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No. 358

TOXICOLOGY AND CARCINOGENESIS STUDIES OF OCHRATOXIN A

(CAS NO. 303-47-9)

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 OCHRATOXIN A

(CAS NO. 303-47-9)

IN F344/N RATS

(GAVAGE STUDIES)

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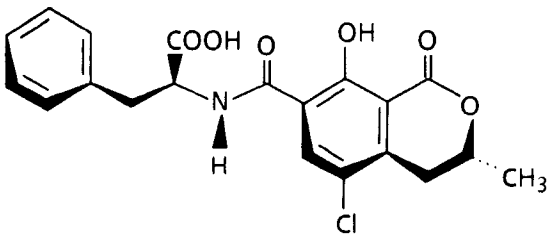

OCHRATOXIN A

CAS No. 303-47-9

$C_{20}H_{18}ClNO_6$ Molecular weight 403.8

Synonyms: (*R*)-*N*[(5-chloro-3,4-dihydro-8-hydroxy-3-methyl-1-oxo-1*H*-2-benzopyran-7-yl)-carbonyl](-L-)phenylalanine

ABSTRACT

Ochratoxin A is a naturally occurring fungal toxin that is a contaminant in corn, peanuts, storage grains, cottonseed, meats, dried fish, and nuts. Toxicology and carcinogenesis studies were conducted by administering ochratoxin A (98% pure) in corn oil by gavage to groups of F344/N rats of each sex for 16 days, 13 weeks, 9 months, 15 months, or 2 years. Only rats were studied because ochratoxin A has been shown to be carcinogenic in mice. Genetic toxicology tests were performed with bacterial and mammalian cells. Urinalysis, hematologic and serum chemical analyses, and bone marrow cellularity determinations were conducted at 9, 15, and 24 months in the 2-year studies.

Sixteen-Day and Thirteen-Week Studies: Rats were administered 0, 1, 4, or 16 mg/kg ochratoxin A in corn oil by gavage 5 days per week for a total of 12 doses over 16 days. All rats that received 16 mg/kg ochratoxin A died within 6 days. Rats that received 4 mg/kg lost weight. Compound-related lesions in rats included bone marrow hypoplasia, thymic atrophy, necrosis and hyperplasia of the forestomach epithelium, renal tubular cell degenerative and regenerative changes (nephropathy), and adrenal gland hemorrhage. Renal tubular changes were most severe in animals that received 4 mg/kg. Rats that received 16 mg/kg had less severe renal lesions than those at 4 mg/kg, perhaps because the acute toxicity and early death did not allow sufficient time for full development of lesions.

No compound-related deaths occurred in the 13-week studies (doses were 0 and 0.0625 to 1 mg/kg). The final mean body weight of rats that received 0.25, 0.5, or 1 mg/kg was 7%, 11%, or 19% lower than that of vehicle controls for males and 3%, 4%, or 9% lower for females. Compound-related lesions in the kidney were characterized as degeneration and regeneration of the epithelium of the proximal convoluted tubules with individual cell necrosis of moderate severity (see following table).

NUMBERS OF RATS WITH RENAL CORTICAL LESIONS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF OCHRATOXIN A (a)

Lesion	Vehicle Control		0.0625 mg/kg		0.125 mg/kg		0.25 mg/kg		0.5 mg/kg		1 mg/kg	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
Degeneration/necrosis	0	0	0	0	6	6	3	5	0	2	10	10
Karyomegaly	0	0	10	9	10	9	10	10	10	10	10	10
Atrophy	0	0	10	9	7	8	9	8	8	8	0	0

(a) 10 animals per group

Karyomegaly of tubular epithelial cells was widespread but most pronounced in the straight portion of the tubules just above the corticomedullary junction. Karyomegaly was present in all dosed groups, and the severity increased as the dose increased. At lower doses, atrophy of the straight portions of the tubules at the corticomedullary junction and in the medulla was observed.

Based on mortality and on the presence and severity of renal lesions, groups of 80 rats per sex and dose group were administered 0, 21, 70, or 210 µg/kg ochratoxin A in corn oil by gavage 5 days per week for up to 2 years. Groups of 15 rats per sex and dose were killed at 9 or at 15 months and the remaining animals at 2 years.

Nine-Month and Fifteen-Month Studies: Administration of ochratoxin A by gavage for 9 months or 15 months to F344/N rats was associated with increased incidences of renal tubular cell neoplasms in males and hyperplasia, degeneration, and karyomegaly of renal tubular epithelial cells in both males and females (see following table).

Body Weight and Survival in the Two-Year Studies: Mean body weights of high dose rats were generally 4%-7% lower than those of vehicle controls. No significant differences in survival were observed between any groups of female rats (vehicle control, 32/50; low dose, 23/51; mid dose, 35/50; high dose, 34/50). Survival was decreased after 77 weeks in high dose male rats and after 96 weeks in low and mid dose male rats (39/50; 26/51; 26/51; 23/50).

Clinical Pathology: Minor differences were observed for hematologic values between dosed and vehicle control animals, but these were not considered to be of biologic significance. Results of serum chemistry analysis were not clearly compound related. Ochratoxin A-dosed animals had slight increases compared with vehicle controls in urine volume and decreases in urine specific gravity in concentration tests, suggesting that exposure resulted in mild to moderate decreases in the ability to concentrate urine.

NUMBERS OF RATS WITH SELECTED RENAL TUBULE LESIONS IN THE NINE- AND FIFTEEN-MONTH GAVAGE STUDIES OF OCHRATOXIN A (a)

	Male				Female			
Age/Lesion	Vehicle Control	21 µg/kg	70 µg/kg	210 µg/kg	Vehicle Control	21 µg/kg	70 µg/kg	210 µg/kg
Nine months								
Karyomegaly	0	0	15	15	0	0	15	15
Hyperplasia	0	0	3	6	0	0	0	3
Adenoma	0	0	0	1	0	0	0	0
Fifteen months								
Degeneration	0	0	0	15	0	0	0	15
Karyomegaly	0	0	14	15	0	0	15	15
Hyperplasia	0	0	6	0	0	0	1	0
Adenoma	0	0	1	1	0	0	0	0
Carcinoma	0	0	1	2	0	0	0	0

(a) 15 animals per group

Nonneoplastic and Neoplastic Effects in the Two-Year Studies: A spectrum of degenerative and proliferative changes occurred in the kidney of male and female rats given ochratoxin A for 2 years. Degeneration of the renal tubular epithelium with formation of tubular cysts, proliferation of the tubular epithelium, and karyomegaly of the nuclei of tubular epithelial cells occurred at increased incidences in dosed rats (see following table). Hyperplasia of the renal tubular epithelium and renal tubular adenomas and carcinomas also occurred at increased incidences in the dosed rats; the tumors were frequently multiple within a single kidney or were bilateral, and many metastasized to other organs.

The incidence of fibroadenomas of the mammary gland in high dose female rats was significantly greater than that in vehicle controls (vehicle control, 17/50; low dose, 23/51; mid dose, 22/50; high dose, 28/50). Multiple fibroadenomas of the mammary gland were observed at an increased incidence in high dose female rats (4/50; 4/51; 5/50; 14/50). One mammary gland adenoma was seen in a mid dose female, and two mammary gland adenocarcinomas were seen in each dosed group; one adenocarcinoma was seen in the vehicle control group.

An adenoma of the pars intermedia of the pituitary gland was observed in one mid dose female rat, and a carcinoma was observed in a second mid dose female rat. Squamous cell papillomas of the tongue were seen in two low dose and two mid dose male rats. Neither the pituitary neoplasms nor the papillomas of the tongue were considered related to ochratoxin A exposure.

Genetic Toxicology: Ochratoxin A was not mutagenic in four strains of *Salmonella typhimurium* (TA97, TA98, TA100, or TA1535) when tested both with and without exogenous metabolic activation. In cultured Chinese hamster ovary (CHO) cells, ochratoxin A induced sister chromatid exchanges (SCEs) in the presence, but not the absence, of metabolic activation; it did not significantly increase the number of chromosomal aberrations in these cells.

Audit: The data, documents, and pathology materials from the 2-year studies of ochratoxin A 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.

NUMBERS OF RATS WITH SELECTED RENAL LESIONS IN THE TWO-YEAR GAVAGE STUDIES OF OCHRATOXIN A

	Male				Female			
Site/Lesion	Vehicle Control	21 µg/kg	70 µg/kg	210 µg/kg	Vehicle Control	21 µg/kg	70 µg/kg	210 µg/kg
Number examined	50	51	51	50	50	51	50	50
Kidney								
Cyst	0	1	0	10	0	0	1	31
Kidney tubule epithelium								
Cytoplasmic alteration	1	0	3	8	0	0	1	2
Degeneration	0	0	50	49	0	0	49	49
Hyperplasia	1	1	16	24	0	0	12	13
Karyomegaly	0	1	51	50	0	8	50	50
Proliferation	0	0	10	26	0	0	3	16
Kidney tubule								
Adenoma	1	1	6	10	0	0	1	5
Carcinoma	0	0	16	30	0	0	1	3
Metastatic renal carcinoma (all sites)	0	0	4	13	0	0	1	0

Conclusions: Under the conditions of these 2-year gavage studies, there was *clear evidence of carcinogenic activity** of ochratoxin A for male F344/N rats as shown by substantially increased incidences of uncommon tubular cell adenomas and of tubular cell carcinomas of the kidney. There was *clear evidence of carcinogenic activity* for female F344/N rats as shown by increased incidences of uncommon tubular cell adenomas and of tubular cell carcinomas of the kidney and by increased incidences and multiplicity of fibroadenomas of the mammary gland.

Ochratoxin A administration also caused nonneoplastic renal changes including tubular cell hyperplasia, tubular cell proliferation, cytoplasmic alteration, karyomegaly, and degeneration of the renal tubular epithelium.

SUMMARY OF THE TWO-YEAR GAVAGE AND GENETIC TOXICOLOGY STUDIES OF OCHRATOXIN A

Male F344/N Rats	Female F344/N Rats
Doses 0, 21, 70, or 210 µg/kg ochratoxin A in corn oil, 5 d/wk	0, 21, 70, or 210 µg/kg ochratoxin A in corn oil, 5 d/wk
Survival rates in the 2-year study 39/50; 26/51; 26/51; 23/50	32/50; 23/51; 35/50; 34/50
Body weights in the 2-year study High dose slightly lower than vehicle controls	High dose slightly lower than vehicle controls
Nonneoplastic effects Degeneration, karyomegaly, proliferation, cytoplasmic alteration, and hyperplasia of the renal tubular epithelium	Degeneration, karyomegaly, proliferation, and hyperplasia of the renal tubular epithelium
Neoplastic effects Renal tubular cell adenomas (1/50; 1/51; 6/51; 10/50) and carcinomas (0/50; 0/51; 16/51; 30/50); metastatic renal carcinomas, all sites (0/50; 0/51; 4/51; 13/50)	Renal tubular cell adenomas (0/50; 0/51; 1/50; 5/50) and carcinomas (0/50; 0/51; 1/50; 3/50); fibroadenomas of the mammary gland (17/50; 23/51; 22/50; 28/50); metastatic renal carcinomas, all sites (0/50; 0/51; 1/50; 0/50)
Level of evidence of carcinogenic activity Clear evidence	Clear evidence
Genetic toxicology	
Salmonella (gene mutation) Negative with and without S9	**CHO cells in vitro** **SCE**: Negative without S9; positive with S9 **Aberration**: Negative with and without S9

*Explanation of Levels of Evidence of Carcinogenic Activity is on page 7.
A summary of the Peer Review comments and the public discussion on this Technical Report appears on page 10.

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 Ochratoxin A is based on 13-week studies that began in November 1981 and ended in February 1982 and on 2-year studies that began in September 1982 and ended in September 1984 at Battelle Columbus Laboratories (Columbus, Ohio).

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PEER REVIEW PANEL

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

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SUMMARY OF PEER REVIEW COMMENTS ON THE TOXICOLOGY AND CARCINOGENESIS STUDIES OF OCHRATOXIN A

On April 18, 1988, the draft Technical Report on the toxicology and carcinogenesis studies of ochratoxin A received peer 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 (NIEHS), Research Triangle Park, North Carolina.

Dr. G.A. Boorman, NIEHS, began the discussion by reviewing the experimental design, results, and proposed conclusions (clear evidence of carcinogenic activity for male and female rats). Ochratoxin A administration also caused nonneoplastic renal changes, including tubular cell hyperplasia, tubular cell proliferation, cytoplasmic alteration, karyomegaly, and degeneration of the renal tubular epithelium.

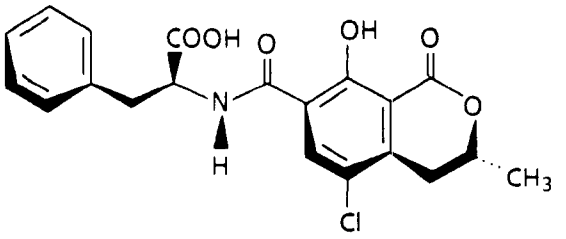
Dr. Capen, Dr. Popp, and Dr. Hughes, the principal reviewers, agreed with the conclusions. All three reviewers indicated that the inclusion of photomicrographs was most useful. In view of the overwhelming carcinogenic response, Dr. Hughes thought it curious that the genetic toxicity assays did not indicate any strong evidence of interaction for the chemical with DNA or adduct formation. Dr. Boorman said that DNA adduct studies had not been done.

Dr. Capen moved that the Technical Report on ochratoxin A be accepted with the conclusions as written for male and female rats, clear evidence of carcinogenic activity. Dr. Popp seconded the motion, which was approved unanimously with 10 votes.

I. INTRODUCTION

Occurrence and Human Exposure
Toxicity
Carcinogenicity Studies
Reproductive and Teratogenic Effects
Absorption, Distribution, and Metabolism
Genetic Toxicology
Study Rationale

I. INTRODUCTION



OCHRATOXIN A

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Synonyms: (*R*)-*N*[(5-chloro-3,4-dihydro-8-hydroxy-3-methyl-1-oxo-1*H*-2-benzopyran-7-yl)-carbonyl](-L-)phenylalanine

Occurrence and Human Exposure

Ochratoxin A is a fungal toxin produced by *Aspergillus ochraceus*, *A. sulphureus*, *Penicillium viridicatum*, *P. cyclopium*, and other species and is present as a contaminant in plant products, especially cereals, beans, and peanuts (Scott et al., 1972; Krogh et al., 1973). Ochratoxin A is also found in meats, dried fish, and nuts (Ueno, 1985). In plant products, concentrations up to 27.5 ppm have been observed, whereas the highest observed concentration of residues in animal products (bacon from pigs) is 0.067 ppm (Krogh, 1977). Human exposure occurs through consumption of contaminated cereals or meat from animals that retain ochratoxin A in their tissues after being fed contaminated feed. Balkan endemic nephropathy and porcine nephropathy occurred in areas where home-grown cereals were contaminated with ochratoxin A (Krogh, 1974; Petkova-Bocharova and Castegnaro, 1985). Balkan endemic nephropathy is seen in areas of Bulgaria, Yugoslavia, and Romania and is associated with a high frequency of carcinomas of the renal pelvis, ureter, and urinary bladder (Castegnaro et al., 1987). The risk of developing tumors is ninetyfold greater in affected villages than in nonaffected villages. Although a number of explanations have been considered, most support is given to the hypothesis involving mycotoxins. Ochratoxin A was found in the blood of people living in areas of endemic nephropathy in Yugoslavia (7% of samples positive, generally containing 2-5 ng ochratoxin A per gram of serum, with the highest concentration being 40 ng/g serum) (Hult et al., 1982). Ochratoxin A was demonstrated to be the cause of porcine nephropathy in Denmark (Castegnaro et al., 1987). In Poland, where a recent increase in porcine nephropathy was found, 148/388 (38%) porcine serum samples were positive for ochratoxin A with concentrations ranging from 1 to 520 ng/ml (Golinski et al., 1985). Galtier et al. (1981) have shown that ochratoxin A persists longer in pigs than in other species, which suggests that problems of ochratoxin A residues in the human food chain may be greater in pork than in other meats.

Toxicity

The nephrotoxic properties of ochratoxin A have been demonstrated in several animal studies. The chemical at concentrations of 3 ppm in feed caused significant depression of weight gain and feed efficiency in chicks (Kubena et al., 1983). Wistar rats dosed with ochratoxin A at 10, 15, 25, or 40 mg/kg body weight by gavage had renal lesions varying from mild dilatation of collecting ducts to severe tubular necrosis (Purchase and Theron, 1968). The LD_{50} values appeared to be 22 mg/kg for males and 20 mg/kg for females. When ochratoxin A was administered for 2 weeks in feed to Wistar rats at concentrations of 0, 2.4, 4.8, 9.6, or 24 ppm, renal effects were seen (Munro et al., 1974). These effects included increased kidney weight relative to body weight, an increase in urinary volume, increased urine pH, increased urine specific gravity, increased blood urea nitrogen, and depressed body weight gain and feed consumption. Other groups of rats fed ochratoxin A at 0, 0.2, 1, or 5 ppm for 90 days

showed renal changes in all dosed groups. A second study showed that ochratoxin A given in feed at concentrations as low as 2 ppm for as little as 1 week caused renal tubular cell injury in rats (Kane et al., 1986a,b).

The initial toxic effect of ochratoxin A is found in the nephron at the level of the proximal convoluted tubule (Ueno, 1985). It appears that the specific effect is on the anion transport mechanism located on the brush border (Endo, 1983). Rats lose the ability to concentrate urine, and excretion of glucose is increased (Krogh, 1977). Biochemically, renal gluconeogenesis and renal phosphoenolpyruvate carboxykinase activity are decreased (Meisner and Selanik, 1979; Meisner et al., 1983). The decreased level of cytosolic phosphoenolpyruvate carboxykinase, involved in gluconeogenesis, is a result of ochratoxin A-induced depression of multiple species of mRNA in renal proximal tubular cells (Meisner and Cimbala, 1986). Ochratoxin A also appears to inhibit protein synthesis by competition with phenylalanine in the phenylalanyl-tRNA synthetase-catalyzed reactions (Bunge et al., 1978; Creppy et al., 1979; Mayura et al., 1984a). Ochratoxin A toxicity in mice can be reduced by administration of phenylalanine (Creppy et al., 1980). As would be expected, ochratoxin A nephrotoxicity is enhanced in rats subjected to a partial nephrectomy (Stein et al., 1984).

Ochratoxin A also affects the hematopoietic system. Female B6C3F$_1$ mice given a total dose of 0, 20, 40, or 80 mg/kg ochratoxin A by intraperitoneal injection every other day for 8 days had atrophy of the thymus at the two highest doses, decreased bone marrow cellularity, and a decreased number of bone marrow progenitor cells in all dosed groups (Boorman et al., 1984). Six weekly injections of ochratoxin A at 5 mg/kg also were reported to cause decreased bone marrow counts in Swiss mice (Gupta et al., 1983). One-day-old chicks given 0.1, 1, 10, or 100 µg ochratoxin A per chick per day for up to 10 days had nephrosis, decreased spleen size, and suppressed hematopoiesis (Peckham et al., 1971).

Depression of the immunologic response by ochratoxin A was reported for BALB/c mice (Roschenthaler et al., 1983). These immunologic and hematologic effects may result from competition between ochratoxin A and phenylalanine, since the immunologic effects in mice can be negated by giving supplemental phenylalnine to ochratoxin A-dosed mice (Haubeck et al., 1981; Roschenthaler et al., 1983). An interesting finding is suppression of natural killer cell activity and enhanced growth of transplanted tumor cells in B6C3F$_1$ mice given 6.7 or 13.4 mg/kg ochratoxin A either orally or systemically (Luster et al., 1987). Nonspecific immunologic effects such as impaired phagocytosis by heterophils has also been reported in chickens (Chang and Hamilton, 1980). At oral doses of 25 or 40 mg/kg in Wistar rats, some evidence of hepatotoxicity was reported (Purchase and Theron, 1968; Peckham et al., 1971). This effect tended to be single-cell necrosis of periportal hepatocytes (Purchase and Theron, 1968). This hepatotoxic effect appears to be less specific, since it occurred only after exposure at higher concentrations of ochratoxin A and the decreased amount of mRNA seen in proximal renal tubular epithelial cells after ochratoxin A exposure was not seen in hepatocytes (Meisner and Cimbala, 1986). Ochratoxin A has a much less pronounced effect on drug-metabolizing systems of the rat liver than does aflatoxin B$_1$ (Galtier et al., 1984).

Carcinogenicity Studies

When Wistar-derived rats were given 2.5 mg/kg ochratoxin A in sunflower oil or sunflower oil alone as a vehicle control (10 rats per group) by subcutaneous injection for 35 doses (given twice per week) and held to week 87, 2 dosed and 2 vehicle control animals had subcutaneous fibrosarcomas at the injection site (Purchase and van der Watt, 1971). In a dermal study in white mice, ochratoxin A used as a promoter following 7,12-dimethylbenz[*a*]anthracene initiation did not affect the incidence of papillomas (Lindenfelser et al., 1973). One-year feed studies in male DDY mice showed that exposure at 40 ppm for 50 weeks caused renal and hepatic tumors (Kanisawa and Suzuki, 1978; Kanisawa, 1984). Nine of 9 mice fed diets containing 40 ppm ochratoxin A had cystic renal adenomas compared with none in 10 control mice. These carcinogenic effects of ochratoxin A in mice were confirmed in a 24-month feed study in male and female B6C3F$_1$ mice (50 per each sex and dose group) exposed to

ochratoxin A at 0, 1, or 40 ppm (Bendele et al., 1983, 1985). Twenty-six of 50 male mice receiving 40 ppm ochratoxin A had renal tumors. No renal tumors were observed in female mice, although there was a slight but significant increase in hepatocellular carcinomas. In males, the incidences of liver tumors were not significantly increased.

Reproductive and Teratogenic Effects

Ochratoxin A given on gestation days 6-15 to pregnant Sprague Dawley-derived rats was found to be embryocidal at doses of 0.75 mg/kg or higher and teratogenic at 0.25 and 0.50 mg/kg (Brown et al., 1976). Deformities included wavy ribs, agenesis of vertebrae, and alterations in the nasal cavity. A single dose of 5 mg/kg ochratoxin A given by intraperitoneal injection to mice on any one of the gestation days between days 7 and 12 resulted in fetal deaths and severe malformations including exencephaly and anomalies of eyes, digits, tail, ribs, vertebrae, and skull (Hayes et al., 1974). The highest incidence of lesions was observed after mice were dosed on day 11 of gestation. Brain necrosis was reported in mice transplacentally exposed to ochratoxin A (Szczech and Hood, 1981), and prenatal exposure caused malformations in hamsters (Hood et al., 1975). With impaired maternal renal function, the teratogenicity of ochratoxin A in rats was increased (Mayura et al., 1984b). Partial protection against ochratoxin A-induced teratogenesis in rats was seen after coadministration of phenylalanine (Mayura et al., 1984a).

Absorption, Distribution, and Metabolism

The primary site of absorption of ochratoxin A appears to be in the small intestine. When ochratoxin A was injected into the lumen of the stomach, small intestine, cecum, or colon of male Wistar rats, the highest absorption was in the proximal jejunum (Kumagai and Aibara, 1982). In mice, when the ochratoxin A was given by oral intubation, the site of highest absorption was the duodenum. In this study, immunohistochemical staining revealed that the highest concentrations of ochratoxin A were in the intestine with decreasing levels in the kidney and liver (Kumagai and Aibara, 1982; Lee et al., 1984).

When ochratoxin A was given orally or by intraperitoneal injection to two strains of rats, 6% of the dose was excreted as ochratoxin A, 1%-1.5% as (4*R*)-4-hydroxyochratoxin A, and 25%-27% as ochratoxin A α in the urine, independent of the route (Storen et al., 1982). The rats were kept in metabolism cages, and 24-hour urine and fecal samples were analyzed for 6 days after the rats were dosed. Only traces of ochratoxin A and ochratoxin A α were found in the feces, as determined by high-performance liquid chromatography and mass spectroscopy.

When ochratoxin A was given orally or intravenously to pigs, rabbits, and chickens at doses of 0.5-2 mg/kg, the biologic half-lives were 88.8, 8.2, and 4.1 hours, respectively, with 65.7%, 55.6%, and 40% of the oral dose being absorbed (Galtier et al., 1981). There are clear pharmacokinetic differences between these three species.

Patients in Bulgaria with Balkan endemic nephropathy and/or renal neoplasms were found to metabolize debrisoquine (a cytochrome P450-dependent reaction) more extensively than did unaffected persons (Castegnaro et al., 1987). Rats with an extensive capacity to metabolize debrisoquine also metabolize ochratoxin A more extensively to its 4-hydroxy metabolite (Storen et al., 1982). Whether this pathway is related to the ability of ochratoxin A to cause renal neoplasms is not known.

Genetic Toxicology

Ochratoxin A has been tested in numerous laboratories for induction of gene mutation in a variety of *Salmonella typhimurium* strains with and without exogenous metabolic activation, and results were uniformly negative (Engel and von Milczewski, 1976; Wehner et al., 1978; Kuczuk et al., 1978; Bartsch et al., 1980; Zeiger et al., 1988). In addition, no growth inhibition due to DNA damage was observed in *Bacillus subtilis* strain M15/H17 (Ueno and Kubota, 1976), and no induction of mitotic recombination was reported in *Saccharomyces cerevisiae* D3 after treatment with ochratoxin A (Kuczuk et al., 1978).

Tests with mammalian cells have indicated some genotoxic activity by ochratoxin A.

Unscheduled DNA synthesis was reported in ACI rat and C3H mouse hepatocyte cultures treated with ochratoxin A (Mori et al., 1984). DNA damage in the form of single strand breaks was observed in the kidney, liver, and spleen of male BALB/c mice injected intraperitoneally with 2.5 mg/kg ochratoxin A in dimethyl sulfoxide-phosphate buffered saline; the DNA damage to splenic cells was confirmed by an in vitro procedure using phytohemagglutinin-stimulated cultured spleen cells incubated for 48 hours with 10 µg/ml ochratoxin A in dimethyl sulfoxide (Creppy et al., 1985). Kane et al. (1986c) reported induction of DNA single strand breaks in renal and hepatic cells of rats administered 288.8 µg/kg ochratoxin A by gavage every 48 hours for 12 weeks (doses were selected to correspond to 4 ppm in feed). Although this observed DNA damage in mammalian cells provides limited evidence of mutagenic potential, no induction of gene mutation was detected in cultured mouse FM3A cells exposed to ochratoxin A at 10 µg/ml in the absence of metabolic activation (Umeda et al., 1977).

Study Rationale

Ochratoxin A was selected for study because it is found in animal products and because a potential for human exposure exists. Although ochratoxin A was found to be carcinogenic for male and female B6C3F$_1$ mice in a Food and Drug Administration study that appeared to be adequate (Bendele et al., 1985), previous studies in rats were considered inadequate by International Agency for Research on Cancer standards (IARC, 1976), and thus, these current studies were conducted in F344/N rats.

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF OCHRATOXIN A

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES

SIXTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

NINE-MONTH, FIFTEEN-MONTH, AND TWO-YEAR STUDIES

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

GENETIC TOXICOLOGY

PROCUREMENT AND CHARACTERIZATION OF OCHRATOXIN A

Ochratoxin A (extracted from rice cultures of *Aspergillus ochraceus*, isolated by liquid chromatography, and recrystallized from chloroform:hexane:acetic acid) was obtained in three lots from the Food and Drug Administration (Table 1). Purity and identity analyses were conducted at Midwest Research Institute (MRI) (Kansas City, Missouri). MRI reports on the analyses performed in support of the ochratoxin A studies are on file at NIEHS.

All lots of the study chemical were a white crystalline powder and were identified as ochratoxin A by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. Infrared, ultraviolet/visible, and nuclear magnetic resonance spectra (representative spectra presented in Figures 1 and 2) were consistent with the structure and with literature spectra (Steyn and Holzapfel, 1967; Van Der Merwe et al., 1965).

Cumulative data indicated that the purity of lot no. 0459-8100 was approximately 94%. This purity was determined by thin-layer chromatography, high-performance liquid chromatography, and gas chromatography. Thin-layer chromatography with a Supelco Aflasil® plate and two different solvent systems--toluene:ethyl acetate:acetic acid (85:5:10) and hexanes: acetone:acetic acid (55:35:10)--and visualization at 366 nm indicated a major spot and a trace impurity (solvent system 1 only). High-performance liquid chromatography with an Altex Ultrasphere ODS column, detection at 254 nm, and a solvent system of 1% aqueous acetic acid:1% acetic acid in methanol (36:64) detected an impurity with an area 0.4% that of the major peak. Quantitation of residual chloroform from the recrystallization of the study material was performed by gas chromatography with flame ionization detection and a 1.8 m × 4 mm 10% SP2100 glass column. Chloroform was determined to be present at a level of 4% in the study material. The nuclear magnetic resonance analysis also indicated the presence of acetic acid in the study material, estimated to be present at approximately 1.4%.

Cumulative data indicated that lot no. 8-29-2 was approximately 98% pure. Results of elemental analyses were in agreement with theoretical values for carbon, hydrogen, nitrogen, and chlorine after correction for the chloroform content. Thin-layer chromatography by the two systems described above indicated a major spot and a trace impurity by both systems. High-performance liquid chromatography with the same system described above indicated two impurities with a combined area of 1.7% relative to the major peak area. Gas chromatographic analysis with the system described above except for the use of a 20% SP2100/0.1% Carbowax column indicated the presence of chloroform, which was quantitated to be present at a level of 0.4%; benzene, quantitated to be present at a level of 0.018%; *o*-xylene, quantitated to be present at a level of 0.001%; and *p*-xylene, quantitated to be present at a level of 0.005%.

TABLE 1. IDENTITY AND SOURCE OF OCHRATOXIN A USED IN THE GAVAGE STUDIES

Sixteen-Day Studies	Thirteen-Week Studies	Nine-Month Studies	Fifteen-Month Studies	Two-Year Studies
Lot Numbers				
0459-8100	8-29-2	9-31-1	Same as 9-mo studies	Same as 9-mo studies
Date of Initial Use				
4/14/81	11/12/81	09/20/82	09/20/82	09/20/82
Supplier				
Food and Drug Administration (Washington, DC)	Same as 16-d studies	Same as 16-d studies	Same as 16-d studies	Same as 16-d studies

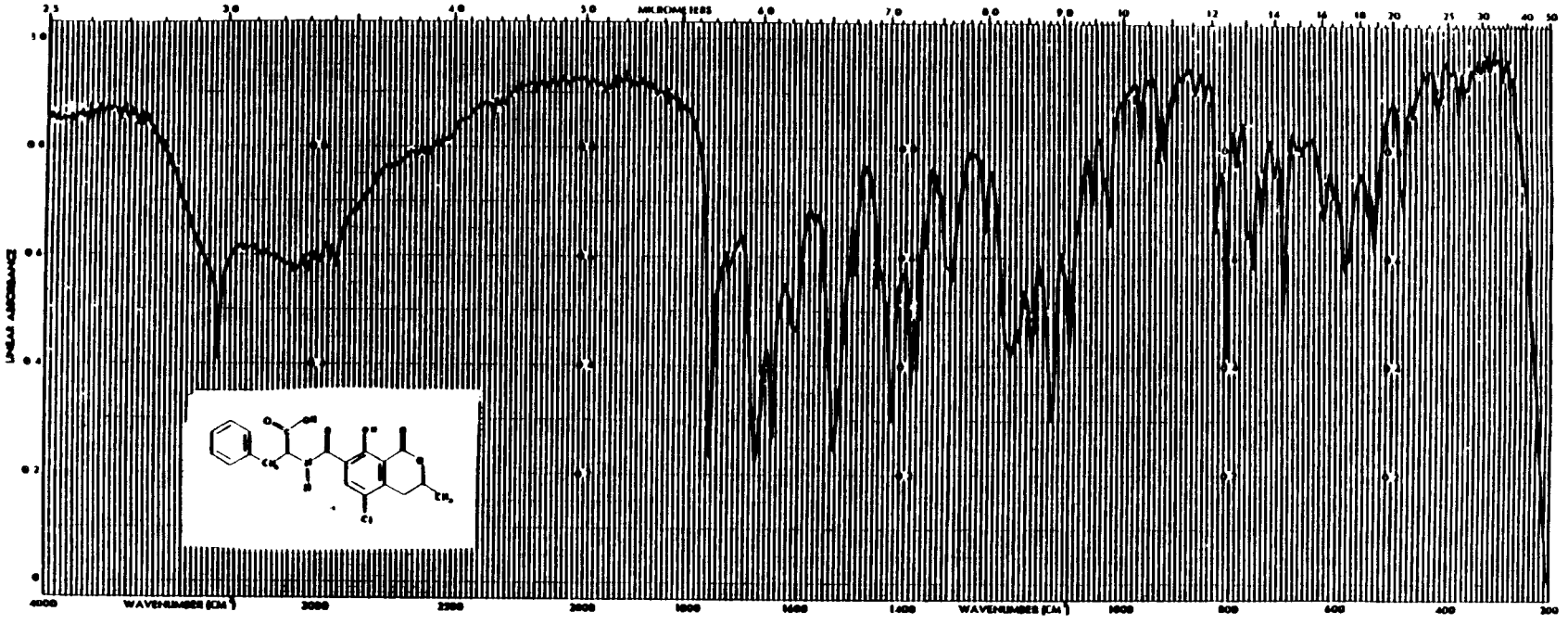

FIGURE 1. INFRARED ABSORPTION SPECTRUM OF OCHRATOXIN A (LOT NO. 9-31-1)

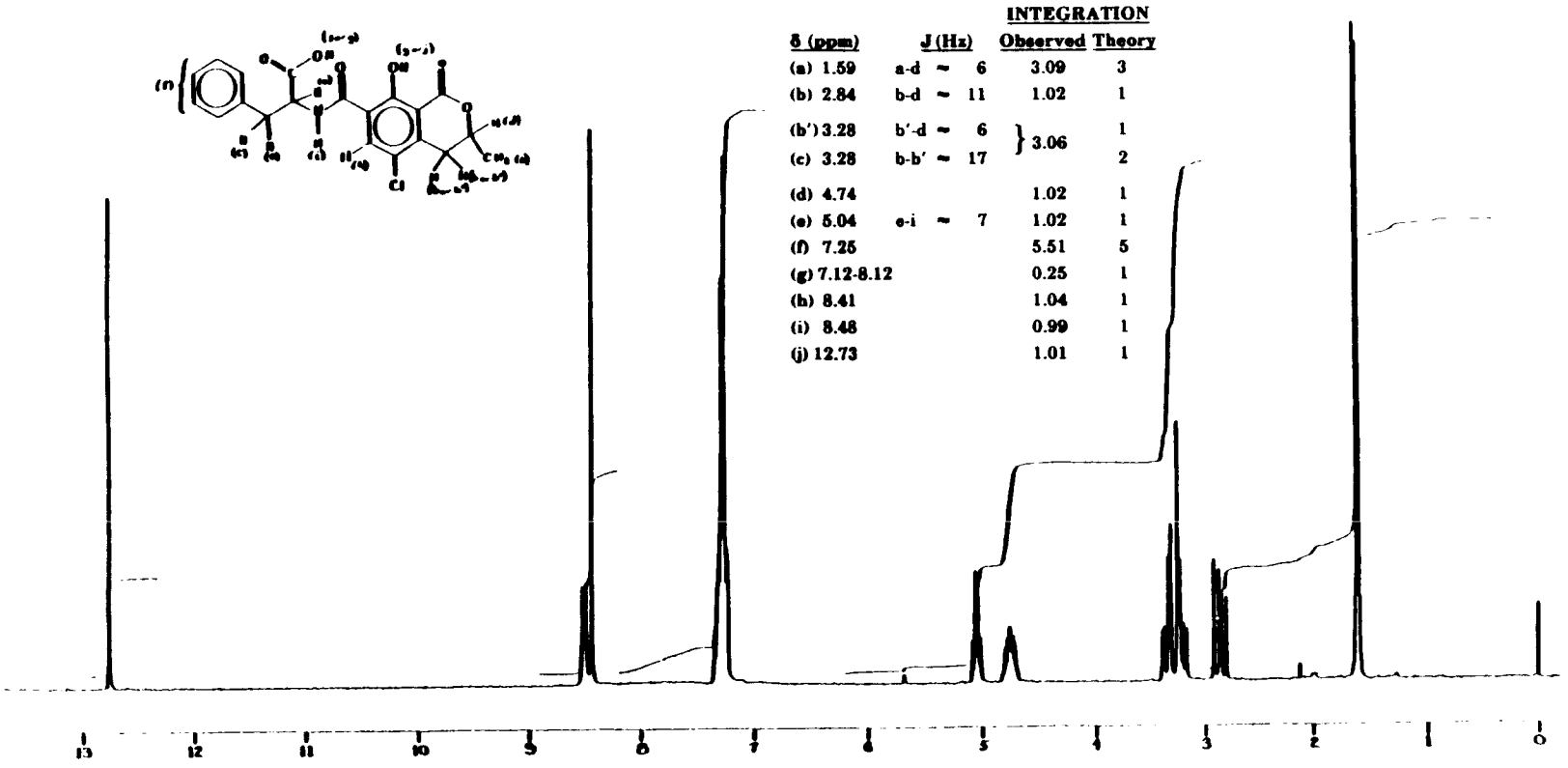

FIGURE 2. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF OCHRATOXIN A (LOT NO. 9-31-1)

Cumulative data indicated that lot no. 9-31-1 was approximately 98% pure. Results of elemental analyses were in agreement with theoretical values for carbon, hydrogen, nitrogen, and chlorine after correction for the chloroform content. Thin-layer chromatography with the two systems previously described indicated a major spot and a trace impurity. High-performance liquid chromatography with a μBondapak C_{18} column and solvent system previously described indicated two impurities, with a combined area of 1.4% relative to the major peak area. Gas chromatographic analysis was performed with flame ionization detection and three different systems: system 1--10% SP2100, system 2--20% SP2100/0.1% Carbowax 1500, and system 3--80/100 Carbopack C/0.1% SP1000. Chloroform content was quantitated as 0.93% (w/w) by system 1. Since the highest dose of ochratoxin A in the 2-year studies was 210 μg/kg, the exposure levels to this contaminant were 2 μg/kg or less. Benzene, *o*-xylene, and *p*-xylene were not present at the detection limits of 100 ppm for benzene or 70 ppm for *o*- or *p*-xylene by system 2. *n*-Hexane was not present at a concentration of greater than 70 ppm, as determined by system 3.

