2%)
Atrium right, thrombus			1 (2%)

TABLE B4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF HEXACHLOROETHANE (Continued)

	Vehicle Control	Low Dose	High Dose
ENDOCRINE SYSTEM			
Adrenal gland, cortex	(50)	(15)	(50)
Accessory adrenal cortical nodule			1 (2%)
Atrophy		1 (7%)	
Congestion	1 (2%)	1 (7%)	
Cytoplasmic alteration, focal	7 (14%)	3 (20%)	5 (10%)
Hypertrophy	1 (2%)		
Adrenal gland, medulla	(50)	(15)	(46)
Hyperplasia, focal	5 (10%)		7 (15%)
Inflammation, focal		1 (7%)	
Islets, pancreatic	(49)	(11)	(49)
Hyperplasia	1 (2%)		
Pituitary gland	(50)	(49)	(49)
Pars distalis, angiectasis	4 (8%)	1 (2%)	7 (14%)
Pars distalis, cyst	25 (50%)	21 (43%)	23 (47%)
Pars distalis, hyperplasia, focal	5 (10%)	11 (22%)	8 (16%)
Pars intermedia, angiectasis			3 (6%)
Pars intermedia, cyst	1 (2%)		
Thyroid gland	(50)	(50)	(50)
Fibrosis	1 (2%)		
Infiltration cellular, histiocytic	1 (2%)		
Pigmentation	1 (2%)		
Ultimobranchial cyst			2 (4%)
C-cell, hyperplasia	19 (38%)	11 (22%)	12 (24%)
Follicle, cyst		1 (2%)	2 (4%)
Follicle, hyperplasia, focal			1 (2%)
GENERAL BODY SYSTEM			
None			
GENITAL SYSTEM			
Clitoral gland	(46)	(10)	(39)
Abscess	3 (7%)		1 (3%)
Atrophy	1 (2%)		
Cyst	1 (2%)		
Dilatation			1 (3%)
Hemorrhage			1 (3%)
Hypertrophy			1 (3%)
Inflammation, acute	1 (2%)		3 (8%)
Inflammation, chronic	11 (24%)	1 (10%)	4 (10%)
Ovary	(50)	(14)	(50)
Congestion	1 (2%)	1 (7%)	2 (4%)
Cyst	7 (14%)	4 (29%)	4 (8%)
Uterus	(48)	(25)	(50)
Abscess			1 (2%)
Dilatation	5 (10%)	5 (20%)	4 (8%)
Exudate	2 (4%)		
Inflammation, acute, focal		1 (4%)	
Inflammation, chronic			1 (2%)
Thrombus	3 (6%)	2 (8%)	2 (4%)
Cervix, hypertrophy		1 (4%)	
Endometrium, cyst	2 (4%)		1 (2%)
Endometrium, hyperplasia	1 (2%)		2 (4%)

TABLE B4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF HEXACHLOROETHANE (Continued)

