NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 235

CARCINOGENESIS BIOASSAY OF ZEARALENONE

(CAS NO. 17924-92-4)

IN F344/N RATS AND B6C3F$_1$ MICE

(FEED STUDY)

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

NATIONAL TOXICOLOGY PROGRAM

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

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

NTP TECHNICAL REPORT
ON THE

CARCINOGENESIS BIOASSAY OF ZEARALENONE

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IN F344/N RATS AND B6C3F$_1$ MICE (FEED STUDY)

NATIONAL TOXICOLOGY PROGRAM
Box 12233
Research Triangle Park
North Carolina 27709
and
Bethesda, Maryland 20205

October 1982

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NOTE TO THE READER

This is one in a series of experiments designed to determine whether selected chemicals produce cancer in animals. Chemicals selected for testing in the NTP carcinogenesis bioassay program are chosen primarily on the bases of human exposure, level of production, and chemical structure. Selection per se is not an indicator of a chemical's carcinogenic potential. Negative results, in which the test animals do not have a greater incidence of cancer than control animals, do not necessarily mean that a test chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of conditions. Positive results demonstrate that a test chemical is carcinogenic for animals under the conditions of the test and indicate that exposure to the chemical is a potential hazard to humans. The determination of the risk to humans from chemicals found to be carcinogenic in animals requires a wider analysis which extends beyond the purview of this study.

This study was initiated by the National Cancer Institute's Carcinogenesis Testing Program, now part of the National Institute of Environmental Health Sciences, National Toxicology Program.

Comments and questions about the National Toxicology Program Technical Reports on Carcinogenesis Bioassays should be directed to the National Toxicology Program, located at Room A-306, Landow Building, Bethesda, MD 20205 (301-496-1152) or at Research Triangle Park, North Carolina 27709 (919-541-3991).

Although every effort is made to prepare the Technical Reports as accurately as possible, mistakes may occur. Readers are requested to communicate any mistakes to the Deputy Director, NTP (P.O. Box 12233, Research Triangle Park, NC 27709), so that corrective action may be taken. Further, anyone who is aware of related ongoing or published studies not mentioned in this report is encouraged to make this information known to the NTP.

These NTP Technical Reports are available for sale from the National Technical Information Service, U.S. Department of Commerce, 5285 Port Royal Road, Springfield, VA 22161 (702-487-4650).

Single copies of this carcinogenesis bioassay technical report are available without charge (and while supplies last) from the NTP Public Information Office, National Toxicology Program, P.O. Box 12233, Research Triangle Park, NC 27709.

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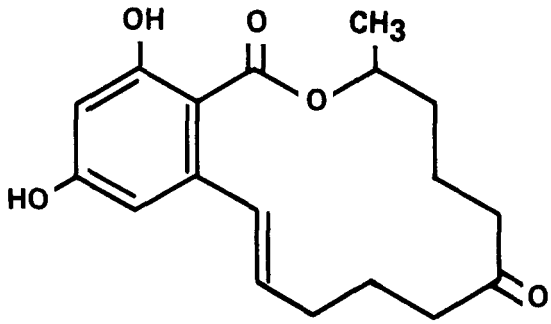

TRANS-ZEARALENONE

CAS NO. 17924-92-4

$C_{18}H_{22}O_5$ Mol. Wt. 318.36

ABSTRACT

A carcinogenesis bioassay of zearalenone, an estrogenic mycotoxin, was conducted by feeding diets containing 25 or 50 ppm zearalenone to groups of 50 F344/N rats of each sex and 50 or 100 ppm to groups of 50 B6C3F1 mice of each sex for 103 weeks. Groups of 50 rats and 50 mice of each sex served as controls. Estimates based on food consumption data indicate that the low- and high-dose rats received daily doses of about 1 and 2 mg, respectively, of zearalenone per kg body weight. Low-dose and high-dose mice received estimated daily doses of about 7-10 and 14-20 mg, respectively, of zearalenone per kg body weight.

Survival of dosed and control rats of each sex was comparable. Mean body weight gains of dosed rats of each sex were lower than those of the corresponding controls; depression in mean body weight gain was dose related. Final body weights of dosed rats were <9% lower than those of control rats. The average daily feed consumption by dosed rats of each sex was 91%-102% that of the controls.

Inflammation of the prostate, testicular atrophy, and hepatocellular cytoplasmic vacuolization (male rats), and nephrosis (male and female rats) were compound-related. Retinopathy and cataracts occurred in low- and high-dose male rats and in low-dose female rats, and were associated with closeness to fluorescent light. No compound-related, increased tumor incidences were observed in rats in the chronic study.

Survival of dosed and control mice of each sex was comparable. Mean body weight gains of high-dose male and low-dose female mice were lower than those of the controls. Terminal body weights of dosed mice were <8% below those of control mice. The average daily feed consumption by dosed mice of each sex was 97%-99% that of the controls.

Myelofibrosis in the bone marrow, uterine fibrosis, and cystic ducts in the mammary gland were related to administration of zearalenone in female mice. The incidence of hepatocellular adenomas in female mice was dose related ($P \leq 0.003$), and the incidence of these tumors in high-dose female mice was significantly higher ($P \leq 0.006$) than those in the controls (control, 0/50; low-dose, 2/49; high-dose, 7/49). Pituitary adenomas occurred with statistically significant positive trends ($P \leq 0.022$ for males and $P \leq 0.001$ for females). The incidences of these tumors in high-dose mice were significantly increased relative to controls ($P \leq 0.032$ for males: 0/40, 4/45, 6/44; and $P \leq 0.003$ for females: 3/46, 2/43, 13/42).

Under the conditions of this bioassay, zearalenone was not carcinogenic for F344/N rats of either sex. Zearalenone should be considered carcinogenic in B6C3F1 mice, as evidenced by the increased proportion of male and female mice with pituitary adenomas and by the increased proportion of female mice with hepatocellular adenomas.

CONTRIBUTORS

The bioassay of zearalenone was conducted at Southern Research Institute under a subcontract to Tracor Jitco, Inc., the prime contractor for the Carcinogenesis Testing Program. The 13-week study was begun in June 1977 and completed in September 1977. The chronic study was begun in February 1978 and completed in February 1980.

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Quality assurance of slides and review of tumor diagnoses were conducted at Experimental Pathology Laboratories, P.O. Box 474, Herndon, VA 22070 by Larry J. Ackerman, D.V.M.

The pathology report from Southern Research Institute, the report from Experimental Pathology Laboratories, and selected slides were evaluated in November 1980 by the National Toxicology Program Pathology Working Group which consisted of:

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The chemicals used in this bioassay of zearalenone were analyzed by the Midwest Research Institute, 425 Volker Blvd., Kansas City, Missouri 64110; reanalysis of the bulk chemical and analyses of dosed feed mixtures were performed by Southern Research Institute.

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SUMMARY OF PEER REVIEW COMMENTS ON THE BIOASSAY OF ZEARALENONE

On December 16, 1981, this report underwent peer review by the National Toxicology Program Board of Scientific Counselors' Technical Reports Review Subcommittee and associated Panel of Experts. The review meeting began at 9:00 a.m. in Conference Room A, Landow Building, 7910 Woodmont Avenue, Bethesda, Maryland.

Dr. Schwetz, a primary reviewer for the report on the bioassay of zearalenone, agreed with the conclusion that zearalenone was not carcinogenic for rats and suggested that the increase in male and female B6C3F1 mice with pituitary adenomas and in females with hepatocellular adenomas should be considered as indirect evidence of carcinogenicity since there were no observed carcinomas in those organs. He suggested that some mention should be made in the discussion about the relationship between exposure to fluorescent lights and the occurrence of retinopathies and cataracts in rats.

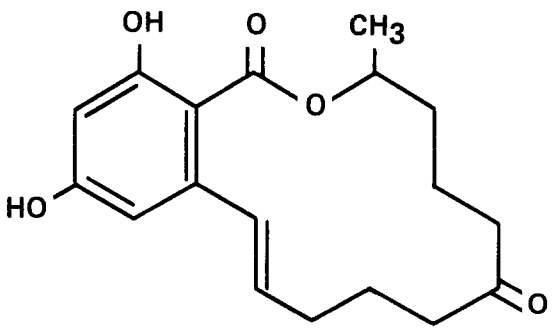
As a second principal reviewer, Dr. Holland pointed out that testicular interstitial tumors in the rat were decreased by zearalenone administration and that potentially serious ophthalmic lesions associated with the compound were induced. He indicated that this latter finding may be one of the more important results to come from the study and should be given more attention. He opined that there was no documentation that this effect was due to fluorescent lights in the animal room.

A discussion followed pertaining to the mechanism(s) by which tumors may be induced in animals exposed to hormonally active chemicals such as zearalenone, which has estrogenic activity. There was some disagreement on the wording of the conclusions based on increased incidences of pituitary and hepatocellular adenomas in mice.

Dr. Schwetz moved that the bioassay report on zearalenone be accepted with revisions as indicated. Dr. Vore seconded the motion and the report was approved by the Peer Review Panel (nine affirmative votes with two abstentions: Dr. Highland and Dr. Mirer).

I. INTRODUCTION

I. INTRODUCTION



TRANS-ZEARALENONE

CAS NO. 17924-92-4

$C_{18}H_{22}O_5$ Mol. Wt. 318.36

Trans-zearalenone — (3,4,5,6,9,10-hexahydro-14,16-dihydroxy-3-methyl-1H-2-benzoxacyclotetradecin-1,7 (8H)-dione)—is a non-steroid estrogenic mycotoxin produced by numerous species of *Fusarium,* but especially *F. roseum* (also known as *F. graminearum*). Under conditions of high moisture *F. roseum* colonizes in maize, barley, oats, and wheat and also invades stored corn (Mirocha et al., 1974). (See the reviews by Christensen, 1979, and by Ciegler, 1975, for a full discussion of the history, production of fungal species, chemistry, and physiological effects of zearalenone and its derivatives).

Mycotoxicosis and swine estrogenism have been associated for over 50 years. Stob et al., (1962) isolated an anabolic uterotophic compound from corn infected with *F. graminearum* (the imperfect stage of *Gibberella zeae*); this material was later identified as zearalenone by Urry et al., (1977). Zearalenone is also known as F-2 toxin and as a resorcylic acid lactone (Christensen et al., 1965; Mirocha et al., 1968).

Outbreaks of this *Fusarium* syndrome have been reported in the United States as well as in Europe (Marasas et al., 1979a); outbreaks are associated with above-average rainfall and infestation of stored corn with *Fusarium* (Mirocha and Christensen, 1974).

The estrogenic syndrome in field and experimental animals is characterized by a number of reproductive organ changes that are probably mediated through the endocrine system. Ingestion of moldy feed by pigs resulted in fetal death, infertility, reduced litter size, abortion, and other related problems (Nelson et al., 1966; Radnai, 1974). Chang et. al. (1979) reported that the feeding of pure zearalenone to healthy, multiparous sows during the pre-estrus or gestation period resulted in these reproductive deficiencies.

Mirocha et al.,(1968) reported that cattle fed hay with a high (14 mg/kg) content of zearalenone showed reduced fertility. In experimental animals (young female pigs), as little as 1 mg of zearalenone per day for 8 days induced vulvar tumefaction (Mirocha and Christensen, 1974). At higher doses of zearalenone, young female pigs developed enlarged vulvae and mammary glands; prolapse of the vagina was commonly seen (Mirocha and Christensen, 1974). These effects were reversible upon cessation of zearalenone administration. Histological effects reported included uterine wall edema and epithelial metaplasia in the cervix and vagina (Kurtz et al., 1969).

The histological changes found in immature female pigs are the same when the gilt is administered pure zearalenone, *Fusarium* infested feed, or estradiol (Kurtz et al., 1969). Zearalenone inhibited the production of follicle stimulating hormone (FSH), depressed the maturation of ovarian follicles, and showed a luteotrophic activity which extended the lifespan of corpora lutea and resulted in pseudopregnancy (Chang et al., 1979). Young male pigs administered zearalenone underwent a feminizing effect with testicular atrophy, mammary gland enlargement, and preputial gland swelling (Mirocha and Christensen, 1974).

Zearalenone may be teratogenic in pigs, but in most reports of stillbirth, fetal resorption, or undersize litters, moldy feed rather than zearalenone specifically was considered to be the causative factor (reviewed by Mirocha and Christensen, 1974). Studies using zearalenone as a teratogenic agent in swine were carried out by Chang et al.(1979). Infertility, pseudopregnancy, reduced litter size, fetal malformation, and probable fetal resorption were noted in this study, but there was no clear evidence of teratogenicity. In multigeneration studies of the teratogenicity of zearalenone in rats, Bailey et al. (1976) were unable to find teratogenic effects at daily intakes of 0.1-10 mg zearalenone per kilogram of body weight. Ruddick et al. (1976) administered zearalenone at levels of 0.075-10 mg/kg to pregnant rats; fetal skeletal anomalies were found in the offspring of rats given oral doses of zearalenone above 1 mg/kg body weight.

The known uterotrophic action of zearalenone is, on a cellular level, translated into cellular proliferation and increased rate of synthesis of target cell protein, DNA, and RNA (Ueno and Yagasaki, 1975; Ueno et al., 1974). Zearalenone and its reduced derivative, zeranol, compete with estradiol for unfilled nuclear estrogen receptor sites in a human breast cancer cell line (Martin et al., 1978), in rat mammary glands (Boyd and Wittliff, 1978), in the immature rat uterus (Katzenellenbogen et al., 1979), in bovine liver (Ingerowski and Stan, 1979), and in the calf uterus (Kiang et al., 1978). The filled cytoplasmic estrogen receptors are translocated to the nucleus, where subsequent biochemical events are influenced. In the immature mouse uterus, zeranol was the strongest competitor for cytoplasmic estradiol receptor sites, stronger than either zearalenone or diethylstilbestrol (DES) (Greenman et al., 1979). In their physiological, cellular, and subcellular actions, zearalenone and zeranol mimic both estradiol, the natural female mammalian circulating hormone, and DES, the synthetic anabolic non-steroid estrogen. The physiological and carcinogenic properties of DES were reviewed in IARC publications in 1974 and 1979.

Zearalenone is produced by large-scale deep fermentation. (See Hidy et al., 1977, for a review of the commercial processes.) The recovered zearalenone is converted via a 4H reduction to its reduced (3*S*,7*R*) derivative zeranol, commercially known as Ralgro®*. Zeranol was approved by the FDA in 1969 for use as a growth promoter in cattle and sheep (Federal Register, 1969). Feedlot cattle and sheep receive ear implants of zeranol; growth, carcass grade, and feed conversion are improved (Brown, 1970; Sharp and Dyer, 1971; Borger et al., 1973). Implantation is discontinued 40-65 days prior to slaughter for sheep and 65 days prior to slaughter for cattle to reach the FDA's zero-residue (less than 20 ppb) requirement for tissue content of zeranol (US CFR, 1973; US CFR, 1974). Zeranol and zearalenone show similar physiological activities in all systems tested.

Zearalenone, when administered to whole animals, is excreted either unchanged or as zearalenol (2H reduction) (Ueno and Tashiro, 1981). The excretory products can be either the intact molecule or the glucuronides (Mirocha et al., 1981). Rat liver homogenates also catalyze both the conjugation and the reduction of zearalenone (Kiessling and Pettersson, 1978). While the reversible reduction of zearalenone to zearalenol can be catalyzed by a bacterial beta-hydroxy steroid dehydrogenase (Kiessling and Pettersson, 1978), there is no evidence for or against this route in mammalian tissue.

There has been no direct evidence that zearalenone, or its metabolic products, are carcinogens. Schoental (1978; 1979) has pointed out that mycotoxins may be responsible for unexplained variations in background tumor rates in laboratory animals. Marasas et al. (1979b) reported that in the African Republic of Transkei there is a correlation between geographical distribution of esophageal cancer and levels of *Fusarium* infestation of corn, the main dietary staple.

Livestock feeds contaminated by mycotoxin-producing microorganisms may present a health hazard to man, because the toxins can pass into milk or edible tissues (Schoental, 1975). When zearalenone was administered to lactating sows, it was metabolized and appeared in the milk as zearalenol (Palyusik et al.,1980). Suckling female piglets fed exclusively on this milk developed red and swollen vulvae, the typical sign of zearalenone mycotoxicosis.

Although zearalenone and zearalenol were positive in the rec$^-$ assay in *Bacillus subtilis* M45 (Ueno and Kubota, 1976), zearalenone is reported to be not mutagenic for *Salmonella typhimurium* TA 1535, TA 1537, TA 1538, TA 98, and TA

*International Minerals and Chemical Corporation, 1331 South First Street, Terra Haute, Indiana 47808.

100, with or without activation by rat liver microsomes (Kuczuk et al., 1978; Wehner et al., 1978; NTP Technical Bulletin, 1980).

Zearalenone was tested by the Bioassay Program because of the potential for chance exposure of the general population to *Fusarium*-infested foods or grains, the use of a chemically reduced (but metabolically unrelated) form, zeranol, as a cattle or lamb growth promoter, and because it is a non-steroidal anabolic estrogenic compound showing physiological and sub-cellular activities similar to those of DES, a non-steroidal anabolic estrogen for which there is sufficient evidence of carcinogenicity in animals and in humans (IARC, 1979).

II. MATERIALS AND METHODS

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PRECHRONIC STUDIES

Single-Dose Study

Fourteen-Day Study

Thirteen-Week Study

CHRONIC STUDY

Clinical Examinations and Pathology

Data Recording and Statistical Methods

CHEMICAL ANALYSIS

The trans-zearalenone (CAS No. 17924-92-4) used in this bioassay was obtained from Commercial Solvents Corp., IMC Chemical Group, Inc. (Terre Haute, IN), in three batches. Lot No. 3-75 (Batch 01) was used for the single-dose and 14-day studies; Lot No. 3-75 (Batch 02) was used for the 13-week studies and for the first 19 months of the chronic studies; and Lot No. 51079 (Batch 03) was used for the remaining 5 months of the chronic studies. The third batch was a homogeneous mixture of two lots obtained from the manufacturers (Lot Nos. 626973 and 626990).

Results of analyses of the three batches of zearalenone at Midwest Research Institute (MRI) were consistent with the literature values (Appendix E). A trace impurity in each of three batches was detected by thin-layer chromatography; and a minor impurity with an area 0.04% that of the major peak was detected before the major peak by high-pressure liquid chromatography only in Lot No. 51079 (Appendix E).

Southern Research Institute (SoRI) reanalyzed the bulk chemical, which was stored in the dark at 5°C, versus a reference sample, which was stored at -20°C, periodically throughout the entire study. Reanalysis included infrared spectroscopy and gas-liquid chromatography (3% OV-1 column after derivatization with a Tri-Sil/BSA reagent). The results of these analyses indicated no change in the chemical throughout the study.

MRI determined that chemical/feed mixtures were stable at temperatures up to 45°C for 2 weeks (Appendix F) and thus required no special storage. (See Table 1 for storage conditions of formulated diets at SoRI.) The GLC procedure (Appendix G, Table G1) utilized by SoRI during the subchronic and the first year of the chronic studies for the analyses of formulated diets was based upon extraction of the dosed feed, cleanup of the extraction on a florasil column, conversion of zearalenone to the trimethylsilyl derivative, and analysis of the derivatized zearalenone by gas chromatography. This procedure proved troublesome in that it produced equivocal results due to reaction of the silylating reagent with feed components. Subsequently, a more reliable procedure was developed based on the HPLC method used for chemical reanalysis. The new method was used during the second year of the chronic study.

Bulk zearalenone was stored in the dark at 5°C.

PRECHRONIC STUDIES

Single-Dose Study

Groups of five male and five female F344/N rats were administered single doses of 250 to 4,000 mg/kg zearalenone in corn oil by gavage. Groups of five male and five female B6C3F1 mice received doses of 125 to 2,000 mg/kg by the same route. Animals were killed on day 16. Details of animal maintenance and examination are provided in Table 1.

Fourteen-Day Study

Groups of five male and five female F344/N rats and groups of five male and five female B6C3F1 mice were fed diets containing 6,000, 12,500, 25,000, 50,000, or 100,000 ppm zearalenone for 14 days (Table 1). Animals were observed twice daily for mortality and were weighed on days 1 and 15. Necropsies were performed on all animals on days 16-21.

Thirteen-Week Study

Subchronic studies were conducted to evaluate the cumulative toxicity of zearalenone and to determine the concentrations to be used in the chronic study.

Groups of 9 or 10 F344/N rats of each sex and groups of 10 B6C3F1 mice of each sex were fed diets containing 0, 30, 100, 300, 1,000, or 3,000 ppm zearalenone for 13 weeks (Table 1). Dosed feed, control diets, and water were available *ad libitum*.

Animals were checked for mortality and signs of morbidity twice daily. Those animals that were judged moribund were killed and necropsied. Each animal was given a clinical examination weekly, including palpation for tissue masses or swelling. Body weight and feed consumption data were collected weekly.

At the end of the 13-week study, survivors were killed with carbon dioxide. Necropsies were performed on all animals found dead during the study, unless precluded in whole or in part by autolysis or cannibalization, and on animals that survived to the end of the study. Thus the number of animals from which particular organs or tissues were examined microscopically varies and does not necessarily represent the number of animals that were placed on study in each group. The following specimens were examined for control and high-dose groups: gross lesions, tissue masses, abnormal lymph nodes, skin, mandibular lymph nodes, mammary gland, salivary gland, thigh muscle, bone marrow, bone (rib), thymus, trachea, lungs and bronchi, heart, thyroid, parathyroid, esophagus, stomach, duodenum, jejunum, ileum, colon, mesenteric lymph nodes, liver, gallbladder (mice), pancreas, spleen, kidneys, adrenals, urinary bladder, seminal vesicles/prostate/testes or ovaries/uterus, brain, and pituitary.

Tissues were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin.

Histopathologic examination for all other dosed groups was limited to the pituitary, adrenals, urinary bladder, bone, bone marrow, testes or ovaries, prostate or uterus, and seminal vesicles.

CHRONIC STUDY

Groups of 50 rats of each sex were fed diets containing 0, 25, or 50 ppm zearalenone for 103 weeks, and groups of 50 mice of each sex were fed diets containing 0, 50, or 100 ppm zearalenone for the same period of time. Control and dosed groups were of the same strain, sex, and age range and from the same source and shipment. All animals shared the same room, and all aspects of animal care and maintenance were similar (Table 1). No other chemicals were on test in that room.

The mixing schedule and storage conditions were based on the results of a stability study. Sample diets formulated with 1,400 or 100,000 ppm zearalenone and stored for 2 weeks at -20° to 45°C were found to be stable (Appendix F). The concentrations of zearalenone were determined in blindly selected batches of formulated diets (Appendix G).

Clinical Examinations and Pathology

Morbidity and mortality checks were made twice daily. Body weights, feed consumption by cage, and clinical signs were recorded monthly. The mean body weight of each group was calculated by dividing the total weight of all surviving animals in the group by the number of surviving animals in the group. The average feed consumption per animal was calculated by dividing the total feed consumption measured for all cages by the number of surviving animals in the group. Moribund animals and animals that survived to the end of the bioassay were killed using carbon dioxide and necropsied.

Examinations for grossly visible lesions were performed on major tissues or organs. Tissues were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. The following were examined microscopically: tissue masses, abnormal lymph nodes, skin, mandibular lymph nodes, mammary gland, salivary gland, thigh muscle, sciatic nerve, bone marrow, femur, thymus, trachea, lungs and bronchi, heart, thyroid, parathyroid, esophagus, stomach, duodenum, jejunum, ileum, colon, mesenteric lymph nodes, liver, gallbladder (mice), pancreas, spleen, kidneys, adrenals, urinary bladder, seminal vesicles/prostate/testes or ovaries/uterus, pituitary, brain, and any grossly abnormal tissues or organs. Special staining techniques were used as necessary.

Necropsies were performed on all animals found dead and on those killed at the end of the study, unless precluded in whole or in part by autolysis or cannibalization. Thus, the number of animals from which particular organs or tissues were examined microscopically varies and is not necessarily equal to the number of animals that were placed on study in each group.

The histopathologic examination for the rat study was performed by Dr. Farnell and for the mouse study by Dr. Giles. The slides, individual animal lifetime records, gross and microscopic necropsy results, animal tumor pathology description, and tumor pathology summary tables were sent to a second pathologist for quality review. This review included reconciliation of the tumor

pathology summary tables with the individual animal records, verification of tissue and slide count, as well as a review of the quality of a percentage of the slides. The second pathologist, in addition, reviewed all tumor diagnoses and all tissues in which there was an increased incidence of tumors. Any discrepancies between the reports of the original pathologist and the reviewing pathologist as well as all tumor target tissue (liver, pituitary) slides were submitted to and evaluated by the NTP Pathology Working Group as described by Ward et al. (1978). The classification of neoplastic nodules was done according to the recommendations of Squire and Levitt (1975) and the National Academy of Sciences (1980). The diagnoses represent a consensus of contracting pathologists and the NTP Pathology Working Group.

Data Recording and Statistical Methods

Data on this experiment were recorded in the Carcinogenesis Bioassay Data System (Linhart et al., 1974). The data elements include descriptive information on the chemicals, animals, experimental design, clinical observations, survival, body weight, and individual pathologic results, as recommended by the International Union Against Cancer (Berenblum, 1969).

Probabilities of survival were estimated by the product-limit procedure of Kaplan and Meier (1958) and are presented in this report in the form of graphs. Animals were statistically censored as of the time that they died of other than natural causes or were found to be missing; animals dying from natural causes were not statistically 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) extensions of Cox's methods for testing for a dose-related trend.

The incidence of neoplastic or nonneoplastic lesions has been 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 included only those animals for which that 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 numbers of animals necropsied.

For the statistical analysis of tumor incidence data, two different methods of adjusting for intercurrent mortality were employed. Each used the classical methods for combining contingency tables developed by Mantel and Haenszel (1959). Tests of significance included pairwise comparisons of high- and low-dosed groups with controls and tests for overall dose-response trends.

The first method of analysis assumed that all tumors of a given type observed in animals dying before the end of the study were "fatal"; i.e., they either directly or indirectly caused the death of the animal. According to this approach, the proportions of tumor-bearing animals in the dosed and 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 methods 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 second method of analysis assumed that all tumors of a given type observed in animals dying before the end of the study were "incidental"; i.e., they were merely observed at autopsy in animals dying of an unrelated cause. According to this approach, the proportions of animals found to have tumors in dosed and control groups were compared in each of the five time intervals: 0-52 weeks, 53-78 weeks, 79-92 weeks, week 93 to the week before terminal kill, and the terminal kill period. The denominators of these proportions were the number of animals actually autopsied during the time interval. The individual time interval comparisons were then combined by the previously described methods to obtain a single overall result. (See Peto et al., 1980, for the computational details of both methods.)

In addition to these tests, one other set of statistical analyses was carried out and reported in the tables analyzing primary tumors: the Fisher exact test for pairwise comparisons and the Cochran-Armitage linear trend test for dose-response trends (Armitage, 1971; Gart et al., 1979). These tests were based on the overall proportion of tumor-bearing animals. All reported P values are one-sided.

For studies in which there is little effect of compound administration 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.

TABLE 1. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS

	Single-Dose	14-Day Study	13-Week Study	2-Year Study
Experimental Design				
Size of Test Groups	5 males and 5 females of each species	5 males and 5 females of each species	9 or 10 male rats; 10 female rats; 10 male and 10 female mice	50 males and 50 females of each species
Doses	Rats: 250, 500, 1,000, 2,000, or 4,000 mg/kg zearalenone in corn oil by gavage Mice: 125, 250, 500, 1,000, or 2,000 mg/kg zearalenone in corn oil by gavage	Rats and Mice: 6,000, 12,500, 25,000, 50,000, or 100,000 ppm zearalenone in feed	Rats and Mice: 0, 30, 100, 300, 1,000, or 3,000 ppm zearalenone in feed	Rats: 0, 25, or 50 ppm zearalenone in feed Mice: 0, 50, or 100 ppm zearalenone in feed
Duration of Dosing	Single dose; killed on day 16	14 days; rats killed on days 16-17; mice killed on days 16-21	13 weeks; killed on days 92-96	Start dates were Feb. 7, 1978, for rats and Feb 14, 1978, for mice. Rats killed on days 729-744; mice on days 735-756.
Type and Frequency of Observation	Observed twice daily for mortality	Same as Single-Dose Study	Observed twice daily; weighed once per week	Observed twice daily; weighed every 4-5 weeks
Necropsy and Histologic Examination	No necropsy or histologic examination	All animals necropsied; no histologic examination	All animals necropsied. Complete histologic exam on controls and high-dose; pituitary, adrenal, urinary bladder, bone, bone marrow, testes or ovaries, prostate or uterus and seminal vesicles examined on all other animals.	All animals necropsied; complete histologic exam on all animals
Animals and Animal Maintenance				
Species	F344/N Rats; $B6C3F_1$ Mice	Same as Single-Dose Study	Same as Single-Dose Study	Same as Single-Dose Study
Animal Source	Frederick Cancer Research Center (Frederick, MD)	Same as Single-Dose Study	Same as Single-Dose Study	Harlan Industries, Inc. (Indianapolis, IN)
Time Held Before Start of Test	Rats, 8 days; mice, 7 days	8 days	7 days	12 days
Age When Placed on Study	6 weeks	5 weeks	5 weeks	Rats: 5 weeks Mice: 7 weeks
Method of Animal Distribution	Animals assigned to cages according to table of random numbers; cages assigned to test group according to new table of random numbers	Same as Single-Dose Study	Same as Single-Dose Study	Same as Single-Dose Study
Feed	Wayne Lab Blox® meal, Allied Mills, Inc. (Chicago, IL) Available *ad libitum*	Same as Single-Dose Study	Same as Single-Dose Study	Same as Single-Dose Study
Bedding	Beta Chips®, Northeastern Products Corp. (Warrensburg, NY); replaced biweekly	Same as Single-Dose Study	Same as Single-Dose Study	Beta Chips® and Sawdust, PWI, Inc. (Lowville, NY)
Water	Water bottles	Tap water via automatic system, Edstrom Industries (Waterford, WI)	Same as 14-Day Study	Same as 14-Day Study

TABLE I. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS (Continued)

	Single-Dose	14-Day Study	13-Week Study	2-Year Study
Cages	Rats and Mice: Stainless steel, Hahn Roofing and Sheet Metal Co. (Birmingham, AL)	Rats: Stainless steel, Hahn Roofing and Sheet Metal Co. (Birmingham, AL) Mice: Polycarbonate, Lab Products, Inc. (Garfield, NJ)	Polycarbonate, Lab Products, Inc. (Garfield, NJ); changed twice per week	Same as 13-Week Study
Animals per Cage	5	5	5	5
Cage Filters	Remay polyester, Dupont #2024 Snow Filtration Co. (Cincinnati, OH); replaced every 2 weeks	Same as Single-Dose Study	Same as Single-Dose Study	Same as Single-Dose Study
Animal Room Environment	Rats and Mice: temperature 23° ± 3°C; uncontrolled humidity	Rats: temperature 23° ± 3°C; uncontrolled humidity; 9 hours fluorescent light; air changed 15 times per hour Mice: temperature 23° ± 3°C; uncontrolled humidity; 12 hours fluorescent light; room air changed 15 times per hour	Temperature 23° ± 3°C; uncontrolled humidity; 12 hours fluorescent light; room air changed 15 times per hour	Same as 13-Week Study
Other Chemicals on Test in Same Room	D-Mannitol, stannous chloride, ziram, propyl gallate	Rats: D-mannitol, ziram, propyl gallate Mice: propyl gallate	None	None
Chemical/Vehicle and Chemical/Feed Mixture Preparation	Weighed amount of zearalenone mixed with corn oil	Weighed amount of zearalenone mixed with small amount of ground feed; premix and additional meal mixed in Patterson-Kelly® Twin-Shell V-Blender (equipped with an intensifier bar) for 5 minutes	Same as 14-Day Study	Same as 14-Day Study
Maximum Storage Time	—	14 days	14 days first 4 weeks; 7 days thereafter	14 days
Storage Conditions	—	Stored in sealed plastic containers at room temperature	Same as 14-Day Study	Stored in plastic bags at 5°C the first week, and at 21° - 23°C the second week

III. RESULTS

RATS

PRECHRONIC STUDIES

Single-Dose Study

Fourteen-Day Study

Thirteen-Week Study

CHRONIC STUDY

Body Weights and Clinical Signs

Zearalenone Intake

Survival

Pathology and Statistical Analyses of Results

MICE

PRECHRONIC STUDIES

Single-Dose Study

Fourteen-Day Study

Thirteen-Week Study

CHRONIC STUDY

Body Weights and Clinical Signs

Zearalenone Intake

Survival

Pathology and Statistical Analyses of Results

PRECHRONIC STUDIES

Single-Dose Study

All rats lived to the end of the 15-day observation period. Rats of each sex receiving 2,000 or 4,000 mg/kg zearalenone were slightly inactive after dosing, but they returned to normal by day 2.