Confirmation of the stability of the chemical during the 2-year studies was obtained by high-performance liquid chromatography and ultraviolet spectroscopy. These methods for analysis were performed by the study laboratory after month 7 of the studies. Results of reanalysis suggested that no degradation of the bulk chemical occurred during the studies.

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES

Appropriate amounts of ochratoxin A and corn oil were mixed (w/v) to give a stock suspension (Table 2). The stability of ochratoxin A in corn oil (350 μg/ml) was determined by high-performance liquid chromatography. The corn oil solution was first diluted with an equal amount of hexanes and then extracted with methanol:water (80:20). The extract was analyzed by high-performance liquid chromatography with a μBondapak C_{18} column, a 1% aqueous acetic acid:1% acetic acid in methanol (30:70) mobile phase, and detection at 333 nm. The study chemical in corn oil was found to be stable for at least 21 days at room temperature in the dark and for at least 3 hours when exposed to air and light at room temperature. Mixtures were stored at 4° C for up to 2 weeks for the 16-day and 13-week studies. During the 9-month,15-month, and 2-year studies, mixtures were kept at room temperature for up to 2 weeks.

TABLE 2. PREPARATION AND STORAGE OF DOSE MIXTURES IN THE GAVAGE STUDIES OF OCHRATOXIN A

Sixteen-Day Studies	Thirteen-Week Studies	Nine-Month Studies	Fifteen-Month Studies	Two-Year Studies
Preparation				
Appropriate amounts of ochratoxin A mixed with corn oil; lower doses prepared by dilution	Appropriate amounts of ochratoxin A diluted to volume in graduated cylinder with corn oil; lower doses prepared by dilution	Appropriate amounts of ochratoxin A mixed with corn oil in Brinkman PT10-35® homogenizer for 30 sec, diluted to volume in a cylinder, and mixed by inversion; lower doses prepared by dilution	Same as 9-mo studies	Same as 9-mo studies
Maximum Storage Time				
2 wk	2 wk	2 wk	2 wk	2 wk
Storage Conditions				
4° C in foil-wrapped bottles	4° C in amber glass bottles	Room temperature in amber glass bottles	Same as 9-mo studies	Same as 9-mo studies

Periodic analysis of ochratoxin A/corn oil mixtures was conducted at the study laboratory and the analytical chemistry laboratory by the high-performance liquid chromatography method described above. During the 2-year studies, the dose preparations were analyzed at the study laboratory at approximately 8-week intervals. Because 38/40 of the dose mixtures were formulated within ±10% of the target concentrations, it is estimated that dose mixtures were prepared within specifications approximately 95% of the time throughout the studies (Table 3). Results of referee analyses performed by the analytical chemistry laboratory were generally in agreement with those of the study laboratory (Table 4).

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

Date Mixed	Concentration of Ochratoxin A in Corn Oil for Target Concentration (μg/ml) (a)		
	4.2	14	42
09/16/82	4.14	13.65	(b) 37.25
		13.35	
09/21/82			(c) 41.80
11/04/82	3.98	15.24	41.69
12/14/82	4.18	14.86	39.46
02/23/83	4.13	14.02	(b) 36.18
02/24/83			(c) 42.90
04/12/83	4.33	13.88	41.79
06/15/83	3.83	12.62	38.39
08/03/83	4.28	(d) 13.15	(d) 39.96
10/04/83	4.35	12.61	39.50
12/07/83	4.23	14.16	44.51
01/24/84	4.20	14.39	40.92
03/27/84	4.18	14.99	41.02
05/22/84	4.39	14.73	43.61
07/17/84	4.07	14.35	41.97
Mean (μg/ml)	4.18	14.00	40.48
Standard deviation	0.155	0.842	2.371
Coefficient of variation (percent)	3.7	6.0	5.9
Range (μg/ml)	3.83-4.39	12.61-15.24	36.18-44.51
Number of samples	13	14	13

(a) Results of duplicate analysis unless otherwise specified
(b) Out of specifications; not used in studies.
(c) Remix; not included in the mean.
(d) Analyzed in quadruplicate

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

Date Mixed	Target Concentration (μg/ml)	Determined Concentration (μg/ml)	
		Study Laboratory (a)	Referee Laboratory (b)
09/16/82	4.2	4.14	4.11
04/12/83	14	13.88	12.6
10/04/83	42	39.50	40.2
05/22/84	14	14.73	13.7

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

SIXTEEN-DAY STUDIES

Male and female F344/N rats were obtained from Harlan Industries and held for 20 days before the studies began. The rats were approximately 7 weeks old when placed on study. Groups of five rats of each sex were administered 0, 1, 4, or 16 mg/kg ochratoxin A in corn oil by gavage, 5 days a week for a total of 12 doses over 16 days.

Animals were housed five per cage. Water and feed were available ad libitum. The rats were observed twice per day and were weighed on days 1 and 7 and at necropsy. Liver, thymus, right kidney, heart, brain, and lungs were weighed. A necropsy was performed on all surviving animals. Histologic examinations were performed on all animals. Details of animal maintenance are presented in Table 5.

THIRTEEN-WEEK STUDIES

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

Four- to six-week-old male and female F344/N rats were obtained from Frederick Cancer Research Facility, observed for 15 days (males) or 16 days (females), distributed to weight classes, and assigned to cages and then to dose groups according to two tables of random numbers. Rats were 7-9 weeks old when placed on study.

Groups of 10 rats of each sex were administered 0, 0.0625, 0.125, 0.25, 0.5, or 1 mg/kg ochratoxin A 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. Animals were checked twice per day; moribund animals were killed. Individual animal weights were recorded once per week.

At the end of the 13-week studies, survivors were killed. The liver, thymus, right kidney, heart, brain, right testis, and lungs were weighed. A necropsy was performed on all animals except those excessively autolyzed or cannibalized. Tissues and groups examined are listed in Table 5.

NINE-MONTH, FIFTEEN-MONTH, AND TWO-YEAR STUDIES

Study Design

Groups of 80 rats of each sex were administered 0, 21, 70, or 210 µg/kg ochratoxin A in corn oil by gavage, 5 days per week for 9 months, 15 months, or 103 weeks. At 9 months and at 15 months, 15 animals of each sex were scheduled to be killed; animals scheduled to be killed at 15 months but which died before the 15-month kill became part of the 2-year studies. All tissues of vehicle control and high dose rats were examined microscopically. The kidneys and pituitary glands of all animals were examined microscopically.

Sixteen-hour samples of urine were collected from 15 rats of each sex from each dose group on days designated for the interim kill--3, 10, and 45--and at months 3, 6, 9, 12, and 15 of the studies. The animals were placed in metabolism cages (Maryland Plastics, New York, New York), and urine was collected overnight. Rats were fasted during urine collection, but water was available ad libitum. Thymol was placed in urine-collecting bottles as a preservative. Urinary creatinine, urea nitrogen, glucose, and total protein were measured on a Gemsaec Centrifugal Analyzer. Urinary pH was measured on a pH meter (Radiometer Copenhagen, Copenhagen, Denmark). Specific gravity was measured directly with a refractometer (American Optical, Buffalo, New York). Total urine volume was measured, and urinary sediment was examined microscopically.

At days 7 and 47 and at months 6 and 12 of the studies, urine was checked for urine-concentrating ability. Rats were deprived of water for 16 hours, their urinary bladders were evacuated, and they were placed in metabolism cages for 4 hours with no feed or water available. Urine was collected, and the specific gravity of the urine was measured with a refractometer.

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

Sixteen-Day Studies	Thirteen-Week Studies	Nine-Month Studies	Fifteen-Month Studies	Two-Year Studies
EXPERIMENTAL DESIGN				
Size of Study Groups				
5 males and 5 females	10 males and 10 females	15 males and 15 females	15 males and 15 females	50 males and 50 females
Doses				
0, 1, 4, or 16 mg/kg ochratoxin A in corn oil by gavage; dose vol--10 ml/kg	0, 0.0625, 0.125, 0.25, 0.5, or 1 mg/kg ochratoxin A in corn oil by gavage; dose vol--10 ml/kg	0, 21, 70, or 210 µg/kg ochratoxin A in corn oil by gavage; dose vol--5 ml/kg	Same as 9-mo studies	Same as 9-mo studies
Date of First Dose				
4/14/81	Male--11/12/81; female--11/13/81	Male--9/21/82; female--9/26/82	Male--9/20/82; female--9/25/82	Male--9/20/82; female--9/21/82
Date of Last Dose				
4/29/81	Male--2/10/82; female--2/11/82	Male--6/23/83; female--6/28/83	Male--12/20/83; female--12/21/83	Male--9/7/84; female--9/10/84
Duration of Dosing				
5 d/wk for 12 doses over 16 d	5 d/wk for 13 wk	5 d/wk for 9 mo	5 d/wk for 15 mo	5 d/wk for 103 wk
Type and Frequency of Observation				
Observed 2 × d; weighed initially and 1 × wk thereafter	Observed 2 × d; weighed initially and 1 × wk thereafter	Observed 2 × d; weighed initially, 1 × wk for 13 wk, and then 1 × mo	Same as 9-mo studies	Same as 9-mo studies
Necropsy, Histologic Examinations, and Supplemental Studies				
Necropsy performed on all surviving animals; histologic exams performed on all animals. Brain, heart, right kidney, liver, lungs, and thymus weighed at necropsy	Necropsy performed on all animals; tissues examined histologically for vehicle control and high dose groups. Tissues examined in lower dose groups include kidney and stomach. Organ weights recorded at necropsy include brain, heart, liver, lungs, right kidney, right testis, and thymus	Necropsy performed on all animals; the following tissues examined histologically for vehicle control and high dose groups and unscheduled deaths before month 21: adrenal glands, brain, colon, esophagus, eyes, femur including marrow, gross lesions and tissue masses with regional lymph nodes, heart, kidneys, liver, lungs and mainstem bronchi, mammary gland, mesenteric lymph nodes, pancreas, parathyroid glands, pituitary gland, prostate/testes or ovaries/uterus, salivary glands, skin, small intestine, spleen, stomach, thymus, thyroid gland, trachea, and urinary bladder. Kidneys and gross lesions examined	Necropsy performed on all animals; the same tissues and groups examined as in the 9-mo studies. Only kidney and pituitary gland examined in low dose groups. Urinalysis and serum chemical analyses performed at 12 and 15 mo. Urine-concentrating ability determined at 12 mo and hematologic analyses at 15 mo	Necropsy performed on all animals; tissues and groups examined are the same as in the 9-mo studies

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

Sixteen-Day Studies	Thirteen-Week Studies	Nine-Month Studies	Fifteen-Month Studies	Two-Year Studies
Necropsy and Histologic Examination (Continued)				
		in lower dose groups. Urinalysis performed on d 3, 10, and 45 and mo 3, 6, and 9; urine-concentrating ability determined at d 7 and 47 and mo 6; hematologic analyses performed at d 45 and mo 3 and 9; serum chemical analyses performed at d 3, 10, and 45 and mo 3, 6, and 9		
ANIMALS AND ANIMAL MAINTENANCE				
Strain and Species				
F344/N rats	F344/N rats	F344/N rats	F344/N rats	F344/N rats
Animal Source				
Harlan Industries (Indianapolis, IN)	Frederick Cancer Research Facility (Frederick, MD)	Frederick Cancer Research Facility (Frederick, MD)	Frederick Cancer Research Facility (Frederick, MD)	Frederick Cancer Research Facility (Frederick, MD)
Study Laboratory				
Battelle Columbus Laboratories	Battelle Columbus Laboratories	Battelle Columbus Laboratories	Battelle Columbus Laboratories	Battelle Columbus Laboratories
Method of Animal Identification				
Toe clip	Toe clip	Toe clip	Toe clip	Toe clip
Time Held Before Study				
20 d	Male--15 d; female--16 d	19-26 d	19-26 d	19-26 d
Age When Placed on Study				
7 wk	7-9 wk	Male--8-9 wk; female--8-10 wk	Same as 9-mo studies	Same as 9-mo studies
Age When Killed				
10 wk	22 wk	Male--47-48 wk; female--48-50 wk	Male--73-74 wk; female--73-75 wk	113-115 wk
Necropsy Dates				
4/30/81	2/11/82; female--2/12/82	Male--6/24/83; female--6/29/83	Male--12/21/83; female--12/22/83	9/17/84-9/20/84
Method of Animal Distribution				
Assigned to weight classes; distributed to cages and then to dose groups according to 2 tables of random numbers	Same as 16-d studies	Same as 16-d studies	Same as 16-d studies	Same as 16-d studies

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

Sixteen-Day Studies	Thirteen-Week Studies	Nine-Month Studies	Fifteen-Month Studies	Two-Year Studies
ANIMALS AND ANIMAL MAINTENANCE (Continued)				
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	Same as 16-d studies	Same as 16-d studies
Bedding				
Absorb-Dri (Absorb-Dri, Inc., Garfield, NJ)	Absorb-Dri (Weisheimers, Columbus, OH)	Same as 16-d studies	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	Same as 16-d studies	Same as 16-d studies	Same as 16-d studies
Cages				
Polycarbonate (Lab Products, Inc., Rochelle Park, NJ)	Same as 16-d studies	Same as 16-d studies	Same as 16-d studies	Same as 16-d studies
Cage Filters				
Spun-bonded polyester, Dupont 2024® (Snow Filtration, Cincinnati, OH)	Same as 16-d studies	Same as 16-d studies	Same as 16-d studies	Same as 16-d studies
Animals per Cage				
5	5	5	5	5
Other Chemicals on Study in the Same Room				
None	None	None	None	None
Animal Room Environment				
Temp--22°-24° C; hum--40%-60%; fluorescent light 12 h/d; 15 room air changes/h	Temp--21°-23° C; hum--40%-60%; fluorescent light 12 h/d; 15 room air changes/h	Temp--17°-23° C; hum--24%-68%; fluorescent light 12 h/d; 15 room air changes/h	Temp--16°-25° C; hum--24%-68%; fluorescent light 12 h/d; 16-24 room air changes/h	Same as 15-mo studies

At day 45 and at months 3, 9, and 15, blood samples were collected from 15 rats of each sex from each dose group by puncture of the orbital sinus. Erythrocyte, leukocyte, and platelet counts were determined with an Ortho ELT-8 laser hematology counter. Hemoglobin was determined spectrophotometrically at 540 nm after reaction of lysed cells with cyanide ferricyanide. Mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration were calculated. The number of nonsegmented neutrophils, segmented neutrophils, eosinophils, basophils, lymphocytes, monocytes, nucleated erythrocytes, and reticulocyte counts was determined microscopically.

At days 3, 10, and 45 and at months 3, 6, 9, 12, and 15, blood was obtained from 15 rats of each sex from each dose group from the orbital sinus. Glucose, urea nitrogen, and creatinine levels were measured on a Gemsaec IV Centrifugal Analyzer.

A femur was taken at necropsy at months 9 and 15; bone marrow cellularity was determined with an Ortho ETL-8 hematology counter, and differential counts were determined from bone marrow smears. A necropsy was performed on all animals including those found dead, unless they were excessively autolyzed or cannibalized, missexed, or found missing.

Source and Specifications of Animals

The male and female F344/N rats used in these studies were produced under strict barrier conditions at Frederick Cancer Research Facility 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. Animals 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 in two shipments at 5 weeks of age for each shipment of males and at 5 and 6 weeks of age for females. The animals were quarantined at the study laboratory for approximately 3-4 weeks. Thereafter, a complete necropsy was performed on five animals of each sex to assess their health status. Male rats were placed on study at 8-9 weeks of age and female rats, at 8-10 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. Males and females were housed in separate rooms. Feed and water were available ad libitum. Cages were rotated. Further details of animal maintenance are given in Table 5.

Clinical Examinations and Pathology

All animals were observed two times per day, and clinical signs were recorded at least once per month. Body weights were recorded once per week for the first 13 weeks of the study and once per month thereafter. Mean body weights were calculated for each group. 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, unless they were excessively autolyzed or cannibalized, missexed, or missing. Thus, the number of animals from which particular organs or tissues were examined microscopically varies and is not necessarily equal to the number of animals that were placed on study.

During necropsy, all organs and tissues were examined for grossly visible lesions. Tissues were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Histopathologic examination of tissues was performed according to an "inverse pyramid" design (McConnell, 1983a,b). That is, complete histopathologic examinations (Table 5) were performed on all high dose and vehicle control animals and on lower 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 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 groups were examined histopathologically. If mortality in the

highest dose group exceeded that in the vehicle control group by 15%, complete histopathologic examinations were performed on all animals in the second highest dose group in addition to those in the high dose group.

A femur taken from rats after killing was flushed with Hank's balanced solution. Suspended cells were counted and reported as cellularity. Differential counts were made from the cell suspensions. Since marrow cellularity was not consistent, these values are not included in this report.

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

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

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

Statistical Methods

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

Survival Analyses: The probability of survival was estimated by the product-limit procedure of Kaplan and Meier (1958) and is presented in the form of graphs. Animals were censored from the survival analyses at the time they were found to be missing or dead from other than natural causes; animals dying from natural causes were not censored. Statistical analyses for a possible dose-related effect on survival used the method of Cox (1972) for testing two groups for equality and Tarone's (1975) life table test for a dose-related trend. When significant survival differences were detected, additional analyses using these procedures were carried out to determine the time point at which significant differences in the survival curves were first detected. All reported P values for the survival analysis are two-sided.

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

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

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

Logistic Regression Analyses--This method of analysis assumes that all tumors of a given type observed in animals that died before the end of the study were "incidental"; i.e., they did not alter the risk of death and were discovered merely as the result of death from an unrelated cause. According to this approach, tumor prevalence was modeled as a logistic function of dose and time. Both linear and quadratic terms in time were incorporated initially, and the quadratic term was eliminated if it did not significantly enhance the fit of the model. The dosed and vehicle control groups were compared on the basis of the likelihood score test for the regression coefficient of dose. This method of adjusting for intercurrent mortality is the prevalence analysis of Dinse and Lagakos (1983), further described and illustrated by Dinse and Haseman (1986). If the tumor type is nonlethal, this comparison of the time-specific tumor also provides a prevalence comparison of the time-specific tumor incidences (McKnight and Crowley, 1984).

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

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

GENETIC TOXICOLOGY

Salmonella Protocol: Testing was performed as reported by Ames et al. (1975) with modifications listed below and described in greater detail by Zeiger et al. (1988) and Mortelmans et al. (1986). Chemicals were sent to the laboratories as coded aliquots from Radian Corporation (Austin, Texas). The study chemical was incubated with the *Salmonella typhimurium* tester strains (TA97, TA98, TA100, and TA1535) 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.

Chemicals were tested in a series (four strains used) or in a hierarchy (initial testing in TA98 and TA100; if results were negative, then the chemical was tested further in additional strains). If all results were negative, the chemical was retested in all strains with a different concentration of S9.

Each test consisted of triplicate plates of concurrent positive and negative controls and of at least five doses of the study chemical. The high dose was limited by toxicity or solubility but did not exceed 10 mg/plate. All negative assays were repeated and all positive assays were repeated under the conditions that elicited the positive response.

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

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

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

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

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

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

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 SCE, both the dose-response curve and individual dose points were statistically analyzed. A statistically significant ($P < 0.003$) effect on the slope of the curve or on a dose point ($P < 0.05$) was sufficient for a conclusion of positive for a test.

III. RESULTS

RATS

SIXTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

NINE-MONTH STUDIES

FIFTEEN-MONTH STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Survival

Hematologic and Clinical Chemical Analysis and Urinalysis

Pathology and Statistical Analyses of Results

GENETIC TOXICOLOGY

SIXTEEN-DAY STUDIES

All rats that received 16 mg/kg ochratoxin A and 1/5 female rats that received 4 mg/kg died before the end of the studies (Table 6). A vehicle control male rat died as a result of gavage error. Diarrhea and nasal discharge were observed for male and female rats that received 16 mg/kg. Rats that received 4 mg/kg lost weight. The relative kidney, heart, and brain weights of rats that received 4 mg/kg were significantly greater than those of vehicle controls (Table 7). Compound-related lesions included bone marrow hypoplasia, thymic atrophy, necrosis and/or hyperplasia of the forestomach, renal tubular degenerative and regenerative changes, and adrenal gland hemorrhage (Table 8). The lesions were most severe at 4 mg/kg (moderate to marked). The lesions were less severe at 16 mg/kg (moderate) because of the shorter survival and reduced period of chemical exposure.

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

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams)			Final Weight Relative to Vehicle Controls (percent)
		Initial	Final	Change (b)	
MALE					
0	(c) 4/5	153	214	+61	
1	5/5	153	202	+49	94.4
4	5/5	150	124	−26	57.9
16	(d) 0/5	147	(e)	(e)	(e)
FEMALE					
0	5/5	121	148	+27	
1	5/5	122	147	+25	99.3
4	(f) 4/5	121	107	−14	72.3
16	(g) 0/5	118	(e)	(e)	(e)

(a) Number surviving/number initially in group
(b) Mean body weight change of the group
(c) Death due to gavage error
(d) Day of death: 4,5,5,5,6
(e) No data are reported due to 100% mortality in this group.
(f) One death occurred on the day of scheduled necropsy.
(g) Day of death: 3,4,4,4,5

TABLE 7. ORGAN WEIGHT TO BODY WEIGHT RATIOS FOR RATS IN THE SIXTEEN-DAY GAVAGE STUDIES OF OCHRATOXIN A (a)

Organ	Vehicle Control	1 mg/kg	4 mg/kg
MALE			
Number weighed (b)	4	5	5
Body weight (grams)	214.2	202.0	124.0
Liver	53.2 ± 2.13	49.0 ± 1.19	(c) 47.3 ± 0.53
Thymus	2.0 ± 0.09	1.9 ± 0.07	(d) 0.4 ± 0.05
Kidney	5.2 ± 0.17	4.6 ± 0.09	(c,e) 6.4 ± 0.48
Heart	3.7 ± 0.11	3.7 ± 0.07	(d) 4.8 ± 0.27
Brain	8.5 ± 0.36	8.8 ± 0.25	(d) 13.6 ± 0.39
Lungs	7.2 ± 0.38	(e) 7.0 ± 0.17	7.4 ± 0.15
FEMALE			
Number weighed	5	5	4
Body weight (grams)	148.4	146.8	107.0
Liver	45.5 ± 1.03	46.8 ± 1.27	45.2 ± 1.29
Thymus	2.3 ± 0.04	2.2 ± 0.10	(d) 0.9 ± 0.21
Kidney	5.1 ± 0.12	5.1 ± 0.15	(d) 6.2 ± 0.25
Heart	4.2 ± 0.08	3.9 ± 0.13	(c) 5.2 ± 0.52
Brain	11.3 ± 0.20	11.5 ± 0.31	(d) 15.3 ± 0.69
Lungs	9.0 ± 0.54	7.9 ± 0.14	7.9 ± 0.22

(a) Mean ± standard error in milligrams per gram unless otherwise specified; P values vs. the vehicle controls by Dunnett's test (Dunnett, 1955).
(b) Unless otherwise specified
(c) $P<0.05$
(d) $P<0.01$
(e) Four weighed

TABLE 8. NUMBERS OF RATS WITH SELECTED LESIONS IN THE SIXTEEN-DAY GAVAGE STUDIES OF OCHRATOXIN A (a)

	Male				Female			
Site/Lesion	Vehicle Control	1 mg/kg	4 mg/kg	16 mg/kg (b)	Vehicle Control	1 mg/kg	4 mg/kg	16 mg/kg (c)
Bone marrow								
Hypoplasia	0	1	5	5	0	3	5	5
Thymus								
Atrophy	0	0	3	5	0	0	2	4
Forestomach								
Necrosis and/or hyperplasia	0	0	5	5	0	0	5	5
Kidney								
Nephropathy	0	5	5	3	0	5	5	3
Adrenal gland								
Hemorrhage	0	0	3	4	0	0	4	4

(a) Five rats examined in each group
(b) All male rats at 16 mg/kg were dead by day 6.
(c) All female rats at 16 mg/kg were dead by day 5.

THIRTEEN-WEEK STUDIES

All deaths were attributed to errors in gavage technique (Table 9). The final mean body weight of rats that received 0.25, 0.5, or 1 mg/kg was 7%, 11%, or 19% lower than that of vehicle controls for males and 3%, 4%, or 9% lower for females (Figures 3 and 4). The relative kidney weights of male rats at 0.125 mg/kg or more were significantly lower than that of vehicle controls (Table 10). Compound-related lesions in the kidney were characterized as degeneration and regeneration of the proximal convoluted tubules with individual tubular cell necrosis of moderate severity (10/10 males and 10/10 females at 1 mg/kg). Karyomegaly (enlargement of the nuclei in the tubular epithelium) was widespread but most pronounced in the straight portion of the tubules in the juxtamedullary cortex. Karyomegaly was present in all dose groups, and the severity was dose related (minimal at 0.0625 mg/kg and moderate at 0.5 mg/kg). Less severe renal lesions, consisting primarily of atrophy of the straight portions of the tubules at the corticomedullary junction and in the medulla, were seen at lower doses (Table 11). Renal lesions were not seen in the vehicle control rats.

TABLE 9. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF OCHRATOXIN A

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams)			Final Weight Relative to Vehicle Controls (percent)
		Initial	Final	Change (b)	
MALE					
0	9/10	136	334	+198	
0.0625	9/10	138	334	+196	100.0
0.125	7/10	138	323	+185	96.7
0.25	9/10	135	311	+176	93.1
0.5	10/10	133	297	+164	88.9
1	10/10	136	272	+136	81.4
FEMALE					
0	10/10	126	192	+66	
0.0625	9/10	126	193	+67	100.5
0.125	8/10	129	195	+66	101.6
0.25	8/10	127	186	+59	96.9
0.5	8/10	124	184	+60	95.8
1	9/10	128	174	+46	90.6

(a) Number surviving/number initially in group; all deaths due to gavage error.
(b) Mean body weight change of the group

TABLE 10. ORGAN WEIGHT TO BODY WEIGHT RATIOS FOR RATS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF OCHRATOXIN A (a)

Organ	Vehicle Control	0.0625 mg/kg	0.125 mg/kg	0.25 mg/kg	0.5 mg/kg	1 mg/kg
MALE						
Body weight (grams)	337 ± 8.6	335 ± 7.8	324 ± 5.1	313 ± 5.0	(b) 300 ± 7.5	(b) 274 ± 7.3
Brain	5.8 ± 0.15	5.8 ± 0.15	5.9 ± 0.07	6.1 ± 0.10	6.3 ± 0.15	(b) 7.1 ± 0.14
Heart	2.9 ± 0.04	2.9 ± 0.05	3.0 ± 0.09	3.0 ± 0.07	3.0 ± 0.06	(b) 3.3 ± 0.08
Right kidney	3.4 ± 0.12	3.5 ± 0.08	3.1 ± 0.07	(b) 2.9 ± 0.06	(b) 2.9 ± 0.06	(b) 3.1 ± 0.08
Liver	39.1 ± 1.29	40.3 ± 0.96	40.2 ± 1.72	39.9 ± 1.65	39.5 ± 0.78	39.0 ± 0.56
Lung	5.4 ± 0.16	5.1 ± 0.19	5.9 ± 0.78	5.0 ± 0.17	5.6 ± 0.24	5.7 ± 0.21
Right testis	4.4 ± 0.05	4.4 ± 0.10	4.5 ± 0.10	4.5 ± 0.09	4.6 ± 0.07	(b) 4.9 ± 0.09
Thymus	0.90 ± 0.037	0.91 ± 0.042	0.95 ± 0.042	0.91 ± 0.073	0.88 ± 0.054	0.82 ± 0.050
FEMALE						
Body weight (grams)	194 ± 3.8	196 ± 4.6	199 ± 6.0	190 ± 4.0	188 ± 2.6	(b) 176 ± 3.9
Brain	9.4 ± 0.19	9.5 ± 0.21	9.2 ± 0.35	9.7 ± 0.27	9.8 ± 0.16	10.3 ± 0.35
Heart	3.2 ± 0.09	3.4 ± 0.06	3.3 ± 0.12	3.6 ± 0.15	3.4 ± 0.07	3.6 ± 0.18
Right kidney	3.4 ± 0.14	3.4 ± 0.08	3.2 ± 0.12	3.2 ± 0.12	3.3 ± 0.09	3.6 ± 0.15
Liver	35.4 ± 1.09	35.6 ± 0.86	34.9 ± 0.69	35.9 ± 0.80	37.0 ± 0.92	34.4 ± 0.91
Lung	6.4 ± 0.50	6.2 ± 0.16	7.0 ± 0.55	6.5 ± 0.24	7.0 ± 0.51	(b) 7.6 ± 0.43
Thymus	1.17 ± 0.039	1.14 ± 0.033	1.13 ± 0.063	1.16 ± 0.031	1.17 ± 0.050	1.11 ± 0.056

(a) Mean ± standard error in milligrams per gram unless otherwise specified. P values vs. the vehicle controls as determined by Dunn's test or Shirley's test (Dunn, 1964; Shirley, 1977).
(b) $P<0.01$

TABLE 11. NUMBERS OF RATS WITH RENAL CORTICAL LESIONS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF OCHRATOXIN A (a)

Lesion	Vehicle Control		0.0625 mg/kg		0.125 mg/kg		0.25 mg/kg		0.5 mg/kg		1 mg/kg	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
Degeneration/necrosis	0	0	0	0	6	6	3	5	0	2	10	10
Karyomegaly	0	0	10	9	10	9	10	10	10	10	10	10
Atrophy	0	0	10	9	7	8	9	8	8	8	0	0

(a) Ten animals per group

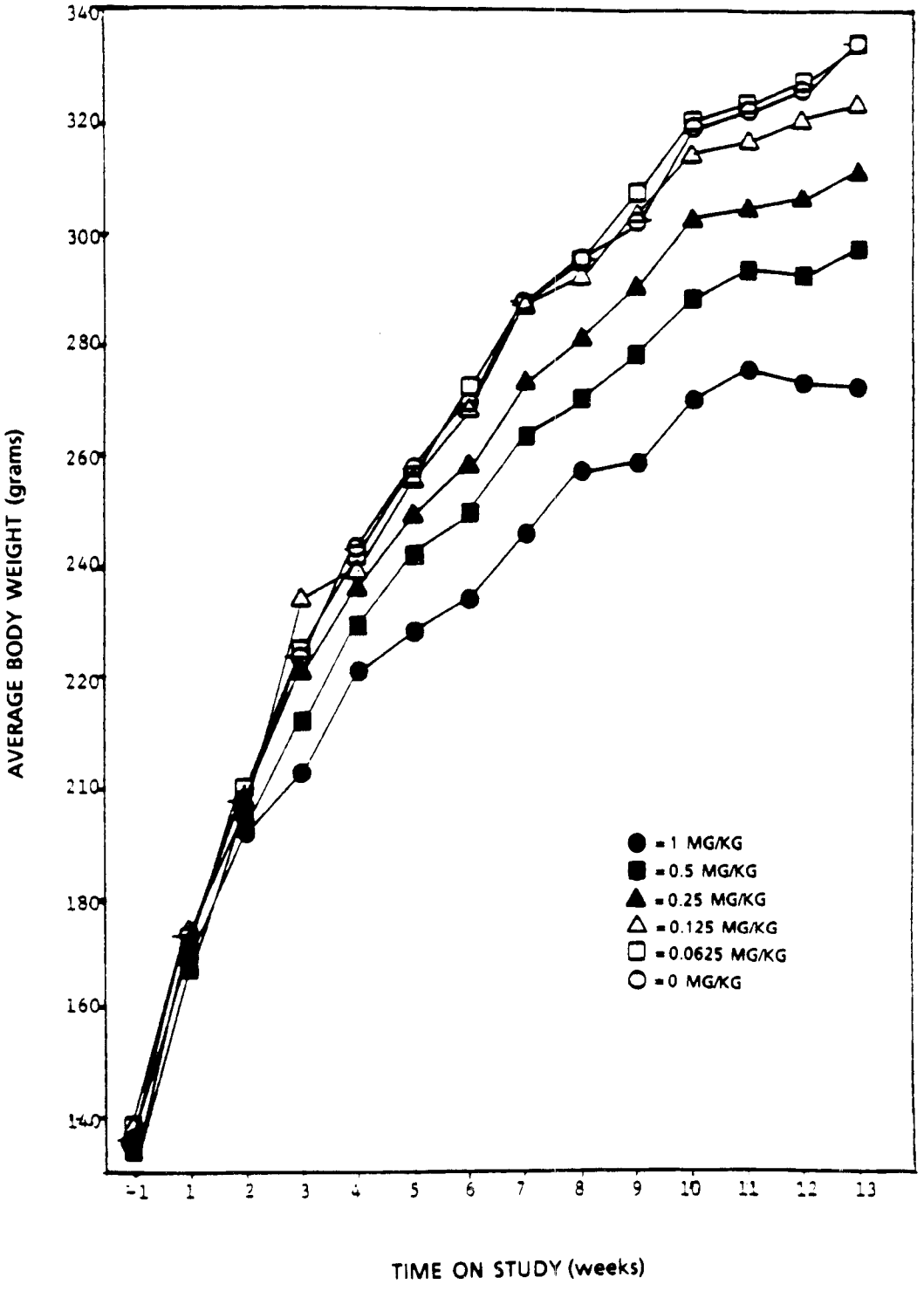

FIGURE 3. AVERAGE BODY WEIGHTS OF MALE RATS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF OCHRATOXIN A

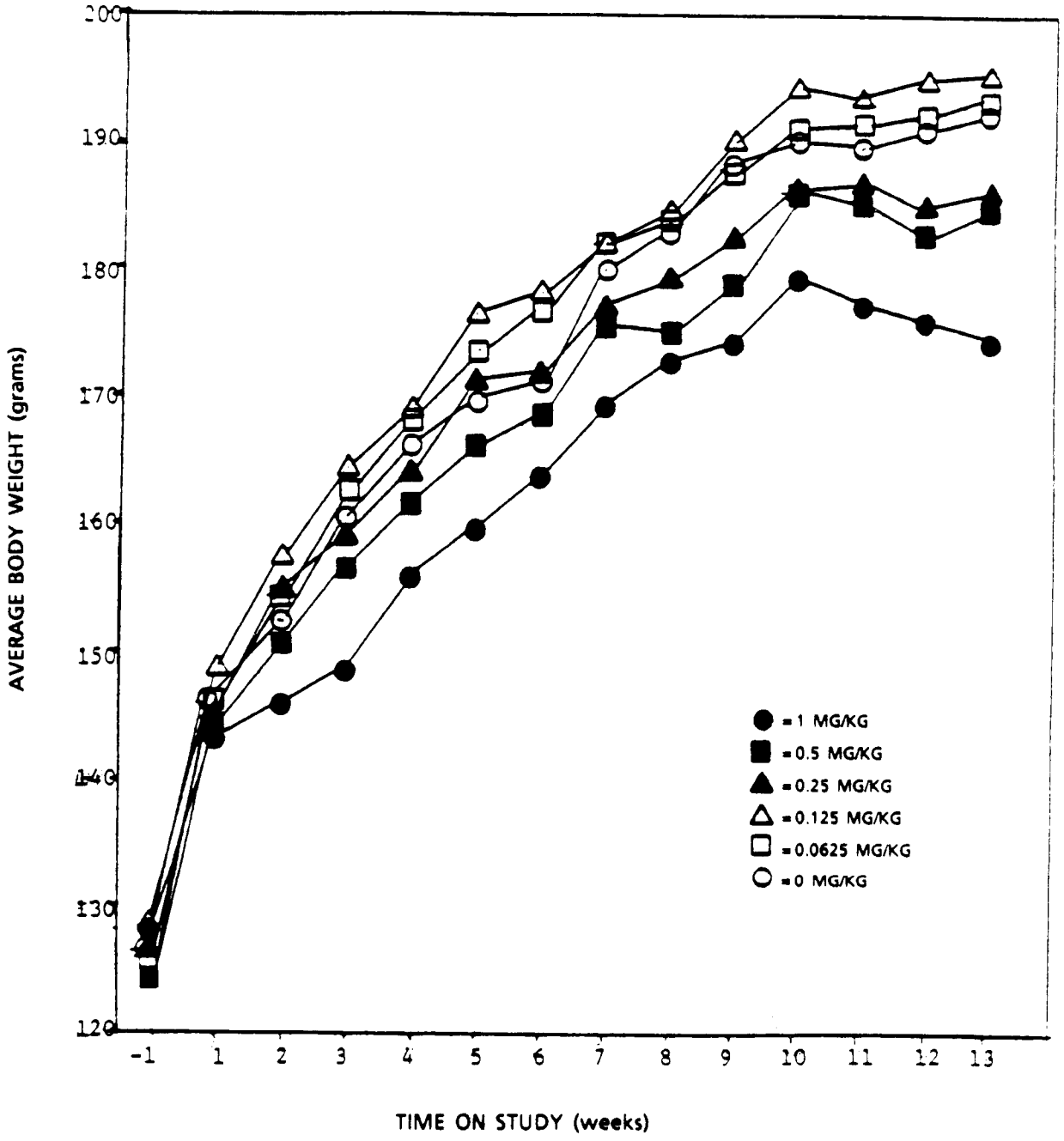

FIGURE 4. AVERAGE BODY WEIGHTS OF FEMALE RATS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF OCHRATOXIN A

Dose Selection Rationale: Dose selection was based largely on body weight data and on changes in the kidney. Rats exposed at 0.25 mg/kg (250 µg/kg) gained approximately 10% less weight than did vehicle controls, whereas the weight difference between the 1 mg/kg (1,000 µg/kg) groups and vehicle controls was nearly 30%. A second factor in dose selection was the presence of karyomegaly and renal tubular atrophy in nearly 100% of the rats in the lowest exposure groups (0.0625 mg/kg [62.5 µg/kg]) in the 13-week studies. Therefore, doses of 21, 70, and 210 µg/kg ochratoxin A were selected for administration in corn oil by gavage 5 days per week for 2 years, with interim kills scheduled for 9 and 15 months. The purpose of the interim-kill examination was to characterize toxic lesions at a time when age-related renal changes would be expected to be minimal and less of a confounding factor, and secondly, to define more clearly time-to-tumor should the study prove to be positive, as was expected, since ochratoxin A exposure in mice had already been reported to cause kidney tumors (Kanisawa and Suzuki, 1978).

