NTP

National Toxicology Program

U.S. Department of Health and Human Services

NTP Technical Report on the Toxicology and Carcinogenesis Studies of

Fumonisin B_1 (CAS No. 116355-83-0) in F344/N Rats and B6C3F$_1$ Mice (Feed Studies)

NTP TR 496

DECEMBER 2001

NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS

STUDIES OF FUMONISIN B_1

(CAS NO. 116355-83-0)

IN F344/N RATS AND $B6C3F_1$ MICE

(FEED STUDIES)

NATIONAL TOXICOLOGY PROGRAM
P.O. Box 12233
Research Triangle Park, NC 27709

December 2001

NTP TR 496

NIH Publication No. 01-3955

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

FOREWORD

The National Toxicology Program (NTP) is made up of four charter agencies of the U.S. Department of Health and Human Services (DHHS): the National Cancer Institute (NCI), National Institutes of Health; the National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health; the National Center for Toxicological Research (NCTR), Food and Drug Administration (FDA); and the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control and Prevention. In July 1981, the Carcinogenesis Bioassay Testing Program, NCI, was transferred to the NIEHS. The NTP coordinates the relevant programs, staff, and resources from these Public Health Service agencies relating to basic and applied research and to biological assay development and validation.

The NTP develops, evaluates, and disseminates scientific information about potentially toxic and hazardous chemicals. This knowledge is used for protecting the health of the American people and for the primary prevention of disease.

The studies on fumonisin B_1 were conducted at the NCTR under an interagency agreement between the FDA and the NIEHS. The studies were designed and monitored by a Toxicology Study Selection and Review Committee, composed of representatives from the NCTR and other FDA product centers, NIEHS, and other *ad hoc* members from other government agencies and academia. The studies were conducted in compliance with NTP laboratory health and safety requirements and must meet or exceed all applicable federal, state, and local health and safety regulations. Animal care and use were in accordance with the Public Health Service Policy on Humane Care and Use of Animals. The prechronic and chronic studies were conducted in compliance with FDA Good Laboratory Practice Regulations.

These studies are designed and conducted to characterize and evaluate the toxicologic potential, including carcinogenic activity, of selected chemicals in laboratory animals (usually two species, rats and mice). Chemicals selected for NTP toxicology and carcinogenesis studies are chosen primarily on the bases of human exposure, level of production, and chemical structure. The interpretive conclusions presented in this Technical Report are based only on the results of these NTP studies. Extrapolation of these results to other species and quantitative risk analyses for humans require wider analyses beyond the purview of these studies. Selection *per se* is not an indicator of a chemical's carcinogenic potential.

Details about ongoing and completed NTP studies are available at the NTP's World Wide Web site: http://ntp-server.niehs.nih.gov. Abstracts of all NTP Technical Reports and full versions of the most recent reports and other publications are available from the NIEHS' Environmental Health Information Service (EHIS) http://ehis.niehs.nih.gov (800-315-3010 or 919-541-3841). In addition, printed copies of these reports are available from EHIS as supplies last. A listing of all NTP reports printed since 1982 appears on the inside back cover.

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CONTRIBUTORS

The studies on fumonisin B_1 were conducted at the FDA's National Center for Toxicological Research under an interagency agreement between the FDA and the NIEHS. The studies were designed and monitored by a Toxicology Study Selection and Review Committee, composed of representatives from the NCTR and other FDA product centers, NIEHS, and other *ad hoc* members from other government agencies and academia. The interagency agreement was designed to use the staff and facilities of the NCTR in testing of FDA priority chemicals and to provide FDA scientists and regulatory policymakers information for hazard identification and risk assessment. The purified fumonisin B_1 was provided by the FDA Center for Food Safety and Applied Nutrition.

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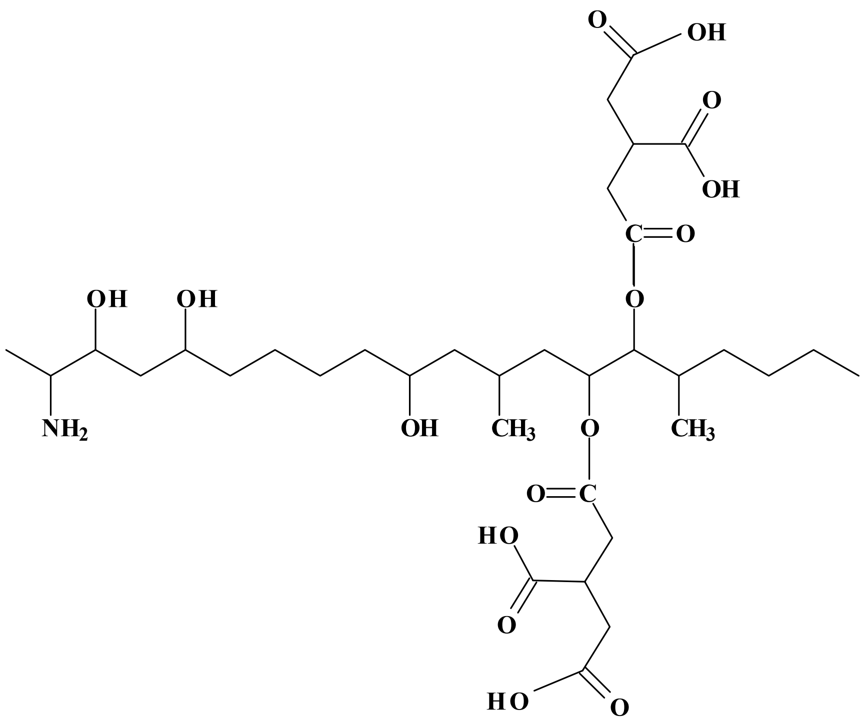
ABSTRACT



FUMONISIN B_1

CAS No. 116355-83-0

Chemical Formula: $C_{34}H_{59}NO_{15}$ Molecular Weight: 721.838

Synonyms: 1,2,3-Propanetricarboxylic acid, 1,1′-[1-(12-amino-4,9,11-trihydroxy-2-methyltridecyl)-2-(1-methylpentyl)-1,2-ethanediyl]ester; macrofusin

Fumonisin B_1 is a mycotoxin produced by the fungus *Fusarium moniliforme*, one of the major species found in corn. There are no known commercial or medical uses of fumonisin B_1. Fumonisin B_1 was nominated by the FDA Center for Food Safety and Applied Nutrition for study because of its occurrence in corn and corn-based products in the United States and its toxicity in field exposure of horses and pigs. Male and female F344/N Nctr BR rats and B6C3F$_1$/Nctr BR (C57BL/6N × C3H/HeN MTV$^-$) mice were exposed to fumonisin B_1 (92% pure) in feed for 28 days or (greater than 96% pure) for 2 years.

28-DAY STUDY IN RATS

Groups of 10 male and 10 female rats were fed diets containing 0, 99, 163, 234, or 484 ppm fumonisin B_1 for 28 days. There were no exposure-related deaths in rats. The mean body weights of the 484 ppm groups were significantly less (−16%) than those of the

controls. Dietary concentrations of 99, 163, 234, and 484 ppm fumonisin B_1 resulted in average daily doses of 12, 20, 28, and 56 mg fumonisin B_1/kg body weight for males and females.

Additional groups of male and female rats were exposed to the same concentrations of fumonisin B_1 for 28 days for clinical pathology studies. The concentrations of creatinine, cholesterol, triglycerides, and total bile acids, as well as activities of the enzymes alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, and γ-glutamyltransferase, were generally significantly greater in the 484 ppm groups than in the control groups at all time points, indicating hyperlipidemia and a hepatic effect. Fumonisin B_1 is an inhibitor of ceramide synthase, resulting in an interruption of *de novo* sphingolipid synthesis. This enzyme inhibition results in increased levels of sphinganine (or increased sphinganine:sphingosine ratio) in tissues and urine. Urinary sphinganine was increased in groups of males exposed to 163 ppm or greater, while urinary sphinganine was increased in all exposed groups of females.

The kidney weights, relative to body weight, of all exposed groups of rats were less than those of the control groups, decreasing by approximately 11% in the females and 20% in the males. Apoptosis and degeneration of the kidney were observed in all exposed males and in most females exposed to 163 ppm or greater. The incidences of minimal to mild apoptosis, degeneration, and mitotic alteration of the liver were significantly increased in 234 and 484 ppm males and in females exposed to 163 ppm or greater. The incidences of bile duct hyperplasia were significantly increased in males and females in the 484 ppm groups. In the core study, male rats in all exposed groups and females exposed to 163 ppm or greater had significantly increased percentages of hepatocytes in one or more proliferative (non-G_0) states.

28-Day Study in Mice

Groups of 12 male and 12 female mice were fed diets containing 0, 99, 163, 234, or 484 ppm fumonisin B_1 for 28 days. There were no exposure-related deaths in mice. The mean body weights of the 484 ppm groups of males were significantly less than those of the controls. Feed consumption by males exposed to 484 ppm was less than that by the controls; dietary concentrations of 99, 163, 234, and 484 ppm fumonisin B_1 resulted in average daily doses of approximately 19, 31, 44, and 93 mg/kg for males and 24, 41, 62, and 105 mg/kg for females.

Additional groups of male and female mice were exposed to the same concentrations of fumonisin B_1 for 28 days for clinical pathology studies. Cholesterol and total bile acid concentrations and alanine aminotransferase and alkaline phosphatase activities were increased at 484 ppm, indicating hyperlipidemia and a hepatic effect. Urinary sphinganine concentrations and sphinganine/sphingosine ratios were increased in 484 ppm male mice.

In 484 ppm males and all exposed groups of females, the incidences of hepatocellular necrosis, diffuse periportal hypertrophy, and diffuse centrilobular hyperplasia, as well as hyperplasia of the bile canaliculi and Kupffer cells, were generally significantly greater than those in the controls. Core study males exposed to 99, 163, or 234 ppm had significantly increased incidences of hepatocellular cytoplasmic alteration. Hepatocytes of 484 ppm male mice and all exposed groups of female mice were induced into proliferative (non-G_0) states.

2-Year Study in Rats

Groups of 48 male and 48 female rats (40 for 5 ppm groups) were fed diets containing 0, 5, 15, 50, or 150 ppm fumonisin B_1 (males) or 0, 5, 15, 50, or 100 ppm fumonisin B_1 (females) (equivalent to average daily doses of approximately 0.25, 0.76, 2.5, or 7.5 mg/kg to males and 0.31, 0.91, 3.0, or 6.1 mg/kg to females) for 105 weeks. Additional groups of four male and four female rats were exposed to the same concentrations as the core study animals and were evaluated at 6, 10, 14 or 26 weeks.

Survival, Body Weights, and Feed Consumption

Survival, mean body weights, and feed consumption of exposed male and female rats were generally similar to the controls throughout the study.

Clinical Pathology Findings

Sphinganine/sphingosine ratios were increased in the urine of 15, 50 and 150 ppm males and 50 and 100 ppm females exposed to fumonisin B_1 for up to 26 weeks. The sphinganine/sphingosine ratios were also increased in kidney tissue of 50 and 150 ppm males (85- and 119-fold) and 50 and 100 ppm females (7.8- and 22-fold) at 2 years.

Cell Proliferation Analyses

Renal tubule epithelial cell proliferation was increased in 50 and 150 ppm male rats exposed to fumonisin B_1 for up to 26 weeks. Renal tubule epithelial cell proliferation was marginally increased in 100 ppm females.

Organ Weights and Pathology Findings

Kidney weights of 50 and 150 ppm males were less than those of the controls at 6, 10, 14, and 26 weeks and at 2 years. Kidney weights of 100 ppm females were less than those of the controls at 26 weeks, and kidney weights of 15, 50, and 100 ppm females were less than those of the controls at 2 years.

At 2 years, there was a significant increase in the incidences of renal tubule adenoma from none in the groups receiving 15 ppm or less to five of 48 in 150 ppm males. Renal tubule carcinomas were not present in male rats receiving 15 ppm or less and occurred in seven of 48 and 10 of 48 male rats in the 50 and 150 ppm groups, respectively. Incidences of apoptosis of the renal tubule epithelium were generally significantly increased in males exposed to 15 ppm or greater for up to 26 weeks. The incidences of focal renal tubule epithelial hyperplasia were significantly increased in 50 and 150 ppm males at 2 years.

2-Year Study in Mice

Groups of 48 male and 48 female mice were fed diets containing 0, 5, 15, 80, or 150 ppm (males) or 0, 5, 15, 50, or 80 ppm (females) fumonisin B_1 (equivalent to average daily doses of approximately 0.6, 1.7, 9.7, or 17.1 mg/kg to males or 0.7, 2.1, 7.1, or 12.4 mg/kg to females) for 105 weeks. Additional groups of four male and four female mice were exposed to the same concentrations as the core study animals and were evaluated at 3, 7, 9, or 24 weeks.

Survival, Body Weights, and Feed Consumption

Survival of males and females in the 15 ppm groups and of 5 ppm females was significantly greater and survival of 80 ppm males and females was significantly less than that of the control groups. Mean body weights and feed consumption of exposed mice were generally similar to the controls.

Organ Weights and Pathology Findings

Liver weights, relative to body weight, were increased 1.3- and 2.9-fold in 50 and 80 ppm females at 2 years. At 2 years, the incidences of hepatocellular adenoma in 50 and 80 ppm females were significantly greater than those in the controls and occurred with a positive trend. Similarly, the incidences of hepatocellular carcinoma increased from none in the groups receiving 0, 5, or 15 ppm fumonisin B_1 to 10 of 47 females at 50 ppm and nine of 45 females at 80 ppm. The incidences of hepatocellular hypertrophy were significantly increased in 15, 80, and 150 ppm males and in 50 and 80 ppm females at 2 years. The incidences of hepatocellular apoptosis were significantly increased in 50 and 80 ppm females at 2 years.

Conclusions

Under the conditions of these 2-year feed studies, there was *clear evidence of carcinogenic activity** of fumonisin B_1 in male F344/N rats based on the increased incidences of renal tubule neoplasms. There was *no evidence of carcinogenic activity* of fumonisin B_1 in female F344/N rats exposed to 5, 15, 50, or 100 ppm. There was *no evidence of carcinogenic activity* of fumonisin B_1 in male B6C3F$_1$ mice exposed to 5, 15, 80, or 150 ppm. There was *clear evidence of carcinogenic activity* of fumonisin B_1 in female B6C3F$_1$ mice based on the increased incidences of hepatocellular neoplasms.

The sphinganine/sphingosine ratios were increased in the urine and the kidney tissue of rats receiving diets containing fumonisin B_1. There was evidence of apoptosis and increased cell proliferation of the renal tubule epithelium in exposed rats, particularly in those groups of males that developed renal tubule neoplasms. Increased incidences of hyperplasia of the renal tubule epithelium also occurred in these groups of male rats.

In mice exposed to the higher concentrations of fumonisin B_1, males and females had increased incidences of hepatocellular hypertrophy and females had increased incidences of hepatocellular apoptosis.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 10. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 12.

Summary of the 2-Year Carcinogenesis Studies of Fumonisin B_1

	Male F344/N Rats	**Female F344/N Rats**	**Male $B6C3F_1$ Mice**	**Female $B6C3F_1$ Mice**
Concentrations in feed	0, 5, 15, 50, or 150 ppm	0, 5, 15, 50, or 100 ppm	0, 5, 15, 80, or 150 ppm	0, 5, 15, 50, or 80 ppm
Body weights	Exposed groups similar to control group	Exposed groups similar to control group	Exposed groups similar to control group	Exposed groups similar to control group
Survival rates	16/48, 17/40, 25/48, 18/48, 25/48	25/48, 22/40, 24/48, 30/48, 29/48	41/48, 39/48, 45/48, 37/48, 42/48	35/48, 44/48, 46/48, 39/48, 28/48
Nonneoplastic effects	Kidney: renal tubule epithelial hyperplasia, focal (2/48, 1/40, 4/48, 14/48, 8/48)	None	Liver: hepatocellular hypertrophy (10/47, 9/47, 24/48, 25/48, 30/48)	Liver: hepatocellular hypertrophy (0/47, 0/48, 0/48, 27/47, 31/45); hepatocellular apoptosis (0/47, 0/48, 0/48, 7/47, 14/45)
Neoplastic effects	Kidney: renal tubule adenoma (0/48, 0/40, 0/48, 2/48, 5/48); renal tubule carcinoma (0/48, 0/40, 0/48, 7/48, 10/48); renal tubule adenoma or carcinoma (0/48, 0/40, 0/48, 9/48, 15/48)	None	None	Liver: hepatocellular adenoma (5/47, 3/48, 1/48, 16/47, 31/45); hepatocellular carcinoma (0/47, 0/48, 0/48, 10/47, 9/45); hepatocellular adenoma or carcinoma (5/47, 3/48, 1/48, 19/47, 39/45)
Level of evidence of carcinogenic activity	Clear evidence	No evidence	No evidence	Clear evidence

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

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

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

- **Clear evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a dose-related (i) increase of malignant neoplasms, (ii) increase of a combination of malignant and benign neoplasms, or (iii) marked increase of benign neoplasms if there is an indication from this or other studies of the ability of such tumors to progress to malignancy.
- **Some evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a chemical-related increased incidence of neoplasms (malignant, benign, or combined) in which the strength of the response is less than that required for clear evidence.
- **Equivocal evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a marginal increase of neoplasms that may be chemical related.
- **No evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing no chemical-related increases in malignant or benign neoplasms.
- **Inadequate study** of carcinogenic activity is demonstrated by studies that, because of major qualitative or quantitative limitations, cannot be interpreted as valid for showing either the presence or absence of carcinogenic activity.

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

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

NATIONAL TOXICOLOGY PROGRAM BOARD OF SCIENTIFIC COUNSELORS TECHNICAL REPORTS REVIEW SUBCOMMITTEE

The members of the Technical Reports Review Subcommittee who evaluated the draft NTP Technical Report on fumonisin B_1 on 21 May 1999 are listed below. Subcommittee members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, subcommittee members have five major responsibilities in reviewing the NTP studies:

- to ascertain that all relevant literature data have been adequately cited and interpreted,
- to determine if the design and conditions of the NTP studies were appropriate,
- to ensure that the Technical Report presents the experimental results and conclusions fully and clearly,
- to judge the significance of the experimental results by scientific criteria, and
- to assess the evaluation of the evidence of carcinogenic activity and other observed toxic responses.

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SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

On 21 May 1999, the draft Technical Report on the toxicology and carcinogenesis studies of fumonisin B_1 received public review by the National Toxicology Program's Board of Scientific Counselors' Technical Reports Review Subcommittee. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Dr. J.R. Bucher reported that the 2-year studies on fumonisin B_1 were the first to come to the Subcommittee for peer review under an Interagency Agreement signed in 1992 between the Food and Drug Administration (FDA) and the National Institute of Environmental Health Sciences (NIEHS) to support the performance of studies evaluating the toxicology and carcinogenic activity of chemicals and agents that were primarily of interest to the FDA.

Dr. P.C. Howard, NCTR, introduced the toxicology and carcinogenesis studies of fumonisin B_1 by noting that fumonisin B_1 is the most prevalent of a number of fungal metabolites of the *Fusaria* species found primarily on corn in the United States and around the world and reporting on the principal mode of action of fumonisin B_1 in interrupting sphingolipid synthesis. Dr. Howard then described the experimental design for 28-day and 2-year studies in rats and mice, including clinical chemistry indicators of hepatotoxicity, renal toxicity, sphingolipid metabolism, and measures of apoptotic activity. He reported on survival and organ and body weight effects and commented on compound-related neoplastic lesions in male rats and female mice and nonneoplastic lesions in male rats and male and female mice. The proposed conclusions for the 2-year studies were *clear evidence of carcinogenic activity* in male F344/N rats, *no evidence of carcinogenic activity* in female F344/N rats, *no evidence of carcinogenic activity* in male B6C3F$_1$ mice, and *clear evidence of carcinogenic activity* in female B6C3F$_1$ mice.

Dr. Fischer, a principal reviewer, agreed with the proposed conclusions. She asked for better definition of the core study group and the additional animals including which animals were being used for which part of the studies. Dr. Howard explained that the core animals were fed continuously for 28 days while the other animals were fasted overnight at intervals for collection of urine or blood, and this distinction would be clarified. Dr. Fischer thought the Abstract would be more complete if information were added indicating that fumonisin B_1 is an inhibitor of ceramide synthase and that this is responsible for the biological consequences of fumonisin B_1 exposure. Dr. Howard agreed. Dr. Fischer noted that because there are major species differences in response to fumonisin B_1 with regard to the particular target tissue affected there should be more discussion about the relevance of all of these animal studies to humans. Dr. Howard commented that the mechanisms of action of these different target organ effects are not well understood, and further, there is no validated biomarker for human exposure, so the relevance of animal to human findings would be hard to discern at this point.

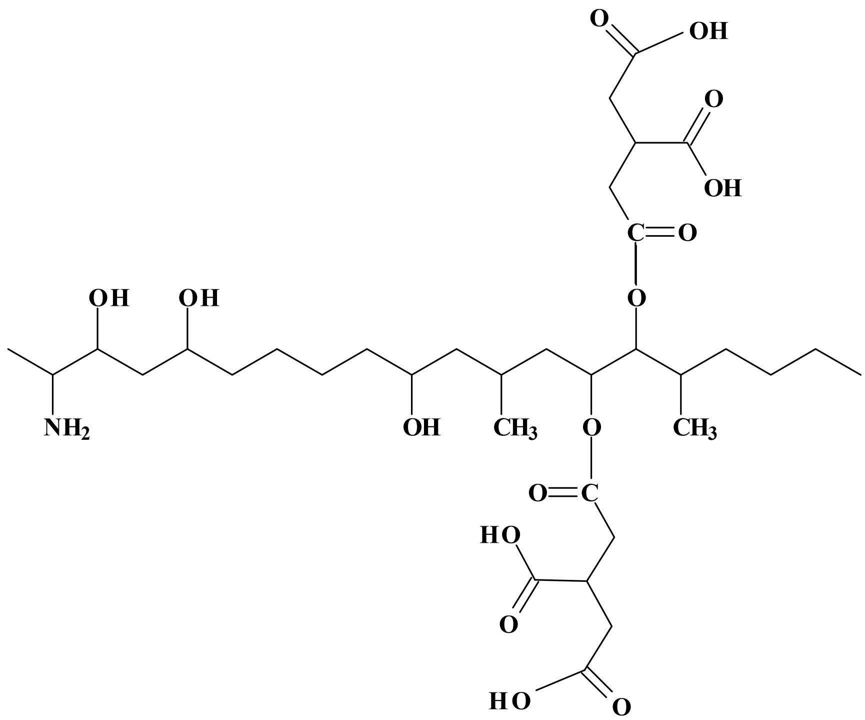
Dr. Bailer, the second principal reviewer, agreed with the proposed conclusions although he thought the increases of the incidences of alveolar/bronchiolar adenoma or carcinoma (combined) in female rats should be listed as an uncertain finding in the Abstract. Dr. Howard said that the 2% incidence in the high exposure group was not considered a significant enough increase, although this could be argued by some as fitting "equivocal evidence." Dr. Bailer questioned not doing complete histopathology on some of the mid exposure groups, clearly decreasing the sensitivity of detecting tumor onset and trend with a loss of dose-response information. Dr. Howard responded that this was the protocol agreed on for the study. However, knowing that liver and kidney were likely target organs, these organs were examined from intermediate exposure groups as well, and of course, animals dying before terminal sacrifice had complete histopathology, regardless of exposure group. Dr. Bucher commented that where there is good interaction among pathologists, study directors, and the test laboratory, there is always the ability to go back and cut in tissues as needed. Dr. Carlson commented that in view of toxicity to heart, lung, and esophagus in other species, one could argue that there should have been complete histopathology on these organs. Dr. Bailer said that incomplete histopathology may have led to some bizarre neoplasm patterns, e.g., the tumor burden for harderian gland adenomas or carcinomas in male mice. Dr. R.L. Kodell, NCTR, said that his opinion was that intermediate dose group data from animals dying before terminal sacrifice should not be used in a statistical analysis.

Dr. Davis, the third principal reviewer, agreed with the proposed conclusions. He had some concerns about the exposure concentration selection noting the lack of tumor response in female rats and male mice and the statement that female rats could have tolerated a higher exposure concentration. Dr. Howard responded that exposure concentrations for the 2-year study were selected based on multiple issues including the hepatotoxicity, nephrotoxicity, and literature information on mechanisms of target organ toxicity. Further, Dr. Davis criticized not doing 90-day studies in conjunction with the 2-year bioassay while relying on 90-day studies done by Voss *et al.* (1993). Dr. Howard stated that it was discussed whether or not to conduct another 90-day study, but since the study by Voss *et al.* (1993) was conducted with test material provided by the NTP and was under NTP guidance, the study was considered adequate for moving ahead to a 2-year study. Dr. Davis also expressed concern about the underfeeding by 30% of the mice in the 2-year study. Dr. Howard explained that the doses in the feed were accurate, but the mice consumed 30% less feed. As a partial explanation, it was realized about nine months into the study that the mice weighed less than the average NTP mouse at that point. The decision was made to continue the study. Dr. Howard said that a factor in the decision not to stop and restart was the cost of the material, $40,000 a gram, and the lengthy time (years) required to purify it.

In other discussion, Dr. Russo asked what human doses from contaminated corn would be in relation to 100 ppm doses in animals. Dr. Howard reported that in South Africa where esophageal cancer is seen and where corn is an everyday staple in the diet, estimates of human intake are around 0.2 mg/kg per day which is within a couple of orders of magnitude of the animal dose. Dr. Russo asked whether there were any pathologic changes in the esophagi of study animals. Dr. Howard responded that there were not, which is at variance with other reported rat studies in which hyperplasia was reported. Dr. Hecht stated that at least 50 nitrosamines can induce esophageal tumors in rats, which suggests that fumonisin B_1 may not be the agent responsible for esophageal cancer in humans. Dr. Howard acknowledged the possible presence of nitrosamines in fungally contaminated corn. He concluded that a proper epidemiological study has not yet been done with fumonisin; rather the best studies available are correlative.

Dr. Fischer moved that under the conditions of this study the Technical Report on fumonisin B_1 be accepted with revisions discussed and the conclusions as written for male rats and female mice, *clear evidence of carcinogenic activity*, and for females rats and male mice, *no evidence of carcinogenic activity*. Dr. Davis seconded the motion, which was accepted unanimously with eight yes votes. Drs. Bailer and Bus were not present for the vote.

INTRODUCTION



FUMONISIN B_1

CAS No. 116355-83-0

Chemical Formula: $C_{34}H_{59}NO_{15}$ Molecular Weight: 721.838

Synonyms: 1,2,3-Propanetricarboxylic acid, 1,1′-[1-(12-amino-4,9,11-trihydroxy-2-methyltridecyl)-2-(1-methylpentyl)-1,2-ethanediyl]ester; macrofusin

Chemical and Physical Properties

Fumonisin B_1 is a colorless powder that is hygroscopic and apparently stable in ultraviolet light. Fumonisin B_1 is stable at 75° C for 135 minutes or 125° C for 5 minutes (Dupuy *et al*., 1993), or at 78° C in solution between pH 4.8 and 9 (Howard *et al*., 1998). The tricarballylic acid groups are hydrolyzed in the presence of 2 N KOH at 70° C for 1 hour (Norred *et al*., 1992a). Fumonisin B_1 does not decompose in corn ammoniated to 2% (Norred *et al*., 1991).

No report concerning the pKs of fumonisin B_1 has been found in the available literature. The pKa values for tricarballylic acid are 3.49, 4.56, and 5.83. The aliphatic amine group would be expected to have a pK greater than 9; therefore, fumonisin B_1 will be a zwitterion at physiological pHs between 6 and 9.

Nuclear magnetic resonance, infrared, and mass spectra data to allow identification of fumonisin B_1 (tetramethyl ester) are given in Bezuidenhout *et al*. (1988) and Savard and Blackwell (1994). Fractionation schemes for the identification, isolation, and purification of fumonisin B_1 are given in Bezuidenhout *et al*. (1988), Shepherd *et al*. (1990, 1992a), Vesonder *et al*. (1990), Ackerman (1991), Cawood *et al*. (1991), Thiel *et al*. (1991a), and Scott and Lawrence (1992).

PRODUCTION, USE, AND HUMAN EXPOSURE

Fumonisin B_1 is available for experimental use as a powder (free acid) from several commercial sources (e.g., Sigma Chemical Co., Cayman Chemical Co.). All commercially available fumonisin B_1 has been purified from cultures of *Fusarium* fungi (Alberts *et al*., 1990, 1994; Cawood *et al*., 1991; Miller *et al*., 1994; Cahagnier *et al*., 1995). Other than experimental use, there are no known commercial or medical uses of fumonisin B_1. Radiolabeled fumonisin B_1 has been produced in solid (Plattner and Shackelford, 1992; Shepherd *et al*., 1992a; Alberts *et al*., 1993) and liquid cultures (Miller *et al*., 1994) of *Fusarium* fungi.

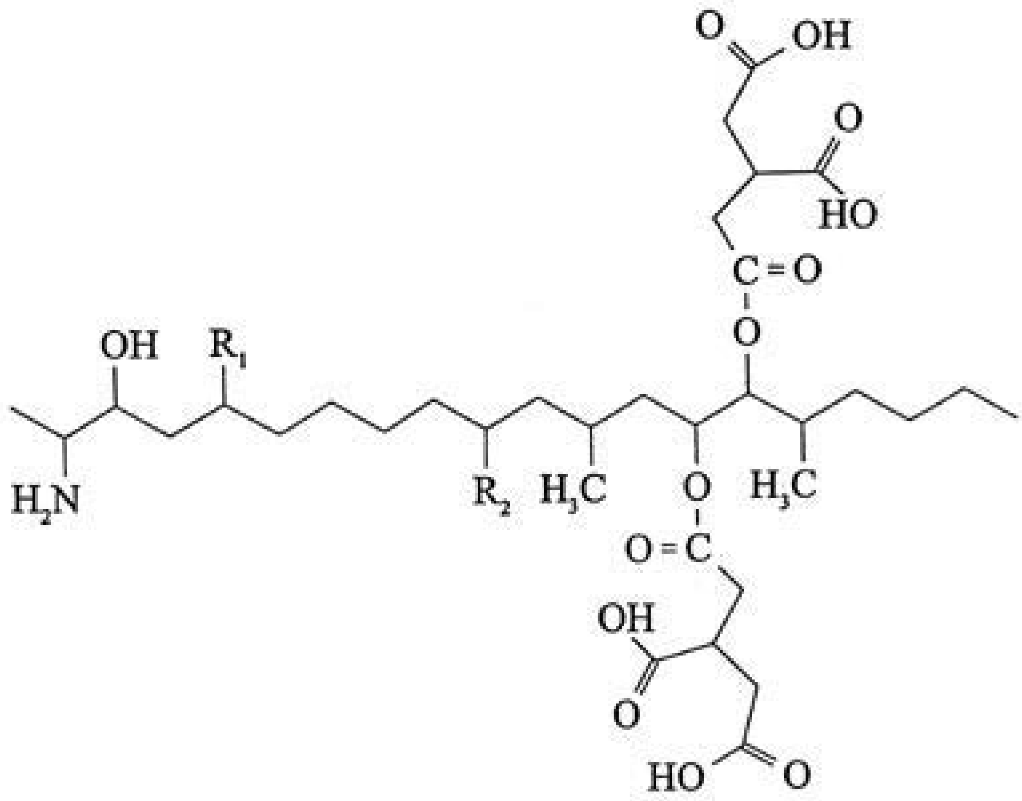
Several different fumonisins have been isolated and structurally identified (Bezuidenhout *et al*., 1988; Plattner *et al*., 1992; Scott, 1993). The structures of the fumonisins B are given in Figure 1, and they differ based on the hydroxyl groups at C4, C5, and C10. *N*-Acetyl derivatives of the fumonisins exist and have been referred to as fumonisins A_1 and A_2 (Bezuidenhout *et al*., 1988). A fumonisin lacking the C1 methyl group was isolated from liquid cultures of *Fusarium moniliforme* and termed fumonisin C_1 (Branham and Plattner, 1993).

Fumonisin B_1 is a secondary metabolite of fungi of the *Fusarium* genus and has been found in several strains including *F. anthophilum, F. dlamini,* and *F. napiforme* (Nelson *et al*., 1992); *F. moniliforme* Sheld, *F. proliferatum*, and *F. nygamai* (Thiel *et al*., 1991b; Nelson, 1992; Norred, 1993; Bullerman and Tsai, 1994; Meireles *et al*., 1994); *F. oxysporum* (Abbas *et al*., 1995); and *F. polyphialidicum* (Abbas and Ocamb, 1995) and the A-mating population of *Gibberella fujikori* (Leslie *et al*., 1992a,b; Desjardins *et al*., 1994). The particular species of fungus that will contaminate corn in a geographic region will differ; however, the contamination of corn with fumonisin B_1 is predominantly through contamination with *F. moniliforme.*

Several reports have described the occurrence of fumonisin B_1 in feed and foodstuffs derived from maize, and an excellent summary was published by Dutton (1996). A summary of reported detection of fumonisin B_1 in corn or corn products is provided in Table 1. Fumonisins seem to be present in the majority of maize-derived products, with a wide variation in the occurrence depending on the maize product, geographical location, and local weather. For instance, approximately 90% of maize from South Africa had detectable fumonisin B_1 with a wide range of contamination (0 to 118 ppm). Gelderblom *et al*. (1988a) sampled corn from an esophageal cancer endemic area of Kentani, Transkei, South Africa, and out of 10 households, an average of 63% of the corn kernels (range, 34%-94%) were infected with *F. moniliforme*. In the United States, fumonisin B_1 was found in all 10 corn grit samples and 15 of 16 corn meal samples from grocers' shelves at mean levels of 0.6 and 1 ppm, respectively, whereas no fumonisins were detected in three cornflake cereals (Sydenham *et al*., 1991). Using canned and frozen sweet corn, Trucksess *et al*. (1995) detected fumonisin B_1 at maximum levels of 0.2 and 0.4 ppm, respectively, in 35 of 97 samples.

The average daily consumption of fumonisin B_1 in the diet in the United States has not been determined accurately. This is due to the widely variable occurrence of fumonisin B_1 in corn-based products and the wide range of corn-based products in the diet.

The highest levels of contamination in corn products are in milled corn that is destined for animal feed. The germ of the corn kernel is used in the production of products for human consumption, while the tip is primarily used in animal feed (referred to as screenings). In the United States, several investigators have measured the levels of fumonisin B_1 in corn screenings or feed, and almost all samples have been found to have detectable fumonisin B_1 concentrations (Plattner *et al*., 1990; Wilson *et al*., 1990; Ross *et al*., 1991a; Thiel *et al*., 1991b; Murphy *et al*., 1993; Price *et al*., 1993). The highest concentration of fumonisin B_1 in maize-containing animal feed was 209 ppm (Ross *et al*., 1991a) with a mean of 12 ppm and a 70-fold range in the samples surveyed in 1991 (Price *et al*., 1993).



Fumonisin B_1: R_1 = OH, R_2 = OH
Fumonisin B_2: R_1 = OH, R_2 = H
Fumonisin B_3: R_1 = H, R_2 = OH

FIGURE 1
Structures of Fumonisins B

TABLE 1
Occurrence of Fumonisin B_1 in Maize and Maize Products

Geographic Region	Positive Samples/ Total Samples	Highest Fumonisin B_1 Level Detected (ppm)	Reference
Argentina	16/17	2	Sydenham *et al*., 1993
Austria	3/9	<15	Lew *et al*., 1991
Benin	9/11	2.3	Doko *et al*., 1995
Brazil	20/21	38.5	Sydenham *et al*., 1992
Canada	1/2	0.05	Sydenham *et al*., 1991
China	5/20	1.7	Yoshizawa *et al*., 1994
	31/31	155	Chu and Li, 1994
Croatia	11/19	0.07	Doko *et al*., 1995
Egypt	2/2	2.4	Sydenham *et al*., 1991
France	95/100	50	LeBars and LeBars, 1995
Honduras	24/24	6.6	Julian *et al*., 1995
Hungary	36/56	334	Fazekas and Tothe, 1995
Italy	?	5.3	Doko *et al*., 1995
Japan	14/17	2.6	Ueno *et al*., 1993
Korea	5/12	1.3	Soo *et al*., 1994
Nepal	12/24	4.6	Ueno *et al*., 1993
Peru	1/2	0.7	Sydenham *et al*., 1991
Poland	2/7	0.03	Doko *et al*., 1995
Portugal	9/9	3.5	Doko *et al*., 1995
Romania	3/6	0.03	Doko *et al*., 1995
Sardinia	6/6	250	Bottalico *et al*., 1995
South Africa	1/1	83	Sydenham *et al*., 1990a
	39/49	47	Sydenham *et al*., 1990b
	10/10	1.9	Sydenham *et al*., 1994
	24/27	118	Rheeder *et al*., 1992
	187/249	7.1	Rheeder *et al*., 1995
Spain	8/50	0.08	Sanchis *et al*., 1994
Switzerland	44/120	0.8	Pittet *et al*., 1992
United States	25/26	1	Sydenham *et al*., 1991
	35/97	0.4	Trucksess *et al*., 1995
	23/28	0.3	Chamberlain *et al*., 1993
	44/160	38	Murphy *et al*., 1993
Zambia	20/20	1.7	Doko *et al*., 1995

One phenomenon that may explain the variability of fumonisin B_1 contamination of maize products is that, under identical conditions, different isolates of *F. moniliforme* are capable of synthesizing differing amounts of fumonisin B_1 (Thiel *et al*., 1991b). Nelson *et al*. (1991) collected 90 isolates of *F. moniliforme* from corn and corn screenings and subsequently produced fumonisin B_1 in identical and ideal conditions. The isolates contained the following amounts of fumonisin B_1 after optimal growth on sterilized corn: corn-based feed associated with outbreaks of leukoencephalomalacia, mean of 1,763 ppm (range, 0-6,090 ppm); Nigerian and Zimbabwean sorghum and millet grain, mean of 380 ppm (range, 0-2,448 ppm); corn-based laboratory rat feed samples from the United States, mean of 385 ppb (range, 10-825 ppb); Nepalese corn kernels, mean of 651 (range, 0-6,397); Australian sorghum, corn, sugarcane, and soil, only trace amounts; good quality poultry corn from Maryland, Pennsylvania, and Virginia, mean of 1,851 ppm (range, 459-3,091 ppm); corn silks from Iowa, mean of 1,817 ppm (range, 310-3,482 ppm).