	Vehicle Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM			
Bone marrow	(50)	(11)	(49)
Hyperplasia	11 (22%)		4 (8%)
Lymph node	(49)	(17)	(50)
Inguinal, infiltration cellular, plasma cell		1 (6%)	
Lumbar, congestion	1 (2%)		
Lumbar, infiltration cellular, plasma cell	1 (2%)		
Lumbar, infiltration cellular, histiocytic	1 (2%)		
Mediastinal, congestion	2 (4%)	1 (6%)	1 (2%)
Mediastinal, infiltration cellular, plasma cell	1 (2%)		
Mediastinal, inflammation, granulomatous	1 (2%)		
Mediastinal, pigmentation		1 (6%)	
Pancreatic, angiectasis			1 (2%)
Pancreatic, congestion			1 (2%)
Pancreatic, hemorrhage		1 (6%)	
Renal, congestion	2 (4%)	1 (6%)	2 (4%)
Renal, granuloma			2 (4%)
Renal, pigmentation		1 (6%)	
Lymph node, mandibular	(46)	(10)	(43)
Angiectasis	1 (2%)		2 (5%)
Congestion	4 (9%)	2 (20%)	
Infiltration cellular, plasma cell	28 (61%)	3 (30%)	29 (67%)
Lymph node, mesenteric	(48)	(12)	(49)
Angiectasis	1 (2%)		
Congestion	2 (4%)		2 (4%)
Granuloma			2 (4%)
Hyperplasia, lymphoid			1 (2%)
Infiltration cellular, plasma cell	1 (2%)		
Pigmentation			2 (4%)
Pigmentation, hemosiderin	3 (6%)	1 (8%)	1 (2%)
Spleen	(50)	(23)	(50)
Congestion			2 (4%)
Hematopoietic cell proliferation	17 (34%)	5 (22%)	18 (36%)
Necrosis, focal	2 (4%)	1 (4%)	
Pigmentation, hemosiderin	5 (10%)	6 (26%)	3 (6%)
INTEGUMENTARY SYSTEM			
Mammary gland	(48)	(28)	(46)
Ectasia	3 (6%)		7 (15%)
Galactocele	10 (21%)	16 (57%)	12 (26%)
Hypertrophy	3 (6%)		
Inflammation, subacute, focal			1 (2%)
Skin	(49)	(12)	(48)
Cyst epithelial inclusion	1 (2%)		
Inflammation, chronic	1 (2%)		
Subcutaneous tissue, abscess		1 (8%)	
MUSCULOSKELETAL SYSTEM			
Bone	(50)	(10)	(50)
Cranium, hyperostosis			1 (2%)

TABLE B4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF HEXACHLOROETHANE (Continued)

	Vehicle Control	Low Dose	High Dose
NERVOUS SYSTEM			
Brain	(50)	(10)	(50)
Congestion			1 (2%)
Hemorrhage	1 (2%)	1 (10%)	1 (2%)
Hydrocephalus	2 (4%)	1 (10%)	1 (2%)
Infarct			1 (2%)
Pigmentation, hemosiderin	1 (2%)		
Spinal cord	(38)		(38)
Degeneration			1 (3%)
RESPIRATORY SYSTEM			
Lung	(50)	(29)	(50)
Congestion	2 (4%)	14 (48%)	4 (8%)
Granuloma	2 (4%)	1 (3%)	3 (6%)
Hemorrhage, focal	1 (2%)	3 (10%)	3 (6%)
Infiltration cellular, histiocytic		1 (3%)	
Pigmentation, hemosiderin, focal	1 (2%)		
Alveolar epithelium, hyperplasia, adenomatous	1 (2%)		
Alveolar epithelium, metaplasia	2 (4%)	1 (3%)	4 (8%)
Alveolus, atypical cells		1 (3%)	
Artery, thrombus			1 (2%)
Peribronchial, inflammation, chronic	29 (58%)	10 (34%)	32 (64%)
Nose	(49)	(9)	(50)
Inflammation, chronic	16 (33%)	3 (33%)	20 (40%)
Metaplasia, squamous	39 (80%)	1 (11%)	41 (82%)
SPECIAL SENSES SYSTEM			
Eye	(6)	(6)	(6)
Cataract	2 (33%)		1 (17%)
Retinal detachment			1 (17%)
Cornea, inflammation, acute			1 (17%)
Lens, mineralization, focal		2 (33%)	
Posterior chamber, hemorrhage		1 (17%)	
Retina, degeneration	2 (33%)	1 (17%)	
Vitreous, degeneration			1 (17%)
Harderian gland		(3)	(1)
Inflammation, chronic, focal		2 (67%)	
URINARY SYSTEM			
Kidney	(50)	(50)	(50)
Casts	1 (2%)		2 (4%)
Inflammation, chronic		1 (2%)	1 (2%)
Mineralization	14 (28%)	22 (44%)	13 (26%)
Nephropathy	22 (44%)	42 (84%)	45 (90%)
Renal tubule, cyst			2 (4%)
Renal tubule, hyperplasia		1 (2%)	
Renal tubule, pigmentation	2 (4%)	2 (4%)	3 (6%)
Renal tubule, regeneration		2 (4%)	1 (2%)
Urinary bladder	(46)	(11)	(47)
Hyperplasia		1 (9%)	
Inflammation, chronic		2 (18%)	
Transitional epithelium, hyperplasia			1 (2%)
Transitional epithelium, hyperplasia, squamous		1 (9%)	
Wall, inflammation, chronic active			1 (2%)