NINE-MONTH STUDIES

Administration of ochratoxin A for 9 months was associated with renal tubular epithelial karyomegalic changes in 100% of the rats in the 70 or 210 µg/kg groups (Table 12). This change was found in the inner cortex and was characterized by renal tubular epithelial cells having nuclei that were hyperchromatic, irregularly shaped, and often up to 10 times normal size. A single renal tubular cell adenoma was present in one high dose male rat. Renal tubular cell hyperplasia was present in both males and females. The hyperplasia was a small circumscribed lesion, often involving only one tubule. The hyperplasia did not cause compression of the adjacent parenchyma and was characterized by small, usually basophilic cells filling the renal tubule. A solitary pituitary gland carcinoma was found in a high dose female. This was not considered remarkable; however, it was felt it would be prudent to examine the pituitary gland as a target tissue for animals killed at 15 months.

FIFTEEN-MONTH STUDIES

Administration of ochratoxin A for 15 months was again associated with karyomegalic changes in 100% of the rats in the 70 and 210 µg/kg exposure groups (Table 13). Five additional renal tubular neoplasms were found, including two carcinomas in high dose males, a carcinoma in a mid dose male, and an adenoma in a mid dose and in a high dose male. An additional change found at 15 months in all high dose males and females was degeneration of the renal tubular epithelium. This lesion was characterized by reduction of the inner cortex, which contained disorganized tubules that were lined by cells containing scant cytoplasm. When the kidney was examined in a blind fashion, a subtle form of this change could be discerned in some rats killed at 9 months and some mid dose animals killed at 15 months. No difference in incidences of pituitary gland lesions between dosed and vehicle control animals was seen for either sex.

TABLE 12. NUMBERS OF RATS WITH SELECTED LESIONS IN THE NINE-MONTH GAVAGE STUDIES OF OCHRATOXIN A (a)

Site/Lesion	Male				Female			
	Vehicle Control	21 µg/kg	70 µg/kg	210 µg/kg	Vehicle Control	21 µg/kg	70 µg/kg	210 µg/kg
Renal tubule								
Cytoplasmic vacuolization	0	0	1	4	0	0	0	2
Karyomegaly	0	0	15	15	0	0	15	15
Epithelial hyperplasia	0	0	3	6	0	0	0	3
Adenoma	0	0	0	1	0	0	0	0
Pituitary gland/pars distalis								
Hyperplasia	0	0	1	1	0	3	0	2
Carcinoma	0	0	0	0	0	0	0	1

(a) Fifteen rats examined in each group

TABLE 13. NUMBERS OF RATS WITH SELECTED RENAL LESIONS IN THE FIFTEEN-MONTH GAVAGE STUDIES OF OCHRATOXIN A

Site/Lesion	Male				Female			
	Vehicle Control	21 µg/kg	70 µg/kg	210 µg/kg	Vehicle Control	21 µg/kg	70 µg/kg	210 µg/kg
Number examined	15	14	14	15	15	14	15	15
Kidney tubule epithelium								
Degeneration	0	0	0	15	0	0	0	15
Cytoplasmic vacuolization	0	0	1	5	0	0	0	0
Karyomegaly	0	0	14	15	0	0	15	15
Hyperplasia	0	0	6	0	0	0	1	0
Kidney tubule								
Adenoma	0	0	1	1	0	0	0	0
Carcinoma	0	0	1	2	0	0	0	0

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of high dose rats were 4%-7% lower than those of vehicle controls between week 18 and week 77 for males and between week 6 and week 89 for females (Table 14 and Figure 5). Mean body weights of rats in the lower dose groups were similar to those of vehicle controls throughout the studies. No compound-related clinical signs were observed.

Survival

Estimates of the probabilities of survival for male and female rats administered ochratoxin A at the doses used in these studies and for vehicle controls are shown in the Kaplan and Meier curves in Figure 6 and in Table 15. The survival of the low (after day 674), mid (after day 674), and high (after day 540) dosed groups of male rats was significantly lower than that of vehicle controls. No significant differences in survival were observed between any groups of female rats.

TABLE 14. MEAN BODY WEIGHTS OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF OCHRATOXIN A

Weeks on Study	Vehicle Control		21 micrograms/kg			70 micrograms/kg			210 micrograms/kg		
	Av. Wt. (grams)	No. Weighed	Av. Wt. (grams)	Wt. (percent of veh. controls)	No. Weighed	Av. Wt. (grams)	Wt. (percent of veh. controls)	No. Weighed	Av. Wt. (grams)	Wt. (percent of veh. controls)	No. Weighed
MALE											
0	172	80	174	101	80	171	99	80	173	101	80
1	194	80	196	101	80	195	101	80	194	100	80
2	213	80	214	100	80	215	101	80	212	100	80
3	234	78	239	102	80	236	101	80	233	100	80
4	249	78	260	104	80	255	102	80	249	100	80
5	269	78	279	104	80	274	102	80	268	100	80
6	284	78	296	104	80	291	102	80	285	100	80
7	295	78	305	103	80	301	102	80	292	99	80
8	303	78	312	103	80	311	103	80	298	98	80
9	319	78	327	103	80	322	101	80	309	97	80
10	326	78	336	103	80	331	102	80	315	97	80
11	342	78	349	102	80	343	100	80	326	95	80
12	350	78	356	102	80	355	101	80	335	96	80
13	353	78	363	103	80	361	102	80	342	97	80
18	382	78	392	103	80	387	101	80	367	96	80
21	402	78	412	102	80	406	101	80	386	96	80
25	416	78	421	101	80	419	101	80	397	95	80
29	434	78	440	101	80	432	100	(a) 79	413	95	(a) 79
33	448	78	456	102	80	448	100	80	425	95	80
37	459	78	466	102	80	457	100	80	430	94	80
41	462	(a,b) 58	465	101	(a,b) 52	457	99	(a,b) 62	431	93	(a,b) 54
45	468	63	468	100	62	463	99	63	439	94	65
49	478	63	478	100	62	475	99	63	448	94	65
53	483	63	479	99	62	477	99	63	453	94	65
57	490	62	492	100	62	485	99	62	461	94	64
61	493	62	497	101	59	490	99	62	470	95	61
65	494	62	501	101	58	491	99	62	476	96	59
69	496	(b) 47	506	102	(b) 44	494	100	(b) 47	478	96	(b) 44
73	493	45	502	102	42	489	99	46	474	96	43
77	493	43	500	101	42	491	100	(a) 43	475	96	(a) 39
81	492	42	498	101	40	492	100	39	478	97	35
85	487	(a) 41	499	102	(a) 39	491	101	(a) 35	478	98	(a) 31
89	486	42	494	102	40	486	100	37	471	97	33
93	485	42	495	102	36	481	99	37	474	98	28
97	480	42	484	101	33	471	98	35	467	97	27
101	473	40	480	101	30	462	98	33	465	98	24
104	464	39	477	103	27	460	99	26	449	97	23
FEMALE											
0	137	80	136	99	80	139	101	80	137	100	80
1	150	80	146	97	80	147	98	80	149	99	80
2	158	80	153	97	79	156	99	80	155	98	80
3	167	80	162	97	79	165	99	80	162	97	80
4	174	80	170	98	79	173	99	80	169	97	80
5	179	80	177	99	79	180	101	80	173	97	80
6	184	80	181	98	79	185	101	80	177	96	80
7	187	80	183	98	79	187	100	80	178	95	80
8	191	80	187	98	79	189	99	80	181	95	80
9	195	80	191	98	79	192	98	80	184	94	80
10	197	80	193	98	79	195	99	80	188	95	80
11	200	80	197	99	79	198	99	80	191	96	80
12	203	80	201	99	79	202	100	80	195	96	80
13	204	80	201	99	79	203	100	80	195	96	80
(c) 14	205	50	204	100	49	205	100	50	196	96	50
18	215	50	214	100	49	212	99	50	202	94	50
21	219	50	219	100	49	218	100	50	208	95	50
25	225	50	229	102	49	226	100	50	216	96	50
29	231	50	234	101	49	233	101	50	221	96	50
33	240	49	239	100	49	239	100	50	225	94	50
37	237	49	240	101	49	239	101	(a) 45	224	95	50
41	242	49	246	102	49	242	100	50	229	95	50
45	251	49	255	102	49	250	100	50	237	94	49
49	262	49	265	101	49	263	100	49	249	95	49
53	270	49	272	101	49	271	100	49	252	93	49
57	280	49	281	100	49	279	100	48	260	93	49
61	288	49	293	102	48	289	100	48	271	94	47
65	296	48	299	101	47	297	100	48	280	95	46
69	302	47	308	102	45	306	101	47	287	95	46
73	304	45	311	102	45	308	101	45	289	95	46
77	307	44	314	102	44	313	102	45	289	94	44
81	314	44	318	101	43	317	101	44	296	94	43
85	312	42	319	102	41	316	101	43	300	96	42
89	318	41	321	101	41	320	101	43	305	96	42
93	321	40	326	102	33	324	101	41	313	98	39
97	325	35	331	102	28	323	99	37	314	97	38
101	326	33	332	102	27	325	100	35	318	98	37
104	326	32	330	101	24	322	99	35	315	97	35

(a) The number of animals weighed was lower than the number of animals surviving.
(b) Interim kill occurred.
(c) Animals designated for interim kills were weighed separately after week 13.

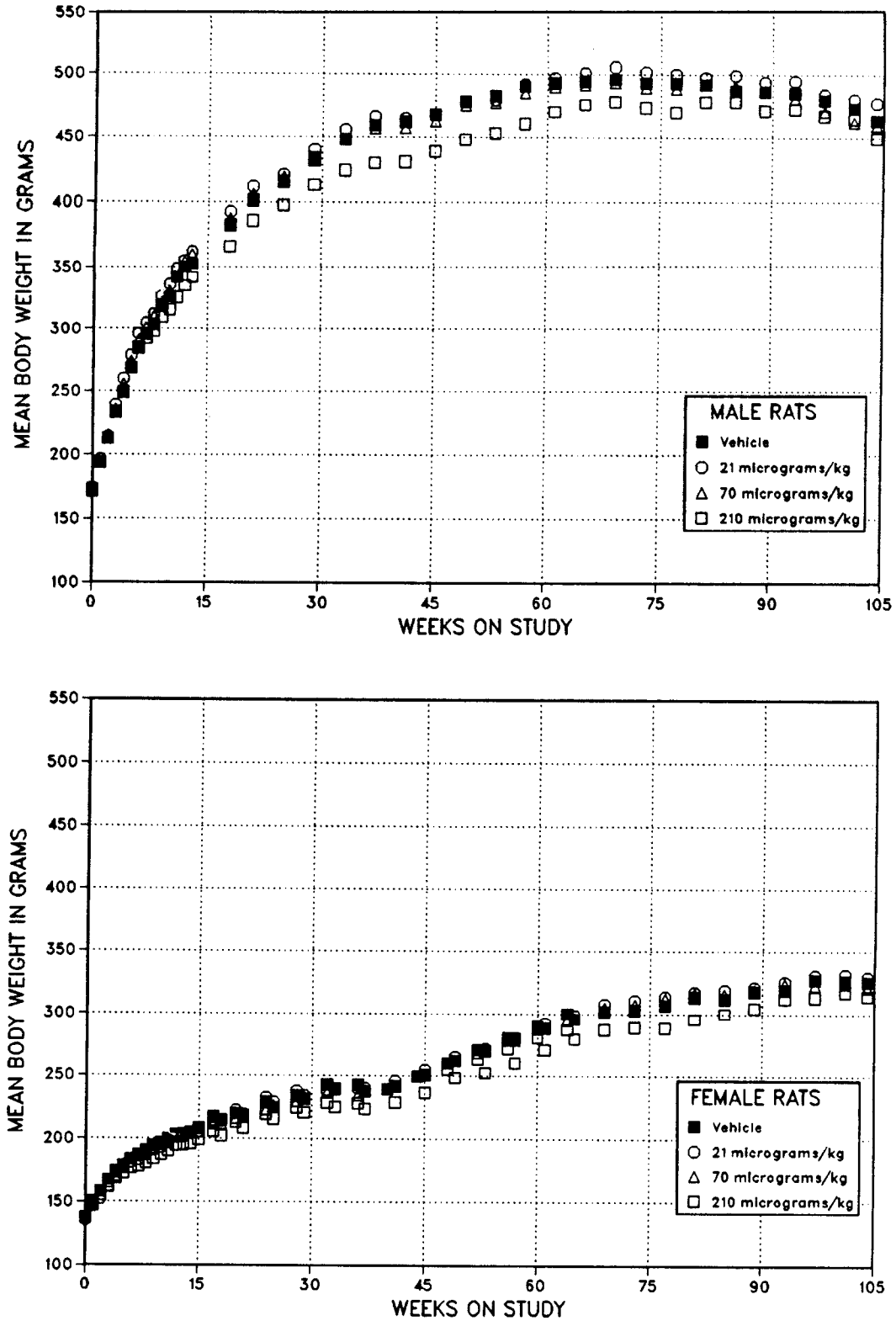

FIGURE 5. GROWTH CURVES FOR RATS ADMINISTERED OCHRATOXIN A IN CORN OIL BY GAVAGE FOR TWO YEARS

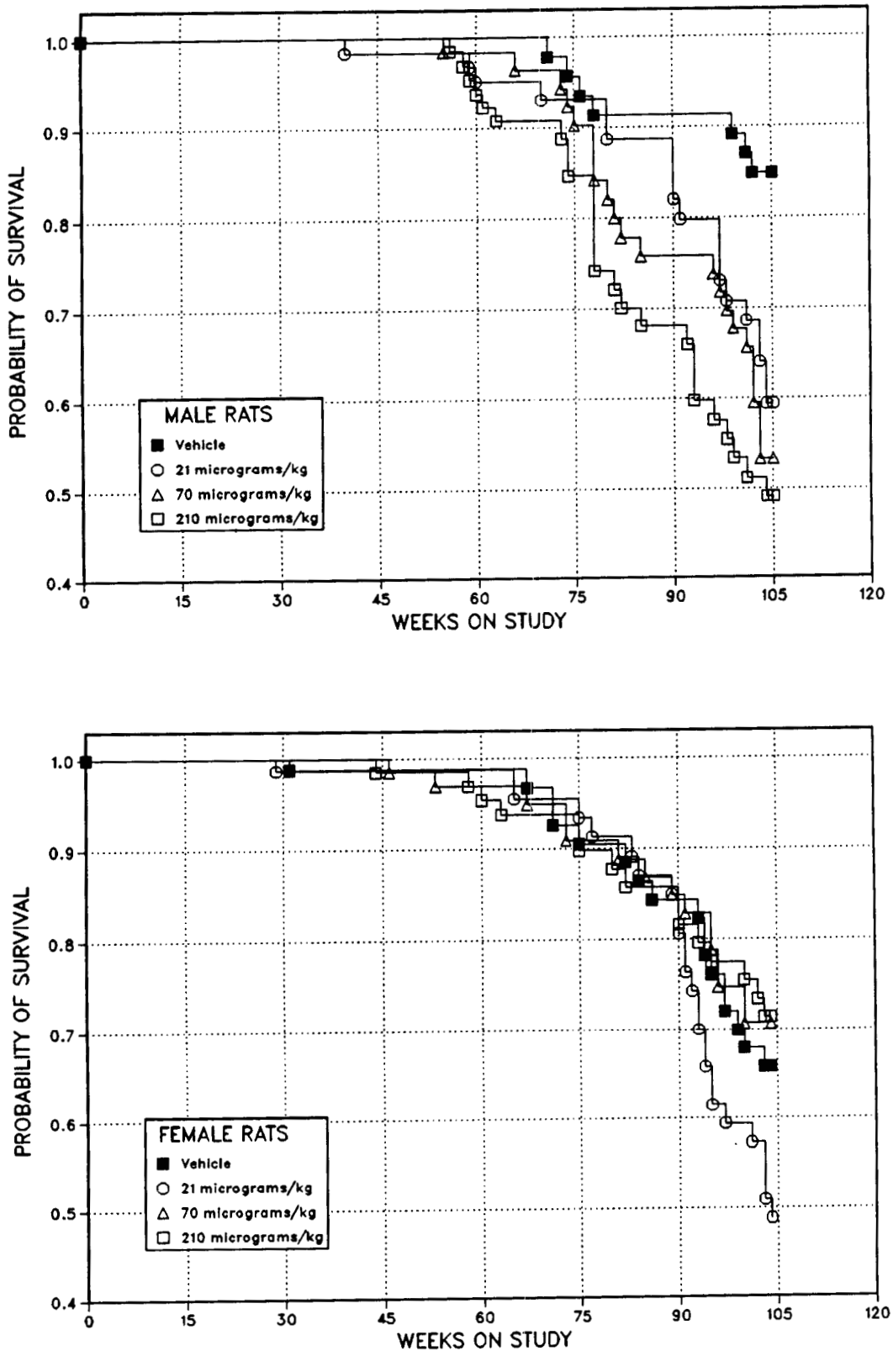

FIGURE 6. KAPLAN-MEIER SURVIVAL CURVES FOR RATS ADMINISTERED OCHRATOXIN A IN CORN OIL BY GAVAGE FOR TWO YEARS

TABLE 15. SURVIVAL OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF OCHRATOXIN A

	Vehicle Control	21 µg/kg	70 µg/kg	210 µg/kg
MALE (a)				
Animals initially in study	80	80	80	80
Nonaccidental deaths before termination (b)	7	19	23	26
Accidentally killed	4	6	2	1
Killed at 9 months	15	15	15	15
Killed at 15 months	15	(c) 14	(c) 14	15
Killed at termination	39	26	26	23
Survival P values (d)	0.001	0.011	0.002	<0.001
FEMALE (a)				
Animals initially in study	80	80	80	80
Nonaccidental deaths before termination (b)	17	25	15	15
Accidentally killed	1	3	0	0
Killed at 9 months	15	15	15	15
Killed at 15 months	15	(c) 14	15	15
Died during termination period	0	0	0	1
Killed at termination	32	23	35	34
Survival P values (d)	0.623	0.833	0.788	0.825

(a) First day of terminal-kill period: male--729, female--726
(b) Includes animals killed in a moribund condition
(c) Animals scheduled to be killed at 15 months but which died before the 15-month kill became part of the 2-year studies. This resulted in 51 rats per group for three groups. See also Table 21.
(d) The result of the life table trend test is in the vehicle control column, and the results of the life table pairwise comparisons with the vehicle controls are in the dosed columns.

Hematologic and Clinical Chemical Analysis and Urinalysis

Minor differences were observed for hematologic values between dosed and vehicle control animals, but none was considered to be of biologic significance (Tables 16 and 17). Results of serum chemical analyses were not clearly compound related (Table 18).

The urinalysis suggests that there may have been mild to moderate decreases in ability to concentrate urine. This was reflected by slight increases in urine volume and decreases in specific gravity in concentration tests in dosed animals as compared with vehicle controls (Tables 19 and 20).

TABLE 16. ANALYSIS OF HEMATOLOGIC DATA FOR MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF OCHRATOXIN A (a)

Analysis	Interval	Vehicle Control	21 µg/kg	70 µg/kg	210 µg/kg
Eosinophils (percent)	45 d	0.8 ± 0.16	1.2 ± 0.20	1.2 ± 0.18	1.2 ± 0.19
	3 mo	1.1 ± 0.18	1.2 ± 0.18	1.4 ± 0.26	1.3 ± 0.29
	9 mo	1.5 ± 0.21	2.0 ± 0.29	1.8 ± 0.21	1.7 ± 0.23
	15 mo	1.6 ± 0.41	2.0 ± 0.31	2.3 ± 0.54	2.4 ± 0.53
Hematocrit (percent)	45 d	52.1 ± 0.42	51.3 ± 0.43	(b) 50.1 ± 0.23	(b) 50.8 ± 0.39
	3 mo	50.0 ± 0.50	49.8 ± 0.45	49.2 ± 0.28	49.2 ± 0.26
	9 mo	46.7 ± 0.56	47.1 ± 0.33	47.5 ± 0.31	45.6 ± 0.39
	15 mo	46.7 ± 0.55	46.4 ± 0.70	46.9 ± 0.72	44.9 ± 0.46
Hemoglobin (g/dl)	45 d	17.0 ± 0.10	16.9 ± 0.11	(b) 16.5 ± 0.07	16.7 ± 0.11
	3 mo	16.4 ± 0.15	16.1 ± 0.12	(b) 15.9 ± 0.08	(b) 15.7 ± 0.09
	9 mo	15.8 ± 0.17	15.7 ± 0.14	15.7 ± 0.10	15.5 ± 0.15
	15 mo	15.9 ± 0.19	15.8 ± 0.25	15.9 ± 0.19	15.4 ± 0.13
Lymphocytes (percent)	45 d	74.2 ± 0.87	75.4 ± 1.12	74.0 ± 1.52	76.3 ± 0.79
	3 mo	77.9 ± 1.61	79.7 ± 1.32	72.9 ± 1.32	76.9 ± 1.63
	9 mo	59.2 ± 2.33	62.6 ± 1.78	65.9 ± 1.60	66 ± 1.14
	15 mo	52.0 ± 2.77	54.9 ± 2.80	55.2 ± 3.71	57 ± 2.55
Mean corpuscular hemoglobin (pg)	15 mo	16.6 ± 0.14	16.6 ± 0.11	16.5 ± 0.15	16.6 ± 0.05
Mean corpuscular hemoglobin concentration (g/dl)	15 mo	34.0 ± 0.20	34.0 ± 0.19	33.9 ± 0.22	34.2 ± 0.19
Mean corpuscular volume (μ^3)	45 d	51.6 ± 0.17	51.9 ± 0.12	51.8 ± 0.09	51.9 ± 0.11
	3 mo	49.6 ± 0.18	50.1 ± 0.15	(b) 50.5 ± 0.13	(b) 50.7 ± 0.15
	9 mo	(d) 46.9 ± 0.36	(d) 47.9 ± 0.27	(d) 48.1 ± 0.21	(d) 47.3 ± 0.25
	15 mo	48.9 ± 0.43	48.1 ± 0.64	48.7 ± 0.40	48.6 ± 0.25
Monocytes (percent)	45 d	1.03 ± 0.277	0.47 ± 0.164	(b) 0.13 ± 0.063	(b) 0.07 ± 0.046
	3 mo	0.53 ± 0.115	0.30 ± 0.128	0.23 ± 0.092	(b) 0.03 ± 0.033
	9 mo	0.23 ± 0.079	0.10 ± 0.056	0.03 ± 0.033	0.03 ± 0.033
	15 mo	0.00 ± 0.000	0.21 ± 0.114	0.07 ± 0.071	0.07 ± 0.067
Nucleated erythrocytes ($10^3/mm^3$)	45 d	0.67 ± 0.161	0.77 ± 0.184	0.60 ± 0.149	0.37 ± 0.176
	3 mo	0.13 ± 0.079	(e) 0.38 ± 0.115	0.37 ± 0.102	0.23 ± 0.149
	9 mo	0.73 ± 0.197	1.30 ± 0.226	0.77 ± 0.157	0.90 ± 0.188
	15 mo	1.20 ± 0.296	1.07 ± 0.355	0.79 ± 0.281	1.33 ± 0.319
Platelets ($10^3/mm^3$)	45 d	513 ± 11.4	511 ± 13.0	(b) 457 ± 12.0	(b) 442 ± 9.9
	3 mo	491 ± 11.7	499 ± 12.6	512 ± 13.9	(b) 441 ± 10.8
	9 mo	545 ± 15.0	(b) 474 ± 14.7	(b) 434 ± 10.6	(b) 338 ± 8.6
	15 mo	402 ± 18.8	435 ± 32.3	474 ± 16.6	462 ± 32.7
Erythrocytes ($10^6/mm^3$)	45 d	10.08 ± 0.07	9.87 ± 0.07	(b) 9.68 ± 0.05	(b) 9.76 ± 0.07
	3 mo	10.07 ± 0.09	9.89 ± 0.08	(b) 9.74 ± 0.05	(b) 9.67 ± 0.04
	9 mo	9.95 ± 0.097	9.82 ± 0.067	9.83 ± 0.058	(b) 9.59 ± 0.079
	15 mo	9.58 ± 0.143	9.53 ± 0.142	9.53 ± 0.139	9.25 ± 0.072
Reticulocytes ($10^6/mm^3$)	45 d	1.85 ± 0.109	1.91 ± 0.079	2.09 ± 0.099	1.84 ± 0.075
	3 mo	1.89 ± 0.087	2.09 ± 0.109	1.96 ± 0.106	2.08 ± 0.102
	9 mo	1.68 ± 0.120	(b) 1.19 ± 0.077	1.35 ± 0.088	(b) 1.19 ± 0.083
	15 mo	1.43 ± 0.072	1.69 ± 0.142	1.75 ± 0.127	1.40 ± 0.104
Segmented neutrophils (percent)	45 d	24.0 ± 0.86	23.0 ± 1.03	25.0 ± 1.44	22.1 ± 0.97
	3 mo	19.9 ± 1.70	18.8 ± 1.34	(b) 25.4 ± 1.23	21.7 ± 1.67
	9 mo	38.4 ± 2.41	34.6 ± 1.61	31.7 ± 1.59	31.4 ± 1.06
	15 mo	41.6 ± 1.93	42.9 ± 2.70	42.4 ± 3.46	40.5 ± 2.49
Leukocytes ($10^3/mm^3$)	45 d	6.27 ± 0.380	5.33 ± 0.241	5.72 ± 0.275	5.48 ± 0.276
	3 mo	6.58 ± 0.271	6.80 ± 0.322	(b) 5.57 ± 0.230	6.25 ± 0.274
	9 mo	6.05 ± 0.174	(b) 5.19 ± 0.156	(b) 5.14 ± 0.136	(b) 4.84 ± 0.166
	15 mo	4.13 ± 0.245	3.67 ± 0.212	5.30 ± 0.238	4.15 ± 0.296

(a) Mean ± standard error, P values vs. the vehicle controls by Dunn's test (Dunn, 1964) or by Shirley's test (Shirley, 1977); number of animals examined except as noted: 45-d, 3-mo, and 9-mo studies, 30; 15-mo studies, 15 for 0 and 210 µg/kg, 14 for 21 and 70 µg/kg.
(b) $P<0.01$
(c) Fourteen examined
(d) Fifteen examined
(e) Twenty-nine examined

TABLE 17. ANALYSIS OF HEMATOLOGIC DATA FOR FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF OCHRATOXIN A (a)

Analysis	Interval	Vehicle Control	21 µg/kg	70 µg/kg	210 µg/kg
Eosinophils (percent)	45 d	0.9 ± 0.20	1.2 ± 0.18	1.4 ± 0.31	1.4 ± 0.35
	3 mo	1.5 ± 0.26	1.4 ± 0.29	1.1 ± 0.20	1.2 ± 0.25
	9 mo	1.6 ± 0.31	1.8 ± 0.35	1.3 ± 0.27	1.7 ± 0.34
	15 mo	2.1 ± 0.30	2.0 ± 0.31	2.5 ± 0.49	1.4 ± 0.34
Hematocrit (percent)	45 d	49.8 ± 0.32	50.1 ± 0.40	50.2 ± 0.36	(b) 51.5 ± 0.40
	3 mo	47.6 ± 0.43	47.5 ± 0.33	48.2 ± 0.30	48.0 ± 0.37
	9 mo	51.7 ± 0.40	50.8 ± 0.39	51.0 ± 0.42	50.8 ± 0.33
	15 mo	47.7 ± 0.57	46.9 ± 0.63	46.8 ± 0.34	45.6 ± 0.59
Hemoglobin (g/dl)	45 d	16.0 ± 0.54	16.6 ± 0.15	16.5 ± 0.11	16.8 ± 0.12
	3 mo	15.6 ± 0.13	15.5 ± 0.13	15.7 ± 0.09	15.6 ± 0.12
	9 mo	16.1 ± 0.13	15.9 ± 0.12	15.8 ± 0.13	15.8 ± 0.09
	15 mo	15.8 ± 0.17	15.7 ± 0.16	15.7 ± 0.12	15.3 ± 0.19
Lymphocytes (percent)	45 d	81.4 ± 1.15	82.3 ± 1.09	82.0 ± 1.30	83.2 ± 0.96
	3 mo	79.4 ± 1.03	76.0 ± 1.31	78.1 ± 1.35	80.7 ± 1.16
	9 mo	77.0 ± 1.79	76.8 ± 1.77	80.8 ± 1.61	77.6 ± 2.01
	15 mo	67.7 ± 1.18	62.4 ± 1.52	61.7 ± 2.07	66.5 ± 1.87
Mean corpuscular hemoglobin (pg)	15 mo	18.4 ± 0.09	18.6 ± 0.13	18.4 ± 0.06	18.4 ± 0.09
Mean corpuscular hemoglobin concentration (g/dl)	15 mo	33.1 ± 0.15	33.5 ± 0.24	33.5 ± 0.17	33.4 ± 0.22
Mean corpuscular volume (μ^3)	45 d	53.6 ± 0.10	53.7 ± 0.13	53.9 ± 0.14	(b) 54.4 ± 0.12
	3 mo	52.4 ± 0.12	52.8 ± 0.14	(b) 52.9 ± 0.10	(b) 53.3 ± 0.18
	9 mo	57.2 ± 0.11	56.8 ± 0.14	57.0 ± 0.23	57.3 ± 0.15
	15 mo	55.6 ± 0.32	55.6 ± 0.20	55.0 ± 0.22	54.9 ± 0.21
Monocytes (percent)	45 d	0.20 ± 0.088	0.17 ± 0.069	0.07 ± 0.046	0.10 ± 0.074
	3 mo	0.03 ± 0.034	0.03 ± 0.034	0.03 ± 0.033	0.07 ± 0.037
	9 mo	0.07 ± 0.067	0.03 ± 0.033	0.03 ± 0.033	0.00 ± 0.000
	15 mo	0.07 ± 0.067	0.29 ± 0.163	0.20 ± 0.107	0.13 ± 0.091
Nucleated erythrocytes ($10^3/mm^3$)	45 d	0.60 ± 0.163	0.77 ± 0.157	0.37 ± 0.112	0.87 ± 0.213
	3 mo	0.40 ± 0.123	0.72 ± 0.148	0.53 ± 0.184	0.97 ± 0.195
	9 mo	1.07 ± 0.253	1.00 ± 0.238	2.13 ± 0.377	1.27 ± 0.291
	15 mo	1.53 ± 0.307	2.29 ± 0.474	2.80 ± 0.757	3.93 ± 0.746
Platelets ($10^3/mm^3$)	45 d	543 ± 15.8	(b) 493 ± 11.9	(e) 504 ± 13.8	(e) 531 ± 12.0
	3 mo	455 ± 21.5	427 ± 20.4	475 ± 13.2	442 ± 20.8
	9 mo	319 ± 14.1	(b) 374 ± 16.0	(b) 381 ± 11.5	(b) 372 ± 15.2
	15 mo	399 ± 24.0	345 ± 16.1	382 ± 11.7	409 ± 9.8
Erythrocytes ($10^6/mm^3$)	45 d	9.30 ± 0.057	9.33 ± 0.072	9.32 ± 0.056	9.44 ± 0.066
	3 mo	9.06 ± 0.073	8.98 ± 0.066	9.13 ± 0.052	8.99 ± 0.067
	9 mo	9.02 ± 0.062	8.94 ± 0.063	8.94 ± 0.066	8.87 ± 0.057
	15 mo	8.59 ± 0.114	8.43 ± 0.113	8.49 ± 0.062	8.29 ± 0.103
Reticulocytes ($10^6/mm^3$)	45 d	1.98 ± 0.057	1.88 ± 0.072	2.37 ± 0.546	1.89 ± 0.085
	3 mo	2.14 ± 0.108	1.82 ± 0.111	1.75 ± 0.107	1.77 ± 0.093
	9 mo	1.95 ± 0.524	1.67 ± 0.095	1.77 ± 0.087	1.62 ± 0.104
	15 mo	1.99 ± 0.150	2.17 ± 0.116	1.64 ± 0.082	1.75 ± 0.154
Segmented neutrophils (percent)	45 d	17.2 ± 1.24	16.5 ± 1.09	16.5 ± 1.25	14.9 ± 0.96
	3 mo	19.1 ± 0.95	22.5 ± 1.27	20.8 ± 1.33	18.0 ± 1.11
	9 mo	21.2 ± 1.67	21.3 ± 1.57	17.8 ± 1.56	20.5 ± 1.86
	15 mo	30.1 ± 1.17	34.4 ± 1.47	35.5 ± 1.83	31.6 ± 1.90
Leukocytes ($10^3/mm^3$)	45 d	5.76 ± 0.269	5.47 ± 0.215	5.07 ± 0.235	5.51 ± 0.251
	3 mo	5.40 ± 0.189	5.38 ± 0.236	5.29 ± 0.137	5.38 ± 0.211
	9 mo	4.41 ± 0.207	(b) 3.78 ± 0.169	(b) 3.30 ± 0.078	(b) 3.16 ± 0.089
	15 mo	(c) 3.80 ± 0.265	3.63 ± 0.317	(b) 2.73 ± 0.172	3.45 ± 0.197

(a) Mean ± standard error, P values vs. the vehicle controls by Dunn's test (Dunn, 1964) or by Shirley's test (Shirley, 1977); number of animals examined except as noted: 45-d and 3-mo studies, 30; 3-mo and 9-mo studies, 30 except for 29 in the 21 µg/kg group; 15-mo studies, 15 except for 14 in the 21 µg/kg group.
(b) $P<0.01$
(c) Fourteen examined
(d) Thirteen examined
(e) Twenty-nine examined

TABLE 18. ANALYSIS OF SERUM CHEMICAL DATA FOR RATS IN THE TWO-YEAR GAVAGE STUDY OF OCHRATOXIN A (a)