Sydenham *et al*. (1991) investigated the occurrence of fumonisins B_1 and B_2 in corn-based foodstuffs (cornmeal, corn grits, cornflakes, and others) from the Transkei region of South Africa. The area with low incidences of esophageal cancer in 1985 averaged

1.6 ppm fumonisin B_1 (range, 0.5-7.9 ppm), while in 1988 these values had decreased slightly to 1.53 ppm fumonisin B_1 (range, 0.21-5.38 ppm). In the high esophageal cancer incidence area of Transkei, the average value in 1985 was 29.3 ppm fumonisin B_1 (range, 3.45-46.9 ppm), increasing by 1988 to 53.74 ppm fumonisin B_1 (range, 3.02-117.52 ppm).

It should be emphasized that the fungus *F. moniliforme* produces several cytotoxic compounds other than the fumonisins. Some of these mycotoxins have the potential for genotoxic, cytotoxic, hormonal, or tumor-promoting activity. These include the fusarins, moniliformin, bikaverin, 8-hydroxy-methyljavanicin, zearalenone, fusaric acid, 10,11-dihydroxyfusaric acid, fusaric diacid, fusariocin C, fusarubin, ipomeanine, 3-ipomeanol, and the trichothecenes such as T-2 toxin, diacetoxyscirpenol, trichothecolon, diplodiatoxin, neosolaniol, and scirpentriol (Cole *et al*., 1973; Ito, 1979; Thiel *et al*., 1982; Burmeister *et al*., 1985; Brückner *et al*., 1989; Vesonder *et al*., 1989; Hassanin and Gabal, 1990). Structurally related heptadecapentol toxins are produced by *Alternaria alternata* f. sp. *lycopersici*, which causes stem canker disease in tomatoes (Bottini and Gilchrist, 1981; Bottini *et al*., 1981), and by *Alternaria alternata* (Fr.) Keissler, which contaminates sunflower seeds (Torres *et al*., 1993). Zearalenone has been associated with hormonal effects (primarily estrogenic) of *F. moniliforme* infections since 1926 (Gordon, 1960; Nelson *et al*., 1973; Ueno and Ueno, 1978). The cocontamination of corn with aflatoxin B_1 and fumonisin B_1 has been reported in the United States and China (Chamberlain *et al*., 1993; Chu and Li, 1994), and *F. moniliforme* isolated from households in China produced nitrosamines in culture (Chu and Li, 1994). As a result, the contamination of corn with *F. moniliforme* may possibly lead to coingestion of other toxins along with fumonisin B_1.

Pharmacokinetic studies (see next section) have shown that fumonisin B_1 is poorly absorbed from the diet. The absorbed fumonisin B_1 is quickly excreted into the feces in the bile, while some remains in the liver and kidney. Therefore, although the possibility of fumonisin B_1 exposure through ingestion of organ meat from animals exposed to fumonisin B_1 cannot be ruled out, this route of exposure would appear to result in minimal exposure given the pharmacokinetics of fumonisin B_1.

There have been several reports on the concentrations of fumonisin B_1 in dairy milk. Scott *et al*. (1994) administered single doses of fumonisin B_1 to dairy cattle at 1 to 5 mg/kg body weight *per os*, or 0.05 to 0.20 mg/kg body weight intravenously. They were unable to detect fumonisin B_1 in the milk of any of the animals. In a survey of 165 milk samples, Margos and Richard (1994) detected fumonisin B_1 (1.3 µg/L) in only one sample. It would seem apparent from these limited studies that consumption of milk is not a significant source of fumonisin B_1 in the human diet. Additionally, the observation that dairy cattle do not excrete fumonisin B_1 in their milk suggests that human neonatal exposure to fumonisin B_1 through maternal milk is a minimal risk.

Fumonisin B_1 levels in some foods change as a result of the cooking process. Jackson *et al*. (1997) showed that up to 43% of fumonisin B_1 spiked in corn meal was lost after baking at 175° to 200° C for 20 minutes. The spiked fumonisin B_1 also decreased in a time- and temperature-dependent manner following the frying of corn chips in soybean oil. Several reports have suggested that the amino group of fumonisin B_1 could react with sugars in foods to form a Schiff's base (Murphy *et al*., 1995; Lu *et al*., 1997). Indeed, Howard *et al*. (1998) characterized *N*-(carboxymethyl)-fumonisin B_1 as a product following the heating of fumonisin B_1 with reducing sugars. *N*-(carboxymethyl)-fumonisin B_1 is formed through sequential Schiff's base formation, an Amadori rearrangement, and oxidative cleavage. *N*-(carboxymethyl)-fumonisin B_1 has been detected in field corn at approximately 4% of the fumonisin B_1 levels (Howard *et al*., 1998).

Fumonisin B_1 can be hydrolyzed during the processing of tortillas. Maza meal is made using calcium hydroxide (nixtamalization), and these alkaline conditions can hydrolyze the tricarballylic acid groups on fumonisin B_1 resulting in the formation of fumonisin aminopentol (Hendrich *et al*., 1993). At present, there are conflicting reports on the relative toxicity of the aminopentol when compared to fumonisin B_1 (Hendrich *et al*., 1993; Voss *et al*., 1996a).

In conclusion, the greatest probable source of fumonisin B_1 exposure for humans is through direct consumption of corn products. The levels of contamination of the corn will differ each year based on fungal growth conditions (e.g., moisture during the growing season). The overall exposure of humans to fumonisin B_1 will depend on the level of contamination, the portion of the diet that is corn or corn-based products, and the cooking habits within each household (e.g., nixtamalization).

ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION

Experimental Animals

Fumonisin B_1 is not readily absorbed from the gastrointestinal tract, which is probably due to the hydrophilic nature of the molecule. No studies have been reported that directly address dermal or pulmonary absorption of fumonisin B_1.

The pharmacokinetics of fumonisin B_1 were studied following intraperitoneal or gavage administration of 7.5 mg unlabeled fumonisin B_1/kg body weight to male BD-IX rats (Shepherd *et al*., 1992b). Fumonisin B_1 was rapidly absorbed from the peritoneal cavity (T_{max} approximately 20 minutes; C_{max}=8.6 µg/mL) and showed a serum half-life of 18 minutes with a one-compartment model for elimination (V_D=132 mL; k_e=0.039/minute). In subsequent studies, Shepherd *et al*. (1992c) administered 7.5 mg/kg [^{14}C]-fumonisin B_1 (28 mCi/mol) by gavage or intraperitoneal injection to male BD-IX rats. After 24 hours, 66% of the intraperitoneal dose and 101% of the gavage dose was recovered in the feces of the rats. In the rats treated intraperitoneally, 32% of the dose was collected in the urine and 1% remained in the liver with trace levels in the kidney and red blood cells. In the gavaged rats, only trace levels were detected in the urine, liver, kidney, and red blood cells, and no ^{14}C was detected in the plasma, heart, or brain. Analysis of the radiolabel excreted in the feces revealed that the majority of the ^{14}C excreted into the feces was unchanged fumonisin B_1.

Shepherd *et al*. (1994a) extended these studies and showed that [^{14}C]-fumonisin B_1 was excreted rapidly into the bile following intraperitoneal injection in rats. Male Wistar rats were cannulated at the bile duct and injected with 7.5 mg/kg [^{14}C]-fumonisin B_1. Approximately 67% of the dose was recovered in the bile within 24 hours, and 88% of this was excreted within the first 4 hours. In contrast, gavage administration of [^{14}C]-fumonisin B_1 resulted in the recovery of only 0.2% of the dose in the bile in 24 hours. This suggests that in the rat, minimal enterohepatic circulation occurs.

Norred *et al*. (1993) studied the toxicokinetics of [^{14}C]-fumonisin B_1 in male Sprague-Dawley rats following intragastric or intravenous administration of 0.045 or 0.0045 µCi/rat, respectively (unspecified amount of fumonisin B_1). In the intragastrically dosed animals, 82% of the dose was excreted in the feces within 48 hours, and 4% was eliminated in the urine. For up to 96 hours postadministration, the blood contained 0.2%, the liver 0.4%, and the kidneys 0.1% of the administered dose. In the animals dosed intravenously, the liver contained 24%, 43%, and 25% of the dose after 10 minutes, 1 hour, and 48 hours, respectively. Blood concentrations declined to 6% of the administered dose in 30 minutes, and were maintained at 1% to 2% thereafter. After 48 hours, 19% of the dose was excreted in the feces and 11% in the urine. These results demonstrated that fumonisin B_1 is poorly absorbed from the stomach and/or intestines and that when fumonisin B_1 enters the blood, it can be eliminated through the biliary system into the feces or it can be excreted via the kidneys into the urine.

In a subsequent study, Voss *et al*. (1996b) determined the distribution of radiolabel in pregnant Sprague-Dawley rats 1 hour after intravenous administration of 330 µg [^{14}C]-fumonisin B_1/kg body weight on gestation day 15. Although this study was not designed to determine the pharmacokinetics of [^{14}C]-fumonisin B_1, the study demonstrated that [^{14}C]-fumonisin B_1 did not cross the placenta because no radiolabel was detected in the fetuses. Approximately 45% of the dose was recovered in the gastrointestinal tract of the dams, while 14% and 4% were recovered in the liver and kidney, respectively.

Shepherd *et al*. (1994b) analyzed the excretion of fumonisin B_1 and metabolites from female vervet monkeys administered 8 mg [^{14}C]-fumonisin B_1/kg body weight by gavage. These authors determined that [^{14}C]-fumonisin B_1 and the products of hydrolysis of the tricarballylic acid groups are excreted into the feces. Therefore, it seems apparent that the only metabolism of fumonisin B_1 that occurred was ester hydrolysis to the less polar aminopentol.

The pharmacokinetics of fumonisin B_1 has been determined in Holstein cows (Prelusky *et al*., 1995). Cows were administered 50 or 200 µg fumonisin B_1/kg body weight intravenously or 1 or 5 mg/kg by gavage. Intravenously administered fumonisin B_1 was cleared from the plasma with biphasic half-lives consisting of a rapid compartment (approximately 2 minutes) and a slow compartment with half-lives of 15.1 and 18.7 minutes for the low and high doses, respectively. The volume of distribution suggested that fumonisin B_1 remained in the extracellular compartment and was not distributed to extravascular tissues. Gavage administration of fumonisin B_1 did not result in the detection of fumonisin B_1 in the blood, suggesting that less than 0.5% to 1% of the fumonisin B_1 was absorbed.

Humans

No reports on the absorption, distribution, metabolism, or excretion of fumonisin B_1 in humans were found in the literature.

TOXICITY

An apparent mechanism of action of fumonisin B_1 is the interruption of sphingolipid synthesis in cells (Riley *et al*., 1996, 1998; Merrill *et al*., 1997). This discovery was the first description of an inhibitor of the pathway for ceramide and sphingolipid synthesis and has led to the discovery of other inhibitors and considerable research into the roles of cellular sphingolipids in cellular homeostasis. Cellular sphingolipids are biosynthesized through a multiple-enzyme pathway in several cellular compartments. The first enzyme in the pathway is serine palmitoyl transferase, which utilizes serine and palmitoyl coenzyme A to produce 3-ketosphinganine (Figure 2) (Sribney, 1966; Kishimoto and Kawamura, 1979). Inhibitors of this enzyme include β-fluoroalanine, 3-chloroalanine, cycloserine, and ISP-1 (Miyake *et al*., 1995; Nakamura *et al*., 1996; Yoo *et al*., 1996). Serine palmitoyl transferase has been purified to homogeneity, and the gene for this enzyme from mice and yeast is known (Mandon *et al*., 1992; Nagiec *et al*., 1994, 1996). The second step in the synthesis of sphingolipids is the reduction of 3-ketosphinganine to sphinganine by 3-ketosphinganine reductase (Stoffel *et al*., 1968). Neither this enzyme nor the corresponding coding gene has been isolated. The third enzyme in the sphingolipid pathway is ceramide synthase (sphinganine *N*-acyl transferase), which catalyzes the transfer of fatty acyl groups to the amino group of sphinganine, forming a dihydroceramide (e.g., *N*-palmitoylsphinganine). This enzyme is inhibited by fumonisin B_1 and appears to catalyze the biologic consequences of fumonisin B_1 exposure. Neither ceramide synthase nor its gene has been identified, although several laboratories have attempted purification of the enzyme (Morell and Radin, 1970; Narimatsu *et al*., 1986; Mandon *et al*., 1992; Shimeno *et al*., 1995). At some point in the metabolism of sphingolipids, the dihydroceramides (e.g., *N*-palmitoylsphinganine) are reduced to ceramides (e.g., *N*-palmitoylsphingosine) via dihydroceramide desaturase.

Ceramides are converted to sphingomyelins via the Golgi complex enzyme phosphatidylcholine:ceramide choline phosphotransferase, which catalyzes the coupling of phosphocholine from phosphatidylcholine to the C1 hydroxyl group on the ceramide (Mathias and Kolesnick, 1993). Additionally, ceramides are used in the synthesis of gangliosides via glucosyl- and galactosyl transferases (Sandhoff and Van Echten, 1993). These complex molecules play an important role in cell membrane function, and their depletion has been suggested as a mechanism for fumonisin action (Yoo *et al*., 1996; Stevens and Tang, 1997; Tolleson *et al*., 1999). It is evident that regulation of the levels of the complex sphingolipids is important because inability to enzymatically degrade specific complex sphingolipids results in developmental and neurological disorders such as Krabbe’s, Fabry’s, Gaucher’s, Farber’s, and Niemann-Pick’s diseases.

Tissue Culture Cells

Wang *et al*. (1991) first observed that fumonisins are structurally related to sphingosine and proposed that the mechanism for fumonisin toxicity might be alterations in sphingomyelin synthesis, affecting production of sphingomyelin, cerebrosides, sulfatides, and gangliosides. To test this hypothesis, the authors demonstrated that the administration of fumonisin B_1 to cultured primary hepatocytes grown in [^{14}C]-serine resulted in increased intracellular levels of [^{14}C]-sphinganine. In further studies with rat liver microsomes and intact hepatocytes, the authors demonstrated that fumonisin B_1 inhibited the sphingosine *N*-acyl transferase-mediated conversion of [^{3}H]-sphinganine to [^{3}H]-dihydroceramide, or [^{3}H]-sphingosine to [^{3}H]-ceramide. As a result of these studies, the authors suggested that the mechanism of action of fumonisin toxicity is interruption of sphingolipid biosynthesis.

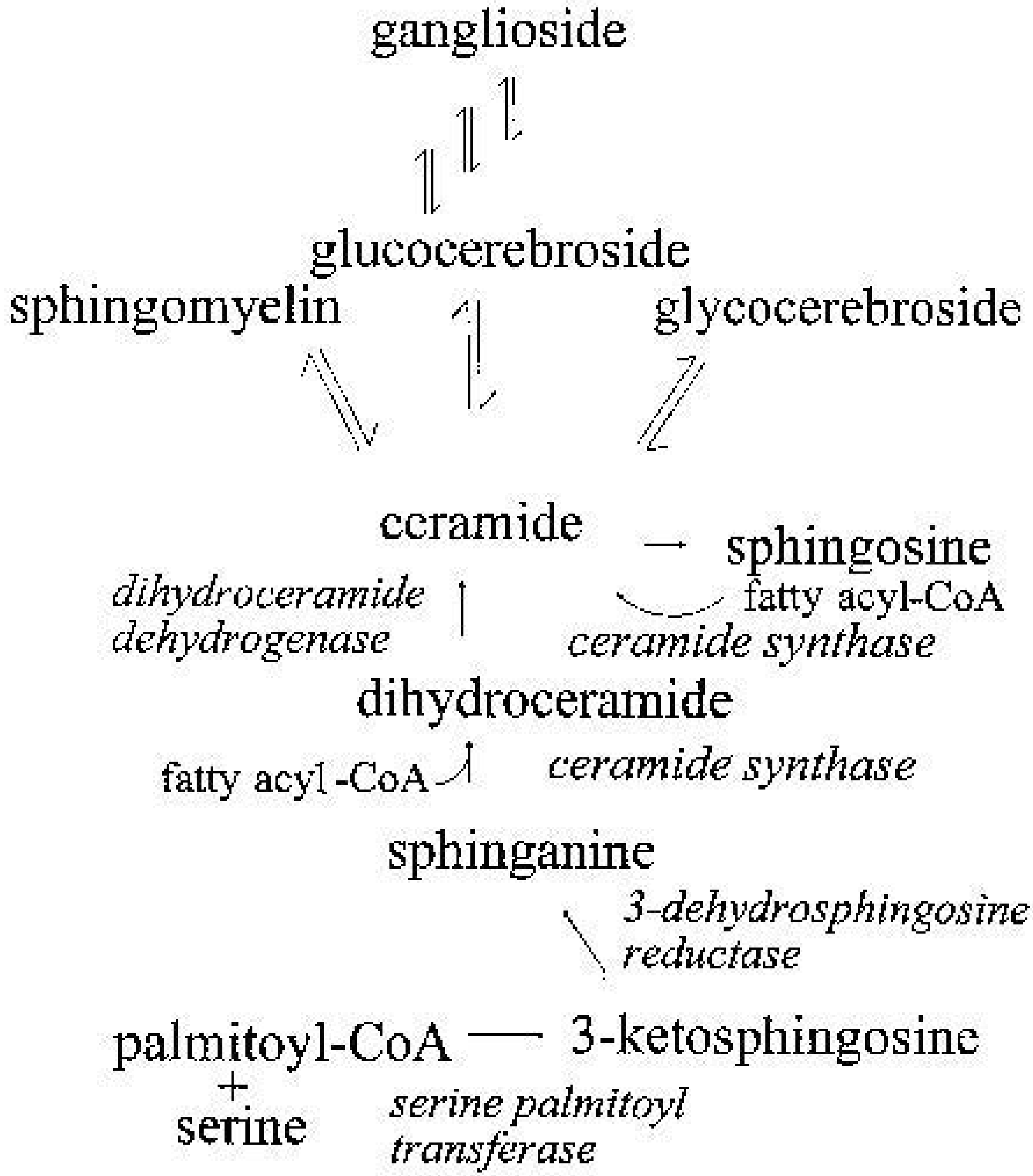


FIGURE 2
Biosynthesis of Cellular Sphingolipids

In subsequent studies by Yoo *et al*. (1992), the fumonisin B_1-based inhibition of sphingolipid synthesis in cultured pig renal epithelial LLC-PK_1 cells was investigated. Fumonisin B_1 (35 μM) inhibited the growth of these nonconfluent cells in a dose-dependent and reversible manner. Low concentrations of fumonisin B_1 (10 to 35 μM) inhibited the incorporation of [^{3}H]-serine into sphingosine, resulting in an accumulation of [^{3}H]-sphinganine, indicating that fumonisins inhibit microsomal ceramide synthase. While the *N*-acetyl transferase inhibition was very rapid, the inhibition of cell proliferation was delayed by 1 to 2 days.

Using LLC-PK_1 cells, Yoo *et al*. (1996) were able to demonstrate that fumonisin B_1 treatment of cells in culture resulted in decreased cell growth, increased release of lactate dehydrogenase into the tissue culture medium, increased intracellular sphinganine (measured as sphinganine/sphingosine ratio), and decreased cellular complex sphingolipid levels. The role of increased intracellular sphinganine levels in the toxicity of fumonisin B_1 was suggested by studies in which the fumonisin B_1 toxicity could be partially inhibited by inclusion of β-fluoroalanine, an inhibitor of serine palmitoyl transferase (Yoo *et al*., 1996).

In studies supported by the NIEHS/FDA research effort, Tolleson *et al*. (1996) demonstrated that administration of fumonisin B_1 to several types of cultured human cells resulted in an increased sphinganine/sphingosine ratio and that this was followed by apoptotic cellular death. The apoptosis was confirmed by several methods including electron microscopy, morphologic changes in the cells, and the production of DNA fragments. There was no evidence of necrosis in the cells. Apoptosis was induced in human cells in culture whether the cells were primary or human papilloma virus immortalized keratinocytes, SV40 large T-antigen immortalized esophageal epithelial cells, or human hepatoblastoma cells (Tolleson *et al*., 1996).

In another study supported by the NIEHS/FDA effort, primary human keratinocytes were exposed to fumonisin B_1, and the increases in intracellular sphinganine or decreases in intracellular ceramides were correlated with cellular apoptosis (Tolleson *et al*., 1999). The incidence of apoptosis more closely correlated with decreased ceramide, and fumonisin B_1-induced apoptosis was partially reversed by addition of *N*-acetylsphingosine. These and other results point out that the mechanism of action of fumonisin B_1 might be different in different cell types and may not be specifically due to sphinganine accumulation. Nevertheless, increased sphinganine levels are a useful biomarker for inhibition of ceramide synthase by fumonisin B_1.

Experimental Animals

The toxicity of cultures of *Fusarium* species following ingestion by animals has been reported. In many cases, the subsequent toxicities are presumed to be due to the fumonisins because *Fusarium* fungi are the predominant sources of fumonisins.

Several studies have shown that exposure of rodents to feeds containing cultures of *F. moniliforme* was hepatotoxic, nephrotoxic, and eventually hepatocarcinogenic; however, interpretation of these studies was complicated by the presence of multiple toxins in the culture material.

The first indication that purified fumonisin B_1 was hepatotoxic and nephrotoxic in rats was published by Voss *et al*. (1993). Male and female Sprague-Dawley rats were given feed containing 0, 15, 50, or 150 ppm fumonisin B_1 for 4 weeks, blood samples were taken, and the liver and kidney were examined following necropsy. Serum cholesterol and triglyceride concentrations and alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase activities were increased in male and female rats at 150 ppm. In male rats, relative liver weights were increased by exposure to 15 or 50 ppm and were decreased by exposure to 150 ppm. Relative kidney weights in male rats were decreased at all exposure concentrations of fumonisin B_1, suggesting nephrotoxicity at lower exposures than required for hepatotoxicity. There were no apparent effects of fumonisin B_1 on organ weights in female rats. The kidneys from male rats were examined by light microscopy, which revealed single cell necrosis accompanied by hyperplastic and eosinophilic cells in the corticomedullary junction. The effect in the liver was characterized as dispersed single cell necrosis accompanied by occasional mitotic cells. These results were further summarized and extended by Riley *et al*. (1994) and Voss *et al*. (1995a,b). In all of the rats exposed to 150 ppm, liver changes were detected by light microscopy, but liver changes were present in only one of three male rats exposed to 50 ppm. Induction of renal necrosis and hyperplasia occurred in all male rats exposed to 15, 50, or 150 ppm, but these lesions occurred only in female rats consuming 50 or 150 ppm. The sphinganine/sphingosine ratios in the liver were increased in males exposed to 150 ppm and in females exposed to 50 or 150 ppm. The sphinganine/sphingosine ratios were increased in the kidney of all exposed groups of rats, while serum sphinganine/sphingosine ratios were increased only at 150 ppm. Increased urinary sphinganine/sphingosine ratios closely paralleled the microscopic detection of nephrotoxicity, where the ratios were increased at all exposure concentrations in males and at 50 and 150 ppm in females. These studies demonstrated that purified fumonisin B_1 was capable of inducing liver and renal toxicity *in vivo* and that the elevation of sphinganine/sphingosine ratios closely paralleled many of the toxicities.

Male F344 rats were given NIH-07 rodent feed containing 1, 3, 9, 27, or 81 ppm fumonisin B_1 for 90 days (Voss *et al*., 1995a,b, 1996c). Exposure concentration-related nephrosis of the outer medulla of the kidney was observed in rats in the 9, 27, and 81 ppm groups. The nephrosis was minimal in the 9 ppm group (14/15), minimal to mild in the 27 ppm group (15/15), and mild in the 81 ppm group (15/15). The nephrosis was characterized by individual enlarged cells (not segments or clusters) with eosinophilic cytoplasm and dark and sometimes pyknotic nuclei. It occurred in the tubules of the outer medulla and in the tubules of the medullary rays that extend into the cortex. In the same study, when fumonisin B_1 was fed to female rats, only the 81 ppm group (15/15) developed minimal nephrosis. The outer medulla and medullary ray lesions in treated animals were very subtle, with a more lightly basophilic hue than those of the control animals.

Male BD-IX rats were fed diets containing 1,000 ppm fumonisin B_1 (92% pure) for 4 weeks, and this resulted in the development of GGT positive foci in the liver (Gelderblom *et al*., 1988b). These rats did not appreciably gain weight, while the animals on the control feed almost doubled their weight over the 4-week period. After 33 days, examination of the liver revealed marked hydropic degeneration, single-cell necrosis, hyaline droplets, bile duct proliferation, enlarged hepatic nuclei, mitotic figures, and fibrosis radiating out from the portal tract. The bile duct proliferation and fibrosis caused distortion of the lobular structure of the liver. Fatty changes and scant necrosis were found in the proximal convoluted tubules of the kidney.

Lim *et al*. (1996) determined the effect of a single intravenous dose of fumonisin B_1 (1.25 mg/kg) on male Sprague-Dawley rats. Organ weights in rats sacrificed 1, 2, 3, or 5 days following treatment were not affected. Serum cholesterol levels were significantly elevated. The single-dose administration of fumonisin B_1 increased the labeling index from approximately 0.1% to 0.5% in liver cells; the labeling index decreased to control values by day 3. In addition, fumonisin B_1 doubled the esophageal labeling index 3 days after treatment. Lim *et al*. (1996) showed that fumonisin B_1 treatment resulted in the induction of renal tubule cell apoptosis and necrosis that began 2 days after treatment and increased in severity by day 5, at which time many of the cells showed marked karyomegaly.

The toxicity of fumonisin B_1 in mice was assessed in a 90-day study in which male and female B6C3F$_1$ mice were given NIH-07 rodent feed containing 1, 3, 9, 27, or 81 ppm fumonisin B_1 (Voss *et al*., 1995a,b). The results showed no fumonisin-related toxic effects in male mice. In female mice, hepatopathy was detected only in the 81 ppm group. The hepatopathy was characterized as predominantly centrilobular, and occasionally midzonal single cell necrosis. The affected hepatocytes were small with hyalinized, hypereosinophilic cytoplasm and pyknotic or karyorrhectic nuclei. The necrosis was distinguished by hepatic cord structural distortion and mitotic division in adjacent cells. All of the female mice exposed to 81 ppm and two of the female mice exposed to 27 ppm had ceroid pigmentation in the macrophages at the corticomedullary junction of the adrenal cortex. There was a minimal to mild accumulation of granular to amorphous yellow-brown material in the cytoplasm of the affected macrophages. Therefore, female mice appeared to be more sensitive than male mice to fumonisin B_1-induced lesions of the liver and adrenal cortex, with a maximum concentration at which no exposure concentration-related effects were observed (no-observed-effect level; NOEL) between 27 and 81 ppm for the liver and 9 and 81 ppm for the adrenal cortex.

The consumption of moldy or *F. moniliforme*-contaminated maize resulted in equine leukoencephalomalacia (Wilson and Maronpot, 1971; Voss, 1990), which was characterized by multifocal liquefactive necrosis of predominantly the white matter in the cerebral hemispheres and by ataxia, oral or facial paresis, apathy, somnolence, hypersensitivity, blindness, head pressing, and eventually frenzy followed by death. This disease was recognized originally in the 1930s as a result of consumption of moldy corn. Equine leukoencephalomalacia has several colloquial names such as blind staggers, corn stalk disease, moldy corn disease, and foraging disease. This disease has been reported sporadically in Argentina, Brazil, China, Egypt, New Caledonia, South Africa, and the United States.

Haliburton *et al*. (1979) grew *F. moniliforme* var. Sheld NRRC 6442 (isolated from the causative corn in an equine leukoencephalomalacia case in the Nile region of Egypt) on sterilized yellow corn for 4 weeks at 25° C. When this corn was fed to two healthy 4-year-old male donkeys, one developed leukoencephalomalacia within 38 days and died on day 39. The other donkey did not develop leukoencephalomalacia but developed symptoms of brain dysfunction. A donkey administered moniliformin at approximately 1 mg/kg body weight per day for 26 days died with heart damage and microhemorrhages in the brain, lungs, and kidney.

Buck *et al*. (1979) compared eight cases of equine leukoencephalomalacia that occurred in Illinois over an 18-month period. In each case the diet contained *F. moniliforme* contaminated corn, and the equids had clinical signs of neurological disorders and liquefactive necrosis, perivascular hemorrhage, satellitosis, and neurophagia of one or both of the cerebral hemispheres.

In order to determine if *F. moniliforme*-contaminated corn was responsible for equine leukoencephalomalacia, Marasas *et al*. (1988a) administered by stomach tube six daily doses of 1.25 g or 2.5 g of corn per kg body weight that had been incubated with *F. moniliforme* MRC 826. The horse on 2.5 g/kg feed developed severe hepatosis and mild brain edema (medulla oblongata), while the horse on 1.25 g/kg feed developed mild hepatosis and moderate brain edema (medulla oblongata). Fumonisin B_1 was purified from *F. moniliforme* and administered to a horse for 8 days at 0.125 mg/kg body weight per day Marasas *et al.*, 1988a). On the ninth day, the horse was incapacitated with symptoms of equine leukoencephalomalacia. Autopsy confirmed focal necrosis of the medulla oblongata and severe edema of the brain.

In a study with two young horses, Kellerman *et al.* (1990) demonstrated the ability of fumonisin B_1 to induce equine leukoencephalomalacia. A 9-month-old filly (150 kg) was administered 50% pure fumonisin B_1 (impurities were stated to be inorganic matter that coeluted with fumonisin B_1 on thin layer chromatography) at a daily dose of 1.25 to 4 mg/kg, while a 16-month-old colt (90 kg) was administered 95% to 98% pure fumonisin B_1 at a daily dose of 1 to 4 mg/kg. The filly was given the dosed feed for 33 days (with a few interspersed days without fumonisin B_1) and was sacrificed on day 35 with clinical signs of equine leukoencephalomalacia and high serum aspartate aminotransferase levels. Pathologic examination confirmed left frontal lobe leukoencephalomalacia. The colt was given the dosed feed for 30 days and was sacrificed at day 33 following severe clinical signs of leukoencephalomalacia. Autopsy confirmed left frontal to occipital lobe leukoencephalomalacia.

Wang *et al*. (1992) found 15 to 44 ppm fumonisins in corn screenings from an outbreak of equine leukoencephalomalacia. Three mares and one stallion (2 to 16 years old) were given corn-based feed that contained 44 ppm fumonisin B_1, and one gelding (4 years old) was given feed containing 15 ppm fumonisin B_1 for 160 days followed by feed containing 22 ppm fumonisin B_1 for 81 additional days until it died. All animals lost weight after consuming the *F. moniliforme*-contaminated feeds, and two of the four animals on the 44 ppm feed died after 10 or 45 days. Each of the equids died of leukoencephalomalacia. Serum sphinganine and sphingosine concentrations and transaminase activities (SGOT/AST) increased following exposure of the ponies.

There is, therefore, considerable evidence to associate the ingestion of feed containing fumonisin B_1 with equine leukoencephalomalacia.

Following the 1989 United States corn harvest, there were outbreaks of equine leukoencephalomalacia concurrent with outbreaks of porcine pulmonary edema in many regions across the United States. Ross *et al.* (1991b, 1992) investigated the levels of fumonisin B_1 and fumonisin B_2 in animal feeds during that period and concluded that, in general, fumonisin B_1 levels higher than 10 ppm were associated with equine leukoencephalomalacia.

Female 4-week-old pathogen-free pigs were exposed to fumonisin B_1 (more than 90% pure) by intravenous administration or to *F. moniliforme*-contaminated corn (Haschek *et al.*, 1992). The corn contained 166 ppm fumonisin B_1, 48 ppm fumonisin B_2, 0.3 ppm deoxynivalenol, and 20 ppb aflatoxin. Of the two pigs administered fumonisin B_1 intravenously, one was dosed at 0.88 mg fumonisin B_1/kg body weight per day for 9 days (72 mg/pig), and the other was dosed at 1.15 mg/kg per day for 4 days (67 mg/pig). The pig dosed with 0.88 mg/kg displayed mild interstitial pulmonary edema characterized by thickened interlobular septa and mild dilation of subpleural lymphatics, diffuse hepatocyte disorganization, scattered hepatocellular degeneration, and mainly centrilobular cell necrosis with mitotic figures. In the pancreas, scattered acinar cell condensation and acidophilic cytoplasm were noted, with pyknotic or occasionally karyorhectic nuclei. The pig dosed with 1.15 mg/kg displayed the same liver and pancreatic disorders but had no changes in the lung. Three of the five pigs exposed through feed consumed daily doses of 4.5 to 6.5 mg fumonisin B_1/kg body weight per day. One of these pigs was euthanized on day 5 because of severe respiratory distress, one died on day 6 with severe respiratory distress, and the third pig displayed intermittent respiratory complications on day 15. All of the pigs exposed to the contaminated feed had elevated serum enzymes indicative of hepatotoxicity. The pathology of the lungs was characterized as severe interstitial edema with alveolar edema and scattered hemorrhages. The livers displayed scattered hepatocellular degeneration, single cell necrosis, and mitotic figures indicating regeneration.

Riley *et al.* (1993) analyzed corn screenings from a field outbreak of acute porcine pulmonary edema and sudden death for the presence of fumonisins and found 166 ppm fumonisin B_1 and 48 ppm fumonisin B_2. They then fed this corn to male SPF cross-bred pigs to yield exposure concentrations of 5 to 175 ppm fumonisins. Histologic examination of the liver and serum chemistry analyses indicated hepatosis in the pigs fed concentrations equal to or greater than 23 ppm. No nephritis was indicated, but lung lesions were noted in the 175 ppm group. When pigs were fed pure fumonisin B_1, the serum sphinganine/sphingosine ratio increased from an average of 0.20 to 0.62, indicating that fumonisin B_1 was inhibiting sphinganine *N*-acyl transferase. Similarly, when pigs were given feed containing 5 to 175 ppm fumonisins, exposure concentration-dependent increases in serum, liver, lung, and kidney sphinganine/sphingosine ratios were detected. The authors concluded that elevation of the sphinganine/sphingosine ratios is an early biomarker of fumonisin B_1 exposure in pigs and that this ratio could be used for field identification of exposed pigs.

The mechanism of induction of pulmonary edema in cross-bred pigs given fumonisin B_1-containing feeds was further examined by Smith *et al.* (1996a,b). Pigs were given feed containing 20 mg fumonisin B_1/kg body weight per day for 7 days and surgically catheterized to enable cardiovascular measurements. In both anesthetized and conscious pigs, the heart rate, cardiac output, and mean aortic pressure were significantly decreased. These changes were accompanied by a 36% to 68% increase in pulmonary arterial pressure and a 142% to 233% increase in pulmonary vascular resistance. The arterial partial pressure of oxygen in the conscious pigs was reduced by 12.5%. These results indicate that one probable mechanism of action for fumonisin B_1 induction of pulmonary edema is the causation of acute left-sided heart failure; the increased sphinganine and sphingosine concentrations due to fumonisin B_1 interruption of sphingolipid synthesis may in turn be responsible for decreased heart function via inhibition of L-type Ca^{2+} channels (Smith *et al.*, 1996b).

Humans

No information on the toxicity of fumonisin B_1 in humans was found in the literature.

Reproductive and Developmental Toxicity

Experimental Animals

The developmental toxicity following administration of fumonisin B_1 to pregnant Syrian hamsters was investigated by Floss *et al.* (1994a). The source of fumonisin B_1 was the aqueous extract from cultures of *F. moniliforme* M1325, and the dose was based on measured fumonisin B_1 content. Date-mated Syrian golden hamsters or nonpregnant controls were administered the extract by gavage between gestation days 8 and 15 at 0, 3, 6, 8, 10, or 12 mg fumonisin B_1/kg body weight per day. Fumonisin B_1 caused a dose-dependent decrease in body weight gain on day 15 in both pregnant and nonpregnant hamsters. Hepatotoxicity was indicated by increases in maternal serum aspartate aminotransferase activities and incidences of maternal hepatocellular karyomegaly. A dose-dependent increase in dead or resorbed fetuses was observed, increasing from 0% at 0 ppm fumonisin B_1, to 3%, 9%, 21%, and 100% at 2, 3, 6, and 12 mg/kg, respectively.

In a subsequent report, the toxicity of fumonisin B_1 or a culture extract containing fumonisin B_1 and fumonisin B_2 to pregnant Syrian hamsters was evaluated at gavage doses of 6, 12, and 18 mg/kg body weight per day (Floss *et al.*, 1994b). The hamsters were dosed on days 8 and 9 of gestation and sacrificed on day 15. While doses as high as 18 mg/kg did not affect maternal indicators of toxicity, the fetal survival was decreased with pure or culture material fumonisin B_1 at 18 mg/kg. Mean weights, crown-rump lengths, and external malformations were evident in the fetuses at 18 mg/kg pure fumonisin B_1 but not at 12 mg/kg.