APPENDIX C

SENTINEL ANIMAL PROGRAM

APPENDIX C. 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 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. 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
PVM (pneumonia virus of mice)	RCV (rat coronavirus) (6,12 mo)	RCV/SDA (sialodacryoadenitis virus) (18,24 mo)
KRV (Kilham rat virus)	Sendai (6 mo)	
H-1 (Toolan's H-1 virus)		
Sendai (12,18,24 mo)		

Results

No positive titers were seen at 6, 12, 18, or 24 months.

APPENDIX D

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

Pellet Diet: March 1982 to April 1984

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

TABLE D1. 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, 1976b; NIH, 1978
(b) Ingredients ground to pass through a U.S. Standard Screen No. 16 before being mixed

TABLE D2. 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 D3. NUTRIENT COMPOSITION OF NIH 07 RAT AND MOUSE RATION

Nutrients	Mean ± Standard Deviation	Range	Number of Samples
Protein (percent by weight)	23.26 ± 1.04	21.3-26.3	26
Crude fat (percent by weight)	5.07 ± 0.55	3.3-5.7	26
Crude fiber (percent by weight)	3.44 ± 0.51	2.9-5.6	26
Ash (percent by weight)	6.56 ± 0.42	5.7-7.3	26
Amino Acids (percent of total diet)			
Arginine	1.32 ± 0.072	1.310-1.390	5
Cystine	0.319 ± 0.088	0.218-0.400	5
Glycine	1.146 ± 0.063	1.060-1.210	5
Histidine	0.571 ± 0.026	0.531-0.603	5
Isoleucine	0.914 ± 0.030	0.881-0.944	5
Leucine	1.946 ± 0.056	1.850-1.990	5
Lysine	1.280 ± 0.067	1.200-1.370	5
Methionine	0.436 ± 0.165	0.306-0.699	5
Phenylalanine	0.938 ± 0.158	0.665-1.05	5
Threonine	0.855 ± 0.035	0.824-0.898	5
Tryptophan	0.277 ± 0.221	0.156-0.671	5
Tyrosine	0.618 ± 0.086	0.564-0.769	5
Valine	1.108 ± 0.043	1.050-1.170	5
Essential Fatty Acids (percent of total diet)			
Linoleic	2.290 ± 0.313	1.83-2.52	5
Linolenic	0.258 ± 0.040	0.210-0.308	5
Vitamins			
Vitamin A (IU/kg)	11,596 ± 4,203	4,200-24,000	26
Vitamin D (IU/kg)	4,450 ± 1,382	3,000-6,300	4
α-Tocopherol (ppm)	43.58 ± 6.92	31.1-48.0	5
Thiamine (ppm)	19.08 ± 4.16	12.0-31.0	26
Riboflavin (ppm)	7.6 ± 0.85	7.58-8.2	5
Niacin (ppm)	97.8 ± 31.68	65.0-150.0	5
Pantothenic acid (ppm)	30.06 ± 4.31	23.0-34.0	5
Pyridoxine (ppm)	7.68 ± 1.31	5.60-8.8	5
Folic acid (ppm)	2.62 ± 0.89	1.80-3.7	5
Biotin (ppm)	0.254 ± 0.053	0.19-0.32	5
Vitamin B_{12} (ppb)	24.21 ± 12.66	10.6-38.0	5
Choline (ppm)	3,122 ± 416.8	2,400-3,430	5
Minerals			
Calcium (percent)	1.25 ± 0.10	1.04-1.43	26
Phosphorus (percent)	0.96 ± 0.05	0.87-1.10	26
Potassium (percent)	0.900 ± 0.098	0.772-0.971	3
Chloride (percent)	0.513 ± 0.114	0.380-0.635	5
Sodium (percent)	0.323 ± 0.043	0.258-0.371	5
Magnesium (percent)	0.167 ± 0.012	0.151-0.181	5
Sulfur (percent)	0.304 ± 0.064	0.268-0.420	5
Iron (ppm)	410.3 ± 94.04	262.0-523.0	5
Manganese (ppm)	90.29 ± 7.15	81.7-99.4	5
Zinc (ppm)	52.78 ± 4.94	46.1-58.2	5
Copper (ppm)	10.72 ± 2.76	8.09-15.39	5
Iodine (ppm)	2.95 ± 1.05	1.52-3.82	4
Chromium (ppm)	1.85 ± 0.25	1.44-2.09	5
Cobalt (ppm)	0.681 ± 0.14	0.490-0.780	4