Analysis	Interval	Vehicle Control	21 µg/kg	70 µg/kg	210 µg/kg
MALE					
Blood urea nitrogen (mg/dl)	3 d	19.9 ± 0.47	19.6 ± 0.86	18.4 ± 0.45	18.8 ± 0.40
	10 d	17.0 ± 0.61	17.4 ± 0.72	(b) 19.0 ± 0.40	(b) 18.9 ± 0.56
	45 d	15.4 ± 0.32	16.1 ± 0.32	15.2 ± 0.32	15.5 ± 0.31
	3 mo	13.5 ± 0.48	13.0 ± 0.36	14.1 ± 0.51	13.2 ± 0.28
	6 mo	13.0 ± 0.35	13.5 ± 0.32	12.9 ± 0.27	12.1 ± 0.18
	9 mo	12.8 ± 0.33	13.4 ± 0.54	12.8 ± 0.30	12.7 ± 0.29
	12 mo	14.1 ± 0.25	14.8 ± 1.44	13.4 ± 0.24	(b) 12.7 ± 0.25
	15 mo	12.1 ± 0.36	11.5 ± 0.34	12.0 ± 0.50	11.3 ± 0.25
Creatinine (mg/dl)	3 d	0.64 ± 0.022	0.66 ± 0.049	0.64 ± 0.036	0.61 ± 0.042
	10 d	0.69 ± 0.033	0.62 ± 0.037	0.62 ± 0.024	0.63 ± 0.033
	45 d	0.67 ± 0.036	0.77 ± 0.059	0.79 ± 0.026	0.74 ± 0.028
	3 mo	0.81 ± 0.072	0.64 ± 0.038	0.69 ± 0.047	0.73 ± 0.027
	6 mo	0.60 ± 0.016	0.67 ± 0.024	(b) 0.71 ± 0.011	(b) 0.75 ± 0.012
	9 mo	0.73 ± 0.023	0.71 ± 0.037	0.68 ± 0.028	0.73 ± 0.024
	12 mo	0.69 ± 0.045	0.67 ± 0.027	0.68 ± 0.040	0.73 ± 0.025
	15 mo	0.80 ± 0.106	0.84 ± 0.060	0.78 ± 0.053	0.77 ± 0.055
Glucose (mg/dl)	3 d	111 ± 5.0	115 ± 6.4	109 ± 3.8	113 ± 4.4
	10 d	121 ± 4.5	115 ± 5.9	130 ± 5.2	129 ± 4.9
	45 d	102 ± 3.8	111 ± 3.2	102 ± 4.6	101 ± 4.6
	3 mo	113 ± 3.5	108 ± 2.6	111 ± 4.3	110 ± 3.1
	6 mo	102 ± 2.0	108 ± 3.3	107 ± 2.7	106 ± 1.8
	9 mo	92 ± 3.0	87 ± 2.0	84 ± 2.2	(b) 81 ± 2.7
	12 mo	121 ± 3.4	116 ± 3.9	113 ± 2.0	116 ± 3.0
	15 mo	115 ± 3.4	137 ± 8.0	122 ± 4.2	116 ± 2.2
FEMALE					
Blood urea nitrogen (mg/dl)	3 d	15.2 ± 0.29	(b) 17.0 ± 0.35	16.6 ± 0.51	15.6 ± 0.32
	10 d	17.8 ± 0.86	18.3 ± 0.63	18.5 ± 0.54	17.7 ± 0.38
	45 d	13.4 ± 0.49	13.4 ± 0.40	13.7 ± 0.35	13.8 ± 0.26
	3 mo	17.9 ± 0.62	17.2 ± 0.55	18.8 ± 0.90	17.3 ± 0.57
	6 mo	13.8 ± 0.29	14.7 ± 0.34	13.8 ± 0.45	14.6 ± 0.35
	9 mo	17.0 ± 1.53	14.6 ± 0.36	14.9 ± 0.40	14.9 ± 0.24
	12 mo	14.2 ± 0.64	14.6 ± 0.43	13.3 ± 0.46	12.7 ± 0.36
	15 mo	12.3 ± 0.28	12.5 ± 0.27	12.6 ± 0.42	11.0 ± 0.28
Creatinine (mg/dl)	3 d	0.61 ± 0.032	0.58 ± 0.019	0.59 ± 0.019	0.59 ± 0.016
	10 d	0.66 ± 0.041	(b) 0.80 ± 0.034	0.67 ± 0.027	0.73 ± 0.033
	45 d	0.60 ± 0.049	0.62 ± 0.021	0.56 ± 0.019	0.61 ± 0.022
	3 mo	0.74 ± 0.029	0.71 ± 0.028	0.75 ± 0.053	0.77 ± 0.035
	6 mo	0.63 ± 0.018	0.57 ± 0.019	0.67 ± 0.027	0.68 ± 0.015
	9 mo	0.91 ± 0.137	(b) 0.65 ± 0.023	(b) 0.64 ± 0.026	0.74 ± 0.023
	12 mo	0.65 ± 0.017	0.59 ± 0.013	0.68 ± 0.031	0.75 ± 0.027
	15 mo	0.75 ± 0.038	0.76 ± 0.039	0.75 ± 0.029	0.81 ± 0.021
Glucose (mg/dl)	3 d	85 ± 2.8	88 ± 4.2	92 ± 3.2	89 ± 3.1
	10 d	119 ± 5.4	126 ± 5.8	128 ± 5.4	128 ± 6.4
	45 d	83 ± 2.7	86 ± 4.9	79 ± 2.5	76 ± 3.6
	3 mo	104 ± 4.0	103 ± 3.5	99 ± 3.2	109 ± 4.4
	6 mo	102 ± 1.7	104 ± 2.3	102 ± 2.2	104 ± 2.3
	9 mo	110 ± 4.4	106 ± 2.8	105 ± 2.8	(b) 94 ± 2.0
	12 mo	110 ± 2.3	103 ± 2.7	108 ± 3.7	115 ± 4.6
	15 mo	102 ± 3.2	114 ± 4.9	99 ± 2.8	93 ± 3.1

(a) Mean ± standard error, P values vs. the vehicle controls by Dunn's test (Dunn, 1964) or by Shirley's test (Shirley, 1977); number of animals examined except as noted: 6 mo or less, 30; 9 mo, 30 except for 29 in the female 21 µg/kg group; 12 and 15 mo, 15 except for 14 in the 21 µg/kg groups and 14 in the male 70 µg/kg group at 15 mo.
(b) $P<0.01$

TABLE 19. RESULTS OF URINALYSIS FOR MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF OCHRATOXIN A (a)

Analysis	Interval	Vehicle Control	21 µg/kg	70 µg/kg	210 µg/kg
Specific gravity	3 d	1.031 ± 0.003	1.027 ± 0.002	1.029 ± 0.003	1.036 ± 0.003
	10 d	(b) 1.026 ± 0.003	1.023 ± 0.003	1.024 ± 0.003	1.033 ± 0.004
	45 d	1.022 ± 0.001	1.024 ± 0.002	1.021 ± 0.002	1.028 ± 0.002
	3 mo	1.041 ± 0.002	1.042 ± 0.005	1.039 ± 0.003	1.037 ± 0.002
	6 mo	1.033 ± 0.002	1.034 ± 0.002	1.029 ± 0.002	1.028 ± 0.002
	9 mo	1.034 ± 0.002	1.032 ± 0.002	1.029 ± 0.001	(c) 1.025 ± 0.001
	12 mo	1.045 ± 0.004	1.047 ± 0.004	1.034 ± 0.002	1.033 ± 0.003
	15 mo	1.035 ± 0.004	1.037 ± 0.004	1.031 ± 0.002	1.027 ± 0.002
Specific gravity (concentration studies)	7 d	1.087 ± 0.002	(d) 1.088 ± 0.001	(d) 1.088 ± 0.002	(b) 1.089 ± 0.002
	47 d	(d) 1.086 ± 0.001	1.088 ± 0.001	1.086 ± 0.001	(c,d) 1.081 ± 0.001
	6 mo	(e) 1.070 ± 0.002	(f) 1.075 ± 0.001	(d) 1.071 ± 0.001	(c) 1.046 ± 0.001
	12 mo	(g) 1.065 ± 0.005	(h) 1.071 ± 0.003	(i) 1.058 ± 0.002	(c) 1.042 ± 0.001
Urea nitrogen (mg/dl)	3 d	1,288 ± 118	1,007 ± 110	1,217 ± 128	1,622 ± 155
	10 d	1,417 ± 213	1,132 ± 173	1,077 ± 157	1,679 ± 212
	45 d	1,406 ± 133	1,393 ± 156	1,312 ± 130	1,614 ± 131
	3 mo	2,105 ± 163	2,283 ± 290	2,197 ± 201	1,710 ± 149
	6 mo	1,720 ± 148	1,787 ± 129	1,588 ± 116	1,272 ± 120
	9 mo	1,804 ± 101	1,612 ± 94	(c) 1,363 ± 83	(c) 1,184 ± 61
	12 mo	2,683 ± 211	2,814 ± 255	(c) 1,787 ± 124	(c) 1,817 ± 164
	15 mo	1,965 ± 227	2,048 ± 213	1,669 ± 107	1,364 ± 81
Creatinine (mg/dl)	3 d	54.6 ± 5.82	51.6 ± 5.68	57.1 ± 6.44	75.1 ± 7.02
	10 d	64.9 ± 10.07	54.8 ± 8.33	50.0 ± 7.40	80.8 ± 9.76
	45 d	70.0 ± 6.90	77.3 ± 9.75	75.8 ± 7.19	92.8 ± 8.26
	3 mo	137.4 ± 10.83	155.3 ± 20.02	152.0 ± 14.64	123.9 ± 10.11
	6 mo	140.0 ± 9.84	142.8 ± 10.02	131.5 ± 9.43	110.8 ± 8.66
	9 mo	170.3 ± 8.58	157.3 ± 9.62	(c) 126.9 ± 9.41	(c) 103.8 ± 5.81
	12 mo	257.5 ± 19.20	334.0 ± 36.10	207.1 ± 13.48	(c) 159.6 ± 12.71
	15 mo	202.3 ± 16.19	232.7 ± 28.91	174.8 ± 11.58	149.4 ± 8.97
Glucose (mg/dl)	3 mo	27.3 ± 1.56	28.0 ± 2.95	26.4 ± 2.44	31.9 ± 2.02
	6 mo	22.3 ± 1.98	20.4 ± 1.65	20.0 ± 1.46	22.5 ± 1.50
	9 mo	45.3 ± 2.05	43.4 ± 2.23	38.8 ± 2.24	(c) 37.1 ± 1.94
	12 mo	59.3 ± 5.45	59.6 ± 6.51	(c) 45.1 ± 1.92	(c) 43.5 ± 2.95
	15 mo	54.0 ± 6.76	53.8 ± 6.47	45.5 ± 3.44	47.1 ± 3.36
Protein (mg/dl)	3 mo	607 ± 33.9	645 ± 63.2	551 ± 48.5	653 ± 40.9
	6 mo	495 ± 34.1	500 ± 33.3	470 ± 31.1	536 ± 30.3
	9 mo	521 ± 27.4	504 ± 26.1	505 ± 24.0	504 ± 25.5
	12 mo	812 ± 87.0	759 ± 71.1	607 ± 54.3	558 ± 34.6
	15 mo	747 ± 95.1	694 ± 86.0	576 ± 62.7	541 ± 41.3
Volume (ml/16 h)	3 d	7.3 ± 0.72	8.3 ± 0.99	8.1 ± 1.06	6.0 ± 0.71
	10 d	7.6 ± 0.83	10.6 ± 1.13	9.3 ± 1.00	6.9 ± 0.90
	45 d	9.2 ± 0.72	9.4 ± 0.83	9.7 ± 0.82	6.9 ± 0.56
	3 mo	4.7 ± 0.39	5.4 ± 0.52	5.3 ± 0.69	5.4 ± 0.52
	6 mo	5.8 ± 0.32	5.9 ± 0.36	6.8 ± 0.41	7.2 ± 0.46
	9 mo	5.3 ± 0.22	5.0 ± 0.30	6.2 ± 0.43	6.9 ± 0.50
	12 mo	3.9 ± 0.40	3.5 ± 0.33	(c) 5.3 ± 0.31	(c) 5.8 ± 0.45
	15 mo	4.7 ± 0.41	4.5 ± 0.46	5.0 ± 0.41	5.7 ± 0.43

(a) Mean ± standard error, P values vs. the vehicle controls by Dunn's test (Dunn, 1964) or by Shirley's test (Shirley, 1977); number of animals examined except as noted: 9 mo or less, 30; 12 mo, 15 except for 14 in the 21 µg/kg group; 15 mo, 15 vehicle controls, 14 in the 21 µg/kg and 210 µg/kg groups; and 13 in the 70 µg/kg group.
(b) Twenty-nine examined
(c) $P<0.01$
(d) Twenty-eight examined
(e) Twenty-three examined
(f) Twenty-five examined
(g) Ten examined
(h) Twelve examined
(i) Thirteen examined

TABLE 20. RESULTS OF URINALYSIS FOR FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF OCHRATOXIN A (a)

Analysis	Interval	Vehicle Control	21 µg/kg	70 µg/kg	210 µg/kg
Specific gravity	3 d	(b) 1.014 ± 0.002	1.020 ± 0.003	1.017 ± 0.002	1.017 ± 0.003
	10 d	1.014 ± 0.001	1.016 ± 0.002	1.016 ± 0.002	1.018 ± 0.002
	45 d	1.018 ± 0.002	1.023 ± 0.002	1.018 ± 0.002	1.014 ± 0.001
	3 mo	1.023 ± 0.001	1.027 ± 0.003	1.022 ± 0.002	(c) 1.017 ± 0.001
	6 mo	1.024 ± 0.002	1.025 ± 0.003	1.024 ± 0.003	(c) 1.017 ± 0.001
	9 mo	1.027 ± 0.002	1.029 ± 0.002	1.022 ± 0.001	1.023 ± 0.002
	12 mo	1.041 ± 0.005	1.036 ± 0.003	1.029 ± 0.002	(c) 1.025 ± 0.003
	15 mo	1.022 ± 0.001	1.026 ± 0.002	1.024 ± 0.001	1.019 ± 0.001
Specific gravity (concentration studies)	7 d	(d) 1.080 ± 0.001	(e) 1.079 ± 0.001	(c) 1.053 ± 0.004	(c) 1.047 ± 0.032
	47 d	1.071 ± 0.002	(b) 1.078 ± 0.002	(b) 1.071 ± 0.001	(c) 1.065 ± 0.002
	6 mo	1.081 ± 0.001	1.079 ± 0.001	(c) 1.062 ± 0.002	(c) 1.052 ± 0.001
	12 mo	1.075 ± 0.002	(f) 1.079 ± 0.002	(c) 1.060 ± 0.002	(c,g) 1.050 ± 0.002
Urea nitrogen (mg/dl)	3 d	(h) 773 ± 145	(i) 960 ± 224	(i) 824 ± 170	(j) 1,081 ± 293
	10 d	801 ± 89	788 ± 111	798 ± 86	829 ± 120
	45 d	1,003 ± 94	1,244 ± 136	933 ± 114	740 ± 59
	3 mo	1,644 ± 116	1,776 ± 184	1,337 ± 169	(c) 1,043 ± 83
	6 mo	1,448 ± 139	1,582 ± 187	1,403 ± 148	(c) 914 ± 71
	9 mo	1,698 ± 117	1,851 ± 145	1,344 ± 82	1,323 ± 103
	12 mo	2,603 ± 292	2,308 ± 180	(c) 1,730 ± 124	(c) 1,375 ± 143
	15 mo	1,423 ± 115	1,688 ± 112	1,390 ± 69	(c) 963 ± 75
Creatinine (mg/dl)	3 d	(h) 28.9 ± 5.01	(i) 36.0 ± 8.97	(i) 32.1 ± 6.80	(j) 37.8 ± 12.35
	10 d	31.4 ± 3.01	32.1 ± 5.04	31.9 ± 3.85	33.2 ± 3.82
	45 d	55.1 ± 5.33	66.0 ± 8.30	50.3 ± 6.38	38.7 ± 3.24
	3 mo	89.9 ± 6.26	101.5 ± 10.96	78.9 ± 7.30	(c) 55.9 ± 4.26
	6 mo	103.9 ± 9.17	107.1 ± 14.62	95.8 ± 11.13	(c) 60.2 ± 4.36
	9 mo	106.4 ± 6.94	122.8 ± 10.67	85.8 ± 5.68	(c) 76.3 ± 5.82
	12 mo	169 ± 20.9	170 ± 16.1	113 ± 8.4	(c) 97 ± 10.7
	15 mo	107 ± 9.0	122 ± 9.5	98 ± 4.7	78 ± 7.1
Glucose (mg/dl)	45 d	14.1 ± 1.61	16.2 ± 2.05	11.8 ± 1.77	11.9 ± 1.60
	3 mo	10.3 ± 0.84	12.9 ± 1.61	12.5 ± 1.32	10.2 ± 0.71
	6 mo	14.5 ± 2.05	12.8 ± 1.88	13.9 ± 1.44	9.7 ± 0.81
	9 mo	28.2 ± 1.88	31.2 ± 2.27	24.0 ± 1.44	26.4 ± 1.72
	12 mo	42.8 ± 3.70	50.4 ± 4.07	39.1 ± 2.46	34.3 ± 3.49
	15 mo	31.5 ± 2.79	37.4 ± 2.18	33.1 ± 1.69	28.9 ± 2.26
Protein (mg/dl)	45 d	175 ± 18.6	205 ± 16.3	158 ± 13.0	158 ± 11.3
	3 mo	230 ± 14.1	267 ± 23.7	228 ± 14.9	204 ± 11.1
	6 mo	262 ± 18.2	284 ± 27.2	283 ± 21.1	228 ± 14.4
	9 mo	297 ± 16.7	327 ± 16.7	274 ± 11.4	307 ± 17.2
	12 mo	358 ± 23.2	369 ± 22.6	326 ± 18.2	348 ± 30.3
	15 mo	247 ± 23.1	265 ± 14.2	265 ± 18.9	283 ± 23.3
Volume (ml/16 h)	3 d	12.7 ± 1.30	10.0 ± 1.18	10.2 ± 1.00	10.8 ± 0.98
	10 d	10.2 ± 0.85	8.7 ± 0.67	9.3 ± 0.84	8.0 ± 0.61
	45 d	6.9 ± 0.75	5.7 ± 0.43	7.5 ± 0.52	8.6 ± 0.69
	3 mo	4.5 ± 0.40	4.4 ± 0.63	5.6 ± 0.54	(c) 6.2 ± 0.49
	6 mo	5.8 ± 0.48	6.3 ± 0.63	6.3 ± 0.55	7.8 ± 0.53
	9 mo	5.2 ± 0.51	4.4 ± 0.30	6.4 ± 0.49	(c) 7.1 ± 0.66
	12 mo	3.2 ± 0.27	3.0 ± 0.26	4.3 ± 0.26	(c) 5.2 ± 0.52
	15 mo	4.7 ± 0.47	4.0 ± 0.33	4.4 ± 0.21	(c) 6.6 ± 0.61

(a) Mean ± standard error, P values vs. the vehicle controls by Dunn's test (Dunn, 1964) or by Shirley's test (Shirley, 1977); number of animals examined except as noted: 9 mo or less, 30 except for 29 in the 21 µg/kg group at 9 mo; 12 and 15 mo, 15 except for 14 in the 21 µg/kg groups.
(b) Twenty-nine examined
(c) $P<0.01$
(d) Twenty-seven examined
(e) Twenty-eight examined
(f) Thirteen examined
(g) Twelve examined
(h) Twenty-four examined
(i) Eighteen examined
(j) Twenty-one examined

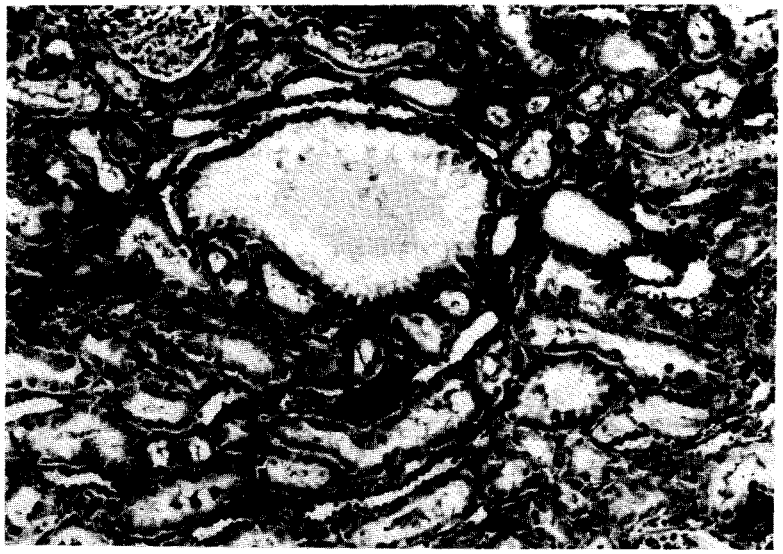

Figure 7. A dilated tubule lined by plump epithelial cells (arrow) was diagnosed as proliferation to distinguish the lesion from typical cysts, which are lined by flattened epithelial cells. Cells lining the proliferations were often 1 to 2 cell layers thick, suggesting that some cell proliferation had occurred. (H&E stain, magnification 40×)

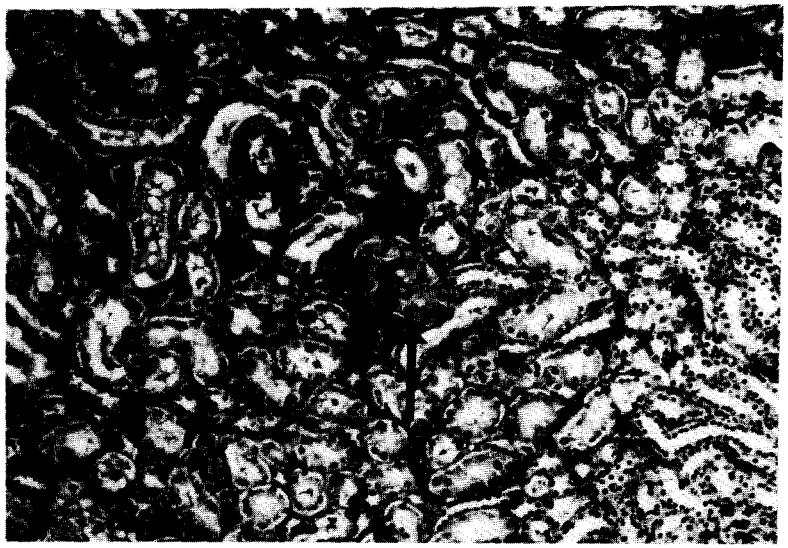

Figure 8. A focal area of hyperplasia involving one tubule. Cells within these lesions often appeared similar to those found within adenomas. (H&E stain, magnification 40×)

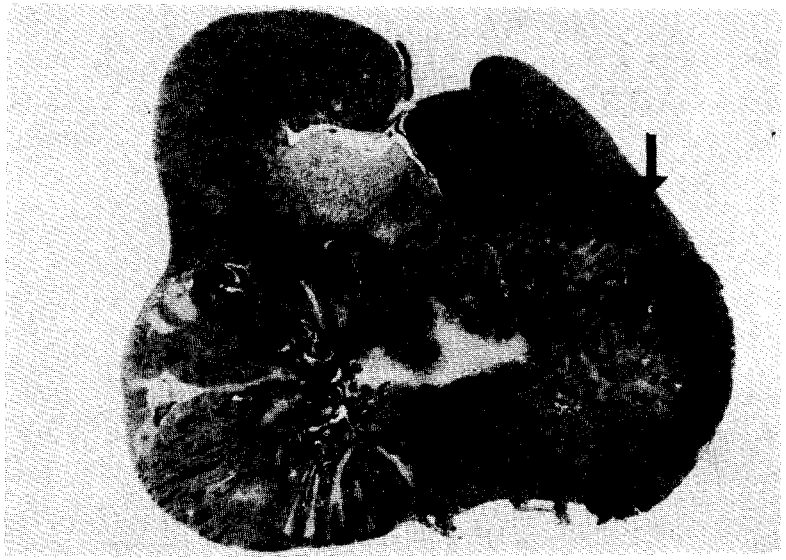

Figure 9. A large tubular cell carcinoma (arrow heads) replacing most of the kidney cortex and bulging above the renal capsule. The pale area in the center of the tumor represents necrosis, where the tumor apparently outgrew its blood supply. A portion of normal renal cortex and medulla can be recognized. (H&E stain, magnification 3.5×)

Figure 10. Much of the lung has been replaced by numerous metastases from a renal cell carcinoma. The lung was the most frequent site of metastases, being involved in 16 of 17 cases. (H&E stain, magnification 7.5×)

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, mammary gland, tongue, and hematopoietic system.

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

Kidney: The administration of ochratoxin A to male and female rats caused a spectrum of degenerative and proliferative changes in the kidney (Tables 21 and 22). The predominant nonneoplastic lesion in dosed rats was degeneration of the renal tubular epithelium in the inner cortex and the outer stripe of the outer medulla. Karyomegaly (the enlargement of nuclei in the tubular epithelium) and cytoplasmic alteration consisting of individual tubules lined by enlarged cells containing granular eosinophilic cytoplasm (onocytes) were also frequent findings. Cysts were characterized by markedly dilated tubules with a single layer of epithelium in the cortex of the kidney. Similarly dilated tubules containing multiple layers of enlarged epithelial cells were diagnosed as proliferation (Figure 7). Foci of hyperplasia consisted of focally enlarged tubules in the cortex filled with epithelial cells (Figure 8). Similar but larger lesions in which all tubular structure was obliterated by the proliferating mass of cells were diagnosed as adenomas. Adenomas were relatively well circumscribed and showed minimal cellular atypia. Carcinomas were generally larger (up to 3 cm in diameter, Figure 9) and were less well circumscribed than adenomas; those that metastasized were at least 1 cm in diameter. Many of the carcinomas had areas of necrosis within the tumor. The neoplastic cells of the carcinomas showed marked cellular atypia, and numerous cells were in mitosis. These neoplasms had a propensity to metastasize, as shown by distant metastases in 17 males and in 1 female with renal tubular cell carcinomas (Figure 10).

TABLE 21. NUMBERS OF RATS WITH RENAL LESIONS IN THE TWO-YEAR GAVAGE STUDIES OF OCHRATOXIN A

	Male				Female			
Site/Lesion	Vehicle Control	21 µg/kg	70 µg/kg	210 µg/kg	Vehicle Control	21 µg/kg	70 µg/kg	210 µg/kg
Number examined	50	51	51	50	50	51	50	50
Kidney								
Cyst	0	1	0	10	0	0	1	31
Kidney tubule epithelium								
Cytoplasmic alteration	1	0	3	8	0	0	1	2
Degeneration	0	0	50	49	0	0	49	49
Hyperplasia	1	1	16	24	0	0	12	13
Karyomegaly	0	1	51	50	0	8	50	50
Proliferation	0	0	10	26	0	0	3	16
Kidney tubule								
Adenoma, solitary	1	1	5	10	0	0	1	3
Adenoma, multiple	0	0	1	0	0	0	0	2
Carcinoma, solitary	0	0	12	20	0	0	1	3
Carcinoma, bilateral/multiple	0	0	4	10	0	0	0	0
Metastatic renal carcinoma (all sites)	0	0	4	13	0	0	1	0

TABLE 22. ANALYSIS OF RENAL TUBULAR CELL TUMORS IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF OCHRATOXIN A (a)

	Vehicle Control	21 µg/kg	70 µg/kg	210 µg/kg
MALE				
Adenoma				
Overall Rates	1/50 (2%)	1/51 (2%)	6/51 (12%)	10/50 (20%)
Adjusted Rates	2.6%	3.8%	19.7%	33.1%
Terminal Rates	1/39 (3%)	1/26 (4%)	4/26 (15%)	5/23 (22%)
Day of First Observation	729	729	524	513
Life Table Tests	P<0.001	P=0.669	P=0.023	P<0.001
Logistic Regression Tests	P<0.001	P=0.669	P=0.053	P=0.004
Carcinoma				
Overall Rates	0/50 (0%)	0/51 (0%)	16/51 (31%)	30/50 (60%)
Adjusted Rates	0.0%	0.0%	43.4%	77.2%
Terminal Rates	0/39 (0%)	0/26 (0%)	7/26 (27%)	15/23 (65%)
Day of First Observation			507	390
Life Table Tests	P<0.001	(b)	P<0.001	P<0.001
Logistic Regression Tests	P<0.001	(b)	P<0.001	P<0.001
Adenoma or Carcinoma (c)				
Overall Rates	1/50 (2%)	1/51 (2%)	20/51 (39%)	36/50 (72%)
Adjusted Rates	2.6%	3.8%	53.4%	87.2%
Terminal Rates	1/39 (3%)	1/26 (4%)	10/26 (38%)	18/23 (78%)
Day of First Observation	729	729	507	390
Life Table Tests	P<0.001	P=0.669	P<0.001	P<0.001
Logistic Regression Tests	P<0.001	P=0.669	P<0.001	P<0.001
FEMALE				
Adenoma				
Overall Rates	0/50 (0%)	0/51 (0%)	1/50 (2%)	5/50 (10%)
Adjusted Rates	0.0%	0.0%	2.4%	14.3%
Terminal Rates	0/32 (0%)	0/23 (0%)	0/35 (0%)	5/35 (14%)
Day of First Observation			637	728
Life Table Tests	P=0.003	(b)	P=0.505	P=0.041
Logistic Regression Tests	P=0.002	(b)	P=0.493	P=0.041
Carcinoma				
Overall Rates	0/50 (0%)	0/51 (0%)	1/50 (2%)	3/50 (6%)
Adjusted Rates	0.0%	0.0%	2.0%	8.6%
Terminal Rates	0/32 (0%)	0/23 (0%)	0/35 (0%)	3/35 (9%)
Day of First Observation			319	728
Life Table Tests	P=0.031	(b)	P=0.504	P=0.137
Logistic Regression Tests	P=0.017	(b)	P=0.500	P=0.137
Adenoma or Carcinoma (d)				
Overall Rates	0/50 (0%)	0/51 (0%)	2/50 (4%)	8/50 (16%)
Adjusted Rates	0.0%	0.0%	4.3%	22.9%
Terminal Rates	0/32 (0%)	0/23 (0%)	0/35 (0%)	8/35 (23%)
Day of First Observation			319	728
Life Table Tests	P<0.001	(b)	P=0.245	P=0.006
Logistic Regression Tests	P<0.001	(b)	P=0.180	P=0.006

(a) The statistical analyses used are discussed in Section II (Statistical Methods) and Table A3 (footnotes).
(b) No P value is reported because no tumors were observed in the 21 µg/kg and the vehicle control groups.
(c) Historical incidence of adenomas or adenocarcinomas (combined) at study laboratory (mean ± SD): 3/248 (1% ± 1%); historical incidence in NTP studies: 10/1,943 (0.5% ± 0.9%)
(d) Historical incidence of adenomas at study laboratory: 0/248; historical incidence in NTP studies (mean ± SD): 2/1,944 (0.1% ± 0.5%); no malignant tumors have been observed.

Mammary Gland: The incidence of fibroadenomas in high dose female rats was significantly greater than that in vehicle controls (Table 23). The neoplasms were usually seen grossly, and histologically they were typical mammary gland fibroadenomas with a mixture of glandular and stromal elements. Multiple fibroadenomas (two per animal) were observed at an increased incidence in high dose female rats (vehicle control, 4/50; low dose, 4/51; mid dose, 5/50; high dose, 14/50).

Tongue: Squamous papillomas were seen in 2/51 low dose and 2/51 mid dose male rats. One low dose and two high dose males also had epithelial hyperplasia of the tongue. Tongues were only examined microscopically if a lesion was seen grossly at necropsy; no tongues of vehicle control male rats were examined microscopically. The mean historical incidence of neoplasms of the oral cavity in corn oil vehicle control male F344/N rats is 0.3% (6/1,949), and the highest observed incidence is 2/50. Oral cavity tumors were not found in female rats; one mid dose female had epithelial hyperplasia of the tongue.

TABLE 23. ANALYSIS OF MAMMARY GLAND TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF OCHRATOXIN A

	Vehicle Control	21 µg/kg	70 µg/kg	210 µg/kg
Fibroadenoma				
Overall Rates	17/50 (34%)	23/51 (45%)	22/50 (44%)	28/50 (56%)
Adjusted Rates	46.6%	70.5%	56.3%	69.9%
Terminal Rates	13/32 (41%)	14/23 (61%)	18/35 (51%)	23/35 (66%)
Day of First Observation	525	436	659	630
Life Table Tests	P=0.205	P=0.021	P=0.313	P=0.052
Logistic Regression Tests	P=0.046	P=0.096	P=0.234	P=0.020
Adenoma				
Overall Rates	0/50 (0%)	0/51 (0%)	1/50 (2%)	0/50 (0%)
Adenocarcinoma				
Overall Rates	1/50 (2%)	2/51 (4%)	2/50 (4%)	2/50 (4%)
Adenoma, Fibroadenoma, or Adenocarcinoma (a)				
Overall Rates	17/50 (34%)	24/51 (47%)	22/50 (44%)	30/50 (60%)
Adjusted Rates	46.6%	73.8%	56.3%	73.1%
Terminal Rates	13/32 (41%)	15/23 (65%)	18/35 (51%)	24/35 (69%)
Day of First Observation	525	436	659	626
Life Table Tests	P=0.127	P=0.012	P=0.313	P=0.024
Logistic Regression Tests	P=0.019	P=0.063	P=0.234	P=0.007

(a) Historical incidence at study laboratory (mean ± SD): 55/250 (22% ± 5%); historical incidence in NTP studies: 588/1,950 (30% ± 10%)

Hematopoietic System: The incidence of mononuclear cell leukemia in high dose female rats was significantly lower than that in vehicle controls (Table 24). Leukemia was seen in 12/50 vehicle control, 7/51 low dose, 7/51 mid dose, and 7/50 high dose male rats.

TABLE 24. ANALYSIS OF MONONUCLEAR CELL LEUKEMIA IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF OCHRATOXIN A (a)

	Vehicle Control	21 µg/kg	70 µg/kg	210 µg/kg
Overall Rates	10/50 (20%)	(b,c) 8/51 (16%)	(b,d) 2/50 (4%)	3/50 (6%)
Adjusted Rates	23.8%			7.9%
Terminal Rates	3/32 (9%)			2/35 (6%)
Day of First Observation	495			568
Life Table Test				P=0.039N
Logistic Regression Test				P=0.037N

(a) Historical incidence of leukemia at study laboratory (mean ± SD): 49/250 (20% ± 8%); historical incidence in NTP studies: 364/1,950 (19% ± 8%)
(b) Incomplete sampling of tissues and thus not statistically analyzed
(c) Twenty-nine livers and 29 spleens were examined microscopically.
(d) Nineteen livers and 16 spleens were examined microscopically.

Ochratoxin A was not mutagenic in S. *typhimurium* strains TA97, TA98, TA100, or TA1535 when tested with a preincubation protocol at doses up to 100 µg/plate in the presence or absence of Aroclor 1254-induced male Sprague Dawley rat or Syrian hamster liver S9 (Table 25; Zeiger et al., 1988). In cytogenic tests with cultured Chinese hamster ovary (CHO) cells, a small but significant and reproducible dose-related increase in sister chromatid exchanges was observed after treatment of CHO cells with ochratoxin A in the presence of S9 (Table 26); ochratoxin A did not induce chromosomal aberrations either with or without Aroclor 1254-induced male Sprague Dawley rat liver S9 (Table 27).

TABLE 25. MUTAGENICITY OF OCHRATOXIN A IN *SALMONELLA TYPHIMURIUM* (a)

Strain	Dose (µg/plate)	Revertants/Plate (b)					
		−S9		+S9 (hamster)		+S9 (rat)	
		Trial 1	Trial 2	10%	30%	10%	30%
TA100	0	107 ± 9.5	113 ± 6.7	86 ± 6.9	102 ± 9.8	89 ± 7.8	115 ± 14.2
	1	91 ± 1.0	102 ± 4.7	80 ± 4.9	105 ± 5.2	99 ± 8.7	117 ± 4.7
	3.3	90 ± 4.4	121 ± 5.8	95 ± 0.9	108 ± 2.9	93 ± 7.2	117 ± 5.5
	10	98 ± 4.6	104 ± 2.4	86 ± 2.0	110 ± 5.9	95 ± 5.0	131 ± 8.2
	33	85 ± 6.2	110 ± 6.4	91 ± 5.5	119 ± 8.5	84 ± 2.5	114 ± 3.2
	100	88 ± 6.1	113 ± 3.1	85 ± 5.9	103 ± 7.3	96 ± 5.5	116 ± 5.5
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control (c)		1,001 ± 29.6	569 ± 15.2	1,543 ± 67.0	1,150 ± 34.1	1,681 ± 32.7	873 ± 11.3
TA1535	0	32 ± 1.2	27 ± 0.9	9 ± 2.4	13 ± 3.6	10 ± 1.7	13 ± 2.8
	1	28 ± 2.0	25 ± 0.6	8 ± 2.2	14 ± 3.5	8 ± 0.9	11 ± 1.9
	3.3	28 ± 2.0	32 ± 2.1	8 ± 1.2	11 ± 2.1	9 ± 1.7	13 ± 2.5
	10	21 ± 3.2	29 ± 3.7	8 ± 0.9	12 ± 1.2	10 ± 1.5	13 ± 3.0
	33	26 ± 3.2	30 ± 1.9	9 ± 1.5	12 ± 0.6	7 ± 2.5	9 ± 2.3
	100	25 ± 0.3	36 ± 3.9	10 ± 0.6	15 ± 2.1	12 ± 0.3	9 ± 1.8
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control (c)		1,080 ± 31.5	757 ± 6.1	186 ± 13.0	204 ± 7.4	198 ± 5.5	168 ± 4.6
TA97	0	89 ± 1.5	114 ± 4.1	131 ± 9.7	156 ± 9.1	129 ± 6.5	120 ± 0.0
	1	92 ± 3.8	107 ± 9.2	125 ± 10.3	169 ± 7.1	113 ± 5.4	117 ± 9.3
	3.3	100 ± 7.0	111 ± 7.4	121 ± 4.8	161 ± 13.0	114 ± 5.9	124 ± 1.5
	10	92 ± 3.1	89 ± 8.0	115 ± 10.5	161 ± 2.9	125 ± 4.6	122 ± 11.4
	33	94 ± 8.7	111 ± 11.9	121 ± 4.0	182 ± 7.8	116 ± 8.1	149 ± 12.0
	100	90 ± 4.2	102 ± 2.3	131 ± 5.8	181 ± 11.9	115 ± 4.1	171 ± 5.7
Trial summary		Negative	Negative	Negative	Negative	Negative	Equivocal
Positive control (c)		1,161 ± 65.5	748 ± 11.2	1,156 ± 15.3	928 ± 18.2	1,371 ± 22.8	655 ± 1.7
TA98	0	15 ± 4.2	16 ± 2.9	21 ± 3.9	31 ± 6.2	22 ± 1.0	34 ± 2.6
	1	12 ± 0.3	19 ± 3.8	26 ± 1.2	25 ± 4.1	22 ± 3.5	32 ± 4.6
	3.3	8 ± 1.7	19 ± 1.7	24 ± 2.6	36 ± 2.6	24 ± 2.6	27 ± 4.1
	10	12 ± 2.9	18 ± 2.1	26 ± 2.9	31 ± 0.3	22 ± 2.1	32 ± 3.8
	33	12 ± 0.3	13 ± 3.8	18 ± 0.3	26 ± 2.1	21 ± 1.5	34 ± 2.3
	100	12 ± 0.7	16 ± 4.3	20 ± 3.6	24 ± 3.2	21 ± 0.9	30 ± 2.2
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control (c)		1,589 ± 106.7	1,785 ± 51.7	1,621 ± 96.9	994 ± 15.4	1,791 ± 12.1	482 ± 21.1

(a) Study performed at Microbiological Associates. The detailed protocol is presented by Zeiger et al. (1988). 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 TA97.