Fourteen-Day Study

All animals survived to the end of the dosing period. A generalized, dose-related decrease in mean body weight gain was observed (Table 2). Male rats fed 100,000 ppm zearalenone lost weight. Ruffled, wet fur and diarrhea were seen in 3/5 or 4/5 rats in each group receiving 12,500 to 100,000 ppm. Distention of the uterine horns was observed in 4/5 or 5/5 females in each dosed group.

Thirteen-Week Study

No compound-related deaths occurred. Weight gain was depressed by more than 17% in rats of either sex receiving 100 ppm or more zearalenone, but feed consumption by dosed and control groups was comparable (Table 3).

Atrophy of the seminal vesicles and testes and fibromuscular hyperplasia of the prostate occurred in 90%-100% of the male rats fed 1,000 or 3,000 ppm zearalenone (Table 4). Ductular hyperplasia of the mammary gland occurred in 6/10 males and 10/10 females fed 3,000 ppm. Chromophobe hyperplasia of the pituitary occurred in 6/10 males and 7/10 females fed 3,000 ppm, 2/9 males and 2/10 females fed 1,000 ppm, and 1/10 females fed 100 ppm; this lesion was not seen in controls. Osteopetrosis was seen in most dosed groups; it was observed in 90%-100% of the females fed 100 ppm or more and in 90%-100% of the males fed 1,000 or 3,000 ppm.

Because of the depression of weight gain, endocrine system involvement, and osteopetrosis at higher dose levels, doses of 25 and 50 ppm zearalenone in feed were selected for both male and female rats in the chronic study.

TABLE 2. DOSAGE, SURVIVAL, AND MEAN BODY WEIGHTS OF RATS FED DIETS CONTAINING ZEARALENONE FOR 14 DAYS

Dose (ppm)	Survival (a)	Mean Body Weight (grams)		
		Initial	Final	Change
Males				
6,000	5/5	80.4 ± 2.11	95.2 ± 1.07	+14.8 ± 1.59
12,500	5/5	82.8 ± 3.87	101.2 ± 2.35	+18.4 ± 4.26
25,000	5/5	85.6 ± 4.31	95.6 ± 2.66	+10.0 ± 5.32
50,000	5/5	80.8 ± 1.56	80.6 ± 1.81	- 0.2 ± 1.66
100,000	5/5	82.4 ± 5.48	76.4 ± 2.77	- 6.0 ± 3.36
Females				
6,000	5/5	67.6 ± 2.86	91.6 ± 2.06	+24.0 ± 1.79
12,500	5/5	67.8 ± 2.56	86.4 ± 2.01	+18.6 ± 1.29
25,000	5/5	73.0 ± 3.11	86.8 ± 1.93	+13.8 ± 1.69
50,000	5/5	61.6 ± 1.63	77.6 ± 1.96	+16.0 ± 1.67
100,000	5/5	60.8 ± 2.06	65.4 ± 4.01	+ 4.6 ± 2.09

(a) Number surviving/number per group.

TABLE 3. DOSAGE, SURVIVAL, MEAN BODY WEIGHTS, AND FEED CONSUMPTION OF RATS FED DIETS CONTAINING ZEARALENONE FOR 13 WEEKS

Dose (ppm)	Survival *(a)*	Mean Body Weight (grams)			Weight Change Relative to Control *(c)* (percent)	Average Daily Feed Consumption (grams)
		Initial	Final *(b)*	Change		
Males						
0	10/10	88.7 ± 2.88	325.5 ± 7.14	+236.8 ± 8.00		19.9
30	9/9 *(d)*	87.0 ± 4.38	304.4 ± 2.87	+214.4 ± 4.51	- 9.5	18.8
100	10/10	81.6 ± 5.25	254.0 ± 2.65	+172.4 ± 4.54	-27.2	18.8
300	10/10	80.5 ± 3.44	201.6 ± 3.69	+121.1 ± 2.57	-48.9	18.6
1,000	9/9 *(d)*	77.1 ± 2.39	179.3 ± 1.78	+102.2 ± 2.59	-56.8	19.5
3,000	10/10	86.6 ± 5.46	173.6 ± 1.90	+ 87.0 ± 5.42	-63.3	19.1
Females						
0	10/10	79.2 ± 2.70	191.7 ± 1.47	+112.5 ± 2.36		13.2
30	10/10	78.5 ± 3.43	187.7 ± 2.09	+109.2 + 3.92	- 2.9	12.4
100	10/10	77.8 ± 2.38	170.2 ± 2.60	+ 92.4 ± 3.80	-17.9	12.7
300	10/10	80.1 ± 3.40	158.1 ± 3.34	+ 78.0 ± 3.41	-30.7	14.2
1,000	10/10	82.6 ± 2.79	149.1 ± 1.91	+ 66.5 ± 3.34	-40.9	13.8
3,000	10/10	77.2 ± 2.51	145.6 ± 3.00	+ 68.4 ± 2.62	-39.2	14.4

(a) Number surviving/number initially in the group.

(b) Mean body weight of survivors of the group ± standard error of the mean.

(c) Weight change of the dosed group relative to that of the controls ◘

$$\frac{\text{Weight Change (Dosed Group)} \quad \text{Weight Change (Control Group)}}{\text{Weight Change (Control Group)}} \times 100$$

(d) One female rat was found in this group of males and was killed.

TABLE 4. INCIDENCE OF COMPOUND-RELATED HISTOPATHOLOGIC EFFECTS IN THE 13-WEEK STUDY OF ZEARALENONE IN RATS

Dose (ppm)	Pituitary		Mammary Gland	Uterus	Prostate	*Seminal* Vesicles	Testes		Bone
	Hyperplasia	Adenoma	Ductular Hyperplasia	Endometrial Hyperplasia	Fibromuscular Hyperplasia	Atrophy	Atrophy	Aspermato-genesis	Osteopetrosis
Males									
0	0/10	0/10	0/10	—	0/10	0/9	0/10	0/10	0/10
30	0/9	0/9	0/9	—	0/9	1/9	0/9	0/9	0/9
100	0/10	0/10	0/10	—	0/10	7/10	0/10	0/10	0/10
300	0/10	0/10	0/10	—	3/10	10/10	7/10	6/10	0/10
1,000	2/9	0/10	0/10	—	9/9	9/9	9/9	9/9	9/9
3,000	6/10	0/10	6/10	—	9/10	9/10	10/10	10/10	10/10
Females									
0	0/10	0/10	0/10	0/10	—	—	—	—	0/10
30	0/10	0/10	0/10	0/10	—	—	—	—	5/10
100	1/10	0/10	0/10	1/10	—	—	—	—	10/10
300	0/10	0/10	0/10	2/10	—	—	—	—	9/10
1,000	2/10	0/10	0/10	8/10	—	—	—	—	10/10
3,000	7/10	0/10	10/10	10/10	—	—	—	—	10/10

CHRONIC STUDY

Body Weights and Clinical Signs

Mean body weight gains of dosed males (throughout the study) and dosed females (during the second year of the study) were lower than those of the controls (Figure 1 and Appendix H, Table H1). The decrement in weight gain was dose related. The average daily feed consumption per rat by low- and high-dose rats was 102% (16.6/16.3) and 91% (14.8/16.3) that of the controls for males and 96% (10.8/11.3) and 98% (11.1/11.3) for females (Appendix I, Table I1). No compound-related clinical signs were observed.

Zearalenone Intake

The average daily intake of zearalenone by male and female rats at various intervals during the 104-week study is shown in Table J1 (Appendix J). The low-dose animals (male and female) received about 1 mg of zearalenone per kg body weight per day during the major portion of the study; high-dose animals received about twice this daily amount. These daily intake amounts should be considered as useful approximations that are dependent on the accuracy of the measurement of feed consumption.

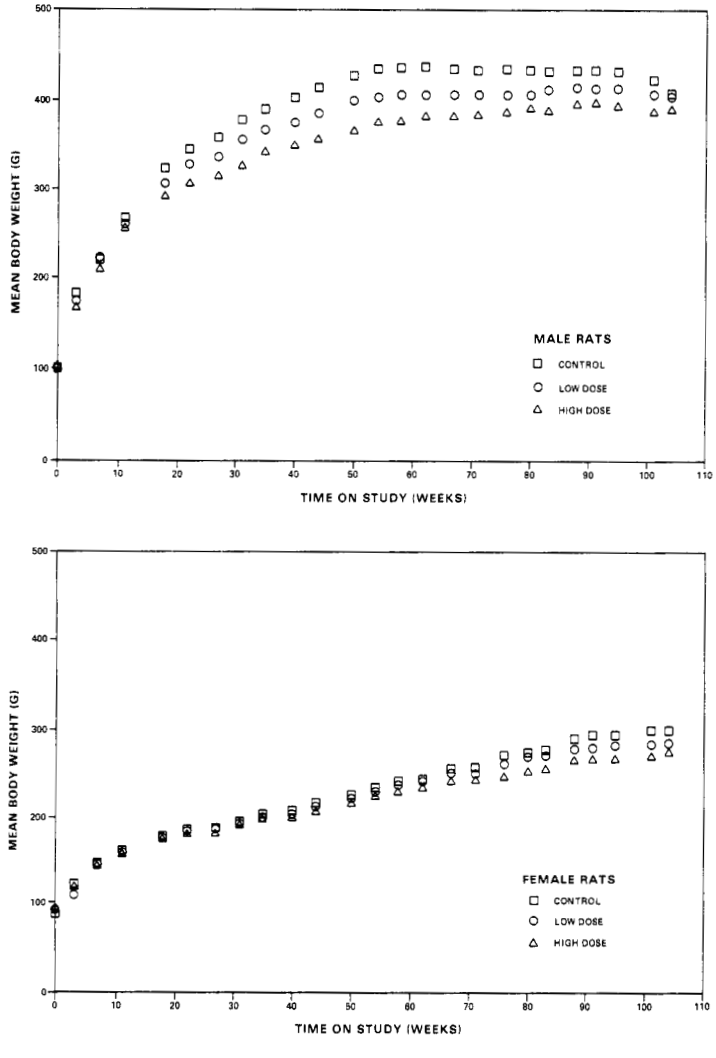

Figure 1. Growth Curves for Rats Fed Diets Containing Zearalenone

Survival

Estimates of the probabilities of survival of male and female rats fed diets containing zearalenone at the concentrations of this bioassay, together with those of the control groups, are shown by the Kaplan and Meier curves in Figure 2. No significant differences in survival were observed between any groups of male or any groups of females.

In male rats, 39/50 (78%) of the controls, 38/50 (76%) of the low-dose, and 37/50 (74%) of the high-dose group lived to the termination period of the study at 104-106 weeks. In female rats, 40/50 (80%) of the controls, 38/50 (76%) of the low-dose, and 41/50 (82%) of the high-dose group lived to the termination period of the study at 104-106 weeks. The survival incidence of control male rats includes one animal that died a natural death during the termination period; this animal is listed in Appendix Table A1 as dying a natural death.

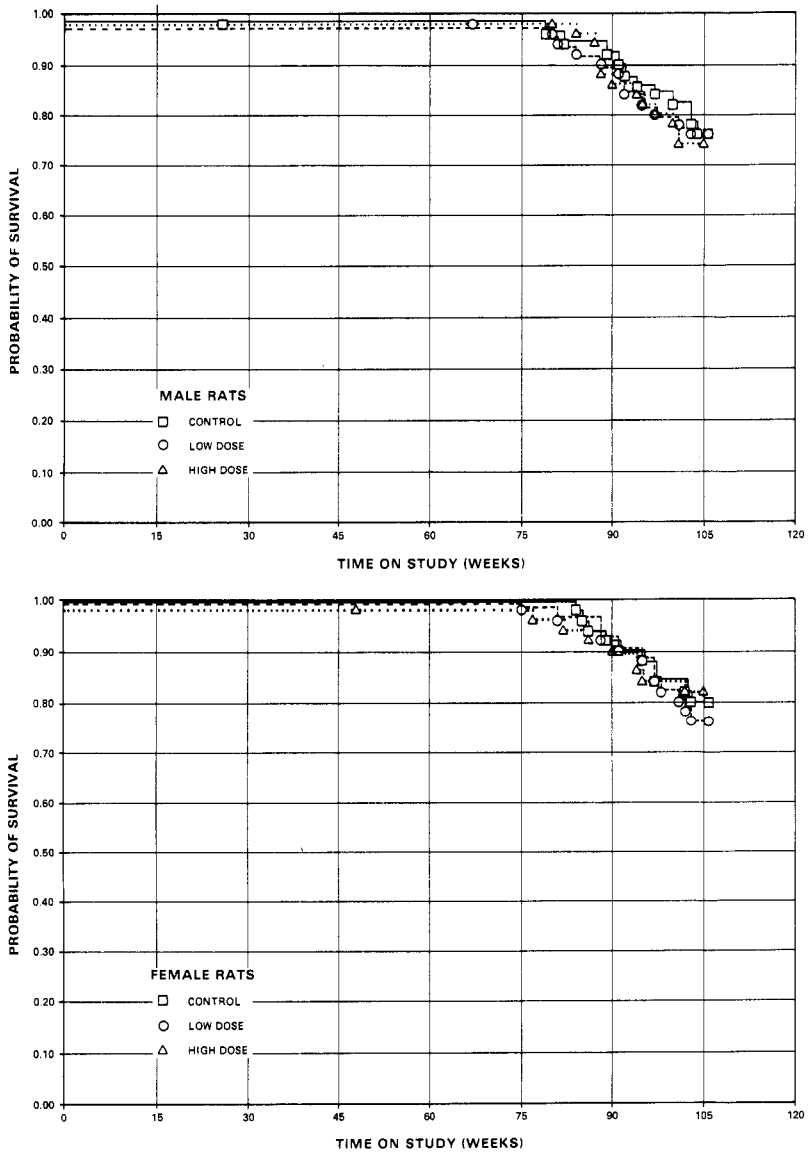

Figure 2. Survival Curves for Rats Fed Diets Containing Zearalenone

Pathology and Statistical Analyses of Results

Histopathologic findings on neoplasms in rats are summarized in Appendix A, Tables A1 and A2; Tables A3 and A4 give the survival and tumor status for each individual animal in the male rat and female rat studies, respectively. Tables 6 and 7 contain the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups.

Findings on nonneoplastic lesions are summarized in Table 5 and Appendix C, Tables C1 and C2.

Kidney: Nephrosis, typical of nephropathy seen in aging F344/N rats, was observed in increased incidence in dosed rats of either sex.

Eye: Retinopathy and cataracts were observed in increased incidence in low- and high-dose male rats (Table C1) and in low-dose female rats (Table C2).

Liver: Cytoplasmic vacuolization was found in increased incidence in dosed male rats.

Prostate: Inflammation was observed in increased incidence in dosed male rats.

Testis: Compound-related atrophy was seen in male rats; incidence: control, 1/50 (2%); low-dose, 26/50 (52%); high-dose, 17/50 (34%). Interstitial-cell tumors occurred with a statistically significant negative trend (P=0.042, incidental tumor test; incidence: control, 45/50, 90%; low-dose, 43/50, 86%; high-dose, 39/50, 78%).

Pituitary: Low-dose male rats showed a significant ($P<0.05$) increase in pituitary adenomas; however, there was no significant dose-related trend (Table 5). When pituitary adenomas and carcinomas were combined for analysis, none of the tests indicated a significant change in tumor rate (Table 5).

TABLE 5. INCIDENCES OF SELECTED NONNEOPLASTIC LESIONS IN RATS ADMINISTERED ZEARALENONE IN THE CHRONIC STUDY

	Controls	Low Dose	High Dose
Kidney: Nephrosis			
Males	30/50 (60%)	43/50 (86%)	41/50 (82%)
Females	10/50 (20%)	24/50 (48%)	26/50 (52%)
Eye: Retinopathy			
Males	0/50 (0%)	14/50 (28%)	27/50 (54%)
Females	3/50 (6%)	28/50 (56%)	8/50 (16%)
Eye: Cataracts			
Males	0/50 (0%)	11/50 (22%)	25/50 (50%)
Females	4/50 (8%)	26/50 (52%)	6/50 (12%)
Liver: Cytoplasmic Vacuolization			
Males	0/50 (0%)	6/50 (12%)	8/50 (16%)
Prostate: Inflammation	15/49 (31%)	31/50 (62%)	22/50 (44%)
Testis: Atrophy	1/50 (2%)	26/50 (52%)	17/50 (34%)

TABLE 6. ANALYSIS OF PRIMARY TUMORS IN MALE RATS *(a)*

	Control	Low Dose	High Dose
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Tumor Rates			
Overall *(b)*	3/49 (6%)	2/50 (4%)	1/47 (2%)
Adjusted *(c)*	7.0%	4.9%	2.8%
Terminal *(d)*	1/39 (3%)	1/38 (3%)	1/36 (3%)
Statistical Tests *(e)*			
Life Table	P=0.246N	P=0.513N	P=0.335N
Incidental Tumor Test	P=0.202N	P=0.474N	P=0.286N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.234N	P=0.490N	P=0.324N
Hematopoietic System: Undifferentiated Leukemia			
Tumor Rates			
Overall *(b)*	9/50 (18%)	4/50 (8%)	7/50 (14%)
Adjusted *(c)*	21.7%	9.6%	15.4%
Terminal *(d)*	7/39 (18%)	2/38 (5%)	2/37 (5%)
Statistical Tests *(e)*			
Life Table	P=0.362N	P=0.135N	P=0.429N
Incidental Tumor Test	P=0.262N	P=0.120N	P=0.310N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.330N	P=0.117N	P=0.393N
Hematopoietic System: Lymphoma or Leukemia			
Tumor Rates			
Overall *(b)*	9/50 (18%)	5/50 (10%)	8/50 (16%)
Adjusted *(c)*	21.7%	12.1%	17.8%
Terminal *(d)*	7/39 (18%)	3/38 (8%)	3/37 (8%)
Statistical Tests *(e)*			
Life Table	P=0.477N	P=0.215N	P=0.534N
Incidental Tumor Test	P=0.376N	P=0.198N	P=0.420N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.444N	P=0.194N	P=0.500N
Pituitary: Adenoma			
Tumor Rates			
Overall *(b)*	5/46 (11%)	13/49 (27%)	9/50 (18%)
Adjusted *(c)*	13.3%	30.3%	22.7%
Terminal *(d)*	4/36 (11%)	8/37 (22%)	7/37 (19%)
Statistical Tests *(e)*			
Life Table	P=0.192	P=0.042	P=0.204
Incidental Tumor Test	P=0.266	P=0.048	P=0.246
Cochran-Armitage Trend, Fisher Exact Tests	P=0.236	P=0.045	P=0.243
Pituitary: Adenoma or Carcinoma			
Tumor Rates			
Overall *(b)*	6/46 (13%)	13/49 (27%)	10/50 (20%)
Adjusted *(c)*	15.1%	30.3%	24.6%
Terminal *(d)*	4/36 (11%)	8/37 (22%)	7/37 (19%)
Statistical Tests *(e)*			
Life Table	P=0.199	P=0.075	P=0.216
Incidental Tumor Test	P=0.290	P=0.095	P=0.290
Cochran-Armitage Trend, Fisher Exact Tests	P=0.246	P=0.082	P=0.262

TABLE 6. ANALYSIS OF PRIMARY TUMORS IN MALE RATS *(a)* (Continued)

	Control	Low Dose	High Dose
Adrenal: Pheochromocytoma			
Tumor Rates			
Overall *(b)*	5/50 (10%)	5/50 (10%)	5/50 (10%)
Adjusted *(c)*	12.3%	11.9%	12.7%
Terminal *(d)*	4/39 (10%)	2/38 (5%)	4/37 (11%)
Statistical Tests *(e)*			
Life Table	P=0.535	P=0.610	P=0.601
Incidental Tumor Test	P=0.530N	P=0.626N	P=0.615N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.566	P=0.630	P=0.630
Adrenal: All Pheochromocytomas			
Tumor Rates			
Overall *(b)*	7/50 (14%)	5/50 (10%)	7/50 (14%)
Adjusted *(c)*	16.8%	11.9%	17.1%
Terminal *(d)*	5/39 (13%)	2/38 (5%)	5/37 (14%)
Statistical Tests *(e)*			
Life Table	P=0.523	P=0.404N	P=0.575
Incidental Tumor Test	P=0.511N	P=0.389N	P=0.576N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.559	P=0.380N	P=0.613
Thyroid: C-Cell Adenoma			
Tumor Rates			
Overall *(b)*	3/49 (6%)	7/50 (14%)	6/50 (12%)
Adjusted *(c)*	7.2%	17.9%	15.4%
Terminal *(d)*	1/39 (3%)	6/38 (16%)	5/37 (14%)
Statistical Tests *(e)*			
Life Table	P=0.189	P=0.153	P=0.224
Incidental Tumor Test	P=0.241	P=0.146	P=0.290
Cochran-Armitage Trend, Fisher Exact Tests	P=0.219	P=0.167	P=0.254
Thyroid: C-Cell Adenoma or Carcinoma			
Tumor Rates			
Overall *(b)*	3/49 (6%)	8/50 (16%)	8/50 (16%)
Adjusted *(c)*	7.2%	19.6%	20.1%
Terminal *(d)*	1/39 (3%)	6/38 (16%)	6/37 (16%)
Statistical Tests *(e)*			
Life Table	P=0.081	P=0.100	P=0.093
Incidental Tumor Test	P=0.118	P=0.102	P=0.136
Cochran-Armitage Trend, Fisher Exact Tests	P=0.095	P=0.106	P=0.106
Pancreatic Islets: Islet-Cell Adenoma or Carcinoma			
Tumor Rates			
Overall *(b)*	3/49 (6%)	3/50 (6%)	0/50 (0%)
Adjusted *(c)*	7.4%	7.9%	0.0%
Terminal *(d)*	2/39 (5%)	3/38 (8%)	0/37 (0%)
Statistical Tests *(e)*			
Life Table	P=0.114N	P=0.648	P=0.136N
Incidental Tumor Test	P=0.098N	P=0.652	P=0.105N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.098N	P=0.651N	P=0.117N

TABLE 6. ANALYSIS OF PRIMARY TUMORS IN MALE RATS *(a)* (Continued)

	Control	Low Dose	High Dose
Mammary Gland: Fibroadenoma			
Tumor Rates			
Overall *(b)*	1/50 (2%)	3/50 (6%)	2/50 (4%)
Adjusted *(c)*	2.6%	6.5%	5.4%
Terminal *(d)*	1/39 (3%)	0/38 (0%)	2/37 (5%)
Statistical Tests *(e)*			
Life Table	P=0.383	P=0.300	P=0.482
Incidental Tumor Test	P=0.451	P=0.390	P=0.482
Cochran-Armitage Trend, Fisher Exact Tests	P=0.400	P=0.309	P=0.500
Testis: All Interstitial-Cell Tumors			
Tumor Rates			
Overall *(b)*	45/50 (90%)	43/50 (86%)	39/50 (78%)
Adjusted *(c)*	97.8%	91.7%	86.4%
Terminal *(d)*	38/39 (97%)	34/38 (89%)	31/37 (84%)
Statistical Tests *(e)*			
Life Table	P=0.231N	P=0.514N	P=0.257N
Incidental Tumor Test	P=0.042N	P=0.396N	P=0.056N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.064N	P=0.380N	P=0.086N

(a) Dosed groups received doses of 25 or 50 ppm of zearalenone in the diet.
(b) Number of tumor bearing animals/number of animals examined at the site.
(c) Kaplan-Meier estimated lifetime tumor incidence after adjusting for intercurrent mortality.
(d) Observed tumor incidence at terminal kill.
(e) Beneath the 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 controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend is indicated by (N).

TABLE 7. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS *(a)*

	Control	Low Dose	High Dose
Hematopoietic System: Undifferentiated Leukemia			
Tumor Rates			
Overall *(b)*	7/50 (14%)	7/50 (14%)	2/50 (4%)
Adjusted *(c)*	16.7%	16.3%	4.9%
Terminal *(d)*	6/40 (15%)	4/38 (11%)	2/41 (5%)
Statistical Tests *(e)*			
Life Table	P=0.075N	P=0.583	P=0.078N
Incidental Tumor Test	P=0.096N	P=0.566	P=0.090N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.073N	P=0.613	P=0.080N
Hematopoietic System: Lymphoma or Leukemia			
Tumor Rates			
Overall *(b)*	8/50 (16%)	7/50 (14%)	3/50 (6%)
Adjusted *(c)*	19.2%	16.3%	6.9%
Terminal *(d)*	7/40 (18%)	4/38 (11%)	2/41 (5%)
Statistical Tests *(e)*			
Life Table	P=0.086N	P=0.529N	P=0.099N
Incidental Tumor Test	P=0.114N	P=0.550N	P=0.123N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.084N	P=0.500N	P=0.100N
Pituitary: Adenoma			
Tumor Rates			
Overall *(b)*	13/49 (27%)	15/50 (30%)	14/49 (29%)
Adjusted *(c)*	28.5%	33.2%	29.9%
Terminal *(d)*	8/40 (20%)	9/38 (24%)	8/40 (20%)
Statistical Tests *(e)*			
Life Table	P=0.446	P=0.382	P=0.488
Incidental Tumor Test	P=0.388	P=0.460	P=0.479
Cochran-Armitage Trend, Fisher Exact Tests	P=0.456	P=0.437	P=0.500
Pituitary: Adenoma or Carcinoma			
Tumor Rates			
Overall *(b)*	14/49 (29%)	16/50 (32%)	14/49 (29%)
Adjusted *(c)*	30.0%	34.8%	29.9%
Terminal *(d)*	8/40 (20%)	9/38 (24%)	8/40 (20%)
Statistical Tests *(e)*			
Life Table	P=0.525	P=0.385	P=0.567
Incidental Tumor Test	P=0.467	P=0.475	P=0.560
Cochran-Armitage Trend, Fisher Exact Tests	P=0.544	P=0.440	P=0.588
Thyroid: C-Cell Adenoma			
Tumor Rates			
Overall *(b)*	5/49 (10%)	6/50 (12%)	4/49 (8%)
Adjusted *(c)*	12.5%	14.7%	9.5%
Terminal *(d)*	5/40 (13%)	4/38 (11%)	3/40 (7%)
Statistical Tests *(e)*			
Life Table	P=0.437N	P=0.470	P=0.500N
Incidental Tumor Test	P=0.463N	P=0.513	P=0.520N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.434N	P=0.514	P=0.500N

TABLE 7. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS *(a)* (Continued)

	Control	Low Dose	High Dose
Thyroid: C-Cell Adenoma or Carcinoma			
Tumor Rates			
Overall *(b)*	5/49 (10%)	7/50 (14%)	6/49 (12%)
Adjusted *(c)*	12.5%	17.2%	14.1%
Terminal *(d)*	5/40 (13%)	5/38 (13%)	4/40 (10%)
Statistical Tests *(e)*			
Life Table	P=0.439	P=0.350	P=0.500
Incidental Tumor Test	P=0.405	P=0.388	P=0.468
Cochran-Armitage Trend, Fisher Exact Tests	P=0.439	P=0.394	P=0.500
Mammary Gland: Fibroadenoma			
Tumor Rates			
Overall *(b)*	9/50 (18%)	14/50 (28%)	9/50 (18%)
Adjusted *(c)*	20.9%	34.7%	20.9%
Terminal *(d)*	7/40 (18%)	12/38 (32%)	7/41 (17%)
Statistical Tests *(e)*			
Life Table	P=0.530N	P=0.148	P=0.587N
Incidental Tumor Test	P=0.513	P=0.152	P=0.546
Cochran-Armitage Trend, Fisher Exact Tests	P=0.548	P=0.171	P=0.602
Uterus: Endometrial Stromal Polyp			
Tumor Rates			
Overall *(b)*	4/50 (8%)	8/49 (16%)	5/49 (10%)
Adjusted *(c)*	10.0%	20.6%	12.1%
Terminal *(d)*	4/40 (10%)	7/37 (19%)	4/40 (10%)
Statistical Tests *(e)*			
Life Table	P=0.437	P=0.146	P=0.500
Incidental Tumor Test	P=0.410	P=0.138	P=0.485
Cochran-Armitage Trend, Fisher Exact Tests	P=0.424	P=0.168	P=0.487

(a) Dosed groups received doses of 25 or 50 ppm of zearalenone in the diet.
(b) Number of tumor bearing animals/number of animals examined at the site.
(c) Kaplan-Meier estimated lifetime tumor incidence after adjusting for intercurrent mortality.
(d) Observed tumor incidence at terminal kill.
(e) Beneath the 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 controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend is indicated by (N).

PRECHRONIC STUDIES

Single-Dose Study

One male mouse administered 1,000 mg/kg zearalenone died due to gavage error. All other mice lived to the end of the observation period.

Fourteen-Day Study

All animals survived to the end of the dosing period. A generalized, dose-related decrease in mean body weight gain was observed (Table 8). Two of five male mice fed 100,000 ppm and 4/5 and 3/5 female mice fed 50,000 or 100,000 ppm, respectively, lost weight. (No controls were used in this study.)

Distention of the uterine horns was observed in 2/5 to 4/5 female mice in each dosed group. All dosed mice had small thymuses. Distention of the urinary bladder was seen in 2/5 and 3/5 male mice receiving 12,500 or 25,000 ppm, respectively.

TABLE 8. DOSAGE, SURVIVAL, AND MEAN BODY WEIGHTS OF MICE FED DIETS CONTAINING ZEARALENONE FOR 14 DAYS

Dose (ppm)	Survival *(a)*	Mean Body Weight (grams)		
		Initial	Final	Change *(b)*
Males				
6,000	5/5	20.4 ± 1.21	21.0 ± 1.14	+0.6 ± 0.24
12,500	5/5	19.8 ± 0.66	20.8 ± 0.66	+1.0 ± 0.00
25,000	5/5	20.4 ± 0.75	21.2 ± 0.58	+0.8 ± 0.49
50,000	5/5	18.4 ± 0.75	19.2 ± 0.86	+0.8 ± 0.20
100,000	5/5	20.0 ± 0.63	19.6 ± 1.03	-0.4 ± 0.51
Females				
6,000	5/5	17.8 ± 0.58	18.6 ± 0.60	+0.8 ± 0.20
12,500	5/5	16.8 ± 0.37	18.8 ± 0.37	+2.0 ± 0.32
25,000	5/5	16.8 ± 0.37	17.2 ± 0.37	+0.4 ± 0.40
50,000	5/5	18.0 ± 0.63	17.4 ± 0.40	-0.6 ± 0.81
100,000	5/5	17.6 ± 0.40	16.8 ± 0.37	-0.8 ± 0.20

(a) Number surviving/number per group.
(b) Weight change of the group ± standard error of the mean.

Thirteen-Week Study

Two of the 10 female mice fed 3,000 ppm died. Weight gain was depressed by 14% or more in male mice fed 300 ppm or more (Table 9). Feed consumption by dosed and control mice was comparable.

Atrophy of the seminal vesicles and cytoplasmic vacuolization of the adrenal were found in 10/10 or 9/10 male mice fed 1,000 or 3,000 ppm zearalenone, and squamous metaplasia of the prostate was seen in 8/10 males fed 3,000 ppm (Table 10). Osteopetrosis was observed in 10/10 males and 6/8 females fed 3,000 ppm, 10/10 males and 5/10 females fed 1,000 ppm, 7/10 males and 5/10 females fed 300 ppm, 4/10 males and 2/10 females fed 100 ppm, and 0/10 male and 0/10 female controls. Myelofibrosis of the bone marrow was seen in 10/10 males fed 3,000 ppm or 1,000 ppm, 6/8 females fed 3,000 ppm, and 3/10 females fed 1,000 ppm. Endometrial hyperplasia of the uterus was seen in 1/10 to 10/10 female mice in all dosed groups, but the incidence was not dose related.

Because of the severity of the lesions observed in mice at doses of 300 ppm or more, doses of 50 and 100 ppm zearalenone in feed were selected for mice in the chronic study.