TABLE D4. CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION

Contaminants	Mean ± Standard Deviation	Range	Number of Samples
Arsenic (ppm)	0.51 ± 0.14	0.18-0.74	26
Cadmium (ppm) (a)	0.11 ± 0.03	0.10-0.20	26
Lead (ppm)	0.79 ± 0.62	0.33-3.37	26
Mercury (ppm) (b)	<0.05		26
Selenium (ppm)	0.31 ± 0.06	0.22-0.45	26
Aflatoxins (ppb) (b)	<5.0		26
Nitrate nitrogen (ppm) (c)	9.25 ± 4.09	2.50-18.0	26
Nitrite nitrogen (ppm) (c)	1.73 ± 1.67	0.10-6.10	26
BHA (ppm) (d)	4.23 ± 4.93	2.0-20.0	26
BHT (ppm) (d)	2.83 ± 2.58	1.0-13.0	26
Aerobic plate count (CFU/g) (d)	137,427 ± 133,363	6,200-420,000	26
Coliform (MPN/g) (f)	695.0 ± 911.0	3.0-2,400	26
E. coli (MPN/g)	10.9 ± 30.0	3.0-150	26
Total nitrosamines (ppb) (g)	5.15 ± 5.9	1.8-30.30	26
N-Nitrosodimethylamine (ppb) (g)	4.38 ± 5.95	0.5-30.0	26
N-Nitrosopyrrolidine (ppb) (g)	0.78 ± 0.60	0.3-2.10	26
Pesticides (ppm)			
α-BHC (b,h)	<0.01		26
β-BHC (b)	<0.02		26
γ-BHC-Lindane (b)	<0.01		26
δ-BHC (b)	<0.01		26
Heptachlor (b)	<0.01		26
Aldrin (b)	<0.01		26
Heptachlor epoxide (b)	<0.01		26
DDE (b)	<0.01		26
DDD (b)	<0.01		26
DDT (b)	<0.01		26
HCB (b)	<0.01		26
Mirex (b)	<0.01		26
Methoxychlor (b)	<0.05		26
Dieldrin (b)	<0.01		26
Endrin (b)	<0.01		26
Telodrin (b)	<0.01		26
Chlordane (b)	<0.05		26
Toxaphene (b)	<0.1		26
Estimated PCBs (b)	<0.2		26
Ronnel (b)	<0.01		26
Ethion (b)	<0.02		26
Trithion (b)	<0.05		26
Diazinon (b)	<0.1		26
Methyl parathion (b)	<0.02		26
Ethyl parathion (b)	<0.02		26
Malathion (i)	0.14 ± 0.17	0.05-0.81	26
Endosulfan I (b)	<0.01		26
Endosulfan II (b)	<0.01		25
Endosulfan sulfate (b)	<0.03		26

(a) Two lots contained more than 0.10 ppm.
(b) All values were less than the detection limit, given in the table as the mean.
(c) Source of contamination: alfalfa, grains, and fish meal
(d) Source of contamination: soy oil and fish meal
(e) CFU = colony-forming unit
(f) MPN = most probable number
(g) All values were corrected for percent recovery.
(h) BHC = hexachlorocyclohexane or benzene hexachloride
(i) Fourteen lots contained more than 0.05 ppm.