TABLE 26. INDUCTION OF SISTER CHROMATID EXCHANGES IN CHINESE HAMSTER OVARY CELLS BY OCHRATOXIN A (a)

Compound	Dose (µg/ml)	Total Cells	No. of Chromosomes	No. of SCEs	SCEs/ Chromosome	SCEs/ Cell	Hours in BrdU	Relative SCEs/Cell (percent) (b)
-S9 (c) Summary: Negative								
Dimethyl sulfoxide		50	1,048	427	0.41	8.5	26.0	--
Ochratoxin A	0.5	50	1,049	444	0.42	8.9	26.0	104.7
	1.6	50	1,050	448	0.43	9.0	26.0	105.9
	5	35	733	297	0.41	8.5	26.0	100.0
Mitomycin C	0.0005	50	1,050	569	0.54	11.4	26.0	134.1
	0.005	10	209	329	1.57	32.9	26.0	387.1
+S9 (d)								
Trial 1--Summary: Weakly positive								
Dimethyl sulfoxide		50	1,051	424	0.4	8.5	26.0	--
Ochratoxin A	5	50	1,050	470	0.45	9.4	26.0	110.6
	16	50	1,050	514	0.49	10.3	26.0	121.2
	50	50	1,049	558	0.53	11.2	26.0	131.8
	160	50	1,050	564	0.54	11.3	26.0	132.9
	500	0					26.0	
Cyclophosphamide	0.1	50	1,049	604	0.58	12.1	26.0	142.4
	0.6	10	210	246	1.17	24.6	26.0	289.4
Trial 2--Summary: Weakly positive								
Dimethyl sulfoxide		50	1,049	437	0.42	8.7	26.0	--
Ochratoxin A	30	50	1,049	462	0.44	9.2	26.0	105.7
	50	50	1,049	504	0.48	10.1	26.0	116.1
	100	50	1,050	525	0.50	10.5	26.0	120.7
	160	50	1,049	597	0.57	11.9	26.0	136.8
	300	0					26.0	
Cyclophosphamide	0.1	50	1,051	547	0.52	10.9	26.0	125.3
	0.6	10	210	265	1.26	26.5	26.0	304.6

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

TABLE 27. INDUCTION OF CHROMOSOMAL ABERRATIONS IN CHINESE HAMSTER OVARY CELLS BY OCHRATOXIN A (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
Harvest time 12.5 h					Harvest time 13.0 h				
Dimethyl sulfoxide					Dimethyl sulfoxide				
	200	2	0.01	1.0		200	2	0.01	1.0
Ochratoxin A					Ochratoxin A				
30	200	0	0.00	0.0	100	200	2	0.01	1.0
50	42	0	0.00	0.0	160	200	1	0.01	0.5
100	200	4	0.02	1.5	300	200	3	0.02	1.5
160	186	5	0.03	2.7					
Summary: Negative					Summary: Negative				
Mitomycin C					Cyclophosphamide				
0.0625	200	52	0.26	22.0	2.5	200	34	0.17	16.5
0.25	50	21	0.42	34.0	7.5	50	49	0.98	56.0

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

IV. DISCUSSION AND CONCLUSIONS

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Ochratoxin A is a fungal toxin found in cereals, grains, nuts, and meat products, with the potential for widespread exposure for both animals and humans. At the time that ochratoxin A was selected for evaluation, epidemiologic data to determine whether ochratoxin A was carcinogenic for humans and studies in animals were considered inadequate. The only data available for ochratoxin A were studies for mice (IARC, 1983). Rats only were selected for the NCI/NTP ochratoxin A studies because the Food and Drug Administration had already contracted for studies to be conducted in $B6C3F_1$ mice. These studies showed that ochratoxin A causes kidney neoplasms in $B6C3F_1$ mice (Bendele et al., 1985). The oral route of exposure was chosen for these studies because this is the typical route of exposure for both animals and humans. Administration by gavage in corn oil as opposed to feed studies was selected because more accurate doses could be administered and because procurement of the fungal toxin is both difficult and expensive.

In NTP genetic toxicology studies, ochratoxin A was not mutagenic in Salmonella assays or in tests for chromosomal aberrations in Chinese hamster ovary (CHO) cells. A small but significant increase in sister chromatid exchanges (SCEs) was observed following treatment of CHO cells with ochratoxin A in the presence of S9. Unscheduled DNA synthesis has been reported in ACI rat and C3H mouse hepatocyte cultures exposed to ochratoxin A (Mori et al., 1984). Since exposure of mammalian cells to ochratoxin A induces unscheduled DNA synthesis and SCEs in vitro and single strand DNA breaks in vivo, one can conclude that ochratoxin A is a genotoxin for mammalian cells. The requirement of S9 for induction of SCEs in mammalian cells suggests that ochratoxin A requires metabolism to some proximate genotoxic form. However, ochratoxin A with or without S9 does not induce gene mutations in bacteria, recombination in fungi, or gene mutations or chromosomal aberrations in cultured mammalian cells. It has not been tested for mutagenicity in vivo.

Sixteen-day and 13-week studies were used to select doses for the 2-year studies. In the 2-year studies, 15 animals were killed at 9 and 15 months for clinical chemical and hematologic analyses, urinalysis, and histologic examinations to determine the incidence and type of toxic lesions occurring early in the studies.

In 16-day studies, ochratoxin A was found to be toxic to F344/N rats; all animals in the 16 mg/kg groups died, and at 4 mg/kg, mean body weight loss exceeded 10% of initial weights. The kidney was shown to be the target organ with necrosis and degenerative changes in the renal tubular epithelial cells. For the 13-week studies, the highest dose selected was 1 mg/kg (the lowest dose in the 16-day studies), and the lowest dose was 0.0625 mg/kg (62.5 µg/kg). Weight gain was clearly lower for both male and female rats receiving 0.25 mg/kg (250 µg/kg) or more. The kidney was the principal tissue affected, with degenerative changes seen in the renal tubular epithelial cells. Since lower weight gain was seen at 250 µg/kg and above and since renal changes, especially karyomegaly, were seen at all doses in the 13-week studies (62.5 µg/kg was the lowest dose), 210 µg/kg was selected as the high dose for the 2-year studies, with mid and low doses of 70 and 21 µg/kg.

All lots of ochratoxin A were greater than 98% pure; chloroform (0.9%) was the major contaminant. Since the doses of ochratoxin A were in the microgram range, the chloroform contamination was not considered to be important for the 2-year studies.

The urinalyses performed after 3, 10, and 45 days and after 3, 6, 9, 12, and 15 months of ochratoxin A exposure suggest a functional defect in renal capacity to concentrate urine. This was reflected in several parameters in both males and females. There was a marginal increase in urine volume in dosed animals for several time periods. The specific gravity of the urine in the 210 µg/kg group was lower at several time points for females and at one time point for males. The most consistent finding was a marginal loss in the ability to concentrate urine during tests conducted after 7 days, 47 days, 6 months, and 12 months of ochratoxin A exposure. Female rats showed lower urine specific gravity in the 210 µg/kg group at all time periods in the concentration studies, whereas males dosed at 210 µg/kg showed lower specific gravity for all but the 7-day exposure period.

Rats were still able to concentrate urine to 1.040 specific gravity or higher, indicating that the functional loss was only moderate. The loss of the concentrating ability of the kidney after ochratoxin A exposure has been shown to be a specific toxic effect on the anion transport mechanism located on the brush border of the proximal convoluted tubules cells (Endo, 1983; Ueno, 1985).

The hematologic changes were not striking except in the 16-day studies in which bone marrow hypocellularity was found histologically in all dosed groups. In the 13-week studies, bone marrow was not originally diagnosed as hypocellular, but when the slides from the high dose and vehicle control groups were reexamined, this time in a blind fashion, a minimal hypocellularity was recognized in the dosed animals (Boorman et al., 1984). When the peripheral blood values were measured 45 days and 3, 9, and 15 months after ochratoxin A exposure, no significant difference in circulating leukocyte values was observed between vehicle control and dosed rats except at 9 and 15 months. At 9 months, values for all dosed animals were marginally below control values for both sexes. A similar decrease was seen at 15 months for mid dose females only. In the differential blood counts, the percentage of monocytes was sometimes lower in dosed males, but the values were variable, and the significance of this finding is unclear. None of the hematologic findings appeared to be biologically significant. Absence of an effect may have been a consequence of the exposure level. In the 16-day studies in which animals were exposed to milligram quantities of ochratoxin A, marrow hypocellularity was obvious. Similarly, mice dosed with up to 80 mg/kg of ochratoxin A showed bone marrow hypocellularity and a marked decrease in macrophage-granulocyte progenitor cells (Boorman et al., 1984). In these same studies, it was shown that following a brief exposure to ochratoxin A, bone marrow cellularity and peripheral blood counts returned to normal in mice by 3 weeks after exposure. However, these ochratoxin A-exposed mice had a residual damage that could be demonstrated by an irradiation stress (Hong et al., 1988). Ochratoxin A inhibits protein synthesis (Haubeck et al., 1981), and the bone marrow effects seen at higher doses may reflect the sensitivity of a rapidly proliferating cell population to this protein inhibition rather than a specific predilection of ochratoxin A for bone marrow progenitor cells.

In the 13-week studies, the kidney clearly had toxic changes, with karyomegaly observed in nearly 100% of all dosed animals. Atrophy of the renal tubular epithelium was present in all dosed animals except at the high doses where necrosis and degeneration were present. The atrophy occurred in the inner cortex and outer medulla, which would be the straight portion of the renal tubules. This finding is in contrast to that from studies on isolated renal segments where the initial effect is on the renal proximal tubule (Ueno, 1985). Morphologic changes in the proximal convoluted tubule would be expected more in the outer cortex of the kidney. Karyomegaly was also a prominent finding, especially in the cells of the inner cortex. This change was characterized by renal tubule nuclei that were often 3-10 times the size of adjacent nuclei. The nuclei were more basophilic, irregular in shape, and often contained prominent nucleoli.

The ochratoxin A doses for the 2-year studies were 0, 21, 70, and 210 µg/kg per day, with 15 animals per dose killed at 9 and 15 months. Again, the kidney was the primary tissue affected. At 9 months, a single renal tubular cell adenoma was present in a high dose male rat. Three high dose females, six high dose males, and three mid dose males also had renal tubular cell hyperplasia, a change where renal tubular cells appear to fill one or more tubules. The lesion is smaller than, but morphologically similar to, a tubular cell adenoma. All of the mid and high dose males and females had karyomegaly of renal tubular epithelial cells; no vehicle controls or low dose animals had this lesion. A renal tubular degenerative change similar to that seen in the 13-week studies was recognized in all high dose animals with subtle changes at lower doses.

At 15 months, one mid dose and one high dose male rat had renal tubular cell adenomas, and one mid dose and two high dose males had carcinomas of the renal tubular epithelium. One hyperplastic lesion was present in a mid dose female, but no neoplasms were observed in

females. Renal neoplasms are uncommon in F344/N rats in 2-year studies, so the presence of adenomas and carcinomas at 9 and 15 months indicated the carcinogenic potential of ochratoxin A for the male rats. At 15 months, the carcinogenic potential for females was unknown, but the presence of hyperplasia suggested that neoplasms of the kidney might be present in the 2-year studies, since these lesions are recognized as part of a biologic continuum. The nonneoplastic lesions in the kidney at 15 months were similar to those seen at 9 months.

In the 2-year studies, the incidences of renal tubular cell adenomas and carcinomas observed in the male rats are the highest seen in any of the NCI/NTP studies to date. The neoplasms were often multiple and bilateral. In 4 mid dose and 13 high dose male rats, metastases, often to multiple sites, were observed. The lung was the most common metastatic site; renal carcinoma cells were present in the lung in 16 of the 17 animals with metastases. Renal tubular neoplasms also were present in females; of the 10 neoplasms, 6 were benign and 4 were malignant, and distant metastases were present in only one animal. Renal tubular cell hyperplasia, renal tubular cell adenomas, and renal tubular cell carcinomas often have similar cytologic features. The size of the lesion and compression of adjacent parenchyma differentiate the lesions. In these studies, the metastases of many neoplasms clearly indicate the malignant potential of neoplasms induced in male rats by ochratoxin A. Several proliferative lesions of the kidney were observed in addition to the neoplasms. Small focal lesions usually involving a single tubule and appearing similar to the adenomas were diagnosed as hyperplasia. This type of lesion is not uncommon in studies in which renal neoplasms are induced, and small focal hyperplasia is considered part of the spectrum of lesions progressing to neoplasms. In the ochratoxin A studies, a second type of proliferative lesion was found and diagnosed as renal tubule proliferation to separate it from the more typical hyperplasia. This lesion consisted of cysts lined by hyperplastic epithelium which appeared to consist of renal tubular epithelial cells. The lesion was both focal and multifocal. Since cystic tumors were not seen, it is not known whether this lesion may progress. In a few animals, renal cysts lined by flattened epithelium were found. These were simply diagnosed as cysts.

In female rats, an increased incidence of mammary gland fibroadenomas was also observed. Although the increase in the number of rats with either fibroadenomas or adenomas (combined) was not striking (vehicle control, 17/50; low dose, 23/51; mid dose, 22/50; high dose, 28/50), there was an increase in multiplicity of tumors: 4 vehicle controls had multiple fibroadenomas compared with 14 high dose animals. No rat had more than two fibroadenomas. The incidence of fibroadenomas in historical corn oil vehicle control female F344/N rats at this laboratory for recent studies is 53/250 (21% ± 5%), and the incidence in the historical corn oil vehicle controls for the NTP is 558/1,950 (29% ± 9%). Thus, the incidence in vehicle controls in this study was greater than normal, and the incidences in all dosed groups exceeded the historical control rates. These high incidences, coupled with the increase in multiplicity of tumors, lead to the conclusion that the mammary gland tumors were associated with ochratoxin A exposure. Adenocarcinomas of the mammary gland, one in the vehicle control and two in each of the dosed groups, did not add or detract from the evidence of carcinogenicity.

Squamous papillomas of the tongue were found in two low dose males and two mid dose males. In addition, epithelial hyperplasia of the tongue was found in one low dose male and two high dose males. The tongue was not included for routine histologic examination. This effect on the tongue was not considered to be compound related, and no other tumors of the oral cavity were seen in dosed males. One squamous papilloma of the palate was found in a vehicle control male. No tumors of the oral cavity were seen in dosed females, but a squamous cell carcinoma of the pharynx was present in a vehicle control female rat.

There appears to be increasing evidence that ochratoxin A may be a carcinogen for humans. In the 1983 International Agency for Research on Cancer (IARC) monograph on food additives, feed additives, and naturally occurring substances, it was concluded that because of a limited positive study in mice and inadequate

epidemiologic data in humans, no evaluation of the carcinogenicity of ochratoxin A to humans could be made (IARC, 1983). Since then, another positive study in mice has been reported (Bendele et al., 1985), and there is increasing evidence that Balkan endemic nephropathy is associated with a dramatic increase in urinary tract tumors (Castegnaro et al., 1987). Balkan endemic nephropathy may be related to ochratoxin A (Hult et al., 1982); ochratoxin A residues are found in pork products and are associated with the presence of nephropathy in swine (Golinski et al., 1985). The current NTP studies show that ochratoxin A is a potent carcinogen for the kidney of F344 rats. From the results of all these studies and because ochratoxin A can be quite widespread in products for human consumption, it would seem that this compound presents a true potential hazard for humans.

The experimental and tabulated data for the NTP Technical Report on ochratoxin A 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.

Under the conditions of these 2-year gavage studies, there was *clear evidence of carcinogenic activity** of ochratoxin A for male F344/N rats as shown by substantially increased incidences of uncommon tubular cell adenomas and of tubular cell carcinomas of the kidney. There was *clear evidence of carcinogenic activity* for female F344/N rats as shown by increased incidences of uncommon tubular cell adenomas and of tubular cell carcinomas of the kidney and by increased incidences and multiplicity of fibroadenomas of the mammary gland.

Ochratoxin A administration also caused nonneoplastic renal changes including tubular cell hyperplasia, tubular cell proliferation, cytoplasmic alteration, karyomegaly, and degeneration of the renal tubular epithelium.

*Explanation of Levels of Evidence of Carcinogenic Activity is on page 7.
A summary of the Peer Review comments and the public discussion on this Technical Report appears on page 10.

V. REFERENCES

V. REFERENCES

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APPENDIX A

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

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

	Vehicle Control	Low Dose	Mid Dose	High Dose
Animals initially in study	80	80	80	80
Animals removed	80	80	80	80
Animals examined histopathologically	50	51	51	50
ALIMENTARY SYSTEM				
Intestine small, ileum	(50)	*(51)	*(51)	(50)
Adenocarcinoma				1 (2%)
Liver	(50)	*(51)	*(51)	(50)
Carcinoma, metastatic, kidney				2 (4%)
Hepatocellular carcinoma				1 (2%)
Hepatocellular carcinoma, multiple	1 (2%)			
Leukemia mononuclear	12 (24%)	6 (12%)	6 (12%)	7 (14%)
Neoplastic nodule				1 (2%)
Mesentery	*(50)	*(51)	*(51)	*(50)
Carcinoma, metastatic, kidney			1 (2%)	8 (16%)
Mesothelioma malignant		3 (6%)		
Sarcoma, metastatic, uncertain primary site		1 (2%)		
Pancreas	(50)	*(51)	*(51)	(50)
Carcinoma, metastatic, kidney			4 (8%)	3 (6%)
Leukemia mononuclear	2 (4%)	2 (4%)	1 (2%)	2 (4%)
Sarcoma, metastatic, uncertain primary site		1 (2%)		
Acinus, adenoma	3 (6%)	3 (6%)		3 (6%)
Acinus, adenoma, multiple	1 (2%)			
Pharynx	*(50)	*(51)	*(51)	*(50)
Palate, papilloma squamous	1 (2%)			
Salivary glands	(50)	*(51)	*(51)	(49)
Acinus, adenoma	1 (2%)			
Stomach, forestomach	(50)	*(51)	*(51)	(50)
Papilloma squamous				1 (2%)
Stomach, glandular	(50)	*(51)	*(51)	(49)
Adenocarcinoma				1 (2%)
Tongue	*(50)	*(51)	*(51)	*(50)
Papilloma squamous		2 (4%)	2 (4%)	
CARDIOVASCULAR SYSTEM				
Heart	(50)	*(51)	*(51)	(50)
Carcinoma, metastatic, kidney				2 (4%)
Leukemia mononuclear		1 (2%)		
Atrium, sarcoma, metastatic, uncertain primary site			1 (2%)	
Epicardium, carcinoma, metastatic, kidney				1 (2%)
ENDOCRINE SYSTEM				
Adrenal gland, cortex	(50)	*(51)	*(51)	(50)
Adenoma	2 (4%)			
Leukemia mononuclear	5 (10%)		1 (2%)	1 (2%)
Medulla, carcinoma, metastatic, kidney				1 (2%)
Adrenal gland, medulla	(50)	*(51)	*(51)	(49)
Leukemia mononuclear			4 (8%)	
Pheochromocytoma malignant			2 (4%)	1 (2%)
Pheochromocytoma complex	1 (2%)		1 (2%)	1 (2%)
Pheochromocytoma benign	13 (26%)	4 (8%)	3 (6%)	9 (18%)
Bilateral, pheochromocytoma benign	4 (8%)		2 (4%)	2 (4%)
Islets, pancreatic	(50)	*(51)	*(51)	(50)
Adenoma	4 (8%)	2 (4%)	3 (6%)	1 (2%)
Adenoma, multiple	1 (2%)			
Carcinoma	1 (2%)		1 (2%)	1 (2%)
Parathyroid gland	(41)	*(51)	*(51)	(47)
Adenoma	2 (5%)			

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

	Vehicle Control	Low Dose	Mid Dose	High Dose
ENDOCRINE SYSTEM (Continued)				
Pituitary gland	(50)	*(51)	*(51)	(49)
Leukemia mononuclear		1 (2%)		
Pars distalis, adenoma	14 (28%)	16 (31%)	7 (14%)	11 (22%)
Pars distalis, carcinoma		2 (4%)	2 (4%)	
Pars intermedia, adenoma	1 (2%)			
Thyroid gland	(50)	*(51)	*(51)	(50)
Carcinoma, metastatic, kidney				2 (4%)
Bilateral, C-cell, adenoma	1 (2%)			
C-cell, adenoma	8 (16%)	5 (10%)	6 (12%)	5 (10%)
C-cell, carcinoma		1 (2%)	1 (2%)	1 (2%)
Follicular cell, adenoma	1 (2%)		1 (2%)	1 (2%)
Follicular cell, carcinoma	2 (4%)	1 (2%)		
GENERAL BODY SYSTEM				
Tissue, NOS	*(50)	*(51)	*(51)	*(50)
Sarcoma			1 (2%)	1 (2%)
Sarcoma, metastatic, uncertain primary site		1 (2%)		
GENITAL SYSTEM				
Epididymis	(49)	*(51)	*(51)	(50)
Carcinoma, metastatic, kidney				1 (2%)
Leukemia mononuclear	1 (2%)			
Mesothelioma malignant		2 (4%)		
Preputial gland	(50)	*(51)	*(51)	(48)
Adenoma	6 (12%)	3 (6%)	1 (2%)	3 (6%)
Testes	(50)	*(51)	*(51)	(50)
Mesothelioma benign		1 (2%)		
Mesothelioma malignant		3 (6%)		
Bilateral, interstitial cell, adenoma	39 (78%)	34 (67%)	32 (63%)	27 (54%)
Interstitial cell, adenoma	5 (10%)	5 (10%)	10 (20%)	13 (26%)
Tunic, carcinoma, metastatic, kidney				1 (2%)
Tunic, mesothelioma malignant	1 (2%)			
HEMATOPOIETIC SYSTEM				
Blood	*(50)	*(51)	*(51)	*(50)
Leukemia mononuclear	1 (2%)			4 (8%)
Bone marrow	(50)	*(51)	*(51)	(50)
Femoral, leukemia mononuclear	5 (10%)	3 (6%)	3 (6%)	1 (2%)
Lymph node	(50)	*(51)	*(51)	(50)
Deep cervical, leukemia mononuclear	2 (4%)			
Inguinal, leukemia mononuclear				1 (2%)
Lumbar, leukemia mononuclear				1 (2%)
Mediastinal, carcinoma, metastatic, kidney			2 (4%)	7 (14%)
Mediastinal, leukemia mononuclear	8 (16%)	3 (6%)	4 (8%)	5 (10%)
Mediastinal, sarcoma, metastatic, uncertain primary site		1 (2%)		
Mediastinal, squamous cell carcinoma, metastatic, lung			1 (2%)	
Mesenteric, leukemia mononuclear	1 (2%)	2 (4%)	1 (2%)	
Pancreatic, adenocarcinoma, metastatic, stomach				1 (2%)
Pancreatic, leukemia mononuclear	1 (2%)		2 (4%)	
Renal, leukemia mononuclear				1 (2%)
Renal, mediastinal, pancreatic, carcinoma, metastatic, kidney			1 (2%)	1 (2%)
Lymph node, mandibular	(49)	*(51)	*(51)	(50)
Carcinoma, metastatic, kidney				1 (2%)
Carcinoma, metastatic, Zymbal gland				1 (2%)
Leukemia mononuclear	10 (20%)	6 (12%)	5 (10%)	7 (14%)

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

	Vehicle Control	Low Dose	Mid Dose	High Dose
HEMATOPOIETIC SYSTEM (Continued)				
Spleen	(50)	*(51)	*(51)	(50)
Carcinoma, metastatic, kidney			1 (2%)	2 (4%)
Fibrosarcoma	1 (2%)		1 (2%)	
Leukemia mononuclear	12 (24%)	7 (14%)	6 (12%)	7 (14%)
Thymus	(41)	*(51)	*(51)	(38)
Carcinoma, metastatic, kidney				1 (3%)
Leukemia mononuclear	1 (2%)	1 (2%)		1 (3%)
INTEGUMENTARY SYSTEM				
Mammary gland	(39)	*(51)	*(51)	(40)
Adenoma			1 (2%)	
Fibroadenoma	3 (8%)	2 (4%)	1 (2%)	3 (8%)
Skin	(49)	*(51)	*(51)	(49)
Basosquamous tumor benign		1 (2%)	1 (2%)	
Keratoacanthoma	1 (2%)	1 (2%)	4 (8%)	2 (4%)
Papilloma squamous	2 (4%)	1 (2%)	4 (8%)	1 (2%)
Trichoepithelioma	1 (2%)			
Sebaceous gland, adenoma	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Subcutaneous tissue, fibroma	4 (8%)	4 (8%)	1 (2%)	2 (4%)
Subcutaneous tissue, fibrosarcoma	1 (2%)		2 (4%)	
Subcutaneous tissue, lipoma				1 (2%)
Subcutaneous tissue, sarcoma	1 (2%)		1 (2%)	
MUSCULOSKELETAL SYSTEM				
Bone	(50)	*(51)	*(51)	(50)
Cranium, osteosarcoma				1 (2%)
Skeletal muscle	*(50)	*(51)	*(51)	*(50)
Diaphragm, sarcoma, metastatic, uncertain primary site		1 (2%)		
NERVOUS SYSTEM				
Brain	(50)	*(51)	*(51)	(50)
Astrocytoma malignant	1 (2%)		1 (2%)	
Leukemia mononuclear		1 (2%)		1 (2%)
Osteosarcoma, metastatic, uncertain primary site			1 (2%)	
RESPIRATORY SYSTEM				
Lung	(50)	*(51)	*(51)	(50)
Alveolar/bronchiolar adenoma		3 (6%)		
Alveolar/bronchiolar carcinoma		1 (2%)		
Carcinoma, metastatic, kidney			3 (6%)	13 (26%)
Carcinoma, metastatic, uncertain primary site				1 (2%)
Leukemia mononuclear	5 (10%)	6 (12%)	4 (8%)	6 (12%)
Pheochromocytoma malignant, metastatic, adrenal gland			2 (4%)	
Squamous cell carcinoma			1 (2%)	
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung		1 (2%)		
SPECIAL SENSES SYSTEM				
Zymbal gland	50)	*(51)	*(51)	*(50)
Carcinoma		2 (4%)		3 (6%)

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

	Vehicle Control	Low Dose	Mid Dose	High Dose
URINARY SYSTEM				
Kidney	(50)	(51)	(51)	(50)
Leukemia mononuclear	1 (2%)	3 (6%)	4 (8%)	2 (4%)
Mixed tumor malignant	1 (2%)			
Sarcoma, metastatic, uncertain primary site		1 (2%)		
Bilateral, renal tubule, carcinoma			1 (2%)	3 (6%)
Bilateral, renal tubule, carcinoma, multiple				1 (2%)
Capsule, carcinoma, metastatic, kidney				1 (2%)
Lymphatic, carcinoma, metastatic, kidney				1 (2%)
Renal tubule, adenoma	1 (2%)	1 (2%)	3 (6%)	10 (20%)
Renal tubule, carcinoma			12 (24%)	20 (40%)
Renal tubule, carcinoma, multiple			3 (6%)	6 (12%)
Renal tubule, epithelium, adenoma			2 (4%)	
Renal tubule, epithelium, adenoma, multiple			1 (2%)	
Urinary bladder	(50)	*(51)	*(51)	(50)
Leukemia mononuclear				1 (2%)
Serosa, mesothelioma malignant	1 (2%)			
SYSTEMIC LESIONS				
Multiple organs	*(50)	*(51)	*(51)	*(50)
Leukemia mononuclear	12 (24%)	7 (14%)	7 (14%)	7 (14%)
Mesothelioma malignant	1 (2%)	4 (8%)		
Mesothelioma benign		1 (2%)		
ANIMAL DISPOSITION SUMMARY				
Animals initially in study	80	80	80	80
Terminal sacrifice	39	26	26	23
Gavage death	4	6	2	1
Moribund	7	13	14	23
Scheduled sacrifice	30	29	29	30
Dead		6	9	3
TUMOR SUMMARY				
Total animals with primary neoplasms **	47	47	50	50
Total primary neoplasms	143	107	123	146
Total animals with benign neoplasms	47	46	48	44
Total benign neoplasms	120	89	86	97
Total animals with malignant neoplasms	22	17	28	39
Total malignant neoplasms	23	18	37	49
Total animals with secondary neoplasms ***		2	9	16
Total secondary neoplasms		7	17	51
Total animals with malignant neoplasms uncertain primary site		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 A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF OCHRATOXIN A: VEHICLE CONTROL

WEEKS ON STUDY	0 0 2	0 0 2	0 5 4	0 7 0	0 7 1	0 7 4	0 7 6	0 7 8	0 9 9	1 0 1	1 0 2	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5
CARCASS ID	0 2 1	0 4 1	0 2 4	0 1 3	0 9 5	0 8 5	0 6 5	0 7 4	0 8 1	0 8 2	0 5 3	0 1 1	0 1 2	0 1 4	0 1 5	0 2 2	0 2 3	0 2 5	0 3 1	0 3 2	0 3 3	0 3 4	0 3 5	0 4 2	0 4 3
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, multiple																			X						
Leukemia mononuclear						X							X					X							X
Mesentery					+																				
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Acinus, adenoma														X											
Acinus, adenoma, multiple																									
Pharynx																									
Palate, papilloma squamous																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinus, adenoma			X																						
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Leukemia mononuclear						X							X												
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma complex																							X		
Pheochromocytoma benign					X										X			X							X
Bilateral, pheochromocytoma benign												X							X		X				
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																	X			X					
Adenoma, multiple																									
Carcinoma																									
Parathyroid gland	M	M	+	M	+	+	M	M	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+
Adenoma																									
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma										X	X	X			X		X			X					
Pars intermedia, adenoma																									X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, C-cell, adenoma																					X				
C cell, adenoma										X		X			X										
Follicular cell, adenoma																									
Follicular cell, carcinoma																	X								
GENERAL BODY SYSTEM																									
None																									

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

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

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

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL
CARCASS ID	0444	0445	0451	0452	0454	0455	0461	0462	0463	0464	0471	0472	0473	0475	0483	0484	0491	0492	0493	0494	0501	0502	0503	0504	0505	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, multiple																										1
Leukemia mononuclear	X						X	X	X	X						X			X					X	12
Mesentery																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear							X	X																		2
Acinus, adenoma									X			X														3
Acinus, adenoma, multiple														X												1
Pharynx		+																								1
Palate, papilloma squamous		X																								1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Acinus, adenoma																										1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma						X							X													2
Leukemia mononuclear							X	X								X										5
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma complex																										1
Pheochromocytoma benign	X				X					X		X					X		X		X		X		X	13
Bilateral, pheochromocytoma benign														X												4
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma					X												X									4
Adenoma, multiple																						X				1
Carcinoma																								X		1
Parathyroid gland	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	41
Adenoma						X													X							2
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma			X			X	X			X		X					X		X			X				14
Pars intermedia, adenoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, C cell, adenoma																										1
C cell, adenoma		X								X									X	X	X					8
Follicular cell, adenoma										X																1
Follicular cell, carcinoma			X																							2
GENERAL BODY SYSTEM																										
None																										

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

WEEKS ON STUDY	002	002	054	070	071	074	076	078	099	101	102	105	105	105	105	105	105	105	105	105	105	105	105	105	105
CARCASS ID	021	041	024	013	095	085	065	074	081	082	053	011	012	014	115	022	023	025	031	032	033	034	035	042	043
GENITAL SYSTEM																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear						X																			
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+
Adenoma									X		X									X					
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma							X	X	X		X	X	X	X			X	X	X	X	X	X	X	X	X
Interstitial cell, adenoma						X				X					X	X									
Tunic, mesothelioma malignant																									
HEMATOPOIETIC SYSTEM																									
Blood													+												
Leukemia mononuclear													X												
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	+	+	-	+	+
Femoral, leukemia mononuclear						X																			
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	+	+	+	+	-
Deep cervical, leukemia mononuclear																		X							
Mediastinal, leukemia mononuclear						X																			
Mesenteric, leukemia mononuclear																									
Pancreatic, leukemia mononuclear													X												
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	-	+	+	+	+	+	+
Leukemia mononuclear						X												X							
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+
Fibrosarcoma															X										
Leukemia mononuclear						X							X					X							X
Thymus	+	+	+	+	+	+	+	+	I	M	M	+	+	+	+	+	+	M	+	+	+	+	+	+	M
Leukemia mononuclear						X																			
INTEGUMENTARY SYSTEM																									
Mammary gland	+	M	+	M	+	+	+	+	+	+	M	+	M	M	+	+	+	+	M	+	+	+	+	+	+
Fibroadenoma						X																			
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+
Keratoacanthoma																									
Papilloma squamous													X												
Trichoepithelioma																									
Sebaceous gland, adenoma																									
Subcutaneous tissue, fibroma								X			X								X						
Subcutaneous tissue, fibrosarcoma																X									
Subcutaneous tissue, sarcoma							X																		
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	+	+	+	+	+
Astrocytoma malignant																									
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear						X							X												
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Eye																								+	
Harderian gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+
Leukemia mononuclear																									
Mixed tumor malignant					X																				
Renal tubule, adenoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	-	+	+	+	+	+	+
Serosa, mesothelioma malignant																									

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

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL
CARCASS ID	044	045	051	052	054	055	061	062	063	064	071	072	073	075	083	084	091	092	093	094	101	102	103	104	105	TISSUES TUMORS
GENITAL SYSTEM																										
Epididymis	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear																										1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma							X					X						X								6
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
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	39
Interstitial cell, adenoma																						X				5
Tunic, mesothelioma malignant																					X					1
HEMATOPOIETIC SYSTEM																										
Blood																										1
Leukemia mononuclear																										1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Femoral, leukemia mononuclear								X		X						X			X							5
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Deep cervical, leukemia mononuclear							X																			2
Mediastinal, leukemia mononuclear	X						X	X	X	X						X			X							8
Mesenteric, leukemia mononuclear								X																		1
Pancreatic, leukemia mononuclear																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear	X						X	X	X	X						X			X						X	10
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma																										1
Leukemia mononuclear	X						X	X	X	X						X			X						X	12
Thymus	+	+	+	+	M	+	M	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	41
Leukemia mononuclear																										1
INTEGUMENTARY SYSTEM																										
Mammary gland	+	M	+	+	+	+	+	+	+	+	M	+	+	M	M	+	+	+	M	+	+	+	+	+	+	39
Fibroadenoma						X																X				3
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	49
Keratoacanthoma																X										1
Papilloma squamous																									X	2
Trichoepithelioma															X											1
Sebaceous gland, adenoma									X																	1
Subcutaneous tissue, fibroma																X										4
Subcutaneous tissue, fibrosarcoma																										1
Subcutaneous tissue, sarcoma																										1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma malignant							X																			1
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear							X	X								X										5
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Eye					+						+															3
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear								X																		1
Mixed tumor malignant																										1
Renal tubule, adenoma																						X				1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Serosa, mesothelioma malignant																					X					1