TABLE 9. DOSAGE, SURVIVAL, MEAN BODY WEIGHTS, AND FEED CONSUMPTION OF MICE FED DIETS CONTAINING ZEARALENONE FOR 13 WEEKS

Dose (ppm)	Survival *(a)*	Mean Body Weight (grams)			Weight Change Relative to Control *(c)* (percent)	Average Daily Feed Consumption (grams)
		Initial	Final *(b)*	Change		
Males						
0	10/10	19.0 ±0.39	31.2 ±0.49	+12.2 ±0.20		7.7
30	10/10	19.6 ±0.34	31.4 ±0.54	+11.8 ±0.36	- 3.3	7.4
100	10/10	19.6 ±0.37	32.2 ±0.65	+12.6 ±0.67	+ 3.3	7.9
300	10/10	19.2 ±0.51	29.6 ±0.64	+10.4 ±0.70	-14.8	7.9
1,000	10/10	18.9 ±0.55	28.3 ±0.82	+ 9.4 ±0.40	-23.0	8.1
3,000	10/10	19.6 ±0.43	26.5 ±0.78	+ 6.9 ±0.55	-43.4	8.1
Females						
0	10/10	16.6 ±0.56	24.8 ±0.20	+ 8.2 ±0.63		8.0
30	10/10	16.2 ±0.47	24.8 ±0.36	+ 8.6 ±0.54	+ 4.9	7.7
100	10/10	16.6 ±0.31	24.8 ±0.33	+ 8.2 ±0.36	0.0	7.8
300	10/10	16.0 ±0.37	24.3 ±0.50	+ 8.3 ±0.30	+ 1.2	7.3
1,000	10/10	15.5 ±0.60	23.6 ±0.65	+ 8.1 ±0.60	- 1.2	6.7
3,000	8/10	15.9 ±0.50	23.8 ±0.53	+ 7.9 ±0.68	- 3.7	7.0

(a) Number surviving/number initially in the group.
(b) Mean weight change of the survivors of the group ± standard error of the mean.
(c) Weight change of the dosed group relative to that of the controls ◘

$$\frac{\text{Weight Change (Dosed Group)} - \text{Weight Change (Control Group)}}{\text{Weight Change (Control Group)}} \times 100$$

TABLE 10. INCIDENCE OF COMPOUND-RELATED HISTOPATHOLOGIC EFFECTS IN THE 13-WEEK STUDY OF ZEARALENONE IN MICE

	Adrenal (Zona Reticularis)	Uterus	Vagina	Prostate	Seminal Vesicles	Testes		Urinary Bladder	Bone	Bone Marrow	
Dose (ppm)	Cytoplasmic Vacuolization	Endometrial Hyperplasia	Hyperkera-tosis	Squamous Metaplasia	Atrophy	Atrophy	Aspermato-genesis	Fibrous hyperplasia	Osteope-trosis	Myelo-fibrosis	Neutrophilic hyperplasia
Males											
0	0/10	—	—	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10
30	0/10	—	—	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10
100	0/10	—	—	0/10	0/10	0/10	0/10	0/10	4/10	0/10	0/10
300	0/10	—	—	0/10	1/10	0/10	0/10	0/10	7/10	1/10	0/10
1,000	9/10	—	—	3/10	10/10	4/10	1/10	0/10	10/10	10/10	0/10
3,000	9/10	—	—	8/10	10/10	4/10	1/10	2/10	10/10	10/10	0/10
Females											
0	0/10	0/10	0/10	—	—	—	—	0/10	0/10	0/10	0/10
30	0/10	10/10	0/10	—	—	—	—	0/10	0/10	0/10	0/10
100	0/10	7/10	0/10	—	—	—	—	0/10	2/10	0/10	0/10
300	6/10	1/10	0/10	—	—	—	—	0/10	5/10	0/10	0/10
1,000	4/10	6/10	0/10	—	—	—	—	0/10	5/10	3/10	2/10
3,000	6/8	7/8	4/8	—	—	—	—	1/8	6/8	6/8	1/8

CHRONIC STUDY

Body Weights and Clinical Signs

No significant reduction in body weight gain was apparent in the male mice during the second half of the chronic study. Low-dose female mice showed a reduced rate of weight gain, but this was not evident in the high-dose female mice (Figure 3 and Appendix H, Table H2). The average daily feed consumption per mouse in the low- and high-dose groups was 99% (6.8/6.9) and 97% (6.7/6.9) that of the controls for males and 97% (6.7/6.9) for both dosed groups of females (Appendix I, Table I2). No other compound-related clinical signs were observed.

Zearalenone Intake

The average daily intake of zearalenone by male and female mice at various intervals during the 104-week study is shown in Table J2 (Appendix J). The low-dose animals (male and female) received about 7-10 mg of zearalenone per kg body weight per day during the major portion of the study; high-dose animals received about twice this daily amount. These daily intake amounts should be considered as useful approximations that are dependent on the accuracy of the measurement of feed consumption.

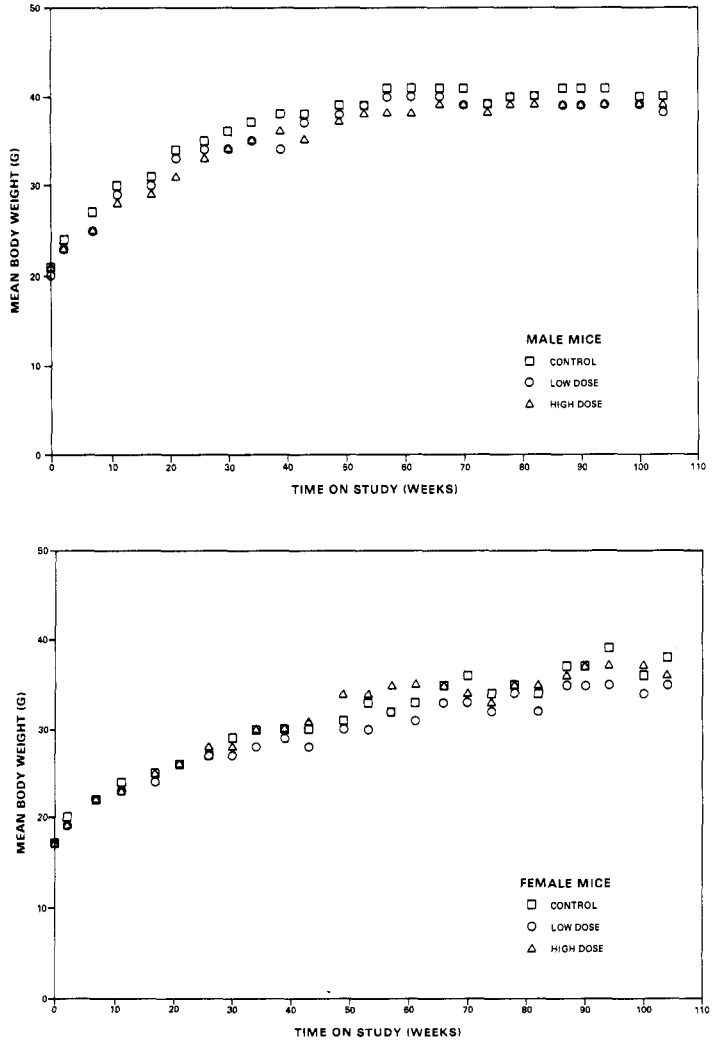

Figure 3. Growth Curves for Mice Fed Diets Containing Zearalenone

Survival

Estimates of the probabilities of survival of male and female mice fed diets containing zearalenone at the concentrations of this bioassay, together with those of the control group, are shown by the Kaplan and Meier curves in Figure 4. No significant differences in survival were observed between any groups of either sex.

In male mice, 42/50 (84%) of the controls, 40/50 (80%) of the low-dose, and 44/50 (88%) of the high-dose group lived to the termination period of the study at 105-108 weeks. In female mice, 37/50 (74%) of the controls, 37/50 (74%) of the low-dose, and 32/50 (64%) of the high-dose group lived to the termination period of the study at 105-108 weeks. The 10 male control mice listed in Appendix B, Table B1, animal disposition summary as "scheduled sacrifice" have been included in the termination period. These animals were killed at week 105. The eight female control mice listed as "scheduled sacrifice" in Appendix B, Table B2, animal disposition summary have also been included in the termination period; these mice were killed at weeks 105 (six animals) and 106 (two animals). In addition, one male and one female mouse in the low-dose groups died natural deaths during the termination period; for statistical purposes, these animals were considered to be killed at termination.

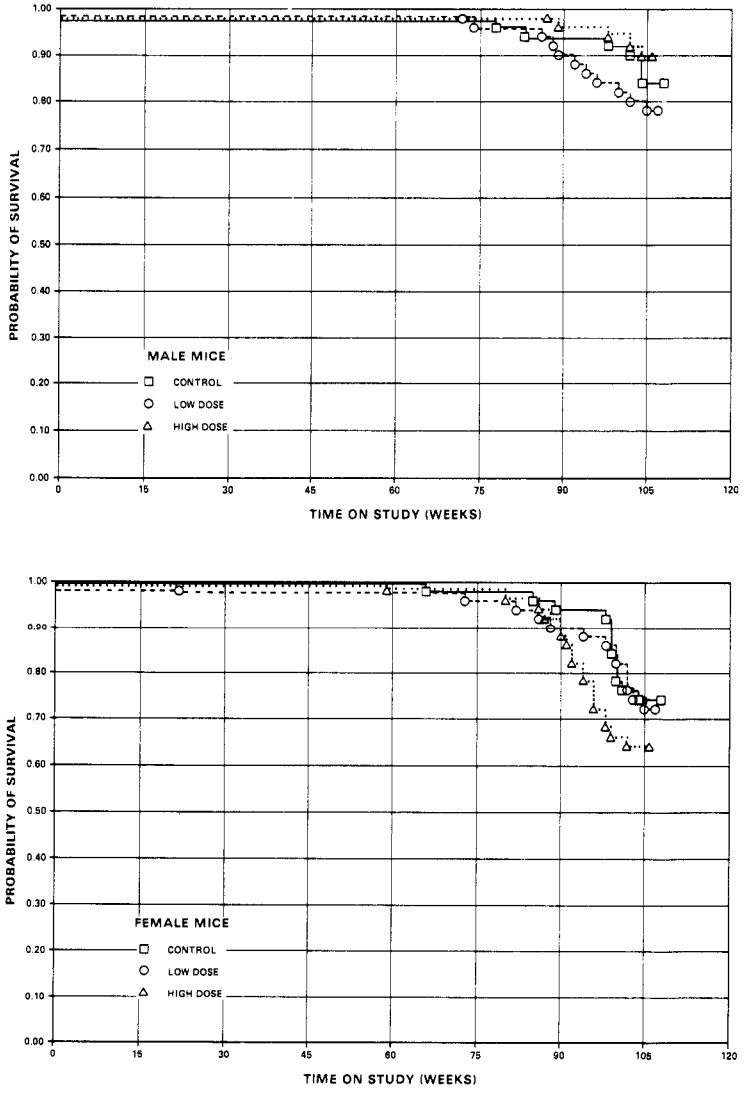

Figure 4. Survival Curves for Mice Fed Diets Containing Zearalenone

Pathology and Statistical Analyses of Results

Histopathologic findings on neoplasms occurring in mice are summarized in Appendix B, Tables B1 and B2; Tables B3 and B4 give the survival and tumor status for each individual animal in the male and female mouse studies, respectively. Findings on nonneoplastic lesions are summarized in Appendix D, Tables D1 and D2. Tables 11 and 12 contain the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups.

Bone Marrow: Myelofibrosis was observed at increased incidences and with increased severity in dosed female mice (control, 8/49, 16%; low-dose, 32/48, 67%; high-dose 34/49, 69%).

Uterus: Fibrosis in the uterus/myometrium was observed at increased incidences in dosed female mice (control, 1/50, 2%; low-dose, 5/49, 10%; high-dose, 17/48, 35%).

Mammary Gland: Dosed females had increased incidences of cystic ducts (control, 0/50, 0%; low-dose, 3/49, 6%; high-dose, 15/49, 31%). Adenocarcinomas were observed at increased incidences in dosed female mice (control, 1/50, 2%; low-dose, 3/49, 6%; high-dose, 3/49, 6%); these increases were not statistically different from controls. The carcinoma in the control animal was type B; in the dosed females, four tumors were type C, one was adenosquamous, and one was type A.

Liver: Hepatocellular adenomas occurred in female mice with a statistically significant ($P \leq 0.003$) positive trend. The incidences in the high-dose group were statistically significant ($P \leq 0.006$) in individual comparisons with the control group (0/50, 2/49, 7/49). The occurrence of liver tumors in dosed male mice was not statistically significant.

Compared with hepatocytes elsewhere in the liver, those in lesions diagnosed as hepatocellular adenomas were often larger, had cytoplasm that was more vacuolated, and often had cytoplasm with a different tinctorial quality. Hepatocellular carcinomas generally had a more disorderly arrangement of hepatocytes than did hepatocellular adenomas, and there was usually evidence of invasive growth into adjoining hepatic tissue. The arrangement of hepatocytes into trabeculae or islands of neoplastic hepatocytes was a criterion for diagnosing lesions as hepatocellular carcinomas. No toxic hepatic lesions were found.

Pituitary: Adenomas occurred in both male and female mice with statistically significant positive trends ($P \leq 0.022$ for males and $P \leq 0.001$ for females). The increased incidences of adenomas were statistically significant in high-dose males ($P \leq 0.032$) and high-dose females ($P \leq 0.003$); see Tables 11 and 12 for incidence rates.

Pituitary adenomas were usually characterized by a nodular, solid proliferation of pleomorphic epithelial cells which was frequently associated with blood-filled vascular spaces and hemosiderin deposition. The diagnosis of pituitary carcinoma was made when one or more of the following were observed: unusually large growths with bizarrely shaped epithelial cells, an increased mitotic index, or invasion into the brain.

TABLE 11. ANALYSIS OF PRIMARY TUMORS IN MALE MICE *(a)*

	Control	Low Dose	High Dose
Lung: Alveolar/Bronchiolar Adenoma			
Tumor Rates			
Overall *(b)*	7/50 (14%)	5/49 (10%)	8/50 (16%)
Adjusted *(c)*	16.7%	12.8%	18.2%
Terminal *(d)*	7/42 (17%)	5/39 (13%)	8/44 (18%)
Statistical Tests *(e)*			
Life Table	P=0.479	P=0.431N	P=0.539
Incidental Tumor Test	P=0.479	P=0.431N	P=0.539
Cochran-Armitage Trend, Fisher Exact Tests	P=0.442	P=0.394N	P=0.500
Lung: Alveolar/Bronchiolar Carcinoma			
Tumor Rates			
Overall *(b)*	4/50 (8%)	3/49 (6%)	3/50 (6%)
Adjusted *(c)*	9.2%	7.3%	6.8%
Terminal *(d)*	4/42 (7%)	2/39 (5%)	3/44 (7%)
Statistical Tests *(e)*			
Life Table	P=0.403N	P=0.543N	P=0.478N
Incidental Tumor Test	P=0.454N	P=0.564N	P=0.517N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.421N	P=0.511N	P=0.500N
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Tumor Rates			
Overall *(b)*	11/50 (22%)	8/49 (16%)	11/50 (22%)
Adjusted *(c)*	25.5%	19.8%	25.0%
Terminal *(d)*	10/42 (24%)	7/39 (18%)	11/44 (25%)
Statistical Tests *(e)*			
Life Table	P=0.505N	P=0.373N	P=0.549N
Incidental Tumor Test	P=0.538	P=0.385N	P=0.573N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.549	P=0.323N	P=0.595
Hematopoietic System: Malignant Lymphoma, Lymphocytic Type			
Tumor Rates			
Overall *(b)*	1/50 (2%)	4/50 (8%)	4/50 (8%)
Adjusted *(c)*	2.4%	10.0%	8.4%
Terminal *(d)*	1/42 (2%)	4/40 (10%)	2/44 (5%)
Statistical Tests *(e)*			
Life Table	P=0.167	P=0.165	P=0.199
Incidental Tumor Test	P=0.206	P=0.165	P=0.319
Cochran-Armitage Trend, Fisher Exact Tests	P=0.147	P=0.181	P=0.181
Hematopoietic System: Malignant Lymphoma, Mixed Type			
Tumor Rates			
Overall *(b)*	5/50 (10%)	2/50 (4%)	2/50 (4%)
Adjusted *(c)*	11.1%	4.9%	4.5%
Terminal *(d)*	2/42 (5%)	1/40 (3%)	2/44 (5%)
Statistical Tests *(e)*			
Life Table	P=0.147N	P=0.259N	P=0.211N
Incidental Tumor Test	P=0.200N	P=0.262N	P=0.290N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.147N	P=0.218N	P=0.218N

TABLE 11. ANALYSIS OF PRIMARY TUMORS IN MALE MICE *(a)* (Continued)

	Control	Low Dose	High Dose
Hematopoietic System: Malignant Lymphoma, All Types			
Tumor Rates			
Overall *(b)*	6/50 (12%)	7/50 (14%)	6/50 (12%)
Adjusted *(c)*	13.3%	16.3%	12.7%
Terminal *(d)*	3/42 (7%)	5/40 (13%)	4/44 (9%)
Statistical Tests *(e)*			
Life Table	P=0.531N	P=0.451	P=0.591N
Incidental Tumor Test	P=0.503	P=0.423	P=0.576N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.559	P=0.500	P=0.620
Liver: Hepatocellular Adenoma			
Tumor Rates			
Overall *(b)*	4/50 (8%)	3/50 (6%)	7/49 (14%)
Adjusted *(c)*	9.5%	7.3%	15.9%
Terminal *(d)*	4/42 (10%)	2/40 (5%)	7/44 (16%)
Statistical Tests *(e)*			
Life Table	P=0.218	P=0.532N	P=0.288
Incidental Tumor Test	P=0.191	P=0.540N	P=0.288
Cochran-Armitage Trend, Fisher Exact Tests	P=0.187	P=0.500N	P=0.251
Liver: Hepatocellular Carcinoma			
Tumor Rates			
Overall *(b)*	15/50 (30%)	19/50 (38%)	7/49 (14%)
Adjusted *(c)*	33.0%	44.0%	15.9%
Terminal *(d)*	12/42 (29%)	16/40 (40%)	7/44 (16%)
Statistical Tests *(e)*			
Life Table	P=0.041N	P=0.217	P=0.040N
Incidental Tumor Test	P=0.071N	P=0.237	P=0.104N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.052N	P=0.263	P=0.050N
Liver: Hepatocellular Adenoma or Carcinoma			
Tumor Rates			
Overall *(b)*	19/50 (38%)	22/50 (44%)	14/49 (29%)
Adjusted *(c)*	41.9%	49.9%	31.8%
Terminal *(d)*	16/42 (38%)	18/40 (45%)	14/44 (32%)
Statistical Tests 2(e)			
Life Table	P=0.147N	P=0.277	P=0.162N
Incidental Tumor Test	P=0.237N	P=0.295	P=0.308N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.196N	P=0.342	P=0.217N
Pituitary: Adenoma			
Tumor Rates			
Overall *(b)*	0/40 (0%)	4/45 (9%)	6/44 (14%)
Adjusted *(c)*	0.0%	9.9%	13.8%
Terminal *(d)*	0/34 (0%)	2/37 (5%)	4/40 (10%)
Statistical Tests *(e)*			
Life Table	P=0.022	P=0.065	P=0.026
Incidental Tumor Test	P=0.010	P=0.046	P=0.032
Cochran-Armitage Trend, Fisher Exact Tests	P=0.017	P=0.074	P=0.017

TABLE 11. ANALYSIS OF PRIMARY TUMORS IN MALE MICE *(a)* (Continued)

	Control	Low Dose	High Dose
Pituitary: Adenoma or Carcinoma			
Tumor Rates			
Overall *(b)*	0/40 (0%)	5/45 (11%)	6/44 (14%)
Adjusted *(c)*	0.0%	11.7%	13.8%
Terminal *(d)*	0/34 (0%)	2/37 (5%)	4/40 (10%)
Statistical Tests *(e)*			
Life Table	P=0.027	P=0.036	P=0.026
Incidental Tumor Test	P=0.006	P=0.025	P=0.032
Cochran-Armitage Trend, Fisher Exact Tests	P=0.022	P=0.037	P=0.017
Adrenal: Cortical Adenoma			
Tumor Rates			
Overall *(b)*	2/50 (4%)	1/50 (2%)	4/49 (8%)
Adjusted *(c)*	4.8%	2.1%	9.0%
Terminal *(d)*	2/42 (5%)	0/40 (0%)	3/43 (7%)
Statistical Tests *(e)*			
Life Table	P=0.250	P=0.511N	P=0.348
Incidental Tumor Test	P=0.255	P=0.367N	P=0.309
Cochran-Armitage Trend, Fisher Exact Tests	P=0.232	P=0.500N	P=0.329
Harderian Gland: Adenoma			
Tumor Rates			
Overall *(b)*	6/50 (12%)	10/50 (20%)	10/50 (20%)
Adjusted *(c)*	14.3%	23.6%	22.1%
Terminal *(d)*	6/42 (14%)	8/40 (20%)	9/44 (20%)
Statistical Tests *(e)*			
Life Table	P=0.209	P=0.179	P=0.236
Incidental Tumor Test	P=0.199	P=0.218	P=0.215
Cochran-Armitage Trend, Fisher Exact Tests	P=0.178	P=0.207	P=0.207

(a) Dosed groups received doses of 50 or 100 ppm of zearalenone in the diet.
(b) Number of tumor bearing animals/number of animals examined at the site.
(c) Kaplan-Meier estimated lifetime tumor incidence after adjusting for intercurrent mortality.
(d) Observed tumor incidence at terminal kill.
(e) Beneath the 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 controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as non-fatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend is indicated by (N).

TABLE 12. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE *(a)*

	Control	Low Dose	High Dose
Lung: Alveolar/Bronchiolar Adenoma			
Tumor Rates			
Overall *(b)*	2/48 (4%)	4/48 (8%)	1/49 (2%)
Adjusted *(c)*	5.6%	10.0%	3.1%
Terminal *(d)*	2/36 (6%)	3/37 (8%)	1/32 (3%)
Statistical Tests *(e)*			
Life Table	P=0.450N	P=0.347	P=0.541N
Incidental Tumor Test	P=0.343N	P=0.427	P=0.541N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.398N	P=0.339	P=0.492N
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Tumor Rates			
Overall *(b)*	3/48 (6%)	4/48 (8%)	1/49 (2%)
Adjusted *(c)*	7.6%	10.0%	3.1%
Terminal *(d)*	2/36 (6%)	3/37 (8%)	1/32 (3%)
Statistical Tests *(e)*			
Life Table	P=0.299N	P=0.504	P=0.363N
Incidental Tumor Test	P=0.209N	P=0.571	P=0.348N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.245N	P=0.500	P=0.301N
Hematopoietic System: Malignant Lymphoma, Lymphocytic Type			
Tumor Rates			
Overall *(b)*	3/50 (6%)	2/49 (4%)	3/49 (6%)
Adjusted *(c)*	8.1%	5.4%	9.0%
Terminal *(d)*	3/37 (8%)	2/37 (5%)	2/32 (6%)
Statistical Tests *(e)*			
Life Table	P=0.513	P=0.500N	P=0.581
Incidental Tumor Test	P=0.524	P=0.500N	P=0.597
Cochran-Armitage Trend, Fisher Exact Tests	P=0.578	P=0.510N	P=0.651
Hematopoietic System: Malignant Lymphoma, Histiocytic Type			
Tumor Rates			
Overall *(b)*	2/50 (4%)	0/49 (0%)	3/49 (6%)
Adjusted *(c)*	5.3%	0.0%	7.2%
Terminal *(d)*	1/37 (3%)	0/37 (0%)	0/32 (0%)
Statistical Tests *(e)*			
Life Table	P=0.339	P=0.243N	P=0.432
Incidental Tumor Test	P=0.358	P=0.264N	P=0.458
Cochran-Armitage Trend, Fisher Exact Tests	P=0.384	P=0.253N	P=0.490
Hematopoietic System: Malignant Lymphoma, Mixed Type			
Tumor Rates			
Overall *(b)*	10/50 (20%)	6/49 (12%)	10/49 (20%)
Adjusted *(c)*	24.4%	15.6%	25.7%
Terminal *(d)*	7/37 (19%)	5/37 (14%)	5/32 (16%)
Statistical Tests *(e)*			
Life Table	P=0.429	P=0.210N	P=0.462
Incidental Tumor Test	P=0.529N	P=0.220N	P=0.547N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.534	P=0.220N	P=0.579

TABLE 12. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE *(a)* (Continued)

	Control	Low Dose	High Dose
Hematopoietic System: Malignant Lymphoma, All Types			
Tumor Rates			
Overall *(b)*	15/50 (30%)	9/49 (18%)	16/49 (33%)
Adjusted *(c)*	36.2%	22.5%	38.0%
Terminal *(d)*	11/37 (30%)	7/37 (19%)	7/32 (22%)
Statistical Tests *(e)*			
Life Table	P=0.307	P=0.129N	P=0.327
Incidental Tumor Test	P=0.428	P=0.138N	P=0.490
Cochran-Armitage Trend, Fisher Exact Tests	P=0.431	P=0.132N	P=0.473
Liver: Hepatocellular Adenoma			
Tumor Rates			
Overall *(b)*	0/50 (0%)	2/49 (4%)	7/49 (14%)
Adjusted *(c)*	0.0%	4.9%	21.0%
Terminal *(d)*	0/37 (0%)	1/37 (3%)	6/32 (19%)
Statistical Tests *(e)*			
Life Table	P=0.002	P=0.235	P=0.005
Incidental Tumor Test	P=0.002	P=0.215	P=0.006
Cochran-Armitage Trend, Fisher Exact Tests	P=0.003	P=0.242	P=0.006
Liver: Hepatocellular Carcinoma			
Tumor Rates			
Overall *(b)*	3/50 (6%)	6/49 (12%)	3/49 (6%)
Adjusted *(c)*	8.1%	14.0%	8.3%
Terminal *(d)*	3/37 (8%)	2/37 (5%)	2/32 (6%)
Statistical Tests *(e)*			
Life Table	P=0.487	P=0.253	P=0.602
Incidental Tumor Test	P=0.564	P=0.194	P=0.636N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.561	P=0.233	P=0.651
Liver: Hepatocellular Adenoma or Carcinoma			
Tumor Rates			
Overall *(b)*	3/50 (6%)	7/49 (14%)	10/49 (20%)
Adjusted *(c)*	8.1%	16.4%	28.7%
Terminal *(d)*	3/37 (8%)	3/37 (8%)	8/32 (25%)
Statistical Tests *(e)*			
Life Table	P=0.014	P=0.169	P=0.019
Incidental Tumor Test	P=0.020	P=0.124	P=0.029
Cochran-Armitage Trend, Fisher Exact Tests	P=0.026	P=0.151	P=0.033
Pituitary: Adenoma			
Tumor Rates			
Overall *(b)*	3/46 (7%)	2/43 (5%)	13/42 (31%)
Adjusted *(c)*	8.6%	5.5%	40.9%
Terminal *(d)*	3/35 (9%)	1/33 (3%)	10/28 (36%)
Statistical Tests *(e)*			
Life Table	P<0.001	P=0.517N	P=0.002
Incidental Tumor Test	P<0.001	P=0.558N	P=0.002
Cochran-Armitage Trend, Fisher Exact Tests	P=0.001	P=0.532N	P=0.003

TABLE 12. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE *(a)* (Continued)

	Control	Low Dose	High Dose
Pituitary: Adenoma or Carcinoma			
Tumor Rates			
Overall *(b)*	3/46 (7%)	2/43 (5%)	15/42 (36%)
Adjusted *(c)*	8.6%	5.5%	44.4%
Terminal *(d)*	3/35 (9%)	1/33 (3%)	10/28 (3%)
Statistical Tests *(e)*			
Life Table	P<0.001	P=0.517N	P<0.001
Incidental Tumor Test	P<0.001	P=0.558N	P<0.001
Cochran-Armitage Trend, Fisher Exact Tests	P<0.001	P=0.532N	P=0.001
Mammary Gland: Adenocarcinoma			
Tumor Rates			
Overall *(b)*	1/50 (2%)	3/49 (6%)	3/49 (6%)
Adjusted *(c)*	2.7%	7.1%	7.4%
Terminal *(d)*	1/37 (3%)	1/37 (3%)	1/32 (3%)
Statistical Tests *(e)*			
Life Table	P=0.209	P=0.311	P=0.275
Incidental Tumor Test	P=0.416	P=0.322	P=0.493
Cochran-Armitage Trend, Fisher Exact Tests	P=0.233	P=0.301	P=0.301
Harderian Gland: Adenoma			
Tumor Rates			
Overall *(b)*	1/50 (2%)	0/49 (0%)	3/49 (6%)
Adjusted *(c)*	2.7%	0.0%	9.4%
Terminal *(d)*	1/37 (3%)	0/37 (0%)	3/32 (9%)
Statistical Tests *(e)*			
Life Table	P=0.144	P=0.500N	P=0.254
Incidental Tumor Test	P=0.144	P=0.500N	P=0.254
Cochran-Armitage Trend, Fisher Exact Tests	P=0.173	P=0.505N	P=0.301

(a) Dosed groups received doses of 50 or 100 ppm of zearalenone in the diet.
(b) Number of tumor bearing animals/number of animals examined at the site.
(c) Kaplan-Meier estimated lifetime tumor incidence after adjusting for intercurrent mortality.
(d) Observed tumor incidence at terminal kill.
(e) Beneath the 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 controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as non-fatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend is indicated by (N).

IV. DISCUSSION AND CONCLUSIONS

Rat Study

Zearalenone and zearalenol have been shown to bind to the uterine cytoplasmic estrogen receptors of Holtzman and Sprague-Dawley rats and to elicit the translocation of the cytosol-receptor complex to the nucleus (Katzenellenbogen et al., 1979; Kiang et al., 1978). Zearalenone has also been found to bind to the mammary gland estrogen receptors of Sprague-Dawley rats (Boyd and Wittliff, 1978). The physiological consequences of these subcellular events were shown clearly in the subchronic tests. In the 14-day study, distention of the uterine horns occurred in 4/5 or 5/5 F344/N rats fed diets containing 6,000-100,000 ppm zearalenone. Endometrial hyperplasia of the uterus was observed in 2/10, 8/10, and 10/10 female rats administered 300, 1,000, or 3,000 ppm for 13 weeks; at the 3,000-ppm dose, ductular gland hyperplasia of the mammary gland was found in 6/10 males and 10/10 females.

Effects on the pituitary, prostate, testes, and bone in rats may also be linked to the binding of zearalenone or its metabolite to steroid receptors. Chromophobe hyperplasia of the pituitary occurred in 1/10 females fed 100 ppm, 2/10 females and 2/9 males fed 1,000 ppm, and 6/10 males and 7/10 females fed 3,000 ppm zearalenone for 13 weeks. Other hyperplastic effects on the pituitary have also been observed in rats administered other estrogenic compounds. Increased incidences of pituitary tumors have been found in rats and mice in other studies after they received implantations of cholesterol pellets containing diethylstilbesterol (Andervont et al., 1960; DeNicola et al., 1978) and after subcutaneous injections of estradiol benzoate (Gardner, 1941) or diethylstilbesterol dipropionate (Jacobi et al., 1975). In this NCI/NTP chronic study an increased incidence of pituitary tumors occurred in B6C3F1 mice but not in F344/N rats.

Implants of zearalenone induce squamous metaplasia and hyperplasia of calf prostate glands (Rothenbacher et al., 1975) as well as testicular atrophy (Ralston, 1978). In the present 13-week study, fibromuscular hyperplasia of the prostate was seen in 9/9 and 9/10 male rats fed diets containing 1,000 or 3,000 ppm. In the chronic study, inflammation of the prostate occurred in 31/50 and 22/50 male rats administered 25 or 50 ppm (control incidence, 15/49).

Atrophy of the seminal vesicles occurred in 90%-100% of the male rats fed 1,000 or 3,000 ppm zearalenone for 13 weeks; atrophy of the testes was found at increased incidences relative to controls in males administered 25 or 50 ppm for 103 weeks. Aspermatogenesis was found in 60%-100% of the animals receiving 300-3,000 ppm in the 13-week study. Interstitial-cell tumors of the testes occurred with a statistically significant negative trend in rats fed 25 or 50 ppm for 103 weeks (P=0.042 in the incidental tumor test; control 45/50, 90%; low-dose, 43/50, 86%; high-dose 39/50, 78%). The decreased incidence of testicular interstitial-cell tumors is probably related to testicular atrophy.