The developmental toxicity of fumonisin B_1 (98% pure) was determined in New Zealand White rabbits as part of the overall NIEHS/FDA effort on fumonisin B_1 (LaBorde *et al.*, 1997). In an initial study, pregnant New Zealand White rabbits were gavaged with 0, 0.25, 0.5, 1, 1.25, or 1.75 mg fumonisin B_1/kg body weight per day between gestation days 3 and 19. By gestation day 20, 40% of the rabbits receiving 1.25 or 1.75 mg/kg had died. An additional study was undertaken to determine the developmental toxicity of fumonisin B_1 in New Zealand White rabbits using gavage doses of 0, 0.1, 0.5, or 1 mg fumonisin B_1/kg body weight per day starting on gestation day 3 (LaBorde *et al.*, 1997). There was a dose-dependent decrease in maternal survival with no deaths at 0 or 0.1 mg/kg, and 9% and 19% maternal deaths at 0.5 and 1 mg/kg, respectively. No dose-related trends were apparent in maternal total body weight or brain, liver, kidney, or uterine weights. Fumonisin B_1-induced changes in the sphinganine/sphingosine ratios were evident in maternal urine, kidney, and liver at 1 mg/kg. The litters of the rabbits that were treated with 0.5 or 1 mg/kg had decreased body, liver, and kidney weights ($P \leq 0.05$), while the organ-to-body-weight ratios did not change. There were no resorptions or evidence of malformations in the fetuses. The sphinganine/sphingosine ratio was unaffected in the fetal liver, kidney, and brain. Taken together, these data suggest that fumonisin B_1 is toxic to pregnant New Zealand White rabbits at concentrations equal to or higher than 0.5 mg/kg per day. Fumonisin B_1 was apparently absorbed from the gavage administration because elevated sphinganine/sphingosine ratios were detected in the maternal kidney and liver at 1 mg/kg. The effect of fumonisin B_1 on fetuses in the dams that survived fumonisin B_1 treatment probably was not due to transplacental transfer of fumonisin B_1 because fetal sphinganine/sphingosine ratios were not elevated. The decreased fetal weight was probably the result of overall direct toxicity to the dam.

The developmental toxicity of fumonisin B_1 (98% pure) was determined in rats as part of the overall NIEHS/FDA effort on fumonisin B_1 (Collins *et al.*, 1998a). Pregnant Charles River rats were gavaged with 0, 1.88, 3.75, 7.5, or 15 mg fumonisin B_1/kg body weight per day from gestation days 3 to 16 and sacrificed on day 17 or 20. Feed consumption, body weight gains, and kidney weights were decreased in rats treated with 15 mg/kg. The sphinganine/sphingosine ratios were elevated in maternal serum and liver at 7.5 and 15 mg/kg. Kidney sphinganine/sphingosine ratios were elevated in all groups of rats treated with fumonisin B_1, increasing from 0.8 in controls to 12.3 at 15 mg/kg. The brain sphinganine/sphingosine ratios were unaffected by fumonisin B_1. Few notable effects were seen in the fetuses of dams treated with fumonisin B_1. The average fetal body weight and crown-rump length were decreased in female fetuses from dams treated until gestation day 20 with 15 mg/kg. The average number of fetuses with two or greater skeletal variations increased at 3.75, 7.5, and 15 mg/kg; however, there was not an overall appearance or indicator of fetal toxicity. This was reflected in the absence of elevated sphinganine/sphingosine ratios in the brain, liver, or kidney of the fetuses from dams exposed to fumonisin B_1.

In a second study, Collins *et al.* (1998b) increased the gavage doses of fumonisin B_1 administered daily by gavage to pregnant Charles River rats to 6.25, 12.5, 25, or 50 mg/kg body weight per day from gestation days 3 to 16 and sacrificed at day 20. Fumonisin B_1 at 25 mg/kg caused decreased feed consumption, while administration at 50 mg/kg resulted in decreased feed consumption, decreased body weight gain, and decreased gravid uterine weight. All doses of fumonisin B_1 resulted in tubule epithelial degeneration and necrosis in the kidney, with an increase in severities of the lesions with increasing dose. The liver of dams treated with 50 mg/kg had increased incidences of hepatocellular necrosis, mitosis, pigmentation, and cytoplasmic alterations. Maternal serum sphinganine/sphingosine ratios were increased at 25 and 50 mg/kg, while liver sphinganine/sphingosine ratios were increased at 12.5, 25, and 50 mg/kg. Maternal kidney sphinganine/sphingosine ratios were increased at all doses, increasing from 1 in control rats to 35.5 in 50 mg/kg rats. The brain sphinganine/sphingosine ratio was unaffected by fumonisin B_1. Decreased numbers of viable fetuses were detected at 50 mg/kg. In fetuses that survived until gestation day 20 in the 50 mg/kg group, the average fetal body weight and crown-rump length were decreased; these decreases were accompanied by increased numbers of skeletal malformations and increased numbers of malformations per fetus. Fetal toxicity was not accompanied by changes in fetal brain, liver, or kidney sphinganine/sphingosine ratios. The absence of induction of sphinganine in the fetus suggests that fumonisin B_1 is unable to cross the placenta. Fetal toxicity may be secondary to maternal toxicity of fumonisin B_1.

The toxicity of fumonisin B_1 was evaluated in pregnant CD-1 mice dosed with 0, 12.5, 25, 50, or 100 mg fumonisin B_1/kg body weight per day between gestation days 7 and 15 (Reddy *et al.*, 1996). Maternal toxicity was indicated at 100 mg/kg by diminished body weight gains compared to controls. Plasma alanine aminotransferase levels were statistically increased at 25 mg/kg and highly increased at 50 and 100 mg/kg. Fetal survival and weights were decreased at 100 mg/kg, and indications of hydrocephaly were present in the fetuses of dams dosed with 25, 50, or 100 mg/kg.

Humans

No information on the reproductive or developmental toxicity of fumonisin B_1 in humans was found in the available literature.

NEUROTOXICITY

Experimental Animals

Porter *et al*. (1990) studied the effects on brain neurotransmitters by feeding 5% or 20% *F. moniliforme*-contaminated corn to male Sprague-Dawley rats. The net exposure in the 20% group was 139 ppm fumonisin B_1 and 131 ppm fumonisin B_2. By inference, the 5% group was exposed to 35 and 33 ppm fumonisins B_1 and B_2, respectively. In comparison to paired control rats fed rat chow supplemented with 20% uncontaminated corn, a dose-dependent decrease in body weight was shown over the 4-week study. This was associated with statistically significant increases in whole brain 5-hydroxyindoleacetic acid and the ratio of 5-hydroxyindoleacetic acid to serotonin. The ratio of brain weight to total body weight was increased by 16% in the 20% exposure group, but this was primarily due to an 18% decrease in body mass accompanied by no net change in relative brain mass. In rats given feed containing 14 or 132 ppm fumonisin B_1, significant differences from the controls were noted for whole brain dihydroxyphenylalanine, homovanillic acid, 5-hydroxyindoleacetic acid, and dihydroxyphenylacetic acid concentrations, while other neurotransmitters remained unchanged.

In a subsequent study, Porter *et al*. (1993) administered feed containing pure fumonisin B_1 at 0, 15, 50, or 150 ppm to male and female Sprague-Dawley rats for 4 weeks. Pure fumonisin B_1 failed to alter the whole brain concentrations of any of the measured neurotransmitters or metabolites, including norepinephrine, dopamine, 3,4-dihydroxyphenylacetic acid, homovanillic acid, 3-methoxytyramine, 5-hydroxyindoleacetic acid, or serotonin. Pineal gland norepinephrine, 5-hydroxyindoleacetic acid, and serotonin concentrations were not affected in either male or female rats. These results suggest that the neurotransmitter effects detected in the previous study with cultured material were the result of a mycotoxin other than fumonisin B_1.

In a study using isolated frog atrial muscle, Sauviat *et al*. (1991) investigated the effect of fumonisin(s) (purity unknown) on transmembrane potentials and currents using the double sucrose gap technique. Exposure to fumonisin(s) shortened the plateau duration of the action potential and, under voltage clamp conditions, evidently inhibited the Ca^{2+} current.

Investigations revealed that the Ca^{2+} effect was probably due to increased Na^+-Ca^{2+} exchange. This may explain some of the cardiotoxic properties that have been reported for fumonisin B_1 and *F. moniliforme*-contaminated feeds.

The effect of fumonisin B_1 on plasma and brain sphingolipid levels was determined in Sprague-Dawley rats as part of the overall NIEHS/FDA effort on fumonisin B_1 (Kwon *et al.*, 1997a). Fumonisin B_1 was administered as a single 0.8 or 8 mg/kg subcutaneous dose to rats on postnatal day 12, and serum and brain sphingolipids were determined for up to 24 hours. Serum and forebrain sphinganine levels increased in a dose- and time-dependent manner, and the extent and duration of the changes were greater in the brain than the serum. Fumonisin B_1 was detected in hindbrain tissue at 40 to 300 ng/g tissue following administration of 8 mg/kg. The rate of decrease in hindbrain fumonisin B_1 levels was less than the rate of elimination of fumonisin B_1 from the serum.

Kwon *et al.* (1997b) extended these studies by the daily subcutaneous administration of fumonisin B_1 at 0.1, 0.4, or 0.8 mg/kg to Sprague-Dawley rat pups from postnatal day 3 to postnatal day 12. The ratios of sphinganine/sphingosine were increased in the forebrain following administration of fumonisin B_1 at 0.8 mg/kg and in the brainstem following treatment with 0.4 or 0.8 mg/kg. The administration of 0.4 or 0.8 mg/kg resulted in decreased body weight gain and decreased survival. Fumonisin B_1 exposure decreased myelination in the corpus callosum. The decreased myelin content was accompanied by a decrease in forebrain myelin-associated 2,3-cyclic nucleotide 3-phosphohydrolase activity at 0.8 mg/kg.

In a study to determine if fumonisin B_1 exposure causes behavioral effects in the offspring, pregnant Sprague-Dawley rats were gavaged daily between gestation days 13 and 20 with 0, 1.6, or 9.6 mg fumonisin B_1/kg body weight (Ferguson *et al.*, 1997). In this study, purified fumonisin B_1 did not affect the total number of pups in each litter, the number of live pups, or the gender ratio. Behavioral activities such as open-field movement, play behavior, wheel-running activity, and maze solving were not affected by fumonisin B_1. Therefore, it appears that fumonisin B_1, at doses that have been shown to be nephrotoxic and cause decreases in body weight, does not affect these behavioral endpoints.

Humans

No information on the neurotoxicity of fumonisin B_1 in humans was found in the available literature.

CARCINOGENICITY

Experimental Animals

Gelderblom *et al.* (1991) reported the results of chronic treatment of male BD-IX rats with purified fumonisin B_1 (purity stated as at least 90%). The diet consisted of 75% sifted white corn meal supplemented with minimal levels of protein and analytical grade minerals and vitamins, along with 50 ppm fumonisin B_1. Feeding 50 ppm fumonisin B_1 to rats resulted in the appearance of liver regenerative nodules and cholangiofibrosis (synonymous with adenofibrosis) in all rats with a progression to hepatic cirrhosis and hepatocellular carcinomas after 20 months (Table 2). The feeding of fumonisin B_1 to the rats caused marked nonneoplastic changes in the liver. Although feeding 50 ppm fumonisin B_1 resulted in 100% incidences of liver dysplasia, the study must be interpreted in light of the possible role that the nutritional deficiencies may have had in the progression of the dysplasia. Diets that include a high percentage of processed corn can result in nutritional deficiencies of several micronutrients, primarily riboflavin and niacin (Darby *et al.*, 1977).

In a subsequent study, Gelderblom *et al.* (1992) used an initiation/promotion protocol to study the effect of fumonisin B_1 ingestion on rats. Fumonisin B_1 (90%-95% pure, with remaining contamination reported as a monoethyl ester derivative as a result of the isolation procedures) was incorporated into either a cereal-based diet or a basal feed. In the first experiment (Table 3), male Fischer 344 rats (100-120 g) were given the basal feed with or without 1,000 ppm fumonisin B_1 for 26 days. Fumonisin B_1-exposed animals had essentially no weight gain, while the rats on the basal feed gained 43% additional total body weight; this is consistent with previous fumonisin feed studies. The rats fed fumonisin B_1 demonstrated a statistically significant increase in the incidences of hepatocellular foci (Table 3) compared to the basal feed animals.

When the feeding of fumonisin B_1 was changed to the selection protocol of the Solt/Farber resistant hepatocyte model (Table 3; Tsuda and Farber, 1980), the induction of hepatocellular GGT^+ foci was more pronounced.

TABLE 2
Pathologic Changes in the Liver of Male BD-IX Rats Fed a Diet Containing 50 ppm Fumonisin B_1[a]

Duration (months)	Body Weight Gain (g)	Liver Weight (% of Body Weight)	Regenerative Nodules	Cholangio-fibrosis	Cirrhosis	Hepato-cellular Carcinoma
6 Months						
Control[b]	381.6 ± 25.4	ND	0/5	0/5	0/5	0/5
50 ppm FB_1	330.2 ± 14.5	ND	5/5	4/5	0/5	0/5
12 Months						
Control	434.0 ± 60.6	ND	0/5	0/5	0/5	0/5
50 ppm FB_1	353.0 ± 18.4	ND	5/5	5/5	0/5	0/5
20 Months						
Control	482.2 ± 53.7	2.6 ± 0.3	0/5	0/5	0/5	0/5
50 ppm FB_1	404.2 ± 24.5	4.2 ± 0.3	5/5	5/5	5/5	3/5
26 Months						
Control	618.4 ± 56.8	2.3 ± 0.2	0/5	0/5	0/5	0/5
50 ppm FB_1	454.8 ± 88.8	8.6 ± 3.4	5/5	5/5	5/5	4/5
18 to 25 Months						
Control	ND	ND	0/5	0/5	0/5	0/5
50 ppm FB_1[c]	ND	ND	5/5	5/5	5/5	3/5

a Data presented in Gelderblom *et al*. (1991); FB_1=fumonisin B_1; ND=not determined
b The control feed was found to contain 0.5 ppm fumonisin B_1 and 0 ppm aflatoxin B_1, and according to the authors, was marginally deficient in some nutritional components.
c These animals died during months 18 to 25.

TABLE 3
Foci Formation in the Liver of Male Fischer 344 Rats by Fumonisin B_1[a]

Treatment	Duration (days)	Liver Weight (% Body Wt)	GGT^+ Foci and Nodules: Number per cm^2	GGT^+ Foci and Nodules: Mean Area (mm^2)	GGT^+ Foci and Nodules: Mean % Area per Liver Section
Feed alone					
0.1% FB_1 in basal feed	26	ND	2.9 ± 0.7***	0.14 ± 0.11*	0.42 ± 0.34*
Basal feed	26	ND	1.0 ± 0.2	0.01 ± 0.00	0.01 ± 0.00
Selection protocol[b]					
0.1% FB_1 in basal feed	53	2.5 ± 0.28***	7.1 ± 0.8****	2.15 ± 1.00**	15.64 ± 8.22**
Basal feed	53	3.1 ± 0.18	1.2 ± 0.3	0.06 ± 0.05	0.07 ± 0.05

* Significantly different ($P<0.01$) from the basal feed control group
** $P<0.005$
*** $P<0.0025$
**** $P<0.0005$
a Data adapted from Table 1 presented in Gelderblom *et al*. (1992); FB_1=fumonisin B_1; ND=not determined
b Solt/Farber model [Tsuda and Farber (1980)]: 26 days of feed, followed at day 27 with basal feed and partial hepatectomy, and 2 weeks later with 3 consecutive days of once-daily gavage of 2-acetylaminofluorene (20 mg/kg) followed on day 4 with 2 mL/kg CCl_4 by gavage. The animals were sacrificed 10 days later.

When the protocol was changed to allow for selection of initiators (Table 4), fumonisin B_1 exposure was not found to result in the initiation of hepatocellular foci, thereby suggesting that fumonisin B_1 modulates carcinogenesis at a postinitiation stage (e.g., proliferation, promotion, and/or progression).

The tumor promotional capacity of fumonisin B_1 was investigated by Gelderblom *et al*. (1996a) using male Fischer rats initiated with 200 mg/kg diethylnitrosamine (DEN) intraperitoneally (Table 5). After initiation, the rats were fed diets containing 10 to 500 ppm fumonisin B_1 for 21 days. Histopathologic analysis of the tissues revealed a significant increase in the number of γ-glutamyl transpepetidase (GGT) foci per cm^2 of liver at 250 and 500 ppm. The mean area of the liver occupied by GGT-positive foci increased from 0.12% in DEN-treated rats maintained on the control feed to 23.59% of the liver in the rats that were DEN treated and given feed containing 500 ppm fumonisin B_1.

Prenoplastic foci were also detected in this study using immunohistochemical staining techniques for the placental form of glutathione-S-transferase (GSTP; Table 5). The mean numbers of foci were increased at 100, 250, and 500 ppm when compared to the value from DEN-initiated rats on control feed. The mean area of liver staining positive for GSTP foci increased from 0.29% in the control rat livers to 13.7%, 13.4%, and 27.6% in rats receiving 100, 250, and 500 ppm, respectively. These results are consistent with fumonisin B_1 exhibiting tumor-promoting activity.

In the study of Gelderblom *et al*. (1996b), rats were fed diets containing 0, 10, 50, 100, 250, or 500 ppm fumonisin B_1 for 21 days, subjected to a partial hepatectomy, and then sacrificed after 24 hours. The rats were treated with [^{3}H]-thymidine 1 hour prior to sacrifice, and an exposure concentration-dependent decrease in [^{3}H]-thymidine incorporation into liver DNA was detected at 50 ppm and greater. Inhibition of regeneration was paralleled by increases in the liver sphinganine/sphingosine ratios, and increases were detected at 100, 250, and 500 ppm ($P \leq 0.05$). These results suggest that the pressure to regenerate liver cells was counterbalanced by the apoptosis induced by fumonisin B_1, as show in other studies.

The results from these studies suggest that fumonisin B_1 is not a classic initiator of cancer in rodents and that the probable neoplastic mechanism of action is the promotion of initiated cells to tumors through continual induction of apoptosis and subsequent cellular regeneration.

Humans

The occurrence of fumonisin B_1 in areas of the world with elevated risks of human esophageal cancer is intriguing, yet there have not been sufficient epidemiologic studies conducted to determine if fumonisin B_1 is causative in any human cancers. The research efforts of the South African Medical Research Council to explain elevated esophageal cancer incidences in the Transkei region have led to the discovery of fusarin C and fumonisin B_1 from corn fungi. For example, the esophageal cytology and taxonomy of fungi on corn were determined in households in low and high esophageal cancer incidence areas (Marasas *et al.*, 1988b; Table 6). There was a statistically significant positive correlation of *F. moniliforme* and total *Fusarium* infection and esophageal cancer risk in both the visibly clean (good) and visibly moldy maize. In the moldy maize, the incidence of *F. moniliforme* infection was more pronounced than in the good maize. *F. graminearum* was more predominant on maize from the lower risk area than in the higher risk area. This work was extended by inclusion of the Butterworth district, an area of intermediate esophageal cancer risk (Table 7). In that study, the esophageal cancer incidences doubled between the low and high risk areas for both men and women and corresponded to an increase in total fungal infection and the level of *F. moniliforme* contamination of the good maize sampled from the respective areas (Marasas *et al.*, 1988b).

Thiel *et al*. (1982) selected infected corn kernels from the Butterworth District of Transkei, South Africa, at the end of the 1978 harvest. This district had the highest esophageal cancer rate (57.9 per 100,000) in Transkei. Extraction of corn kernels that were moldy or visibly infected yielded a variety of *Fusarium*

TABLE 4
Foci Formation in the Liver of Male Fischer 344 Rats by Fumonisin B_1[a]

Treatment	Protocol[b]	Liver Weight (% Body Wt)	GGT$^+$ Foci and Nodules Number per cm^2	Mean Area (mm^2)	Mean % Area per Liver Section
FB_1 (50 mg/kg)	1	3.7 ± 0.20	1.0 ± 0.26	0.1 ± 0.02	0.1 ± 0.04
FB_1 (100 mg/kg)	1	3.9 ± 0.28	1.6 ± 0.39	0.1 ± 0.09	0.2 ± 0.10
FB_1 (200 mg/kg + 50 mg/kg)	2	4.4 ± 0.04	1.2 ± 0.16	0.2 ± 0.19	0.3 ± 0.25
FB_1 (50 mg/kg + 50 mg/kg)	3	3.4 ± 0.23	1.0 ± 0.27	0.1 ± 0.01	0.1 ± 0.01
FB_1 (100 mg/kg + 50 mg/kg)	3	3.5 ± 0.07	1.0 ± 0.18	0.1 ± 0.02	0.1 ± 0.01
DEN (30 mg/kg)	1	4.3 ± 0.18	32.2 ± 14.0*	0.5 ± 0.11	15.5 ± 3.63*
Control (DMSO)	1	3.6 ± 0.23	0.9 ± 0.03	0.1 ± 0.01	0.1 ± 0.01

* Significantly different (P<0.05) from the control group
[a] Data adapted from Table II presented in Gelderblom *et al*. (1992); values are mean ± standard deviation of 3 animals per group. GGT=γ-glutamyl transpeptidase; FB_1=fumonisin B_1; DEN=diethylnitrosamine
[b] Treatment protocols:
1. Animals were orally gavaged with DMSO (controls), fumonisin B_1 in DMSO, or intraperitoneally injected with DEN, 18 hours after partial hepatectomy. Two weeks later they were gavaged once-daily with 2-acetylaminofluorene (20 mg/kg) for 3 consecutive days followed by a single gavage dose of 2 mL/kg CCl_4 on the fourth day. The animals were sacrificed 14 days later.
2. Same as in protocol 1, except animals were given 200 mg/kg of fumonisin B_1 4 hours prior to partial hepatectomy.
3. Same as in protocol 1, except 24 hours after the first treatment of chemical, the animals received an additional dose of fumonisin B_1.

TABLE 5
Foci Formation in the Liver of Male Fischer 344 Rats by Fumonisin B_1[a]

Treatment[b]	GGT$^+$ Foci Number per cm^2	GGT$^+$ Foci Mean % Area per Liver Section	GSTP$^+$ Foci Number per cm^2	GSTP$^+$ Foci Mean % Area per Liver Section
Control	0.55	0.12	3.59	0.29
FB_1 (10 mg/kg)	0.44	0.08	6.5	0.31
FB_1 (50 mg/kg)	0.87	0.15	12.76	0.97
FB_1 (100 mg/kg)	6.67	0.84	47.83*	13.73*
FB_1 (250 mg/kg)	36.85*	10.15*	43.61*	13.43*
FB_1 (500 mg/kg)	66.00*	23.59	56.99*	27.56*

* Significantly different (P<0.01) from the control group
[a] Data presented in Gelderblom *et al*. (1996a); values are the means of 5 animals per group. GGT=γ-glutamyl transpeptidase; GSTP=placental form of glutathione-S-transferase; FB_1=fumonisin B_1
[b] Male Fischer rats received 200 mg/kg diethylnitrosamine intraperitoneally and were then placed on the fumonisin B_1 feeds for 21 days.

TABLE 6
Prevalence of Esophageal Cytologic Abnormalities in Occupants and of Fungi in Homegrown Maize from Households in a Low Esophageal Cancer Rate Area (Bizana) and a High Rate Area (Kentani) in Transkei During 1985[a]

	Low Rate Area	High Rate Area	P Value
Esophageal cytology			
Number of occupants[b]	24	30	
Normal epithelial cells (%)	83.3	30	
Mild cellular changes (%)	12.5	50.0	
Advanced cellular changes (%)	4.2	36.7	
Incidence of fungi[c] (%)			
Good maize			
F. moniliforme	8.3 ± 13.1	42.0 ± 18.0	<0.001
F. subglutinans	1.6 ± 1.5	3.5 ± 4.8	NS
F. graminearum	4.2 ± 8.2	2.5 ± 3.6	NS
TOTAL *Fusarium* spp.[d]	14.1 ± 14.6	48.3 ± 17.9	<0.001
Diplodia spp.[e]	2.9 ± 5.5	4.5 ± 9.1	NS
Other fungi	14.1 ± 13.5	26.9 ± 21.0	NS
TOTAL fungal spp.	31.1 ± 6.7	79.7 ± 20.8	<0.001
Moldy maize			
F. moniliforme	34.5 ± 16.3	67.7 ± 21.0	<0.01
F. subglutinans	10.1 ± 8.9	4.7 ± 3.4	NS
F. graminearum	34.9 ± 26.7	8.0 ± 12.8	<0.01
TOTAL *Fusarium* spp.[d]	79.5 ± 20.0	81.0 ± 21.5	NS
Diplodia spp.[e]	0.5 ± 1.4	6.8 ± 7.6	<0.01
Other fungi	7.4 ± 9.6	18.8 ± 22.3	NS
TOTAL fungal spp.	87.4 ± 17.3	106.7 ± 20.4	<0.05

[a] Data presented in Marasas *et al*. (1988b); NS=not statistically significant
[b] Gender and age distribution of occupants: low rate area, 9 men (48 ± 19 years), 15 women (48 ± 21 years); high rate area, 13 men (48 ± 18 years), 17 women (45 ± 16 years)
[c] Means and standard deviations are based on 1,200 surface-sterilized maize kernels (100 kernels/household from 12 households) from each area.
[d] Total number of *Fusarium* colonies isolated; some kernels were infected by more than one *Fusarium* species.
[e] *Diplodia maydis* and a few isolates of *D. macrospora* from the low rate area (Bizana)

TABLE 7
Prevalence of Esophageal Cytologic Abnormalities in Occupants and of Fungi in Homegrown Maize from Households in Low Esophageal Cancer Rate (Bizana), Intermediate Rate (Butterworth), and High Rate (Kentani) Areas of Transkei During 1986[a]

	Low Rate Area	Intermediate Rate Area	High Rate Area	P Value
Esophageal cancer rate (per 100,000)				
Men	19.5	31.5	45.0	
Women	15.0	19.0	29.3	
Esophageal cytology				
Number of occupants[b]	39	73	32	
Normal epithelial cells (%)	87.1	63.0	59.4	
Mild cellular changes (%)	10.3	27.4	21.9	
Advanced cellular changes (%)	2.6	9.6	18.7	
Incidence of fungi in good maize[c]				
F. moniliforme	9.0 ± 8.1	24.7 ± 30.1	43.0 ± 26.5	<0.01
F. subglutinans	14.9 ± 18.4	43.5 ± 32.4	11.2 ± 11.9	<0.01
F. graminearum	6.1 ± 10.8	6.5 ± 6.9	7.7 ± 8.4	NS
TOTAL *Fusarium* spp.[d]	30.3 ± 21.7	77.5 ± 44.2	63.2 ± 29.3	<0.01
Diplodia spp.[e]	19.6 ± 19.4	2.1 ± 4.9	14.6 ± 18.4	<0.01
Other fungi	23.7 ± 25.5	34.8 ± 24.3	53.0 ± 23.4	<0.05
TOTAL fungal spp.	73.7 ± 30.7	114.6 ± 50.9	130.8 ± 30.6	<0.01

a Data presented in Marasas *et al*. (1988b); NS=not statistically significant
b Gender and age distribution of occupants: low rate area, 11 men (48 ± 16 years), 28 women (43 ± 15 years); intermediate rate area, 17 men (53 ± 9 years), 56 women (47 ± 14 years); high rate area, 10 men (51 ± 19 years), 22 women (48 ± 17 years)
c Means and standard deviations are based on 1,200 surface-sterilized maize kernels (100 kernels/household from 12 households) each from low (Bizana) and high (Kentani) rate areas, and 2,400 kernels from 24 households in the intermediate rate area (Butterworth).
d Total number of *Fusarium* colonies isolated; some kernels were infected by more than one *Fusarium* species.
e *Diplodia maydis* and a few isolates of *D. macrospora* from the low rate area (Bizana)

species (Table 8). The predominant species in the moldy corn was *F. verticillioides* (same as *F. moniliforme*) at 37% of the fungi. However, hand selection of corn with visible signs of *Fusarium* infection resulted in selecting corn that had a predominance of *F. sacchari* var. *subglutinans* infection, rather than *F. moniliforme*. Corn isolated in the field from an endemic area of esophageal cancer contained a variety of *Fusarium* spp. that produce a mixture of toxins, while each individual *Fusarium* sp. does not produce all of the toxins of the mixture. In a subsequent study, the natural occurrence of mycotoxins in areas with low and high human esophageal cancer incidence was determined, and the analytical results are shown in Table 9 (Sydenham *et al*., 1990b). In corn isolated from an area of Transkei that is low in esophageal cancer incidence, 34.5% of the *Fusarium* spp. present was *F. moniliforme*, while another third was *F. graminearum*. When the corn was selected from a high-incidence area, the dominant *Fusarium* sp. was *F. moniliforme*. This shift towards *F. moniliforme* in the corn from the high-incidence area resulted in a decrease in mycotoxins that are associated with *Fusarium* spp. other than *F. moniliforme*, namely moniliformin, zearalenone, nivalenol, and deoxynivalenol. The shift towards *F. moniliforme* was accompanied by an increase in the detectable fumonisin B_1, fumonisin B_2, and tricarballylic acid in the corn samples. This strongly suggests that the presence of fumonisins correlates with the occurrence of esophageal cancer in South Africa. The reasons for the differences in the results shown in Tables 8 and 9 are not known; however, they may be due to the differences in the years of harvest (1978 and 1985).

Several areas of the People's Republic of China have high incidences of esophageal cancer. These areas

TABLE 8
Incidences of *Fusarium* Species in Moldy Corn Kernels and in Hand-selected Visibly *Fusarium*-infected Corn Kernels from Butterworth, Transkei[a]

Fusarium Species	% of Kernels Infected[b] Moldy Corn Kernels	Hand-selected *Fusarium*-infected Corn Kernels
F. graminearum	19	21
F. sacchari var. *subglutinans*	30	43
F. verticillioides[c]	37	35
TOTAL *Fusarium* spp.	86	99

[a] Data presented in Thiel *et al*. (1982)
[b] Based on 100 surface-sterilized kernels of each sample; some kernels were infected by more than one *Fusarium* species.
[c] Same as *F. moniliforme*

TABLE 9
Differences in the Mean Incidence of *Fusarium* Species and Mycotoxin Levels in Moldy Corn from Esophageal Cancer Areas in the Transkei in 1985[a]

	Low-incidence Area	High-incidence Area	P Value
Fusarium species (%)			
F. subglutinans	10.1 ± 8.9	4.7 ± 3.4	NS
F. graminearum	34.9 ± 26.7	8.0 ± 12.8	<0.01
F. moniliforme	34.5 ± 16.3	67.7 ± 21.0	<0.01
Mycotoxins (ppm)			
Moniliformin	3.5 ± 3.7	0.8 ± 0.4	<0.01
Zearalenone	1.2 ± 1.0	0.4 ± 1.0	<0.01
Nivalenol	4.6 ± 5.0	1.8 ± 2.8	<0.05
Deoxynivalenol	2.9 ± 4.3	0.3 ± 2.9	NS
Tricarballylic acid	12.4 ± 5.6	77.7 ± 146.3	<0.01
Fumonisin B_1	6.5 ± 5.3	23.9 ± 14.6	<0.01
Fumonisin B_2	2.5 ± 2.2	7.6 ± 4.6	<0.01
Diacetoxyscirpenol	ND	ND	NA
T-2 toxin	ND	ND	NA

[a] Data presented in Sydenham *et al*. (1990b); NS=not statistically significant; ND=not detected. Means and standard deviations are based on 12 samples/area.

within Linxian County of the Henan Province have age-adjusted esophageal cancer mortality rates of 135 to 140 per 100,000, compared with rates of 1.4 to 2.8 per 100,000 in neighboring counties (Yang, 1980). Records dating back 2,000 years document the incidence of dysphagia syndromes among these inhabitants. One cultural habit that appears to be associated with the esophageal cancer incidence is the consumption of the solids or liquor from fermented leaves of Chinese cabbage, turnips, soybeans, sweet potatoes, sesame, and other vegetables (Yang, 1980). In addition, from data reported by this author, it was suggested that *F. moniliforme* was cultured from bread samples in this area (Yang, 1980).

The cause of the esophageal cancer in this area of China seems to be epizootic because chickens from this area also have a high incidence of pharyngeal and esophageal cancer (Preister, 1975). Fungal infections are common among the inhabitants of this area, occurring at rates of 31%, 72%, and 90% for patients with normal, mildly dysplastic, and severely dysplastic esophagi, respectively (Yang, 1980). Accordingly, it is possible to conclude that mycotoxins are involved in esophageal cancer incidence in this area of China; however, residents of these areas also have a high intake of nitrosamines (Lu *et al*., 1980; Yang, 1980). Specifically, *N,N*-dimethylnitrosamine, *N,N*-diethylnitrosamine, *N,N*-methylbenzylnitrosamine, and *N*-3-methylbutyl-*N*-1-methylacetonylnitrosamine have been found in local cornbread contaminated with *F. moniliforme* and $NaNO_2$ (Li *et al*., 1980).

In regions other than South Africa and China, incidences of esophageal cancer have been epidemiologically associated with corn and alcohol consumption. Franceschi *et al*. (1990) found that in individuals in the Pordenone province of Northern Italy with heavy intake of alcoholic beverages (0.9 to 1.65 L/day of wine, 1.98 to 3.6 L/day of beer, or 0.18 to 0.33 L/day of hard liquor), the odds ratios for oral, pharyngeal, and esophageal cancers from corn consumption were 3.3, 3.2, and 2.8, respectively.

Studies have recently attributed an outbreak of human mycotoxicoses to *Fusarium* species and fumonsin B_1 contamination of food in India (Bhat *et al.*, 1997). This study reported that *Fusarium* species were the predominant fungi present in foods that induced diarrhea and borborygmi in humans and that fumonisin B_1 was also detected in the contaminated food. A previous study had demonstrated that the induction of diarrhea in chickens accompanied by mortality and reduced egg production was attributable to *Fusarium* fungi contaminated chicken feed and that the condition could be reproduced by adding fumonisin B_1 to control chicken feed (Prathapkumar *et al.*, 1997). Although these reports suggest that the human diseases may be attributable to *Fusarium* fungi, the reports are not sufficient to indicate that fumonisin B_1 was causative in the outbreaks of human diarrhea in India.

The International Agency for Research on Cancer (1993) has evaluated the carcinogenicity of *Fusarium* fungi and fumonisin B_1. The conclusion was that there is sufficient evidence in experimental animals for the carcinogenicity of *Fusarium moniliforme* cultures that contain significant amounts of fumonisins and that there is limited evidence for the carcinogenicity of fumonisin B_1.

Genetic Toxicity

There is little information describing the genetic toxicity of fumonisin B_1; results of all but one reported assay were negative.

The mutagenicity of fumonisin B_1 in *Salmonella typhimurium* was investigated by Knasmuller *et al*. (1997). Seven concentration levels of fumonisin B_1 (98% pure), from 0.7 to 500 µg/plate, were tested in plate incorporation experiments with *S. typhimurium* strains TA98 and TA100 in the presence and absence of rat liver S9. No increase in the number of mutant colonies was seen in either strain; the authors do not describe the dose-limiting factors.

The effects of fumonisin B_1 on SOS and repairable DNA damage induction were measured in *Escherichia coli* strain PQ37 (Knasmuller *et al*., 1997). Fumonisin B_1 concentrations as high as 500 µg/assay in the presence or absence of rat liver S9 were unable to induce an SOS response. Similarly, there was no evidence of differential survival in repair proficient and deficient *E. coli* strains, indicating that cytotoxic DNA damage was not induced by fumonisin B_1.

Norred *et al*. (1992b) investigated the ability of fumonisin B_1 (up to 250 µM) to induce unscheduled DNA synthesis (UDS) in primary hepatocytes isolated from male Sprague-Dawley rats. No increase in UDS, as measured by [^{3}H]-thymidine incorporation, was detected.

Knasmuller *et al.* (1997) also conducted genetic toxicity studies with fumonisin B_1 in metabolically competent primary rat hepatocytes *in vitro*. They saw no induction of micronuclei in hepatocytes treated for three hours with 0.010 to 100 µg/ml fumonisin B_1 and harvested 51 hours later, but with this same protocol, they observed a significant increase in the number of chromosomal aberrations per diploid cell. The increases in aberrations they observed were dose-related, except at the highest dose tested (100 µg/ml), where the number of aberrations was observed to decline, and this decrease was suggested to result from an inhibition of cell division (measured as a decrease in mitotic index) at the high dose. The lack of concordance between the results of the micronucleus and chromosomal aberrations tests (both of which measure structural chromosomal damage), was not discussed. Knasmuller *et al.* (1997) did not indicate whether the actual frequency of aberrant cells was increased following treatment with fumonisin B_1; they only reported that overall damage was increased. It may be that cells suffered increased chromosomal damage as a result of fumonisin B_1 exposure to an extent that prevented them from continuing to cycle through to the subsequent interphase stage, which would be necessary to view micronuclei.

STUDY RATIONALE

Fumonisin B_1, a contaminant in corn, was nominated by the FDA Center for Food Safety and Applied Nutrition for study because of its occurrence in corn and corn-based products in the United States, the toxicity of fumonisin B_1 in field exposure of horses and pigs, and the reports on carcinogenicity in rats.

MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF FUMONISIN B_1

Fumonisin B_1 was obtained from the Center for Food Safety and Applied Nutrition (CFSAN) (Food and Drug Administration, Washington, DC) in three lots (E12-27-1, E12-83, and E12-89). Lot E12-27-1 (a fumonisin B_1 free acid) was used during the 28-day studies, and lots E12-83 and E12-89 were used during the 2-year studies. Based on the purity analyses of lot E12-27-1, lots E12-83 and E12-89 were purified as an ammonium salt from cultures of *Fusarium proliferatum* at CFSAN. Identity and purity analyses were conducted by the study laboratory.

All lots of the compound were identified through structural confirmation as fumonisin B_1 by ^{1}H- and ^{13}C-nuclear magnetic resonance (NMR) spectroscopy (Figures H1 and H2). NMR analyses of lot E12-27-1 confirmed that the major component of lot E12-27-1 was the same as a South African fumonisin B_1 standard (PROMEC, C/93). Mass spectral analysis of all lots confirmed the presence of a compound with mass fragmentation characteristics of fumonisin B_1. The solubility of lot E12-27-1 in deionized water was determined to be approximately 20 mg/mL.