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

WEEKS ON STUDY	038	040	041	059	060	060	062	070	070	080	080	090	090	090	091	097	097	097	097	098	101	103	103	104	104	105
CARCASS ID	245	175	285	254	223	242	195	203	263	214	233	252	184	232	244	174	235	172	212	255	265	201	251	204	194	171
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Intestine large, cecum	+	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+		+	+	+	+	
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	
Intestine large, rectum	+	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+		+	+	+	+	
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	
Intestine small, ileum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Leukemia mononuclear						X	X			X										X	X	X				
Mesentery						+		+					+	+					+					+		
Mesothelioma malignant								X											X							
Sarcoma, metastatic, uncertain primary site														X												
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Leukemia mononuclear																				X		X				
Sarcoma, metastatic, uncertain primary site														X												
Acinus, adenoma												X							X							
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	
Tongue																						+				
Papilloma squamous																										
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Leukemia mononuclear																				X						
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Adrenal gland, cortex	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Adrenal gland, medulla	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Pheochromocytoma benign													X					X		X			X		
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Adenoma															X								X			
Parathyroid gland	+	+	M	+	+	+	+	+	M	M	+	A	+	+	+	+	+	+	+	+	+	+	M	+	+	
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Leukemia mononuclear																				X						
Pars distalis, adenoma				X					X	X	X		X			X		Y			X		X			
Pars distalis, carcinoma																								X		
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	
C cell, adenoma																	X			X						
C-cell, carcinoma																										
Follicular cell, carcinoma																										
GENERAL BODY SYSTEM																										
Tissue, NOS														+												
Sarcoma, metastatic, uncertain primary site														X												
GENITAL SYSTEM																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Mesothelioma malignant							X								X											
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Adenoma																										
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Seminal vesicle												+														
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma benign																X										
Mesothelioma malignant								X											X							
Bilateral, interstitial cell, adenoma								X			X		X	X		X		X	X	X	X	X	X	X	X	X
Interstitial cell, adenoma							X			X																
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Femoral, leukemia mononuclear							X				X										X					
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Mediastinal, leukemia mononuclear							X													X		X				
Mediastinal, sarcoma, metastatic, uncertain primary site														X												
Mesenteric, leukemia mononuclear							X													X						
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Leukemia mononuclear						X	X				X									X	X	X				
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Leukemia mononuclear						X	X				X									X	X	X				
Thymus	+	+	+	+	+	+	+	M	+	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	173	181	182	183	185	191	192	193	202	205	211	213	215	221	222	224	225	231	234	241	243	253	261	262	264	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+																									26
Intestine large	+																									26
Intestine large, cecum	+																									23
Intestine large, colon	+																									25
Intestine large, rectum	+																									23
Intestine small	+																									26
Intestine small, duodenum	+																									25
Intestine small, ileum	+																									24
Intestine small, jejunum	+																									25
Liver	+																									26
Leukemia mononuclear																										6
Mesentery							+																			7
Mesothelioma malignant							X																			3
Sarcoma, metastatic, uncertain primary site																										1
Pancreas	+																									26
Leukemia mononuclear																										2
Sarcoma, metastatic, uncertain primary site																										1
Acinus, adenoma	X																									3
Salivary glands	+																									26
Stomach	+																									26
Stomach, forestomach	+																									25
Stomach, glandular	+																									25
Tongue														+		+										3
Papilloma squamous														X		X										2
CARDIOVASCULAR SYSTEM																										
Heart	+																									26
Leukemia mononuclear																										1
ENDOCRINE SYSTEM																										
Adrenal gland	+																									25
Adrenal gland, cortex	+																									25
Adrenal gland, medulla	+																									25
Pheochromocytoma benign																										4
Islets, pancreatic	+																									26
Adenoma																										2
Parathyroid gland	+																									21
Pituitary gland	+	+			+	+			+			+		+					+							33
Leukemia mononuclear																										1
Pars distalis, adenoma	X	X			X	X			X			X							X							16
Pars distalis, carcinoma														X												2
Thyroid gland	+	+					+									+								+		29
C-cell, adenoma	X	X														X										5
C-cell, carcinoma																								X		1
Follicular cell, carcinoma							X																			1
GENERAL BODY SYSTEM																										
Tissue, NOS																										1
Sarcoma, metastatic, uncertain primary site																										1
GENITAL SYSTEM																										
Epididymis	+																									26
Mesothelioma malignant																										2
Preputial gland	+		+											+	+											28
Adenoma			X											X	X											3
Prostate	+																									26
Seminal vesicle																										1
Testes	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma benign																										1
Mesothelioma malignant							X																			3
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	34
Interstitial cell, adenoma													X						X	X						5
HEMATOPOIETIC SYSTEM																										
Bone marrow	+																									25
Femoral, leukemia mononuclear																										3
Lymph node	+								+					+												28
Mediastinal, leukemia mononuclear																										3
Mediastinal, sarcoma, metastatic, uncertain primary site																										1
Mesenteric, leukemia mononuclear																										2
Lymph node, mandibular	+								+					+												28
Leukemia mononuclear																										6
Spleen	+			+				+		+																29
Leukemia mononuclear										X																7
Thymus	+																									22
Leukemia mononuclear																										1

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

WEEKS ON STUDY	038	040	041	059	060	060	062	070	070	080	080	090	090	090	091	097	097	097	097	098	101	103	103	104	104	105
CARCASS ID	245	175	285	254	223	242	195	203	263	214	233	252	184	232	244	174	235	172	212	255	265	201	251	204	194	171
INTEGUMENTARY SYSTEM																										
Mammary gland	M	+	+	+	+	+	+	+	M	+	M	+	+	+	M	+	+	+	M	+	+	+	+	+	+	
Fibroadenoma																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basosquamous tumor benign																										
Keratoacanthoma																										
Papilloma squamous																										
Sebaceous gland, adenoma																										
Subcutaneous tissue, fibroma																							X		X	X
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Skeletal muscle													+													
Diaphragm, sarcoma, metastatic, uncertain primary site													X													
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	
Leukemia mononuclear																				X						
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Alveolar/bronchiolar adenoma															X							X				
Alveolar/bronchiolar carcinoma																										
Leukemia mononuclear						X	X				X									X	X	X				
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung																										
Nose	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
SPECIAL SENSES SYSTEM																										
Eye																										
Harderian gland	M	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	
Zymbal gland				+						+																
Carcinoma				X						X																
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear											X										X	X				
Sarcoma, metastatic, uncertain primary site													X													
Renal tubule, adenoma																										
Urethra	+																									
Urinary bladder	A	A	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	

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	105	TOTAL
CARCASS ID	173	181	182	183	185	191	192	193	202	205	211	213	215	221	222	224	225	231	234	241	243	253	261	262	264		TISSUES TUMORS
INTEGUMENTARY SYSTEM																											
Mammary gland	M											+	+														22
Fibroadenoma												X	X														2
Skin	+							+			+						+		+		+						32
Basosquamous tumor benign											X																1
Keratoacanthoma	X																										1
Papilloma squamous																			X								1
Sebaceous gland, adenoma																			X								1
Subcutaneous tissue, fibroma								X																			4
MUSCULOSKELETAL SYSTEM																											
Bone	+																										26
Skeletal muscle																											1
Diaphragm, sarcoma, metastatic, uncertain primary site																											1
NERVOUS SYSTEM																											
Brain	+																										25
Leukemia mononuclear																											1
RESPIRATORY SYSTEM																											
Lung	+						+	+							+					+							30
Alveolar/bronchiolar adenoma																				X							3
Alveolar/bronchiolar carcinoma	X																										1
Leukemia mononuclear																											6
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung	X																										1
Nose	+																										25
Trachea	+																										26
SPECIAL SENSES SYSTEM																											
Eye				+																							1
Harderian gland	+																										22
Zymbal gland																											2
Carcinoma																											2
URINARY SYSTEM																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		51
Leukemia mononuclear																											3
Sarcoma, metastatic, uncertain primary site																											1
Renal tubule, adenoma	X																										1
Urethra																											1
Urinary bladder	+																										23

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF OCHRATOXIN A: MID DOSE

WEEKS ON STUDY	042	043	055	066	073	074	075	078	078	078	080	081	082	085	096	097	098	099	101	102	102	102	103	103	103	105
CARCASS ID	415	405	444	335	365	364	333	404	392	353	352	381	393	425	402	413	354	411	341	384	373	424	412	374	342	331
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Intestine large, cecum	+	+	A	+	+	+	A		+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	A	
Intestine large, colon	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Intestine large, rectum	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Intestine small, duodenum	+	+	A	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Intestine small, ileum	+	+	A	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	A	
Intestine small, jejunum	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	A	
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Leukemia mononuclear									X				X	X		X		X								
Mesentery					+			+	+				+								+					
Carcinoma, metastatic, kidney					X																					
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	
Carcinoma, metastatic, kidney					X						X	X										X				
Leukemia mononuclear																		X								
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Tongue														+								+				
Papilloma squamous														X								X				
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Atrium, sarcoma, metastatic, uncertain primary site																									X	
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Leukemia mononuclear																X										
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+		+	+		+	+	
Leukemia mononuclear									X				X			X		X								
Pheochromocytoma malignant																										X
Pheochromocytoma complex				X																						
Pheochromocytoma benign															X					X					X	
Bilateral, pheochromocytoma benign																										
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+
Adenoma									X																	X
Carcinoma																										X
Parathyroid gland	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	M	
Pituitary gland	+	I	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Pars distalis, adenoma								X												X	X			X		
Pars distalis, carcinoma																							X			
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	
C cell, adenoma						X		X										X						X		
C cell, carcinoma																						X				
Follicular cell, adenoma																			X							
GENERAL BODY SYSTEM																										
Tissue, NOS																									+	
Sarcoma																									X	
GENITAL SYSTEM																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Adenoma						X																				
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+
Bilateral, interstitial cell, adenoma					X		X		X		X			X		X	X	X	X			X	X	X	X	X
Interstitial cell, adenoma						X				X		X	X		X					X						

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: MID 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	332	334	343	344	345	351	355	361	362	363	371	372	375	382	383	385	391	394	395	401	403	414	421	422	423	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus																										25
Intestine large																										25
Intestine large, cecum																										20
Intestine large, colon																										24
Intestine large, rectum																										24
Intestine small																										25
Intestine small, duodenum																										23
Intestine small, ileum																										21
Intestine small, jejunum																										22
Liver									+																	26
Leukemia mononuclear									X																	6
Mesentery																										5
Carcinoma, metastatic, kidney																										1
Pancreas																										24
Carcinoma, metastatic, kidney																										4
Leukemia mononuclear																										1
Salivary glands																										25
Stomach																										25
Stomach, forestomach																										25
Stomach, glandular																										25
Tongue																										2
Papilloma squamous																										2
CARDIOVASCULAR SYSTEM																										
Heart																										25
Atrium, sarcoma, metastatic, uncertain primary site																										1
ENDOCRINE SYSTEM																										
Adrenal gland		+				+														+						28
Adrenal gland, cortex																				+						25
Leukemia mononuclear																										1
Adrenal gland, medulla		+				+														+						26
Leukemia mononuclear																										4
Pheochromocytoma malignant						X																				2
Pheochromocytoma complex																										1
Pheochromocytoma benign																										3
Bilateral, pheochromocytoma benign		X																		X						2
Islets, pancreatic				+																						26
Adenoma				X																						3
Carcinoma																										1
Parathyroid gland																										21
Pituitary gland		+												+						+					+	27
Pars distalis, adenoma		X																		X					X	7
Pars distalis, carcinoma														X												2
Thyroid gland						+																			+	26
C cell, adenoma						X																			X	6
C cell, carcinoma																										1
Follicular cell, adenoma																										1
GENERAL BODY SYSTEM																										
Tissue, NOS																										1
Sarcoma																										1
GENITAL SYSTEM																										
Epididymis																										25
Preputial gland																										25
Adenoma																										1
Prostate																										25
Testes	+	+	+	+	+	+	+			+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	48
Bilateral, interstitial cell, adenoma	X	X	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	10

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

WEEKS ON STUDY	042	043	055	066	073	074	075	078	078	078	080	081	082	085	096	097	098	099	101	102	102	103	103	103	105
CARCASS ID	415	405	444	335	365	364	333	404	392	353	352	381	393	425	402	413	354	411	411	384	373	424	412	374	331
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Femoral, leukemia mononuclear									X					X				X							
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Mediastinal, carcinoma, metastatic, kidney					X							X													
Mediastinal, leukemia mononuclear									X				X	X				X							
Mediastinal, squamous cell carcinoma, metastatic, lung				X																					
Mesenteric, leukemia mononuclear																		X							
Pancreatic, leukemia mononuclear														X				X							
Renal, mediastinal, pancreatic, carcinoma, metastatic, kidney											X														
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	M		+	+	+	+	+	+	+	+	+	+	+	+	
Leukemia mononuclear									X				X	X		X		X							
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	
Carcinoma, metastatic, kidney					X																				
Fibrosarcoma																									
Leukemia mononuclear									X				X	X		X		X							
Thymus	+	+	+	M	+	+	+	+	+	M	+	+	+	M	+	+	+	M	+	+	+	+	+	+	M	
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	M	+	+	+	+	
Adenoma																								X	
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Basosquamous tumor benign																									
Keratoacanthoma														X								X			
Papilloma squamous				X										X						X					
Sebaceous gland, adenoma																	X								
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, fibrosarcoma	X																								
Subcutaneous tissue, sarcoma												X													
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Astrocytoma malignant		X																							
Osteosarcoma, metastatic, uncertain primary site																						X			
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, kidney					X						X	X													
Leukemia mononuclear									X					X		X		X							
Pheochromocytoma malignant, metastatic, adrenal gland																									X
Squamous cell carcinoma				X																					
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
SPECIAL SENSES SYSTEM																									
Eye							+															+			
Harderian gland	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	M	M	+	+	M	M	+	+	
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear									X				X	X				X							
Bilateral, renal tubule, carcinoma																									
Renal tubule, adenoma							X																		X
Renal tubule, carcinoma					X							X	X				X	X			X	X			
Renal tubule, carcinoma, multiple											X								X						
Renal tubule, epithelium, adenoma																		X							
Renal tubule, epithelium, adenoma, multiple																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: MID 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 TISSUES TUMORS
CARCASS ID	332	334	343	344	345	351	355	361	362	363	371	372	375	382	383	385	391	394	395	401	403	414	421	422	423		
HEMATOPOIETIC SYSTEM																											
Bone marrow																											25
Femoral, leukemia mononuclear																											3
Lymph node																											25
Mediastinal, carcinoma, metastatic, kidney																											2
Mediastinal, leukemia mononuclear																											4
Mediastinal, squamous cell carcinoma, metastatic, lung																											1
Mesenteric, leukemia mononuclear																											1
Pancreatic, leukemia mononuclear																											2
Renal, mediastinal, pancreatic, carcinoma, metastatic, kidney																											1
Lymph node, mandibular																											23
Leukemia mononuclear																											5
Spleen			+	+															+								27
Carcinoma, metastatic, kidney																											1
Fibrosarcoma																			X								1
Leukemia mononuclear				X																							6
Thymus																											20
INTEGUMENTARY SYSTEM																											
Mammary gland											+																23
Adenoma																											1
Fibroadenoma											X																1
Skin								+						+		+	+		+			+					30
Basosquamous tumor benign														X													1
Keratoacanthoma								X									X										4
Papilloma squamous																X											4
Sebaceous gland, adenoma																											1
Subcutaneous tissue, fibroma																			X								1
Subcutaneous tissue, fibrosarcoma																						X					2
Subcutaneous tissue, sarcoma																											1
MUSCULOSKELETAL SYSTEM																											
Bone																											25
NERVOUS SYSTEM																											
Brain																											25
Astrocytoma malignant																											1
Osteosarcoma, metastatic, uncertain primary site																											1
RESPIRATORY SYSTEM																											
Lung						+																					27
Carcinoma, metastatic, kidney																											3
Leukemia mononuclear																											4
Pheochromocytoma malignant, metastatic, adrenal gland						X																					2
Squamous cell carcinoma																											1
Nose																											24
Trachea																											25
SPECIAL SENSES SYSTEM																											
Eye										+				+													4
Harderian gland																											19
URINARY SYSTEM																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		51
Leukemia mononuclear																											4
Bilateral, renal tubule carcinoma															X												1
Renal tubule, adenoma																								X			3
Renal tubule, carcinoma			X	X	X				X			X															12
Renal tubule, carcinoma, multiple																							X				3
Renal tubule, epithelium, adenoma									X																		2
Renal tubule, epithelium, adenoma, multiple										X																	1
Urinary bladder																											24

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

WEEKS ON STUDY	056	058	059	060	061	063	073	074	074	078	078	078	078	081	082	085	092	093	093	093	093	096	098	099
CARCASS ID	534	513	551	501	494	535	554	493	495	514	525	545	584	541	561	562	522	503	504	553	555	515	581	521	512
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma							X																		
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, kidney				X		X																			
Hepatocellular carcinoma																	X								
Leukemia mononuclear			X						X										X						X
Neoplastic nodule																									
Mesentery	+	+		+		+		+		+		+								+	+			+	
Carcinoma, metastatic, kidney	X	X		X		X				X		X								X				X	
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, kidney	X			X																				X	
Leukemia mononuclear			X																X						
Acinus, adenoma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous																									
Stomach, glandular	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma								X																	
Tongue												+													
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, kidney		X				X																			
Epicardium, carcinoma, metastatic, kidney														X											
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									X
Medulla, carcinoma, metastatic, kidney		X																							
Adrenal gland, medulla	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																									
Pheochromocytoma complex																									
Pheochromocytoma benign			X																	X			X		
Bilateral, pheochromocytoma benign																								X	
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																						X			
Carcinoma																									
Parathyroid gland	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma											X						X					X			
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, kidney														X				X							
C cell, adenoma									X																
C cell, carcinoma																									X
Follicular cell, adenoma																									
GENERAL BODY SYSTEM																									
Tissue, NOS															+										+
Sarcoma																									X

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

WEEKS ON STUDY	101	104	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	563	552	491	492	502	505	511	523	524	531	532	533	542	543	544	564	565	571	572	573	574	575	582	583	585	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	47
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	50
Adenocarcinoma																										1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, kidney																										2
Hepatocellular carcinoma																										1
Leukemia mononuclear										X									X	X						7
Neoplastic nodule																			X							1
Mesentery	+																									11
Carcinoma, metastatic, kidney																										8
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, kidney																										3
Leukemia mononuclear																										2
Acinus, adenoma				X						X						X										3
Salivary glands	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	50
Papilloma squamous					X																					1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma																										1
Tongue																+										2
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, kidney																										2
Epicardium, carcinoma, metastatic, kidney																										1
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Medulla, carcinoma, metastatic, kidney																										1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma malignant															X											1
Pheochromocytoma complex											X															1
Pheochromocytoma benign		X						X	X			X						X			X					9
Bilateral, pheochromocytoma benign																				X						2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Carcinoma					X																					1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Pituitary gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma				X	X		X			X					X			X			X			X		11
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, kidney																										2
C cell, adenoma								X			X							X		X						5
C-cell, carcinoma																										1
Follicular cell, adenoma												X														1
GENERAL BODY SYSTEM																										
Tissue, NOS																										2
Sarcoma																										1

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

WEEKS ON STUDY	056	058	059	060	061	063	073	074	074	078	078	078	078	081	082	085	092	093	093	093	093	096	098	099
CARCASS ID	53 4	51 3	55 1	50 1	49 4	53 5	55 4	49 3	49 5	51 4	52 5	54 5	58 4	54 1	56 1	56 2	52 2	50 3	50 4	55 3	55 5	51 5	58 1	52 1	51 2
GENITAL SYSTEM																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, kidney				X																					
Preputial gland		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			+	+
Adenoma																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle																				+					
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma									X	X		X		X					X	X			X	X	X
Interstitial cell, adenoma					X			X			X		X		X			X			X				
Tunic, carcinoma, metastatic, kidney				X																					
HEMATOPOIETIC SYSTEM																									
Blood									+		+					+	+		+	+				+	
Leukemia mononuclear									X										X						
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Femoral, leukemia mononuclear			X																						
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Inguinal, leukemia mononuclear																			X						
Lumbar, leukemia mononuclear			X																						
Mediastinal, carcinoma, metastatic, kidney	X					X				X				X	X									X	
Mediastinal, leukemia mononuclear			X						X										X						
Pancreatic, adenocarcinoma, metastatic, stomach								X																	
Renal, leukemia mononuclear			X																						
Renal, mediastinal, pancreatic, carcinoma, metastatic, kidney				X																					
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, kidney		X																							
Carcinoma, metastatic, Zymbal gland											X														
Leukemia mononuclear			X						X										X						X
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, kidney															X									X	
Leukemia mononuclear			X						X										X						X
Thymus	+	+	M	M	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	M	+
Carcinoma, metastatic, kidney		X																							
Leukemia mononuclear																			X						
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	+	+	M	M	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma								X																	
Skin	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																				X					
Papilloma squamous																									
Sebaceous gland, adenoma																									
Subcutaneous tissue, fibroma					X																				
Subcutaneous tissue, lipoma																									
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cranium, osteosarcoma																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X																						
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, kidney	X	X		X		X				X				X				X						X	
Carcinoma, metastatic, uncertain primary site																									
Carcinoma, metastatic, kidney												X			X					X					
Leukemia mononuclear			X						X										X						X
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Eye																									
Harderian gland	M	M	M	+	M	M	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Zymbal gland											+		+									+			
Carcinoma											X		X									X			
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X																						
Bilateral, renal tubule, carcinoma															X					X					
Bilateral, renal tubule, carcinoma, multiple																									
Capsule, carcinoma, metastatic, kidney				X																					
Lymphatic, carcinoma, metastatic, kidney	X																								
Renal tubule, adenoma								X				X		X											X
Renal tubule, carcinoma	X	X		X		X				X		X				X	X	X			X			X	
Renal tubule, carcinoma, multiple														X											
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X																						

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

WEEKS ON STUDY	1 0 1	1 0 4	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	
CARCASS ID	5 5 6 3	5 5 5 2	4 9 1	4 9 2	5 0 2	5 0 5	5 1 1	5 2 3	5 2 4	5 3 1	5 3 2	5 3 3	5 4 2	5 4 3	5 4 4	5 4 6	5 6 5	5 7 1	5 7 2	5 7 3	5 7 4	5 7 5	5 8 2	5 8 3	5 8 5	TOTAL TISSUES TUMORS
GENITAL SYSTEM																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, kidney																										1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma		X							X										X							3
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle																										1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma	X	X	X	X		X		X	X		X	X		X	X	X		X	X	X		X	X		X	27
Interstitial cell, adenoma					X		X			X			X				X							X		3
Tunic, carcinoma, metastatic, kidney																										1
HEMATOPOIETIC SYSTEM																										
Blood																			+	+						9
Leukemia mononuclear																			X	X						4
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Femoral, leukemia mononuclear																										1
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Inguinal, leukemia mononuclear																										1
Lumbar, leukemia mononuclear																										1
Mediastinal, carcinoma, metastatic kidney														X												7
Mediastinal, leukemia mononuclear																			X	X						5
Pancreatic, adenocarcinoma, metastatic, stomach																										1
Renal, leukemia mononuclear																										1
Renal, mediastinal, pancreatic, carcinoma, metastatic, kidney																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, kidney																										1
Carcinoma, metastatic, Zymbal gland																										1
Leukemia mononuclear											X								X	X						7
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, kidney																										2
Leukemia mononuclear											X								X	X						7
Thymus	M	M	+	+	+	+	M	+		+	+	+	+	+	+	M	+	+	+	M	M	M	+	+	+	38
Carcinoma, metastatic, kidney																										1
Leukemia mononuclear																										1
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	M	+	+	+	+	M	+	+	M	+	+	+	+	+	+	M	M	M	+	+	+	+	+	40
Fibroadenoma						X																	X			3
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	49
Keratoacanthoma											X															2
Papilloma squamous																				X						1
Sebaceous gland, adenoma							X																			1
Subcutaneous tissue, fibroma	X																									2
Subcutaneous tissue, lipoma																									X	1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cranium, osteosarcoma	X																									1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, kidney														X												9
Carcinoma, metastatic, uncertain primary site															X											1
Carcinoma, metastatic, kidney																		X								4
Leukemia mononuclear																			X	X						5
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Eye														+									+			2
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Zymbal gland																										3
Carcinoma																										3
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																				X						2
Bilateral, renal tubule, carcinoma									X																	3
Bilateral, renal tubule, carcinoma, multiple																								X		1
Capsule, carcinoma, metastatic, kidney																										1
Lymphatic, carcinoma, metastat , kidney																										1
Renal tubule, adenoma		X	X									X				X	X				X					10
Renal tubule, carcinoma	X											X			X		X		X	X		X	X		X	20
Renal tubule, carcinoma, multiple					X					X	X			X				X								8
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1

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

	Vehicle Control	21 µg/kg	70 µg/kg	210 µg/kg
Adrenal Gland Medulla: Pheochromocytoma				
Overall Rates (a)	17/50 (34%)	(b) 4/25 (16%)	(b) 5/26 (19%)	11/50 (22%)
Adjusted Rates (c)	42.3%			37.6%
Terminal Rates (d)	16/39 (41%)			6/23 (26%)
Day of First Observation	495			408
Life Table Test (e)				P=0.547
Logistic Regression Test (e)				P=0.279N
Fisher Exact Test (e)				P=0.133N
Adrenal Gland Medulla: Pheochromocytoma, Benign, Complex, or Malignant				
Overall Rates (a)	18/50 (36%)	(b) 4/25 (16%)	(b) 8/26 (31%)	13/50 (26%)
Adjusted Rates (c)	44.8%			44.9%
Terminal Rates (d)	17/39 (44%)			8/23 (35%)
Day of First Observation	495			408
Life Table Test (e)				P=0.390
Logistic Regression Test (e)				P=0.414N
Fisher Exact Test (e)				P=0.194N
Preputial Gland: Adenoma				
Overall Rates (a)	6/50 (12%)	(b) 3/28 (11%)	(b) 1/25 (4%)	3/48 (6%)
Adjusted Rates (c)	14.6%			12.5%
Terminal Rates (d)	4/39 (10%)			2/23 (9%)
Day of First Observation	691			723
Life Table Test (e)				P=0.541N
Logistic Regression Test (e)				P=0.456N
Fisher Exact Test (e)				P=0.264N
Pancreatic Islets: Adenoma				
Overall Rates (a)	5/50 (10%)	(b) 2/26 (8%)	(b) 3/26 (12%)	1/50 (2%)
Adjusted Rates (c)	12.8%			3.4%
Terminal Rates (d)	5/39 (13%)			0/23 (0%)
Day of First Observation	729			649
Life Table Test (e)				P=0.254N
Logistic Regression Test (e)				P=0.176N
Fisher Exact Test (e)				P=0.102N
Kidney Tubule: Adenoma				
Overall Rates (a)	1/50 (2%)	1/51 (2%)	6/51 (12%)	10/50 (20%)
Adjusted Rates (c)	2.6%	3.8%	19.7%	33.1%
Terminal Rates (d)	1/39 (3%)	1/26 (4%)	4/26 (15%)	5/23 (22%)
Day of First Observation	729	729	524	513
Life Table Tests (e)	P<0.001	P=0.669	P=0.023	P<0.001
Logistic Regression Tests (e)	P<0.001	P=0.669	P=0.053	P=0.004
Cochran-Armitage Trend Test (e)	P<0.001			
Fisher Exact Test (e)		P=0.748N	P=0.059	P=0.004
Kidney Tubule: Carcinoma				
Overall Rates (a)	0/50 (0%)	0/51 (0%)	16/51 (31%)	30/50 (60%)
Adjusted Rates (c)	0.0%	0.0%	43.4%	77.2%
Terminal Rates (d)	0/39 (0%)	0/26 (0%)	7/26 (27%)	15/23 (65%)
Day of First Observation			507	390
Life Table Tests (e)	P<0.001	(f)	P<0.001	P<0.001
Logistic Regression Tests (e)	P<0.001	(f)	P<0.001	P<0.001
Cochran-Armitage Trend Test (e)	P<0.001			
Fisher Exact Test (e)		(f)	P<0.001	P<0.001

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

	Vehicle Control	21 µg/kg	70 µg/kg	210 µg/kg
Kidney Tubule: Adenoma or Carcinoma				
Overall Rates (a)	1/50 (2%)	1/51 (2%)	20/51 (39%)	36/50 (72%)
Adjusted Rates (c)	2.6%	3.8%	53.4%	87.2%
Terminal Rates (d)	1/39 (3%)	1/26 (4%)	10/26 (38%)	18/23 (78%)
Day of First Observation	729	729	507	390
Life Table Tests (e)	P<0.001	P=0.669	P<0.001	P<0.001
Logistic Regression Tests (e)	P<0.001	P=0.669	P<0.001	P<0.001
Cochran-Armitage Trend Test (e)	P<0.001			
Fisher Exact Test (e)		P=0.748N	P<0.001	P<0.001
Mammary Gland: Fibroadenoma				
Overall Rates (a)	3/50 (6%)	2/51 (4%)	1/51 (2%)	3/50 (6%)
Adjusted Rates (c)	7.2%	7.7%	3.8%	10.8%
Terminal Rates (d)	2/39 (5%)	2/26 (8%)	1/26 (4%)	2/23 (9%)
Day of First Observation	516	729	729	513
Life Table Tests (e)	P=0.361	P=0.650N	P=0.416N	P=0.483
Logistic Regression Tests (e)	P=0.473	P=0.512N	P=0.301N	P=0.661
Cochran-Armitage Trend Test (e)	P=0.504			
Fisher Exact Test (e)		P=0.491N	P=0.301N	P=0.661
Mammary Gland: Adenoma or Fibroadenoma				
Overall Rates (a)	3/50 (6%)	2/51 (4%)	2/51 (4%)	3/50 (6%)
Adjusted Rates (c)	7.2%	7.7%	7.3%	10.8%
Terminal Rates (d)	2/39 (5%)	2/26 (8%)	1/26 (4%)	2/23 (9%)
Day of First Observation	516	729	717	513
Life Table Tests (e)	P=0.358	P=0.650N	P=0.635N	P=0.483
Logistic Regression Tests (e)	P=0.473	P=0.512N	P=0.502N	P=0.661
Cochran-Armitage Trend Test (e)	P=0.512			
Fisher Exact Test (e)		P=0.491N	P=0.491N	P=0.661
Pancreas: Adenoma				
Overall Rates (a)	4/50 (8%)	(b) 3/26 (12%)	(b) 0/24 (0%)	3/50 (6%)
Adjusted Rates (c)	10.3%			13.0%
Terminal Rates (d)	4/39 (10%)			3/23 (13%)
Day of First Observation	729			729
Life Table Test (e)				P=0.532
Logistic Regression Test (e)				P=0.532
Fisher Exact Test (e)				P=0.500N
Pituitary Gland/Pars Distalis: Adenoma				
Overall Rates (a)	14/50 (28%)	(b,g) 16/33 (48%)	(b,g) 7/27 (26%)	11/49 (22%)
Adjusted Rates (c)	34.1%			40.4%
Terminal Rates (d)	12/39 (31%)			8/23 (35%)
Day of First Observation	704			540
Life Table Test (e)				P=0.318
Logistic Regression Test (e)				P=0.560
Fisher Exact Test (e)				P=0.343N
Skin: Keratoacantoma				
Overall Rates (a)	1/50 (2%)	1/51 (2%)	4/51 (8%)	2/50 (4%)
Adjusted Rates (c)	2.6%	3.8%	13.2%	7.3%
Terminal Rates (d)	1/39 (3%)	1/26 (4%)	2/26 (8%)	1/23 (4%)
Day of First Observation	729	729	589	647
Life Table Tests (e)	P=0.268	P=0.669	P=0.100	P=0.349
Logistic Regression Tests (e)	P=0.345	P=0.669	P=0.165	P=0.433
Cochran-Armitage Trend Test (e)	P=0.409			
Fisher Exact Test (e)		P=0.748N	P=0.187	P=0.500

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

	Vehicle Control	21 µg/kg	70 µg/kg	210 µg/kg
Skin: Squamous Papilloma				
Overall Rates (a)	2/50 (4%)	1/51 (2%)	4/51 (8%)	1/50 (2%)
Adjusted Rates (c)	5.1%	3.8%	11.2%	4.3%
Terminal Rates (d)	2/39 (5%)	1/26 (4%)	1/26 (4%)	1/23 (4%)
Day of First Observation	729	729	459	729
Life Table Tests (e)	P=0.608N	P=0.640N	P=0.233	P=0.681N
Logistic Regression Tests (e)	P=0.489N	P=0.640N	P=0.348	P=0.681N
Cochran-Armitage Trend Test (e)	P=0.469N			
Fisher Exact Test (e)		P=0.492N	P=0.348	P=0.500N
Subcutaneous Tissue: Fibroma				
Overall Rates (a)	4/50 (8%)	4/51 (8%)	1/51 (2%)	2/50 (4%)
Adjusted Rates (c)	9.7%	14.2%	3.8%	6.1%
Terminal Rates (d)	2/39 (5%)	2/26 (8%)	1/26 (4%)	0/23 (0%)
Day of First Observation	540	717	729	425
Life Table Tests (e)	P=0.387N	P=0.459	P=0.278N	P=0.507N
Logistic Regression Tests (e)	P=0.265N	P=0.607	P=0.181N	P=0.328N
Cochran-Armitage Trend Test (e)	P=0.245N			
Fisher Exact Test (e)		P=0.631N	P=0.175N	P=0.339N
Subcutaneous Tissue: Fibroma or Fibrosarcoma				
Overall Rates (a)	5/50 (10%)	4/51 (8%)	3/51 (6%)	2/50 (4%)
Adjusted Rates (c)	12.1%	14.2%	9.5%	6.1%
Terminal Rates (d)	3/39 (8%)	2/26 (8%)	2/26 (8%)	0/23 (0%)
Day of First Observation	540	717	290	425
Life Table Tests (e)	P=0.320N	P=0.571	P=0.512N	P=0.393N
Logistic Regression Tests (e)	P=0.186N	P=0.550N	P=0.342N	P=0.214N
Cochran-Armitage Trend Test (e)	P=0.184N			
Fisher Exact Test (e)		P=0.487N	P=0.346N	P=0.218N
Subcutaneous Tissue: Sarcoma or Fibrosarcoma				
Overall Rates (a)	2/50 (4%)	0/51 (0%)	3/51 (6%)	0/50 (0%)
Adjusted Rates (c)	4.8%	0.0%	8.1%	0.0%
Terminal Rates (d)	1/39 (3%)	0/26 (0%)	1/26 (4%)	0/23 (0%)
Day of First Observation	526		290	
Life Table Tests (e)	P=0.356N	P=0.289N	P=0.429	P=0.306N
Logistic Regression Tests (e)	P=0.306N	P=0.229N	P=0.487	P=0.232N
Cochran-Armitage Trend Test (e)	P=0.302N			
Fisher Exact Test (e)		P=0.243N	P=0.509	P=0.247N
Subcutaneous Tissue: Fibroma, Sarcoma, or Fibrosarcoma				
Overall Rates (a)	6/50 (12%)	4/51 (8%)	4/51 (8%)	2/50 (4%)
Adjusted Rates (c)	14.1%	14.2%	11.8%	6.1%
Terminal Rates (d)	3/39 (8%)	2/26 (8%)	2/26 (8%)	0/23 (0%)
Day of First Observation	526	717	290	425
Life Table Tests (e)	P=0.251N	P=0.566N	P=0.514N	P=0.273N
Logistic Regression Tests (e)	P=0.132N	P=0.385N	P=0.354N	P=0.127N
Cochran-Armitage Trend Test (e)	P=0.135N			
Fisher Exact Test (e)		P=0.358N	P=0.358N	P=0.134N
Testis: Adenoma				
Overall Rates (a)	44/50 (88%)	39/50 (78%)	42/48 (88%)	40/50 (80%)
Adjusted Rates (c)	97.8%	100.0%	100.0%	97.5%
Terminal Rates (d)	38/39 (97%)	25/25 (100%)	23/23 (100%)	22/23 (96%)
Day of First Observation	516	428	507	425
Life Table Tests (e)	P=0.019	P=0.018	P=0.002	P=0.004
Logistic Regression Test (e)	P=	P=	P=	P=0.573N
Cochran-Armitage Trend Test (e)	P=0.224N			
Fisher Exact Test (e)		P=0.143N	P=0.591N	P=0.207N