Osteopetrosis occurred with a dose-related incidence in female rats administered diets containing 30-3,000 ppm zearalenone for 13 weeks. Incidences of 90%-100% were found in groups of females administered 100 ppm or more and in males administered 1,000 or 3,000 ppm. Female rats were considerably more sensitive to this chemically-induced effect (5/10 at 30 ppm) than were males. Yet, osteopetrosis was not observed in either male or female rats in the chronic study. Bailey et al. (1976) reported that ingestion of more than 0.1 mg zearalenone per kg per day increased the number and extent of distribution of medullary trabeculae in the femurs of male and female rats in a multigeneration study of the toxic effects of zearalenone. The absence of this response in the current study is unexplainable.

Studies on the metabolic fate of ^{3}H-zearalenone in Wistar rats have shown that radioactivity accumulates in both the liver and kidney (Ueno et al., 1977). Cytoplasmic vacuolization of the liver was observed at increased incidences in male rats fed diets containing 25 or 50 ppm zearalenone in the chronic study. The vacuolization, however, was minimal and was focal in most instances. Nephrosis, typical of that seen in aging F344/N rats, was observed at increased incidences in males and females fed 25 or 50 ppm zearalenone (control males, 30/50, 60%; low-dose males, 43/50, 86%; high-dose males, 41/50, 82%; control females, 10/50, 20%; low-dose females, 24/50, 48%; high-dose females, 26/50, 52%).

Clinically, opacity or cloudiness of the lens was noted at increased incidences in male rats fed diets containing 25 or 50 ppm zearalenone and in female rats fed 25 ppm. The increased incidences were also associated with animals in the uppermost rows of cages and with proximity to fluorescent light. Inasmuch as the eye was not one of the organs sampled routinely, only those eyes with clinical or gross abnormalities were examined microscopically. Almost all rats in which opacity or cloudiness of the lens was

observed were also found to have cataractous or shrunken lenses and retinal degeneration or atrophy. The relationship between cataracts, the test chemical, light intensity, and retinal degeneration (which was usually severe in the present study) is not known.

Lenticular problems associated with exposure of test or control animals to fluorescent light have been noted in several Bioassay Program studies at this same laboratory (NTP 1982a; NTP 1982b; NTP 1982c).

For male and female rats there were no compound-related increases in any tumor type.

Mouse Study

Effects similar to those found in rats were also observed in mice. Distention of the uterine horns occurred in 2/5 to 4/5 females receiving 6,000-100,000 ppm zearalenone for 14 days. Fibrosis of the uterus/myometrium was seen at increased incidences in mice administered 50 or 100 ppm for 103 weeks. The number of females with cystic ducts in the mammary glands was increased in the dosed groups in the chronic study.

Atrophy of the seminal vesicles was seen in all male mice fed diets containing 1,000 or 3,000 ppm zearalenone in the 13-week subchronic study and vacuolization of the adrenal glands was observed in 90% of the male mice fed diets containing the same doses of the test chemical; squamous metaplasia of the prostate occurred in 8/10 males administered the 3,000-ppm dose.

Osteopetrosis was observed in 10/10 males and 6/8 females fed diets containing 3,000 ppm zearalenone for 13 weeks, in 10/10 males and 5/10 females administered 1,000 ppm, in 7/10 males and 5/10 females receiving 300 ppm, and in 4/10 males and 2/10 females administered 100 ppm. Osteopetrosis, noted at most dose levels in the 13-week study, was not seen in the chronic study. Certain minimal bony changes were noted in the femurs of the chronic study high-dose female mice; these changes were characterized by increased fibrous osteodystrophy. Sass and Montali (1980) recently reported that the spontaneous myelofibrosis found in B6C3F1 mice resembles the estrogen-induced myelofibrosis described by other investigators (Seaman et al., 1979; Sokoloff et al., 1967; Silberberg and Silberberg, 1970). In the current experiment, myelofibrosis of the bone marrow occurred in 10/10 males fed diets containing 3,000 or 1,000 ppm for 13 weeks and in 6/8 females fed 3,000 ppm and 3/10 females fed 1,000 ppm; this effect occurred with increased incidence and severity (compared with the controls) for females receiving 50 or 100 ppm zearalenone for 103 weeks.

Administration of zearalenone to mice in the present study was associated with increased incidences of neoplastic lesions of the liver and of the pituitary.

The incidence of hepatocellular adenomas was dose-related in female mice administered diets containing 0, 50, or 100 ppm zearalenone for 103 weeks ($P \leq 0.003$); the incidences in females receiving the highest dose were significantly ($P \leq 0.006$) higher than those in the controls. The incidence of hepatocellular adenomas for females administered 50 or 100 ppm zearalenone was 2/49 (4%) and 7/49 (14%), respectively. The incidence in the control group was 0/50 (0%), compared with an average rate of 14/498 (2.8%) for control female B6C3F1 mice at this laboratory. The historical incidence of liver tumors in untreated control female B6C3F1 mice in all Bioassay Program laboratories is summarized in Appendix K, Table K1. The incidence of hepatocellular carcinomas (3/50, 6/49, 3/49) was similar for the control and dosed groups.

Pituitary adenomas occurred with statistically significant positive trends in mice administered 50 or 100 ppm zearalenone for 103 weeks ($P \leq 0.022$ for males and $P \leq 0.001$ for females). The increased incidences of pituitary adenomas in mice receiving the higher dose were each statistically significant ($P \leq 0.032$ in males, $P \leq 0.003$ in females). These increases are considered to be due to the dietary administration of zearalenone. In addition to the pituitary adenomas, two other high-dose female mice had pituitary carcinoma. The incidence of pituitary adenomas and carcinomas (of all types) in untreated control B6C3F1 mice at this laboratory is 0/399 for males and 21/428 (4.9%) for females (individual group incidences ranged from 0% to 6/48, 12.5%) (Appendix K, Tables K2 and K3). Pituitary tumors have also been found at increased incidences in various strains of rats and mice, including F344 males and C57BL males, administered other estrogenic compounds such as diethylstilbesterol (Andervont et al., 1960), estradiol benzoate (Gardner, 1941), or diethylstilbesterol dipropionate (Jacobi et al., 1975).

The body weight gain reduction anticipated from the 13-week study was not duplicated throughout the chronic study. Based on weight gain data only, it appears that the mice could have tolerated higher doses of zearalenone. However, based on histological findings in both male and female mice, it appears likely that the

levels used in the chronic study approached a maximum tolerated dose.

As can be observed from the analysis of the data given in Tables 11 and 12, the significance of the dose-related increase in hepatocellular adenomas in female mice is not markedly affected when adenomas or carcinomas are considered together. Hepatocellular adenomas are considered to be part of the process of hepatic carcinogenesis (Stewart et al., 1980) which is induced by hepatocarcinogens but not by non-carcinogens. National and international agencies (IARC, 1980; IRLG, 1979) have stated that few, if any, chemicals produce only benign tumors in any species; agents that significantly increase the incidence of benign tumors are today viewed with as much suspicion as they would have been had the induced tumors been diagnosed as malignant. In general, existing evidence supports the progression, in many tissues, of adenomas to carcinomas and, accordingly, a chemical that induces adenomas represents a potential carcinogenic risk to humans (IARC, 1980).

Despite the similarities between zearalenone and DES in their physiological responses and subcellular actions, there appear to be significant differences in tumor target tissues. Following oral doses of DES, Sprague-Dawley rats developed mammary fibroadenomas, pituitary tumors (not specified as adenomas or carcinomas), hepatomas, and a hemangio-endothelioma (Gibson et al., 1967). Such tumors were not seen in the F344/N rats in this study. Various strains of mice receiving oral doses of DES (gavage or feed) developed mammary tumors, uterine horn adenocarcinomas, cervical adenocarcinomas, and osteosarcomas (reviewed in IARC, 1979). The B6C3F1 mice used in this study did not develop tumors in these locations. It is not presently clear if these target tissue differences are due to strain, to the chemical tested (despite physiologically similar mechanisms), or to both.

Administration of zearalenone was related to the occurrence of inflammation of the prostate, testicular atrophy, and cytoplasmic vacuolization of the liver in male F344/N rats and to nephrosis in rats of either sex. In female B6C3F1 mice, zearalenone increased the incidence of bone marrow myelofibrosis, uterine fibrosis, and mammary cystic ducts.

Conclusions: Under the conditions of this bioassay, zearalenone was not carcinogenic for F344/N rats of either sex. Zearalenone should be considered carcinogenic in B6C3F1 mice, as evidenced by the increased proportion of male and female mice with pituitary adenomas and by the increased proportion of female mice with hepatocellular adenomas.

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APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS FED DIETS CONTAINING ZEARALENONE

TABLE A1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS FED DIETS CONTAINING ZEARALENONE

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*MEDIASTINUM	(50)	(50)	(50)
FIBROUS HISTIOCYTOMA, MALIGNANT	1 (2%)		
*SKIN	(50)	(50)	(50)
PAPILLOMA, NOS			1 (2%)
SQUAMOUS CELL PAPILLOMA	2 (4%)	1 (2%)	
BASAL-CELL TUMOR	1 (2%)		
SEBACEOUS ADENOMA			1 (2%)
ADENOSQUAMOUS CARCINOMA			1 (2%)
*SUBCUT TISSUE	(50)	(50)	(50)
FIBROMA	2 (4%)		
FIBROSARCOMA	1 (2%)		1 (2%)
LIPOMA			1 (2%)
RESPIRATORY SYSTEM			
*NOSE	(50)	(50)	(50)
SQUAMOUS CELL PAPILLOMA		1 (2%)	
#TRACHEAL GLAND	(49)	(43)	(46)
ADENOCARCINOMA, NOS	1 (2%)		
#LUNG	(49)	(50)	(47)
CARCINOMA, NOS, METASTATIC		1 (2%)	
SQUAMOUS CELL CARCINOMA	1 (2%)		
ALVEOLAR/BRONCHIOLAR ADENOMA	3 (6%)	1 (2%)	
ALVEOLAR/BRONCHIOLAR CARCINOMA	2 (4%)	1 (2%)	1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		1 (2%)	
MALIGNANT LYMPHOMA, MIXED TYPE			1 (2%)
UNDIFFERENTIATED LEUKEMIA	9 (18%)	4 (8%)	7 (14%)
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(49)	(49)	(50)
SARCOMA, NOS	1 (2%)		
#LIVER	(50)	(50)	(50)

\# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
NEOPLASTIC NODULE	2 (4%)		1 (2%)
HEPATOCELLULAR CARCINOMA			1 (2%)
#COLONIC MUCOUS MEMBR	(49)	(49)	(48)
ADENOMATOUS POLYP, NOS		1 (2%)	
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
SARCOMA, NOS	1 (2%)		
NEPHROBLASTOMA	1 (2%)		
ENDOCRINE SYSTEM			
#PITUITARY	(46)	(49)	(50)
NEOPLASM, NOS	1 (2%)		
CARCINOMA,NOS	1 (2%)		1 (2%)
ADENOMA, NOS	5 (11%)	13 (27%)	9 (18%)
#ADRENAL	(50)	(50)	(50)
PHEOCHROMOCYTOMA	5 (10%)	5 (10%)	5 (10%)
PHEOCHROMOCYTOMA, MALIGNANT	2 (4%)		2 (4%)
#THYROID	(49)	(50)	(50)
FOLLICULAR-CELL ADENOMA			1 (2%)
C-CELL ADENOMA	3 (6%)	7 (14%)	6 (12%)
C-CELL CARCINOMA		1 (2%)	2 (4%)
#PANCREATIC ISLETS	(49)	(50)	(50)
ISLET-CELL ADENOMA	2 (4%)	2 (4%)	
ISLET-CELL CARCINOMA	1 (2%)	1 (2%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
CARCINOMA,NOS	1 (2%)		
ADENOMA, NOS			1 (2%)
FIBROMA	1 (2%)		
FIBROADENOMA	1 (2%)	3 (6%)	2 (4%)
*PREPUTIAL GLAND	(50)	(50)	(50)
CARCINOMA,NOS	1 (2%)		
SQUAMOUS CELL CARCINOMA	1 (2%)		
ADENOMA, NOS	1 (2%)	2 (4%)	1 (2%)
#PROSTATE	(49)	(50)	(49)
ADENOCARCINOMA, NOS			1 (2%)
#TESTIS	(50)	(50)	(50)
INTERSTITIAL-CELL TUMOR	45 (90%)	42 (84%)	39 (78%)
INTERSTITIAL-CELL TUMOR, MALIGNA		1 (2%)	
*SCROTUM	(50)	(50)	(50)
SQUAMOUS CELL PAPILLOMA		1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
NERVOUS SYSTEM			
#BRAIN	(50)	(50)	(50)
ASTROCYTOMA	1 (2%)		
#PALLIUM	(50)	(50)	(50)
GLIOMA, NOS		1 (2%)	
SPECIAL SENSE ORGANS			
*ZYMBAL'S GLAND	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA		1 (2%)	
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*MEDIASTINUM	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA, METASTA	1 (2%)		
*ABDOMINAL CAVITY	(50)	(50)	(50)
MESOTHELIOMA BENIGN	1 (2%)		
*MESENTERY	(50)	(50)	(50)
MESOTHELIOMA BENIGN		1 (2%)	
*TUNICA VAGINALIS	(50)	(50)	(50)
MESOTHELIOMA BENIGN	1 (2%)		
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
ALVEOLAR/BRONCHIOLAR CA, METASTA	1 (2%)	1 (2%)	
PHEOCHROMOCYTOMA, METASTATIC			1 (2%)
MESOTHELIOMA, NOS		1 (2%)	1 (2%)
THIGH			
CARCINOMA,NOS		1	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	6	4	3
MORIBUND SACRIFICE	6	8	10
SCHEDULED SACRIFICE	6		
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	32	38	37
ANIMAL MISSING			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	50	50	48
TOTAL PRIMARY TUMORS	102	93	87
TOTAL ANIMALS WITH BENIGN TUMORS	47	47	46
TOTAL BENIGN TUMORS	73	80	67
TOTAL ANIMALS WITH MALIGNANT TUMORS	21	10	15
TOTAL MALIGNANT TUMORS	26	12	18
TOTAL ANIMALS WITH SECONDARY TUMORS#	2	2	1
TOTAL SECONDARY TUMORS	2	2	1
TOTAL ANIMALS WITH TUMORS UNCERTAIN- BENIGN OR MALIGNANT	3	1	2
TOTAL UNCERTAIN TUMORS	3	1	2
TOTAL ANIMALS WITH TUMORS UNCERTAIN- PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

@ INCLUDES AUTOLYZED ANIMALS

* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

TABLE A2.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS FED DIETS CONTAINING ZEARALENONE

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
SQUAMOUS CELL PAPILLOMA		1 (2%)	
KERATOACANTHOMA	1 (2%)		
*SUBCUT TISSUE	(50)	(50)	(50)
CARCINOMA,NOS		1 (2%)	
SARCOMA, NOS		2 (4%)	
FIBROMA		2 (4%)	
RESPIRATORY SYSTEM			
#TRACHEA	(42)	(46)	(47)
C-CELL CARCINOMA, INVASIVE			1 (2%)
#LUNG	(48)	(50)	(50)
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (2%)	2 (4%)	1 (2%)
ALVEOLAR/BRONCHIOLAR CARCINOMA			1 (2%)
SARCOMA, NOS, METASTATIC		1 (2%)	
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)
UNDIFFERENTIATED LEUKEMIA	7 (14%)	7 (14%)	2 (4%)
#BONE MARROW	(49)	(48)	(48)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (2%)		
CIRCULATORY SYSTEM			
NONE			

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
#LIVER	(50)	(50)	(50)
NEOPLASTIC NODULE		1 (2%)	1 (2%)
HEPATOCELLULAR CARCINOMA			1 (2%)
#STOMACH	(50)	(50)	(50)
SARCOMA, NOS	1 (2%)		
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#PITUITARY	(49)	(50)	(49)
CARCINOMA,NOS	1 (2%)	1 (2%)	
ADENOMA, NOS	13 (27%)	15 (30%)	14 (29%)
#ADRENAL	(50)	(50)	(50)
CORTICAL ADENOMA			1 (2%)
PHEOCHROMOCYTOMA		1 (2%)	
#THYROID	(49)	(50)	(49)
ADENOMA, NOS	1 (2%)		
FOLLICULAR-CELL ADENOMA	1 (2%)		
C-CELL ADENOMA	5 (10%)	6 (12%)	4 (8%)
C-CELL CARCINOMA		1 (2%)	2 (4%)
#PARATHYROID	(43)	(45)	(44)
ADENOMA, NOS			1 (2%)
#PANCREATIC ISLETS	(50)	(50)	(50)
ISLET-CELL ADENOMA	1 (2%)		
ISLET-CELL CARCINOMA		1 (2%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
ADENOCARCINOMA, NOS	1 (2%)	2 (4%)	1 (2%)
CYSTADENOMA, NOS			1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
FIBROADENOMA	9 (18%)	14 (28%)	9 (18%)
*PREPUTIAL GLAND	(50)	(50)	(50)
CARCINOMA,NOS	1 (2%)		
ADENOMA, NOS			2 (4%)
*VAGINA	(50)	(50)	(50)
GRANULAR-CELL TUMOR, BENIGN	1 (2%)		
#UTERUS	(50)	(49)	(49)
ENDOMETRIAL STROMAL POLYP	4 (8%)	8 (16%)	5 (10%)
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*EYELID	(50)	(50)	(50)
FIBROSARCOMA		1 (2%)	
*ZYMBAL'S GLAND	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA	1 (2%)		
MUSCULOSKELETAL SYSTEM			
*MUSCLE OF BACK	(50)	(50)	(50)
RHABDOMYOSARCOMA			1 (2%)
BODY CAVITIES			
*THORAX	(50)	(50)	(50)
FIBROMA			1 (2%)
*MEDIASTINUM	(50)	(50)	(50)
ADENOCARCINOMA, NOS		1 (2%)	
*ABDOMINAL WALL	(50)	(50)	(50)
FIBROMA	1 (2%)		
*MESENTERY	(50)	(50)	(50)
LIPOMA	1 (2%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
C-CELL CARCINOMA, METASTATIC			1 (2%)
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	2		
MORIBUND SACRIFICE	8	12	9
SCHEDULED SACRIFICE	6		
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	34	38	41
ANIMAL MISSING			
@ INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	32	40	33
TOTAL PRIMARY TUMORS	52	67	49
TOTAL ANIMALS WITH BENIGN TUMORS	29	35	28
TOTAL BENIGN TUMORS	39	49	39
TOTAL ANIMALS WITH MALIGNANT TUMORS	13	15	9
TOTAL MALIGNANT TUMORS	13	17	9
TOTAL ANIMALS WITH SECONDARY TUMORS#		1	1
TOTAL SECONDARY TUMORS		1	2
TOTAL ANIMALS WITH TUMORS UNCERTAIN- BENIGN OR MALIGNANT		1	1
TOTAL UNCERTAIN TUMORS		1	1
TOTAL ANIMALS WITH TUMORS UNCERTAIN- PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

TABLE A3.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE 2-YEAR STUDY OF ZEARALENONE

CONTROL

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	104	104	104	026	104	106	106	106	103	106	106	106	106	101	106	106	106	106	106	104	106	094	103	106	079
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL PAPILLOMA																								X	
BASAL-CELL TUMOR																									
SUBCUTANEOUS TISSUE	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FIBROMA																					X				
FIBROSARCOMA																									
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+
SQUAMOUS CELL CARCINOMA													X												
ALVEOLAR/BRONCHIOLAR ADENOMA													X	X											
ALVEOLAR/BRONCHIOLAR CARCINOMA													X												
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+
ADENOCARCINOMA, NOS																							X		
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	+	+	+	+	+	-	+	+	+	+	-	+	-	+	+	+	+	+	+	+	+	-	+	+	-
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+
SARCOMA, NOS																									
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NEOPLASTIC NODULE									X					X											
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+
ESOPHAGUS	+	-	-	+	+	-	+	-	+	-	+	+	+	+	-	+	-	+	+	+	+	-	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SARCOMA, NOS													X												
NEPHROBLASTOMA					X																				
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	-
ENDOCRINE SYSTEM																									
PITUITARY	-	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+
NEOPLASM, NOS																									X
CARCINOMA,NOS																									
ADENOMA, NOS				X								X											X		
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PHEOCHROMOCYTOMA			X																						X
PHEOCHROMOCYTOMA, MALIGNANT									X																
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+
C-CELL ADENOMA																					X		X		
PARATHYROID	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	-	+	-	-	-	+	+	+
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+
ISLET-CELL ADENOMA																					X		X		
ISLET-CELL CARCINOMA																									
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARCINOMA,NOS																		X							
FIBROMA						-																			
FIBROADENOMA																									
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
INTERSTITIAL-CELL TUMOR	X	X	X		X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
PROSTATE	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
CARCINOMA,NOS																		X							
SQUAMOUS CELL CARCINOMA																									
ADENOMA, NOS																									
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ASTROCYTOMA																									
BODY CAVITIES																									
MEDIASTINUM	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
SQUAMOUS CELL CARCINOMA, METASTAT																									
FIBROUS HISTIOCYTOMA, MALIGNANT																									
PERITONEUM	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
MESOTHELIOMA BENIGN																									
TUNICA VAGINALIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MESOTHELIOMA BENIGN																									
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ALVEOLAR/BRONCHIOLAR CA, METASTAT																									
UNDIFFERENTIATED LEUKEMIA			X											X							X				

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: *ANIMAL MISSING*
B: NO NECROPSY PERFORMED

TABLE A3. MALE RATS: TUMOR PATHOLOGY (CONTINUED) CONTROL

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL
WEEKS ON STUDY	106	104	106	106	106	106	106	106	092	082	106	061	091	106	097	106	106	089	106	106	106	106	106	106	106	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
SKIN	+	N	+	+	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
SQUAMOUS CELL PAPILLOMA				X																						2
BASAL-CELL TUMOR																						X				1
SUBCUTANEOUS TISSUE	+	N	+	+	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
FIBROMA															X											2
FIBROSARCOMA																				X						1
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SQUAMOUS CELL CARCINOMA										X																1
ALVEOLAR/BRONCHIOLAR ADENOMA													X													3
ALVEOLAR/BRONCHIOLAR CARCINOMA													X													2
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ADENOCARCINOMA, NOS																										1
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	49
SPLEEN	+	+	•	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	•	+	50
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
THYMUS	+	-	+	-	-	+	-	+	+	+	+	+	+	+	+	+	-	+	-	-	+	+	-	+	+	37
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SARCOMA, NOS															X											1
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NEOPLASTIC NODULE																										2
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ESOPHAGUS	+	+	+	-	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	39
STOMACH	+	+	+	+	•	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SARCOMA, NOS																										1
NEPHROBLASTOMA																										1
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	-	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
NEOPLASM, NOS																										1
CARCINOMA,NOS																										1
ADENOMA, NOS						X								X					X							5
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
PHEOCHROMOCYTOMA									X												X				X	5
PHEOCHROMOCYTOMA, MALIGNANT																				X						2
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-CELL ADENOMA															X											3
PARATHYROID	-	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	-	+	+	-	+	+	41
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ISLET-CELL ADENOMA																					X					2
ISLET-CELL CARCINOMA																										1
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	N	+	+	+	+	50*
CARCINOMA,NOS																						X				1
FIBROMA																										1
FIBROADENOMA							X																			1
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
INTERSTITIAL-CELL TUMOR	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	45
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
CARCINOMA,NOS																					X					1
SQUAMOUS CELL CARCINOMA																										1
ADENOMA, NOS						X																				1
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ASTROCYTOMA												X														1
BODY CAVITIES																										
MEDIASTINUM	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
SQUAMOUS CELL CARCINOMA, METASTAT										X																1
FIBROUS HISTIOCYTOMA, MALIGNANT										X																1
PERITONEUM	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
MESOTHELIOMA BENIGN																					N					1
TUNICA VAGINALIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
MESOTHELIOMA BENIGN										X																1
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
ALVEOLAR/BRONCHIOLAR CA, METASTAT													X													1
UNDIFFERENTIATED LEUKEMIA	X	X						X	X			X								X						9

* ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A3.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE 2-YEAR STUDY OF ZEARALENONE

LOW DOSE

ANIMAL NUMBER	0011	0012	0013	0014	0015	0016	0017	0018	0019	0110	0111	0112	0113	0114	0115	0116	0117	0118	0119	0120	0121	0122	0123	0124	0125
WEEKS ON STUDY	101	084	105	105	095	095	105	105	080	105	105	105	105	105	105	092	105	105	105	105	105	105	105	105	092
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+
SQUAMOUS CELL PAPILLOMA																									
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARCINOMA, NOS, METASTATIC									X																
ALVEOLAR/BRONCHIOLAR ADENOMA																				X					
ALVEOLAR/BRONCHIOLAR CARCINOMA						X																			
TRACHEA	+	+	+	+	+	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+
NASAL CAVITY	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
SQUAMOUS CELL PAPILLOMA							X																		
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	+	+	+	+	+	–	+	–	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOMATOUS POLYP, NOS			X																						
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+
ADENOMA, NOS			X	X												X	X						X		
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PHEOCHROMOCYTOMA	X																	X							X
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-CELL ADENOMA	X																								
C-CELL CARCINOMA																									
PARATHYROID	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	–	+	–	
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ISLET-CELL ADENOMA																			X						
ISLET-CELL CARCINOMA																									
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	N	+	+	+	+
FIBROADENOMA																									X
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
INTERSTITIAL-CELL TUMOR	X	X	X		X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
INTERSTITIAL-CELL TUMOR, MALIGNAN									X																
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ADENOMA, NOS														X	X										
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GLIOMA, NOS																					X				
SPECIAL SENSE ORGANS																									
ZYMBAL'S GLAND	N	N	N	N	N	N	N	N	N	+	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N
SQUAMOUS CELL CARCINOMA																									
BODY CAVITIES																									
MESENTERY	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
MESOTHELIOMA BENIGN																									
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ALVEOLAR/BRONCHIOLAR CA, METASTAT						X																			
MESOTHELIOMA, NOS																									
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE																									
UNDIFFERENTIATED LEUKEMIA	X	X																							
THIGH NOS																									
CARCINOMA,NOS									X																
SCROTUM NOS																									
SQUAMOUS CELL PAPILLOMA	X																								

+: TISSUE EXAMINED MICROSCOPICALLY
–: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCO
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A3. MALE RATS: TUMOR PATHOLOGY (CONTINUED) LOW DOSE

ANIMAL NUMBER	0261	0277	0281	0291	0310	0311	0323	0331	0334	0335	0336	0337	0338	0339	0340	0341	0342	0343	0344	0345	0346	0347	0348	0349	0350	TOTAL
WEEKS ON STUDY	105	105	105	105	105	105	088	103	106	106	067	091	106	106	106	081	106	106	106	106	106	106	097	106	106	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
SKIN	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SQUAMOUS CELL PAPILLOMA		X																								1
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CARCINOMA, NOS, METASTATIC																										1
ALVEOLAR/BRONCHIOLAR ADENOMA																										1
ALVEOLAR/BRONCHIOLAR CARCINOMA																										1
TRACHEA	-	+	+	+	-	+	+	+	+	-	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	43
NASAL CAVITY	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50
SQUAMOUS CELL PAPILLOMA																										1
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
THYMUS	+	+	-	+	+	+	+	+	+	+	+	+	+	+	-	+	-	+	-	+	+	+	+	+	+	43
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ADENOMATOUS POLYP, NOS																										1
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ADENOMA, NOS				X	X			X				X				X								X	X	X	13
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
PHEOCHROMOCYTOMA																				X				X		5
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-CELL ADENOMA	X	X	X							X								X			X					7
C-CELL CARCINOMA																X										1
PARATHYROID	+	+	+	+	-	+	+	+	+	+	+	+	-	+	+	+	+	-	+	+	+	+	+	+	+	43
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ISLET-CELL ADENOMA				X																						2
ISLET-CELL CARCINOMA									X																	1
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
FIBROADENOMA							X					X														3
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
INTERSTITIAL-CELL TUMOR	X	X	X			X	X	X		X			X	X	X		X	X	X	X	X	X	X	X	X	42
INTERSTITIAL-CELL TUMOR, MALIGNAN																										1
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50
ADENOMA, NOS																										2
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GLIOMA, NOS																										1
SPECIAL SENSE ORGANS																										
ZYMBAL'S GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	50
SQUAMOUS CELL CARCINOMA																			X							1
BODY CAVITIES																										
MESENTERY	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50
MESOTHELIOMA BENIGN				X																						1
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50
ALVEOLAR/BRONCHIOLAR CA, METASTAT																										1
MESOTHELIOMA, NOS												X														1
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE										X																1
UNDIFFERENTIATED LEUKEMIA																			X					X		4
THIGH NOS																										
CARCINOMA,NOS																										1
SCROTUM NOS																										
SQUAMOUS CELL PAPILLOMA																										1

* ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A3.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE 2-YEAR STUDY OF ZEARALENONE

HIGH DOSE

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	104	095	104	097	104	100	041	041	088	041	046	044	041	041	044	041	041	087	044	088	080	085	085	085	101
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PAPILLOMA, NOS				X																					
SEBACEOUS ADENOMA																									
ADENOSQUAMOUS CARCINOMA									X																
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FIBROSARCOMA																									
LIPOMA																									X
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+
ALVEOLAR/BRONCHIOLAR CARCINOMA																									
TRACHEA	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	-
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	-	+	+	+	+	-	+	-	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NEOPLASTIC NODULE																									
HEPATOCELLULAR CARCINOMA																									
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	-	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARCINOMA,NOS																									
ADENOMA, NOS	X															X	X			X		X			
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PHEOCHROMOCYTOMA																X			X	X					
PHEOCHROMOCYTOMA, MALIGNANT																					X				
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FOLLICULAR-CELL ADENOMA																X									
C-CELL ADENOMA																	X							X	
C-CELL CARCINOMA																									X
PARATHYROID	+	+	+	+	-	+	+	+	-	+	+	+	+	-	+	+	+	+	+	-	+	+	+	-	+
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOMA, NOS																									
FIBROADENOMA			X							X															
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
INTERSTITIAL-CELL TUMOR				X	X		X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X
PROSTATE	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOCARCINOMA, NOS																									
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ADENOMA, NOS		X																							
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
PHEOCHROMOCYTOMA, METASTATIC											X														
MESOTHELIOMA, NOS																									
MALIGNANT LYMPHOMA, MIXED TYPE				X	X	X														X	X				
UNDIFFERENTIATED LEUKEMIA																									

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION

: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A3. MALE RATS: TUMOR PATHOLOGY (CONTINUED) HIGH DOSE

ANIMAL NUMBER / WEEKS ON STUDY	TOTAL TISSUES TUMORS
INTEGUMENTARY SYSTEM	
SKIN	50*
PAPILLOMA, NOS	1
SEBACEOUS ADENOMA	1
ADENOSQUAMOUS CARCINOMA	1
SUBCUTANEOUS TISSUE	50*
FIBROSARCOMA	1
LIPOMA	1
RESPIRATORY SYSTEM	
LUNGS AND BRONCHI	47
ALVEOLAR/BRONCHIOLAR CARCINOMA	1
TRACHEA	46
HEMATOPOIETIC SYSTEM	
BONE MARROW	50
SPLEEN	50
LYMPH NODES	50
THYMUS	43
CIRCULATORY SYSTEM	
HEART	50
DIGESTIVE SYSTEM	
SALIVARY GLAND	50
LIVER	50
NEOPLASTIC NODULE	1
HEPATOCELLULAR CARCINOMA	1
BILE DUCT	50
GALLBLADDER & COMMON BILE DUCT	50*
PANCREAS	50
ESOPHAGUS	49
STOMACH	50
SMALL INTESTINE	49
LARGE INTESTINE	48
URINARY SYSTEM	
KIDNEY	50
URINARY BLADDER	49
ENDOCRINE SYSTEM	
PITUITARY	50
CARCINOMA,NOS	1
ADENOMA, NOS	9
ADRENAL	50
PHEOCHROMOCYTOMA	5
PHEOCHROMOCYTOMA, MALIGNANT	2
THYROID	50
FOLLICULAR-CELL ADENOMA	1
C-CELL ADENOMA	6
C-CELL CARCINOMA	2
PARATHYROID	43
REPRODUCTIVE SYSTEM	
MAMMARY GLAND	50*
ADENOMA, NOS	1
FIBROADENOMA	2
TESTIS	50
INTERSTITIAL-CELL TUMOR	39
PROSTATE	49
ADENOCARCINOMA, NOS	1
PREPUTIAL/CLITORAL GLAND	50*
ADENOMA, NOS	1
NERVOUS SYSTEM	
BRAIN	50
ALL OTHER SYSTEMS	
MULTIPLE ORGANS NOS	50*
PHEOCHROMOCYTOMA, METASTATIC	1
MESOTHELIOMA, NOS	1
MALIGNANT LYMPHOMA, MIXED TYPE	1
UNDIFFERENTIATED LEUKEMIA	2

* ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
~: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: *NECROPSY*, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
-: NO TISSUE INFORMATION *SUBMITTED*
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY *PERFORMED*

TABLE A4.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE 2-YEAR STUDY OF ZEARALENONE

CONTROL

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	091	113	114	104	095	097	097	104	081	104	104	061	102	105	106	106	106	106	061	106	106	106	106	106	106
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	N	+	+	+	N	+	+	N	+	+	+	+	N	N	+	+	+	+	N
KERATOACANTHOMA			X																						
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+
ALVEOLAR/BRONCHIOLAR ADENOMA																									
TRACHEA	-	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																X									
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	-	+	+	+	+	+	+	+	+	+	+	-	+	-	+	+	+	-	+	+	+	+	+	+	-
CIRCULATORY SYSTEM																									
HEART	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	-	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SARCOMA, NOS					X																				
SMALL INTESTINE	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARCINOMA,NOS																									
ADENOMA, NOS	X			X		X	X						X			X			X					
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYROID	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOMA, NOS																									
FOLLICULAR-CELL ADENOMA																									X
C-CELL ADENOMA								X												X					
PARATHYROID	-	+	+	+	+	-	-	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ISLET-CELL ADENOMA									X																
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	N
ADENOCARCINOMA, NOS							X																		
FIBROADENOMA			X						X			X		X		X			X						
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
CARCINOMA,NOS												X													
VAGINA	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
GRANULAR-CELL TUMOR, BENIGN		X																							
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOMETRIAL STROMAL POLYP								X																	
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
ZYMBAL'S GLAND	+	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
SQUAMOUS CELL CARCINOMA																									
BODY CAVITIES																									
PERITONEUM	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
FIBROMA																									
MESENTERY	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
LIPOMA			X																						
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
UNDIFFERENTIATED LEUKEMIA				X																X	X				

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A4. FEMALE RATS: TUMOR PATHOLOGY (CONTINUED) CONTROL

ANIMAL NUMBER / WEEKS ON STUDY	TOTAL TISSUES / TUMORS
INTEGUMENTARY SYSTEM	
SKIN	50M
KERATOACANTHOMA	1
RESPIRATORY SYSTEM	
LUNGS AND BRONCHI	48
ALVEOLAR/BRONCHIOLAR ADENOMA	1
TRACHEA	42
HEMATOPOIETIC SYSTEM	
BONE MARROW	49
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1
SPLEEN	50
LYMPH NODES	50
THYMUS	43
CIRCULATORY SYSTEM	
HEART	49
DIGESTIVE SYSTEM	
SALIVARY GLAND	50
LIVER	50
BILE DUCT	50
GALLBLADDER & COMMON BILE DUCT	50M
PANCREAS	50
ESOPHAGUS	48
STOMACH	50
SARCOMA, NOS	1
SMALL INTESTINE	49
LARGE INTESTINE	49
URINARY SYSTEM	
KIDNEY	50
URINARY BLADDER	49
ENDOCRINE SYSTEM	
PITUITARY	49
CARCINOMA,NOS	1
ADENOMA, NOS	13
ADRENAL	50
THYROID	49
ADENOMA, NOS	1
FOLLICULAR-CELL ADENOMA	1
C-CELL ADENOMA	5
PARATHYROID	43
PANCREATIC ISLETS	50
ISLET-CELL ADENOMA	1
REPRODUCTIVE SYSTEM	
MAMMARY GLAND	50M
ADENOCARCINOMA, NOS	1
FIBROADENOMA	9
PREPUTIAL/CLITORAL GLAND	50M
CARCINOMA,NOS	1
VAGINA	50M
GRANULAR-CELL TUMOR, BENIGN	1
UTERUS	50
ENDOMETRIAL STROMAL POLYP	4
OVARY	50
NERVOUS SYSTEM	
BRAIN	49
SPECIAL SENSE ORGANS	
ZYMBAL'S GLAND	50M
SQUAMOUS CELL CARCINOMA	1
BODY CAVITIES	
PERITONEUM	50M
FIBROMA	1
MESENTERY	50M
LIPOMA	1
ALL OTHER SYSTEMS	
MULTIPLE ORGANS NOS	50M
UNDIFFERENTIATED LEUKEMIA	7

* ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A4.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE 2-YEAR STUDY OF ZEARALENONE

LOW DOSE

ANIMAL NUMBER	0001	0002	0003	0004	0005	0006	0007	0008	0009	0010	0011	0012	0013	0014	0015	0016	0017	0018	0019	0020	0021	0022	0023	0024	0025
WEEKS ON STUDY	101	105	102	105	105	105	105	105	098	105	105	105	105	105	105	105	105	103	105	105	105	088	085	105	105
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL PAPILLOMA																									
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARCINOMA,NOS																									
SARCOMA, NOS																									
FIBROMA	X																		X						
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALVEOLAR/BRONCHIOLAR ADENOMA																	X								
SARCOMA, NOS, METASTATIC	X																								
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	-
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NEOPLASTIC NODULE																									X
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARCINOMA,NOS			X																						
ADENOMA, NOS					X	X				X	X	X												X	X
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PHEOCHROMOCYTOMA			X																						
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-CELL ADENOMA	X																		X						X
C-CELL CARCINOMA																				X					
PARATHYROID	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ISLET-CELL CARCINOMA							X																		
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOCARCINOMA, NOS			X			X											X	X							
FIBROADENOMA								X	X	X											X		X	X	
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOMETRIAL STROMAL POLYP													X					X		X					
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
EYE APPENDAGES	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
FIBROSARCOMA							X																		
BODY CAVITIES																									
MEDIASTINUM	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ADENOCARCINOMA, NOS																									
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
UNDIFFERENTIATED LEUKEMIA									X													X			X

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION

: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A4. FEMALE RATS: TUMOR PATHOLOGY (CONTINUED) LOW DOSE

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL
WEEKS ON STUDY	105	105	075	097	115	106	106	081	061	106	097	061	061	061	061	061	061	061	088	095	091	061	061	061	061	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	50*
SQUAMOUS CELL PAPILLOMA																									X	1
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	50*
CARCINOMA,NOS																			X							1
SARCOMA, NOS			X																							2
FIBROMA															X											2
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALVEOLAR/BRONCHIOLAR ADENOMA																								X		2
SARCOMA, NOS, METASTATIC																										1
TRACHEA	+	-	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	46
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	48
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
THYMUS	+	+	+	-	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	47
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	49
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NEOPLASTIC NODULE																										1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CARCINOMA,NOS																										1
ADENOMA, NOS				X		X		X	X		X								X	X	X					15
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
PHEOCHROMOCYTOMA																										1
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-CELL ADENOMA	X										X															6
C-CELL CARCINOMA																								X		1
PARATHYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	+	+	+	+	+	45
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ISLET-CELL CARCINOMA																										1
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
ADENOCARCINOMA, NOS			X		X					X	X				X											2
FIBROADENOMA									X															X		14
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	49
ENDOMETRIAL STROMAL POLYP		X					X			X		X							X							8
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	49
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
EYE APPENDAGES	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
FIBROSARCOMA																										1
BODY CAVITIES																										
MEDIASTINUM	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
ADENOCARCINOMA, NOS																				X						1
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
UNDIFFERENTIATED LEUKEMIA		X				X								X					X							7

* ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: *REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY*
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION

: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A4.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE 2-YEAR STUDY OF ZEARALENONE

HIGH DOSE

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	048	104	104	104	104	105	105	104	105	105	105	105	105	105	090
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALVEOLAR/BRONCHIOLAR ADENOMA																									
ALVEOLAR/BRONCHIOLAR CARCINOMA																									
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+
C-CELL CARCINOMA, INVASIVE																									
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+
THYMUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NEOPLASTIC NODULE																									
HEPATOCELLULAR CARCINOMA																									
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	+	+	•	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	-	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOMA, NOS	X				X								X		X		X					X			
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CORTICAL ADENOMA																									
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+
C-CELL ADENOMA									X															X	X
C-CELL CARCINOMA																									
PARATHYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	-
ADENOMA, NOS			X																						
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOCARCINOMA, NOS										X															
CYSTADENOMA, NOS																X	X								
FIBROADENOMA																								X	
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ADENOMA, NOS																									
UTERUS	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOMETRIAL STROMAL POLYP												X			X							X			
OVARY	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MUSCULOSKELETAL SYSTEM																									
MUSCLE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RHABDOMYOSARCOMA										X															
BODY CAVITIES																									
PLEURA	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
FIBROMA													X												
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
C-CELL CARCINOMA, METASTATIC																									
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																									
UNDIFFERENTIATED LEUKEMIA																		X							X

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION

: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A4. FEMALE RATS: TUMOR PATHOLOGY (CONTINUED) HIGH DOSE

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL
WEEKS ON STUDY	105	105	105	082	103	105	105	105	094	105	105	102	105	105	071	105	105	086	105	105	105	095	094	105	105	TISSUES TUMORS
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	•	+	+	+	+	+	•	+	+	+	+	+	+	+	+	+	+	+	+	50
ALVEOLAR/BRONCHIOLAR ADENOMA							X																			1
ALVEOLAR/BRONCHIOLAR CARCINOMA			X																							1
TRACHEA	+	+	+	+	+	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
C-CELL CARCINOMA, INVASIVE												X														1
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
THYMUS	+	+	+	+	+	+	+	+	-	+	+	+	+	+	-	+	+	-	+	+	+	+	+	+	+	46
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NEOPLASTIC NODULE																X										1
HEPATOCELLULAR CARCINOMA		X																								1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50M
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	49
ADENOMA, NOS		X		X	X				X						X			X				X	X			14
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CORTICAL ADENOMA																			X							1
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-CELL ADENOMA								X																		4
C-CELL CARCINOMA							X					X														2
PARATHYROID	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	-	+	+	+	-	+	-	+	44
ADENOMA, NOS																										1
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50M
ADENOCARCINOMA, NOS																										1
CYSTADENOMA, NOS																								X		1
FIBROADENOMA	X										X	X	X							X		X				9
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50M
ADENOMA, NOS								X		X																2
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOMETRIAL STROMAL POLYP							X					X														5
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
MUSCULOSKELETAL SYSTEM																										
MUSCLE	+	+	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50M
RHABDOMYOSARCOMA																										1
BODY CAVITIES																										
PLEURA	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50M
FIBROMA																										1
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50M
C-CELL CARCINOMA, METASTATIC												X														1
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																										1
UNDIFFERENTIATED LEUKEMIA																X										2

* ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

APPENDIX B

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE FED DIETS CONTAINING ZEARALENONE

TABLE B1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE FED DIETS CONTAINING ZEARALENONE

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
SQUAMOUS CELL PAPILLOMA	1 (2%)		
FIBROSARCOMA		1 (2%)	
*SUBCUT TISSUE	(50)	(50)	(50)
SARCOMA, NOS	1 (2%)	1 (2%)	
FIBROSARCOMA		1 (2%)	
NEURILEMOMA, MALIGNANT			1 (2%)
RESPIRATORY SYSTEM			
#LUNG	(50)	(49)	(50)
HEPATOCELLULAR CARCINOMA, METAST	1 (2%)	3 (6%)	
ALVEOLAR/BRONCHIOLAR ADENOMA	7 (14%)	5 (10%)	8 (16%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	4 (8%)	3 (6%)	3 (6%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	1 (2%)	1 (2%)	4 (8%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)	
MALIGNANT LYMPHOMA, MIXED TYPE	5 (10%)	2 (4%)	1 (2%)
#SPLEEN	(50)	(50)	(49)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		1 (2%)	
#PEYER'S PATCH	(49)	(49)	(49)
MALIGNANT LYMPHOMA, MIXED TYPE			1 (2%)
#DUODENUM	(49)	(49)	(49)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		2 (4%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
CIRCULATORY SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
HEMANGIOSARCOMA	1 (2%)		1 (2%)
*SUBCUT TISSUE	(50)	(50)	(50)
HEMANGIOSARCOMA	1 (2%)		
#SPLEEN	(50)	(50)	(49)
HEMANGIOMA		1 (2%)	1 (2%)
HEMANGIOSARCOMA	1 (2%)	1 (2%)	
#PANCREAS	(50)	(49)	(49)
HEMANGIOMA	1 (2%)		
DIGESTIVE SYSTEM			
#LIVER	(50)	(50)	(49)
HEPATOCELLULAR ADENOMA	4 (8%)	3 (6%)	7 (14%)
HEPATOCELLULAR CARCINOMA	15 (30%)	19 (38%)	7 (14%)
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
HEPATOCELLULAR CARCINOMA, METAST	1 (2%)		
ENDOCRINE SYSTEM			
#PITUITARY	(40)	(45)	(44)
CARCINOMA,NOS		1 (2%)	
ADENOMA, NOS		4 (9%)	6 (14%)
#ADRENAL	(50)	(50)	(49)
CORTICAL ADENOMA	2 (4%)	1 (2%)	4 (8%)
PHEOCHROMOCYTOMA			1 (2%)
#THYROID	(50)	(49)	(49)
FOLLICULAR-CELL ADENOMA	2 (4%)	1 (2%)	
#PANCREATIC ISLETS	(50)	(49)	(49)
ISLET-CELL ADENOMA		1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM			
#TESTIS	(50)	(50)	(50)
INTERSTITIAL-CELL TUMOR	1 (2%)		
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
#HARDERIAN GLAND	(50)	(50)	(50)
ADENOMA, NOS	6 (12%)	10 (20%)	10 (20%)
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
SARCOMA, NOS	1 (2%)		
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	6	4	1
MORIBUND SACRIFICE	2	7	4
SCHEDULED SACRIFICE	10		
TERMINAL SACRIFICE	32	39	44
ACCIDENTALLY KILLED			1
ANIMAL MISSING			

@ INCLUDES AUTOLYZED ANIMALS

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	37	41	38
TOTAL PRIMARY TUMORS	54	60	55
TOTAL ANIMALS WITH BENIGN TUMORS	20	21	29
TOTAL BENIGN TUMORS	24	26	37
TOTAL ANIMALS WITH MALIGNANT TUMORS	24	29	17
TOTAL MALIGNANT TUMORS	30	34	18
TOTAL ANIMALS WITH SECONDARY TUMORS#	1	3	
TOTAL SECONDARY TUMORS	2	3	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			
TOTAL UNCERTAIN TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
\# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

TABLE B2.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE FED DIETS CONTAINING ZEARALENONE

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	49	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	49	49
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(49)	(49)
SQUAMOUS CELL CARCINOMA	1 (2%)		
*SUBCUT TISSUE	(50)	(49)	(49)
FIBROSARCOMA		1 (2%)	
OSTEOSARCOMA			1 (2%)
RESPIRATORY SYSTEM			
#LUNG	(48)	(48)	(49)
HEPATOCELLULAR CARCINOMA, METAST		1 (2%)	1 (2%)
ALVEOLAR/BRONCHIOLAR ADENOMA	2 (4%)	4 (8%)	1 (2%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	1 (2%)		
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(49)	(49)
MALIGNANT LYMPHOMA, NOS		1 (2%)	
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	2 (4%)	2 (4%)	3 (6%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	2 (4%)		3 (6%)
MALIGNANT LYMPHOMA, MIXED TYPE	9 (18%)	5 (10%)	9 (18%)
#SPLEEN	(50)	(49)	(49)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	1 (2%)		
MALIGNANT LYMPHOMA, MIXED TYPE	1 (2%)		
#MESENTERIC L. NODE	(50)	(48)	(49)
MALIGNANT LYMPHOMA, MIXED TYPE		1 (2%)	
#PEYER'S PATCH	(48)	(45)	(49)
MALIGNANT LYMPHOMA, MIXED TYPE			1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
CIRCULATORY SYSTEM			
*MULTIPLE ORGANS	(50)	(49)	(49)
HEMANGIOSARCOMA			1 (2%)
#SPLEEN	(50)	(49)	(49)
HEMANGIOSARCOMA	1 (2%)		1 (2%)
#UTERUS	(50)	(49)	(48)
HEMANGIOMA	1 (2%)		
#OVARY	(44)	(48)	(48)
HEMANGIOMA		1 (2%)	
DIGESTIVE SYSTEM			
#LIVER	(50)	(49)	(49)
HEPATOCELLULAR ADENOMA		2 (4%)	7 (14%)
HEPATOCELLULAR CARCINOMA	3 (6%)	6 (12%)	3 (6%)
#STOMACH	(48)	(48)	(49)
SQUAMOUS CELL PAPILLOMA		1 (2%)	
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#PITUITARY	(46)	(43)	(42)
CARCINOMA,NOS			2 (5%)
ADENOMA, NOS	3 (7%)	2 (5%)	13 (31%)
#ADRENAL	(50)	(49)	(47)
CORTICAL ADENOMA		1 (2%)	1 (2%)
PHEOCHROMOCYTOMA		1 (2%)	
#THYROID	(47)	(48)	(47)
FOLLICULAR-CELL ADENOMA	1 (2%)	1 (2%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(49)	(49)
ADENOCARCINOMA, NOS	1 (2%)	3 (6%)	3 (6%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
ADENOSQUAMOUS CARCINOMA		1 (2%)	
#UTERUS	(50)	(49)	(48)
ENDOMETRIAL STROMAL POLYP	1 (2%)		
#CERVIX UTERI	(50)	(49)	(48)
SQUAMOUS CELL CARCINOMA	1 (2%)		
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*HARDERIAN GLAND	(50)	(49)	(49)
ADENOMA, NOS	1 (2%)		3 (6%)
MUSCULOSKELETAL SYSTEM			
*BONE	(50)	(49)	(49)
OSTEOSARCOMA			1 (2%)
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
LEG			
OSTEOSARCOMA	1		
NEURILEMOMA, MALIGNANT	1		
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	7	10	4
MORIBUND SACRIFICE	6	4	14
SCHEDULED SACRIFICE	8		
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	29	36	32
ANIMAL MISSING			

@ INCLUDES AUTOLYZED ANIMALS

\# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	28	25	40
TOTAL PRIMARY TUMORS	34	33	53
TOTAL ANIMALS WITH BENIGN TUMORS	8	13	22
TOTAL BENIGN TUMORS	9	13	25
TOTAL ANIMALS WITH MALIGNANT TUMORS	23	18	27
TOTAL MALIGNANT TUMORS	25	20	28
TOTAL ANIMALS WITH SECONDARY TUMORS#		1	1
TOTAL SECONDARY TUMORS		1	1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			
TOTAL UNCERTAIN TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
\# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

TABLE B3.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE 2-YEAR STUDY OF ZEARALENONE

CONTROL

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	105	115	115	105	105	105	105	105	104	105	105	107	102	107	107	108	108	108	108	108	108	104	078	108	104
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL PAPILLOMA										X															
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SARCOMA, NOS																									
HEMANGIOSARCOMA																									
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR CARCINOMA, METASTA																						X			
ALVEOLAR/BRONCHIOLAR ADENOMA			X		X						X														
ALVEOLAR/BRONCHIOLAR CARCINOMA								X																	X
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMANGIOSARCOMA																									
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR ADENOMA			X											X											
HEPATOCELLULAR CARCINOMA				X							X				X			X	X		X	X	X		
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	N	N	+	+	N	+	+	+	+
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMANGIOMA																									
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR CARCINOMA, METASTA																					X				
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	-	+	+	+	+	-	+	+	+	+	+	+	-	+	+	-	+	
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CORTICAL ADENOMA								X																	
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FOLLICULAR-CELL ADENOMA								X																	
PARATHYROID	+	+	-	-	+	+	+	+	+	+	+	+	+	-	+	+	-	+	+	+	+	+	-	+	+
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
INTERSTITIAL-CELL TUMOR												X													
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
HARDERIAN GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOMA, NOS						X					X								X	X					
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
SARCOMA, NOS				X																					
HEMANGIOSARCOMA													X												
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE																									
MALIGNANT LYMPHOMA, MIXED TYPE	X								X								X					X		X

* ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION

: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B3. MALE MICE: TUMOR PATHOLOGY (CONTINUED) CONTROL

ANIMAL NUMBER	0026	0027	0028	0029	0030	0031	0032	0033	0034	0035	0036	0037	0038	0039	0040	0041	0042	0043	0044	0045	0046	0047	0048	0049	0050	TOTAL
WEEKS ON STUDY	1108	1108	1108	1108	1108	1108	1108	1108	1108	0883	1108	1108	1108	1108	1098	1108	1108	1108	1108	0779	1108	1108	1108	1108	1108	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
SQUAMOUS CELL PAPILLOMA																										1
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
SARCOMA, NOS														X												1
HEMANGIOSARCOMA										X																1
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEPATOCELLULAR CARCINOMA, METASTA																										1
ALVEOLAR/BRONCHIOLAR ADENOMA					X	X						X					X									7
ALVEOLAR/BRONCHIOLAR CARCINOMA											X					X										4
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	49
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMANGIOSARCOMA										X																1
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
THYMUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	48
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEPATOCELLULAR ADENOMA	X							X																		4
HEPATOCELLULAR CARCINOMA		X			X									X			X		X		X		X			15
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	+	+	N	N	N	+	+	+	+	+	N	+	+	+	+	+	N	+	+	N	+	+	+	+	+	50*
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMANGIOMA											X															1
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	49
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEPATOCELLULAR CARCINOMA, METASTA																										1
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
PITUITARY	-	+	+	+	+	+	+	+	+	-	+	+	+	-	+	+	-	+	+	-	-	+	+	+	+	40
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CORTICAL ADENOMA							X																			2
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
FOLLICULAR-CELL ADENOMA														X												2
PARATHYROID	+	+	+	+	-	+	-	+	+	-	+	+	+	-	+	+	+	-	+	+	+	+	+	-	+	39
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
INTERSTITIAL-CELL TUMOR																										1
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
HARDERIAN GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ADENOMA, NOS					X															X						6
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
SARCOMA, NOS																										1
HEMANGIOSARCOMA																										1
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE																	X									1
MALIGNANT LYMPHOMA, MIXED TYPE																										5

* ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B3.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE 2-YEAR STUDY OF ZEARALENONE

LOW DOSE

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	100	106	092	106	106	096	106	106	106	106	106	106	106	106	106	074	106	106	102	106	106	106	106	106	106
INTEGUMENTARY SYSTEM																									
SKIN	+	N	+	+	N	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+
FIBROSARCOMA																									
SUBCUTANEOUS TISSUE	+	N	+	+	N	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+
SARCOMA, NOS																									
FIBROSARCOMA																									
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR CARCINOMA, METASTA																									
ALVEOLAR/BRONCHIOLAR ADENOMA											X											X			
ALVEOLAR/BRONCHIOLAR CARCINOMA																									
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMANGIOMA															X										
HEMANGIOSARCOMA																			X						
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE																									
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+
THYMUS	+	-	+	+	-	+	+	-	-	+	+	+	+	+	+	-	+	+	+	-	+	+	+	+	-
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR ADENOMA																			X	X					X
HEPATOCELLULAR CARCINOMA	X					X						X	X		X			X				X			
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE																									
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	-	+	+	+	-	+	+	+	+	+	+	+	+	-	+	+
CARCINOMA,NOS																X									
ADENOMA, NOS	X			X					X										X						
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CORTICAL ADENOMA																									
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FOLLICULAR-CELL ADENOMA																									
PARATHYROID	+	+	+	+	-	+	+	-	-	-	+	-	+	-	-	-	+	+	-	+	-	+	-	+	-
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ISLET-CELL ADENOMA																								X	
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	N	+	N	N	+	N	N	N	+	N	N	N	N	N	+	N	N	N	N	+	N	N	N	+
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
BRAIN	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
HARDERIAN GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOMA, NOS		X	X		X	X		X	X											X					
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE							X																		
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																									
MALIGNANT LYMPHOMA, MIXED TYPE		X																	X						

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B3. MALE MICE: TUMOR PATHOLOGY (CONTINUED) LOW DOSE

ANIMAL NUMBER	0122	0227	0286	0219	0301	0332	0346	0349	0354	0361	0375	0383	0391	0401	0411	0422	0433	0441	0445	0456	0467	0489	0491	0501	TOTAL
WEEKS ON STUDY	072	096	106	151	096	096	096	094	096	096	096	077	071	071	088	071	086	097	097	097	097	089	097	097	TISSUES TUMORS
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	X	+	+	N	+	+	+	+	+	50*
FIBROSARCOMA																									1
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	50*
SARCOMA, NOS																		X							1
FIBROSARCOMA								X																	1
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	49
HEPATOCELLULAR CARCINOMA, METASTA												X	X										X		3
ALVEOLAR/BRONCHIOLAR ADENOMA				X			X				X														5
ALVEOLAR/BRONCHIOLAR CARCINOMA			X						X	X															3
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMANGIOMA																									1
HEMANGIOSARCOMA																									1
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE													X												1
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
THYMUS	-	+	+	-	+	+	+	+	+	+	+	+	-	-	+	+	+	+	+	+	+	+	+	+	39
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEPATOCELLULAR ADENOMA																									3
HEPATOCELLULAR CARCINOMA				X	X	X		X		X	X		X	X			X		X			X	X		19
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	N	+	+	N	+	+	+	+	N	+	+	N	+	+	+	+	+	+	+	+	+	+	+	N	50*
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	49
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SMALL INTESTINE	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE												X				X									2
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	-	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	45
CARCINOMA,NOS																									1
ADENOMA, NOS																									4
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	X	+	+	+	+	+	+	+	+	50
CORTICAL ADENOMA																									1
THYROID	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
FOLLICULAR-CELL ADENOMA												X													1
PARATHYROID	+	+	-	-	-	-	-	+	+	-	-	-	+	-	+	+	+	+	-	+	-	-	+	-	24
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	49
ISLET-CELL ADENOMA																									1
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	N	N	N	N	N	+	N	N	N	N	+	N	N	N	N	+	+	+	N	N	N	N	+	+	50*
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPECIAL SENSE ORGANS																									
HARDERIAN GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ADENOMA, NOS							X	X						X											10
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE																									1
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	X																								1
MALIGNANT LYMPHOMA, MIXED TYPE																									2

* ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B3.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE 2-YEAR STUDY OF ZEARALENONE

HIGH DOSE

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	105	105	105	105	087	105	105	105	087	105	105	098	105	105	104	105	105	105	105	105	105	105	105	105	105
INTEGUMENTARY SYSTEM																									
SUBCUTANEOUS TISSUE NEURILEMOMA, MALIGNANT	+	+	+	+	+	+	+	+	+	+	+	+ X	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI *ALVEOLAR/BRONCHIOLAR ADENOMA* ALVEOLAR/BRONCHIOLAR CARCINOMA	+	+	+	+	+	+ X	+	+	+	+	+	+	+ X	+	+	+	+ X	+	+ X	+ X	+ X	+	+	+	+
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN HEMANGIOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	-	+	+	-	+	+	
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER HEPATOCELLULAR ADENOMA *HEPATOCELLULAR CARCINOMA*	+ X	+	+ X	+ X	+	+ X	+ X	+	+	+	+ X	+	+	+	+	+	+	+ X	+ X	+ X	+	+	+ X	+	+
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	N	+	+	N	+	+	+	+
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE MALIGNANT LYMPHOMA, MIXED TYPE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY ADENOMA, NOS	+	+	+	+	-	-	+	+	+	+	+	+	+ X	+	+ X	+	+ X	+	+	-	+	+	+	+	+
ADRENAL CORTICAL ADENOMA PHEOCHROMOCYTOMA	+	+	+	+	+	+	+	+ X	+	+	+	+ X	+	+	+	+	+ X	+	+	+	+ X	+	-	+	+
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PARATHYROID	+	+	+	+	+	+	+	+	+	+	+	-	-	+	-	+	-	-	-	-	+	-	+	+	+
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	N	N	N	N	+	+	+	+	N	N	+	+	+	+	+	+	N	+	+	+	N	N	N	N	N
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
HARDERIAN GLAND ADENOMA, NOS	+	+	+	+	+	+ X	+	+	+	+	+	+ X	+	+	+	+	+ X	+	+	+	+	+ X	+ X	+	+
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS HEMANGIOSARCOMA MALIG.LYMPHOMA, LYMPHOCYTIC TYPE MALIGNANT LYMPHOMA, MIXED TYPE	N	N	N	N	N X	N	N	N	N X	N	N	N	N	N	N X	N	N	N	N	N	N	N	N	N X	N

+: TISSUE EXAMINED MICROSCOPICALLY
~: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION

: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B3. MALE MICE: TUMOR PATHOLOGY (CONTINUED) HIGH DOSE

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL
WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	102	105	105	105	105	106	106	089	106	106	106	106	106	106	106	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
NEURILEMOMA, MALIGNANT																										1
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALVEOLAR/BRONCHIOLAR ADENOMA						X	X		X																	8
ALVEOLAR/BRONCHIOLAR CARCINOMA								X									X									3
TRACHEA	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPLEEN	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMANGIOMA				X																						1
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
THYMUS	+	-	+	+	+	+	+	+	-	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LIVER	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEPATOCELLULAR ADENOMA										X																7
HEPATOCELLULAR CARCINOMA								X								X				X						7
BILE DUCT	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	+	N	+	+	+	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
PANCREAS	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ESOPHAGUS	+	+	+	+	-	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
STOMACH	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
MALIGNANT LYMPHOMA, MIXED TYPE							X																			1
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	-	+	+	+	+	-	+	+	+	+	+	-	+	+	+	+	+	+	+	+	44
ADENOMA, NOS	X																	X						X		6
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
CORTICAL ADENOMA			X																							4
PHEOCHROMOCYTOMA																										1
THYROID	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
PARATHYROID	+	+	+	+	-	-	-	-	+	-	+	-	-	+	+	-	+	+	+	+	+	+	+	+	+	34
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	N	N	N	N	N	+	N	N	N	N	N	N	+	+	N	N	+	+	+	+	+	+	+	+	N	50*
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
HARDERIAN GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ADENOMA, NOS								X						X	X				X						X	10
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
HEMANGIOSARCOMA																										1
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE																			X							4
MALIGNANT LYMPHOMA, MIXED TYPE																							X			1

* ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B4.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE 2-YEAR STUDY OF ZEARALENONE

CONTROL

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	105	099	095	100	051	015	015	015	056	046	077	071	011	077	077	088	088	088	088	088	088	088	088	080	099
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL CARCINOMA													X												
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALVEOLAR/BRONCHIOLAR ADENOMA												X													
ALVEOLAR/BRONCHIOLAR CARCINOMA																									
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMANGIOSARCOMA													X												
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE																									
MALIGNANT LYMPHOMA, MIXED TYPE																									
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR CARCINOMA														X								X			
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOMA, NOS	X														X										
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FOLLICULAR-CELL ADENOMA																									
PARATHYROID	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	-	-	+	+	-	+	-	+	+	
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOCARCINOMA, NOS															X										
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL CARCINOMA			X																						
ENDOMETRIAL STROMAL POLYP								X																	
HEMANGIOMA																	X								
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	-	-	+	+	+	+	+	+
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
HARDERIAN GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ADENOMA, NOS												X													
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE													X												
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																									
MALIGNANT LYMPHOMA, MIXED TYPE	X		X	X		X			X	X															
LEG NOS																									
OSTEOSARCOMA																									
NEURILEMOMA, MALIGNANT																									