The purity of lots E12-27-1, E12-83, and E12-89 was determined by elemental analyses (lots E12-27-1 and E12-83), Karl Fischer water analysis, ^{1}H-NMR spectroscopy, and high-performance liquid chromatography (HPLC). Trace metals analyses for 39 elements were performed on lots E12-27-1 and E12-83. For lot E12-27-1, the principal impurities were silicon (368 ppm), calcium (125 ppm), magnesium (51.8 ppm), iron (25 ppm), zinc (15.9 ppm), and tin (12.5 ppm). For lot E12-83, the impurities totaled 37 ppm; the principal impurities were tin (7.9) and selenium (7.0 ppm). Karl Fischer water analysis indicated 0.10% water for lot E12-27-1, 0.00% water for lot E12-83, and 0.04% water for lot E12-89. HPLC indicated a purity of 92.0% ± 0.3% for lot E12-27-1, 96.9% ± 0.6% for lot E12-83, and 97.6% ± 0.2% for lot E12-89. ^{1}H-NMR spectroscopy indicated a purity of 92% for lot E12-27-1 with pyridine detected as an impurity. HPLC was used to quantify pyridine in lots E12-27-1 and E12-83. HPLC indicated the presence of 0.51% pyridine in lot E12-27-1, and pyridine was not present at the 50 ppb limit of detection in lot E12-83. The overall purity was determined to be 92% for lot E12-27-1, greater than 96% for lot E12-83, and greater than 97% for lot E12-89. Lot E12-27-1 was used to prepare diets for the 28-day studies, and lots E12-83 and E12-89 were used to prepare diets for the 2-year studies.

Fumonisin B_1 was stored at room temperature in a dry and inert atmosphere; there was no apparent degradation of the fumonisin B_1 during the course of the study.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

The dose formulations were prepared once for the 28-day studies and as needed during the 2-year studies by mixing fumonisin B_1 with feed (Table H1). NIH-31 feed was obtained from Purina Corporation (St. Louis, MO). This feed is an open formulation that contains approximately 20% corn by weight. Samples of the corn for the NIH-31 diet were sent from Purina Corporation to the study laboratory for analysis of fumonisin B_1 content using HPLC/mass spectroscopy. Only corn samples containing less than 60 ppb fumonisin B_1 were accepted. During the 28-day and 2-year studies, the dose formulations were stored in stainless steel cans at 4° to 8° C; dose formulations for the 2-year studies were stored for up to 16 weeks.

Homogeneity studies of 100 and 500 ppm formulations for the 28-day studies and of the 5 and 150 ppm dose formulations for the 2-year studies and stability studies of a 100 ppm formulation for the 28-day studies and of the 5 ppm dose formulation for the 2-year studies, were performed by the study laboratory using HPLC. Homogeneity was confirmed. Stability of the 100 ppm formulation was confirmed for up to 16 weeks for dose formulations stored in stainless steel cans at 2° to 6° C and for up to 14 days when stored at room temperature, open to air and light. Stability of the 5 ppm dose formulation was confirmed for up to 16 weeks for dose formulations stored in stainless steel cans at 4° to 8° C and for up to 30 days when stored at room temperature, open to air and light.

Prior to the start of the 28-day studies, the dose formulations were analyzed at the study laboratory using HPLC. The exposure concentrations for the 28-day studies were determined to be 99, 163, 234, and 484 ppm. Dose formulations of fumonisin B_1 used in the 2-year studies were analyzed approximately every 1 to 4 weeks at the study laboratory using HPLC (Table H2). The acceptable deviations from the target concentrations were 5 ± 2 ppm, 15 ± 3 ppm, 50 ± 5 ppm, 80 ± 8 ppm, 100 ± 10 ppm, and 150 ± 15 ppm. During the 2-year studies, 96% (152/158) of the dose formulations for rats and 99% (149/151) of the dose formulations for mice were within the acceptable target concentration range. The dose formulations that were outside the acceptable range were used due to the limited availability of fumonisin B_1.

28-DAY STUDIES

Male and female F344/N Nctr BR rats and $B6C3F_1$/Nctr BR (C57BL/6N × C3H/HeN MTV^-) mice were obtained from the study laboratory's breeding colony and were 4 weeks old at receipt. Animals were 6 weeks old on the first day of exposure to fumonisin B_1.

Groups of 10 male and 10 female rats and 12 male and 12 female mice received fumonisin B_1 in feed at concentrations of 0, 99, 163, 234, or 484 ppm for 28 days. Additional groups of eight male and eight female rats and seven or eight male and four or eight female mice designated for clinical pathology testing were maintained along with the core study animals and received the same exposure concentrations. Rats were housed two per cage, and mice were housed four per cage; microisolator bonnets were used to prevent contamination of the study room with scattered dosed feed. Feed and water were available *ad libitum*, except feed was not available during urine collection periods. Additional details on animal maintenance are provided in Table 10.

Clinical pathology studies were performed on rats and mice designated for clinical pathology testing and on all core study animals. Blood for clinical chemistry evaluations and urine for urinalyses were collected from up to four clinical pathology study animals per group on day 7 and from the remaining animals per group on day 14. At the end of the studies, blood and urine samples were collected from all clinical pathology study animals, and blood was collected from four core study rats and three core study mice per group. Animals were housed individually in metabolism cages and fasted overnight before blood was collected.

Animals were anesthetized with carbon dioxide, and blood was withdrawn from the retroorbital sinus. Blood samples were placed in tubes, allowed to clot, and then centrifuged, and the serum was removed. Clinical chemistry parameters were measured with a Roche Diagnostics Cobas Mira-Plus analyzer. The parameters that were evaluated are listed in Table 10. Reagents were obtained from the equipment manufacturer.

Clinical pathology study animals were housed overnight in metabolism cages prior to blood collection, and urine was collected on ice. Urine creatinine and protein concentrations for rats and mice, as well as urinary glucose concentrations and *N*-acetyl-β-D-glucosaminidase activities for rats were measured with a Roche Cobas Mira Plus automated analyzer (Roche Diagnostic Systems, Inc., Branchburg, NJ). Additional urine samples were analyzed at Emory University (Atlanta, GA) for sphingosine and sphinganine concentrations using HPLC and fluorescence detection methods (Wang *et al*., 1992).

Complete necropsies were performed on all animals. Organs and tissues were examined for gross lesions and fixed in 10% neutral buffered formalin. Tissues to be examined microscopically were trimmed, embedded in paraffin, sectioned, and stained with hematoxylin and eosin for microscopic examination. Complete histopathologic examinations were performed on all core study animals in the 0 and 484 ppm groups and all animals that died early; histopathologic examinations of the kidney, liver, and gross lesions were performed on rats and mice in the lower exposure groups and all clinical pathology study animals. Table 10 lists the organs weighed and tissues examined microscopically.

Sections of liver tissue from core study rats and mice were stained with antibodies to proliferating cell nuclear antigens (PCNA). At least 2,000 cells per slide were scored for each cell cycle phase (G_0, G_1, S, G_2, and M), and the percentages of cells in each phase were calculated.

2-YEAR STUDIES

Study Design

Groups of 48 male and 48 female rats were fed diets containing 0, 15, 50, or 150 ppm fumonisin B_1 (males) or 0, 15, 50, or 100 ppm fumonisin B_1 (females) for 105 weeks. The groups of rats that received diets containing 5 ppm for the same period were reduced to 40 males and 40 females in order to accommodate logistical constraints. Groups of 48 male and 48 female mice were fed diets containing 0, 5, 15, 80, or 150 ppm (males) or 0, 5, 15, 50, or 80 ppm (females). Additional groups of four male and four female rats and mice were fed diets containing the same concentrations of fumonisin B_1 as the core study groups and evaluated at 6, 10, 14, or 26 weeks (rats) or 3, 7, 9, or 24 weeks (mice) for differences in cell proliferation, apoptosis, hematology, clinical chemistry, urinalysis, and tissue sphingolipid parameters, and were necropsied.

Source and Specification of Animals

Male and female F344/N Nctr BR rats and B6C3F$_1$/Nctr BR (C57BL/6N × C3H/HeN MTV$^-$) mice were obtained from the study laboratory's breeding colony. Rats and mice were approximately 6 weeks old on the first day of exposure. The health of the animals was monitored during the studies according to the protocols of the study laboratory's Sentinel Animal Program (Appendix K).

Animal Maintenance

The health status of the sentinel rodents in the colony was excellent, and they were free from *Syphacia* infections typical to nonbarrier studies. The mice were not tested for *Helicobacter hepaticus*. Rats were housed two per cage, and mice four per cage. Feed and water were available *ad libitum*, except feed was not available during urine collection periods. Feed consumption was measured weekly. Cages were changed twice weekly for rats and once weekly for mice; cages were rotated weekly. Further details of animal maintenance are given in Table 10. Information on feed composition and contaminants is provided in Appendix J.

Clinical Examinations and Pathology

All animals were observed twice daily. Clinical findings and body weights were recorded weekly. At the 6-, 10-, 14-, and 26-week evaluations (rats) and 3-, 7-, 9-, and 24-week evaluations (mice), animals were housed individually overnight in metabolism cages to collect urine. They were then injected with 5-bromo-2-deoxyuridine (BrdU); 2 hours later, they were anesthetized with CO_2 and blood was collected from the retroorbital sinus for hematology and clinical chemistry analyses. The blood was placed in tubes containing EDTA as the anticoagulant. The assessment of blood cells was determined by blood smears and light microscopy. Serum was prepared as described in the 28-day studies. The parameters measured are listed in Table 10. Tissue and urinary sphingolipids were analyzed at the study laboratory using HPLC methods following derivitization with *o*-pthaldialdehyde (LaBorde *et al*., 1997). Kidney samples from rats at the 6-, 10-, 14-, and 26-week evaluations and rats at 2-year evaluations and liver samples from rats at the 6-, 10-, 14-, and 26-week evaluations, male mice at the 3-, 7-, and 9-week evaluations, and female mice at 3-, 7-, 9-, and 24-week evaluations were analyzed for sphinganine and sphingosine concentrations. Up to four animals from groups exposed for up to 26 weeks and up to seven animals per group from the 2-year studies were evaluated for tissue sphingolipid concentrations. Urinary and tissue sphingolipid analyses are detailed in Table 10.

Complete necropsies were performed on all animals. The brain, heart, left and right kidneys, liver, and left and right testes were weighed at 3, 7, 9, or 24 weeks (mice), 6, 10, 14, or 26 weeks (rats), and at 2 years. At necropsy, all organs and tissues were examined for grossly visible lesions, and all major tissues were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in Tissue-Prep II, sectioned to a thickness of 4 to 6 µm, and stained with hematoxylin and eosin for microscopic examination. Complete histopathology was performed on all animals that died during the study, 0 ppm animals, and 150 ppm male rats and mice, 100 ppm female rats, and 80 ppm female mice at 2 years. The kidneys and livers from all other animals were examined at the 3-, 7-, 9-, and 24-week (mice) and 6-, 10-, 14-, and 26-week (rats) evaluations and at 2 years. The lungs of female rats were examined at 2 years. Tissues examined microscopically are listed in Table 10.

Microscopic evaluations were completed by the study laboratory pathologist, and the pathology data were entered into the study laboratory's Micropath Data Collection System. The slides, paraffin blocks, and residual wet tissues were sent to the study laboratory's Quality Assurance Archives for inventory, slide/block match, and wet tissue audit. The slides, individual animal data records, and pathology tables were eval-

evaluations and at 2 years. The lungs of female rats were examined at 2 years. Tissues examined microscopically are listed in Table 10.

Microscopic evaluations were completed by the study laboratory pathologist, and the pathology data were entered into the study laboratory's Micropath Data Collection System. The slides, paraffin blocks, and residual wet tissues were sent to the study laboratory's Quality Assurance Archives for inventory, slide/block match, and wet tissue audit. The slides, individual animal data records, and pathology tables were evaluated by an independent quality assessment group. The individual animal records and tables were compared for accuracy, the slide and tissue counts were verified, and the histotechnique was evaluated. For the 2-year studies, a quality assessment pathologist evaluated slides from all tumors and all potential target organs, which included the kidney and liver of male and female rats, the lung of female rats, the liver of male and female mice, and the harderian gland and lung of 0 and 150 ppm male mice.

Differences of opinion were reconciled between the study and quality assessment pathologist. The quality assessment pathologist served as chairperson of the Pathology Working Group (PWG), and presented histopathology slides containing the diagnoses made by the laboratory and quality assessment pathologists. Representative histopathology slides containing examples of lesions related to chemical administration, examples of disagreements in diagnoses between the laboratory and quality assessment pathologists, or lesions of general interest were presented by the chairperson to the PWG for review. The PWG consisted of the quality assessment pathologists, study pathologist, and other pathologists experienced in rodent toxicologic pathology. This group examined the tissues without any knowledge of dose groups or previously rendered diagnoses. When the PWG consensus differed from the opinion of the laboratory pathologist, the diagnosis was changed. Final diagnoses for reviewed lesions represent a consensus between the laboratory pathologist, reviewing pathologist(s), and the PWG. Details of these review procedures have been described, in part, by Maronpot and Boorman (1982) and Boorman *et al*. (1985). For subsequent analyses of the pathology data, the decision of whether to evaluate the diagnosed lesions for each tissue type separately or combined was generally based on the guidelines of McConnell *et al*. (1986).

Cell proliferation rates were evaluated in formalin-fixed liver and kidney tissue from the clinical pathology study animals. Liver BrdU and kidney BrdU proliferation rates were calculated as the number of labeled cells per 2,000 ± 75 hepatocytes or 2,100 ± 50 proximal tubule epithelial cells. Antibodies against PCNA were used to evaluate rates of cellular proliferation in the liver and kidneys. PCNA proliferation rates were calculated as the number of cells labeled with anti-PCNA antibodies per 2,000 ± 75 hepatocytes or 2,100 ± 50 proximal tubule epithelial cells. The presence of apoptosis-induced cellular changes was identified in hematoxylin- and eosin-stained sections of liver and kidneys.

TABLE 10
Experimental Design and Materials and Methods in the Feed Studies of Fumonisin B_1

28-Day Studies	2-Year Studies
Study Laboratory	
National Center for Toxicological Research (NCTR; Jefferson, AR)	National Center for Toxicological Research (NCTR; Jefferson, AR)
Strain and Species	
Rats: F344/N Nctr BR Mice: $B6C3F_1$/Nctr BR (C57BL/6N × C3H/HeN MTV$^-$)	Rats: F344/N Nctr BR Mice: $B6C3F_1$/Nctr BR (C57BL/6N × C3H/HeN MTV$^-$)
Animal Source	
NCTR breeding colony (Jefferson, AR)	NCTR breeding colony (Jefferson, AR)
Time Held Before Studies	
2 weeks	2 weeks
Average Age When Studies Began	
6 weeks	6 weeks
Date of First Day on Study	
Rats: core groups - 13 to 17 February 1994 clinical pathology study groups - 12, 13, 15, or 16 February 1994 Mice: core groups - 16 to 18 January 1994 clinical pathology study groups - 15 to 17 January 1994	Rats: 6-week evaluation - 24 February or 10 March 1995 10-week evaluation - 17 February or 3 March 1995 14-week evaluation - 24 February or 10 March 1995 26-week evaluation - 17 February or 3 March 1995 2-year study - 17 February, 3, 24, or 31 March, or 7 or 14 April 1995 Mice: 3-week evaluation - 12 April 1995 7-week evaluation - 29 March 1995 9-week evaluation - 5 April 1995 24-week evaluation - 22 March 1995 2-year study - 1, 8, 15, 22, or 29 March or 5 or 12 April 1995
Duration of Study	
28 days	Rats: 106 weeks (exposed for 105 weeks) Mice: 106 weeks (exposed for 105 weeks)
Date of Last Exposure	
Rats: core groups - 21 to 25 March 1994 clinical pathology study groups - 21, 22, 24, or 25 March 1994 Mice: 21 to 23 February 1994	Rats: 6-week evaluation - 3 or 17 April (males) or 6 or 20 April (females) 1995 10-week evaluation - 24 April or 8 May (males) or 27 April or 11 May (females) 1995 14-week evaluation - 30 May or 12 June (males) or 1 or 15 June (females) 1995 26-week evaluation - 14 or 28 August (males) or 17 or 31 August (females) 1995 2-year study - 24 February, 11 or 31 March, or 2, 7, 14, or 21 April 1997 Mice: 3-week evaluation - 1 (males) or 4 (females) May 1995 7-week evaluation - 15 (males) or 18 (females) May 1995 9-week evaluation - 5 (males) or 8 (females) June 1995 24-week evaluation - 5 (males) or 7 (females) September 1995 2-year study - 9, 16, 17, 23, or 30 March or 6 or 13 April 1997

TABLE 10
Experimental Design and Materials and Methods in the Feed Studies of Fumonisin B_1

28-Day Studies	2-Year Studies
Necropsy Dates	
Rats: 22 to 26 March 1994 Mice: 22 to 26 February 1994	Rats: 6-week evaluation - 4 or 18 April (males) or 7 or 21 April (females) 1995 10-week evaluation - 25 April or 9 May (males) or 28 April or 12 May (females) 1995 14-week evaluation - 31 May or 13 June (males) or 2 or 16 June (females) 1995 26-week evaluation - 15 or 29 August (males) or 18 August or 1 September (females) 1995 2-year study - 25 February, 12 March, or 1, 3, 8, 15, or 22 April 1997 Mice: 3-week evaluation - 2 (males) or 5 (females) May 1995 7-week evaluation - 16 (males) or 19 (females) May 1995 9-week evaluation - 6 (males) or 9 (females) June 1995 24-week evaluation - 6 (males) or 8 (females) September 1995 2-year study - 10, 17, 18, 24, or 31 March or 7 or 14 April 1997
Average Age at Necropsy	
10 weeks	Rats: 6-week evaluation: 12 weeks 10-week evaluation: 16 weeks 14-week evaluation: 20 weeks 26-week evaluation: 32 weeks 2-year study: 112 weeks Mice: 3-week evaluation: 9 weeks 7-week evaluation: 13 weeks 9-week evaluation: 15 weeks 24-week evaluation: 30 weeks 2-year study: 112 weeks
Size of Study Groups	
Rats: 10 males and 10 females (core); 8 males and 8 females (clinical pathology) Mice: 12 males and 12 females (core); 7 or 8 males and 4 or 8 females (clinical pathology)	Rats: 6-, 10-, 14-, and 26-week evaluations: 4 males and 4 females 2-year study: 48 males (0, 15, 50, 150 ppm), 48 females (0, 15, 50, 100 ppm), 40 males and 40 females (5 ppm) Mice: 3-, 7-, 9-, 24-week evaluations: 4 males and 4 females 2-year study: 48 males and 48 females
Method of Distribution	
Animals were distributed randomly into groups of approximately equal initial mean body weights.	Animals were distributed randomly into groups of approximately equal initial mean body weights.
Animals per Cage	
Rats: 2 Mice: 4	Rats: 2 Mice: 4
Method of Animal Identification	
Ear clip	Ear clip
Diet	
NIH-31 open formula meal (pellets were autoclaved, then ground to powder) (Purina Mills, Richmond, IN), available *ad libitum* except when animals were housed overnight in metabolism cages the night before necropsy for urine collection.	Same as 28-day studies

TABLE 10
Experimental Design and Materials and Methods in the Feed Studies of Fumonisin B_1

28-Day Studies	2-Year Studies
Water	
Millipore-filtered water (Jefferson municipal supply) via 16-oz water bottle, available *ad libitum*	Same as 28-day studies
Cages	
Polycarbonate (Allentown Caging Equipment Co., Allentown, NJ), changed twice weekly (rats) or weekly (mice); cages rotated weekly	Same as 28-day studies
Bedding	
Hardwood chips (Northeastern Products Inc., Warrensburg, NY), changed twice weekly (rats) or weekly (mice)	Same as 28-day studies
Cage Bonnets	
Microisolator tops (Lab Products, Inc, Maywood, NJ)	Same as 28-day studies
Racks	
Metal animal cage racks (Allentown Caging Equipment Co., Allentown, NJ), changed weekly	Same as 28-day studies
Animal Room Environment	
Temperature: 23° ± 3° C Relative humidity: 50% ± 20% Room fluorescent light: 12 hours/day Room air changes: at least 10/hour	Temperature: 23° ± 3° C Relative humidity: 50% ± 20% Room fluorescent light: 12 hours/day Room air changes: 10-15/hour
Exposure Concentrations	
0, 99, 163, 234, or 484 ppm in feed, available *ad libitum*	Rats: males - 0, 5, 15, 50, or 150 ppm in feed, available *ad libitum* females - 0, 5, 15, 50, or 100 ppm in feed, available *ad libitum* Mice: males - 0, 5, 15, 80, or 150 ppm in feed, available *ad libitum* females - 0, 5, 15, 50, or 80 ppm in feed, available *ad libitum*
Type and Frequency of Observation	
Animals were observed twice daily (rats) or once daily (mice); animals were weighed initially, weekly, and at the end of the studies. Feed consumption by core study animals was measured weekly. Clinical findings were recorded once weekly.	Observed twice daily; animals were weighed weekly and at the end of the studies. Clinical findings and feed consumption (by cage) were recorded weekly.
Method of Sacrifice	
Asphyxiation with carbon dioxide, following overnight fasting	Same as 28-day studies
Necropsy	
Necropsies were performed on all animals. Organs weighed were brain, heart, left and right kidneys, liver, and left and right testes.	Necropsies were performed on all animals. Organs weighed were brain, heart, left and right kidneys, liver, and left and right testes.

TABLE 10
Experimental Design and Materials and Methods in the Feed Studies of Fumonisin B_1

28-Day Studies	2-Year Studies
Clinical Pathology	
Blood was collected from the retroorbital sinus of rats anesthetized with carbon dioxide. Rats and mice in the clinical pathology study groups were evaluated on days 7 and 14 and at the end of the studies (day 28). Core study animals were evaluated at the end of the studies. Animals were housed overnight in metabolism cages for urine collection prior to necropsy. ***Clinical chemistry:*** urea nitrogen, creatinine, total protein, albumin, albumin/total protein ratio, cholesterol, triglycerides, alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, sorbitol dehydrogenase (rats), γ-glutamyltransferase, total bile acids ***Urinalysis:*** creatinine, glucose (rats), proteins, *N*-acetyl-β-D-glucosaminidase (rats), sphingosine, sphinganine, sphinganine/sphingosine ratio	Blood was collected from the retroorbital sinus of rats evaluated at 6, 10, 14, or 26 weeks and mice evaluated at 3, 7, 9, or 24 weeks for hematology and clinical chemistry analyses. Whole blood, urine, and tissues for sphingolipid analyses were collected from up to four rats and mice at each time point. Animals were housed overnight in metabolism cages for urine collection prior to necropsy. In addition, kidney sphingolipids were evaluated in up to seven rats at 2 years. ***Hematology:*** hematocrit; hemoglobin; erythrocyte, platelets, and leukocyte counts; mean cell volume; mean cell hemoglobin; mean cell hemoglobin concentration ***Clinical chemistry:*** Rats - urea nitrogen, creatinine, total protein, albumin, cholesterol, triglycerides, alanine aminotrasferase, alkaline phosphatase, creatine kinase, sorbitol dehydrogenase, γ-glutamyltransferase, total bile acids Mice - creatinine, albumin, cholesterol, triglycerides, alanine aminotrasferase, alkaline phosphatase ***Urinalysis:*** creatinine, protein, sphingosine (rats), sphinganine (rats), sphinganine/sphingosine ratio (rats) ***Tissue Sphingolipids:*** kidney (rats) and liver
Histopathology	
Complete histopathologic evaluations were performed on all core study rats and mice in the 0 and 484 ppm groups and all animals that died early. In addition to gross lesions and tissue masses, the following tissues were examined: adrenal gland, aorta, bone (femur), bone marrow (sternum), brain (cerebellum, cerebrum, stem), clitoral gland (rats), esophagus, gallbladder (mice), harderian gland, heart, large intestine (cecum, colon, rectum), small intestine (duodenum, jejunum, ileum), kidney, larynx, liver, lung, lymph nodes (mandibular and mesenteric), nose, ovary (with oviduct), pancreas, parathyroid gland, pharynx, pituitary gland, preputial gland, prostate gland, salivary gland, sciatic nerve, seminal vesicle, skin (mammary), spinal cord (thoracic), spleen, stomach (forestomach and glandular stomach), testis (with epididymis), thigh muscle, thymus, thyroid gland, tongue, trachea, ureter (mice), urethra (mice), urinary bladder, uterus, vagina (rats), and Zymbal's gland (rats). The kidney, liver, and gross lesions were examined in rats and mice in the lower exposure groups and all clinical pathology study animals.	Complete histopathology was performed on all animals that died during the study, 0 ppm animals, and 150 ppm male rats and mice, 100 ppm female rats, and 80 ppm female mice at 2 years. In addition to gross lesions and tissue masses, the following tissues were examined: adrenal gland, blood vessel, bone with marrow, brain (cerebellum, cerebrum), clitoral gland, coagulating gland, esophagus, eye, gallbladder (mice only), harderian gland, heart, large intestine (cecum, colon, rectum), small intestine (duodenum, jejunum, ileum), kidney, lacrimal gland, larynx, liver, lung, lymph nodes (mandibular and mesenteric), mammary gland, mesentery, nose, ovary, pancreas, parathyroid gland, peripheral nerve, pituitary gland, preputial gland, prostate gland, salivary gland, skeletal muscle, skin, spinal cord, spleen, stomach (forestomach and glandular), testis with epididymis and seminal vesicle, thymus, thyroid gland, tongue, trachea, urinary bladder, uterus, vagina, and Zymbal's gland. The kidney and liver from all other animals were examined at the 3-, 7-, 9-, and 24-week (mice) and 6-, 10-, 14-, and 26-week (rats) evaluations and at 2 years. The lung of female rats was examined at 2 years.
Cell Proliferation, Cell Cycle Analyses, and Apoptosis	
Sections of liver tissue from all core study rats and mice were stained with antibodies to PCNA. At least 2,000 cells per slide were scored for the presence of the antigen. The percentage of labeled cells in each cycle phase (G_0, G_1, G_2, S, or M), the sum of these percentages, and the sum of the percentages of cells in the S and M phases were calculated.	All rats evaluated at 6, 10, 14, or 26 weeks and all mice evaluated at 3, 7, 9, or 24 weeks were injected with 5-bromo-2-deoxyuridine (BrdU). Liver BrdU and kidney BrdU proliferation rates were calculated as the number of labeled cells per 2,000 ± 75 hepatocytes or 2,100 ± 50 proximal tubule epithelial cells. Antibodies against PCNA were used to evaluate at least 2,000 ± 75 hepatocytes or 2,100 ± 50 proximal tubule epithelial cells for cellular proliferation in the liver and kidneys. The percentage of labeled cells in each cycle phase (G_0, G_1, G_2, S, or M) and the sum of these percentages were calculated. The presence of apoptosis-induced cellular changes was identified in hematoxylin- and eosin-stained sections of liver and kidneys.

STATISTICAL METHODS

Survival Analyses

The probability of survival was estimated by the product-limit procedure of Kaplan and Meier (1958) and is presented in the form of graphs. Animals found dead of other than natural causes, missing, or removed from the study were censored from the survival analyses; animals dying from natural causes were not censored. Statistical analyses for possible dose-related effects on survival used Cox's (1972) method for testing two groups for equality and Tarone's (1975) life table test to identify dose-related trends. All reported P values for the survival analyses are two sided.

Calculation of Incidence

The Fisher exact test, a procedure based on the overall proportion of affected animals (Gart *et al.*, 1979), was used to determine significance of lesion incidences in the 28-day studies. The P values were adjusted with a modified Bonferroni procedure (Holm, 1979). The Cochran-Armitage test for dose-response trend of proportions (Thomas *et al.*, 1977) was used to determine the probability of trends across exposure concentrations. All tests were one sided; decreases in incidence with increasing exposure concentration were not considered.

The incidences of neoplasms or nonneoplastic lesions in the 2-year studies as presented in Tables A1, A4, B1, B4, C1, C4, D1, and D4 are given as the numbers of animals bearing such lesions at a specific anatomic site and the numbers of animals with that site examined microscopically. For calculation of statistical significance, the incidences of neoplasms (Tables A3, B3, C3, and D3) and nonneoplastic lesions are given as the numbers of animals affected at each site examined microscopically. Tables A3, B3, C3, and D3 also give the survival-adjusted neoplasm rate for each group and each site-specific neoplasm. This survival-adjusted rate (based on the Poly-3 method described below) accounts for differential mortality by assigning a reduced risk of neoplasm, proportional to the third power of the fraction of time on study, to animals not reaching terminal sacrifice.

Analysis of Neoplasm and Nonneoplastic Lesion Incidences

The Poly-k test (Bailer and Portier, 1988; Portier and Bailer, 1989; Piegorsch and Bailer, 1997) was used to assess neoplasm and nonneoplastic lesion prevalence. This test is a survival-adjusted quantal-response procedure that modifies the Cochran-Armitage linear trend test to take survival differences into account. More specifically, this method modifies the denominator in the quantal estimate of lesion incidence to approximate more closely the total number of animal years at risk. For analysis of a given site, each animal is assigned a risk weight. This value is one if the animal had a lesion at that site or if it survived until terminal sacrifice; if the animal died prior to terminal sacrifice and did not have a lesion at that site, its risk weight is the fraction of the entire study time that it survived, raised to the kth power.

This method yields a lesion prevalence rate that depends only upon the choice of a shape parameter for a Weibull hazard function describing cumulative lesion incidence over time (Bailer and Portier, 1988). Unless otherwise specified, a value of k=3 was used in the analysis of site-specific lesions. This value was recommended by Bailer and Portier (1988) following an evaluation of neoplasm onset time distributions for a variety of site-specific neoplasms in control F344 rats and $B6C3F_1$ mice (Portier *et al.*, 1986). Bailer and Portier (1988) showed that the Poly-3 test gave valid results if the true value of k was anywhere in the range from 1 to 5. A further advantage of the Poly-3 method is that it does not require lesion lethality assumptions.

Tests of significance included pairwise comparisons of each exposed group with controls and a test for an overall exposure-related trend. Continuity-corrected Poly-3 tests were used in the analysis of lesion incidence, and reported P values are one sided. The significance of lower incidences or decreasing trends in lesions are represented as 1–P with the letter N added (e.g., P=0.99 is presented as P=0.01N).

Analysis of Continuous Variables

Body weight and feed consumption data from the 28-day studies were analyzed using a repeated-measures analysis of variance, while organ weights were analyzed in a one-way analysis. The procedure of Holm (1979) was used to adjust for multiple comparisons of exposed groups to controls for each endpoint. For all other studies, a one-way analysis of variance was used for organ weights, with pairwise comparisons to controls adjusted by the procedure of Dunnett (1955).

Clinical chemistry data for core study animals in the 28-day studies were analyzed using a one-way analysis of variance, along with Holm's procedure to adjust for multiple comparisons to controls. Clinical chemistry and nonsphingolipid urinalysis data from the 28-day clinical pathology studies were analyzed using a multivariate generalized growth curve model to account for differences in the day of observation (Kleinbaum, 1973). Urinary sphingolipid data for the clinical pathology animals were analyzed with a repeated measures analysis of variance to account for the day effect. In both cases, comparisons of means of exposed groups to controls were adjusted by Holm's procedure. For all other studies, clinical pathology data were analyzed using a one-way analysis of variance at each time point, in conjunction with Dunnett's procedure for comparing exposed groups to controls.

Hepatocyte cell cycle data from the 28-day studies were analyzed with a one-way analysis of variance, with Holm's procedure to adjust for multiple comparisons of exposed groups to controls. Liver and kidney cell proliferation data from all other studies were analyzed individually for each study week using a one-way analysis of variance, with Dunnett's test for comparisons of exposed groups to controls.

Quality Assurance Methods

The 28-day and 2-year studies were conducted in compliance with Food and Drug Administration Good Laboratory Practice Regulations (21 CFR, Part 58). The Quality Assurance Unit of the National Center for Toxicological Research performed audits and inspections of protocols, procedures, data, and reports throughout the course of the studies. Separate audits covering completeness and accuracy of the pathology data, pathology specimens, final pathology tables, and a draft of this NTP Technical Report were conducted. Audit procedures and findings are presented in the reports and are on file at NCTR. The audit findings were reviewed and assessed by NCTR staff, and all comments resolved or otherwise addressed during the preparation of this Technical Report.

RESULTS

RATS

28-DAY STUDY

All core and clinical pathology study rats survived to the end of the study (Tables 11 and 12). The final mean body weights and body weight gains of core and clinical pathology study males and females in the 484 ppm groups, core study males and females in the 163 and 234 ppm groups, and clinical pathology study males in the 234 ppm group were significantly less than those of the controls (Tables 11 and 12). Feed consumption by core study males in the 484 ppm group was less than that by the controls at weeks 1 and 4; feed consumption by core study females exposed to 484 ppm was also less than that by the controls at week 1. In the core studies, dietary concentrations of 99, 163, 234, and 484 ppm fumonisin B_1 resulted in average daily doses of approximately 12, 20, 28, and 56 mg fumonisin B_1/kg body weight to males and females. There were no apparent exposure-related clinical findings in male or female rats.

TABLE 11
Survival, Body Weights, and Feed Consumption of Core Study Rats in the 28-Day Feed Study of Fumonisin B_1

Concentration (ppm)	Survival[a]	Mean Body Weight[b] (g) Initial	Final	Change	Final Weight Relative to Controls (%)	Feed Consumption[c] Week 1	Week 4
Male							
0	10/10	89 ± 4	223 ± 2	134		17.5	18.8
99	10/10	88 ± 3	218 ± 2	130	98	17.9	19.0
163	10/10	90 ± 3	216 ± 2**	126	97	17.7	19.4
234	10/10	90 ± 4	216 ± 2**	126	97	18.0	18.8
484	10/10	88 ± 5	187 ± 1****	99	84	15.7***	16.2**
Female							
0	10/10	84 ± 3	148 ± 1	64		13.5	14.1
99	10/10	84 ± 3	147 ± 1	63	99	13.7	14.9
163	10/10	84 ± 3	143 ± 1**	59	97	13.8	14.5
234	10/10	84 ± 3	136 ± 1****	52	92	13.7	13.3
484	10/10	85 ± 3	131 ± 1****	47	89	12.3*	12.7

* Significantly different ($P \leq 0.05$) from the control group by a repeated measures analysis of variance with application of Holm's procedure
** $P \leq 0.01$
*** $P \leq 0.001$
**** $P \leq 0.0001$
a Number of animals surviving at 28 days/number initially in group
b Weights are given as mean ± standard error, and weight changes are given as the mean.
c Feed consumption is expressed as grams of feed consumed per animal per day.

TABLE 12
Survival and Body Weights of Clinical Pathology Study Rats in the 28-Day Feed Study of Fumonisin B_1

Concentration (ppm)	Survival[a]	Mean Body Weight[b] (g) Initial	Final	Change	Final Weight Relative to Controls (%)
Male					
0	8/8	102 ± 5	198 ± 8	96	
99	8/8	97 ± 4	190 ± 3	93	96
163	8/8	89 ± 4	185 ± 3	96	93
234	8/8	95 ± 4	178 ± 7*	83	90
484	8/8	96 ± 5	164 ± 4***	68	83
Female					
0	8/8	92 ± 3	137 ± 3	45	
99	8/8	88 ± 4	136 ± 4	48	99
163	8/8	88 ± 4	128 ± 3	40	93
234	8/8	91 ± 5	127 ± 4	36	93
484	8/8	91 ± 3	118 ± 3**	27	86

* Significantly different ($P \leq 0.05$) from the control group by a repeated measures analysis of variance with application of Holm's procedure
** $P \leq 0.01$
*** $P \leq 0.001$
a Number of animals surviving at 28 days/number initially in group
b Weights are given as mean ± standard error, and weight changes are given as the mean.

The clinical pathology data for rats in the 28-day feed study of fumonisin B_1 are listed in Tables 13 and F1. A treatment-related hypercholesterolemia, demonstrated by increased cholesterol concentrations, occurred at all time points for 484 ppm male and females and 234 ppm females; increases occurred sporadically in 234 ppm males and 163 ppm females. Increased triglyceride concentrations accompanied the hypocholesterolemia and occurred at all time points in 484 ppm males, at most time points in 484 ppm females, and occasionally in the 163 and 234 ppm groups. At all time points, alanine aminotransferase activities, a marker of hepatocellular injury or leakage, were strongly increased in 484 ppm males and females; they also demonstrated sporadic increases in the 234 ppm groups. At the end of the study, aspartate aminotransferase activity, a marker of soft tissue injury, was increased in 234 and 484 ppm males and females; this would be consistent with the alanine aminotransferase activity increases. Sorbitol dehydrogenase activity, another marker of hepatocellular injury, was also evaluated at the end of the study but was unaffected. Total bile acid concentrations, a marker of cholestasis or altered hepatic function, were markedly increased at all time points for rats exposed to 484 ppm and were occasionally increased in females in the 163 and 234 ppm groups. Alkaline phosphatase and γ-glutamyltransferase activities, other markers of cholestasis, were also moderately to markedly increased in 484 ppm males and females and 234 ppm females. At study termination, serum creatinine concentration, a marker of renal function, was increased in 484 ppm males and females.