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

	Vehicle Control	21 µg/kg	70 µg/kg	210 µg/kg
Thyroid Gland: C-Cell Adenoma				
Overall Rates (a)	9/50 (18%)	(b) 5/29 (17%)	(b) 6/26 (23%)	5/50 (10%)
Adjusted Rates (c)	22.5%			19.3%
Terminal Rates (d)	8/39 (21%)			4/23 (17%)
Day of First Observation	704			513
Life Table Test (e)				P=0.546N
Logistic Regression Test (e)				P=0.358N
Fisher Exact Test (e)				P=0.194N
Thyroid Gland: C-Cell Adenoma or Carcinoma				
Overall Rates (a)	9/50 (18%)	(b) 6/29 (21%)	(b) 7/26 (27%)	6/50 (12%)
Adjusted Rates (c)	22.5%			22.4%
Terminal Rates (d)	8/39 (21%)			4/23 (17%)
Day of First Observation	704			513
Life Table Test (e)				P=0.544
Logistic Regression Test (e)				P=0.481N
Fisher Exact Test (e)				P=0.288N
Thyroid Gland: Follicular Cell Adenoma or Carcinoma				
Overall Rates (a)	3/50 (6%)	(b) 1/29 (3%)	(b) 1/26 (4%)	1/50 (2%)
Adjusted Rates (c)	7.7%			4.3%
Terminal Rates (d)	3/39 (8%)			1/23 (4%)
Day of First Observation	729			729
Life Table Test (e)				P=0.507N
Logistic Regression Test (e)				P=0.507N
Fisher Exact Test (e)				P=0.309N
Zymbal Gland: Carcinoma				
Overall Rates (a)	0/50 (0%)	2/51 (4%)	0/51 (0%)	3/50 (6%)
Adjusted Rates (c)	0.0%	4.4%	0.0%	8.2%
Terminal Rates (d)	0/39 (0%)	0/26 (0%)	0/26 (0%)	0/23 (0%)
Day of First Observation		409		540
Life Table Tests (e)	P=0.088	P=0.242	(f)	P=0.097
Logistic Regression Tests (e)	P=0.092	P=0.215	(f)	P=0.120
Cochran-Armitage Trend Test (e)	P=0.105			
Fisher Exact Test (e)		P=0.252	(f)	P=0.121
Hematopoietic System: Mononuclear Leukemia				
Overall Rates (a)	12/50 (24%)	(b,h) 7/51 (14%)	(b,i) 7/51 (14%)	7/50 (14%)
Adjusted Rates (c)	29.8%			22.5%
Terminal Rates (d)	11/39 (28%)			3/23 (13%)
Day of First Observation	516			408
Life Table Test (e)				P=0.504N
Logistic Regression Test (e)				P=0.198N
Fisher Exact Test (e)				P=0.154N
All Sites: Mesothelioma				
Overall Rates (a)	1/50 (2%)	4/51 (8%)	0/51 (0%)	0/50 (0%)
Adjusted Rates (c)	2.6%	11.4%	0.0%	0.0%
Terminal Rates (d)	1/39 (3%)	1/26 (4%)	0/26 (0%)	0/23 (0%)
Day of First Observation	729	487		
Life Table Tests (e)	P=0.155N	P=0.118	P=0.581N	P=0.605N
Logistic Regression Tests (e)	P=0.108N	P=0.184	P=0.581N	P=0.605N
Cochran-Armitage Trend Test (e)	P=0.108N			
Fisher Exact Test (e)		P=0.187	P=0.495N	P=0.500N

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

(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) No P value is reported because no tumors were observed in the dosed and vehicle control groups.
(g) Two carcinomas were also observed.
(h) Twenty-six livers and 29 spleens were examined microscopically.
(i) Twenty-six livers and 27 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 Battelle Columbus Laboratories	
Chlorobenzene	0/50
1,2-Dichlorobenzene	0/50
1,4-Dichlorobenzene	(b) 1/50
Benzene	(b) 1/50
Xylenes	(b) 1/48
TOTAL	3/248 (1.2%)
SD (c)	1.11%
Range (d)	
High	1/48
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, two adenocarcinomas, NOS, and five tubular cell adenocarcinomas

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

Study	Incidence of Squamous Cell Papillomas in Vehicle Controls
Historical Incidence at Battelle Columbus Laboratories	
Chlorobenzene	0/50
1,2-Dichlorobenzene	0/50
1,4-Dichlorobenzene	1/50
Benzene	1/50
Xylenes	0/50
TOTAL	2/250 (0.8%)
SD (b)	1.10%
Range (c)	
High	1/50
Low	0/50
Overall Historical Incidence	
TOTAL	6/1,949 (0.3%)
SD (b)	0.86%
Range (c)	
High	2/50
Low	0/50

(a) Data as of April 29, 1987, for studies of at least 104 weeks; no malignant tumors have been observed.
(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 OCHRATOXIN A

	Vehicle Control	Low Dose	Mid Dose	High Dose
Animals initially in study	80	80	80	80
Animals removed	80	80	80	80
Animals examined histopathologically	50	51	51	50
ALIMENTARY SYSTEM				
Intestine large, cecum	(50)	(23)	(20)	(50)
Inflammation, chronic active, diffuse			1 (5%)	
Intestine large, colon	(50)	(25)	(24)	(50)
Parasite metazoan	1 (2%)			2 (4%)
Intestine large, rectum	(48)	(23)	(24)	(47)
Parasite metazoan	6 (13%)	2 (9%)		3 (6%)
Intestine small, duodenum	(50)	(25)	(23)	(50)
Necrosis, acute, focal				1 (2%)
Liver	(50)	(26)	(26)	(50)
Angiectasis, multifocal				1 (2%)
Basophilic focus, multiple	40 (80%)	13 (50%)	8 (31%)	33 (66%)
Clear cell focus	9 (18%)			6 (12%)
Clear cell focus, multiple				1 (2%)
Congestion	1 (2%)	1 (4%)		
Cytoplasmic alteration, focal			1 (4%)	2 (4%)
Degeneration, cystic, focal	2 (4%)	1 (4%)	1 (4%)	1 (2%)
Eosinophilic focus				2 (4%)
Hematopoietic cell proliferation, multifocal	2 (4%)			1 (2%)
Inflammation, chronic active, multifocal	8 (16%)	1 (4%)		3 (6%)
Mixed cell focus		1 (4%)		
Necrosis, acute	1 (2%)	5 (19%)	1 (4%)	1 (2%)
Thrombus				1 (2%)
Bile duct, hyperplasia, multifocal	38 (76%)	16 (62%)	14 (54%)	30 (60%)
Centrilobular, vacuolization cytoplasmic, diffuse	23 (46%)	5 (19%)	2 (8%)	13 (26%)
Periportal, vacuolization cytoplasmic, diffuse		1 (4%)	1 (4%)	1 (2%)
Mesentery	(1)	(7)	(5)	(11)
Inflammation, chronic active		3 (43%)	4 (80%)	3 (27%)
Pancreas	(50)	(26)	(24)	(50)
Inflammation, acute, multifocal				1 (2%)
Inflammation, chronic, diffuse	1 (2%)			1 (2%)
Acinus, atrophy	17 (34%)	8 (31%)	1 (4%)	14 (28%)
Acinus, focal cellular change	6 (12%)			5 (10%)
Acinus, hyperplasia, focal	6 (12%)		2 (8%)	8 (16%)
Duct, ectasia, multifocal	1 (2%)			
Perivascular, inflammation, chronic active, multifocal		1 (4%)		3 (6%)
Salivary glands	(50)	(26)	(25)	(49)
Acinus, atrophy, multifocal				2 (4%)
Stomach, forestomach	(50)	(25)	(25)	(50)
Acanthosis		1 (4%)		8 (16%)
Acanthosis, focal	1 (2%)			1 (2%)
Acanthosis, multifocal				1 (2%)
Cyst epithelial inclusion				1 (2%)
Erosion				1 (2%)
Inflammation, chronic active	1 (2%)	2 (8%)	2 (8%)	6 (12%)
Ulcer	1 (2%)	2 (8%)	2 (8%)	2 (4%)
Stomach, glandular	(50)	(25)	(25)	(49)
Hyperplasia, multifocal				1 (2%)
Inflammation, acute		1 (4%)		
Ulcer				4 (8%)
Tongue		(3)	(2)	(2)
Epithelium, hyperkeratosis, focal				1 (50%)
Epithelium, hyperplasia		1 (33%)		2 (100%)

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

	Vehicle Control	Low Dose	Mid Dose	High Dose
CARDIOVASCULAR SYSTEM				
Heart	(50)	(26)	(25)	(50)
Degeneration, chronic, multifocal	47 (94%)	26 (100%)	22 (88%)	47 (94%)
Inflammation, chronic, focal	1 (2%)			
Epicardium, fibrosis, multifocal				1 (2%)
ENDOCRINE SYSTEM				
Adrenal gland, cortex	(50)	(25)	(25)	(50)
Cytoplasmic alteration			1 (4%)	1 (2%)
Degeneration				2 (4%)
Degeneration, fatty	6 (12%)	2 (8%)	3 (12%)	12 (24%)
Hyperplasia	18 (36%)	3 (12%)	2 (8%)	13 (26%)
Hyperplasia, multifocal				1 (2%)
Hypertrophy	5 (10%)		1 (4%)	2 (4%)
Bilateral, atrophy, diffuse			1 (4%)	
Adrenal gland, medulla	(50)	(25)	(26)	(49)
Hyperplasia	7 (14%)	2 (8%)	4 (15%)	10 (20%)
Hyperplasia, focal				1 (2%)
Islets, pancreatic	(50)	(26)	(26)	(50)
Hyperplasia, focal	1 (2%)			
Pituitary gland	(50)	(33)	(27)	(49)
Pars distalis, cyst	1 (2%)	1 (3%)	2 (7%)	3 (6%)
Pars distalis, hyperplasia	6 (12%)	4 (12%)	3 (11%)	14 (29%)
Pars intermedia, cyst	1 (2%)			1 (2%)
Pars nervosa, hyperplasia				1 (2%)
Rathke's cleft, cyst, multiple				1 (2%)
Thyroid gland	(50)	(29)	(26)	(50)
C-cell, hyperplasia	24 (48%)	6 (21%)	10 (38%)	16 (32%)
Follicle, cyst	1 (2%)			2 (4%)
Follicular cell, hyperplasia	1 (2%)			3 (6%)
GENERAL BODY SYSTEM				
Tissue, NOS		(1)	(1)	(2)
Inflammation, chronic active, diffuse				1 (50%)
GENITAL SYSTEM				
Epididymis	(49)	(26)	(25)	(50)
Atrophy, diffuse			1 (4%)	
Preputial gland	(50)	(28)	(25)	(48)
Hyperplasia		1 (4%)	1 (4%)	
Inflammation, chronic active, multifocal	44 (88%)	11 (39%)	11 (44%)	38 (79%)
Duct, ectasia	8 (16%)	1 (4%)		3 (6%)
Prostate	(50)	(26)	(25)	(50)
Atrophy, diffuse			1 (4%)	
Cyst				1 (2%)
Dilatation, diffuse				1 (2%)
Inflammation, acute		1 (4%)		
Inflammation, chronic active, multifocal	15 (30%)	2 (8%)		12 (24%)
Epithelium, hyperplasia, multifocal			1 (4%)	
Seminal vesicle		(1)		(1)
Dilatation		1 (100%)		
Inflammation, acute		1 (100%)		
Testes	(50)	(50)	(48)	(50)
Inflammation, necrotizing, chronic active, diffuse				1 (2%)
Germinal epithelium, atrophy	43 (86%)	1 (2%)	40 (83%)	33 (66%)
Interstitial cell, hyperplasia	22 (44%)	13 (26%)	14 (29%)	24 (48%)
Perivascular, inflammation, chronic, multifocal				1 (2%)

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

	Vehicle Control	Low Dose	Mid Dose	High Dose
HEMATOPOIETIC SYSTEM				
Blood	(1)			(9)
Neutrophilia				5 (56%)
Bone marrow	(50)	(25)	(25)	(50)
Femoral, hyperplasia, neutrophil, diffuse		1 (4%)		1 (2%)
Lymph node	(50)	(28)	(25)	(50)
Inguinal, sinus, ectasia		1 (4%)		
Lumbar, sinus, ectasia		1 (4%)		
Mediastinal, congestion		1 (4%)		
Mediastinal, hemorrhage, multifocal				1 (2%)
Mesenteric, cyst				1 (2%)
Mesenteric, inflammation, chronic active, multifocal				1 (2%)
Mesenteric, sinus, ectasia		1 (4%)		
Lymph node, mandibular	(49)	(28)	(23)	(50)
Hemorrhage, multifocal				2 (4%)
Infiltration cellular, plasma cell		3 (11%)		1 (2%)
Necrosis, acute, multifocal	1 (2%)			
Spleen	(50)	(29)	(27)	(50)
Angiectasis		1 (3%)		
Depletion lymphoid	3 (6%)	5 (17%)		
Infiltration cellular, lipocyte, multifocal	1 (2%)			
Red pulp, fibrosis	2 (4%)	2 (7%)	1 (4%)	2 (4%)
Red pulp, hematopoietic cell proliferation, diffuse	3 (6%)	1 (3%)	1 (4%)	8 (16%)
Red pulp, infiltration cellular, lipocyte, multifocal				1 (2%)
INTEGUMENTARY SYSTEM				
Mammary gland	(39)	(22)	(23)	(40)
Hyperplasia, cystic, multifocal	37 (95%)	18 (82%)	18 (78%)	38 (95%)
Skin	(49)	(32)	(30)	(49)
Cyst epithelial inclusion	1 (2%)			
Hyperkeratosis		1 (3%)	1 (3%)	
Subcutaneous tissue, fibrosis		1 (3%)		
Subcutaneous tissue, inflammation, chronic active, diffuse	1 (2%)			
MUSCULOSKELETAL SYSTEM				
None				
NERVOUS SYSTEM				
Brain	(50)	(25)	(25)	(50)
Compression	1 (2%)	1 (4%)	1 (4%)	1 (2%)
Ventricle, hydrocephalus	1 (2%)	2 (8%)	1 (4%)	
RESPIRATORY SYSTEM				
Lung	(50)	(30)	(27)	(50)
Congestion	2 (4%)		2 (7%)	
Edema, acute, diffuse	3 (6%)			
Foreign body, multifocal	11 (22%)	9 (30%)	5 (19%)	6 (12%)
Mineralization, focal	1 (2%)			
Pigmentation		2 (7%)		
Alveolar epithelium, hyperplasia	3 (6%)	1 (3%)	2 (7%)	1 (2%)
Interstitium, inflammation, acute, multifocal		2 (7%)	1 (4%)	
Interstitium, inflammation, chronic active, multifocal	21 (42%)	5 (17%)	2 (7%)	14 (28%)
Perivascular, edema, acute		4 (13%)		

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

	Vehicle Control	Low Dose	Mid Dose	High Dose
RESPIRATORY SYSTEM (Continued)				
Nose	(50)	(25)	(24)	(50)
Lumen, foreign body				2 (4%)
Nasolacrimal duct, hyperplasia			1 (4%)	
SPECIAL SENSES SYSTEM				
Eye	(3)	(1)	(4)	(2)
Lens, cataract	3 (100%)	1 (100%)	2 (50%)	2 (100%)
Retina, atrophy, diffuse	3 (100%)	1 (100%)	2 (50%)	2 (100%)
URINARY SYSTEM				
Kidney	(50)	(51)	(51)	(50)
Cyst				6 (12%)
Cyst, multiple		1 (2%)		4 (8%)
Fibrosis, focal			1 (2%)	
Hydronephrosis		1 (2%)		1 (2%)
Nephropathy, chronic, diffuse	48 (96%)	51 (100%)	51 (100%)	48 (96%)
Pelvis, epithelium, hyperplasia, multifocal				1 (2%)
Pelvis, epithelium, hyperplasia, papillary, multifocal				1 (2%)
Renal tubule, hyperplasia	1 (2%)			
Renal tubule, epithelium, cytoplasmic alteration, focal	1 (2%)		2 (4%)	7 (14%)
Renal tubule, epithelium, cytoplasmic alteration, multifocal			1 (2%)	1 (2%)
Renal tubule, epithelium, degeneration, multifocal			50 (98%)	49 (98%)
Renal tubule, epithelium, hyperplasia, focal	1 (2%)		11 (22%)	15 (30%)
Renal tubule, epithelium, hyperplasia, multifocal		1 (2%)	5 (10%)	9 (18%)
Renal tubule, epithelium, karyomegaly, multifocal		1 (2%)	51 (100%)	50 (100%)
Renal tubule, epithelium, proliferation, focal			4 (8%)	13 (26%)
Renal tubule, epithelium, proliferation, multifocal			6 (12%)	13 (26%)
Vein, dilatation, focal	1 (2%)			
Urethra		(1)		
Calculus micro observation only		1 (100%)		
Urinary bladder	(50)	(23)	(24)	(50)
Calculus micro observation only	2 (4%)			1 (2%)
Ectasia		1 (4%)		
Inflammation, acute		1 (4%)		
Mucosa, hyperplasia, diffuse				1 (2%)
Serosa, necrosis, chronic active, multifocal				1 (2%)
Submucosa, inflammation, chronic active, multifocal				1 (2%)

APPENDIX B

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

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

	Vehicle Control	Low Dose	Mid Dose	High Dose
Animals initially in study	80	80	80	80
Animals removed	80	80	80	80
Animals examined histopathologically	50	51	50	50
ALIMENTARY SYSTEM				
Liver	(50)	*(51)	*(50)	(50)
Carcinoma, metastatic, kidney			1 (2%)	
Leukemia mononuclear	10 (20%)	8 (16%)	2 (4%)	2 (4%)
Mesentery	*(50)	*(51)	*(50)	*(50)
Carcinoma, metastatic, kidney			1 (2%)	
Pancreas	(50)	*(51)	*(50)	(50)
Carcinoma, metastatic, kidney			1 (2%)	
Leukemia mononuclear	1 (2%)	1 (2%)		
Acinus, adenoma				1 (2%)
Pharynx	*(50)	*(51)	*(50)	*(50)
Squamous cell carcinoma	1 (2%)			
CARDIOVASCULAR SYSTEM				
Heart	(50)	*(51)	*(50)	(50)
Leukemia mononuclear		1 (2%)		
Sarcoma		1 (2%)		
ENDOCRINE SYSTEM				
Adrenal gland, cortex	(50)	*(51)	*(50)	(50)
Adenoma	2 (4%)			
Carcinoma				1 (2%)
Leukemia mononuclear	5 (10%)	1 (2%)		
Medulla, carcinoma, metastatic, kidney			1 (2%)	
Adrenal gland, medulla	(50)	*(51)	*(50)	(50)
Leukemia mononuclear	5 (10%)	2 (4%)	1 (2%)	
Pheochromocytoma complex		1 (2%)		
Pheochromocytoma benign	3 (6%)	1 (2%)	2 (4%)	4 (8%)
Islets, pancreatic	(50)	*(51)	*(50)	(50)
Adenoma			1 (2%)	
Carcinoma, multiple	1 (2%)			
Parathyroid gland	(39)	*(51)	*(50)	(42)
Adenoma				1 (2%)
Pituitary gland	(49)	*(51)	*(50)	(49)
Leukemia mononuclear		1 (2%)		
Pars distalis, adenoma	16 (33%)	19 (37%)	15 (30%)	22 (45%)
Pars distalis, carcinoma	1 (2%)	2 (4%)	1 (2%)	
Pars intermedia, adenoma			1 (2%)	
Pars intermedia, carcinoma			1 (2%)	
Thyroid gland	(50)	*(51)	*(50)	(50)
Bilateral, C-cell, adenoma			1 (2%)	1 (2%)
C-cell, adenoma	7 (14%)	7 (14%)	4 (8%)	2 (4%)
C-cell, carcinoma	1 (2%)			
Follicular cell, adenoma		1 (2%)		
Follicular cell, carcinoma		1 (2%)	1 (2%)	
GENERAL BODY SYSTEM				
None				

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

	Vehicle Control	Low Dose	Mid Dose	High Dose
GENITAL SYSTEM				
Clitoral gland	(49)	*(51)	*(50)	(47)
Adenoma	7 (14%)	4 (8%)	2 (4%)	3 (6%)
Carcinoma			1 (2%)	1 (2%)
Bilateral, adenoma			1 (2%)	
Ovary	(49)	*(51)	*(50)	(50)
Carcinoma, metastatic, kidney			1 (2%)	
Leukemia mononuclear		1 (2%)		
Uterus	(49)	*(51)	*(50)	(50)
Leiomyosarcoma			1 (2%)	
Leukemia mononuclear		1 (2%)		
Polyp stromal	2 (4%)	7 (14%)	2 (4%)	6 (12%)
Polyp stromal, multiple				1 (2%)
Sarcoma stromal			1 (2%)	
HEMATOPOIETIC SYSTEM				
Blood	*(50)	*(51)	*(50)	*(50)
Leukemia mononuclear	2 (4%)			
Bone marrow	(49)	*(51)	*(50)	(50)
Femoral, leukemia mononuclear	1 (2%)	4 (8%)	1 (2%)	
Lymph node	(50)	*(51)	*(50)	(50)
Mediastinal, basosquamous tumor malignant, metastatic, thymus				1 (2%)
Mediastinal, leukemia mononuclear	7 (14%)	3 (6%)		1 (2%)
Mesenteric, leukemia mononuclear	2 (4%)	2 (4%)		
Lymph node, mandibular	(50)	*(51)	*(50)	(50)
Leukemia mononuclear	9 (18%)	6 (12%)	2 (4%)	3 (6%)
Spleen	(50)	*(51)	*(50)	(50)
Leukemia mononuclear	10 (20%)	8 (16%)	2 (4%)	3 (6%)
Thymus	(43)	*(51)	*(50)	(44)
Basosquamous tumor malignant				1 (2%)
Leukemia mononuclear	1 (2%)			
Thymoma benign				1 (2%)
INTEGUMENTARY SYSTEM				
Mammary gland	(47)	*(51)	*(50)	(49)
Adenocarcinoma	1 (2%)	2 (4%)	2 (4%)	2 (4%)
Adenoma			1 (2%)	
Fibroadenoma	13 (28%)	19 (37%)	17 (34%)	14 (29%)
Fibroadenoma, multiple	4 (9%)	4 (8%)	5 (10%)	14 (29%)
Skin	(49)	*(51)	*(50)	(50)
Basosquamous tumor benign		1 (2%)		
Papilloma squamous		2 (4%)		1 (2%)
Subcutaneous tissue, fibroma		1 (2%)	1 (2%)	
Subcutaneous tissue, fibrosarcoma	1 (2%)	2 (4%)		2 (4%)
Subcutaneous tissue, lipoma		1 (2%)		
MUSCULOSKELETAL SYSTEM				
None				
NERVOUS SYSTEM				
Brain	(50)	*(51)	*(50)	(50)
Astrocytoma malignant		2 (4%)		
Carcinoma, metastatic, pituitary gland	1 (2%)			
Oligodendroglioma malignant			1 (2%)	

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

	Vehicle Control	Low Dose	Mid Dose	High Dose
RESPIRATORY SYSTEM				
Lung	(50)	*(51)	*(50)	(50)
Alveolar/bronchiolar adenoma		1 (2%)		1 (2%)
Basosquamous tumor malignant, metastatic, thymus				1 (2%)
Carcinoma, metastatic, kidney			1 (2%)	
Leukemia mononuclear	9 (18%)	5 (10%)	1 (2%)	2 (4%)
SPECIAL SENSES SYSTEM				
Zymbal gland	50)	*(51)	*(50)	*(50)
Carcinoma		1 (2%)	2 (4%)	
URINARY SYSTEM				
Kidney	(50)	(51)	(50)	(50)
Leukemia mononuclear	5 (10%)	4 (8%)		
Renal tubule, adenoma			1 (2%)	3 (6%)
Renal tubule, adenoma, multiple				2 (4%)
Renal tubule, carcinoma			1 (2%)	3 (6%)
SYSTEMIC LESIONS				
Multiple organs	*(50)	*(51)	*(50)	*(50)
Leukemia mononuclear	10 (20%)	8 (16%)	2 (4%)	3 (6%)
ANIMAL DISPOSITION SUMMARY				
Animals initially in study	80	80	80	80
Terminal sacrifice	32	23	35	34
Moribund	10	22	11	11
Dead	7	3	4	5
Gavage death	1	3		
Scheduled sacrifice	30	29	30	30
TUMOR SUMMARY				
Total animals with primary neoplasms **	39	44	40	45
Total primary neoplasms	70	88	68	90
Total animals with benign neoplasms	34	38	34	42
Total benign neoplasms	54	68	54	77
Total animals with malignant neoplasms	14	19	13	10
Total malignant neoplasms	16	20	14	13
Total animals with secondary neoplasms ***	1		1	1
Total secondary neoplasms	1		6	2

* 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 OCHRATOXIN A: VEHICLE CONTROL

WEEKS ON STUDY	0 3 1	0 6 1	0 6 7	0 7 1	0 7 1	0 7 5	0 8 2	0 8 4	0 8 6	0 9 3	0 9 4	0 9 4	0 9 5	0 9 7	0 9 7	0 9 9	1 0 0	1 0 3	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4
CARCASS ID	7 0 5	7 3 3	7 1 1	7 6 5	7 3 2	7 1 5	7 5 5	7 1 2	7 3 5	6 8 5	7 0 1	7 2 5	7 0 2	7 2 3	7 6 4	6 9 2	6 8 2	7 5 3	6 8 1	6 8 3	6 8 4	6 9 1	6 9 3	6 9 4	6 9 5
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	M	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X	X		X	X		X						X	X								
Mesentery																	+								
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																	X								
Pharynx												+													
Squamous cell carcinoma												X													
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue												+													
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Leukemia mononuclear				X			X	X								X	X								
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X			X	X								X	X								
Pheochromocytoma benign															X						X				
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, multiple																									
Parathyroid gland	+	+	+	+	+	+	M	+	M	+	M	+	M	+	+	M	+	+	+	+	M	M	+	+	+
Pituitary gland	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma			X						X		X	X	X	X				X	X		X		X		
Pars distalis, carcinoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C cell, adenoma							X		X							X					X			X	
C cell, carcinoma																									
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma					X	X				X								X			X		X		
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Polyp stromal														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	104	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL TISSUES TUMORS
CARCASS ID	703	704	713	714	721	722	724	731	734	741	742	743	744	745	751	752	754	761	762	763	771	772	773	774	775	
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																		X		X					X	10
Mesentery																										1
Pancreas			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Pharynx																										1
Squamous cell carcinoma																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue																										1
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma					X																		X			2
Leukemia mononuclear																										5
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										5
Pheochromocytoma benign														X												3
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, multiple								X																		1
Parathyroid gland	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	M	39
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma						X	X										X	X			X				X	16
Pars distalis, carcinoma													X													1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C cell, adenoma		X									X															7
C cell, carcinoma																		X								1
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																	X									7
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Polyp stromal														X												2

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

WEEKS ON STUDY	031	061	067	071	071	075	082	084	086	093	094	094	095	097	097	099	100	103	104	104	104	104	104	104	104
CARCASS ID	705	733	711	765	732	715	755	712	735	685	701	725	702	723	764	692	682	753	681	683	684	691	693	694	695
HEMATOPOIETIC SYSTEM																									
Blood							+										+								
Leukemia mononuclear							X										X								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+
Femoral, leukemia mononuclear				X																					
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mediastinal, leukemia mononuclear				X	X		X									X	X								
Mesenteric, leukemia mononuclear				X													X								
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X	X		X	X								X	X								
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	-	+
Leukemia mononuclear				X	X		X	X		X						X	X								
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M
Leukemia mononuclear					X																				
INTEGUMENTARY SYSTEM																									
Mammary gland	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Fibroadenoma						X									X			X	X	X	X				
Fibroadenoma, multiple											X												X		
Skin	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma																									
MUSCULOSKELETAL SYSTEM																									
Bone	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pituitary gland																									
RESPIRATORY SYSTEM																									
Lung	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X	X		X	X		X						X	X								
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Ear								+																	
Eye							+																	+	
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	M	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	-	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X			X		X						X	X								
Urinary bladder	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+

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

WEEKS ON STUDY	104	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	
CARCASS ID	703	704	713	714	721	722	724	731	734	741	742	743	744	745	751	752	754	761	762	763	771	772	773	774	775	TOTAL TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Blood																										2
Leukemia mononuclear																										2
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Femoral, leukemia mononuclear																										1
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mediastinal, leukemia mononuclear																		X							X	7
Mesenteric, leukemia mononuclear																										2
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																		X		X					X	9
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																		X		X					X	10
Thymus	+	+	+	+	M	M	M	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	43
Leukemia mononuclear																										1
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	47
Adenocarcinoma																		X								1
Fibroadenoma						X					X		X			X			X	X				X		13
Fibroadenoma, multiple																		X							X	4
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Subcutaneous tissue, fibrosarcoma			X																							1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, pituitary gland													X													1
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																				X					X	9
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Ear																										1
Eye	+				+																					4
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										5
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

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

WEEKS ON STUDY	001	029	060	063	065	065	075	077	083	084	089	090	090	091	091	092	093	093	094	094	095	095	097	101	103	103
CARCASS ID	8864	9051	8535	9255	8554	8884	9055	9233	9311	8411	9211	9332	8574	8711	9114	8444	9334	8994	8772	8993	8883	9335	8555	9001	8773	8992
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear										X			X	X		X	X			X			X	X		
Mesentery																										
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear													X													
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																								X		
Sarcoma																										
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear														X												
Adrenal gland, medulla	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+
Leukemia mononuclear													X	X												
Pheochromocytoma complex																										
Pheochromocytoma benign																										
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	M	M	+	+	M	+	M	M	+	M	+	M	M	+	+	+	+	+	M	M	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																								X		
Pars distalis, adenoma										X	X				X			X		X	X	X	X		X	X
Pars distalis, carcinoma																			X							
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C cell, adenoma															X	X					X					
Follicular cell, adenoma																										
Follicular cell, carcinoma																										
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Adenoma											X								X						X	
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear													X													
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear													X													
Polyp stromal												X	X	X												
HEMATOPOIETIC SYSTEM																										
Blood															+								+			
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Femoral, leukemia mononuclear													X	X		X								X		
Lymph node	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mediastinal, leukemia mononuclear													X										X	X		
Mesenteric, leukemia mononuclear																	X						X			
Lymph node, mandibular	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+
Leukemia mononuclear										X			X	X		X	X							X		
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear										X			X	X		X	X			X			X	X		
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+

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

WEEKS ON STUDY	103	104	104	104	104	104	104	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL
CARCASS ID	8422	9232	8433	8445	8451	8525	8616	8626	8633	8665	8675	8681	8822	8855	8991	9095	9102	9103	9104	9111	9121	9131	9155	9244	9333	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+																								28
Intestine large	+	+																								28
Intestine large, cecum	+	+																								28
Intestine large, colon	+	+																								28
Intestine large, rectum	+	+																								28
Intestine small	+	+																								28
Intestine small, duodenum	+	+																								28
Intestine small, ileum	+	+																								28
Intestine small, jejunum	+	+																								28
Liver	+	+							+																	29
Leukemia mononuclear																										8
Mesentery																			+							1
Pancreas	+	+																	+							29
Leukemia mononuclear																										1
Salivary glands	+	+																								28
Stomach	+	+																								28
Stomach, forestomach	+	+																								28
Stomach, glandular	+	+																								28
CARDIOVASCULAR SYSTEM																										
Heart	+	+																								28
Leukemia mononuclear																										1
Sarcoma		X																								1
ENDOCRINE SYSTEM																										
Adrenal gland	+	+									+															29
Adrenal gland, cortex	+	+									+															29
Leukemia mononuclear																										1
Adrenal gland, medulla	+	+									+															27
Leukemia mononuclear																										2
Pheochromocytoma complex											X															1
Pheochromocytoma benign	X																									1
Islets, pancreatic	+	+																								28
Parathyroid gland	+	+																								17
Pituitary gland	+	+		+		+	+	+		+	+				+	+	+	+				+	+	+		41
Leukemia mononuclear																										1
Pars distalis, adenoma	X									X					X	X	X	X				X	X	X		19
Pars distalis, carcinoma	X																									2
Thyroid gland	+	+									+					+		+						+		32
C-cell, adenoma											X					X		X						X		7
Follicular cell, adenoma	X																									1
Follicular cell, carcinoma																		X								1
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Clitoral gland	+	+	+				+																			29
Adenoma			X																							4
Ovary	+	+				+																				29
Leukemia mononuclear																										1
Uterus	+	+		+	+						+							+								32
Leukemia mononuclear																										1
Polyp stromal				X	X						X							X								7
HEMATOPOIETIC SYSTEM																										
Blood																										2
Bone marrow	+	+																								28
Femoral, leukemia mononuclear																										4
Lymph node	+	+																								27
Mediastinal, leukemia mononuclear																										3
Mesenteric, leukemia mononuclear																										2
Lymph node, mandibular	+	+																								26
Leukemia mononuclear																										6
Spleen	+	+						+																		29
Leukemia mononuclear																										8
Thymus	+	+																								27

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

WEEKS ON STUDY	001	029	060	063	065	065	075	077	083	084	089	090	090	091	091	092	093	093	094	094	095	095	097	101	103	103
CARCASS ID	864	951	853	925	854	884	905	923	931	841	921	932	874	871	914	844	934	894	872	893	883	935	855	901	873	892
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+		+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									X	
Fibroadenoma				X		X								X					X			X	X	X		
Fibroadenoma, multiple																									X	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basosquamous tumor benign																										
Papilloma squamous																										
Subcutaneous tissue, fibroma												X														
Subcutaneous tissue, fibrosarcoma							X																			
Subcutaneous tissue, lipoma																										
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant								X																		
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma															X											
Leukemia mononuclear														X			X			X			X	X		
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																										
Eye																						+				
Harderian gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Zymbal gland									+																	
Carcinoma									X																	
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear													X			X	X							X		
Urinary bladder	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

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

WEEKS ON STUDY	103	104	104	104	104	104	104	104	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	
CARCASS ID	842	922	843	845	851	852	861	862	863	865	875	881	882	885	891	895	902	903	904	911	912	913	915	924	933	TOTAL TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Mammary gland	+	M		+		+	+	+	+	+				+	+	+	+				+		+	+	+	+	40
Adenocarcinoma														X												2
Fibroadenoma	X					X	X	X		X					X	X					X		X	X	X	X	19
Fibroadenoma, multiple				X					X								X									4
Skin	+	+											+				+					+				31
Basosquamous tumor benign																						X				1
Papilloma squamous													X				X									2
Subcutaneous tissue, fibroma																										1
Subcutaneous tissue, fibrosarcoma																						X				2
Subcutaneous tissue, lipoma													X													1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+																								28
NERVOUS SYSTEM																										
Brain	+	+																								28
Astrocytoma malignant	X																									2
RESPIRATORY SYSTEM																										
Lung	+	+				+									+						+			+		32
Alveolar/bronchiolar adenoma																										1
Leukemia mononuclear																										5
Nose	+	+																								28
Trachea	+	+																								28
SPECIAL SENSES SYSTEM																										
Eye													+													2
Harderian gland	+	+																								27
Zymbal gland																										1
Carcinoma																										1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Leukemia mononuclear																										4
Urinary bladder	+	+																								27

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF OCHRATOXIN A: MID DOSE

WEEKS ON STUDY	046	053	067	073	077	081	085	089	091	095	095	096	096	100	100	104	104	104	104	104	104	104	104	104	104	105	105
CARCASS ID	10555	10754	10664	10055	10995	10933	10443	10711	10524	10224	10222	10115	10441	10811	10444	10101	10102	10103	10044	10111	10112	10113	10114	10121	10123		
ALIMENTARY SYSTEM																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+												
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+												
Intestine large, cecum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+												
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+												
Intestine large, rectum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+												
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+												
Intestine small, duodenum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+												
Intestine small, ileum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+												
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+												
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				+	+	+						
Carcinoma, metastatic, kidney	X																										
Leukemia mononuclear												X	X														
Mesentery	+																										
Carcinoma, metastatic, kidney	X																										
Pancreas	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+												
Carcinoma, metastatic, kidney	X																										
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+												
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+												
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+												
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+												
Tongue																											
CARDIOVASCULAR SYSTEM																											
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+												
ENDOCRINE SYSTEM																											
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+												
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+												
Medulla, carcinoma, metastatic, kidney	X																										
Adrenal gland, medulla		+	+	+	+	+	+	+	+	+	+	+	+	+	+												
Leukemia mononuclear													X														
Pheochromocytoma benign															X												
Islets, pancreatic	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+												
Adenoma									X																		
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+												
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			+	+	+	+			+	+	
Pars distalis, adenoma							X							X					X	X	X	X					
Pars distalis, carcinoma												X															
Pars intermedia, adenoma																											
Pars intermedia, carcinoma									X																		
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+							
Bilateral, C-cell, adenoma																											
C cell, adenoma													X		X					X							
Follicular cell, carcinoma											X																
GENERAL BODY SYSTEM																											
None																											
GENITAL SYSTEM																											
Clitoral gland	+	+	+	+	+	+	+	+	M	+	+	+	M	M	+			+									
Adenoma																											
Carcinoma																											
Bilateral, adenoma																											
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			+									
Carcinoma, metastatic, kidney	X																										
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+									+			
Leiomyosarcoma																								X			
Polyp stromal													X														
Sarcoma stromal				X																							