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION

: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B4. FEMALE MICE: TUMOR PATHOLOGY (CONTINUED) CONTROL

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL TISSUES TUMORS
WEEKS ON STUDY	108	091	108	108	108	108	108	108	108	108	099	108	104	108	108	099	108	108	108	108	108	085	091	100	096	
INTEGUMENTARY SYSTEM																										
SKIN	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	50M
SQUAMOUS CELL CARCINOMA																										1
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+		48
ALVEOLAR/BRONCHIOLAR ADENOMA	X																									2
ALVEOLAR/BRONCHIOLAR CARCINOMA		X																								1
TRACHEA	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+		48
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+		49
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
HEMANGIOSARCOMA																										1
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	X																									1
MALIGNANT LYMPHOMA, MIXED TYPE									X																	1
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
THYMUS	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	-	~	-	+		45
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+		49
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
HEPATOCELLULAR CARCINOMA															X											3
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
GALLBLADDER & COMMON BILE DUCT	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	N	50M
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+		49
ESOPHAGUS	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+		48
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+		48
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+		48
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	+	-	+	+	-	-	+	+	+	+	+	+	+	+	+	-	+	+		46
ADENOMA, NOS																				X						3
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
THYROID	+	+	+	-	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+		47
FOLLICULAR-CELL ADENOMA																	X									1
PARATHYROID	+	+	-	-	+	-	+	-	-	+	+	+	-	-	+	+	+	+	+	~	+	+	-	+		36
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	+	+	+	+	+	+	+	N	+	+	+	N	+	+	+	+	+	N	+	+	+	+	+	+		50M
ADENOCARCINOMA, NOS																										1
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
SQUAMOUS CELL CARCINOMA																										1
ENDOMETRIAL STROMAL POLYP																										1
HEMANGIOMA							-																			1
OVARY	+	•	-	•	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+		44
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
SPECIAL SENSE ORGANS																										
HARDERIAN GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N		50M
ADENOMA, NOS																										1
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N		50M
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE			X																							2
MALIG.LYMPHOMA, HISTIOCYTIC TYPE							X						X													2
MALIGNANT LYMPHOMA, MIXED TYPE																			X			X		X		9
LEG NOS																										
OSTEOSARCOMA																								X		1
NEURILEMOMA, MALIGNANT																									X	1

* ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
~: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: *NO NECROPSY PERFORMED*

TABLE B4.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE 2-YEAR STUDY OF ZEARALENONE

LOW DOSE

ANIMAL NUMBER	0011	0012	0013	0014	0015	0016	0017	0018	0019	0110	0111	0112	0113	0114	0115	0116	0117	0118	0119	0120	0121	0122	0123	0124	0125
WEEKS ON STUDY	106	106	100	022	106	106	106	106	106	094	106	106	106	106	106	106	106	088	106	106	086	106	106	106	102
INTEGUMENTARY SYSTEM																									
SUBCUTANEOUS TISSUE FIBROSARCOMA	N	+	+	A	+	+	N	+	+	+	+	N	+	N	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI HEPATOCELLULAR CARCINOMA, METASTA ALVEOLAR/BRONCHIOLAR ADENOMA	+	+	+	A	+	+	+	X	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	X	+
TRACHEA	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES MALIGNANT LYMPHOMA, MIXED TYPE	+	+	+	A	+	+	+	+	+	+	+	+	+	+	X	+	+	+	+	+	+	+	+	+	+
THYMUS	+	+	+	A	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER HEPATOCELLULAR ADENOMA HEPATOCELLULAR CARCINOMA	+	+	X	A	+	+	+	+	+	X	+	+	+	+	+	+	+	+	X	X	+	+	+	+	X
BILE DUCT	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	+	+	+	A	+	N	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+
PANCREAS	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+
STOMACH SQUAMOUS CELL PAPILLOMA	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	X	+	+	+	+	+
SMALL INTESTINE	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-
LARGE INTESTINE	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-
URINARY SYSTEM																									
KIDNEY	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY ADENOMA, NOS	+	+	+	A	+	+	+	+	+	-	-	+	+	+	+	+	+	+	+	+	+	+	-	+	+ X
ADRENAL CORTICAL ADENOMA PHEOCHROMOCYTOMA	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+ X	+	+	+	+	+	+
THYROID FOLLICULAR-CELL ADENOMA	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+
PARATHYROID	+	+	+	A	+	+	+	+	-	-	-	+	-	+	+	+	+	-	-	-	+	-	+	+	+
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND ADENOCARCINOMA, NOS ADENOSQUAMOUS CARCINOMA	+	+	+	A	+	+	+	+	+	•	•	•	+	+	+	+	+	+ X	+	+	+	+	+	+	+ X
UTERUS	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
OVARY HEMANGIOMA	+	+	+	A	+	+	+ X	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
BRAIN	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS MALIGNANT LYMPHOMA, NOS MALIG.LYMPHOMA, LYMPHOCYTIC TYPE MALIGNANT LYMPHOMA, MIXED TYPE	N	N	N	A	N X	N X	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N X	N	N

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B4. FEMALE MICE: TUMOR PATHOLOGY (CONTINUED) LOW DOSE

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL
WEEKS ON STUDY	106	061	073	106	096	098	096	106	096	096	102	107	107	107	103	107	102	107	107	107	107	107	082	051	097	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
SUBCUTANEOUS TISSUE FIBROSARCOMA	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+ X	+	+	+	+	N	+	+	+	49M 1
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
HEPATOCELLULAR CARCINOMA, METASTA																										1
ALVEOLAR/BRONCHIOLAR ADENOMA																X						X			X	4
TRACHEA	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LYMPH NODES	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
MALIGNANT LYMPHOMA, MIXED TYPE																										1
THYMUS	+	+	+	+	+	+	+	+	+	+	+	+	-	-	+	+	+	+	+	+	-	+	+	+	+	45
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEPATOCELLULAR ADENOMA																				X						2
HEPATOCELLULAR CARCINOMA				X																						6
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
GALLBLADDER & COMMON BILE DUCT	+	+	+	N	+	+	+	+	N	+	+	+	+	+	N	+	+	+	+	+	+	N	N	+	+	49M
PANCREAS	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
STOMACH	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
SQUAMOUS CELL PAPILLOMA																										1
SMALL INTESTINE	+	+	-	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	-	+	+	45
LARGE INTESTINE	+	+	-	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	-	+	+	45
URINARY SYSTEM																										
KIDNEY	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
URINARY BLADDER	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	-	-	+	+	-	+	+	+	+	•	+	+	+	+	+	+	+	+	+	43
ADENOMA, NOS	X																									2
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
CORTICAL ADENOMA																		X								1
PHEOCHROMOCYTOMA																										1
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
FOLLICULAR-CELL ADENOMA																								X		1
PARATHYROID	+	-	-	+	+	+	+	+	-	+	+	+	+	-	-	-	+	+	-	+	+	+	+	+	+	34
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+ X	+	+	+	•	+	+	+	•	+	+	49M 3
ADENOCARCINOMA, NOS																								X		1
ADENOSQUAMOUS CARCINOMA																										
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
OVARY	+	+	-	+	+	+	+	+	+	+	+	+	•	+	+	+	+	+	+	+	+	+	+	+	+	48
HEMANGIOMA																										1
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	49M 1
MALIGNANT LYMPHOMA, NOS			X																							
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE																								X		2
MALIGNANT LYMPHOMA, MIXED TYPE										X	X									X						5

M ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION

: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B4.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE 2-YEAR STUDY OF ZEARALENONE

HIGH DOSE

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	105	105	092	105	105	105	105	105	086	105	105	105	105	059	098	101	105	087	096	099	105	105	105	105	092
INTEGUMENTARY SYSTEM																									
SUBCUTANEOUS TISSUE	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+
OSTEOSARCOMA																									
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR CARCINOMA, METASTA				X																					
ALVEOLAR/BRONCHIOLAR ADENOMA										X															
TRACHEA	+	+	A	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMANGIOSARCOMA									X																
LYMPH NODES	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	A	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR ADENOMA	X							X					X		X	X									
HEPATOCELLULAR CARCINOMA				X															X						
BILE DUCT	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	+	+	A	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+
PANCREAS	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	A	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MALIGNANT LYMPHOMA, MIXED TYPE																									
LARGE INTESTINE	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	-	+	-
CARCINOMA,NOS															X										
ADENOMA, NOS	X			X	X								X			X						X			
ADRENAL	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CORTICAL ADENOMA																									
THYROID	+	+	A	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+
PARATHYROID	+	+	A	+	+	+	+	+	-	+	+	+	-	+	+	+	+	+	-	+	+	+	+	+	+
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOCARCINOMA, NOS		X																							
UTERUS	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
OVARY	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
BRAIN	+	+	A	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
HARDERIAN GLAND	N	N	A	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ADENOMA, NOS																									
MUSCULOSKELETAL SYSTEM																									
BONE	N	N	A	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
OSTEOSARCOMA																			X						
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	A	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
HEMANGIOSARCOMA																X									
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE					X		X														X				
MALIG.LYMPHOMA, HISTIOCYTIC TYPE						X					X			X			X			X					X
MALIGNANT LYMPHOMA, MIXED TYPE																									

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION

: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B4. FEMALE MICE: TUMOR PATHOLOGY (CONTINUED) HIGH DOSE

ANIMAL NUMBER / WEEKS ON STUDY	TOTAL TISSUES TUMORS
INTEGUMENTARY SYSTEM	
SUBCUTANEOUS TISSUE	49M
OSTEOSARCOMA	1
RESPIRATORY SYSTEM	
LUNGS AND BRONCHI	49
HEPATOCELLULAR CARCINOMA, METASTA	1
ALVEOLAR/BRONCHIOLAR ADENOMA	1
TRACHEA	48
HEMATOPOIETIC SYSTEM	
BONE MARROW	49
SPLEEN	49
HEMANGIOSARCOMA	1
LYMPH NODES	49
THYMUS	48
CIRCULATORY SYSTEM	
HEART	49
DIGESTIVE SYSTEM	
SALIVARY GLAND	48
LIVER	49
HEPATOCELLULAR ADENOMA	7
HEPATOCELLULAR CARCINOMA	3
BILE DUCT	49
GALLBLADDER & COMMON BILE DUCT	49M
PANCREAS	49
ESOPHAGUS	48
STOMACH	49
SMALL INTESTINE	49
MALIGNANT LYMPHOMA, MIXED TYPE	1
LARGE INTESTINE	49
URINARY SYSTEM	
KIDNEY	49
URINARY BLADDER	49
ENDOCRINE SYSTEM	
PITUITARY	42
CARCINOMA,NOS	2
ADENOMA, NOS	13
ADRENAL	47
CORTICAL ADENOMA	1
THYROID	47
PARATHYROID	40
REPRODUCTIVE SYSTEM	
MAMMARY GLAND	49M
ADENOCARCINOMA, NOS	3
UTERUS	48
OVARY	48
NERVOUS SYSTEM	
BRAIN	48
SPECIAL SENSE ORGANS	
HARDERIAN GLAND	49M
ADENOMA, NOS	3
MUSCULOSKELETAL SYSTEM	
BONE	49M
OSTEOSARCOMA	1
ALL OTHER SYSTEMS	
MULTIPLE ORGANS NOS	49M
HEMANGIOSARCOMA	1
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	3
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	3
MALIGNANT LYMPHOMA, MIXED TYPE	9

* ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

APPENDIX C

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS FED DIETS CONTAINING ZEARALENONE

TABLE C1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS FED DIETS CONTAINING ZEARALENONE

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
EPIDERMAL INCLUSION CYST		1 (2%)	
ATROPHY, NOS			1 (2%)
HYPERPLASIA, FOCAL			1 (2%)
SKIN TAG	2 (4%)		
*SUBCUT TISSUE	(50)	(50)	(50)
EPIDERMAL INCLUSION CYST	2 (4%)	1 (2%)	
RESPIRATORY SYSTEM			
#LUNG/BRONCHIOLE	(49)	(50)	(47)
HYPERPLASIA, NOS	3 (6%)	1 (2%)	1 (2%)
HYPERPLASIA, ADENOMATOUS		1 (2%)	
#LUNG	(49)	(50)	(47)
INFLAMMATION, INTERSTITIAL	1 (2%)		
PNEUMONIA, CHRONIC MURINE	1 (2%)		
HYPERPLASIA, ALVEOLAR EPITHELIUM	3 (6%)	1 (2%)	1 (2%)
#ALVEOLAR EPITHELIUM	(49)	(50)	(47)
HYPERPLASIA, ADENOMATOUS		1 (2%)	
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(49)	(49)	(50)
HISTIOCYTOSIS		1 (2%)	
HYPOPLASIA, HEMATOPOIETIC	1 (2%)		
#SPLEEN	(50)	(50)	(50)
INFLAMMATION, CHRONIC			1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
FIBROSIS, FOCAL		1 (2%)	
HEMATOPOIESIS	1 (2%)	2 (4%)	
#MANDIBULAR L. NODE	(50)	(50)	(50)
DILATATION, NOS			1 (2%)
INFLAMMATION, NOS			2 (4%)
HYPERPLASIA, NOS		5 (10%)	1 (2%)
HYPERPLASIA, CYSTIC	2 (4%)		
HYPERPLASIA, LYMPHOID		1 (2%)	
#MESENTERIC L. NODE	(50)	(50)	(50)
HYPERPLASIA, NOS		1 (2%)	
HYPERPLASIA, RETICULUM CELL			1 (2%)
#LIVER	(50)	(50)	(50)
LEUKOCYTOSIS, NOS		5 (10%)	
HEMATOPOIESIS		1 (2%)	
#KIDNEY	(50)	(50)	(50)
HYPERPLASIA, LYMPHOID	1 (2%)	1 (2%)	
CIRCULATORY SYSTEM			
#LUNG	(49)	(50)	(47)
THROMBOSIS, NOS	1 (2%)		
#HEART	(49)	(50)	(50)
INFLAMMATION, CHRONIC	1 (2%)		4 (8%)
#MYOCARDIUM	(49)	(50)	(50)
INFLAMMATION, NOS		2 (4%)	
INFLAMMATION, INTERSTITIAL			1 (2%)
INFLAMMATION, CHRONIC	18 (37%)		3 (6%)
FIBROSIS	1 (2%)	6 (12%)	
FIBROSIS, FOCAL		1 (2%)	
FIBROSIS, DIFFUSE	2 (4%)	2 (4%)	6 (12%)
#CARDIAC VALVE	(49)	(50)	(50)
INFLAMMATION, FIBRINOUS	1 (2%)		
*ARTERY	(50)	(50)	(50)
INFLAMMATION, FOCAL	1 (2%)		
DIGESTIVE SYSTEM			
#LIVER	(50)	(50)	(50)
FIBROSIS		1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
CHOLANGIOFIBROSIS	1 (2%)		
NECROSIS, NOS	1 (2%)		
CYTOPLASMIC VACUOLIZATION		6 (12%)	8 (16%)
BASOPHILIC CYTO CHANGE			1 (2%)
ATROPHY, FOCAL	1 (2%)		
HYPERPLASIA, FOCAL	1 (2%)		
ANGIECTASIS			1 (2%)
#HEPATIC LOBULE	(50)	(50)	(50)
HYPERPLASIA, NOS		1 (2%)	
#LIVER/CENTRILOBULAR	(50)	(50)	(50)
ATROPHY, NOS	1 (2%)		3 (6%)
#BILE DUCT	(50)	(50)	(50)
HYPERPLASIA, NOS	7 (14%)	4 (8%)	1 (2%)
HYPERPLASIA, FOCAL			1 (2%)
#PANCREAS	(49)	(50)	(50)
INFLAMMATION, CHRONIC	9 (18%)	1 (2%)	
INFLAMMATION, CHRONIC FOCAL	1 (2%)		
ATROPHY, NOS		1 (2%)	
ATROPHY, FOCAL			2 (4%)
#PANCREATIC ACINUS	(49)	(50)	(50)
ATROPHY, NOS		1 (2%)	
ATROPHY, FOCAL		4 (8%)	3 (6%)
#GASTRIC MUCOSA	(50)	(50)	(50)
INFLAMMATION, NOS			1 (2%)
HYPERPLASIA, NOS			1 (2%)
#GASTRIC SUBMUCOSA	(50)	(50)	(50)
INFLAMMATION, NOS			1 (2%)
#CARDIAC STOMACH	(50)	(50)	(50)
ULCER, NOS		1 (2%)	
INFLAMMATION ACTIVE CHRONIC		1 (2%)	
HYPERPLASIA, EPITHELIAL		1 (2%)	
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
HYDRONEPHROSIS		1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
CYST, NOS			1 (2%)
INFLAMMATION, CHRONIC	1 (2%)		
INFLAMMATION, GRANULOMATOUS	1 (2%)		
NEPHROPATHY			1 (2%)
NEPHROSIS, NOS	30 (60%)	43 (86%)	41 (82%)
INFARCT, NOS	1 (2%)		
HEMOSIDEROSIS		1 (2%)	
#URINARY BLADDER	(48)	(50)	(49)
INFLAMMATION, HEMORRHAGIC		1 (2%)	
*URETHRA	(50)	(50)	(50)
HEMORRHAGE		1 (2%)	
INFLAMMATION, NOS		1 (2%)	
ENDOCRINE SYSTEM			
#PITUITARY	(46)	(49)	(50)
HYPERPLASIA, NOS		2 (4%)	3 (6%)
HYPERPLASIA, FOCAL	1 (2%)		1 (2%)
#ADRENAL	(50)	(50)	(50)
CYTOPLASMIC VACUOLIZATION			1 (2%)
#ADRENAL CORTEX	(50)	(50)	(50)
CYTOPLASMIC VACUOLIZATION		2 (4%)	1 (2%)
CYTOLOGIC ALTERATION, NOS		1 (2%)	
HYPERPLASIA, FOCAL	1 (2%)		
#ADRENAL MEDULLA	(50)	(50)	(50)
FOCAL CELLULAR CHANGE			1 (2%)
#THYROID	(49)	(50)	(50)
CYSTIC FOLLICLES			1 (2%)
DEGENERATION, CYSTIC		7 (14%)	5 (10%)
HYPERPLASIA, CYSTIC			2 (4%)
HYPERPLASIA, C-CELL	1 (2%)	1 (2%)	3 (6%)
#PARATHYROID	(41)	(43)	(43)
HYPERPLASIA, NOS		1 (2%)	
#PANCREATIC ISLETS	(49)	(50)	(50)
HYPERPLASIA, NOS	1 (2%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
CYST, NOS	3 (6%)	13 (26%)	5 (10%)
CYSTIC DUCTS	1 (2%)		14 (28%)
INFLAMMATION, CHRONIC		1 (2%)	
HYPERPLASIA, NOS	1 (2%)		
HYPERPLASIA, CYSTIC	1 (2%)		2 (4%)
*PREPUTIAL GLAND	(50)	(50)	(50)
CYST, NOS		1 (2%)	1 (2%)
CYSTIC DUCTS			1 (2%)
INFLAMMATION, NOS		1 (2%)	
INFLAMMATION, SUPPURATIVE	1 (2%)	1 (2%)	
INFLAMMATION ACTIVE CHRONIC		1 (2%)	
INFLAMMATION, GRANULOMATOUS	1 (2%)		
HYPERPLASIA, NOS	3 (6%)	1 (2%)	2 (4%)
HYPERPLASIA, CYSTIC		1 (2%)	1 (2%)
#PROSTATE	(49)	(50)	(49)
CYST, NOS		1 (2%)	
HEMORRHAGE		1 (2%)	
INFLAMMATION, NOS			1 (2%)
INFLAMMATION, SUPPURATIVE	10 (20%)	29 (58%)	20 (41%)
INFLAMMATION ACUTE AND CHRONIC			1 (2%)
INFLAMMATION, CHRONIC	3 (6%)	2 (4%)	
INFLAMMATION, CHRONIC SUPPURATIV	2 (4%)		
FIBROSIS, DIFFUSE	2 (4%)		
HYPERPLASIA, FOCAL	1 (2%)	2 (4%)	1 (2%)
*SEMINAL VESICLE	(50)	(50)	(50)
HYPERPLASIA, NOS	1 (2%)		
*COAGULATING GLAND	(50)	(50)	(50)
HEMORRHAGE		1 (2%)	
#TESTIS	(50)	(50)	(50)
INFARCT, NOS		1 (2%)	
CALCIFICATION, FOCAL		1 (2%)	
ATROPHY, NOS	1 (2%)	26 (52%)	17 (34%)
HYPERPLASIA, INTERSTITIAL CELL			2 (4%)
*EPIDIDYMIS	(50)	(50)	(50)
GRANULOMA, SPERMATIC		1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
NERVOUS SYSTEM			
#BRAIN	(50)	(50)	(50)
HEMORRHAGE	3 (6%)		
#HYPOTHALAMUS	(50)	(50)	(50)
COMPRESSION	1 (2%)	2 (4%)	1 (2%)
SPECIAL SENSE ORGANS			
*EYE	(50)	(50)	(50)
HEMORRHAGE		1 (2%)	
RETINOPATHY		14 (28%)	27 (54%)
CATARACT		11 (22%)	25 (50%)
*EYE/RETINA	(50)	(50)	(50)
DEFORMITY, NOS			1 (2%)
INFLAMMATION, CHRONIC			1 (2%)
ATROPHY, NOS	7 (14%)		2 (4%)
*EYE/CRYSTALLINE LENS	(50)	(50)	(50)
MINERALIZATION			1 (2%)
FIBROSIS	1 (2%)		
*ZYMBAL'S GLAND	(50)	(50)	(50)
HYPERPLASIA, CYSTIC			1 (2%)
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*MESENTERY	(50)	(50)	(50)
STEATITIS	3 (6%)	3 (6%)	2 (4%)
INFLAMMATION, CHRONIC		1 (2%)	
LIPOGRANULOMA		1 (2%)	
ADHESION, NOS			1 (2%)
NECROSIS, FAT		5 (10%)	3 (6%)
ALL OTHER SYSTEMS			
OMENTUM			
NECROSIS, FAT	1	2	1

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
SPECIAL MORPHOLOGY SUMMARY			
NONE			

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C2.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS FED DIETS CONTAINING ZEARALENONE

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
ULCER, NOS		1 (2%)	
HYPERPLASIA, NOS	1 (2%)		
*SUBCUT TISSUE	(50)	(50)	(50)
INFLAMMATION, SUPPURATIVE			2 (4%)
RESPIRATORY SYSTEM			
#LUNG/BRONCHIOLE	(48)	(50)	(50)
HYPERPLASIA, ADENOMATOUS		1 (2%)	
#LUNG	(48)	(50)	(50)
CONGESTION, NOS		1 (2%)	
EDEMA, NOS		1 (2%)	
HYPERPLASIA, ALVEOLAR EPITHELIUM	1 (2%)		1 (2%)
#ALVEOLAR EPITHELIUM	(48)	(50)	(50)
HYPERPLASIA, ADENOMATOUS		2 (4%)	
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(49)	(48)	(48)
HYPERPLASIA, NOS	1 (2%)		
#SPLEEN	(50)	(50)	(50)
HEMOSIDEROSIS	2 (4%)		3 (6%)
ATROPHY, FOCAL	1 (2%)		
HYPERPLASIA, HEMATOPOIETIC	1 (2%)		
HEMATOPOIESIS		2 (4%)	
#MANDIBULAR L. NODE	(50)	(50)	(49)
HEMOSIDEROSIS			1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
HYPERPLASIA, NOS		3 (6%)	3 (6%)
#MEDIASTINAL L.NODE	(50)	(50)	(49)
HYPERPLASIA, NOS		1 (2%)	
*FEMUR	(50)	(50)	(50)
MYELOFIBROSIS			1 (2%)
#LUNG	(48)	(50)	(50)
HYPERPLASIA, LYMPHOID		2 (4%)	
#LIVER	(50)	(50)	(50)
LEUKOCYTOSIS, NOS	1 (2%)	5 (10%)	
#THYMUS	(43)	(47)	(46)
HYPERPLASIA, EPITHELIAL		1 (2%)	
CIRCULATORY SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
PERIARTERITIS	1 (2%)		
*MEDIASTINUM	(50)	(50)	(50)
THROMBUS, MURAL			1 (2%)
#HEART	(49)	(50)	(50)
INFLAMMATION, CHRONIC		1 (2%)	
#BASE OF HEART	(49)	(50)	(50)
INFLAMMATION, FOCAL		1 (2%)	
#MYOCARDIUM	(49)	(50)	(50)
INFLAMMATION, NOS	1 (2%)		
INFLAMMATION, MULTIFOCAL		1 (2%)	
INFLAMMATION, CHRONIC	1 (2%)		
FIBROSIS		1 (2%)	
FIBROSIS, DIFFUSE	2 (4%)		1 (2%)
*MESENTERIC ARTERY	(50)	(50)	(50)
INFLAMMATION, CHRONIC	1 (2%)		
NECROSIS, FIBRINOID	1 (2%)		
#LIVER	(50)	(50)	(50)
THROMBOSIS, NOS			1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
#PAROTID GLAND	(50)	(49)	(50)
INFLAMMATION, CHRONIC FOCAL		1 (2%)	
#LIVER	(50)	(50)	(50)
INFLAMMATION, FOCAL GRANULOMATOU		1 (2%)	
NECROSIS, FOCAL	1 (2%)		
METAMORPHOSIS FATTY	1 (2%)	2 (4%)	
CYTOPLASMIC CHANGE, NOS			1 (2%)
CYTOPLASMIC VACUOLIZATION	2 (4%)	2 (4%)	2 (4%)
BASOPHILIC CYTO CHANGE	1 (2%)	1 (2%)	3 (6%)
FOCAL CELLULAR CHANGE		1 (2%)	
HYPERPLASIA, FOCAL	1 (2%)		
#LIVER/CENTRILOBULAR	(50)	(50)	(50)
DEGENERATION, NOS	1 (2%)		
METAMORPHOSIS FATTY		2 (4%)	1 (2%)
CYTOPLASMIC VACUOLIZATION		1 (2%)	1 (2%)
ATROPHY, NOS	3 (6%)	1 (2%)	1 (2%)
#LIVER/MIDLOBULAR	(50)	(50)	(50)
METAMORPHOSIS FATTY		1 (2%)	
#LIVER/PERIPORTAL	(50)	(50)	(50)
METAMORPHOSIS FATTY		1 (2%)	
#LIVER/HEPATOCYTES	(50)	(50)	(50)
HYPERPLASIA, FOCAL		1 (2%)	
#BILE DUCT	(50)	(50)	(50)
CYST, NOS		1 (2%)	
HYPERPLASIA, NOS	5 (10%)		
#PANCREAS	(50)	(50)	(50)
CYSTIC DUCTS		1 (2%)	
#PANCREATIC ACINUS	(50)	(50)	(50)
ATROPHY, NOS	2 (4%)	1 (2%)	
ATROPHY, FOCAL	1 (2%)	5 (10%)	1 (2%)
#ESOPHAGUS	(48)	(50)	(50)
INFLAMMATION, NOS		1 (2%)	
#CARDIAC STOMACH	(50)	(50)	(50)
INFLAMMATION, VESICULAR	1 (2%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
HYDRONEPHROSIS	1 (2%)		
NEPHROSIS, NOS	10 (20%)	24 (48%)	26 (52%)
NECROSIS, NOS		1 (2%)	
#KIDNEY/PELVIS	(50)	(50)	(50)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)		
CALCIFICATION, NOS		1 (2%)	
#URINARY BLADDER	(49)	(48)	(48)
HYPERPLASIA, EPITHELIAL		1 (2%)	
ENDOCRINE SYSTEM			
#PITUITARY	(49)	(50)	(49)
HYPERPLASIA, NOS	6 (12%)	4 (8%)	7 (14%)
HYPERPLASIA, FOCAL	1 (2%)		1 (2%)
#ANTERIOR PITUITARY	(49)	(50)	(49)
HEMORRHAGIC CYST			1 (2%)
ANGIECTASIS			1 (2%)
#ADRENAL	(50)	(50)	(50)
CALCIFICATION, FOCAL		1 (2%)	
CYTOPLASMIC VACUOLIZATION	2 (4%)		
#ADRENAL CORTEX	(50)	(50)	(50)
HEMORRHAGIC CYST		1 (2%)	
CYTOPLASMIC VACUOLIZATION	1 (2%)	1 (2%)	
HYPERPLASIA, FOCAL		1 (2%)	
#ADRENAL MEDULLA	(50)	(50)	(50)
HEMORRHAGIC CYST			1 (2%)
HYPERPLASIA, NOS		1 (2%)	
#THYROID	(49)	(50)	(49)
ULTIMOBRANCHIAL CYST	2 (4%)		
CYSTIC FOLLICLES			1 (2%)
HYPERPLASIA, CYSTIC	1 (2%)		
HYPERPLASIA, C-CELL	9 (18%)	6 (12%)	7 (14%)
#THYROID PARAFOLLICUL	(49)	(50)	(49)
HYPERTROPHY, FOCAL		1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
GALACTOCELE			1 (2%)
CYST, NOS	10 (20%)	34 (68%)	10 (20%)
CYSTIC DUCTS	18 (36%)		18 (36%)
ABSCESS, NOS		1 (2%)	
INFLAMMATION, CHRONIC			1 (2%)
HYPERPLASIA, CYSTIC	1 (2%)		1 (2%)
ADENOSIS		2 (4%)	2 (4%)
*MAMMARY LOBULE	(50)	(50)	(50)
HYPERPLASIA, NOS		1 (2%)	1 (2%)
*PREPUTIAL GLAND	(50)	(50)	(50)
CYSTIC DUCTS			1 (2%)
INFLAMMATION, NOS		1 (2%)	
INFLAMMATION, SUPPURATIVE		1 (2%)	2 (4%)
HYPERPLASIA, CYSTIC	2 (4%)	2 (4%)	1 (2%)
*CLITORAL GLAND	(50)	(50)	(50)
HYPERPLASIA, FOCAL	1 (2%)		
#UTERUS	(50)	(49)	(49)
HYDROMETRA	1 (2%)	3 (6%)	
HEMATOMETRA			1 (2%)
#CERVIX UTERI	(50)	(49)	(49)
HYPERPLASIA, EPITHELIAL			1 (2%)
#UTERUS/ENDOMETRIUM	(50)	(49)	(49)
HYPERPLASIA, FOCAL	1 (2%)	1 (2%)	
HYPERPLASIA, CYSTIC	2 (4%)	5 (10%)	
#OVARY	(50)	(49)	(49)
CYST, NOS	2 (4%)	1 (2%)	
FOLLICULAR CYST, NOS			4 (8%)
CORPUS LUTEUM	1 (2%)		
NERVOUS SYSTEM			
*CHOROID PLEXUS LATER	(50)	(50)	(50)
ANGIECTASIS	1 (2%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#HYPOTHALAMUS	(49)	(50)	(50)
COMPRESSION	1 (2%)	2 (4%)	3 (6%)
SPECIAL SENSE ORGANS			
*EYE	(50)	(50)	(50)
HEMORRHAGE		6 (12%)	1 (2%)
INFLAMMATION, CHRONIC		1 (2%)	
RETINOPATHY	3 (6%)	28 (56%)	8 (16%)
CATARACT	4 (8%)	26 (52%)	6 (12%)
*EYE/CORNEA	(50)	(50)	(50)
INFLAMMATION, FOCAL			1 (2%)
*EYE/RETINA	(50)	(50)	(50)
ATROPHY, NOS		3 (6%)	1 (2%)
*EYE/CRYSTALLINE LENS	(50)	(50)	(50)
MINERALIZATION		1 (2%)	
*ZYMBAL'S GLAND	(50)	(50)	(50)
HYPERPLASIA, CYSTIC			1 (2%)
*MIDDLE EAR	(50)	(50)	(50)
INFLAMMATION, SUPPURATIVE			1 (2%)
MUSCULOSKELETAL SYSTEM			
*MUSCLE OF HEAD	(50)	(50)	(50)
INFLAMMATION, NOS		1 (2%)	
BODY CAVITIES			
*MESENTERY	(50)	(50)	(50)
STEATITIS	3 (6%)	2 (4%)	
INFLAMMATION, CHRONIC		1 (2%)	
NECROSIS, FAT	3 (6%)	2 (4%)	4 (8%)
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
HEMORRHAGE	1 (2%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
TAIL			
HYPERKERATOSIS			1
FOOT			
HYPERKERATOSIS			1
OMENTUM			
NECROSIS, FAT	2		1
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	4		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

APPENDIX D

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE FED DIETS CONTAINING ZEARALENONE