TABLE 13
Selected Clinical Chemistry and Urinalysis Data for Rats in the 28-Day Feed Study of Fumonisin B_1[a]

	0 ppm	99 ppm	163 ppm	234 ppm	484 ppm
n					
Day 7	4	4	4	4	4
Day 14	4	4	4	4	4
Day 28	8	8	8	8	8
Core study	4	4	4	4	4
Male					
Clinical Chemistry					
Creatinine (mg/dL)					
Day 28	0.41 ± 0.01	0.46 ± 0.02	0.50 ± 0.04	0.53 ± 0.04**	0.63 ± 0.03****
Core study	0.56 ± 0.04	0.56 ± 0.06	0.55 ± 0.05[b]	0.69 ± 0.08	0.73 ± 0.03*[b]
Total protein (g/dL)					
Day 28	6.3 ± 0.1	6.3 ± 0.1	6.3 ± 0.1	6.9 ± 0.5	7.0 ± 0.3
Core study	6.6 ± 0.1	6.6 ± 0.1	6.6 ± 0.1	6.6 ± 0.1	7.0 ± 0.1*
Cholesterol (mg/dL)					
Day 7	85 ± 5	92 ± 4	96 ± 5	103 ± 7	266 ± 30****
Day 14	88 ± 8	80 ± 7	83 ± 5	136 ± 13*	220 ± 18****
Day 28	48 ± 2	49 ± 1	54 ± 2	75 ± 8	225 ± 24****
Core study	60 ± 1	61 ± 2	60 ± 2	62 ± 3	212 ± 20****
Triglycerides (mg/dL)					
Day 7	82 ± 12	88 ± 4	83 ± 7	89 ± 11	175 ± 11****
Day 14	75 ± 12	100 ± 10	79 ± 4	133 ± 13**	163 ± 18****
Day 28	54 ± 3	66 ± 5	74 ± 5*	86 ± 7**	107 ± 7****
Core study	120 ± 17	122 ± 19	107 ± 18	101 ± 15	143 ± 9
Alanine aminotransferase (IU/L)					
Day 7	42 ± 2	42 ± 3	46 ± 2	61 ± 5	188 ± 46****[b]
Day 14	52 ± 14	40 ± 1	36 ± 5	83 ± 6	118 ± 15***
Day 28	35 ± 3	34 ± 1	48 ± 10	58 ± 7	156 ± 27****
Core study	24 ± 1	27 ± 1	34 ± 5	45 ± 4**	174 ± 29****
Alkaline phosphatase (IU/L)					
Day 7	360 ± 8	382 ± 11	388 ± 11	423 ± 3	846 ± 134****[b]
Day 14	379 ± 8[b]	346 ± 9	362 ± 12	336 ± 48	732 ± 81****
Day 28	259 ± 10	258 ± 8	284 ± 11	333 ± 19	623 ± 37****
Core study	266 ± 7	254 ± 8	260 ± 12	277 ± 14	577 ± 42****
Aspartate aminotransferase (IU/L)					
Day 28	75 ± 6	72 ± 3	94 ± 11	96 ± 8	248 ± 20****
Core study	50 ± 4	60 ± 4	65 ± 4*	69 ± 1**	238 ± 31****
γ-Glutamyltransferase (IU/L)					
Day 28	0.4 ± 0.1	0.5 ± 0.1	0.4 ± 0.1	0.8 ± 0.2	5.8 ± 0.6****
Core study	0.8 ± 0.4	0.9 ± 0.3	1.2 ± 0.2	0.7 ± 0.2	5.0 ± 0.5****
Total bile acids (μmol/L)					
Day 7	17.4 ± 2.1	15.9 ± 1.0[c]	23.8 ± 1.6	29.2 ± 6.0	130.1 ± 66.4*[b]
Day 14	19.0 ± 2.6[b]	21.5 ± 6.5[c]	15.3[d]	52.6 ± 14.1[c]	117.2 ± 36.8***[c]
Day 28	10.3 ± 1.1	10.5 ± 1.3	20.0 ± 9.5	18.7 ± 2.7	72.4 ± 11.5****
Core study	18.2 ± 0.8	12.4 ± 1.4	12.7 ± 1.7	20.7 ± 1.6	115.7 ± 28.9****

TABLE 13
Selected Clinical Chemistry and Urinalysis Data for Rats in the 28-Day Feed Study of Fumonisin B_1

	0 ppm	99 ppm	163 ppm	234 ppm	484 ppm
n					
Day 7	4	4	4	4	4
Day 14	4	4	4	4	4
Day 28	8	8	8	8	8
Core study	4	4	4	4	4
Male (continued)					
Urinalysis					
Sphingosine (pmol/mL)					
Day 7	31.48 ± 7.19	76.15 ± 23.78	50.37 ± 13.24	41.48 ± 11.26	46.20 ± 13.73
Day 14	49.93 ± 1.95	176.21 ± 50.00	292.42 ± 68.27*[b]	225.74 ± 37.46	213.74 ± 43.33
Day 28	27.76 ± 3.13	166.38 ± 25.63*	346.15 ± 64.77*	152.76 ± 14.01*	171.90 ± 24.86*
Sphinganine (pmol/mL)					
Day 7	74.35 ± 45.59	320.24 ± 19.49	453.93 ± 136.30	365.62 ± 114.68	542.33 ± 211.84
Day 14	82.34 ± 20.80	805.32 ± 224.43	1,720.68 ± 327.04*[b]	1,583.51 ± 282.51*	1,579.41 ± 600.55*
Day 28	33.28 ± 3.53	880.46 ± 118.38*	2,137.35 ± 374.58*	1,103.07 ± 110.26*	1,326.02 ± 162.32*
Sphinganine/sphingosine ratio					
Day 7	2.29 ± 1.40	5.42 ± 1.51	8.70 ± 0.89*	9.13 ± 1.66*	10.04 ± 2.20*
Day 14	1.65 ± 0.41	4.56 ± 0.23	5.99 ± 0.29[b]	6.98 ± 0.20*	7.04 ± 2.02*
Day 28	1.35 ± 0.28	5.39 ± 0.18*	6.27 ± 0.11*	7.24 ± 0.26*	8.12 ± 0.59*
Female					
Clinical Chemistry					
Creatinine (mg/dL)					
Day 28	0.45 ± 0.02	0.45 ± 0.03	0.51 ± 0.01	0.51 ± 0.01	0.60 ± 0.02****
Core study	0.51 ± 0.04	0.54 ± 0.05	0.56 ± 0.04	0.59 ± 0.06*	0.65 ± 0.04***
Total protein (g/dL)					
Day 28	7.0 ± 0.4	6.7 ± 0.5	6.6 ± 0.0	7.3 ± 0.3	7.5 ± 0.3
Core study	6.5 ± 0.1	6.4 ± 0.0	6.7 ± 0.1	6.8 ± 0.1	7.1 ± 0.1**
Cholesterol (mg/dL)					
Day 7	103 ± 8	95 ± 2	120 ± 6	195 ± 12****	272 ± 21****
Day 14	91 ± 3	97 ± 3	170 ± 14**	240 ± 19****	255 ± 34****
Day 28	117 ± 17	109 ± 17	130 ± 5	205 ± 22**	280 ± 32****
Core study	101 ± 4	106 ± 3	147 ± 9	189 ± 12**	244 ± 30***
Triglycerides (mg/dL)					
Day 7	62 ± 7	62 ± 11	60 ± 5	83 ± 11	82 ± 5
Day 14	45 ± 5	44 ± 2	68 ± 7*	94 ± 11****	128 ± 4****
Day 28	64 ± 6	60 ± 3	63 ± 4	74 ± 5	97 ± 8***
Core study	68 ± 9	80 ± 11	111 ± 12**	132 ± 11***	139 ± 13***
Alanine aminotransferase (IU/L)					
Day 7	35 ± 3	33 ± 2	38 ± 3	71 ± 3***	146 ± 12****
Day 14	30 ± 1	33 ± 0	50 ± 7	64 ± 9	165 ± 47***
Day 28	37 ± 5	35 ± 5	33 ± 2	59 ± 8	119 ± 22****
Core study	38 ± 3	43 ± 4	44 ± 9	59 ± 8	120 ± 14***
Alkaline phosphatase (IU/L)					
Day 7	287 ± 3	277 ± 11	278 ± 15	343 ± 4*	792 ± 27****
Day 14	234 ± 3	240 ± 6	265 ± 14	350 ± 23**	711 ± 48****
Day 28	196 ± 15	177 ± 14	177 ± 5	262 ± 16	529 ± 45****
Core study	166 ± 5	164 ± 7	177 ± 10	235 ± 9*	490 ± 36****

TABLE 13
Selected Clinical Chemistry and Urinalysis Data for Rats in the 28-Day Feed Study of Fumonisin B_1

	0 ppm	99 ppm	163 ppm	234 ppm	484 ppm
n					
Day 7	4	4	4	4	4
Day 14	4	4	4	4	4
Day 28	8	8	8	8	8
Core study	4	4	4	4	4
Female (continued)					
Clinical Chemistry (continued)					
Aspartate aminotransferase (IU/L)					
Day 28	80 ± 5	71 ± 5	82 ± 4	119 ± 8**	194 ± 15****
Core study	73 ± 5	70 ± 5	70 ± 7	97 ± 9	201 ± 20****
γ-Glutamyltransferase (IU/L)					
Day 28	0.7 ± 0.2	0.6 ± 0.1	0.9 ± 0.2	1.5 ± 0.5	6.8 ± 1.1****
Core study	0.6 ± 0.2	0.9 ± 0.4	0.8 ± 0.1	1.7 ± 0.3*	10.8 ± 2.7****
Total bile acids (μmol/L)					
Day 7	16.1 ± 8.2[b]	18.6 ± 3.2[b]	26.3 ± 2.0	77.4 ± 8.9*	192.8 ± 27.0****
Day 14	13.3 ± 6.4[c]	14.9[d]	35.4 ± 1.2[c]	73.1 ± 13.4[c]	193.8 ± 42.0**
Day 28	11.3 ± 2.2	10.5 ± 1.6	19.0 ± 3.4	31.8 ± 4.5	110.9 ± 25.4****
Core study	13.7 ± 1.4	16.9 ± 2.3	29.9 ± 4.7**	47.0 ± 6.1****	109.8 ± 23.4****
Urinalysis					
Sphingosine (pmol/mL)					
Day 7	10.59 ± 1.62	38.24 ± 20.02*	139.55 ± 28.12*	237.10 ± 83.99*	204.79 ± 103.37*
Day 14	14.73 ± 2.41	39.83 ± 5.77*	68.07 ± 16.77*	142.68 ± 43.29*	107.71 ± 24.37*
Day 28	15.44 ± 3.87	20.55 ± 4.78	38.24 ± 9.48*	80.31 ± 21.19*	86.17 ± 10.03*
Sphinganine (pmol/mL)					
Day 7	18.39 ± 5.27	208.21 ± 68.31*	1,141.94 ± 223.65*	2,256.62 ± 1141.94*	1,236.29 ± 131.84*
Day 14	39.12 ± 3.14	195.36 ± 15.84*	448.32 ± 95.07*	1,306.99 ± 331.51*	1,166.06 ± 302.75*
Day 28	22.11 ± 9.34	112.72 ± 24.61*	358.41 ± 87.42*	824.14 ± 204.25*	887.02 ± 149.43*
Sphinganine/sphingosine ratio					
Day 7	1.73 ± 0.39	7.49 ± 3.16*	8.20 ± 0.16*	8.92 ± 1.68*	9.34 ± 2.23*
Day 14	2.90 ± 0.59	5.15 ± 0.69*	7.05 ± 0.72*	9.63 ± 0.94*	10.58 ± 0.36*
Day 28	2.18 ± 1.31	5.67 ± 0.47	9.69 ± 0.87*	10.78 ± 0.98*	10.11 ± 0.76*

* Significantly different (P≤0.05) from the control group by Kleinbaum's procedure (clinical chemistry data) or a repeated measures analysis of variance (urinalysis data), with application of Holm's procedure
** P≤0.01
*** P≤0.001
**** P≤0.0001
a Mean ± standard error. Statistical tests were performed on unrounded data. Core study animals were evaluated on day 28; clinical pathology study animals were evaluated on days 7, 14, and 28.
b n=3
c n=2
d n=1; no standard error was calculated because fewer than two measurements were available.

Urine sphinganine and sphingosine concentrations and sphinganine/sphingosine ratios of clinical pathology study females were increased at 99 ppm and generally increased with increasing exposure concentration. The ratio of these sphingolipids in fluids and tissues has been used as an indicator of fumonisin B_1 inhibition of ceramide synthase (Wang *et al.*, 1991). In clinical pathology study males, these concentrations were increased in exposed groups. However, the differences were significant in all exposed groups only on day 28. The sphinganine/sphingosine ratios were also significantly increased in males exposed to 163 ppm or greater on days 7 and 28. The sphinganine concentrations in males exposed to 163 ppm or greater and the ratios in the 234 and 484 ppm groups were significantly increased on day 14.

The absolute and relative kidney weights of core and clinical pathology study males and all exposed groups of females were less than those of the control groups (Tables 14, 15, G1, and G2). The absolute and relative liver weights of core and clinical pathology study males exposed to 484 ppm were significantly less than those of the controls. Other differences in organ weights generally reflected body weight changes and were not biologically significant.

TABLE 14
Selected Organ Weight Data for Core Study Rats in the 28-Day Feed Study of Fumonisin B_1[a]

	0 ppm	99 ppm	163 ppm	234 ppm	484 ppm
n	10	10	10	10	10
Male					
Final body wt	223 ± 2	218 ± 2	216 ± 2**	216 ± 2**	187 ± 1****
L. and R. Kidneys					
Absolute	1.874 ± 0.044	1.603 ± 0.038****	1.515 ± 0.024****	1.476 ± 0.033****	1.279 ± 0.028****
Relative	8.408 ± 0.082	7.364 ± 0.085****	7.025 ± 0.125****	6.846 ± 0.059****	6.836 ± 0.140****
Liver					
Absolute	8.802 ± 0.239	9.088 ± 0.312	8.848 ± 0.204	8.522 ± 0.267	6.216 ± 0.123****
Relative	39.492 ± 0.598	41.692 ± 0.749	40.950 ± 0.638	39.478 ± 0.722	33.227 ± 0.656****
Female					
Final body wt	148 ± 1	147 ± 1	143 ± 1**	136 ± 1****	131 ± 1****
L. and R. Kidneys					
Absolute	1.315 ± 0.025	1.160 ± 0.023****	1.155 ± 0.018****	1.076 ± 0.021****	1.042 ± 0.026****
Relative	8.907 ± 0.119	7.901 ± 0.112****	8.082 ± 0.079****	7.915 ± 0.110****	7.955 ± 0.122****
Liver					
Absolute	5.231 ± 0.112	5.203 ± 0.124	5.264 ± 0.114	4.581 ± 0.081***	4.641 ± 0.149***
Relative	35.452 ± 0.616	35.451 ± 0.713	36.815 ± 0.416	33.704 ± 0.538	35.435 ± 0.875

** Significantly different (P≤0.01) from the control group by a one-way analysis of variance with application of Holm's procedure
*** P≤0.001
**** P≤0.0001
a Organ weights (absolute weights) and body weights are given in grams; organ-weight-to-body-weight ratios (relative weights) are given as mg organ weight/g body weight (mean ± standard error).

TABLE 15
Selected Organ Weight Data for Clinical Pathology Study Rats in the 28-Day Feed Study of Fumonisin B_1[a]

	0 ppm	99 ppm	163 ppm	234 ppm	484 ppm
n	8	8	8	8	8
Male					
Final body wt	198 ± 8	190 ± 3	185 ± 3	178 ± 7*	164 ± 4***
L. and R. Kidneys					
Absolute	1.737 ± 0.059	1.459 ± 0.022****	1.380 ± 0.029****	1.272 ± 0.054****	1.210 ± 0.022****
Relative	8.791 ± 0.207	7.678 ± 0.092****	7.468 ± 0.141****	7.145 ± 0.105****	7.399 ± 0.125****
Liver					
Absolute	8.244 ± 0.312	8.153 ± 0.225	7.936 ± 0.208	7.230 ± 0.376*	6.089 ± 0.128****
Relative	41.746 ± 1.301	42.879 ± 0.871	42.915 ± 0.927	40.493 ± 0.819	37.194 ± 0.444**
Female					
Final body wt	137 ± 3	136 ± 4	128 ± 3	127 ± 4	118 ± 3**
L. and R. Kidneys					
Absolute	1.301 ± 0.044	1.190 ± 0.100	1.039 ± 0.031**	1.071 ± 0.029**	0.937 ± 0.029***
Relative	9.489 ± 0.172	8.683 ± 0.484*	8.092 ± 0.162**	8.450 ± 0.170*	7.954 ± 0.179***
Liver					
Absolute	5.090 ± 0.150	5.152 ± 0.144	4.818 ± 0.176	4.689 ± 0.144	4.291 ± 0.093**
Relative	37.166 ± 0.784	37.968 ± 0.936	37.457 ± 0.775	36.966 ± 0.622	36.432 ± 0.404

* Significantly different ($P \leq 0.05$) from the control group by a one-way analysis of variance with application of Holm's procedure
** $P \leq 0.01$
*** $P \leq 0.001$
**** $P \leq 0.0001$
[a] Organ weights (absolute weights) and body weights are given in grams; organ-weight-to-body-weight ratios (relative weights) are given as mg organ weight/g body weight (mean ± standard error).

Apoptosis and degeneration of the kidney were observed in all exposed males in the core and clinical pathology studies, in all core study females exposed to 163 ppm or greater, and in all clinical pathology study females in the 234 and 484 ppm groups (Tables 16 and 17). Apoptotic kidney cells were noted by cellular shrinkage from adjacent cells, cytoplasmic eosinophilia, and chromatin condensation and margination in the nucleus. Although apoptotic bodies were not detected, the clear morphologic markers of apoptosis were present. Apoptotic tubular epithelial cells were additionally indicated using an *in situ* method for detecting DNA fragmentation. In the clinical pathology study females, the incidences of kidney degeneration and apoptosis were also significantly increased in the 163 ppm group. The severities of apoptosis and degeneration were mild in males; severities ranged from minimal to mild in core study females and minimal to moderate in clinical pathology study females. These lesions were noted in the inner cortex of the tubule epithelium in males and females.

In the core and clinical pathology study rats, the incidences of apoptosis and degeneration of the liver were significantly increased in males in the 234 and 484 ppm groups and females exposed to 163 ppm or greater (Tables 16 and 17). Hepatocytes undergoing apoptosis were clearly evident through morphologic analysis. The cell volumes were decreased, causing withdrawal from neighboring cells. The apoptotic hepatocytes were eosinophilic with condensed and marginated nuclei. There was an apparent lack of necrosis in the tissues, with disorganization of the sinusoidal structure (hepatocellular degeneration) being the result of the apoptosis of hepatocytes. Apototic cells were confirmed using an *in situ* method for the detection of

TABLE 16
Incidence of Kidney and Liver Lesions in Core Study Rats in the 28-Day Feed Study of Fumonisin B_1

	0 ppm	99 ppm	163 ppm	234 ppm	484 ppm
Male					
Kidney[a]	10	10	10	10	10
Apoptosis[b]	0	10** (2.0)[c]	10** (2.0)	10** (2.0)	10** (2.0)
Degeneration	0	10** (1.9)	10** (2.0)	10** (2.0)	10** (2.0)
Liver	10	10	10	10	10
Apoptosis	0	0	0	9** (1.1)	10** (2.3)
Degeneration	0	0	0	10** (1.0)	10** (2.0)
Mitotic Alteration	0	0	0	0	10** (2.0)
Bile Duct, Hyperplasia	0	0	0	0	9** (1.2)
Female					
Kidney	10	10	10	10	10
Apoptosis	0	0	10** (1.0)	10** (1.0)	10** (2.4)
Degeneration	0	0	10** (1.3)	10** (2.0)	10** (2.0)
Liver	10	10	10	10	10
Apoptosis	0	2 (1.0)	9** (1.2)	10** (1.9)	10** (2.2)
Degeneration	0	0	8** (1.1)	10** (2.0)	10** (2.3)
Mitotic Alteration	0	0	4* (1.0)	10** (2.0)	10** (2.2)
Bile Duct, Hyperplasia	0	0	0	4* (1.0)	10** (1.9)

* Significantly different ($P \leq 0.05$) from the control group by the Fisher exact test
** $P \leq 0.01$
[a] Number of animals with organ examined microscopically
[b] Number of animals with lesion
[c] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

TABLE 17
Incidence of Kidney and Liver Lesions in Clinical Pathology Study Rats in the 28-Day Feed Study of Fumonisin B_1

	0 ppm	99 ppm	163 ppm	234 ppm	484 ppm
Male					
Kidney[a]	8	8	8	8	8
Apoptosis[b]	0	8** (1.8)[c]	8** (2.0)	8** (2.0)	8** (2.0)
Degeneration	0	8** (1.9)	8** (2.0)	8** (2.0)	8** (2.0)
Liver	8	8	8	8	8
Apoptosis	0	0	0	5* (1.2)	8** (2.4)
Degeneration	0	0	0	8** (1.1)	8** (2.5)
Mitotic Alteration	0	1 (2.0)	0	4* (1.5)	8** (2.6)
Bile Duct, Hyperplasia	0	0	0	1 (1.0)	8** (1.4)
Female					
Kidney	8	8	8	8	8
Apoptosis	0	0	5* (1.0)	8** (1.5)	8** (2.5)
Degeneration	0	2 (1.0)	8** (1.4)	8** (2.0)	8** (2.0)
Liver	8	8	8	8	8
Apoptosis	0	0	5* (1.2)	7** (2.0)	8** (2.0)
Degeneration	1 (1.0)	0	8** (1.1)	8** (1.8)	8** (2.0)
Mitotic Alteration	0	0	7** (1.3)	6** (2.0)	8** (2.1)
Bile Duct, Hyperplasia	0	0	1 (1.0)	2 (1.0)	8** (2.1)

* Significantly different ($P \leq 0.05$) from the control group by the Fisher exact test
** $P \leq 0.01$
[a] Number of animals with organ examined microscopically
[b] Number of animals with lesion
[c] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

DNA fragmentation. The severities of these lesions increased with increasing exposure concentration. Core and clinical pathology study females exposed to 163 ppm or greater also had significantly increased incidences of minimal to mild mitotic alteration. The incidences of mitotic alteration were also increased in core study males in the 484 ppm group and clinical pathology study males in the 234 and 484 ppm groups; the severity was mild in core study males and minimal to moderate in clinical pathology study males. The incidences of bile duct hyperplasia were significantly increased in core and clinical pathology study males and females in the 484 ppm groups; the severity was minimal in males and mild in females.

The hepatocytes of males in all exposed groups and females exposed to 163 ppm or greater were induced into proliferative (non-G_0) states, as determined by anti-PCNA immunohistochemical methods (Table E1). In males, the percentage of hepatocytes in G_0 decreased with increasing exposure concentration; in females, the response reached a plateau between 234 and 484 ppm.

All groups of males and females exposed to 163 ppm or greater had significantly increased percentages of cells in G_1 and G_2. Males exposed to 163 ppm or greater and females in the 234 and 484 ppm groups had significantly increased percentages of cells in S-phase (S). Males exposed to 484 ppm and females exposed to 163 ppm or greater also had significantly increased percentages of cells in mitosis (M). In exposed males and females, the percentages of cells in S + M reflected the high percentages of cells in S-phase.

Exposure Concentration Selection Rationale: Exposure concentrations for the 2-year study in male rats were based on increased incidences of kidney lesions and elevations in clinical pathology parameters indicative of nephrotoxicity in all exposed groups of males and evidence of hepatotoxicity in males exposed to 484 ppm. The findings of a 90-day study using F344/N rats in which nephrosis was detected in male rats fed diets containing 9, 27, or 81 ppm fumonisin B_1 suggested that exposure to 150 ppm would induce the renal changes detected in male rats (Voss *et al*., 1993). Therefore, 150 ppm was selected as the highest exposure concentration for the 2-year study in male rats. The other exposure concentrations selected were 5, 15, and 50 ppm.

Exposure concentrations for the 2-year study in female rats were based on increased incidences of liver and kidney lesions in groups of females exposed to 163 ppm or greater and evidence of greater sensitivity than males to alterations of associated clinical pathology parameters. These results suggested that the hepatotoxic effects of fumonisin B_1 occurred at lower exposure concentrations in females than in males. Therefore, 100 ppm was selected as the highest exposure concentration for the 2-year study in female rats. The other exposure concentrations selected were 5, 15, and 50 ppm.

2-YEAR STUDY

Survival

Estimates of 2-year survival probabilities for male and female rats are shown in Table 18 and in the Kaplan-Meier survival curves (Figure 3). Survival of exposed males and females was similar to that of the controls.

TABLE 18
Survival of Rats in the 2-Year Feed Study of Fumonisin B_1

	0 ppm	5 ppm	15 ppm	50 ppm	150 ppm
Male					
6-Week evaluation	4	4	4	4	4
10-Week evaluation	4	4	4	4	4
14-Week evaluation	4	4	4	4	4
26-Week evaluation	4	4	4	4	4
Animals initially in 2-year study	48	40	48	48	48
Removed from study[a]	2	0	0	2	0
Moribund	24	19	19	19	21
Natural deaths	6	4	4	9	2
Animals surviving to study termination	16	17	25	18	25
Percent probability of survival at end of study[b]	35	48	52	39	52
Mean survival (days)[c]	664	675	671	654	668
Survival analysis[d]	P=0.1352N	P=0.3796	P=0.1463N	P=0.1622	P=0.1095N
	0 ppm	**5 ppm**	**15 ppm**	**50 ppm**	**100 ppm**
Female					
6-Week evaluation	4	4	4	4	4
10-Week evaluation	4	4	4	4	4
14-Week evaluation	4	4	4	4	4
26-Week evaluation	4	4	4	4	4
Animals initially in 2-year study	48	40	48	48	48
Removed from study	1	2	0	2	0
Moribund	20	15	23	16	16
Natural deaths	2	1	1	0	3
Animals surviving to study termination	25	22	24	30	29
Percent probability of survival at end of study	53	58	50	65	60
Mean survival (days)	693	663	674	684	699
Survival analysis	P=0.1346N	P=0.4182	P=0.0913	P=0.1219N	P=0.2604N

[a] Censored from survival analyses
[b] Kaplan-Meier determinations
[c] Mean of all deaths in 2-year study (uncensored, censored, and terminal sacrifice)
[d] The result of the life table trend test (Tarone, 1975) is in the control column, and the results of the life table pairwise comparisons (Cox, 1972) with the controls are in the exposed group columns. A negative trend or lower mortality in an exposure group is indicated by **N**.

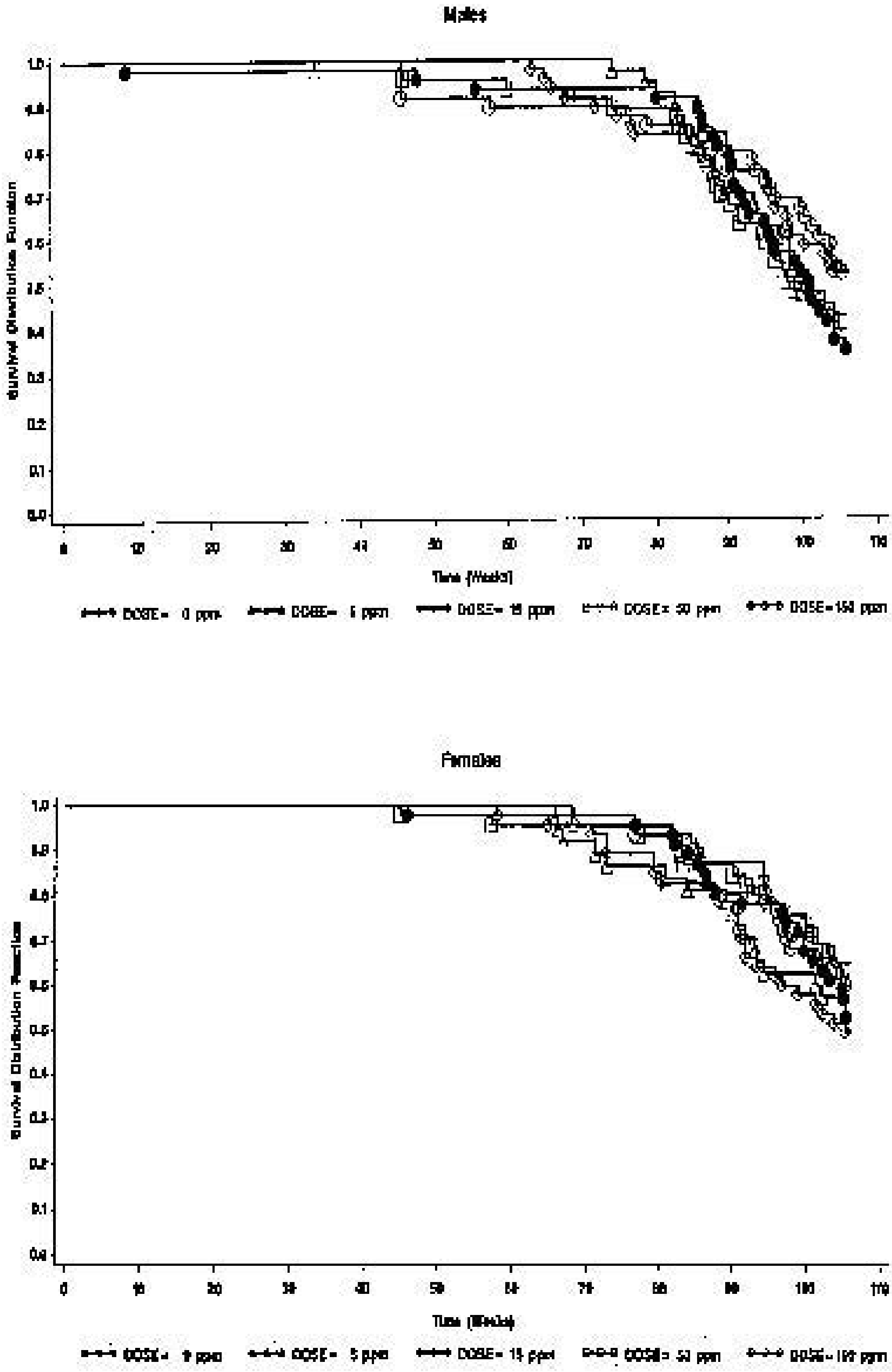


FIGURE 3
Kaplan-Meier Survival Curves for Male and Female Rats Administered Fumonisin B_1 in Feed for 2 Years

Body Weights, Feed and Compound Consumption, and Clinical Findings

Mean body weights of exposed males and females were similar to those of the controls throughout the 2-year study (Tables 19 and 20 and Figure 4).

Feed consumption by males and females exposed for up to 26 weeks (Tables I1 and I2) or for 2 years (Tables I5 and I6) was similar to that by the controls.

Dietary concentrations of 5, 15, 50, and 150 ppm fumonisin B_1 resulted in average daily doses of approximately 0.25, 0.76, 2.5, and 7.5 mg fumonisin B_1/kg body weight to male rats, and dietary concentrations of 5, 15, 50, and 100 ppm resulted in average daily doses of approximately 0.31, 0.91, 3.0, and 6.1 mg/kg to female rats. There were no apparent exposure-related clinical findings in male or female rats.

Clinical Pathology Findings

Clinical pathology data for rats exposed to fumonisin B_1 for up to 26 weeks are presented in Table F2. Although some statistical differences were noted in some of the test parameters, essentially no exposure-related results were detected in the analyzed parameters. The exceptions to the lack of changes in clinical pathology data were increases in the sphinganine content in the urine and tissues (Table F2). The ratios of urinary sphinganine to sphingosine for 15, 50, and 150 ppm males increased after 10 weeks and for 5 ppm males at 10 and 26 weeks. The sphinganine/sphingosine ratios in the urine of 50 and 100 ppm females increased after 10 weeks of exposure. The sphinganine/sphingosine ratios increased in kidney tissue of 15, 50, and 150 ppm males at 6, 10, and 14 weeks and also increased in 50 and 150 ppm males at 2 years. The kidney tissue sphinganine/sphingosine ratios increased in 50 and 100 ppm females at 6, 14, and 26 weeks and at 2 years. Liver sphinganine/sphingosine ratios were unchanged in males at 6, 10, 14, and 26 weeks, while they increased in 100 ppm females at 6, 10, and 14 weeks.

Cell Proliferation Analyses

The data for the cell proliferation analyses are summarized in Tables E3 and E4. Proliferation was determined in the kidney and liver of rats using two immunohistochemical methods measuring PCNA expression and BrdU incorporation. Renal tubule epithelial cell proliferation was increased consistently in 50 and 150 ppm male rats at 6, 10, 14, and 26 weeks and marginally in 100 ppm females (anti-BrdU only). Proliferation was not detected to any significant extent in the liver of male or female rats at 6, 10, 14, or 26 weeks (Tables E3 and E4).

TABLE 19
Mean Body Weights and Survival of Male Rats in the 2-Year Feed Study of Fumonisin B_1

Weeks on Study	0 ppm		5 ppm			15 ppm		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
2	130.45	48	133.46	102.31	40	131.81	101.04	48
3	165.58	48	166.32	100.45	40	164.96	99.63	48
4	197.70	48	199.39	100.85	40	197.23	99.76	48
5	225.08	48	226.30	100.54	40	222.88	99.02	48
6	246.27	48	247.37	100.45	40	243.79	98.99	48
7	268.54	48	267.65	99.67	40	263.14	97.99	48
8	282.22	48	284.35	100.75	40	278.58	98.71	48
9	299.23	48	300.36	100.38	40	294.63	98.46	48
10	313.78	47	314.06	100.09	40	307.43	97.98	48
11	327.53	47	326.15	99.58	40	318.61	97.28	48
12	338.14	47	336.83	99.61	40	328.74	97.22	48
16	363.43	47	361.48	99.46	40	351.18	96.63	48
20	392.53	47	389.87	99.32	40	381.59	97.21	48
24	409.38	47	408.64	99.82	40	402.21	98.25	48
28	419.77	47	421.14	100.33	40	416.38	99.19	48
32	434.95	47	433.71	99.71	40	432.03	99.33	48
36	450.20	47	448.53	99.63	40	446.89	99.26	48
40	461.11	47	460.45	99.86	40	458.65	99.47	48
44	469.09	45	470.38	100.28	40	467.54	99.67	48
48	479.82	45	478.82	99.79	40	477.98	99.62	48
52	488.91	44	489.74	100.17	40	488.10	99.83	48
56	495.99	44	497.62	100.33	40	497.58	100.32	48
60	502.18	43	503.84	100.33	40	505.25	100.61	48
64	508.47	43	509.92	100.29	40	513.54	101.00	47
68	514.79	43	514.68	99.98	40	516.13	100.26	45
72	520.42	43	518.09	99.55	40	516.06	99.16	44
76	525.19	43	521.43	99.28	39	520.43	99.09	42
80	529.42	43	524.23	99.02	38	520.57	98.33	40
84	519.97	42	521.13	100.22	35	516.16	98.27	40
88	510.89	39	510.50	99.92	31	510.59	99.94	39
92	513.41	33	507.28	98.81	28	507.80	98.91	36
96	509.57	29	506.59	99.42	25	498.76	97.88	34
100	481.77	25	496.19	102.99	20	492.73	102.27	29
104	470.56	19	486.23	103.33	18	489.99	104.13	27
106	453.92	17	477.67	105.23	17	481.07	105.98	25
Mean for weeks								
2-13	254.05		254.75	100.28		250.16	98.47	
14-52	436.92		436.28	99.85		432.26	98.93	
53-106	504.04		506.81	100.55		506.19	100.43	

TABLE 19
Mean Body Weights and Survival of Male Rats in the 2-Year Feed Study of Fumonisin B_1

Weeks on Study	50 ppm Av. Wt. (g)	50 ppm Wt. (% of controls)	50 ppm No. of Survivors	150 ppm Av. Wt. (g)	150 ppm Wt. (% of controls)	150 ppm No. of Survivors
2	128.63	98.60	48	133.51	102.35	48
3	161.39	97.47	48	164.63	99.43	48
4	192.18	97.21	48	194.37	98.32	48
5	215.86	98.90	48	217.43	96.60	48
6	236.87	96.18	48	238.76	96.95	48
7	257.05	95.72	48	257.14	95.75	48
8	270.63	95.89	48	270.72	95.93	48
9	286.98	95.91	48	287.33	96.02	48
10	300.31	95.71	48	300.39	95.73	48
11	311.49	95.10	48	312.65	95.46	48
12	322.30	95.32	48	323.81	95.76	48
16	346.16	95.25	48	346.38	95.31	48
20	374.08	95.30	48	376.18	95.83	48
24	389.77	95.21	48	394.69	96.41	48
28	401.46	95.64	48	406.89	96.93	48
32	416.66	95.79	48	420.49	96.68	48
36	432.33	96.03	47	433.09	96.20	48
40	444.14	96.32	47	447.54	97.06	48
44	454.13	96.81	45	456.96	97.41	48
48	465.14	96.94	44	465.29	96.97	44
52	475.55	97.27	44	474.79	97.11	44
56	486.32	98.05	44	483.07	97.40	44
60	492.07	97.99	44	488.74	97.32	43
64	499.60	98.26	43	495.88	97.52	43
68	505.33	98.16	43	502.71	97.65	43
72	511.59	98.30	42	508.11	97.63	43
76	513.85	97.84	41	509.39	96.99	43
80	516.11	97.49	41	507.30	95.82	41
84	511.72	98.41	39	504.73	97.07	41
88	506.70	99.18	36	504.14	98.68	40
92	505.31	98.42	31	505.97	98.55	38
96	500.68	98.26	27	507.44	99.58	35
100	486.04	100.89	22	504.15	104.65	33
104	476.78	101.32	20	491.46	101.44	29
106	483.58	106.53	18	481.50	106.08	25
Mean for weeks						
2-13	243.97	96.03		245.52	96.64	
14-52	419.94	96.11		422.23	96.64	
53-106	499.69	99.14		499.61	99.12	

TABLE 20
Mean Body Weights and Survival of Female Rats in the 2-Year Feed Study of Fumonisin B_1