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: MID 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	10255	10311	10322	10333	10344	10355	10422	10455	10511	10533	10544	10611	10622	10633	10655	10722	10733	10755	10822	10833	10844	10855	10911	10922	10944	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus																										15
Intestine large																										15
Intestine large, cecum																										14
Intestine large, colon																										15
Intestine large, rectum																										14
Intestine small																										15
Intestine small, duodenum																										14
Intestine small, ileum																										14
Intestine small, jejunum																										15
Liver																				+						19
Carcinoma, metastatic, kidney																										1
Leukemia mononuclear																										2
Mesentery																										1
Carcinoma, metastatic, kidney																										1
Pancreas																										14
Carcinoma, metastatic, kidney																										1
Salivary glands																										15
Stomach																										15
Stomach, forestomach																										15
Stomach, glandular																										15
Tongue								+																		1
CARDIOVASCULAR SYSTEM																										
Heart																										15
ENDOCRINE SYSTEM																										
Adrenal gland																							+			16
Adrenal gland, cortex																										15
Medulla, carcinoma, metastatic, kidney																										1
Adrenal gland, medulla																							+			15
Leukemia mononuclear																										1
Pheochromocytoma benign																							X			2
Islets, pancreatic																										14
Adenoma																										1
Parathyroid gland																										13
Pituitary gland	+		+			+	+	+						+		+	+	+	+	+		+	+			35
Pars distalis, adenoma			X			X	X	X									X		X	X		X	X			15
Pars distalis, carcinoma																										1
Pars intermedia, adenoma														X												1
Pars intermedia, carcinoma																										1
Thyroid gland							+																+			18
Bilateral, C cell, adenoma																							X			1
C cell, adenoma							X																			4
Follicular cell, carcinoma																										1
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Clitoral gland	+																				+	+	+			17
Adenoma	X																						X			2
Carcinoma																						X				1
Bilateral, adenoma																					X					1
Ovary			+						+												+					19
Carcinoma, metastatic, kidney																										1
Uterus					+									+				+								19
Leiomyosarcoma																										1
Polyp stromal					X																					2
Sarcoma stromal																										1

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

WEEKS ON STUDY	046	053	067	073	073	081	085	089	091	095	095	096	096	100	100	104	104	104	104	104	104	104	104	104	105	105
CARCASS ID	1055	1074	1064	1005	1095	1093	1043	1071	1052	1024	1022	1015	1041	1081	1044	1001	1002	1003	1004	1011	1012	1013	1014	1021	1023	
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+											
Femoral, leukemia mononuclear													X													
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+											
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+											
Leukemia mononuclear												X	X													
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+											+
Leukemia mononuclear												X	X													
Thymus	M	M	+	+	+	+	+	+	M	+	+	+	+	M	+											
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+			+	+	+			+	+		
Adenocarcinoma										X																
Adenoma																										
Fibroadenoma										X		X	X						X					X	X	
Fibroadenoma, multiple														X						X						
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								+			
Subcutaneous tissue, fibroma								X																		
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+											
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+											
Oligodendroglioma malignant						X																				
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+											+
Carcinoma, metastatic, kidney	X																									
Leukemia mononuclear													X													
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+											
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+											
SPECIAL SENSES SYSTEM																										
Eye			+										+											+		
Harderian gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+											
Zymbal gland			+		+																					
Carcinoma			X		X																					
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Renal tubule adenoma									X																	
Renal tubule, carcinoma	X																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+											

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: MID 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	1025	1031	1032	1033	1034	1035	1042	1045	1051	1053	1054	1061	1062	1063	1065	1072	1073	1075	1082	1083	1084	1085	1091	1092	1094	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Bone marrow																										15
Femoral, leukemia mononuclear																										1
Lymph node																						+				16
Lymph node, mandibular																										15
Leukemia mononuclear																										2
Spleen																										16
Leukemia mononuclear																										2
Thymus																										11
INTEGUMENTARY SYSTEM																										
Mammary gland	+		+	+		+		+			+	+	+		+		+			+	+	+		+	+	34
Adenocarcinoma			X																							2
Adenoma				X																						1
Fibroadenoma	X		X			X		X			X	X	X		X						X	X		X		17
Fibroadenoma, multiple				X																X					X	5
Skin																										16
Subcutaneous tissue, fibroma																										1
MUSCULOSKELETAL SYSTEM																										
Bone																										15
NERVOUS SYSTEM																										
Brain																										15
Oligodendroglioma malignant																										1
RESPIRATORY SYSTEM																										
Lung										+							+									18
Carcinoma, metastatic, kidney																										1
Leukemia mononuclear																										1
Nose																										15
Trachea																										15
SPECIAL SENSES SYSTEM																										
Eye			+													+										5
Harderian gland																										14
Zymbal gland																										2
Carcinoma																										2
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	50
Renal tubule, adenoma																										1
Renal tubule, carcinoma																										1
Urinary bladder																										15

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

WEEKS ON STUDY	044	058	060	063	075	075	080	082	090	090	093	095	100	102	103	104	104	104	104	104	104	104	104	105
CARCASS ID	12005	11884	12553	12221	11665	12255	12552	11711	12233	12212	12424	12323	12113	11774	11773	11161	11662	11663	11664	11772	11775	11881	11882	11885
ALIMENTARY SYSTEM																								
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	A	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	A	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	A	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X																
Mesentery											+													
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinus, adenoma																				X				
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARDIOVASCULAR SYSTEM																								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																								
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma													X											
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign			X												X					X				
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	+	+	+	+	M	+	M	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+
Adenoma																								
Pituitary gland	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma					X		X			X			X	X	X			X	X		X	X	X	X	X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, C cell, adenoma																								
C cell, adenoma												X			X									
GENERAL BODY SYSTEM																								
None																								
GENITAL SYSTEM																								
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+
Adenoma																				X				
Carcinoma													X											
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal	X											X			X		X							
Polyp stromal, multiple																								

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

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	095	105	105	105	105	105	105	105	105	TOTAL
CARCASS ID	11901	11902	11903	11904	11905	12002	12003	12001	12004	12011	12014	12015	12022	12024	12031	12033	12034	12035	12041	12043	12044	12045	12051	12054	12055	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	47
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																			X							2
Mesentery																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Acinus, adenoma																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	-	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	50
Pheochromocytoma benign						X																				4
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	M	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	42
Adenoma				X																						1
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	49
Pars distalis, adenoma					X			X			X	X							X	X	X	X		X		22
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, C cell, adenoma																								X		1
C cell, adenoma																										2
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	47
Adenoma	X									X																3
Carcinoma																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal					X						X															6
Polyp stromal, multiple														X												1

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

WEEKS ON STUDY	044	058	060	063	075	075	080	082	090	090	093	095	100	102	103	104	104	104	104	104	104	104	104	104	105
CARCASS ID	12005	11843	12853	12221	11655	12255	12522	11717	12233	12212	12242	12232	12213	11174	11773	11761	11662	11663	11684	11772	11775	11881	11882	11883	11885
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mediastinal, basosquamous tumor malignant, metastatic thymus	X																								
Mediastinal, leukemia mononuclear								X																	
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X																	
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X																	
Thymus	+	+	+	+	+	M	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	M	+	+	
Basosquamous tumor malignant	X																								
Thymoma benign																									
INTEGUMENTARY SYSTEM																									
Mammary gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma									X																
Fibroadenoma										X									X		X	X			X
Fibroadenoma, multiple											X	X		X	X	X		X		X				X	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous																									
Subcutaneous tissue, fibrosarcoma											X														
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Basosquamous tumor malignant, metastatic, thymus	X																								
Leukemia mononuclear								X																	
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Eye														+	+	+									
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule adenoma																							X		
Renal tubule, adenoma multiple																			X						X
Renal tubule, carcinoma																		X							
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

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

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL
CARCASS ID	11991	11992	11993	11994	11995	12002	12003	12001	12004	12111	12114	12115	12222	12224	12231	12233	12234	12235	12241	12243	12244	12245	12251	12254	12255	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mediastinal, basosquamous tumor malignant, metastatic, thymus																										1
Mediastinal, leukemia mononuclear																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																			X						X	3
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																			X						X	3
Thymus	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	I	+	M	+	44
Basosquamous tumor malignant																										1
Thymoma benign																			X							1
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma																			X							2
Fibroadenoma		X	X					X		X		X					X	X				X	X			14
Fibroadenoma, multiple	X				X				X		X				X									X		14
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Papilloma squamous				X																						1
Subcutaneous tissue, fibrosarcoma											X															2
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																X										1
Basosquamous tumor malignant, metastatic, thymus																										1
Leukemia mononuclear																									X	2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	-	-	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Eye												+														4
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma	X				X																					3
Renal tubule, adenoma, multiple																										2
Renal tubule, carcinoma																			X			X				3
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	-	+	50

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

	Vehicle Control	21 µg/kg	70 µg/kg	210 µg/kg
Adrenal Gland Medulla: Pheochromocytoma				
Overall Rates (a)	3/50 (6%)	(b,c) 1/27 (4%)	(b) 2/15 (13%)	4/50 (8%)
Adjusted Rates (d)	8.9%			10 2%
Terminal Rates (e)	2/32 (6%)			2/35 (6%)
Day of First Observation	675			415
Life Table Test (f)				P=0 537
Logistic Regression Test (f)				P=0.500
Fisher Exact Test (f)				P=0.500
Clitoral Gland: Adenoma				
Overall Rates (a)	7/49 (14%)	(b) 4/29 (14%)	(b) 3/17 (18%)	3/47 (6%)
Adjusted Rates (d)	18.3%			9 1%
Terminal Rates (e)	3/31 (10%)			3/33 (9%)
Day of First Observation	497			728
Life Table Test (f)				P=0 150N
Logistic Regression Test (f)				P=0.175N
Fisher Exact Test (f)				P=0.176N
Clitoral Gland: Adenoma or Carcinoma				
Overall Rates (a)	7/49 (14%)	(b) 4/29 (14%)	(b) 4/17 (24%)	4/47 (9%)
Adjusted Rates (d)	18.3%			11.5%
Terminal Rates (e)	3/31 (10%)			3/33 (9%)
Day of First Observation	497			699
Life Table Test (f)				P=0.242N
Logistic Regression Test (f)				P=0.285N
Fisher Exact Test (f)				P=0 287N
Kidney Tubule: Adenoma				
Overall Rates (a)	0/50 (0%)	0/51 (0%)	1/50 (2%)	5/50 (10%)
Adjusted Rates (d)	0.0%	0.0%	2 4%	14.3%
Terminal Rates (e)	0/32 (0%)	0/23 (0%)	0/35 (0%)	5/35 (14%)
Day of First Observation			637	728
Life Table Tests (f)	P=0.003	(g	P=0.505	P=0.041
Logistic Regression Tests (f)	P=0.002	(g)	P=0 493	P=0 041
Cochran-Armitage Trend Test (f)	P=0.001			
Fisher Exact Test (f)		(g)	P=0.500	P=0.028
Kidney Tubule: Carcinoma				
Overall Rates (a)	0/50 (0%)	0/51 (0%)	1/50 (2%)	3/50 (6%)
Adjusted Rates (d)	0.0%	0.0%	2.0%	8.6%
Terminal Rates (e)	0/32 (0%)	0/23 (0%)	0/35 (0%)	3/35 (9%)
Day of First Observation			319	728
Life Table Tests (f)	P=0 031	(g)	P=0 504	P=0.137
Logistic Regression Tests (f)	P=0.017	(g)	P=0.500	P=0.137
Cochran-Armitage Trend Test (f)	P=0.021			
Fisher Exact Test (f)		(g)	P=0.500	P=0.121
Kidney Tubule: Adenoma or Carcinoma				
Overall Rates (a)	0/50 (0%)	0/51 (0%)	2/50 (4%)	8/50 (16%)
Adjusted Rates (d)	0.0%	0 0%	4 3%	22 9%
Terminal Rates (e)	0/32 (0%)	0/23 (0%)	0/35 (0%)	8/35 (23%)
Day of First Observation			319	728
Life Table Tests (f)	P<0.001	(g)	P=0.245	P=0 006
Logistic Regression Tests (f)	P<0.001	(g)	P=0.180	P=0.006
Cochran-Armitage Trend Test (f)	P<0.001			
Fisher Exact Test (f)		(g)	P=0.247	P=0.003

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

	Vehicle Control	21 µg/kg	70 µg/kg	210 µg/kg
Mammary Gland: Fibroadenoma				
Overall Rates (a)	17/50 (34%)	23/51 (45%)	22/50 (44%)	28/50 (56%)
Adjusted Rates (d)	46.6%	70.5%	56.3%	69.9%
Terminal Rates (e)	13/32 (41%)	14/23 (61%)	18/35 (51%)	23/35 (66%)
Day of First Observation	525	436	659	630
Life Table Tests (f)	P=0.205	P=0.021	P=0.313	P=0.052
Logistic Regression Tests (f)	P=0.046	P=0.096	P=0.234	P=0.020
Cochran-Armitage Trend Test (f)	P=0.030			
Fisher Exact Test (f)		P=0.174	P=0.206	P=0.022
Mammary Gland: Adenoma, Fibroadenoma, or Adenocarcinoma				
Overall Rates (a)	17/50 (34%)	24/51 (47%)	22/50 (44%)	30/50 (60%)
Adjusted Rates (d)	46.6%	73.8%	56.3%	73.1%
Terminal Rates (e)	13/32 (41%)	15/23 (65%)	18/35 (51%)	24/35 (69%)
Day of First Observation	525	436	659	626
Life Table Tests (f)	P=0.127	P=0.012	P=0.313	P=0.024
Logistic Regression Tests (f)	P=0.019	P=0.063	P=0.234	P=0.007
Cochran-Armitage Trend Test (f)	P=0.012			
Fisher Exact Test (f)		P=0.128	P=0.206	P=0.008
Pituitary Gland/Pars Distalis: Adenoma				
Overall Rates (a)	16/49 (33%)	(b) 19/41 (46%)	(b) 15/35 (43%)	22/49 (45%)
Adjusted Rates (d)	40.0%	54.3%		53.4%
Terminal Rates (e)	9/32 (28%)			16/35 (46%)
Day of First Observation	466			520
Life Table Test (f)				P=0.246
Logistic Regression Test (f)				P=0.149
Fisher Exact Test (f)				P=0.150
Pituitary Gland/Pars Distalis: Adenoma or Carcinoma				
Overall Rates (a)	17/49 (35%)	(b) 20/41 (49%)	(b) 16/35 (46%)	22/49 (45%)
Adjusted Rates (d)	42.6%			53.4%
Terminal Rates (e)	10/32 (31%)			16/35 (46%)
Day of First Observation	466			520
Life Table Test (f)				P=0.312
Logistic Regression Test (f)				P=0.204
Fisher Exact Test (f)				P=0.205
Subcutaneous Tissue: Fibroma or Fibrosarcoma				
Overall Rates (a)	1/50 (2%)	3/51 (6%)	1/50 (2%)	2/50 (4%)
Adjusted Rates (d)	3.1%	8.8%	2.3%	5.3%
Terminal Rates (e)	1/32 (3%)	1/23 (4%)	0/35 (0%)	1/35 (3%)
Day of First Observation	728	525	622	645
Life Table Tests (f)	P=0.623	P=0.249	P=0.745N	P=0.518
Logistic Regression Tests (f)	P=0.574	P=0.317	P=0.762	P=0.504
Cochran-Armitage Trend Test (f)	P=0.580			
Fisher Exact Test (f)		P=0.316	P=0.753N	P=0.500
Thyroid Gland: C-Cell Adenoma				
Overall Rates (a)	7/50 (14%)	(b) 7/32 (22%)	(b) 5/18 (28%)	3/50 (6%)
Adjusted Rates (d)	18.9%			8.0%
Terminal Rates (e)	4/32 (13%)			1/35 (3%)
Day of First Observation	568			659
Life Table Test (f)				P=0.144N
Logistic Regression Test (f)				P=0.157N
Fisher Exact Test (f)				P=0.159N

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

	Vehicle Control	21 µg/kg	70 µg/kg	210 µg/kg
Thyroid Gland: C-Cell Adenoma or Carcinoma				
Overall Rates (a)	8/50 (16%)	(b) 7/32 (22%)	(b) 5/18 (28%)	3/50 (6%)
Adjusted Rates (d)	21.8%			8.0%
Terminal Rates (e)	5/32 (16%)			1/35 (3%)
Day of First Observation	568			659
Life Table Test (f)				P=0.090N
Logistic Regression Test (f)				P=0.099N
Fisher Exact Test (f)				P=0.100N
Uterus: Stromal Polyp				
Overall Rates (a)	2/49 (4%)	(b) 7/32 (22%)	(b) 2/19 (11%)	7/50 (14%)
Adjusted Rates (d)	5.7%			17.8%
Terminal Rates (e)	1/32 (3%)			4/35 (11%)
Day of First Observation	673			305
Life Table Test (f)				P=0.105
Logistic Regression Test (f)				P=0.085
Fisher Exact Test (f)				P=0.085
Hematopoietic System: Mononuclear Leukemia				
Overall Rates (a)	10/50 (20%)	(b,h) 8/51 (16%)	(b,i) 2/50 (4%)	3/50 (6%)
Adjusted Rates (d)	23.8%			7.9%
Terminal Rates (e)	3/32 (9%)			2/35 (6%)
Day of First Observation	495			568
Life Table Test (f)				P=0.039N
Logistic Regression Test (f)				P=0.037N
Fisher Exact Test (f)				P=0.036N

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Incomplete sampling of tissues
(c) A complex pheochromocytoma was also observed.
(d) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(e) Observed tumor incidence at terminal kill
(f) Beneath the vehicle control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the vehicle controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The 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).
(g) No P value is reported because no tumors were observed in the dosed and vehicle control groups.
(h) Twenty-nine livers and 29 spleens were examined microscopically.
(i) Nineteen livers and 16 spleens were examined microscopically.

TABLE B4a. HISTORICAL INCIDENCE OF RENAL TUBULAR CELL TUMORS IN FEMALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence of Adenomas in Vehicle Controls
Historical Incidence at Battelle Columbus Laboratories	
Chlorobenzene	0/50
1,2-Dichlorobenzene	0/49
1,4-Dichlorobenzene	0/49
Benzene	0/50
Xylenes	0/50
TOTAL	0/248 (0.0%)
SD (c)	0.00%
Range (d)	
High	0/50
Low	0/50
Overall Historical Incidence	
TOTAL	(d) 2/1,944 (0.1%)
SD (c)	0.45%
Range (d)	
High	1/50
Low	0/50

(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.
(d) Includes one adenoma, NOS, and one tubular cell adenoma; no malignant tumors have been observed.

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

Study	Incidence in Vehicle Controls		
	Fibroadenoma	Adenocarcinoma	Fibroadenoma or Adenocarcinoma
Historical Incidence at Battelle Columbus Laboratories			
Chlorobenzene	9/50	0/50	9/50
1,2-Dichlorobenzene	8/50	1/50	9/50
1,4-Dichlorobenzene	12/50	0/50	12/50
Benzene	10/50	2/50	10/50
Xylenes	14/50	1/50	15/50
TOTAL	(b) 53/250 (21.2%)	(c) 4/250 (1.6%)	(b,c) 55/250 (22.0%)
SD (d)	4.82%	1.67%	5.10%
Range (e)			
High	14/50	2/50	15/50
Low	8/50	0/50	9/50
Overall Historical Incidence			
TOTAL	(f) 558/1,950 (28.6%)	(g) 44/1,950 (2.3%)	(f,g) 588/1,950 (30.2%)
SD (d)	9.09%	2.01%	9.76%
Range (e)			
High	26/50	5/50	28/50
Low	7/50	0/50	7/50

(a) Data as of April 29, 1987, for studies of at least 104 weeks
(b) Includes one papillary adenoma, one cystadenoma, NOS, one adenoma, NOS, and one papillary cystadenoma, NOS
(c) Includes one papillary cystadenoma, NOS
(d) Standard deviation
(e) Range and SD are presented for groups of 35 or more animals.
(f) Includes 16 adenomas, NOS, 1 papillary adenoma, 5 cystadenomas, NOS, and 1 papillary cystadenoma, NOS
(g) Includes two carcinomas, NOS, and one papillary cystadenocarcinoma, NOS

TABLE B4c. HISTORICAL INCIDENCE OF LEUKEMIA IN FEMALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls
Historical Incidence at Battelle Columbus Laboratories	
Chlorobenzene	8/50
1,2-Dichlorobenzene	13/50
1,4-Dichlorobenzene	15/50
Benzene	6/50
Xylenes	7/50
TOTAL	49/250 (19.6%)
SD (c)	7.92%
Range (d)	
High	15/50
Low	6/50
Overall Historical Incidence	
TOTAL	364/1,950 (18.7%)
SD (c)	7.93%
Range (d)	
High	21/50
Low	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 B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF OCHRATOXIN A

	Vehicle Control	Low Dose	Mid Dose	High Dose
Animals initially in study	80	80	80	80
Animals removed	80	80	80	80
Animals examined histopathologically	50	51	50	50
ALIMENTARY SYSTEM				
Intestine large, colon	(49)	(28)	(15)	(48)
Parasite metazoan	1 (2%)			1 (2%)
Intestine large, rectum	(48)	(28)	(14)	(47)
Parasite metazoan	1 (2%)			2 (4%)
Liver	(50)	(29)	(19)	(50)
Basophilic focus, multiple	41 (82%)	15 (52%)	11 (58%)	45 (90%)
Clear cell focus	4 (8%)			
Cytoplasmic alteration, focal		2 (7%)	2 (11%)	4 (8%)
Cytoplasmic alteration, multifocal				1 (2%)
Eosinophilic focus	1 (2%)			1 (2%)
Inflammation, chronic active, multifocal	15 (30%)	3 (10%)	2 (11%)	8 (16%)
Necrosis, acute				1 (2%)
Regeneration, focal				1 (2%)
Bile duct, hyperplasia, multifocal	13 (26%)	3 (10%)	2 (11%)	18 (36%)
Centrilobular, degeneration	2 (4%)			
Centrilobular, vacuolization cytoplasmic, diffuse	1 (2%)	3 (10%)	1 (5%)	
Periportal, fibrosis, chronic, multifocal				1 (2%)
Periportal, vacuolization cytoplasmic, diffuse	3 (6%)	2 (7%)		1 (2%)
Mesentery	(1)	(1)	(1)	(1)
Inflammation, chronic active	1 (100%)			1 (100%)
Perivascular, inflammation, chronic active		1 (100%)		
Pancreas	(50)	(29)	(14)	(50)
Acinus, atrophy	12 (24%)	2 (7%)	2 (14%)	14 (28%)
Acinus, degeneration, multifocal	1 (2%)			
Acinus, focal cellular change				1 (2%)
Duct, ectasia				3 (6%)
Perivascular, inflammation, chronic active, multifocal		1 (3%)		
Salivary glands	(50)	(28)	(15)	(50)
Inflammation, chronic active, multifocal	1 (2%)			
Acinus, atrophy, focal				1 (2%)
Stomach, forestomach	(50)	(28)	(15)	(49)
Cyst epithelial inclusion	1 (2%)			
Inflammation, chronic active		1 (4%)		1 (2%)
Ulcer				1 (2%)
Stomach, glandular	(50)	(28)	(15)	(49)
Ulcer	1 (2%)			
Tongue	(1)		(1)	
Epithelium, hyperkeratosis, focal			1 (100%)	
Epithelium, hyperplasia			1 (100%)	
CARDIOVASCULAR SYSTEM				
Heart	(50)	(28)	(15)	(50)
Degeneration, chronic, multifocal	34 (68%)	10 (36%)	9 (60%)	41 (82%)
Epicardium, inflammation, chronic, multifocal				1 (2%)
ENDOCRINE SYSTEM				
Adrenal gland	(50)	(29)	(16)	(50)
Accessory adrenal cortical nodule			1 (6%)	
Adrenal gland, cortex	(50)	(29)	(15)	(50)
Atrophy, diffuse				1 (2%)
Degeneration	2 (4%)			
Degeneration, fatty	13 (26%)	3 (10%)	5 (33%)	13 (26%)
Degeneration, fatty, focal			1 (7%)	

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

	Vehicle Control	Low Dose	Mid Dose	High Dose
ENDOCRINE SYSTEM				
Adrenal gland, cortex (Continued)	(50)	(29)	(15)	(50)
Hematopoietic cell proliferation, multifocal	1 (2%)			
Hyperplasia	14 (28%)	6 (21%)		13 (26%)
Hypertrophy	2 (4%)	2 (7%)		3 (6%)
Necrosis, acute		1 (3%)	2 (13%)	3 (6%)
Adrenal gland, medulla	(50)	(27)	(15)	(50)
Hyperplasia	1 (2%)	1 (4%)	1 (7%)	7 (14%)
Pituitary gland	(49)	(41)	(35)	(49)
Pars distalis, cyst	21 (43%)	9 (22%)	9 (26%)	17 (35%)
Pars distalis, hyperplasia	15 (31%)	9 (22%)	8 (23%)	16 (33%)
Pars nervosa, hyperplasia, glandular		1 (2%)		
Rathke's cleft, cyst		3 (7%)		
Thyroid gland	(50)	(32)	(18)	(50)
C-cell, hyperplasia	24 (48%)	14 (44%)	9 (50%)	27 (54%)
Follicle, cyst	1 (2%)			
Follicular cell, hyperplasia	1 (2%)	1 (3%)		
GENERAL BODY SYSTEM				
None				
GENITAL SYSTEM				
Clitoral gland	(49)	(29)	(17)	(47)
Hyperplasia	3 (6%)			8 (17%)
Infiltration cellular, lipocyte, focal	1 (2%)			
Inflammation, chronic active		1 (3%)	2 (12%)	6 (13%)
Duct, cyst	1 (2%)	1 (3%)		1 (2%)
Duct, hyperplasia, squamous, multifocal			1 (6%)	1 (2%)
Ovary	(49)	(29)	(19)	(50)
Edema, diffuse				1 (2%)
Follicle, cyst		2 (7%)		2 (4%)
Periovarian tissue, cyst	1 (2%)	3 (10%)	4 (21%)	1 (2%)
Uterus	(49)	(32)	(19)	(50)
Dilatation	1 (2%)	1 (3%)		
Inflammation, chronic active		1 (3%)		
Endometrium, hyperplasia, cystic, glandular, multifocal	3 (6%)	4 (13%)	2 (11%)	3 (6%)
HEMATOPOIETIC SYSTEM				
Bone marrow	(49)	(28)	(15)	(50)
Femoral, hyperplasia, reticulum cell				2 (4%)
Lymph node	(50)	(27)	(16)	(50)
Lumbar, cyst			1 (6%)	
Lumbar, inflammation, chronic active, multifocal			1	(6%)
Mesenteric, hyperplasia, lymphoid, multifocal				1 (2%)
Mesenteric, sinus, ectasia		1 (4%)		
Pancreatic, inflammation, chronic active, multifocal	1 (2%)			
Lymph node, mandibular	(50)	(26)	(15)	(50)
Hemorrhage, multifocal	1 (2%)			
Hyperplasia, lymphoid, multifocal			1 (7%)	
Hyperplasia, reticulum cell, multifocal	1 (2%)			

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

	Vehicle Control	Low Dose	Mid Dose	High Dose
HEMATOPOIETIC SYSTEM (Continued)				
Spleen	(50)	(29)	(16)	(50)
Degeneration, fatty, focal			1 (6%)	
Depletion lymphoid		1 (3%)		
Edema, diffuse				1 (2%)
Red pulp, fibrosis		1 (3%)		
Red pulp, hematopoietic cell proliferation, diffuse	2 (4%)	3 (10%)	2 (13%)	5 (10%)
Thymus	(43)	(27)	(11)	(44)
Depletion lymphoid, multifocal	1 (2%)			
INTEGUMENTARY SYSTEM				
Mammary gland	(47)	(40)	(34)	(49)
Hyperplasia, cystic, multifocal	46 (98%)	22 (55%)	17 (50%)	48 (98%)
Skin	(49)	(31)	(16)	(50)
Acanthosis, multifocal			1 (6%)	
Subcutaneous tissue, inflammation, chronic active, diffuse			1 (6%)	
MUSCULOSKELETAL SYSTEM				
Bone	(50)	(28)	(15)	(50)
Femur, hyperostosis	1 (2%)			
Femur, osteopetrosis				1 (2%)
NERVOUS SYSTEM				
Brain	(50)	(28)	(15)	(50)
Compression	5 (10%)	7 (25%)	2 (13%)	3 (6%)
Cyst	1 (2%)			
Hemorrhage, multifocal	1 (2%)			
Inflammation, chronic, multifocal	1 (2%)			
Ventricle, hydrocephalus	5 (10%)	7 (25%)	2 (13%)	2 (4%)
RESPIRATORY SYSTEM				
Lung	(50)	(32)	(18)	(50)
Foreign body, multifocal	4 (8%)	5 (16%)	1 (6%)	2 (4%)
Alveolar epithelium, hyperplasia		3 (9%)	1 (6%)	4 (8%)
Interstitium, inflammation, chronic active, multifocal	30 (60%)	12 (38%)	8 (44%)	24 (48%)
Perivascular, edema, acute		4 (13%)		1 (2%)
Nose	(50)	(28)	(15)	(50)
Lumen, foreign body	7 (14%)			6 (12%)
Mucosa, inflammation, acute, multifocal	5 (10%)			5 (10%)
Mucosa, inflammation, chronic active, multifocal				2 (4%)
Nasolacrimal duct, inflammation, acute, multifocal				1 (2%)
SPECIAL SENSES SYSTEM				
Eye	(4)	(2)	(5)	(4)
Cornea, hyperplasia		1 (50%)		
Lens, cataract	2 (50%)	1 (50%)	5 (100%)	4 (100%)
Retina, atrophy, diffuse	2 (50%)	1 (50%)	5 (100%)	4 (100%)

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

	Vehicle Control	Low Dose	Mid Dose	High Dose
URINARY SYSTEM				
Kidney	(50)	(51)	(50)	(50)
Cyst			1 (2%)	25 (50%)
Cyst, multiple				6 (12%)
Hydronephrosis			1 (2%)	
Mineralization, multifocal			1 (2%)	
Nephropathy, chronic, diffuse	35 (70%)	40 (78%)	44 (88%)	46 (92%)
Cortex, hemorrhage, focal			1 (2%)	
Pelvis, epithelium, hyperplasia, multifocal				2 (4%)
Renal tubule, epithelium, cytoplasmic alteration, focal			1 (2%)	2 (4%)
Renal tubule, epithelium, degeneration, multifocal			49 (98%)	49 (98%)
Renal tubule, epithelium, hyperplasia, focal			6 (12%)	12 (24%)
Renal tubule, epithelium, hyperplasia, multifocal			6 (12%)	1 (2%)
Renal tubule, epithelium, karyomegaly, multifocal		8 (16%)	50 (100%)	50 (100%)
Renal tubule, epithelium, pigmentation, diffuse	1 (2%)			
Renal tubule, epithelium, proliferation, focal			1 (2%)	7 (14%)
Renal tubule, epithelium, proliferation, multifocal			2 (4%)	9 (18%)
Urinary bladder	(50)	(27)	(15)	(50)
Calculus gross observation			1 (7%)	
Ectasia			2 (13%)	
Hemorrhage		1 (4%)		
Inflammation, acute		1 (4%)		
Mucosa, hyperplasia, diffuse			1 (7%)	1 (2%)

APPENDIX C

SENTINEL ANIMAL PROGRAM

APPENDIX C. SENTINEL ANIMAL PROGRAM

I. Methods

Rodents used in the Carcinogenesis Program of the National Toxicology Program are produced in optimally clean facilities to eliminate potential pathogens that may affect 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)	RCV/SDA (sialodacryoadenitis virus)
KRV (Kilham rat virus)	(6 mo)	(12,18,24 mo)
H-1 (Toolan's H-1 virus)		
Sendai		

II. 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: July 1982 to July 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, 1976; 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
Crude protein (percent by weight)	23.13 ± 1.08	21.3-26.3	25
Crude fat (percent by weight)	5.13 ± 0.59	3.3-6.3	25
Crude fiber (percent by weight)	3.47 ± 0.53	2.8-5.6	25
Ash (percent by weight)	6.63 ± 0.38	5.7-7.3	25
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)	12,584 ± 4,612	4,100-24,000	25
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)	17.6 ± 3.8	12.0-27.0	25
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)	1.30 ± 0.13	1.11-1.63	25
Phosphorus (percent)	0.97 ± 0.06	0.87-1.10	25
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)	0.53 ± 0.15	0.17-0.77	25
Cadmium (ppm) (a)	<0.10		25
Lead (ppm)	0.74 ± 0.62	0.33-3.37	25
Mercury (ppm) (a)	<0.05		25
Selenium (ppm)	0.32 ± 0.07	0.13-0.42	25
Aflatoxins (ppb) (a)	<5.0		25
Nitrate nitrogen (ppm) (b)	9.20 ± 4.64	0.10-22.0	25
Nitrite nitrogen (ppm) (b)	1.37 ± 1.69	0.10-7.20	25
BHA (ppm) (c)	4.08 ± 4.76	2.0-17.0	25
BHT (ppm) (c)	2.80 ± 2.57	1.0-12.0	25
Aerobic plate count (CFU/g) (d)	46,112 ± 34,525	6,600-130,000	25
Coliform (MPN/g) (e)	49.2 ± 125	3.0-460	25
E. coli (MPN/g) (a,e)	<3.0		25
Total nitrosamines (ppb) (f)	5.67 ± 5.81	1.8-30.9	25
N-Nitrosodimethylamine (ppb) (f)	4.61 ± 5.81	0.8-30.0	25
N-Nitrosopyrrolidine (ppb) (f)	1.06 ± 0.26	0.81-1.70	25
Pesticides (ppm)			
α-BHC (a,g)	<0.01		25
β-BHC (a)	<0.02		25
γ-BHC-Lindane (a)	<0.01		25
δ-BHC (a)	<0.01		25
Heptachlor (a)	<0.01		25
Aldrin (a)	<0.01		25
Heptachlor epoxide (a)	<0.01		25
DDE (a)	<0.01		25
DDD (a)	<0.01		25
DDT (a)	<0.01		25
HCB (a)	<0.01		25
Mirex (a)	<0.01		25
Methoxychlor (a)	<0.05		25
Dieldrin (a)	<0.01		25
Endrin (a)	<0.01		25
Telodrin (a)	<0.01		25
Chlordane (a)	<0.05		25
Toxaphene (a)	<0.1		25
Estimated PCBs (a)	<0.2		25
Ronnel (a)	<0.01		25
Ethion (a)	<0.02		25
Trithion (a)	<0.05		25
Diazinon (a)	<0.1		25
Methyl parathion (a)	<0.02		25
Ethyl parathion (a)	<0.02		25
Malathion (h)	0.12 ± 0.09	<0.05-0.45	25
Endosulfan I (a)	<0.01		25
Endosulfan II (a)	<0.01		25
Endosulfan sulfate (a)	<0.03		25

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

APPENDIX E

AUDIT SUMMARY

APPENDIX E. AUDIT SUMMARY

The experimental data, documents, draft Technical Report, and pathology specimens for the 9-month, 15-month, and 2-year studies of ochratoxin A in rats were audited for accuracy, consistency, completeness, and compliance with Good Laboratory Practice regulations of the Food and Drug Administration (fully implemented by the NTP beginning October 1, 1981). The laboratory studies were conducted for the NTP by the Battelle Columbus Laboratories, Columbus, Ohio. Exposure of animals to the chemical in corn oil by gavage began in September 1982. The retrospective audit was conducted for the NIEHS at the NTP Archives during December 1987 by Dynamac Corporation. The full audit report is on file at the NIEHS. The audit included a review of the following:

(1) All records concerning animal receipt, quarantine, randomization, and disposition prior to study start.
(2) All inlife records, including protocol, correspondence, dosing, environmental conditions, animal husbandry, mortality, inlife animal identification, serology, and correlation between clinical and necropsy observations of masses recorded during the last 3 months of life.
(3) Body weight and clinical observation data for a random 10% sample of the study animals in each dose group.
(4) All chemistry records.
(5) All postmortem records for individual animals concerning disposition codes, condition codes, correlations between necropsy observations, and microscopic diagnoses.
(6) Individual Animal Necropsy Record forms from a random 10% sample of animals for data entry errors, and the quality assessment report and Individual Animal Tumor Pathology Tables for tissue accountability (100%).
(7) All wet tissue bags for inventory and wet tissues from a random 20% sample of the study animals, plus other relevant cases, to verify animal identity and to examine for untrimmed potential lesions.
(8) Blocks and slides of tissues from a random 20% sample of animals to examine for proper match and inventory.
(9) All red-lined diagnoses on the pathology table (PEIRPT14) to verify update changes on the final PEIRPT14.

Procedures and events generally were adequately documented in the archival records. Of the 228 external masses observed inlife, 218 had a corresponding observation at necropsy.

Inspection of wet tissues for individual animal identifiers showed that 123/145 rats examined were identified correctly by their residual tissues. The other 22 animals were evaluated by further review of toxicology and pathology study records. The apparent identification discrepancies for 16/22 rats were not a result of misidentification during life or subsequent tissue mixup but appeared to be related to inconsistent saving of the identifiers. For the remaining six rats, there were not sufficient pathology or toxicology records to resolve the issue. Review of the wet tissues identified 32 untrimmed potential lesions in 26/145 rats examined. NTP staff considered that these findings did not affect the interpretation of the study. Full details about these and other audit findings are presented in the audit report. In conclusion, the data and results presented in the Technical Report for the 2-year studies of ochratoxin A are supported by the records at the NTP Archives.