TABLE D1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE FED DIETS CONTAINING ZEARALENONE

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
INFLAMMATION, ACUTE FOCAL	3 (6%)		
INFLAMMATION, CHRONIC	1 (2%)		
INFLAMMATION, CHRONIC FOCAL	3 (6%)	2 (4%)	
*SUBCUT TISSUE	(50)	(50)	(50)
INFLAMMATION ACUTE AND CHRONIC			1 (2%)
INFLAMMATION, CHRONIC FOCAL		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(50)	(49)	(50)
CONGESTION, NOS	1 (2%)		
BRONCHOPNEUMONIA, FOCAL	14 (28%)	6 (12%)	12 (24%)
PNEUMONIA, CHRONIC MURINE			1 (2%)
HYPERPLASIA, ADENOMATOUS	1 (2%)		
HYPERPLASIA, ALVEOLAR EPITHELIUM	1 (2%)		
HEMATOPOIETIC SYSTEM			
#HARDERIAN GLAND	(50)	(50)	(50)
HYPERPLASIA, LYMPHOID	7 (14%)	7 (14%)	8 (16%)
#SPLEEN	(50)	(50)	(49)
HYPERPLASIA, NOS		1 (2%)	
HYPERPLASIA, LYMPHOID		1 (2%)	
#PANCREATIC L.NODE	(50)	(49)	(50)
INFLAMMATION, GRANULOMATOUS		1 (2%)	
#MESENTERIC L. NODE	(50)	(49)	(50)
ANGIECTASIS	1 (2%)		1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#SACRAL LYMPH NODE	(50)	(49)	(50)
HYPERPLASIA, LYMPHOID	1 (2%)		
#INGUINAL LYMPH NODE	(50)	(49)	(50)
HYPERPLASIA, LYMPHOID	3 (6%)		
#PEYER'S PATCH	(49)	(49)	(49)
HYPERPLASIA, LYMPHOID		1 (2%)	
#THYMUS	(48)	(39)	(44)
CYST, NOS		1 (3%)	
CIRCULATORY SYSTEM			
#HEART	(50)	(50)	(50)
INFLAMMATION, CHRONIC FOCAL	1 (2%)		
DIGESTIVE SYSTEM			
#LIVER	(50)	(50)	(49)
CYST, NOS	1 (2%)	1 (2%)	
INFLAMMATION, CHRONIC		1 (2%)	
FIBROSIS		1 (2%)	
NECROSIS, NOS	1 (2%)	2 (4%)	
NECROSIS, CASEOUS			1 (2%)
CYTOLOGIC ALTERATION, NOS	4 (8%)	1 (2%)	1 (2%)
#PANCREAS	(50)	(49)	(49)
DILATATION/DUCTS	1 (2%)		
ATROPHY, NOS	1 (2%)		
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
HYDRONEPHROSIS		1 (2%)	
CYST, NOS	1 (2%)		
INFLAMMATION, SUPPURATIVE		1 (2%)	
INFLAMMATION, ACUTE SUPPURATIVE	1 (2%)		
#URINARY BLADDER	(49)	(50)	(50)
LYMPHOCYTIC INFLAMMATORY INFILTR		1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM			
#PITUITARY	(40)	(45)	(44)
HYPERPLASIA, FOCAL			1 (2%)
#ADRENAL CORTEX	(50)	(50)	(49)
HYPERPLASIA, FOCAL			1 (2%)
#ADRENAL MEDULLA	(50)	(50)	(49)
HYPERPLASIA, FOCAL		1 (2%)	
#THYROID	(50)	(49)	(49)
CYST, NOS			1 (2%)
CYSTIC FOLLICLES		1 (2%)	2 (4%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
CYSTIC DUCTS			2 (4%)
*PREPUTIAL GLAND	(50)	(50)	(50)
CYST, NOS	3 (6%)	2 (4%)	3 (6%)
CYSTIC DUCTS		1 (2%)	1 (2%)
INFLAMMATION, ACUTE SUPPURATIVE			1 (2%)
INFLAMMATION ACUTE AND CHRONIC	2 (4%)	2 (4%)	1 (2%)
#PROSTATE	(50)	(50)	(50)
INFLAMMATION, ACUTE SUPPURATIVE	1 (2%)		
*SEMINAL VESICLE	(50)	(50)	(50)
DISTENTION		1 (2%)	
INFLAMMATION, CHRONIC	1 (2%)		
#TESTIS	(50)	(50)	(50)
FIBROSIS		1 (2%)	
NECROSIS, NOS		1 (2%)	
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
#HARDERIAN GLAND	(50)	(50)	(50)
INFLAMMATION, ACUTE SUPPURATIVE	1 (2%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
INFLAMMATION, ACUTE/CHRONIC	1 (2%)		
MUSCULOSKELETAL SYSTEM			
*ABDOMINAL MUSCLE	(50)	(50)	(50)
INFLAMMATION, ACUTE SUPPURATIVE	1 (2%)		
BODY CAVITIES			
*PERITONEUM	(50)	(50)	(50)
INFLAMMATION, SUPPURATIVE		1 (2%)	
INFLAMMATION, ACUTE SUPPURATIVE			1 (2%)
*MESENTERY	(50)	(50)	(50)
NECROSIS, FAT	2 (4%)	1 (2%)	
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	1	4	6

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D2.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE FED DIETS CONTAINING ZEARALENONE

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	49	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	49	49
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(49)	(49)
EDEMA, NOS		1 (2%)	
INFLAMMATION ACUTE AND CHRONIC			1 (2%)
INFLAMMATION, FOCAL GRANULOMATOU	1 (2%)		
*SUBCUT TISSUE	(50)	(49)	(49)
INFLAMMATION ACUTE AND CHRONIC		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(48)	(48)	(49)
BRONCHOPNEUMONIA, FOCAL	3 (6%)	4 (8%)	3 (6%)
BRONCHOPNEUMONIA, CHRONIC			1 (2%)
CHOLESTEROL DEPOSIT			1 (2%)
HYPERPLASIA, ALVEOLAR EPITHELIUM			1 (2%)
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(49)	(48)	(49)
MYELOFIBROSIS	8 (16%)	32 (67%)	34 (69%)
#SPLEEN	(50)	(49)	(49)
ABSCESS, NOS	1 (2%)		
#MEDIASTINAL L.NODE	(50)	(48)	(49)
ABSCESS, NOS	1 (2%)		
HYPERPLASIA, NOS			1 (2%)
#CELIAC LYMPH NODE	(50)	(48)	(49)
HYPERPLASIA, LYMPHOID	1 (2%)		
#RENAL LYMPH NODE	(50)	(48)	(49)
HYPERPLASIA, LYMPHOID	1 (2%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#ILIAC LYMPH NODE	(50)	(48)	(49)
HYPERPLASIA, NOS			1 (2%)
#LIVER	(50)	(49)	(49)
MYELOPOIESIS	1 (2%)		
#PEYER'S PATCH	(48)	(45)	(49)
HYPERPLASIA, LYMPHOID	1 (2%)		
CIRCULATORY SYSTEM			
*MUSCLE HIP/THIGH	(50)	(49)	(49)
PERIVASCULITIS			1 (2%)
#THYROID	(47)	(48)	(47)
PERIVASCULITIS			1 (2%)
DIGESTIVE SYSTEM			
#LIVER	(50)	(49)	(49)
CYST, NOS		1 (2%)	3 (6%)
INFLAMMATION, CHRONIC FOCAL		1 (2%)	
NECROSIS, NOS		3 (6%)	
CYTOPLASMIC VACUOLIZATION			1 (2%)
CYTOLOGIC ALTERATION, NOS	2 (4%)		
HEPATOCYTOMEGALY		1 (2%)	2 (4%)
ATROPHY, NOS		1 (2%)	
ANGIECTASIS			3 (6%)
#PANCREAS	(49)	(48)	(49)
INFLAMMATION ACUTE AND CHRONIC	1 (2%)		1 (2%)
INFLAMMATION, CHRONIC	1 (2%)		
INFLAMMATION, CHRONIC FOCAL		1 (2%)	
FIBROSIS			1 (2%)
FIBROSIS, FOCAL	1 (2%)		
ATROPHY, NOS	3 (6%)	1 (2%)	1 (2%)
#STOMACH	(48)	(48)	(49)
FOREIGN BODY, NOS		1 (2%)	
INFLAMMATION, ACUTE FOCAL		1 (2%)	
INFLAMMATION, ACUTE SUPPURATIVE			1 (2%)
INFLAMMATION, FOCAL GRANULOMATOU		1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
URINARY SYSTEM			
#KIDNEY	(50)	(48)	(49)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)		
#URINARY BLADDER	(49)	(48)	(49)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)		
INFLAMMATION, ACUTE FOCAL			1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(46)	(43)	(42)
HYPERPLASIA, FOCAL		3 (7%)	
ANGIECTASIS			1 (2%)
#ADRENAL CORTEX	(50)	(49)	(47)
CYST, NOS		1 (2%)	
CYTOPLASMIC VACUOLIZATION			1 (2%)
ATROPHY, NOS			1 (2%)
#THYROID	(47)	(48)	(47)
CYSTIC FOLLICLES	2 (4%)		
DEGENERATION, CYSTIC	1 (2%)		6 (13%)
HYPERPLASIA, FOCAL		1 (2%)	
HYPERPLASIA, CYSTIC			2 (4%)
HYPERPLASIA, FOLLICULAR-CELL	3 (6%)	1 (2%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(49)	(49)
CYSTIC DUCTS		3 (6%)	15 (31%)
METAPLASIA, SQUAMOUS		1 (2%)	
*VAGINA	(50)	(49)	(49)
INFLAMMATION, ACUTE SUPPURATIVE	3 (6%)	2 (4%)	5 (10%)
HYPERKERATOSIS			1 (2%)
#UTERUS	(50)	(49)	(48)
INFLAMMATION, SUPPURATIVE	10 (20%)	1 (2%)	
INFLAMMATION, ACUTE SUPPURATIVE	2 (4%)	5 (10%)	1 (2%)
#CERVIX UTERI	(50)	(49)	(48)
INFLAMMATION, ACUTE SUPPURATIVE	3 (6%)	5 (10%)	16 (33%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#UTERUS/ENDOMETRIUM	(50)	(49)	(48)
INFLAMMATION, SUPPURATIVE		2 (4%)	
HYPERPLASIA, CYSTIC	49 (98%)	48 (98%)	47 (98%)
#ENDOMETRIAL GLAND	(50)	(49)	(48)
HYPERPLASIA, CYSTIC			1 (2%)
#UTERUS/MYOMETRIUM	(50)	(49)	(48)
FIBROSIS, FOCAL	1 (2%)	5 (10%)	17 (35%)
#OVARY	(44)	(48)	(48)
CYST, NOS	6 (14%)	2 (4%)	3 (6%)
INFLAMMATION, SUPPURATIVE	2 (5%)		
INFLAMMATION, ACUTE SUPPURATIVE	1 (2%)	1 (2%)	
NERVOUS SYSTEM			
#BRAIN/MENINGES	(50)	(49)	(48)
LYMPHOCYTIC INFLAMMATORY INFILTR		1 (2%)	
SPECIAL SENSE ORGANS			
*EYE	(50)	(49)	(49)
RETINOPATHY			1 (2%)
MUSCULOSKELETAL SYSTEM			
*MUSCLE HIP/THIGH	(50)	(49)	(49)
INFLAMMATION, CHRONIC FOCAL		1 (2%)	
BODY CAVITIES			
*PERITONEUM	(50)	(49)	(49)
INFLAMMATION, ACUTE SUPPURATIVE	1 (2%)	1 (2%)	
*MESENTERY	(50)	(49)	(49)
INFLAMMATION, SUPPURATIVE	2 (4%)		
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(49)	(49)
LYMPHOCYTIC INFLAMMATORY INFILTR		1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

APPENDIX E

ANALYSIS OF ZEARALENONE (MIDWEST RESEARCH INSTITUTE)

APPENDIX E

A. ELEMENTAL ANALYSIS

	Element	C	H
	Theory	67.90	6.97
Batch 01	Determined	67.78	6.88
		67.92	6.95
Batch 02	Determined	67.76	6.82
		67.87	6.95
Batch 03	Determined	68.12	7.05
		68.14	7.04

B. WATER ANALYSIS (Karl Fischer)

Batch 01 0.14 ± 0.01 (δ)%

Batch 03 0.05%

C. MELTING POINT

	Determined	Literature Values
Batch 01	m.p.: 162° to 164°C (visual, capillary)	164° to 165°C (Urry et al., 1977)
Batch 02	m.p.: 162°-163°C (visual, capillary)	

D. OPTICAL ROTATION

Determined	Literature Values
Batch 01 $[\alpha]_{589}^{25}$ = -137.2 ± 0.9 (δ)° concentration = 1.0% in methanol	$[\alpha]_{546}^{25}$ = -170.5 (Urry et al., 1977) concentration = 1.0% in methanol

E. THIN-LAYER CHROMATOGRAPHY

1. Batch 01

Plates: Silica Gel 60 F-254	Ref. Standard: Resorcinol
Amounted spotted: 100 and 300 μg	Visualization: Ultraviolet, 254 and 366 nm and 50% sulfuric acid
System 1: Chloroform:acetone (90:10)	System 2: Benzene:methanol (90:10)
R_f: 0.53, origin (trace) R_{st}: 2.0, origin	R_f: 0.56, origin (trace) R_{st}: 3.5, origin

2. Batch 02

Plates: Silica gel G F-254	Ref. Standard: Resorcinol
Amount Spotted: 10 and 30 μl, 10 μg/μl in methanol	Visualization: Ultraviolet, 254 and 366 nm and 50% aqueous sulfuric acid
System 1: Chloroform:acetone (90:10)	System 2: Benzene:methanol (90:10)
R_f: 0.61, origin R_{st}: 2.65, origin	R_f: 0.63 R_{st}: 3.00

3. Batch 03

Plates: Silica gel 60 F-254 Amount Spotted: 10, 100, and 300 μg (10 μg/μl in acetone)	Ref. Standard: Resorcinol, 10 μg (10 μg/μl in acetone) Visualization: Ultraviolet (254 and 366 nm) and 50% aqueous sulfuric acid
System 1: Chloroform:acetone (90:10)	System 2: Toluene:methanol (90:10)
R_f: 0.58 (major); 0.20 (slight trace) R_{st}: 3.45 (major); 1.18 (slight trace)	R_f: 0.35 (major); 0.14 (trace) R_{st}: 3.19 (major); 1.33 (trace)

F. HIGH PERFORMANCE LIQUID CHROMATOGRAPHY

1. Batch 01:

   Instrument: Waters ALC 202 with Model 660 Solvent Programmer

   Detection: Ultraviolet 254 nm

   a. System 1:

      Column: μBondapak C_{18} - 300 x 4 mm ID, stainless steel

      Solvent: A:B (80:20) to 100% B
      A - 10% acetonitrile in water
      B - 100% acetonitrile

      Program: Six (linear)

      Program time: 15 min

      Flow: 1 ml/min

      Results: Single homogeneous peak

      Retention time: 14.5 min

   b. System 2:

      Column: μPorsasil - 300 x 4 mm ID,

      Solvent: Chloroform:tetrahydrofuran (95:5), isocratic

      Flow: 1 ml/min

      Results: Single homogeneous peak

      Retention time: 7.0 min

2. Batch 02:

   Instrument: Waters ALC 202

   Detection: Ultraviolet, 280 nm

   Column: μBondapak C_{18}, 300 mm x 4 mm ID

   Solvent: Acetonitrile:water (60:40), isocratic

   Flow Rate: 1 ml/min

   Amount Injected: 2 μl, 1.9 μg/μl in acetonitrile

   Results: Single homogeneous peak, retention time 5.5 min

3. Batch 03:

Instrument: Waters ALC 202 with Waters 6000A pump with Model 660 Solvent Programmer and Waters 440 detector

Detection: Ultraviolet, 254 nm

Column: μBondapak C_{18}, 300 mm x 3.9 mm ID

Guard Column: CO:PELL ODS, 72 mm x 2.3 mm ID

Solvent: Acetonitrile: water (60:40), isocratic:

Flow Rate: 1 ml/min

Samples Injected: Solution (10 μl) of 1.0 mg/ml Zearalenone in methanol, filtered

Results: Major peak and one impurity before the major peak

Peak No.	Retention Time (min)	Retention Time (Relative to Major Peak)	Area (Percent of Major Peak)
1	12.8	0.67	0.04
2	19.2	1.00	100

Using isocratic solvent systems of 35% A:65% B, 30% A:70% B, and 20% A:80% B, no additional impurities were observed.

G. SPECTRAL DATA

1. Infrared

a. Batch 01:

Instrument: Beckman IR-12

Cell: Neat, melt on sodium chloride plates

Results: Figure 5 — Consistent with literature spectrum (Mirocha et al., 1967)

b. Batch 02:

Instrument: Perkin Elmer Model 137 Infracord

Cell: Melt on sodium chloride plates

Results: Figure 6 — Consistent with literature spectrum (Mirocha et al., 1967)

c. Batch 03:

Instrument: Beckman IR-12

Cell: 1% in KBr pellet

Results: Figure 7 — Consistent with literature spectrum (Mirocha et al., 1967)

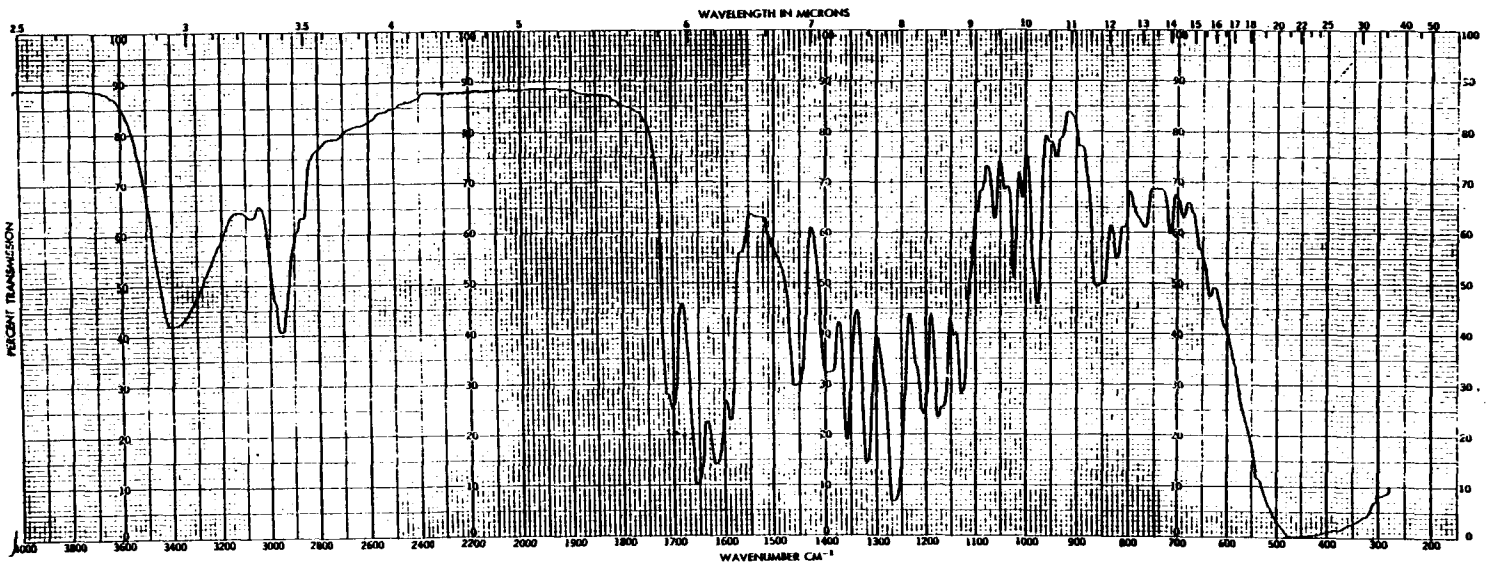

Figure 5. Infrared Absorption Spectrum of Zearalenone (Lot No. 3-75; Batch 01)

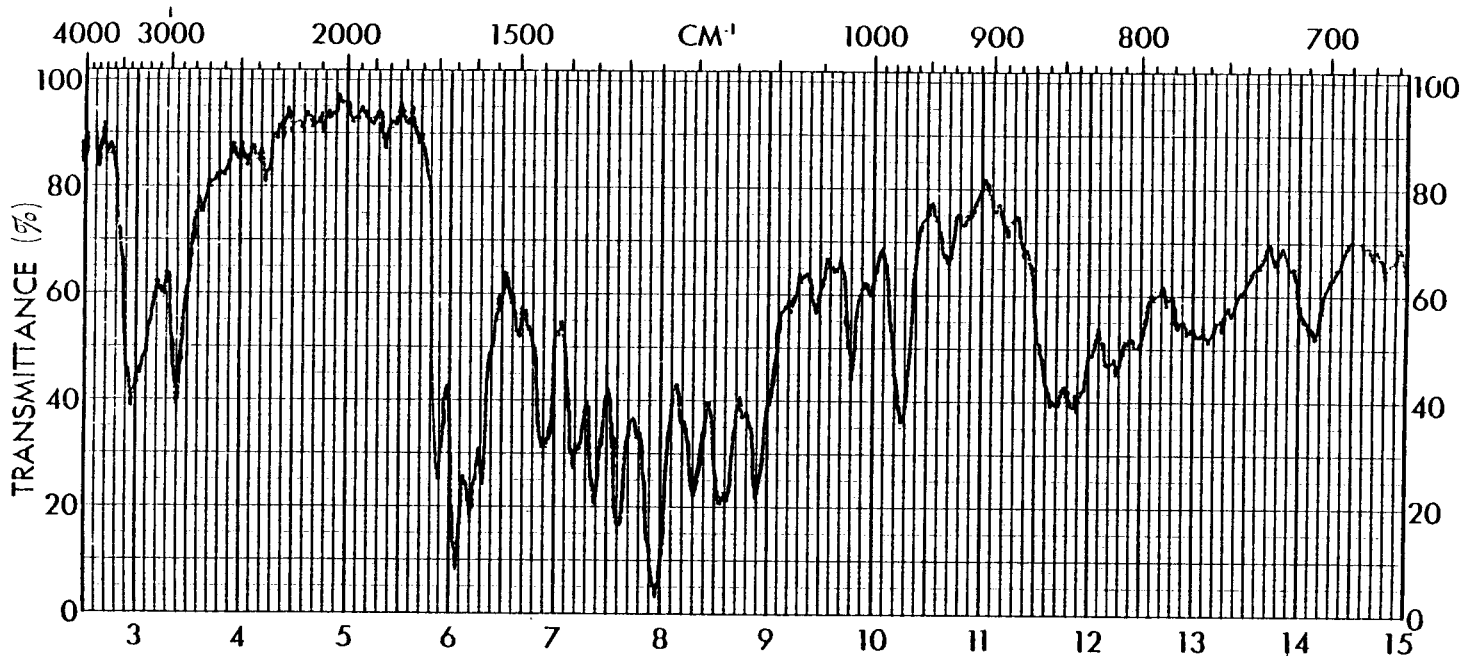

Figure 6. Infrared Absorption Spectrum of Zearalenone (Lot No. 3-75; Batch 02)

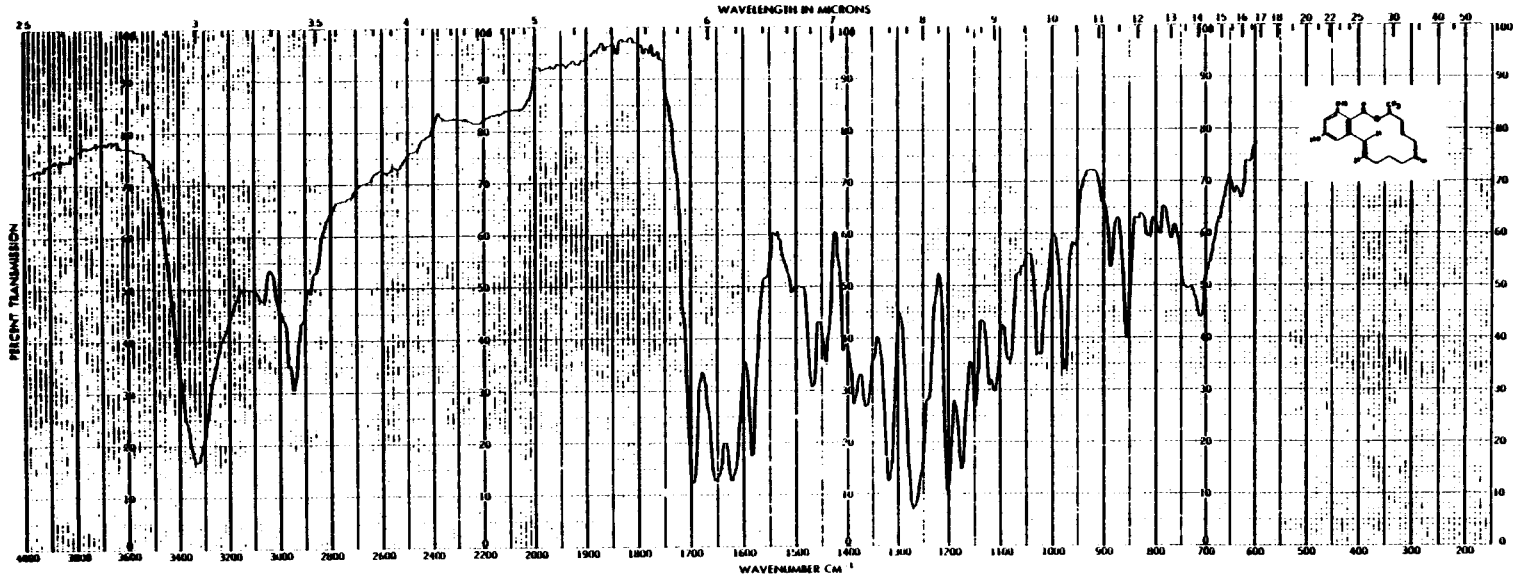

Figure 7. Infrared Absorption Spectrum of Zearalenone (Lot No. 51079; Batch 03)

2. Ultraviolet/Visible:

Instrument: Cary 118

a. Batch 01:

Determined		Literature Values (Urry et al., 1977)	
λ max(nm)	**ε x 10^{-3}**	**λ max(nm)**	**ε x 10^{-3}**
235.5	27.9 ± 0.2 (δ)	236	29.7
273.5	12.3 ± 0.1 (δ)	274	13.9
314.5	5.60 ± 0.06 (δ)	316	6.02

No absorbance between 350 and 800 nm (visible range) at a concentration of 0.1 mg/ml

Solvent: Methanol

b. Batch 03:

Instrument: Cary 118

No maxima from 800 to 350 nm (visible region) but an increase in absorbance toward 350 nm at a concentration of 0.1%.

λ max(nm)	**ε x 10^{-3}**	**λ max(nm)**	**ε x 10^{-3}**
236	29.25 ± 0.0056(δ)	236	29.7
274	13.36 ± 0.0077(δ)	274	13.9
314	15.87 ± 0.0017(δ)	316	60.2

Solvent: Methanol

3. Nuclear Magnetic Resonance:

a. Batch 01:

Instrument: Varian HA-100

Solvent: Methanol-d-4 with internal tetramethylsilane

Assignments: Figure 8

(The proton designations are shown in Figure 10)

(a) d, δ 1.35 ppm, J_{af} = 6 Hz
(b) m, δ 1.65 ppm
(c) m, δ 2.19 ppm
(d) m, δ 2.48 to 3.16 ppm
(e) m, δ 4.95 ppm, not resolved
(f) m, δ 4.95 ppm
(g) m, δ 5.73 ppm
(h) d, δ 6.30 ppm, J_{hi} ◻ 2 Hz
(i) d, δ 6.44 ppm
(j) d, δ 7.05 ppm, J_{gi} ◻ 16 Hz

Experimental spectrum consistent with structure.
Literature spectrum (Urry et al., 1977) differs in the following respects:
Protons (h) and (i) are *not* resolved. The -OH protons are resolved into singlets further downfield than the other signals from zearalenone.
Solvent: $CDCl_3$

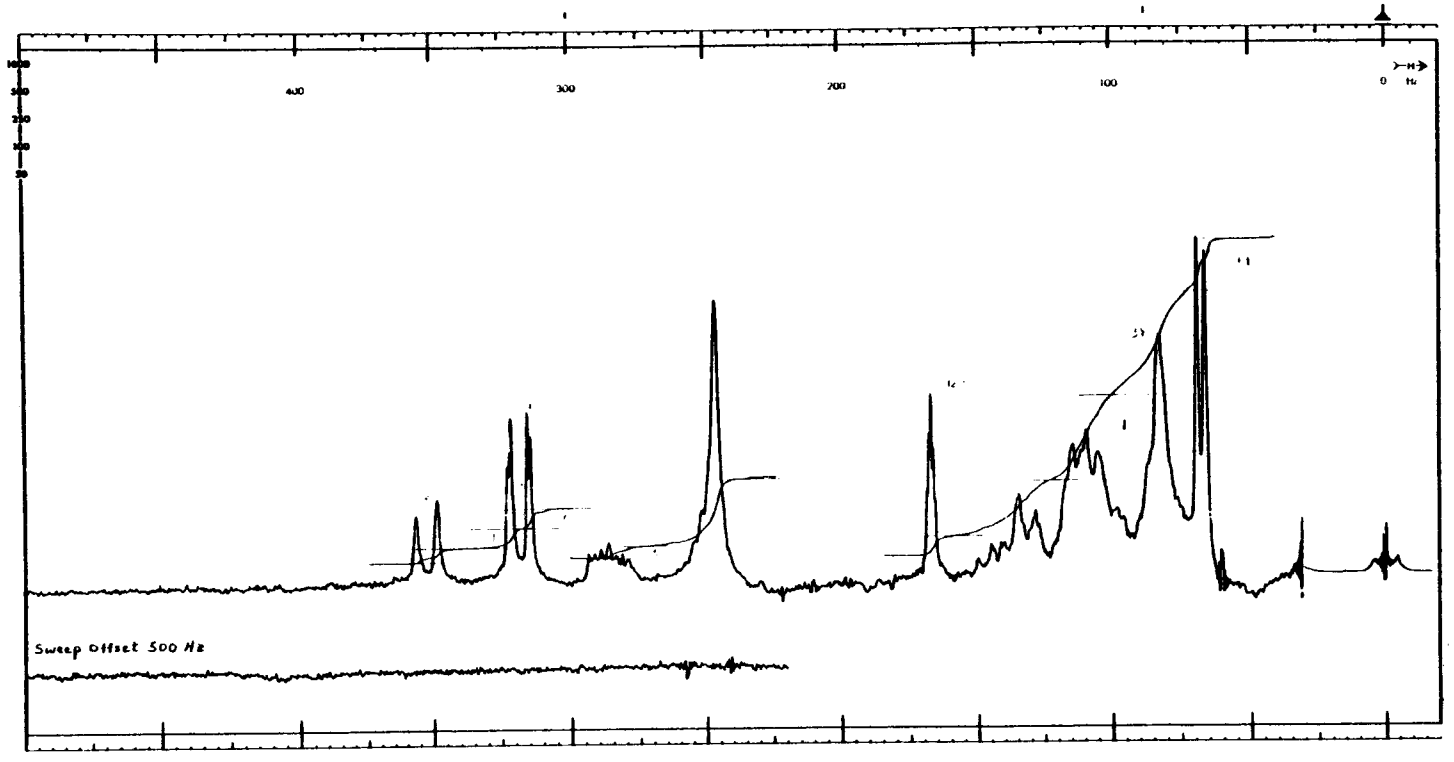

Figure 8. Nuclear Magnetic Resonance Spectrum of Zearalenone (Lot No. 3-75; Batch 01)

Integration ratios:

(a) 2.74
(b) 5.48
(c) 4.47
(d) 2.88
(e,f) -OH from solvent and protons from zearalenone
(g) 0.72
(h) 1.01
(i) 1.01
(j) 0.72

b. Batch 02:

Instrument: Varian HA-100
Solvent: Methanol-d-4 with
internal tetramethylsilane

Assignments: Figure 9

(a) d, δ 1.32 ppm, J_{af} = 6 Hz;
(b) m, δ 1.64 ppm;
(c) t, δ 2.14 ppm, J_{bc} = 9 Hz;
(d) m, δ 2.44-2.98 ppm;
(e,f) m, δ 4.77 ppm;
(g) m, δ 5.64 ppm, J_{gi} = 15 Hz;
(h) d, δ 6.15 ppm, J_{gh} ¤ 2 Hz;
(i) d, δ 6.30 ppm;
(j) d, δ 6.90 ppm

Integration ratios:

(a) 3.37
(b) 5.28
(c) 4.43
(d) 1.90
(e,f) -OH from solvent and protons from zearalenone,
(g) 1.06
(h) 0.95
(i) 1.06
(j) 0.95

c. Batch 03:

Instrument: Varian EM-360A

Solvent: Methanol-d-4 with
internal tetramethylsilane

Assignments: Figure 10

(a) d, δ 1.37 ppm, J_{a-f} = 6 Hz
(b) m, δ 1.68 ppm
(c) m, δ 2.23 ppm
(d) m, δ 2.50-3.18 ppm
(e) s, δ 4.85 ppm
(f) m, δ 4.95 ppm
(g) m, δ 5.67 ppm
(h) d, δ 6.23 ppm, J_{h-i} = 2 Hz
(i) d, δ 6.35 ppm
(j) d, δ 6.97 ppm, J_{g-j} = 15 Hz

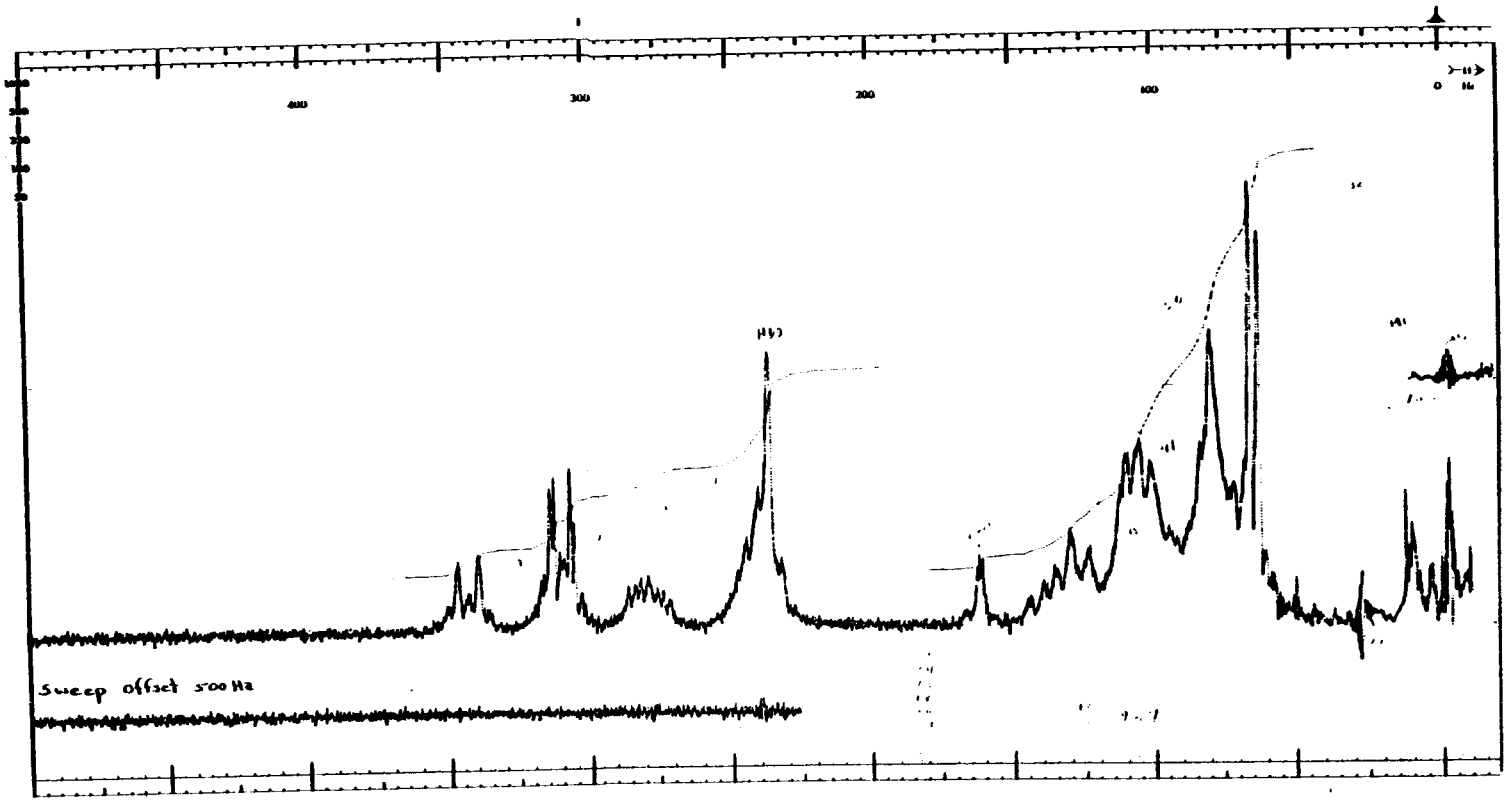

Figure 9. Nuclear Magnetic Resonance Spectrum of Zearalenone (Lot No. 3-75; Batch 02)

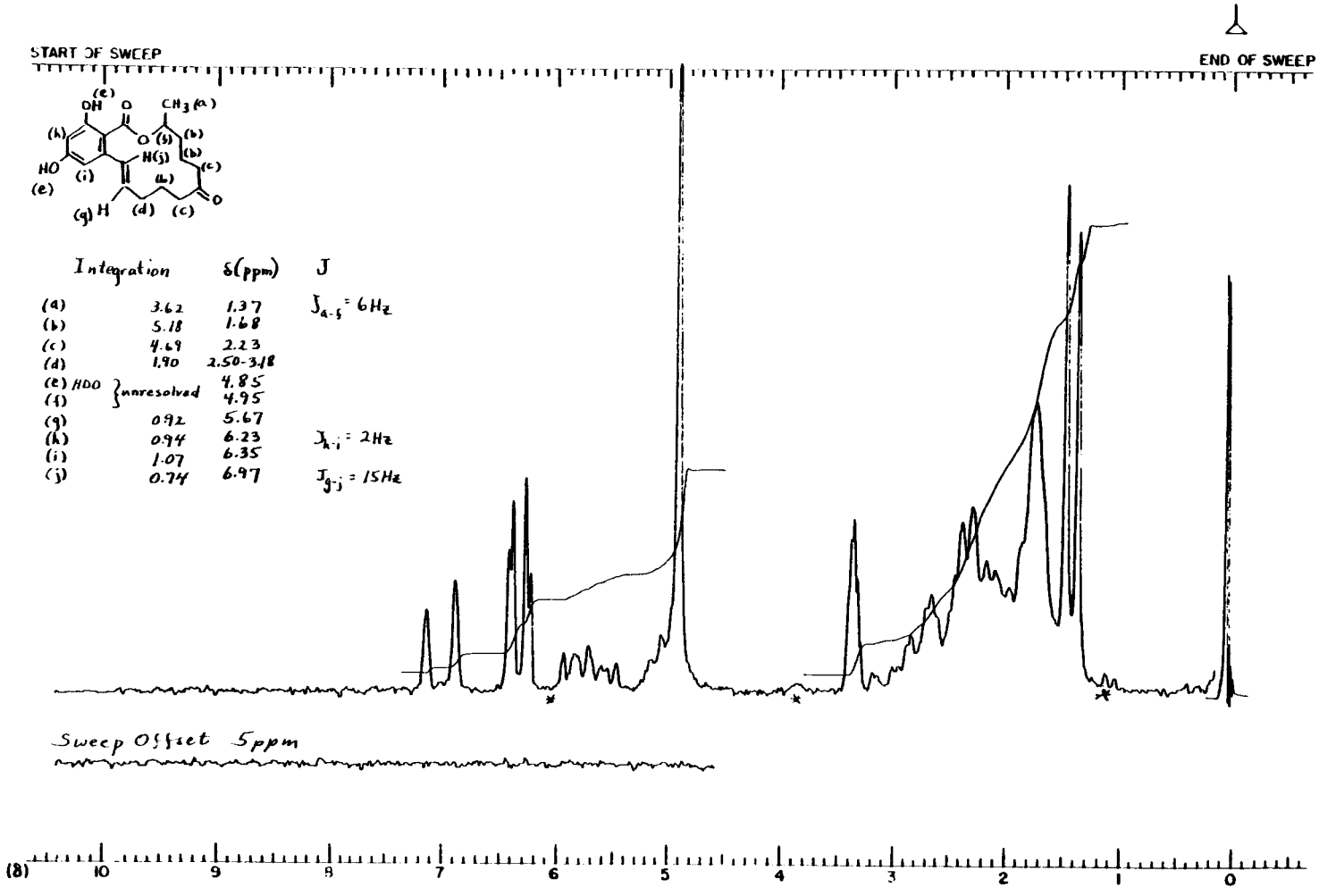

Figure 10. Nuclear Magnetic Resonance Spectrum of Zearalenone (Lot No. 51079; Batch 03)

APPENDIX E

Integration ratios:

(a)	3.62
(b)	5.18
(c)	4.69
(d)	1.90
(e)	-OH and MeOH unresolved
(f)	-OH and MeOH unresolved
(g)	0.92
(h)	0.94
(i)	1.07
(j)	0.74

APPENDIX F

ANALYSIS OF FORMULATED DIETS FOR STABILITY OF ZEARALENONE (MIDWEST RESEARCH INSTITUTE)

APPENDIX F

A. Mixing and storage: Zearalenone and Wayne Lab-Blox® rodent feed were mixed in a mortar in two different concentrations: high (100,000 ppm) and low (1,400 ppm). Samples of the mixtures were removed and stored at 2 weeks at -20°C, 5°C, 25°C, and 45°C, respectively. The samples of high zearalenone concentration were analyzed by high-pressure liquid chromatography and those of low zearalenone concentration were analyzed by ultraviolet spectrophotometric analysis.

B. Extraction: One-gram samples of each of the above mixtures were mixed with 50 ml of methanol in an ultrasonic vibratory bath for 30 seconds and then were triturated for 1 minute using a Polytron® high-speed blender. The mixture was centrifuged, and the supernatant solution was decanted into a 100-ml volumetric flask. This extraction was repeated on the feed residue, and the combined supernatant solutions were brought to volume with fresh methanol.

C. Analysis

1. High zearalenone concentration (100,000 ppm ▫ 10.0%)

   Instrument: Waters ALC 202

   Column: μ-Bondapak C_{18}, 300 x 4 mm ID

   Solvent: Acetonitrile:Water (60:40)

   Detection: Ultraviolet, 254 nm

   Flow rate: 1.0 ml/min

   Results:

Sample (°C)	Average Percent of Recovered Compound (*a*)
-20	10.8 ± 0.5
5	10.2 ± 0.5
25	10.4 ± 0.5
45	9.7 ± 0.5

(a) Corrected for a spiked recovery value of 99.1%; theoretical 100% value ▫ 10.0%.

2. Low zearalenone concentration (1,400 ppm ▫ 0.14%)

   Instrument: Cary 118 Spectrophotometer
   Absorbance wavelength: 236 nm
   Results:

Sample (°C)	Average Percent of Compound Recovered (*a*)
-20	0.14 ± 0.02
5	0.14 ± 0.02
25	0.15 ± 0.02
45	0.12 ± 0.02

(*a*) Corrected for a spiked recovery value of 100%; theoretical 100% value ▫ 0.14%

D. Conclusion: Zearalenone mixed with feed is stable for 2 weeks at temperatures of up to 45°C.

APPENDIX G

ANALYSIS OF FORMULATED DIETS FOR CONCENTRATIONS OF ZEARALENONE (SOUTHERN RESEARCH INSTITUTE)

APPENDIX G

A. Gas Chromatography Method

Five-gram samples of the chemical feed mixture were triturated with 50 ml of chloroform with a Polytron® high-speed blender for 90 seconds. The mixture was filtered through a glass fiber filter and the extraction tube was rinsed with two 20-ml portions of chloroform which were used to wash the filtered feed residue. The feed was washed with a final 10 ml of chloroform. The combined chloroform extract was transferred to a 150-ml beaker and evaporated to dryness. The oil-like residue was transferred to a heptane-packed florisil column, 1 cm by 25 cm, with a few ml of chloroform. The column was eluted with successive portions of solvent: 50 ml of heptane, 100 ml of chloroform, and 65 ml of ether. The ether fraction was evaporated to dryness and reserved for GC analyses of zearalenone.

The oil residue from the ether fraction was derivatized with 0.5 ml of Tri-Sil/BSA reagent. The plain feed, spiked plain feed, and chemical/feed samples were analyzed by vapor-phase chromatography.

GC Conditions:

Column: 3% OV-1 on 80/100 supelcoport,
1.8 m x 4mm ID, glass

Temperatures: Oven 260°C, isothermal
Inlet 260°C
FID 300°C

Carrier Flow: N_2, 40cc/min

Retention time: 3.3 min

Sample size: 2 μl

B. High Pressure Liquid Chromatography Method

Extraction: Ten-gram samples of the chemical/vehicle mixture were accurately weighed and transferred into large sample tubes. Acetonitrile (40 m) was added to each sample. Plain feed blanks and spiked plain feeds were prepared by weighing undosed feed (10 g) into large sample tubes and spiking each sample with acetonitrile or zearalenone in acetonitrile. A stock solution of zeralenone in acetonitrile was prepared and used to spike samples at several concentrations in the specified dosage range of 0.001-0.05%.

The samples were extracted by triturating with acetonitrile using the Polytron® High Speed Blender. After triturating for 60 seconds, the samples were filtered through a Fiberglas® filter using a Millipore® filtering apparatus. The feed residue was then reextracted with another 40 ml aliquot of acetonitrile. The combined extracts were then brought to a 100-ml volume with acetonitrile. These extract solutions were then evaporated to an oily residue on a rotary evaporator.

Column Chromatography: Silica gel columns were prepared by first placing a ball of glass wool loosely in the bottom of the chromatographic column. Approximately 5 g of anhydrous sodium sulfate was added to give an even base for the silica gel. Chloroform was added until the columns were about one-half full; then 10 g of silica gel (ICN Pharmaceuticals, Inc., 100-200μ m, activated by drying overnight at 105°C, then adding 1% water by weight, sealing, shaking until thoroughly mixed, and stored in an airtight container). The sides of the column were washed with approximately 20 ml chloroform, and the silica gel was stirred to disperse it into the chloroform. When the rate of settling slowed, some of the chloroform was drawn off to aid in settling, leaving 2 to 3 in. of chloroform above the silica gel. Fifteen grams of anhydrous sodium sulfate was then slowly added and the chloroform was drawn off to the top of the sodium sulfate.

The oil residue of the acetonitrile extraction was mixed with 5 ml chloroform, followed by a 10-ml chloroform rinse, and transferred to 150 ml hexane. This solution was added to the chromatographic column and eluted at a maximum flow rate of 10-20 ml/min. The elution was continued with 150 ml of benzene. These hexane and benzene eluates were discarded, and the zearalenone was eluted from the column with 250 ml acetone:benzene (5:95, v/v).

The acetone:benzene fraction was evaporated on a rotary evaporator until only an oil residue was left. The residue was dissolved in 4 ml of methanol, and filtered solutions were analyzed by high-pressure liquid chromatography.

High Pressure Liquid Chromatography:

Instrument System:

Pumps: Waters 6000 A

Programmer: Waters 660

Detector: Waters 440 at x 0.1 attenuation

Injector: Waters U6K

Detection: Ultraviolet, 313 nm

Column: μBondapak C_{18}, 300 x 3.9 mm ID with CO-Pell ODS guard column, 72 x 2.3 mm ID

Solvent System: Ion Pairing

A: 0.005 M tetrabutylammonium hydroxide (TBA) in water, adjusted to pH 7.3-7.4 with 1% phosphoric acid

B: 0.005 M tetrabutylammonium hydroxide (TBA) in methanol, adjusted to pH 7.3-7.4 with 1% phosphoric acid

Program: 60% B, 40% A isocratic

Flow Rate: 1 ml/min

Sample Injected: 10 μl

Data Recorded on Hewlett-Packard 3380S Integrator

Retention Time of Zearalenone: 13 min

C. Results

See Table G1.

TABLE G1. ANALYSIS OF FORMULATED DIETS

Week Mixed	Week Used	Concentration *(a)* of Zearalenone for Target Concentration of: 100 ppm	50 ppm	25 ppm
Analyses Performed Using *Original Procedure* for Gas Chromatography				
02/14/78	02/21/78	96	50	19
03/21/78	03/28/79		52	28
04/11/78	04/18/78	115	55	
			58	
05/09/78	05/16/78			38
				38
06/13/78	06/20/78		30	16
				21
08/01/78	08/08/78	81	37	18
08/29/78	09/05/78	92	40	19
09/26/78	10/03/78	96	53	27
10/24/78	10/31/78		57	27
11/28/78	12/05/78		46	24
			45	
12/19/78	12/26/78	110	41	16
Mean (ppm)		98.3	47.0	24.3
Standard Deviation		12.4	8.7	7.7
Coefficient of Variation (%)		12.6	18.5	31.7
Range (ppm)		81-115	30-58	16-38
No analysis performed on batches mixed after 12/19/78 pending development of new procedure				
Analyses Performed Using *New Procedure* for High-Pressure Liquid Chromatography				
04/17/79	04/24/79	110	50	27
05/08/79	05/15/79		52	26
06/05/79	06/12/79		51	25
07/03/79	07/10/79		52	25
			56	
07/31/79	08/07/79	95	52	23
08/28/79	09/04/79		55	27
			52	
09/25/79	10/02/79	93	49	23
10/23/79	10/30/79		49	24
			52	
11/27/79	12/04/79	96	48	28
12/18/79	12/25/79		60	29
01/15/80	01/22/80	101	53	26
Mean (ppm)		99.0	52.2	25.7
Standard Deviation		6.8	3.1	2.0
Coefficient of Variation (%)		6.9	5.9	7.8
Range (ppm)		93-110	49-60	23-29

(a) The data presented are the average of the results of duplicate analyses.

APPENDIX H

CUMULATIVE MEAN BODY WEIGHT CHANGE OF RATS AND MICE FED DIETS CONTAINING ZEARALENONE

TABLE H1. CUMULATIVE MEAN BODY WEIGHT CHANGE (RELATIVE TO CONTROLS) OF RATS FED DIETS CONTAINING ZEARALENONE

		Cumulative Mean Body Weight Change *(a)*			Weight Change Relative to Controls	
	Week No.	Control	Low Dose	High Dose	Low Dose	High Dose
Males	0	100 *(b)*	100 *(b)*	101 *(b)*		
	3	81	72	64	-11	-21
	22	246	228	207	-7	-16
	44	314	286	255	-9	-19
	62	338	308	280	-9	-17
	83	332	311	288	-6	-13
	104	308	305	288	-1	-6
		408 *(c)*	405 *(c)*	389 *(c)*	-1 *(d)*	-5 *(d)*
Females	0	88 *(b)*	90 *(b)*	91 *(b)*		
	3	33	19	27	-42	-18
	22	98	94	89	-4	-9
	44	129	124	115	-4	-11
	62	157	153	144	-3	-8
	83	190	181	165	-5	-13
	104	212	195	183	-8	-14
		300 *(c)*	285 *(c)*	274 *(c)*	-5 *(d)*	-9 *(d)*

(a) Weight change of the dosed group relative to that of the controls =

$$\frac{\text{Weight Change (Dosed Group)} - \text{Weight Change (Control Group)}}{\text{Weight Change (Control Group)}} \times 100$$

(b) Initial weight

(c) Mean body weight at week 104.

(d) Mean body weight relative to controls.

TABLE H2. CUMULATIVE MEAN BODY WEIGHT CHANGE (RELATIVE TO CONTROLS) OF MICE FED DIETS CONTAINING ZEARALENONE

		Cumulative Mean Body Weight Change *(a)* (grams)			Weight Change Relative to Controls (percent)	
	Week No.	Control	Low Dose	High Dose	Low Dose	High Dose
Males	0	21 *(b)*	20 *(b)*	21(b)		
	2	3	3	2	0	-33
	21	13	13	10	0	-23
	43	17	17	14	0	-18
	61	20	20	17	0	-15
	82	19	20	18	+5	5
	104	19	18	18	-5	-5
		40 *(c)*	38 *(c)*	39 *(c)*	-5 *(d)*	-3 *(d)*
Females	0	17 *(b)*	17 *(b)*	17 *(b)*		
	2	3	2	2	-33	-33
	21	9	9	9	0	0
	43	13	11	14	-15	+8
	61	16	14	18	-12	+12
	82	17	15	18	-12	+6
	104	21	18	19	-14	-10
		38 *(c)*	35 *(c)*	36 *(c)*	-8 *(d)*	-5 *(d)*

(a) Weight change of the dosed group relative to that of the controls =

$$\frac{\text{Weight Change (Dosed Group)} - \text{Weight Change (Control Group)}}{\text{Weight Change (Control Group)}} \times 100$$

(b) Initial weight

(c) Mean body weight at week 104.

(d) Mean body weight relative to controls.

APPENDIX I

FEED CONSUMPTION BY RATS AND MICE RECEIVING ZEARALENONE IN THE CHRONIC STUDY

TABLE I1. FEED CONSUMPTION BY RATS RECEIVING ZEARALENONE IN THE CHRONIC STUDY

		Control	Low Dose		High Dose	
	Week	Grams Feed/ Day *(a)*	Grams Feed/ Day *(a)*	Low/ Control *(b)*	Grams Feed/ Day *(a)*	High/ Control *(b)*
Males						
	3	16.0	16.0	1.0	13.0	0.8
	22	18.0	20.0	1.1	15.0	0.8
	44	16.0	15.0	0.9	14.0	0.9
	62	17.0	17.0	1.0	16.0	0.9
	83	15.7	16.7	1.1	15.8	1.0
	104	15.0	15.0	1.0	15.0	1.0
Mean		16.3	16.6	1.0	14.8	0.9
SD *(c)*		1.1	1.9	0.1	1.1	0.1
CV *(d)*		6.7	11.4	10.0	7.4	11.1
Females						
	3	13.0	12.0	0.9	12.0	0.9
	22	10.0	11.0	1.1	11.0	1.1
	44	10.0	9.0	0.9	10.0	1.0
	62	11.0	11.0	1.0	11.0	1.0
	83	12.6	10.5	0.8	11.6	0.9
	104	11.0	11.0	1.0	11.0	1.0
Mean		11.3	10.8	1.0	11.1	1.0
SD *(c)*		1.3	1.0	0.1	0.7	0.1
CV *(d)*		11.5	9.3	10.0	6.3	10.0

(a) Grams of feed consumed per animal per day.
(b) Grams of feed consumed per day by the dosed group divided by that for the controls.
(c) Standard deviation.
(d) Coefficient of variation ▫ (Standard deviation/mean) x 100.

TABLE I2. FEED CONSUMPTION BY MICE RECEIVING ZEARALENONE IN THE CHRONIC STUDY

		Control	Low Dose		High Dose	
	Week	Grams Feed/ Day *(a)*	Grams Feed/ Day *(a)*	Low/ Control *(b)*	Grams Feed/ Day *(a)*	High/ Control *(b)*
Males						
	2	8.6	8.6	1.0	7.5	0.9
	21	8.0	8.0	1.0	9.0	1.1
	43	6.0	6.0	1.0	6.0	1.0
	61	7.0	6.0	0.9	6.0	0.9
	82	5.1	5.1	1.0	5.1	1.0
	104	6.8	6.8	1.0	6.8	1.0
Mean		6.9	6.8	1.0	6.7	1.0
SD *(c)*		1.3	1.3	0.0	1.4	0.1
CV *(d)*		18.8	19.1	0.0	20.9	10.0
Females						
	2	7.5	7.5	1.0	7.5	1.0
	21	8.0	8.0	1.0	8.0	1.0
	43	7.0	6.0	0.9	6.0	0.9
	61	6.0	7.0	1.2	6.0	1.0
	82	6.0	5.1	0.9	5.1	0.9
	104	6.8	6.8	1.0	7.7	1.1
Mean		6.9	6.7	1.0	6.7	1.0
SD *(c)*		0.8	1.0	0.1	1.2	0.1
CV *(d)*		11.6	14.9	10.0	17.9	10.0

(a) Grams of feed consumed per animal per day.
(b) Grams of feed consumed per day by the dosed group divided by that for the controls.
(c) Standard deviation.
(d) Coefficient of variation = (Standard deviation/mean) x 100.

APPENDIX J

COMPOUND CONSUMPTION BY RATS AND MICE FED DIETS CONTAINING ZEARALENONE

TABLE J1. COMPOUND CONSUMPTION BY RATS FED DIETS CONTAINING ZEARALENONE

Week No.	Low Dose			High Dose		
	Body Weight *(a)*	Grams Feed/Day *(b)*	Dose mg/kg/day *(c)*	Body Weight *(a)*	Grams Feed/Day *(b)*	Dose mg/kg/day *(d)*
Males						
3	172	16.0	2.33	165	13.0	3.94
22	328	20.0	1.52	308	15.0	2.44
44	386	15.0	0.97	356	14.0	1.97
62	408	17.0	1.04	381	16.0	2.10
83	411	16.7	1.02	389	15.8	2.03
104	405	15.0	0.93	389	15.0	1.93
Females						
3	109	12.0	2.75	118	12.0	5.08
22	184	11.0	1.49	180	11.0	3.06
44	214	9.0	1.05	206	10.0	2.43
62	243	11.0	1.13	235	11.0	2.34
83	271	10.5	0.97	256	11.6	2.26
104	285	11.0	0.96	274	11.0	2.01

(a) Group body weight average, from Table H1.
(b) From Table I1.
(c) Low Dose = 25 mg/kg of feed. Dose calculation =

$$\left[\frac{\text{Grams Feed/Day}}{\text{Body Wt. (kg)}} \times 25\right] / 1000$$

(d) High Dose = 50 mg/kg of feed. Dose calculation =

$$\left[\frac{\text{Grams Feed/Day}}{\text{Body Wt. (kg)}} \times 50\right] / 1000$$

TABLE J2. COMPOUND CONSUMPTION BY MICE FED DIETS CONTAINING ZEARALENONE

Week No.	Low Dose			High Dose		
	Body Weight *(a)*	Grams Feed/Day *(b)*	Dose mg/kg/day *(c)*	Body Weight *(a)*	Grams Feed/Day *(b)*	Dose mg/kg/day *(d)*
Males						
2	23	8.6	18.7	23	7.5	32.6
21	33	8.0	12.1	31	9.0	29.0
43	37	6.0	8.1	35	6.0	17.1
61	40	6.0	7.5	38	6.0	15.8
82	40	5.1	6.4	39	5.1	13.1
104	38	6.8	8.9	39	6.8	17.4
Females						
2	19	7.5	19.7	19	7.5	39.5
21	26	8.0	15.4	26	8.0	30.8
43	28	6.0	10.7	31	6.0	19.4
61	31	7.0	11.3	35	6.0	17.1
82	32	5.1	8.0	35	5.1	14.6
104	35	6.8	9.7	36	7.7	21.4

(a) Group body weight average, from Table H2.
(b) From Table I2.
(c) Low Dose = 50 mg/kg of feed. Dose calculation =

$$\left[\frac{\text{Grams Feed/Day}}{\text{Body Wt. (kg)}} \times 50\right] / 1000$$

(d) High Dose = 100 mg/kg of feed. Dose calculation =

$$\left[\frac{\text{Grams Feed/Day}}{\text{Body Wt. (kg)}} \times 100\right] / 1000$$

APPENDIX K

HISTORICAL INCIDENCE OF TUMORS IN CONTROL B6C3F1 MICE

TABLE K1. HISTORICAL INCIDENCE OF LIVER TUMORS IN UNTREATED CONTROL FEMALE B6C3F1 MICE *(a)*

Laboratory	Adenoma	Carcinoma	Combined
Battelle	5/348 (1.4%)	21/348 (6.0%)	25/348 (7.2%)
Dow	3/98 (3.1%)	5/98 (5.1%)	7/98 (7.1%)
Frederick	10/431 (2.3%)	13/431 (3.0%)	22/431 (5.1%)
Hazleton	1/100 (1.0%)	4/100 (4.0%)	5/100 (5.0%)
Litton	21/511 (4.1%)	11/511 (2.2%)	32/511 (6.3%)
Mason	35/809 (4.3%)	39/809 (4.8%)	73/809 (9.0%)
Southern *(b)*	14/498 (2.8%)	18/498 (3.6%)	31/498 (6.2%)
Total	89/2795 (3.2%)	111/2795 (4.0%)	195/2795 (7.0%)
Overall Historical Range			
High *(c)*	9/49	7/48	10/49
Low *(d)*	0/50	0/50	0/50

(a) Data as of January 17, 1981 for studies of at least 104 weeks. Range is presented for groups in which at least 35 animals were examined microscopically. Interim death (<104 weeks) animals are included.
(b) Southern Research Institute conducted the current bioassay.
(c) Highest incidence in group of 35 or more animals.
(d) Lowest incidence in group of 35 or more animals.

TABLE K2. HISTORICAL INCIDENCE OF PITUITARY TUMORS IN UNTREATED CONTROL MALE B6C3F1 MICE *(a)*

Laboratory	Carcinoma NOS	Adenoma NOS	Chromophobe Adenoma	Chromophobe Carcinoma
Battelle	0/276 (0.0%)	0/276 (0.0%)	0/276 (0.0%)	1/276 (0.4%)
Dow	0/67 (0.0%)	0/67 (0.0%)	0/67 (0.0%)	0/67 (0.0%)
Frederick	0/358 (0.0%)	2/358 (0.6%)	0/358 (0.0%)	1/358 (0.3%)
Hazleton	0/40 (0.0%)	0/40 (0.0%)	0/40 (0.0%)	0/40 (0.0%)
Litton	0/341 (0.0%)	0/341 (0.0%)	1/341 (0.3%)	0/341 (0.0%)
Mason	0/647 (0.0%)	7/647 (1.1%)	1/647 (0.2%)	0/647 (0.0%)
Southern *(b)*	0/399 (0.0%)	0/399 (0.0%)	0/399 (0.0%)	0/399 (0.0%)
Total	0/2128 (0.0%)	9/2128 (0.4%)	2/2128 (0.1%)	2/2128 (0.1%)
Overall Historical Range				
High *(c)*	0/46	2/42	1/46	1/43
Low *(d)*	0/43	0/43	0/43	0/46

(a) Data as of January 17, 1981 for studies of at least 104 weeks. The range is presented for groups in which at least 35 animals were examined microscopically. Interim death (<104 weeks) animals are included.
(b) Southern Research Institute conducted the current study.
(c) Highest incidence in group of 35 or more animals.
(d) Lowest incidence in group of 35 or more animals.

TABLE K3. HISTORICAL INCIDENCE OF PITUITARY TUMORS IN UNTREATED CONTROL FEMALE B6C3F1 MICE *(a)*

Laboratory	Carcinoma (Unspecified)	Adenoma (Unspecified)	Chromophobe Adenoma	Chromophobe Carcinoma
Battelle	1/298 (0.3%)	3/298 (1.0%)	7/298 (2.3%)	1/298 (0.3%)
Dow	0/77 (0.0%)	0/77 (0.0%)	7/77 (9.1%)	0/77 (0.0%)
Frederick	1/403 (0.2%)	15/403 (3.7%)	6/403 (1.5%)	1/403 (0.2%)
Hazleton	0/93 (0.0%)	8/93 (8.6%)	0/93 (0.0%)	0/93 (0.0%)
Litton	0/369 (0.0%)	5/369 (1.4%)	11/369 (3.0%)	2/369 (0.5%)
Mason	0/666 (0.0%)	57/666 (8.6%)	4/666 (0.6%)	0/666 (0.0%)
Southern *(b)*	2/428 (0.5%)	8/428 (1.9%)	10/428 (2.3%)	1/428 (0.2%)
Total	4/2334 (0.2%)	96/2334 (4.1%)	45/2334 (1.9%)	5/2334 (0.2%)
Overall Historical Range				
High *(c)*	1/43	11/41	4/38	2/44
Low *(d)*	0/49	0/47	0/49	0/49

(a) Data as of January 17, 1981 for studies of at least 104 weeks. Range is presented for groups in which at least 35 animals were examined microscopically. Interim death (< 104 weeks) animals are included.
(b) Southern Research Institute conducted the current bioassay. The combined incidence of female B6C3F1 mice at Southern with either adenomas or carcinomas in the pituitary gland is 21/428 (4.9%). The highest combined incidence in a group of 35 or more animals at Southern is 6/48 (12.5%).
(c) Highest incidence in group of 35 or more animals.
(d) Lowest incidence in group of 35 or more animals.

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