Weeks on Study	0 ppm Av. Wt. (g)	0 ppm No. of Survivors	5 ppm Av. Wt. (g)	5 ppm Wt. (% of controls)	5 ppm No. of Survivors	15 ppm Av. Wt. (g)	15 ppm Wt. (% of controls)	15 ppm No. of Survivors
2	106.71	48	105.60	98.96	40	107.36	100.61	48
3	124.34	48	123.73	99.51	40	123.44	99.28	48
4	137.20	48	136.55	99.53	40	136.31	99.35	48
5	148.79	48	146.49	98.45	40	146.70	98.60	48
6	157.57	48	155.22	98.51	40	155.34	98.58	48
7	164.53	48	161.66	98.26	40	161.20	97.98	48
8	170.56	48	168.15	98.59	40	168.45	98.76	48
9	176.17	48	174.15	98.85	40	171.98	97.62	48
10	181.14	48	179.15	98.90	40	177.23	97.84	48
11	185.89	48	183.52	98.73	40	181.04	97.39	48
12	191.92	48	188.26	98.09	40	188.96	98.46	48
16	200.95	48	199.71	99.38	40	198.19	98.63	48
20	211.58	48	212.70	100.53	40	209.88	99.20	48
24	221.60	48	222.09	100.22	40	219.53	99.07	48
28	230.54	48	231.52	100.43	40	229.79	99.67	48
32	238.72	48	240.50	100.75	40	238.11	99.74	48
36	245.42	47	248.15	101.11	40	245.46	100.02	48
40	250.90	47	253.62	101.08	40	250.56	99.86	48
44	256.21	47	258.43	100.87	40	256.96	100.29	48
48	264.52	46	265.87	100.51	38	265.67	100.43	48
52	274.13	46	277.68	101.30	38	276.73	100.95	48
56	284.46	46	288.42	101.39	38	288.04	101.26	48
60	295.59	46	299.27	101.24	38	299.97	101.48	47
64	305.64	46	309.47	101.25	38	310.15	101.48	47
68	315.80	46	318.66	100.91	35	320.11	101.36	46
72	324.55	46	330.45	101.82	34	328.95	101.36	45
76	330.92	46	337.74	102.06	33	336.77	101.77	43
80	336.29	45	344.22	102.36	33	341.83	101.65	41
84	340.46	43	345.68	101.53	32	343.86	101.00	40
88	342.04	39	349.22	102.10	31	340.10	99.43	39
92	350.20	37	351.40	100.34	28	341.88	97.62	34
96	351.95	37	361.68	102.76	24	348.02	98.88	31
100	347.89	34	353.65	101.66	24	357.47	102.75	28
104	342.70	29	355.17	103.64	22	358.87	101.72	26
106	356.39	25	360.23	101.08	22	362.04	101.59	24
Mean for weeks								
2-13	158.62		156.59	98.72		156.18	98.46	
14-52	239.46		241.03	100.66		239.09	99.85	
53-106	330.35		336.09	101.74		334.15	100.15	

TABLE 20
Mean Body Weights and Survival of Female Rats in the 2-Year Feed Study of Fumonisin B_1

Weeks on Study	50 ppm Av. Wt. (g)	50 ppm Wt. (% of controls)	50 ppm No. of Survivors	100 ppm Av. Wt. (g)	100 ppm Wt. (% of controls)	100 ppm No. of Survivors
2	106.12	99.45	48	108.22	101.42	48
3	123.31	99.17	48	124.43	100.07	48
4	137.23	100.02	48	137.02	99.87	48
5	148.12	99.55	48	146.43	98.41	48
6	156.20	99.13	48	155.11	98.44	48
7	163.68	99.48	48	160.26	97.40	48
8	170.26	99.82	48	166.61	97.68	48
9	175.85	99.82	48	170.73	96.91	48
10	181.37	100.13	48	176.66	97.53	48
11	184.24	99.11	48	179.15	96.37	48
12	191.00	99.52	48	186.77	97.32	48
16	199.81	99.43	48	194.61	96.84	48
20	209.34	98.94	48	203.02	95.95	48
24	218.29	98.51	48	210.80	95.13	48
28	227.71	98.77	48	219.52	95.22	48
32	235.51	98.66	48	227.31	95.22	48
36	242.91	98.98	48	234.23	95.44	48
40	248.64	99.10	48	238.91	95.22	48
44	253.83	99.07	48	244.30	95.35	48
48	262.34	99.18	45	251.07	94.92	48
52	274.40	100.10	45	261.81	95.51	48
56	284.33	99.95	45	272.66	95.85	48
60	296.01	100.14	44	282.26	95.49	48
64	306.53	100.29	44	293.02	95.87	48
68	317.05	100.40	44	301.72	95.54	48
72	325.93	100.43	44	310.37	95.63	46
76	333.68	100.83	44	316.51	95.65	46
80	339.43	100.93	43	321.26	95.53	45
84	341.85	100.41	40	322.77	94.80	45
88	345.92	101.13	40	326.43	95.44	42
92	350.89	100.20	39	330.46	94.36	42
96	354.74	100.79	36	328.65	93.38	38
100	350.38	100.72	35	347.61	99.92	33
104	351.94	100.27	30	352.25	102.79	32
106	357.40	100.28	30	355.70	99.81	29
Mean for weeks						
2-13	157.94	99.57		155.58	98.08	
14-52	237.28	99.09		228.56	95.45	
53-106	332.58	100.68		318.69	96.47	

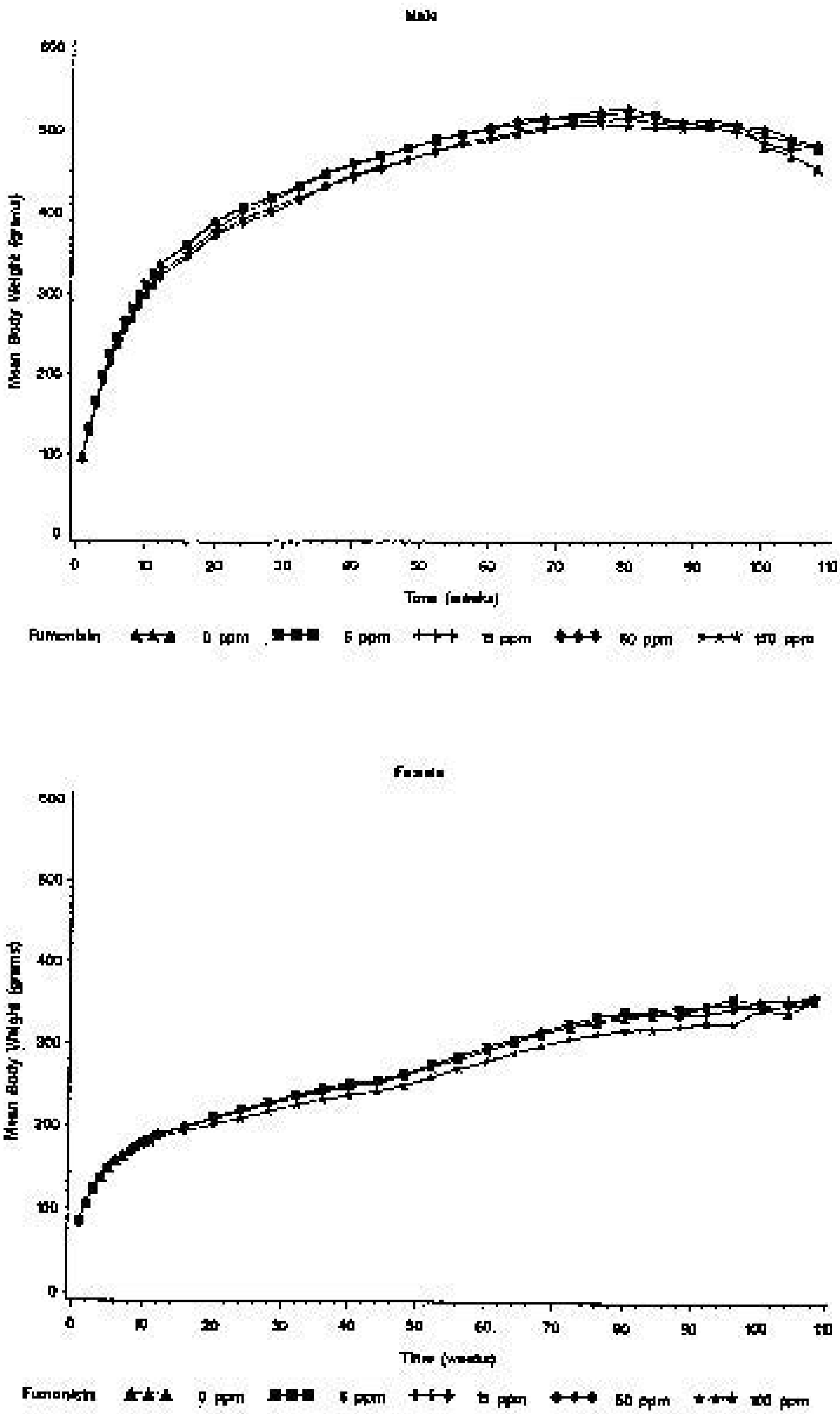


FIGURE 4
Growth Curves for Male and Female Rats Administered Fumonisin B_1 in Feed for 2 Years

Organ Weights, Pathology, and Statistical Analyses

This section describes the statistically significant or biologically noteworthy changes in organ weights and in the incidences of neoplasms and/or nonneoplastic lesions of the kidney, liver, and lung. Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, and statistical analyses of neoplasms in the control and highest exposed groups are presented in Appendix A for male rats and Appendix B for female rats.

Kidney: Absolute left and right kidney weights of 50 and 150 ppm males at 6 and 14 weeks, 150 ppm males at 10 weeks, 15, 50, and 150 ppm males at 26 weeks, and 50 ppm males at 2 years were significantly less than those of the controls (Tables G3 to G7). Generally, the ratios of kidney weights to brain and body weights were significantly less for 50 and 150 ppm males at 6, 10, 14, and 26 weeks and for 50 and 150 ppm males at 2 years. The right kidney weights of 100 ppm females at 26 weeks and the left and right kidney weights of 15, 50, and 100 ppm females at 2 years were less than those of the controls (Table G7).

At 2 years, the incidence of renal tubule adenoma in 150 ppm males was significantly greater than that in the controls, and the incidences in males occurred with a positive trend (Tables 21 and A3). The incidences of renal tubule carcinoma and renal tubule adenoma or carcinoma (combined) were significantly increased in the 50 and 150 ppm males; these neoplasms also occurred with positive trends. One 50 ppm female had a renal tubule adenoma, and one 100 ppm female had a renal tubule carcinoma (Tables 21 and B1). Renal tubule adenoma was characterized as an expansive proliferation of renal tubule epithelial cells that tended to be separated into lobules by a delicate fibrous stroma. The neoplastic cells had nuclei that were slightly larger with increased cytoplasmic volume. The cytoplasmic changes were uniform within individual lesions and varied from clear to basophilic. Renal tubule carcinomas were characterized by cellular atypia, necrosis within the lesion, invasion of the adjacent normal renal parenchyma, or metastasis to distant organs.

Frequent metastatic sites included the lung and the lymph node (Table A1). The individual cells in the carcinomas tended to be large with hyperchromatic nuclei and abundant basophilic cytoplasm.

At 2 years, incidences of focal renal tubule epithelial hyperplasia were significantly greater than those in the controls in 50 and 150 ppm males (Tables 21 and A4). The lesion was characterized as a dilated tubule lined by multiple layers of hypertrophic epithelium or by a tubular lumen occluded by a solid proliferation of epithelial cells. Nucleoli of cells with solid proliferations were usually more prominent and the cell cytoplasm less abundant when compared to normal renal tubule epithelium. Renal tubule epithelial hyperplasia also occurred in exposed groups of females, but the incidences were not significantly different from those in the controls (Tables 21 and B4).

The only significant treatment-related lesion observed microscopically at the early evaluations was apoptosis of the renal tubule epithelium in male rats exposed to 15 ppm or greater (Tables 21 and A4). Apoptosis did not occur in female rats. Apoptosis was confined to tubules of the inner cortex and was characterized by cells with shrunken condensed nuclei and deeply eosinophilic cytoplasm. The cells either were present in the tubule lining or were free in the tubule lumina. The severity of renal tubule apoptosis ranged from minimal to mild and was not related to exposure concentration.

TABLE 21
Incidences of Neoplasms and Nonneoplastic Lesions of the Kidney in Rats in the 2-Year Feed Study of Fumonisin B_1

	0 ppm	5 ppm	15 ppm	50 ppm	150 ppm
Male					
6-Week Evaluation					
Number Examined Microscopically	4	4	4	4	4
Renal Tubule Epithelial Apoptosis, Cortex[a]	0	0	4* (1.0)[b]	4* (2.3)	4* (2.0)
10-Week Evaluation					
Number Examined Microscopically	4	4	4	4	4
Renal Tubule Epithelial Apoptosis, Cortex	0	0	4* (1.0)	4* (2.0)	4* (2.0)
14-Week Evaluation					
Number Examined Microscopically	4	4	4	4	4
Renal Tubule Epithelial Apoptosis, Cortex	0	0	4* (1.0)	4* (1.5)	4* (1.8)
26-Week Evaluation					
Number Examined Microscopically	4	4	4	4	4
Renal Tubule Epithelial Apoptosis, Cortex	0	1 (1.0)	0	4* (1.5)	4* (1.0)
2-Year Study					
Number Examined Microscopically	48	40	48	48	48
Renal Tubule Epithelial Hyperplasia, Focal	2 (2.0)	1 (3.0)	4 (2.0)	14***(2.6)	8* (2.0)
Renal Tubule Adenoma					
Overall rate[c]	0/48 (0%)	0/40 (0%)	0/48 (0%)	2/48 (4%)	5/48 (10%)
Adjusted rate[d]	0.0%	0.0%	0.0%	5.7%	12.9%
Terminal rate[e]	0/18 (0%)	0/17 (0%)	0/25 (0%)	2/20 (10%)	5/25 (20%)
First incidence (days)	—[g]	—	—	740 (T)	740 (T)
Poly-3 test[f]	P=0.0004	—[h]	—	P=0.2293	P=0.0314
Renal Tubule Carcinoma					
Overall rate	0/48 (0%)	0/40 (0%)	0/48 (0%)	7/48 (15%)	10/48 (21%)
Adjusted rate	0.0%	0.0%	0.0%	20.0%	25.4%
Terminal rate	0/18 (0%)	0/17 (0%)	0/25 (0%)	6/20 (30%)	8/25 (32%)
First incidence (days)	—	—	—	680	594
Poly-3 test	P=0.0001	—	—	P=0.0059	P=0.0008
Renal Tubule Adenoma or Carcinoma					
Overall rate	0/48 (0%)	0/40 (0%)	0/48 (0%)	9/48 (19%)	15/48 (31%)
Adjusted rate	0.0%	0.0%	0.0%	25.7%	38.1%
Terminal rate	0/18 (0%)	0/17 (0%)	0/25 (0%)	8/20 (40%)	13/25 (52%)
First incidence (days)	—	—	—	680	594
Poly-3 test	P=0.0001	—	—	P=0.0011	P=0.0001

TABLE 21
Incidences of Neoplasms and Nonneoplastic Lesions of the Kidney in Rats in the 2-Year Feed Study of Fumonisin B_1

	0 ppm	5 ppm	15 ppm	50 ppm	100 ppm
Female					
2-Year Study					
Number Examined Microscopically	48	40	48	48	48
Renal Tubule Epithelial Hyperplasia, Focal, Bilateral	0	0	0	0	1 (4.0)
Renal Tubule Epithelial Hyperplasia, Focal (includes bilateral)	0	1 (1.0)	1 (1.0)	2 (1.5)	3 (3.7)
Renal Tubule Adenoma	0	0	0	1	0
Renal Tubule Carcinoma	0	0	0	0	1

* Significantly different ($P \leq 0.05$) from the control group by the Fisher exact test (6-, 10-, 14-, and 26-week evaluations) or Poly-3 test (2-year study)
*** $P \leq 0.001$
(T) Terminal sacrifice
[a] Number of animals with lesion
[b] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked
[c] Number of animals with neoplasm per number of animals with kidney examined microscopically
[d] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[e] Observed incidence at terminal kill
[f] Beneath the control incidence is the P value associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice.
[g] Not applicable; no neoplasms in animal group
[h] Value of statistic cannot be computed.

Liver: Relative liver weights of all exposed groups of male rats were less than those of the controls.

Hepatocellular adenoma was detected in two males at 5 and 15 ppm, one male at 150 ppm, and one 15 ppm female (Tables 22, A1, A3 and B1). Hepatocellular carcinoma was detected in one 5 ppm male and one 15 ppm male. These lesions were not considered exposure related.

Some rats had nonneoplastic focal cellular alterations of the liver (Tables 22, A4, and B4). Altered foci consisted of clusters of hepatocytes with a tinctorially distinct cytoplasm (basophilic, clear cell, eosinophilic, or mixed) that blended with or marginally compressed the adjacent normal hepatic parenchyma. The liver of individual animals often had multiple altered foci of the same or different types. Basophilic foci formation is a common occurrence in F344/N rats, and although NTP does not maintain a database of this lesion, it occurred at a frequency of 42%, 40%, and 50% in the liver of control male rats in the NTP studies of gallium arsenide (NTP, 2000a), emodin (NTP, 2001a), and anthraquinone (NTP, 2001b). The occurrence of basophilic foci in the present study in 150 ppm male rats was 48%, within the range in the studies mentioned above. The statistical increase in the incidences of basophilic foci in 5 and 150 ppm males is considered to be due to a relatively low incidence in the control group. Additionally, there were no significant increases in the incidences of other types of foci. Basophilic foci occurred in 65% to 83% of the control and exposed female rats with no exposure concentration-relation.

TABLE 22
Incidences of Neoplasms and Nonneoplastic Lesions of the Liver in Rats in the 2-Year Feed Study of Fumonisin B_1

	0 ppm	5 ppm	15 ppm	50 ppm	150 ppm
Male					
2-Year Study					
Number Examined Microscopically	48	40	48	48	48
Basophilic Focus[a]	3	11**	7	9*	23***
Clear Cell Focus	5	10	14*	6	10
Eosinophilic Focus	5	6	10	5	10
Mixed Cell Focus	5	6	5	4	9
Hepatocellular Adenoma	0	2	2	0	1
Hepatocellular Carcinoma	0	1	1	0	0
Hepatocellular Adenoma or Carcinoma	0	3	3	0	1
	0 ppm	**5 ppm**	**15 ppm**	**50 ppm**	**100 ppm**
Female					
2-Year Study					
Number Examined Microscopically	48	40	48	48	48
Basophilic Focus	35	26	32	38	40
Clear Cell Focus	4	5	6	6	5
Eosinophilic Focus	7	3	11	11	4
Mixed Cell Focus	19	12	11	17	16
Hepatocellular Adenoma	0	0	1	0	0

* Significantly different ($P \leq 0.05$) from the control group by the Poly-3 test
** $P \leq 0.01$
*** $P \leq 0.001$
[a] Number of animals with lesion

Lung: An alveolar/bronchiolar carcinoma occurred in the lung of one 100 ppm female (Tables 23 and B1). Adenomas were present in one 5 ppm, one 50 ppm, and two 100 ppm females. The lungs were examined for nonneoplastic lesions to determine if any correlative indications of lesions were present. Although alveolar epithelial hyperplasia was present in some tissues, the incidences were not supportive of an exposure-related effect (Tables 23, A4, and B4). Although the incidences of alveolar/bronchiolar adenoma or carcinoma (combined) occurred with a positive trend in females (Tables 23 and B3), the low incidence, lack of significant difference from controls at any exposure concentration, and lack of correlative nonneoplastic lesions did not support a conclusion for an exposure-related effect.

TABLE 23
Incidences of Neoplasms and Nonneoplastic Lesions of the Lung in Rats in the 2-Year Feed Study of Fumonisin B_1

	0 ppm	5 ppm	15 ppm	50 ppm	150 ppm
Male					
2-Year Study					
Number Examined Microscopically	48	24	23	32	48
Hyperplasia, Alveolar, Epithelial[a]	0	1 (2.0)[b]	0	2 (3.5)	1 (2.0)
	0 ppm	**5 ppm**	**15 ppm**	**50 ppm**	**100 ppm**
Female					
2-Year Study					
Number Examined Microscopically	47	40	48	48	48
Hyperplasia, Alveolar, Epithelial	0	2 (1.5)	1 (3.0)	2 (2.5)	2 (3.0)
Alveolar/bronchiolar Adenoma	0	1	0	1	2
Alveolar/bronchiolar Carcinoma	0	0	0	0	1
Alveolar/bronchiolar Adenoma or Carcinoma	0	1	0	1	3
Alveolar/bronchiolar Adenoma or Carcinoma					
Overall rate[c]	0/47 (0%)	1/40 (3%)	0/48 (0%)	1/48(2%)	3/48 (6%)
Adjusted rate[d]	0.0%	3.2%	0.0%	2.5%	7.1%
Terminal rate[e]	0/26 (0%)	1/24 (4%)	0/24 (0%)	1/32 (3%)	2/29 (7%)
First incidence (days)	—[f]	740 (T)	—	740 (T)	680
Poly-3 test[g]	P=0.0340	P=0.4534	—[h]	P=0.5032	P=0.1218

(T)Terminal sacrifice
[a] Number of animalswith lesion
[b] Average severity of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked
[c] Number of neoplasm-bearing animals/number of animals examined microscopically
[d] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[e] Observed incidence at terminal kill
[f] Not applicable; no neoplasms in animal group
[g] Beneath the control incidence is the P value associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice.
[h] Value of statistic cannot be computed.

MICE

28-DAY STUDY

All core study mice survived to the end of the study (Table 24). In the clinical pathology study, one male and one female in the 99 ppm groups, two males and one female in the 234 ppm groups, and two males in the 484 ppm group died while being bled for clinical chemistry measurements (Table 25). The final mean body weights and body weight gains of core study and clinical pathology study males in the 484 ppm groups were significantly less than those of the controls (Tables 24 and 25); the final mean body weights and body weight gains of clinical pathology study males in the 99 and 163 ppm groups were significantly greater. Feed consumption by core study males in the 484 ppm group was less than that by the controls (Table 24). The lower mean body weight of 484 ppm core study males may be related to reduced feed consumption. In the core study, dietary concentrations of 99, 163, 234, and 484 ppm fumonisin B_1 resulted in average daily doses of approximately 19, 31, 44, and 93 mg fumonisin B_1/kg body weight to males and 24, 41, 62, and 105 mg/kg to females. There were no exposure-related clinical findings in male or female mice.

TABLE 24
Survival, Body Weights, and Feed Consumption of Core Study Mice in the 28-Day Feed Study of Fumonisin B_1

Concentration (ppm)	Survival[a]	Mean Body Weight[b] (g) Initial	Final	Change	Final Weight Relative to Controls (%)	Feed Consumption[c] Week 1	Week 4
Male							
0	12/12	18.9 ± 0.4	22.1 ± 0.4	3.2		4.1	4.1
99	12/12	19.0 ± 0.3	22.3 ± 0.3	3.3	100.9	3.9	3.8
163	12/12	18.7 ± 0.3	21.2 ± 0.2	2.5	95.9	3.8	3.7
234	12/12	19.0 ± 0.3	21.6 ± 0.2	2.6	97.7	3.9	3.9
484	12/12	18.9 ± 0.2	20.1 ± 0.3***	1.2	91.0	3.9	3.6
Female							
0	12/12	14.8 ± 0.2	15.7 ± 0.2	0.9		3.5	3.4
99	12/12	15.2 ± 0.2	15.7 ± 0.1	0.5	100.0	4.1	3.3
163	12/12	16.0 ± 0.2	16.2 ± 0.2	0.2	103.2	4.6	3.4
234	12/12	15.2 ± 0.2	15.6 ± 0.1	0.4	99.4	3.9	4.2
484	12/12	15.6 ± 0.3	15.4 ± 0.2	–0.2	98.1	3.6	3.1

*** Significantly different ($P \leq 0.001$) from the control group by a repeated measures analysis of variance with application of Holm's procedure
[a] Number of animals surviving at 28 days/number initially in group
[b] Weights are given as mean ± standard error, and weight changes are given as the mean.
[c] Feed consumption is expressed as grams of feed consumed per animal per day.

TABLE 25
Survival and Body Weights of Clinical Pathology Study Mice in the 28-Day Feed Study of Fumonisin B_1

Concentration (ppm)	Survival[a]	Mean Body Weight[b] (g) Initial	Final	Change	Final Weight Relative to Controls (%)
Male					
0	8/8	17.5 ± 0.4	20.3 ± 0.2	2.8	
99	6/7[c]	16.8 ± 0.3	21.4 ± 0.3*	4.6	105.4
163	8/8	18.1 ± 0.3	21.9 ± 0.3***	3.8	107.9
234	6/8[d]	17.8 ± 0.5	20.9 ± 0.4	3.1	103.0
484	6/8[e]	18.0 ± 0.3	19.1 ± 0.3*	1.1	94.1
Female					
0	8/8	14.6 ± 0.5	15.3 ± 0.3	0.7	
99	3/4[f]	14.6 ± 0.8	15.6 ± 0.4	1.0	102.0
163	8/8	16.1 ± 0.3	15.5 ± 0.5	–0.6	101.3
234	7/8[c]	15.7 ± 0.4	15.0 ± 0.6	–0.7	98.0
484	8/8	16.0 ± 0.4	14.8 ± 0.4	–1.2	96.7

* Significantly different ($P \leq 0.05$) from the control group by a repeated measures analysis of variance with application of Holm's procedure
*** $P \leq 0.001$
a Number of animals surviving at 28 days/number initially in group
b Weights are given as mean ± standard error, and weight changes are given as the mean. Subsequent calculations are based on animals surviving to the end of the study.
c Day of death: 7 (accidental death)
d Day of death: 7, 28 (accidental deaths)
e Day of death: 14, 14 (accidental deaths)
f Day of death: 28 (accidental death)

Clinical pathology and urinalysis data are provided in Tables 26 and F3. In the core and clinical pathology study groups, cholesterol and total bile acid concentrations and alanine aminotransferase and alkaline phosphatase activities of males in the 484 ppm groups and females in all exposed groups were greater than those of the controls at all time points for which measurements were available. In core study males, alkaline phosphatase activities of the lower exposed groups were also significantly increased at the end of the study. Triglyceride concentrations increased with increasing exposure concentration in females at all time points, and triglyceride concentrations were significantly increased for males in the 484 ppm groups on day 28. In core study females, urea nitrogen concentrations of all exposed groups were significantly decreased and aspartate aminotransferase activities of the 234 and 484 ppm groups were increased. Other differences in clinical chemistry parameters were random and were not considered to be biologically significant.

In males, sphinganine concentrations increased with increasing exposure concentration at all time points, and the differences were significant in the 484 ppm group. In males in the 234 and 484 ppm groups, sphingosine concentrations were significantly decreased and sphinganine/sphingosine ratios were significantly increased on day 7. Urinary sphinganine/sphingosine ratios in female mice were unaffected by exposure.

Organ weight changes were minor and did not show good consistency between core study and clinical pathology study mice. In core study mice, the liver weights of females in the 484 ppm group were significantly greater than those of the controls (Table G8). The heart weights of clinical pathology study males and females in the 484 ppm groups and females in the 163 ppm group were significantly less (Table G9).

TABLE 26
Selected Clinical Chemistry and Urinalysis Data for Mice in the 28-Day Feed Study of Fumonisin B_1[a]

	0 ppm	99 ppm	163 ppm	234 ppm	484 ppm
Male					
Clinical Chemistry					
n					
Day 7	4	4	4	4	4
Day 14	4	3	4	2	4
Day 28	7	6	8	7	6
Core study	3	3	3	3	3
Cholesterol (mg/dL)					
Day 7	136 ± 1	151 ± 3	142 ± 4	162 ± 8**	232 ± 13***
Day 14	148 ± 5	132 ± 2	165 ± 5	159 ± 7[b]	245 ± 17***
Day 28	130 ± 2[c]	126 ± 4	147 ± 4	160 ± 11**	233 ± 10***
Core study	138 ± 7	149 ± 9	160 ± 12	169 ± 12	253 ± 9****
Triglycerides (mg/dL)					
Day 7	49 ± 6	50 ± 6	59 ± 4	60 ± 6	78 ± 18
Day 14	66 ± 1	54 ± 2	50 ± 7	45 ± 8	87 ± 9
Day 28	43 ± 2[c]	47 ± 4	46 ± 3	51 ± 3	112 ± 12***
Core study	82 ± 2	86 ± 5	85 ± 5	77 ± 6	123 ± 12**
Alanine aminotransferase (IU/L)					
Day 7	29 ± 5	25 ± 3	19 ± 2	62 ± 31	634 ± 183***
Day 14	37 ± 14	28 ± 3	30 ± 5	25 ± 1	455 ± 88***[d]
Day 28	37 ± 9	40 ± 12	30 ± 6	122 ± 62	556 ± 232***[d]
Core study	67 ± 22	51 ± 7	36 ± 3	75 ± 23	384 ± 51*
Alkaline phosphatase (IU/L)					
Day 7	149 ± 3	211 ± 5	181 ± 5	228 ± 14	500 ± 95***
Day 14	135 ± 8	135 ± 5	152 ± 16	—[e]	621 ± 50***[d]
Day 28	121 ± 5	138 ± 7	—	—	579 ± 68***[f]
Core study	112 ± 3	122 ± 2*	136 ± 4*	145 ± 8*	426 ± 32**
Total bile acids (µmol/L)					
Day 7	25.0 ± 2.3	25.5 ± 1.3	26.3 ± 3.5	25.8 ± 4.8[d]	275.3 ± 59.1***[d]
Day 14	15.2 ± 1.4	20.2 ± 2.4	16.2 ± 0.2[f]	—	179.4 ± 8.8***[f]
Day 28	14.0 ± 1.4	21.5 ± 0.6	—	—	207.3 ± 93.3***[f]
Core study	22.0 ± 1.4	20.5 ± 2.3	18.0 ± 1.0	26.0 ± 5.1	153.4 ± 5.7****
Urinalysis					
n					
Day 7	4	4	4	4	4
Day 14	4	3	4	4	4
Day 28	8	6	8	7	6
Sphingosine (pmol/mL urine)					
Day 7	13.94 ± 1.30	11.97 ± 2.06	13.75 ± 1.84	8.20 ± 0.71*	6.06 ± 1.71**
Day 14	7.00 ± 3.58	9.80 ± 1.98	7.62 ± 3.52	5.36 ± 1.05	12.45 ± 4.21
Day 28	10.27 ± 2.99	18.70 ± 1.96	11.25 ± 1.89	11.44 ± 2.79	9.83 ± 2.89
Sphinganine (pmol/mL urine)					
Day 7	17.75 ± 2.48	59.65 ± 9.05*	46.13 ± 10.00	63.87 ± 9.72**	84.95 ± 15.30***
Day 14	9.84 ± 3.08	41.19 ± 12.61	38.52 ± 7.07	47.32 ± 3.92	100.30 ± 23.13***
Day 28	15.77 ± 2.56	42.78 ± 10.72	58.90 ± 5.68	57.68 ± 5.75	113.88 ± 36.23***
Sphinganine/sphingosine ratio					
Day 7	1.32 ± 0.26	5.45 ± 1.25	3.25 ± 0.30	8.03 ± 1.58*	15.92 ± 2.95****
Day 14	2.20 ± 0.89	4.87 ± 1.92	6.72 ± 1.46	9.56 ± 1.42	10.89 ± 4.17
Day 28	2.12 ± 0.48	2.33 ± 0.60	6.67 ± 1.37	9.33 ± 4.16	22.02 ± 12.20*

TABLE 26
Selected Clinical Chemistry and Urinalysis Data for Mice in the 28-Day Feed Study of Fumonisin B_1

	0 ppm	99 ppm	163 ppm	234 ppm	484 ppm
Female					
n					
Day 7	4	4	3	4	4
Day 14	4	0	3	3	4
Day 28	8	4	8	7	8
Core study	3	3	3	3	3
Clinical Chemistry					
Urea nitrogen (mg/dL)					
Core study	23.1 ± 0.7	18.1 ± 0.6*	16.3 ± 0.9**	16.6 ± 0.8**	19.0 ± 0.5*
Cholesterol (mg/dL)					
Day 7	96 ± 3	165 ± 5***	175 ± 4***[b]	218 ± 5***	222 ± 3***
Day 14	98 ± 3	—	165 ± 5***[b]	199 ± 5***[b]	210 ± 5***
Day 28	87 ± 2	145 ± 11***	176 ± 7***	212 ± 5***	256 ± 10***
Core study	110 ± 11	173 ± 12****	197 ± 13****	228 ± 8****	259 ± 11****
Triglycerides (mg/dL)					
Day 7	58 ± 7	44 ± 1	62 ± 1	94 ± 1***	128 ± 9***
Day 14	43 ± 6	—	97 ± 7***[b]	98 ± 7***	124 ± 7***
Day 28	35 ± 2	84 ± 9***	97 ± 5***	115 ± 6***	162 ± 8***
Core study	63 ± 10	118 ± 6**	151 ± 19***	192 ± 4****	215 ± 10****
Alanine aminotransferase (IU/L)					
Day 7	64 ± 39	304 ± 118	247 ± 54	630 ± 115***	605 ± 91***
Day 14	29 ± 8	—	413 ± 84***	417 ± 98***	472 ± 43***
Day 28	28 ± 9	273 ± 66	596 ± 98***	419 ± 47***[g]	343 ± 33***
Core study	47 ± 3	170 ± 58	257 ± 26**	415 ± 59*	399 ± 44*
Alkaline phosphatase (IU/L)					
Day 7	163 ± 3	343 ± 45***	301 ± 33***	590 ± 26***	702 ± 16***
Day 14	174 ± 3	—	421 ± 16***	—	794 ± 12***
Day 28	164 ± 3	311 ± 15***	—	512 ± 11***[b]	793 ± 27***
Core study	176 ± 7	377 ± 38****	458 ± 31****	589 ± 19****	786 ± 16****
Aspartate aminotransferase (IU/L)					
Core study	113 ± 16	157 ± 30	208 ± 17	329 ± 59*	288 ± 53*
Total bile acids (µmol/L)					
Day 7	22.7 ± 0.8[d]	198.5 ± 79.3	175.8 ± 3.4[f]	420.6 ± 31.1***[d]	446.6 ± 61.4***
Day 14	19.1 ± 1.3[f]	—	184.1 ± 47.2***	—	543.4 ± 15.0***
Day 28	15.1 ± 1.3	118.4 ± 14.4[d]	—	—	359.9 ± 130.6***[d]
Core study	20.4 ± 2.0	103.6 ± 16.0*	139.7 ± 6.0****	228.4 ± 64.2	306.2 ± 50.0

* Significantly different ($P \leq 0.05$) from the control group by Kleinbaum's procedure (clinical chemistry data) or a repeated measures analysis of variance (urinalysis data) with application of Holm's procedure
** $P \leq 0.01$
*** $P \leq 0.001$
**** $P \leq 0.0001$
a Mean ± standard error. Statistical tests were performed on unrounded data. Core study animals were evaluated on day 28; clinical pathology study animals were evaluated on days 7, 14, and 28.
b n=4
c n=8
d n=3
e Not examined for this exposure group
f n=2
g n=6

In the core and clinical pathology study mice, the incidences of hepatocellular necrosis, diffuse periportal hypertrophy, and diffuse centrilobular hyperplasia, as well as hyperplasia of the bile canaliculi and Kupffer cells in 484 ppm male groups and all exposed groups of females were generally significantly greater than those in the controls (Tables 27 and 28). The incidences of multifocal subacute inflammation of the liver in core study females in the 163 and 484 ppm groups were also significantly increased. Core study males exposed to 99, 163, or 234 ppm had significantly increased incidences of hepatocellular cytoplasmic alteration characterized by reduced cytoplasm, absent cytoplasmic vacuolation, and a blue rather than pink appearance.

The hepatocytes of males in the 484 ppm group and females in all exposed groups were induced into non-G_0 states (Table E2). In males in the 484 ppm group, the percentages of hepatocytes in all non-G_0 phases were significantly increased, with the highest percentages of non-G_0 cells in G_1 and S. In exposed females, the response for G_1 and G_2 reached a plateau between 163 and 234 ppm. The percentages of cells in S increased with increasing exposure concentration in females. Only females in the 99 and 163 ppm groups exhibited significantly increased percentages of cells in M, with the higher percentage occurring in the 99 ppm group. In exposed males and females, the percentages of cells in S + M reflected the high percentages of cells in S.