APPENDIX E

AUDIT SUMMARY

APPENDIX E. AUDIT SUMMARY

The pathology specimens, experimental data, study documents, and draft NTP Technical Report No. 361 for the 2-year studies of hexachloroethane in rats were audited for the National Institute of Environmental Health Sciences (NIEHS) at the National Toxicology Program (NTP) Archives by Dynamac Corporation and by Argus Research Laboratories. The audit included review of:

(1) All records concerning animal receipt, quarantine, randomization, and disposition prior to study start.
(2) All inlife records including protocol, correspondence, animal husbandry, environmental conditions, dosing, external masses, mortality, animal identification, and serology.
(3) Body weight and clinical observation data; all data were scanned before a random 10% sample of animals in each study group were reviewed in detail.
(4) All chemistry records.
(5) All postmortem records for individual animals concerning date of death, disposition codes, condition codes, tissue accountability, correlation of masses or clinical signs recorded at the last inlife observation with gross observations and microscopic diagnoses, and correlations between gross observations and microscopic diagnoses.
(6) All wet tissue bags for inventory and wet tissues from a random 20% sample of animals in all study groups, plus other relevant cases, to evaluate the integrity of individual animal identity and to examine for untrimmed potential lesions.
(7) Blocks and slides of tissues from a random 20% sample of animals from each study group, plus animals with less than complete or correct identification.
(8) Necropsy record forms for data entry errors and all original and updated microscopic diagnoses for a random 10% sample of animals to verify computer data entry and their incorporation into final pathology tables.
(9) Correlation between the data, factual information, and procedures for the 2-year studies presented in the draft Technical Report and the records available at the NTP Archives.

In most cases, procedures and events during the exposure phase of the studies were documented adequately by the archival records. The procedure for randomizing animals was present at the NTP Archives, but the table of random numbers and body weights were not; however, the group mean body weights at the start of the studies indicate that uniform distribution was achieved. Animal room temperatures were recorded two times per day for 103 weeks, but data for 22 measurements were not present. Data for peroxide analyses and analytical chemistry support work and for light cycle and air change rates for the animal room were not documented other than in the laboratory report. Tissue bags were not received at the Archives for one high dose male rat and one low dose female rat, but, for both these animals, the blocks and slides were present. Review of data from the entire exposure phase indicated that husbandry practices were consistently followed during the course of the studies. Records documented that doses were prepared, stored, analyzed, and administered according to protocols. Recalculation of 24 group mean body weights showed all to be correct. Of the 204 masses noted in the inlife records, all correlated with necropsy observations. Survival records for all animals were reviewed and found to be correct, except for the date (different by 1 day) and reason for removal (natural death vs. moribund kill) of one high dose male rat.

Individual animal identifiers (ears) were present and correct for 73/75 animals examined. One ear for each of the two other animals examined was correct, whereas marking on the second ear could not be read unambiguously; review of data trails for these animals provided evidence that the integrity of their individual animal identity had been preserved throughout the study. The residual wet tissues contained 12 untrimmed potential lesions that were in nontarget organs, and some intestinal segments were partially unopened in 74/75 rats examined. Gross observations made at necropsy correlated with microscopic diagnoses, except for 16 observations that involved nontarget organs.

Full details about these and other audit findings are presented in audit reports on file at the NIEHS. In conclusion, the data and factual information in the preliminary draft of the Technical Report for the 2-year gavage studies of hexachloroethane are supported by the records at the NTP Archives.

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