TABLE 27
Incidence of Liver Lesions in Core Study Mice in the 28-Day Feed Study of Fumonisin B_1

	0 ppm	99 ppm	163 ppm	234 ppm	484 ppm
Male					
Number Examined Microscopically	12	12	12	12	12
Hepatocellular Cytoplasmic Alteration[a]	0	12** (1.0)[b]	12** (1.0)	11** (1.0)	0
Hepatocellular Necrosis	0	0	0	1 (1.0)	10** (1.3)
Hepatocellular Diffuse Periportal Hypertrophy	0	0	0	1 (1.0)	12** (1.8)
Hepatocellular Diffuse Centrilobular Hyperplasia	0	0	0	1 (1.0)	12** (1.8)
Bile Canaliculi, Hyperplasia	0	0	0	0	8** (1.0)
Kupffer Cell, Diffuse Hyperplasia	0	0	0	1 (1.0)	12** (2.0)
Female					
Number Examined Microscopically	12	12	12	12	12
Multifocal Subacute Inflammation	2 (1.0)	3 (1.0)	8* (1.0)	1 (1.0)	9** (1.0)
Hepatocellular Necrosis	0	8** (1.0)	11** (1.0)	12** (1.0)	10** (1.0)
Hepatocellular Diffuse Periportal Hypertrophy	0	12** (1.0)	12** (1.9)	12** (2.3)	12** (2.0)
Hepatocellular Diffuse Centrilobular Hyperplasia	0	12** (1.0)	12** (1.9)	12** (2.0)	12** (3.0)
Bile Canaliculi, Hyperplasia	0	1 (1.0)	7** (1.0)	10** (1.1)	12** (1.0)
Kupffer Cell, Diffuse Hyperplasia	0	12** (1.0)	12** (1.9)	12** (2.3)	12** (1.8)

* Significantly different ($P \leq 0.05$) from the control group by the Fisher exact test
** $P \leq 0.01$
[a] Number of animals with lesion
[b] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

TABLE 28
Incidence of Liver Lesions in Clinical Pathology Study Mice in the 28-Day Feed Study of Fumonisin B_1

	0 ppm	99 ppm	163 ppm	234 ppm	484 ppm
Male					
Number Examined Microscopically	8	7	8	8	8
Hepatocellular Necrosis[a]	0	0	0	1 (1.0)[b]	8** (1.2)
Hepatocellular Diffuse Periportal Hypertrophy	0	0	0	1 (1.0)	8** (2.0)
Hepatocellular Diffuse Centrilobular Hyperplasia	0	0	0	1 (1.0)	8** (3.0)
Bile Canaliculi, Hyperplasia	0	0	0	0	6** (1.2)
Kupffer Cell, Diffuse Hyperplasia	0	0	0	1 (1.0)	8** (2.0)
Female					
Number Examined Microscopically	8	4	8	8	8
Hepatocellular Necrosis	0	4** (1.0)	6** (1.0)	8** (1.0)	8** (1.0)
Hepatocellular Diffuse Periportal Hypertrophy	0	3* (1.0)	8** (2.0)	8** (2.0)	8** (2.0)
Hepatocellular Diffuse Centrilobular Hyperplasia	0	4** (1.0)	8** (2.0)	8** (3.0)	8** (3.0)
Bile Canaliculi, Hyperplasia	0	0	7** (1.1)	7** (1.3)	8** (1.9)
Kupffer Cell, Diffuse Hyperplasia	0	4** (1.0)	8** (2.0)	8** (2.0)	8** (2.0)

* Significantly different ($P \leq 0.05$) from the control group by the Fisher exact test
** $P \leq 0.01$
[a] Number of animals with lesion
[b] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

Exposure Concentration Selection Rationale: Exposure concentrations for the 2-year study in male mice were based on increased incidences of liver lesions and elevations in clinical pathology parameters indicative of hepatotoxicity or nephrotoxicity in males exposed to 484 ppm. The findings of a 90-day study using B6C3F$_1$ mice in which no exposure concentration-related lesions were detected in males fed diets containing concentrations of fumonisin B_1 up to 81 ppm suggested that the minimal concentration of fumonisin B_1 required for achieving a demonstrated biologic effect was greater than 81 ppm (Voss *et al*., 1993). Therefore, 150 ppm was selected as the highest exposure concentration for the 2-year study in male mice. The other exposure concentrations selected were 5, 15, and 80 ppm.

Exposure concentrations for the 2-year study in female mice were based on increased incidences of liver lesions in all exposed groups of females and evidence of greater sensitivity than males to alterations of associated clinical pathology parameters. These results suggested that the hepatotoxic effects of fumonisin B_1 occurred at lower exposure concentrations in females than in males. In the Voss *et al*. (1993) study, 81 ppm fumonisin B_1 resulted in hepatocellular changes in female mice, while none were detected at 27 ppm. Therefore, 80 ppm was selected as the highest exposure concentration for the 2-year study in female mice. The other exposure concentrations selected were 5, 15, and 50 ppm.

2-Year Study

Survival

Estimates of 2-year survival probabilities for male and female mice are shown in Table 29 and in the Kaplan-Meier survival curves (Figure 5). Survival of males and females in the 15 ppm groups and of 5 ppm females was significantly greater than that of the control groups, and survival of 80 ppm males and females was significantly less than that of the control groups.

Table 29
Survival of Mice in the 2-Year Feed Study of Fumonisin B_1

	0 ppm	5 ppm	15 ppm	80 ppm	150 ppm
Male					
3-Week evaluation	4	4	4	4	4
7-Week evaluation	4	4	4	4	4
9-Week evaluation	4	4	4	4	4
24-Week evaluation	4	4	4	4	4
Animals initially in the 2-year study	48	48	48	48	48
Removed from study[a]	0	1	0	0	0
Moribund	4	3	1	5	4
Natural deaths	3	5	2	6	2
Animals surviving to study termination	41	39	45	37	42
Percent probability of survival at end of study[b]	85	83	94	77	88
Mean survival (days)[c]	658	688	667	653	730
Survival analysis[d]	P=0.3934	P=0.2960	P=0.0346N	P=0.0276	P=0.2886N
	0 ppm	**5 ppm**	**15 ppm**	**50 ppm**	**80 ppm**
Female					
3-Week evaluation	4	4	4	4	4
7-Week evaluation	4	4	4	4	4
9-Week evaluation	4	4	4	4	4
24-Week evaluation	4	4	4	4	4
Animals initially in the 2-year study	48	48	48	48	48
Removed from study	4	0	0	0	0
Missing[a]	1	0	0	0	0
Moribund	7	3	2	3	6
Natural deaths	1	1	0	6	14
Animals surviving to study termination	35	44	46	39	28
Percent probability of survival at end of study	81	92	96	81	58
Mean survival (days)	713	724	725	708	654
Survival analysis	P<0.0001	P=0.0264N	P=0.0030N	P=0.4648	P<0.0001

[a] Censored from survival analyses
[b] Kaplan-Meier determinations
[c] Mean of all deaths in 2-year study (uncensored, censored, and terminal sacrifice)
[d] The result of the life table trend test (Tarone, 1975) is in the control column, and the results of the life table pairwise comparisons (Cox, 1972) with the controls are in the exposed group columns. A lower mortality in an exposure group is indicated by **N**.

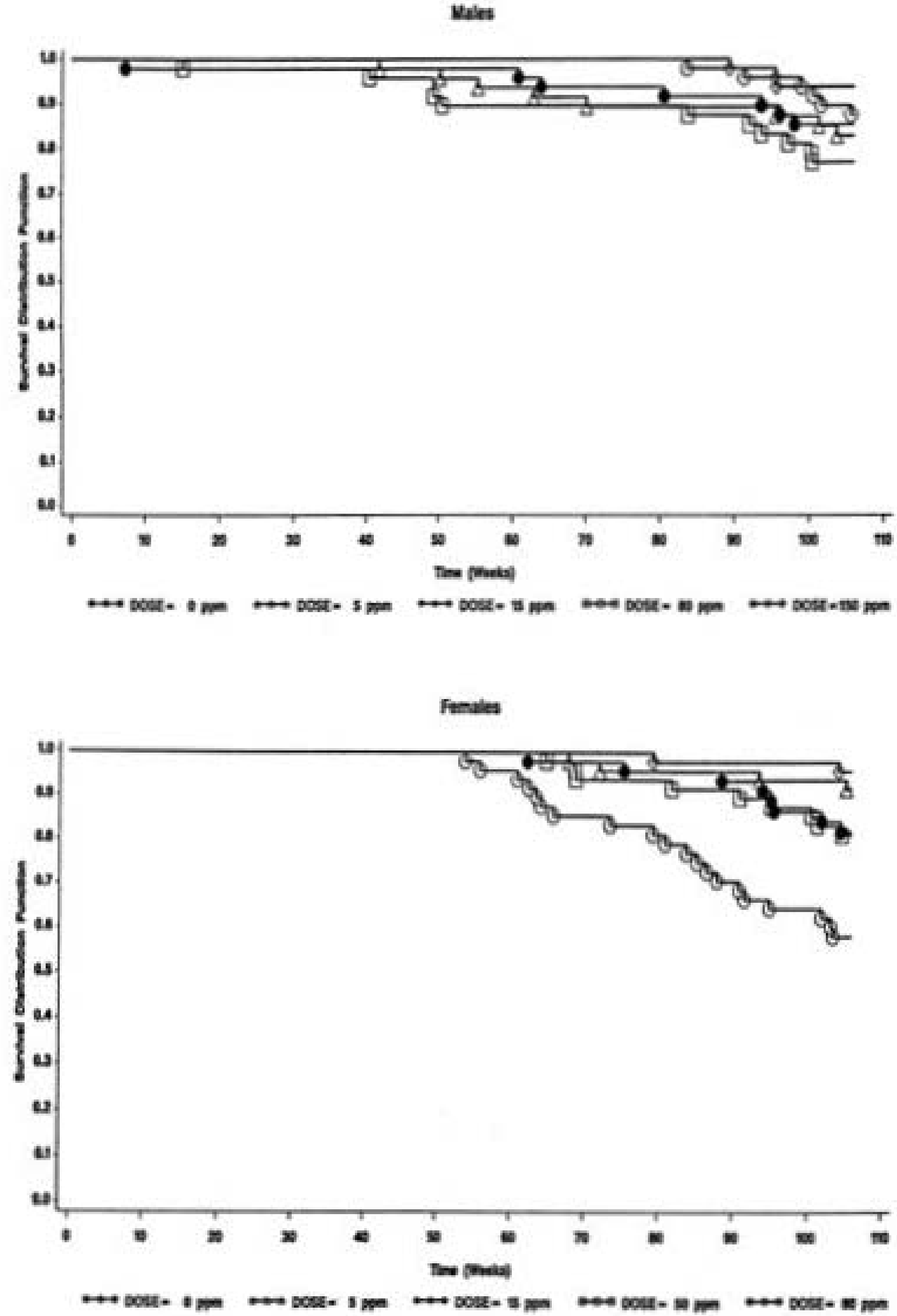


FIGURE 5
Kaplan-Meier Survival Curves for Male and Female Mice Administered Fumonisin B_1 in Feed for 2 Years

Body Weights, Feed and Compound Consumption, and Clinical Findings

Mean body weights of mice exposed to fumonisin B_1 for 2 years were generally similar to those of the controls throughout the study (Figure 6 and Tables 30 and 31).

The mean body weight of the male and female mice at 52 weeks was 33.3 and 25.4 grams compared to 39 and 32 grams on similar studies at this facility.

The reduced body weight was apparently due to an inadvertent restriction of the free flow of the powdered feed through the wire feeder screens. This resulted in an approximate 30% reduction in the amount of feed consumed daily by the mice on this study compared to animals under similar conditions at this facility; however, feed consumption by males and females exposed for up to 24 weeks (Tables I3 and I4) or for 2 years (Tables I7 and I8) was generally similar to that by the controls. The impact of this restriction on the analysis of the results is presented in the Discussion.

Dietary concentrations of 5, 15, 80, or 150 ppm fumonisin B_1 resulted in average daily doses of approximately 0.6, 1.7, 9.7, or 17.1 mg fumonisin B_1/kg body weight to male mice exposed for 2 years. Dietary concentrations of 5, 15, 50, or 80 ppm fumonisin B_1 resulted in average daily doses of approximately 0.7, 2.1, 7.1, or 12.4 mg/kg to female mice. There were no exposure-related clinical findings in male or female mice.

Clinical Pathology Findings

Clinical pathology data for mice exposed to fumonisin B_1 for up to 24 weeks are presented in Table F4. There was no consistent exposure-related effect on any of the serum analytes in males or females. Neither urinary creatinine nor protein was significantly affected by exposure. The sphinganine/sphingosine ratios were significantly increased in the liver of 50 and 80 ppm female groups at week 3 and of all exposed groups of females at week 9. Due to a high sphinganine/sphingosine ratio in the liver of control females at week 7, fumonisin B_1 exposure was not found to affect sphingolipid synthesis at this intermediate time point. Because the sphinganine/sphingosine ratio was also unaffected by exposure at 24 weeks, the reliability of this biomarker as an indicator of exposure in female mice is questionable. Liver sphinganine/sphingosine ratios were significantly increased in 80 and 150 ppm male groups at 7 weeks but were not significantly changed at 3 or 9 weeks.

Cell Proliferation Analyses

Cell proliferation was determined in the liver and kidney of mice evaluated at 3, 7, 9, and 24 weeks using immunohistochemical methods for determining BrdU uptake and PCNA expression (Tables E5 and E6). Consistent increases in cell proliferation were not detected in the liver or kidney of male or female mice.

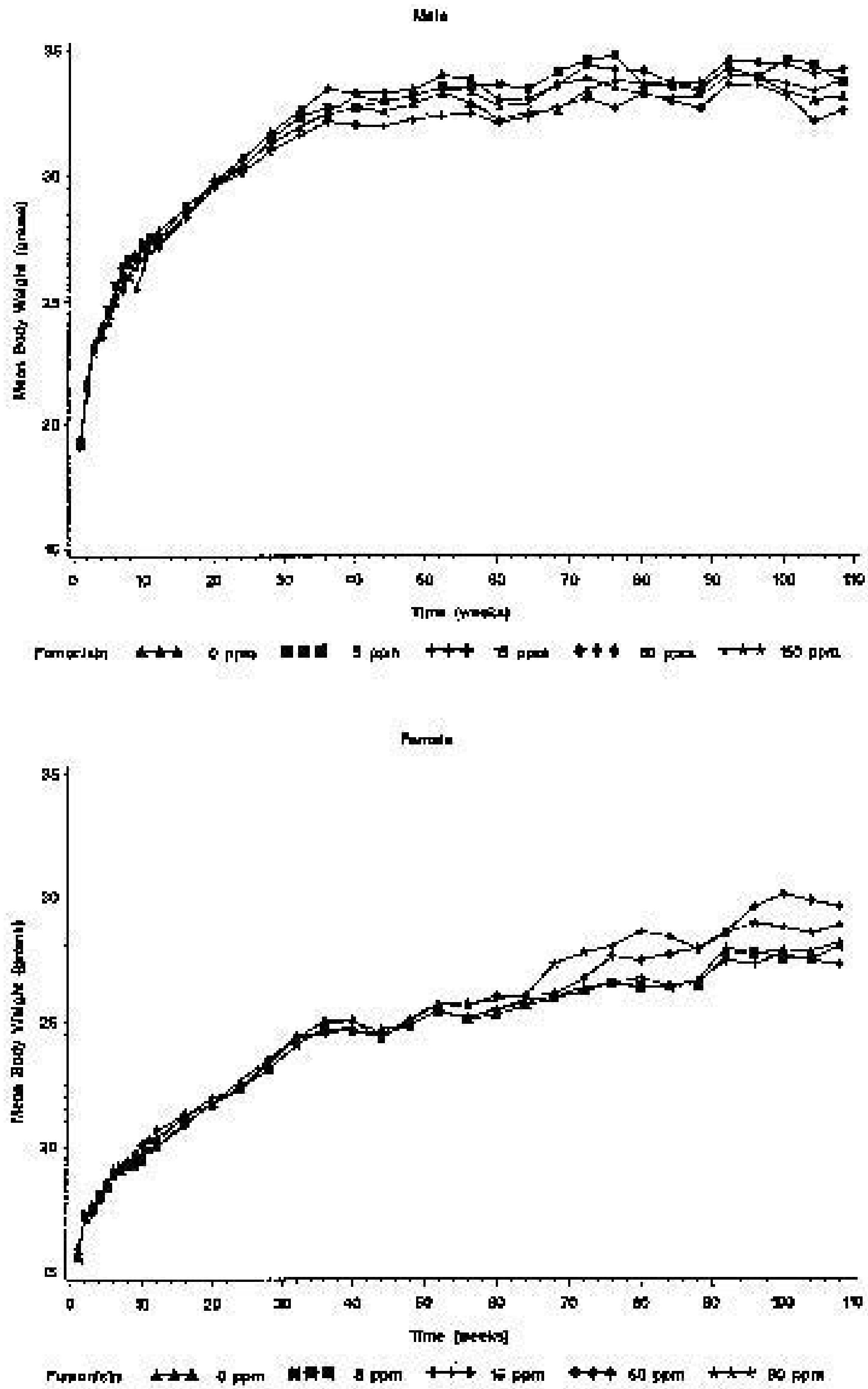


FIGURE 6
Growth Curves for Male and Female Mice Administered Fumonisin B_1 in Feed for 2 Years

TABLE 30
Mean Body Weights and Survival of Male Mice in the 2-Year Feed Study of Fumonisin B_1

Weeks on Study	0 ppm		5 ppm			15 ppm		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
2	21.79	48	21.55	98.90	48	21.68	99.50	48
3	23.26	48	23.05	99.10	48	22.97	98.75	48
4	23.94	48	23.74	99.16	48	23.54	98.33	48
5	24.54	48	24.67	100.53	48	24.31	99.06	48
6	25.31	48	25.68	101.46	48	25.19	99.53	48
7	26.11	48	26.48	101.42	48	25.46	97.51	48
8	26.04	47	26.79	102.88	48	26.09	100.19	48
9	26.88	47	26.89	100.04	48	26.45	98.40	48
10	26.79	47	27.34	102.05	48	26.73	99.78	48
11	27.43	47	27.62	100.69	48	27.05	98.61	48
12	27.80	47	27.47	98.81	48	27.19	97.81	48
16	28.78	47	28.80	100.07	48	28.35	98.51	48
20	29.67	47	29.61	99.80	48	29.55	99.60	48
24	30.36	47	30.26	99.67	48	30.11	99.18	48
28	31.26	47	31.44	100.58	47	30.98	99.10	48
32	31.88	47	32.31	101.35	47	31.56	99.00	48
36	32.40	47	32.67	100.83	47	32.10	99.07	48
40	32.64	47	32.66	100.06	47	31.96	97.92	48
44	32.52	47	32.92	101.23	46	31.94	98.22	48
48	32.82	47	33.14	100.98	46	32.19	98.08	48
52	33.28	47	33.52	100.72	45	32.33	97.15	48
56	32.87	47	33.52	101.98	45	32.46	98.75	48
60	32.18	47	33.59	104.38	44	32.08	99.69	48
64	32.51	46	33.45	102.89	43	32.33	99.45	48
68	32.57	45	34.08	104.64	43	32.69	100.37	48
72	33.40	45	34.56	103.47	42	33.06	98.98	48
76	33.79	45	34.74	102.81	42	32.66	96.66	48
80	33.65	45	33.56	99.73	42	33.26	98.84	48
84	33.65	44	33.57	99.76	42	32.93	97.86	48
88	33.48	44	33.37	99.67	42	32.65	97.52	48
92	34.29	44	34.25	99.88	42	33.60	97.99	47
96	33.87	43	33.87	100.00	42	33.60	99.20	47
100	33.30	41	34.60	103.90	41	33.11	99.43	45
104	32.96	41	34.35	104.22	40	32.09	97.36	45
106	33.08	41	33.64	101.69	39	32.53	98.34	45
Mean for weeks								
2-13	25.44		25.57	100.51		25.15	98.86	
14-52	31.56		31.73	100.54		31.11	98.57	
53-106	33.26		33.94	102.04		32.79	98.59	

TABLE 30
Mean Body Weights and Survival of Male Mice in the 2-Year Feed Study of Fumonisin B_1

Weeks on Study	80 ppm Av. Wt. (g)	80 ppm Wt. (% of controls)	80 ppm No. of Survivors	150 ppm Av. Wt. (g)	150 ppm Wt. (% of controls)	150 ppm No. of Survivors
2	21.65	99.36	48	21.29	97.71	48
3	23.14	99.48	48	22.84	98.19	48
4	23.89	99.79	48	23.54	98.33	48
5	24.64	100.41	48	24.10	98.21	48
6	24.94	98.54	48	24.94	98.54	48
7	25.96	99.43	48	25.61	98.09	48
8	26.51	101.80	48	26.04	100.00	48
9	26.65	99.14	48	25.51	94.90	48
10	27.11	101.19	48	26.41	98.58	48
11	27.43	100.00	48	27.40	99.89	48
12	27.36	98.42	48	27.29	98.17	48
16	28.51	99.06	47	28.34	98.47	48
20	29.71	100.13	47	29.87	100.67	48
24	30.64	100.92	47	30.38	100.07	48
28	31.68	101.34	47	31.24	99.94	48
32	32.54	102.07	47	31.94	100.19	48
36	33.41	103.12	47	32.46	100.19	48
40	33.23	101.81	47	33.14	101.53	48
44	33.28	102.34	46	32.91	101.20	48
48	33.38	101.71	46	33.15	101.01	48
52	33.96	102.04	43	33.44	100.48	48
56	33.82	102.89	43	33.31	101.34	48
60	32.99	102.52	43	32.73	101.71	48
64	33.05	101.66	43	32.84	101.02	48
68	33.59	103.13	43	33.63	103.25	48
72	34.37	102.90	43	33.83	101.29	48
76	34.20	101.21	43	33.50	99.14	48
80	34.17	101.55	43	33.21	98.69	48
84	33.67	100.06	43	33.05	98.22	48
88	33.68	100.60	42	33.14	98.98	47
92	34.58	100.85	42	33.99	99.13	46
96	34.48	101.80	40	33.87	100.00	46
100	34.36	103.18	39	33.64	101.02	45
104	34.02	103.22	37	33.31	101.06	43
106	34.18	103.33	37	33.76	102.06	43
Mean for weeks						
2-13	25.39	99.80		25.00	98.27	
14-52	32.03	101.49		31.69	100.41	
53-106	33.94	102.04		33.42	100.48	

TABLE 31
Mean Body Weights and Survival of Female Mice in the 2-Year Feed Study of Fumonisin B_1

Weeks on Study	0 ppm		5 ppm			15 ppm		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
2	17.17	48	17.28	100.64	52	17.13	99.77	48
3	17.68	48	17.53	99.15	52	17.48	98.87	48
4	17.98	48	18.07	100.50	48	18.12	100.78	48
5	18.57	48	18.39	99.03	48	18.50	99.62	48
6	19.13	47	18.98	99.22	48	18.83	98.43	48
7	19.06	47	19.22	100.84	48	19.09	100.16	48
8	19.27	47	19.33	100.31	48	19.42	100.78	48
9	19.66	47	19.26	97.97	48	19.60	99.69	48
10	19.73	47	19.46	98.63	48	20.07	101.72	48
11	20.32	47	19.89	97.88	48	20.28	99.80	48
12	20.39	47	20.04	98.28	48	20.25	99.31	48
16	21.23	47	21.02	99.01	48	21.26	100.14	48
20	21.79	47	21.71	99.63	48	22.00	100.96	48
24	22.64	47	22.32	98.59	48	22.39	98.90	48
28	23.54	47	23.11	98.17	48	23.45	99.62	48
32	24.43	47	24.09	98.61	48	24.32	99.55	48
36	24.61	47	24.75	100.57	48	24.55	99.76	48
40	24.81	47	24.60	99.15	48	24.68	99.48	48
44	24.70	47	24.40	98.79	48	24.49	99.15	48
48	24.87	47	24.84	99.88	48	24.86	99.96	48
52	25.38	47	25.44	100.24	48	25.37	99.96	48
56	25.14	47	25.06	99.68	48	25.11	99.88	48
60	25.42	47	25.26	99.37	48	25.48	100.24	48
64	25.75	46	25.61	99.46	48	25.86	100.43	48
68	25.99	46	25.90	99.65	48	25.98	99.96	48
72	26.37	46	26.18	99.28	47	26.17	99.24	48
76	26.53	46	26.57	100.15	46	26.55	100.08	48
80	26.33	45	26.42	100.34	46	26.74	101.56	48
84	26.40	45	26.38	99.92	46	26.44	100.15	47
88	26.63	45	26.46	99.36	46	26.61	99.92	47
92	27.92	40	27.61	98.89	46	27.42	98.21	47
96	27.68	38	27.78	100.36	45	27.29	98.59	47
100	27.85	37	27.48	98.67	45	27.66	99.32	47
104	27.77	36	27.46	98.88	45	27.41	98.70	47
106	28.12	35	27.96	99.43	44	27.26	96.94	46
Mean for weeks								
2-13	19.00		18.86	99.26		18.98	99.89	
14-52	23.80		23.63	99.29		23.74	99.75	
53-106	26.71		26.58	99.51		26.57	99.48	

TABLE 31
Mean Body Weights and Survival of Female Mice in the 2-Year Feed Study of Fumonisin B_1

Weeks on Study	50 ppm Av. Wt. (g)	50 ppm Wt. (% of controls)	50 ppm No. of Survivors	80 ppm Av. Wt. (g)	80 ppm Wt. (% of controls)	80 ppm No. of Survivors
2	17.21	100.23	48	17.16	99.94	48
3	17.38	98.30	48	17.63	99.72	48
4	17.89	99.50	48	18.09	100.61	48
5	18.46	99.41	48	18.57	100.00	48
6	19.07	99.69	48	18.77	98.12	48
7	19.03	99.84	48	19.21	100.79	48
8	19.41	100.73	48	19.22	99.74	48
9	19.69	100.15	48	19.63	99.85	48
10	20.11	101.93	48	19.54	99.04	48
11	20.28	99.80	48	19.95	98.18	48
12	20.63	101.18	48	20.00	98.09	48
16	21.33	100.47	48	20.88	98.35	48
20	21.73	99.72	48	21.83	100.18	48
24	22.41	98.98	48	22.37	98.81	48
28	23.51	99.87	48	23.31	99.02	48
32	24.41	99.92	48	24.32	99.55	48
36	24.90	101.18	48	25.06	101.83	48
40	25.02	100.85	48	25.02	100.85	48
44	24.54	99.35	48	24.28	98.30	48
48	25.02	100.60	48	25.11	100.97	48
52	25.62	100.95	48	25.69	101.22	48
56	25.65	102.03	48	25.61	101.87	47
60	26.00	102.28	48	25.86	101.73	46
64	26.00	100.97	48	26.05	101.17	44
68	26.08	100.35	47	27.29	105.00	41
72	26.72	101.33	45	27.73	105.16	41
76	27.59	104.00	45	27.99	105.50	40
80	27.44	104.22	45	28.58	108.55	40
84	27.69	104.89	44	28.40	107.58	38
88	27.89	104.73	44	27.84	104.54	35
92	28.56	102.29	43	28.50	102.08	33
96	29.58	106.86	42	28.92	104.48	31
100	30.10	108.08	42	28.74	103.20	31
104	29.83	107.42	40	28.50	102.63	29
106	29.60	105.26	39	28.82	102.49	28
Mean for weeks						
2-13	19.01	100.05		18.89	99.42	
14-52	23.85	100.21		23.79	99.96	
53-106	27.77	103.97		27.77	103.97	

Organ Weights, Pathology, and Statistical Analyses

This section describes the statistically significant or biologically noteworthy changes in organ weights and in the incidences of neoplasms and nonneoplastic lesions of the liver. Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, and statistical analyses of neoplasms in the control and highest exposed groups are presented in Appendix C for male mice and Appendix D for female mice.

Organ weight changes in mice exposed to fumonisin B_1 were not very remarkable. Right kidney-to-brain-weight ratios of 15, 80, and 150 ppm males at 9 weeks were significantly greater than that of the controls (Table G12). In 80 ppm males and 50 ppm females at 2 years, the kidney weights were greater than those of the controls (Table G14).

Liver: In 50 and 80 ppm females at 2 years, liver weights were increased (Table G14).

At 2 years, hepatocellular adenomas and carcinomas were detected in all groups of male mice, but none of the incidences in the exposed groups were significantly different from the incidences in the control group, and no exposure-related trends were present. At 2 years, the incidences of hepatocellular neoplasms in 50 and 80 ppm females were significantly greater than those in the controls and occurred with positive trends (Tables 32 and D3). Hepatocellular adenomas were characterized as discrete lesions with compression of adjacent normal tissue. The normal hepatic lobular structure was absent with uneven growth patterns. The cells in the adenoma appeared to be well differentiated and either eosinophilic, basophilic, or vacuolated. Hepatocellular carcinomas were characterized as foci of cells with distinct trabecular or adenoid structure. Histological evidence of local invasiveness or metastasis was usually evident. The cells within the carcinoma were poorly differentiated or anaplastic. Some of the carcinomas appeared to arise within adenomas.

Several nonneoplastic lesions were observed in the liver of females exposed to fumonisin B_1 for up to 24 weeks, including centrilobular apoptosis, centrilobular necrosis, cytoplasmic alteration, centrilobular hypertrophy, cytoplasmic vacuolization, Kupffer cell hyperplasia, and centrilobular pigmentation (Tables 32 and D4).

Although significantly increased incidences of centrilobular apoptosis occurred, neither the incidences nor severities appeared to be related to exposure concentration or time. Centrilobular necrosis was characterized by focal lytic necrosis. This was observed in 80 ppm females after 3 and 7 weeks of exposure. Necrosis was present in 15 and 80 ppm females at 9 weeks and was not observed at 24 weeks. Hepatocytes were identified with increased eosinophilia and fine granularity in the cytoplasm (cytoplasmic alteration). This change has been referred to as cloudy swelling in the past, and it is inferred to represent increased content of smooth and/or rough endoplasmic reticulum. This lesion was observed in 50 and 80 ppm females evaluated at 3 weeks and in the 5 and 15 ppm groups at later time points. Enlarged centrilobular hepatocytes were characterized as hypertrophic hepatocytes in females. This lesion was observed in 50 and 80 ppm females at 3 and 7 weeks and in 5 and 15 ppm females at 9 weeks. At 24 weeks, this lesion was observed in one control female, one 15 ppm female, and all 80 ppm females. Cytoplasmic vacuolization occurred in the centrilobular region of one 50 ppm female and in the periportal region of all 80 ppm females at 3 weeks. Following 7 weeks of exposure, two females in the 5 and 50 ppm groups and one in the 80 ppm group had centrilobular cytoplasmic vacuolization. At 9 weeks, one female in the 5 and 80 ppm groups had this lesion, and there was no evidence of this lesion at 24 weeks. Kupffer cell hyperplasia was only evident in 80 ppm females. This lesion was observed in two females at 3 and 7 weeks and in all 80 ppm females at 9 weeks, and this lesion was not observed in mice at 24 weeks. Macrophages containing yellow-gray pigmented material (centrilobular pigmentation) were detected on a sporadic basis. Livers of all 80 ppm females contained the pigmented macrophages at 7 weeks, whereas all 15 ppm females had this lesion after 9 weeks. At the 24-week evaluation, all control and 80 ppm females displayed this lesion. In summary, the nonneoplastic lesions noted in mice exposed for up to 24 weeks were detected only in the liver of females. After 3 and 7 weeks of exposure, lesions were observed predominantly in 50 and 80 ppm mice. The pattern of lesions observed after 9 and 24 weeks of exposure was not as consistent.

TABLE 32
Incidences of Neoplasms and Nonneoplastic Lesions of the Liver in Mice in the 2-Year Feed Study of Fumonisin B_1

	0 ppm	5 ppm	15 ppm	80 ppm	150 ppm
Male					
2-Year Study					
Number Examined Microscopically	47	47	48	48	48
Apoptosis, Hepatocyte[a]	0	0	0	0	3 (2.0)[b]
Hypertrophy, Hepatocyte	10 (1.2)	9 (2.1)	24** (2.0)	25***(1.9)	30***(3.1)
Hepatocellular Adenoma	9	7	7	6	8
Hepatocellular Carcinoma	4	3	4	3	2
Hepatocellular Adenoma or Carcinoma	12	9	9	9	10

	0 ppm	5 ppm	15 ppm	50 ppm	80 ppm
Female					
3-Week Evaluation					
Number Examined Microscopically	4	4	4	4	4
Apoptosis, Centrilobular	0	0	0	0	4* (2.0)
Necrosis, Centrilobular	0	0	0	0	1 (1.0)
Cytoplasmic Alteration, Centrilobular	0	0	0	2 (1.0)	4* (2.0)
Hypertrophy, Centrilobular	0	0	0	2 (1.0)	4* (1.0)
Cytoplasmic Vacuolization, Centrilobular	0	0	0	1 (1.0)	0
Cytoplasmic Vacuolization, Portal	0	0	0	0	4* (1.0)
Hyperplasia, Centrilobular, Kupffer Cell	0	0	0	0	2 (1.5)
7-Week Evaluation					
Number Examined Microscopically	4	4	4	4	4
Apoptosis, Centrilobular	0	0	0	0	4* (1.0)
Necrosis, Centrilobular	0	0	0	0	2 (1.0)
Cytoplasmic Alteration, Centrilobular	0	0	2 (1.0)	3 (1.0)	4* (1.0)
Hypertrophy, Centrilobular	0	0	0	2 (1.0)	4* (1.0)
Cytoplasmic Vacuolization, Centrilobular	0	2 (1.0)	0	2 (1.0)	1 (3.0)
Hyperplasia, Centrilobular, Kupffer Cell	0	0	0	0	2 (1.5)
Pigment, Centrilobular	0	0	0	0	4* (1.0)
9-Week Evaluation					
Number Examined Microscopically	4	4	4	4	4
Apoptosis, Centrilobular	0	0	4* (2.8)	0	0
Necrosis, Centrilobular	0	0	4* (2.0)	0	0
Necrosis, Focal	0	0	0	0	1 (2.0)
Cytoplasmic Alteration, Centrilobular	0	0	3 (2.0)	0	0
Cytoplasmic Alteration, Diffuse	0	1 (1.0)	1 (2.0)	4* (1.8)	0
Hypertrophy, Centrilobular	0	1 (1.0)	3 (2.0)	0	0
Cytoplasmic Vacuolization, Centrilobular	0	1 (1.0)	0	0	1 (3.0)
Hyperplasia, Diffuse, Kupffer Cell	0	0	0	0	4* (1.3)
Pigment, Centrilobular	0	0	4* (2.0)	0	0
24-Week Evaluation					
Number Examined Microscopically	4	4	4	4	4
Apoptosis, Centrilobular	4 (1.3)	0*	0*	0*	1 (2.0)
Cytoplasmic Alteration, Centrilobular	0	0	0	0	4* (1.0)
Cytoplasmic Alteration, Diffuse	0	0	1 (2.0)	4* (2.0)	0
Hypertrophy, Centrilobular	1 (1.0)	0	1 (2.0)	0	4 (2.0)
Pigment, Centrilobular	4 (1.8)	0*	0*	0*	4 (2.5)

TABLE 32
Incidences of Neoplasms and Nonneoplastic Lesions of the Liver in Mice in the 2-Year Feed Study of Fumonisin B_1

	0 ppm	5 ppm	15 ppm	50 ppm	80 ppm
Female (continued)					
2-Year Study					
Number Examined Microscopically	47	48	48	47	45
Apoptosis, Hepatocyte	0	0	0	7* (1.1)	14** (2.0)
Hypertrophy, Diffuse, Hepatocyte	0	0	0	27***(1.9)	31***(3.2)
Hepatocellular Adenoma					
Overall rate[c]	5/47 (11%)	3/48 (6%)	1/48 (2%)	16/47 (34%)	31/45 (69%)
Adjusted rate[d]	11.7%	6.5%	2.1%	36.3%	73.7%
Terminal rate[e]	5/39 (13%)	3/44 (7%)	1/46 (2%)	14/39 (36%)	21/28 (75%)
First incidence (days)	740 (T)	740 (T)	740 (T)	703	391
Poly-3 test[f]	P=0.0001	P=0.3314N	P=0.0862N	P=0.0047	P=0.0001
Hepatocellular Carcinoma					
Overall rate	0/47 (0%)	0/48 (0%)	0/48 (0%)	10/47 (21%)	9/45 (20%)
Adjusted rate	0.0%	0.0%	0.0%	22.5%	23.1%
Terminal rate	0/39 (0%)	0/44 (0%)	0/46 (0%)	8/39 (21%)	3/28 (11%)
First incidence (days)	—[g]	—	—	636	437
Poly-3 test	P=0.0001	—[h]	—	P=0.0007	P=0.0007
Hepatocellular Adenoma or Carcinoma					
Overall rate	5/47 (11%)	3/48 (6%)	1/48 (2%)	19/47 (40%)	39/45 (87%)
Adjusted rate	11.7%	6.5%	2.1%	42.7%	88.3%
Terminal rate	5/39 (13%)	3/44 (7%)	1/46 (2%)	16/39 (41%)	24/28 (86%)
First incidence (days)	740 (T)	740 (T)	740 (T)	636	391
Poly-3 test	P=0.0001	P=0.3314N	P=0.0862N	P=0.0005	P=0.0001

* Significantly different ($P \leq 0.05$) from the control group by the Fisher exact test (3-, 7-, 9-, and 24-week evaluations) or Poly-3 test (2-year study)
** $P \leq 0.01$
*** $P \leq 0.001$
(T) Terminal sacrifice
a Number of animals with lesion
b Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked
c Number of animals with neoplasm per number of animals with liver examined microscopically
d Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
e Observed incidence at terminal kill
f Beneath the control incidence is the P value associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A lower incidence in an exposure group is indicated by **N**.
g Not applicable; no neoplasms in animal group
h Value of statistic cannot be computed.

Hepatocellular hypertrophy was the only significant nonneoplastic lesion that was considered to be exposure related in mice exposed to fumonisin B_1 for 2 years. The incidences of hepatocellular hypertrophy were significantly increased relative to controls in 15, 80, and 150 ppm males and in 50 and 80 ppm females.

DISCUSSION AND CONCLUSIONS

Fumonisin B_1 is a mycotoxin produced by several fungi of the *Fusarium* genus (Thiel *et al.*, 1991a; Leslie *et al.*, 1992a,b; Nelson, 1992; Norred, 1993; Bullerman and Tsai, 1994; Desjardins *et al.*, 1994; Meireles *et al.*, 1994; Abbas *et al.*, 1995). These fungi contaminate corn and other grain crops worldwide (Sydenham *et al.*, 1991; Dutton, 1996). The growth of the fungus and production of the mycotoxins are based on a variety of environmental conditions such as temperature and moisture during growth. As a consequence, human exposure to fumonisin B_1 varies depending on the environmental conditions during plant growth, the percentage of the diet that contains contaminated food, and the methods that are employed in food processing and preparation.

The 2-year feed studies described in this report were initiated to determine the tumorigenicity of fumonisin B_1 in two rodent species. In the 2-year study, renal tubule adenomas and carcinomas were seen in the kidney of male rats exposed to 50 or 150 ppm. Significant increases in the incidences of hyperplasia of the renal tubule epithelium were seen in the same exposed groups. Proliferation of the renal tubule epithelial cells was also revealed early in the study both by incorporation of BrdU into the DNA and by PCNA using immunohistochemical techniques. Renal tubule epithelial apoptosis was detected at the 6-, 10-, and 14-week evaluations in male rats exposed to 15, 50, or 150 ppm and at 26 weeks in the 50 and 150 ppm groups of males. The occurrence of renal tubule epithelial apoptosis was expected since the incidences of this lesion were increased in male rats exposed to 99 ppm or greater in the 28-day study. Single cell necrosis and renal tubule hyperplasia were also seen in male Sprague-Dawley rats exposed to 15, 50, or 150 ppm fumonisin B_1 (Voss *et al.*, 1993). As a result, a consistent observation in male rats is the induction of renal apoptosis at a low exposure concentration (15 ppm) of fumonisin B_1.

An association between α2u-globulin and the development of renal tubule neoplasms in male rats has been described for several compounds; however, based on the absence of characteristic renal tubule lesions, α2u-globulin does not appear to be a contributing factor in the development of renal tubule neoplasms in male rats exposed to fumonisin B_1. This globulin is found primarily more proximally in the tubule (Segment S2 or P2), whereas the hyperplasias, apoptoses, and neoplasms in the fumonisin B_1-treated rats were primarily in the more distal S3 or P3 segments.

In the 2-year study, the absolute and relative kidney weights in the 50 and 150 ppm groups of male rats were less than those of the controls. These differences were expected, since rats exposed to 99 or 163 ppm fumonisin B_1 for 28 days had decreased kidney weights. In the 2-year study, the exposure concentrations that resulted in decreased kidney weights were also responsible for increased incidences of renal tubule epithelial cell apoptosis, increased cell proliferation, and renal tubule neoplasm formation. Decreased kidney weights were also seen in Sprague-Dawley rats exposed to 15, 50, or 150 ppm fumonisin B_1 (Voss *et al.*, 1993).

Exposure to fumonisin B_1 for 28 days resulted in decreased relative liver weights in the 484 ppm groups of male rats, while exposure for 2 years resulted in reduced relative liver weights in all exposed groups of male rats. In the 28-day feed studies conducted by Voss *et al.* (1993), the relative liver weights of Sprague-Dawley rats were increased in groups exposed to 15 or 50 ppm fumonisin B_1 and decreased in the 150 ppm group.

Increase in cellular sphinganine (expressed as sphinganine to sphingosine ratio) in tissues, serum, and urine has been well characterized as a biomarker for fumonisin B_1-based inhibition of ceramide synthase (Riley *et al.*, 1996, 1998; Merrill *et al.*, 1997). The concentrations of sphinganine and the sphinganine/sphingosine ratios were increased in the kidney of male rats exposed to 15, 50, or 150 ppm at the 6-, 10-, 14-, and 26-week evaluations and in the 50 and 150 ppm male groups at 2 years. The sphinganine/sphingosine ratios in the kidney varied depending on the age of the rat but increased from approximately 0.6 at week 6 to 3 at week 26 in the male rat control group and from 14 to 28 in 150 ppm male rats over the same period. The sphinganine/sphingosine ratios in the urine of male rats were also increased in the 15, 50, and 150 ppm groups at 10, 14, and 26 weeks, increasing from 0.1 to 0.5 in the controls and from 7 to 26 in the 150 ppm group. These results are consistent with the observations in the 28-day study in which urinary sphinganine/sphingosine ratios were increased in all exposed groups of male rats with the highest ratio (10) in the 484 ppm group on day 7. Similar increases in urinary and kidney sphinganine concentrations have been reported in male Sprague-Dawley rats fed diets containing 15, 50, or 150 ppm fumonisin B_1 for 28 days (Riley *et al*., 1994; Voss *et al*., 1995a,b).

In male rats, there was a demonstrable inhibition of ceramide synthase (i.e., elevated sphinganine/sphingosine ratios) at the same exposure concentrations that resulted in increased incidences of renal tubule epithelial cell apoptosis and renal tubule adenomas and carcinomas, decreased kidney weights, and increased cell proliferation. Therefore, the data suggest that fumonisin B_1 induced renal tubule epithelial cell apoptosis and that this apoptosis was followed by tubule epithelial cell regeneration and eventually formation of the renal tubule neoplasms. This hypothesis is supported by *in vitro* studies in which fumonisin B_1 induced interruption of sphingolipid synthesis which resulted in apoptosis in rodent and human cells (Wang *et al*., 1991; Yoo *et al*., 1992, 1996; Tolleson *et al*., 1996, 1999).

There is an apparent gender difference in the response of the F344/N rat to fumonisin B_1 exposure. This difference was detected in the 28-day study. Hepatic toxicity, as evidenced by increased cholesterol and triglyceride concentrations and alanine aminotransferase and alkaline phosphatase activities, was increased in male rats only at 484 ppm, while the increases were detected at 234 and 484 ppm in female rats. While the impact of fumonisin B_1 on urinary sphinganine/sphingosine ratios and on liver and kidney weights was equivalent in males and females, the impact on liver and kidney nonneoplastic lesions was quite different. The incidence of renal tubule epithelial cell apoptosis was increased at 99 ppm in male rats, while the incidences of this lesion were increased in female rats at 163 ppm. Conversely, hepatocellular apoptosis was increased in male rats at 234 and 484 ppm, while the incidences of these lesions were increased in female rats starting at 163 ppm. In the 2-year study, there was no indication of renal tubule epithelial cell apoptosis in female rats exposed to concentrations up to 100 ppm at the 6-, 10-, 14-, and 26-week evaluations, while this lesion was induced in male rats at 15 ppm. Additionally, the incidences of renal tubule epithelial cell hyperplasia were not significantly increased in female rats at 2 years, but were increased in male rats starting at 50 ppm. Kidney tissue sphinganine concentrations were increased in male rats exposed to 15 ppm or greater and were increased in 50 and 100 ppm female rats. The reasons for the difference in the response of male and female rats to fumonisin B_1 is not understood at this time but has been documented for Sprague-Dawley rats (Voss *et al*., 1993, 1995a,b, 1996c). This gender difference is most apparent in the incidence of renal tubule neoplasms in the 2-year study in which male rats exposed to 50 or 150 ppm had increased incidences of renal tubule neoplasms while no such increases were detected in females. A difference in the consumption of fumonisin B_1 has been offered as an explanation of the gender differences in the response to fumonisin B_1 in rats (Voss *et al*., 1995a,b). This was apparently not the case in the present 2-year study in which the feed consumption by male and female rats was comparable. The mean body weights of male and female rats in this study at 52 weeks were 483 g and 273 g, respectively. The mean body weights of control F344/N rats at 49 to 52 weeks were 465 g for males and 276 g for females in six recent NTP studies (NTP, 1999a,b; 2000a,b; 2001, 2002).

Based on the results of the 28-day rat study and other toxicity studies in rats (Voss *et al*., 1993), the highest fumonisin B_1 exposure concentrations used in the 2-year study in F344/N rats were 150 ppm (males) and 100 ppm (females). While mean body weights and survival of rats exposed to fumonisin B_1 for 2 years were not significantly different from rats receiving control diets, 150 ppm resulted in the induction of kidney neoplasms in males. In female rats, the highest exposure concentration (100 ppm) did not have this result. Although the highest exposure concentrations were selected based on kidney and liver toxicities that developed in short-term studies, these types or extents of toxicities did not occur in the 2-year study. As a result, it appears that female rats could have tolerated somewhat higher exposure concentrations.

Histopathologic examination did not reveal any neoplastic or nonneoplastic changes in the liver or kidney of male mice at the 3-, 7-, 9-, or 24-week evaluations. No neoplastic changes were detected in female mice at the 3-, 7-, 9-, or 24-week evaluations; however, nonneoplastic lesions were seen in the liver of females during the evaluations. Centrilobular hepatocellular apoptosis and hypertrophy were detected in 80 ppm female mice at the 3- and 7-week evaluations. After 9 weeks of exposure, these lesions were increased only at 15 ppm, and at 26 weeks the incidence of hepatocellular apoptosis was increased in the control females but not in females exposed to 80 ppm. Whether these results reflect a temporal pattern or variations from small sample groups is not clear. Voss *et al*. (1995a,b) determined that following exposure to 81 ppm fumonisin B_1 for 90 days, hepatocellular apoptosis was induced in female B6C3F$_1$ mice but not in males, which supports the finding of the present study that fumonisin B_1 is more hepatotoxic to female mice than to male mice.

In the 2-year mouse study, the incidences of hepatocellular adenomas and carcinomas were significantly increased in females exposed to 50 or 80 ppm. The decreased survival of female mice exposed to 80 ppm was probably due to the increased incidences of hepatocellular neoplasms. The liver weights of female mice were increased in the 50 and 80 ppm groups, as were the incidences of hepatocellular hypertrophy and apoptosis. There were no apparent exposure concentration-related differences in the incidences of hepatocellular adenomas or carcinomas in male mice exposed to up to 150 ppm. There was an increase in the incidences of hepatocellular hypertrophy in male mice at 2 years in the 15, 80, and 150 ppm groups; however, this did not result in altered livers weights or neoplasm development.

The exposure concentrations of fumonisin B_1 required to increase the incidences of neoplastic and nonneoplastic changes in the liver of female mice in the 2-year study are consistent with the exposure concentrations that were required for clinical chemistry alterations in the 28-day study. Serum cholesterol and triglyceride concentrations and alanine aminotransferase and alkaline phosphatase activities were consistently elevated in 163 ppm female mice and occasionally in 99 ppm females. This is in contrast to male mice, for which serum analytes were increased only in the 484 ppm group. Similar results have been reported by Bondy *et al.* (1997) in which a daily dose of 35 mg/kg fumonisin B_1 induced alanine aminotransferase activities in female but not in male mice after 14 days. The daily doses of fumonisin B_1 in the 28-day study were approximately 93 and 105 mg/kg per day for male and female mice fed diets containing 484 ppm fumonisin B_1.

The liver was the only tissue from mice in the 2-year study that was examined for cellular sphingolipid changes. Liver sphinganine concentrations and the sphinganine/sphingosine ratios were increased in female mice exposed to 50 or 80 ppm fumonisin B_1 for 3 or 9 weeks but were not elevated after 7 or 24 weeks. These increases were modest compared to the increases detected in male and female rat urine and tissues. The sphinganine/sphingosine ratios were increased in male mice exposed to 80 or 150 ppm only at 7 weeks. This apparent lack of induction of the sphinganine/sphingosine ratios in mice is consistent with the observations from the 28-day study. Urinary sphinganine/sphingosine ratios were increased in 484 ppm male mice, while they were not increased in female mice exposed to concentrations up to 484 ppm. Additional analyses of the tissue sphinganine/sphingosine concentrations are being conducted for mice from the 28-day and 2-year studies. These analyses should clarify the extent of increase in this biomarker for fumonisin B_1 exposure; however, the lack of consistent increases in the liver sphinganine/sphingosine ratios in female mice in relationship to the increased incidences of hepatocellular neoplasms suggests that, in mice, the sphinganine/sphingosine ratio may not be the best biomarker for fumonisin B_1 exposure and tumorigenic risk.

There is not an adequate explanation for the gender differences in the response of male and female mice to fumonisin B_1; however, the differences do not appear to be due to exposure to fumonisin B_1. The daily doses were approximately 9.5 and 17 mg fumonisin B_1/kg per day for males fed diets containing 80 and 150 ppm. Female mice consumed approximately 7 and 12.5 mg fumonisin B_1/kg per day when fed diets containing 50 and 80 ppm. Therefore, if fumonisin B_1 was equipotent in males and females, increases in the incidences of hepatocellular neoplasms in males in the two highest exposure groups would have been expected.

The highest fumonisin B_1 exposure concentrations used in the 2-year study in $B6C3F_1$ mice were 150 ppm (males) and 80 ppm (females). Mean body weights of males and females and survival of males were not markedly different from those of the controls. Fumonisin B_1 caused concentration-related increases in the incidences of hepatocellular adenomas and carcinomas in female mice beginning at 50 ppm. Therefore, it appears that the exposure concentrations selected for the 2-year female mouse study were adequate. There were no concentration-related increases in the incidences of neoplasms in male mice exposed to concentrations of fumonisin B_1 up to 150 ppm. In the 28-day mouse study, the incidences of hepatocellular nonneoplastic lesions and clinical chemistry parameters were increased in females at 99 ppm but were increased in males only at 484 ppm. Although the exposure concentrations for male mice in the 2-year study were set almost twofold higher than those for females, it is possible that this was insufficient to fully compensate for the gender difference in sensitivity to fumonisin B_1 toxicity.

There was an apparent inadvertent restriction of feed for mice in the 2-year study. The male and female mice in the current 2-year study weighed 33.3 g and 25.4 g, respectively, after 52 weeks, compared with means of 38 to 40 g for males and 32 g for females for other NCTR studies. The $B6C3F_1$/Nctr BR (C57BL/6N × C3H/HeN MTV−) mice used in this study are from an on-site breeding colony at NCTR; by contrast, the mean body weights of male and female $B6C3F_1$ mice from different breeding colonies and fed control NIH-07 diets in five recent NTP studies were 50 g and 49 g, respectively, at 49 to 52 weeks (NTP, 1999b; 2000a,b; 2001a,b). The lower body weights were probably due to a minimal restriction of feed in the mouse cages. Deionized water or fumonisin B_1 in deionized water were mixed into powdered NIH-31 open formula diet using commercial blenders. Particle size analysis did not detect a significant alteration in the size distribution of the fumonisin B_1-containing feed (data not presented); however, the free flow of control as well as dosed feed through the wire screens was apparently restricted, as the mice consumed approximately 30% less than the typical daily quantity of feed when compared to mice of similar age at NCTR.

Reduced body weight through dietary restriction has been shown to increase longevity and reduce the incidence of spontaneous tumors in mice (Sheldon *et al*., 1995). An analysis of the effects of dietary restriction showed that the spontaneous liver tumor incidence was reduced from 55% to 24% in male $B6C3F_1$ mice and from 44% to 12% in female $B6C3F_1$ mice (Haseman, 1998). The decreases in 12-month body weights were 20% for males and 30% for females. Leakey *et al*. (1998) determined that male $B6C3F_1$ mice weighing approximately 33 grams at 12 months should have liver tumor incidences of approximately 20%. The liver neoplasm incidences in mice given control diets in the present 2-year study were 26% for males and 11% for females. Therefore, it appears that the effect of the restriction of feed in the mouse component of this 2-year study was to reduce the liver neoplasm incidence to levels consistent with a 20% food restriction model (Kari and Abdo, 1995; Haseman, 1998). The reduction of the liver tumor rates in the control male and female mice though reduction in feed consumption and body weight would have the advantage of increasing the statistical sensitivity of the bioassay for a liver carcinogen (Turturro *et al*., 1998).

Gelderblom *et al.* (1991) demonstrated that the inclusion of 50 ppm fumonisin B_1 in the diet resulted in increased incidences of hepatocellular carcinomas in male BD-IX rats. Gelderblom *et al.* (1992) used an initiation/promotion assay to demonstrate that fumonisin B_1 was probably a tumor promoter and not a complete carcinogen or initiator. In subsequent studies, dietary fumonisin B_1 at 50 ppm and higher was able to promote diethylnitrosamine-initiated rats to form hepatocellular foci after 21 days (Gelderblom *et al*., 1996a). The studies in this Technical Report have extended these observations and demonstrated that the consumption of diets containing 50 ppm or higher concentrations of fumonisin B_1 for 2 years results in the formation of renal tubule neoplasms in male rats. The difference in the neoplasm site between F344/N rats (kidney) and BD-IX rats (liver) cannot be explained at this time.

Conclusions

Under the conditions of these 2-year feed studies, there was *clear evidence of carcinogenic activity** of fumonisin B_1 in male F344/N rats based on the increased incidences of renal tubule neoplasms. There was *no evidence of carcinogenic activity* of fumonisin B_1 in female F344/N rats exposed to 5, 15, 50, or 100 ppm. There was *no evidence of carcinogenic activity* of fumonisin B_1 in male B6C3F$_1$ mice exposed to 5, 15, 80, or 150 ppm. There was *clear evidence of carcinogenic activity* of fumonisin B_1 in female B6C3F$_1$ mice based on the increased incidences of hepatocellular neoplasms.

The sphinganine/sphingosine ratios were increased in the urine and the kidney tissue of rats receiving diets containing fumonisin B_1. There was evidence of apoptosis and increased cell proliferation of the renal tubule epithelium in exposed rats, particularly in those groups of males that developed renal tubule neoplasms. Increased incidences of hyperplasia of the renal tubule epithelium also occurred in these groups of male rats.

In mice exposed to the higher concentrations of fumonisin B_1, males and females had increased incidences of hepatocellular hypertrophy and females had increased incidences of hepatocellular apoptosis.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 10. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 12.

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APPENDIX A
SUMMARY OF LESIONS IN MALE RATS
IN THE 2-YEAR FEED STUDY
OF FUMONISIN B_1

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of Fumonisin B_1[a]

	0 ppm		5 ppm		15 ppm		50 ppm		150 ppm	
Disposition Summary										
6-Week evaluation	4		4		4		4		4	
10-Week evaluation	4		4		4		4		4	
14-Week evaluation	4		4		4		4		4	
26-Week evaluation	4		4		4		4		4	
Animals initially in 2-year study	48		40		48		48		48	
Early deaths										
Removed from study	2						2			
Moribund	24		19		19		19		21	
Natural deaths	6		4		4		9		2	
Survivors										
Terminal sacrifice	16		17		25		18		25	
Animals examined microscopically	64		56		64		64		64	

Tissues Examined at 6 Weeks with No Neoplasms Observed

Kidney
Liver

Tissues Examined at 10 Weeks with No Neoplasms Observed

Kidney
Liver
Mesentery

Tissues Examined at 14 Weeks with No Neoplasms Observed

Kidney
Liver
Testes

Tissues Examined at 26 Weeks with No Neoplasms Observed

Intestine large
Kidney
Liver

2-Year Study

	0 ppm		5 ppm		15 ppm		50 ppm		150 ppm	
Adrenal gland	(47)		(22)		(25)		(31)		(47)	
Adenoma, cortex							1	(3%)	2	(4%)
Carcinoma, cortex									1	(2%)
Leukemia monuc	9	(19%)	3	(14%)	5	(20%)	3	(10%)	4	(9%)
Pheochrom bgn, bilateral, medulla									2	(4%)
Pheochrom bgn, medulla	11	(23%)	4	(18%)	6	(24%)	3	(10%)	6	(13%)
Pheochrom mal, medulla	1	(2%)			1	(4%)				
Bone	(48)		(23)		(23)		(30)		(48)	
Osteoma, scapula	1	(2%)								
Sarcoma, synovial tiss					1	(4%)				
Bone marrow	(47)		(23)		(23)		(30)		(48)	
Leukemia monuc	15	(32%)	12	(52%)	10	(43%)	10	(33%)	10	(21%)

Table A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of Fumonisin B_1

	0 ppm		5 ppm		15 ppm		50 ppm		150 ppm	
2-Year Study (continued)										
Brain	(48)		(24)		(23)		(31)		(48)	
Leukemia monuc	2	(4%)			4	(17%)	2	(6%)		
Leukemia monuc, medulla									1	(2%)
Oligodendr mal, pons	1	(2%)								
Brain, cerebellum	(48)		(24)		(23)		(31)		(47)	
Gra cl tum bgn, meninges	2	(4%)								
Brain, cerebrum	(48)		(24)		(23)		(31)		(48)	
Astrocyto mal					1	(4%)				
Oligodendr mal							1	(3%)		
Ear							(1)			
Keratoacanthma							1	(100%)		
Epididymis	(48)		(23)		(22)		(28)		(47)	
Leukemia monuc					1	(5%)				
Mesothelio mal	2	(4%)							3	(6%)
Eye	(47)		(24)		(26)		(35)		(48)	
Leukemia monuc, retrobulbar			1	(4%)						
Harderian gland	(48)		(23)		(23)		(30)		(48)	
Carcinoma					1	(4%)				
Leukemia monuc			1	(4%)	1	(4%)				
Heart	(48)		(23)		(24)		(30)		(48)	
Leukemia monuc	6	(13%)	3	(13%)	6	(25%)	3	(10%)	4	(8%)
Schwannoma mal							1	(3%)		
Intestine large, cecum	(45)		(23)		(23)		(25)		(47)	
Leukemia monuc			1	(4%)	1	(4%)				
Intestine large, colon	(47)		(23)		(23)		(28)		(47)	
Leukemia monuc	1	(2%)	1	(4%)						
Intestine small, duodenum	(47)		(23)		(23)		(30)		(47)	
Leukemia monuc	1	(2%)			1	(4%)				
Mesothelio mal							1	(3%)		
Intestine small, ileum	(45)		(23)		(22)		(26)		(47)	
Leukemia monuc	2	(4%)			1	(5%)				
Intestine small, jejunum	(44)		(21)		(21)		(26)		(47)	
Carcinoma							1	(4%)		
Leukemia monuc					1	(5%)				
Sarcoma							1	(4%)		
Kidney	(48)		(40)		(48)		(48)		(48)	
Adenoma, bilateral, renal tubule							1	(2%)		
Adenoma, renal tubule							1	(2%)	5	(10%)
Carcinoma, bilateral, renal tubule							1	(2%)		
Carcinoma, renal tubule							6	(13%)	10	(21%)
Leukemia monuc	6	(13%)	4	(10%)	9	(19%)	4	(8%)	3	(6%)
Liposarc	1	(2%)								
Mesothelio mal	1	(2%)							1	(2%)
Nephroblastoma							1	(2%)		
Lacrimal gland	(47)		(23)		(22)		(30)		(48)	
Leukemia monuc	3	(6%)			1	(5%)	1	(3%)		
Liver	(48)		(40)		(48)		(48)		(48)	
Carcinoma, metastatic, thyroid gland					1	(2%)				
Fib histiocyt, metastatic, skin									1	(2%)
Hepatoclr aden			2	(5%)	2	(4%)			1	(2%)
Hepatoclr carc			1	(3%)	1	(2%)				
Histio sarc, metastatic, skin									1	(2%)
Leukemia monuc	20	(42%)	20	(50%)	17	(35%)	18	(38%)	12	(25%)
Mesothelio mal									1	(2%)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of Fumonisin B_1

	0 ppm		5 ppm		15 ppm		50 ppm		150 ppm	
2-Year Study (continued)										
Lung	(48)		(24)		(23)		(32)		(48)	
Alv bron aden			1	(4%)			1	(3%)		
Alv bron carc			1	(4%)						
Carcinoma, metastatic, adrenal gland									1	(2%)
Carcinoma, metastatic, kidney							2	(6%)	4	(8%)
Carcinoma, metastatic, thyroid gland					1	(4%)				
Fib histiocyt, metastatic, skin									1	(2%)
Histio sarc, metastatic, skin									1	(2%)
Leukemia monuc	16	(33%)	9	(38%)	8	(35%)	9	(28%)	7	(15%)
Sarcoma, metastatic, skin	1	(2%)								
Lung, bronchus	(48)		(24)		(23)		(31)		(48)	
Squam cel carc			1	(4%)			1	(3%)	1	(2%)
Lymph node	(48)		(24)		(27)		(33)		(48)	
Carcinoma, metastatic, kidney									1	(2%)
Carcinoma, metastatic, mediastinal, kidney									1	(2%)
Carcinoma, metastatic, mediastinal, lung			1	(4%)						
Carcinoma, metastatic, renal, kidney									1	(2%)
Leukemia monuc	1	(2%)	2	(8%)						
Leukemia monuc, axillary					1	(4%)				
Leukemia monuc, deep cervical					1	(4%)				
Leukemia monuc, thoracic			1	(4%)						
Lymph node, mandibular	(48)		(23)		(26)		(32)		(48)	
Leukemia monuc	16	(33%)	11	(48%)	7	(27%)	8	(25%)	10	(21%)
Lymph node, mesenteric	(47)		(23)		(23)		(30)		(48)	
Leukemia monuc	12	(26%)	11	(48%)	8	(35%)	9	(30%)	7	(15%)
Mammary gland	(40)		(20)		(24)		(24)		(42)	
Carcinoma					1	(4%)				
Fibroadenoma	2	(5%)							4	(10%)
Mesentery	(4)		(3)		(3)		(4)		(4)	
Carcinoma, metastatic, kidney									1	(25%)
Fibroma							1	(25%)		
Mesothelio mal	1	(25%)								
Nose	(48)		(23)		(23)		(29)		(48)	
Leukemia monuc			1	(4%)						
Pancreas	(47)		(24)		(25)		(30)		(48)	
Adenoma	4	(9%)					2	(7%)	3	(6%)
Adenoma, acinar cell	2	(4%)			2	(8%)	2	(7%)	2	(4%)
Adenoma, duct									1	(2%)
Carcinoma	3	(6%)	2	(8%)	2	(8%)			3	(6%)
Carcinoma, metastatic, kidney									1	(2%)
Histio sarc, metastatic, skin									1	(2%)
Leukemia monuc	1	(2%)	1	(4%)	2	(8%)	1	(3%)	2	(4%)
Mesothelio mal							1	(3%)	1	(2%)
Mixd tumor bgn									1	(2%)
Parathyroid gland	(46)		(21)		(22)		(26)		(47)	
Adenoma	1	(2%)								
Pituitary gland	(43)		(28)		(33)		(33)		(45)	
Adenoma, pars distalis	30	(70%)	18	(64%)	23	(70%)	18	(55%)	24	(53%)
Adenoma, pars intermed							1	(3%)		
Carcinoma, pars distalis			1	(4%)					1	(2%)
Leukemia monuc	5	(12%)	3	(11%)	1	(3%)	1	(3%)	1	(2%)
Preputial gland	(43)		(19)		(20)		(30)		(44)	
Adenoma	2	(5%)	2	(11%)	1	(5%)	2	(7%)	2	(5%)
Carcinoma					1	(5%)			1	(2%)
Prostate	(48)		(22)		(23)		(30)		(48)	
Adenoma	1	(2%)					1	(3%)	1	(2%)
Histio sarc, metastatic, skin									1	(2%)
Leukemia monuc							2	(7%)		

Table A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of Fumonisin B_1

	0 ppm		5 ppm		15 ppm		50 ppm		150 ppm	
2-Year Study (continued)										
Salivary glands	(48)		(23)		(23)		(30)		(48)	
Leukemia monuc							1	(3%)		
Seminal vesicle	(48)		(23)		(24)		(30)		(48)	
Leukemia monuc	1	(2%)								
Mesothelio mal									1	(2%)
Skeletal muscle	(48)		(23)		(24)		(30)		(48)	
Fibrosarc					1	(4%)				
Mesothelio mal, abdominal									1	(2%)
Skin	(48)		(27)		(28)		(32)		(48)	
Adenoma, sebaceous gland					1	(4%)				
Basal cel aden	3	(6%)					1	(3%)	3	(6%)
Fib histiocyt, subcut tiss									1	(2%)
Fibroma, subcut tiss	3	(6%)	3	(11%)	2	(7%)	2	(6%)		
Hemangioma							1	(3%)		
Hemangioma, subcut tiss					1	(4%)				
Histio sarc									1	(2%)
Histio sarc, subcut tiss							1	(3%)	1	(2%)
Keratoacanthma	2	(4%)			3	(11%)			1	(2%)
Keratoacanthma, multiple			1	(4%)						
Lipoma, subcut tiss	1	(2%)	1	(4%)	1	(4%)	1	(3%)	1	(2%)
Papilloma squa	1	(2%)								
Papilloma squa, tail							1	(3%)		
Sarcoma, subcut tiss	1	(2%)			1	(4%)				
Trichoepithel			1	(4%)	1	(4%)			1	(2%)
Spinal cord, thoracic	(47)		(23)		(23)		(30)		(48)	
Leukemia monuc	1	(2%)			1	(4%)				
Spleen	(48)		(29)		(33)		(41)		(48)	
Carcinoma, metastatic, kidney									1	(2%)
Histio sarc, metastatic, skin									1	(2%)
Leukemia monuc	24	(50%)	20	(69%)	20	(61%)	18	(44%)	16	(33%)
Liposarc			1	(3%)						
Mesothelio mal							1	(2%)	1	(2%)
Stomach, forestomach	(48)		(23)		(23)		(30)		(48)	
Leukemia monuc	2	(4%)			1	(4%)	1	(3%)	1	(2%)
Papilloma squa	1	(2%)	1	(4%)						
Stomach, glandular	(48)		(23)		(23)		(30)		(48)	
Mesothelio mal	1	(2%)					1	(3%)		
Testes	(48)		(39)		(46)		(46)		(48)	
Adenoma, bilateral, interstit cell	19	(40%)	24	(62%)	20	(43%)	22	(48%)	26	(54%)
Adenoma, interstit cell	14	(29%)	6	(15%)	14	(30%)	13	(28%)	11	(23%)
Mesothelio mal	1	(2%)					2	(4%)	4	(8%)
Thymus	(37)		(19)		(21)		(24)		(41)	
Leukemia monuc	8	(22%)	6	(32%)	5	(24%)	4	(17%)	3	(7%)
Thyroid gland	(48)		(24)		(25)		(31)		(48)	
Adenoma, c cell	9	(19%)	2	(8%)	4	(16%)	2	(6%)	10	(21%)
Adenoma, multiple, c cell									1	(2%)
Carcinoma, c cell	1	(2%)	1	(4%)	2	(8%)	2	(6%)		
Carcinoma, follicular cel			1	(4%)						
Leukemia monuc					1	(4%)	1	(3%)		
Tissue NOS	(2)				(2)		(1)		(1)	
Chordoma					1	(50%)				
Mesothelio mal, pelvic	1	(50%)								
Mesothelio mal, scrotal							1	(100%)		

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of Fumonisin B_1

	0 ppm	5 ppm	15 ppm	50 ppm	150 ppm
2-Year Study (continued)					
Tongue	(48)	(23)	(23)	(30)	(48)
Leukemia monuc			1 (4%)		
Urinary bladder	(47)	(22)	(23)	(30)	(48)
Leukemia monuc	1 (2%)			2 (7%)	
Mesothelio mal				1 (3%)	1 (2%)
Zymbal's gland	(33)	(19)	(17)	(21)	(33)
Carcinoma	1 (3%)	1 (5%)	1 (6%)	1 (5%)	
Neoplasm Summary					
Total animals with primary neoplasms[b]					
2-Year study	46	38	48	46	44
Total primary neoplasms					
2-Year study	278	187	211	201	223
Total animals with benign neoplasms					
2-Year study	45	36	45	44	43
Total benign neoplasms					
2-Year study	109	66	81	78	108
Total animals with malignant neoplasms					
2-Year study	30	26	28	30	30
Total malignant neoplasms					
2-Year study	169	121	130	123	115
Total animals with metastatic neoplasms					
2-Year study	1	1	1	2	7
Total metastatic neoplasms					
2-Year study	1	1	2	2	18

[a] Number of animals examined microscopically at the site and the number of animals with neoplasm
[b] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Fumonisin B_1: 0 ppm

Carcass ID Number	001	012	013	019	030	056	087	091	102	107	114	116	123	125	133	137	139	146	148	154	158	170	172	191	201
Adrenal gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia monuc												X							X	X			X	X	
Pheochrom bgn, medulla										X								X			X	X			X
Pheochrom mal, medulla																		X							
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Blood vessel, aorta	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteoma, scapula	X																								
Bone, femur	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bone, sternum	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bone marrow	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia monuc					X							X				X		X	X	X	X		X	X	X
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia monuc					X																X				
Oligodendr mal, pons																									
Brain, cerebellum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gra cl tum bgn, meninges																		X							
Brain, cerebrum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Coagulating gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelio mal																					X				
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia monuc					X													X			X			X	X
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	M	M	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia monuc									X																
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia monuc																		X							
Intestine small, ileum	+	+	+	+	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Leukemia monuc																				X			X		
Intestine small, jejunum	+	+	+	+	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia monuc					X													X		X				X	
Liposarc													X												
Mesothelio mal														X											
Lacrimal gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia monuc																					X		X		
Larynx	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia monuc					X				X			X				X		X	X	X	X		X	X	X
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia monuc					X				X			X				X		X	X	X	X		X	X	X
Sarcoma, metastatic, skin																	X								
Lung, bronchus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia monuc																									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia monuc					X				X			X						X	X	X	X		X	X	X
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Leukemia monuc					X							X				X		X		X	X		X	X	

+: Tissue examined microscopically
A: Autolysis precludes examination
M: Missing tissue
I: Insufficient tissue
X: Lesion present
Blank: Not examined

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Fumonisin B_1: 0 ppm

Carcass ID Number	213	214	256	260	267	278	310	311	312	321	326	327	328	332	368	369	386	387	404	405	451	452	453	Total Tissues/ Tumors
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Leukemia monuc	X				X	X																	X	9
Pheochrom bgn, medulla											X						X	X		X	X		X	11
Pheochrom mal, medulla																								1
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	47
Blood vessel, aorta	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	47
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Osteoma, scapula																								1
Bone, femur	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Bone, sternum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Leukemia monuc	X				X	X								X									X	15
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia monuc																								2
Oligodendr mal, pons																					X			1
Brain, cerebellum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Gra cl tum bgn, meninges						X																		2
Brain, cerebrum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Coagulating gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Mesothelio mal										X														2
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Eye	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia monuc					X																			6
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Leukemia monuc																								1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Leukemia monuc																								1
Intestine small, ileum	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Leukemia monuc																								2
Intestine small, jejunum	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia monuc							X																X	6
Liposarc																								1
Mesothelio mal																								1
Lacrimal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Leukemia monuc																							X	3
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia monuc	X	X	X		X	X	X							X		X							X	20
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia monuc	X				X	X	X																X	16
Sarcoma, metastatic, skin																								1
Lung, bronchus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia monuc																							X	1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia monuc	X		X		X	X	X																X	16
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Leukemia monuc	X				X		X																X	12

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Fumonisin B_1: 0 ppm

Carcass ID Number	001	012	013	019	030	056	087	091	102	107	114	116	123	125	133	137	139	146	148	154	158	170	172	191	201
Mammary gland	M	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Fibroadenoma																							X		
Mesentery								+						+		+									
Mesothelio mal														X											
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																		X						X	
Adenoma, acinar cell								X																	
Carcinoma																									
Leukemia monuc																		X							
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Adenoma																									
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve, sciatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	M	+	+	+	M
Adenoma, pars distalis		X				X	X	X	X		X				X	X	X			X		X		X	
Leukemia monuc																		X					X	X	
Preputial gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	M	M	+	+	+	+
Adenoma										X															
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																						X			
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia monuc																		X							
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle, thigh	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cel aden						X	X																		X
Fibroma, subcut tiss													X												
Keratoacanthma										X															
Lipoma, subcut tiss																									
Papilloma squa													X												
Sarcoma, subcut tiss																	X								
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Spinal cord, thoracic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Leukemia monuc																					X				
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia monuc					X	X			X			X				X		X	X	X	X		X	X	X
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia monuc																		X							
Papilloma squa																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelio mal														X											
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, bilateral, interstit cell								X					X	X					X	X			X		X
Adenoma, interstit cell										X	X	X			X	X	X				X				
Mesothelio mal																					X				
Thymus	+	+	+	M	+	+	+	M	+	M	M	+	M	M	+	+	+	+	+	+	+	+	+	+	+
Leukemia monuc					X													X		X	X		X	X	
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, c cell															X					X					
Carcinoma, c cell																									
Tissue NOS																					+				
Mesothelio mal, pelvic																					X				
Tongue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Leukemia monuc																		X							
Zymbal's gland	+	+	M	M	+	+	+	+	+	+	M	M	M	+	M	+	+	+	+	+	+	M	+	+	M
Carcinoma																								X	

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Fumonisin B$_1$: 0 ppm

Carcass ID Number	213	214	256	260	267	278	310	311	312	321	326	327	328	332	368	369	386	387	404	405	451	452	453	Total Tissues/ Tumors
Mammary gland	M	M	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	40
Fibroadenoma																			X					2
Mesentery										+														4
Mesothelio mal																								1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma									X				X											4
Adenoma, acinar cell							X																	2
Carcinoma	X									X													X	3
Leukemia monuc																								1
Parathyroid gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Adenoma																							X	1
Peripheral nerve	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Peripheral nerve, sciatic	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	43
Adenoma, pars distalis			X		X	X	X	X	X	X	X	X	X	X	X		X		X	X	X	X	X	30
Leukemia monuc	X						X																	5
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	43
Adenoma																				X				2
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma																								1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia monuc																								1
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Skeletal muscle, thigh	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Basal cel aden																								3
Fibroma, subcut tiss					X													X						3
Keratoacanthma																							X	2
Lipoma, subcut tiss														X										1
Papilloma squa																								1
Sarcoma, subcut tiss																								1
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Spinal cord, thoracic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Leukemia monuc																								1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia monuc	X	X	X		X	X	X							X		X	X		X			X	X	24
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia monuc			X																					2
Papilloma squa				X																				1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Mesothelio mal																								1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma, bilateral, interstit cell		X		X	X		X				X		X	X	X		X				X	X	X	19
Adenoma, interstit cell	X					X				X		X				X		X		X				14
Mesothelio mal																								1
Thymus	M	+	+	+	+	+	+	M	M	+	+	M	+	+	+	+	+	+	+	M	+	+	+	37
Leukemia monuc					X																		X	8
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma, c cell	X							X	X		X						X	X			X			9
Carcinoma, c cell																		X						1
Tissue NOS																				+				2
Mesothelio mal, pelvic																								1
Tongue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Leukemia monuc																								1
Zymbal's gland	+	M	M	+	M	+	+	M	+	M	+	+	+	+	+	M	+	M	+	+	+	+	+	33
Carcinoma																								1

Table A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Fumonisin B_1: 5 ppm

Carcass ID Number	055	066	068	076	078	081	083	088	099	112	120	127	131	138	156	166	179	185	193	204	218	219	220	221	228
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
Leukemia monuc			X			X											X								
Pheochrom bgn, medulla				X									X				X								
Blood vessel	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
Blood vessel, aorta	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
Bone, femur	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
Bone, sternum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
Leukemia monuc		X	X	X		X			X				X	X	X	X	X		X						
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
Brain, cerebellum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
Brain, cerebrum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
Coagulating gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
Esophagus	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+					
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Leukemia monuc, retrobulbar													X												
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
Leukemia monuc		X																							
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
Leukemia monuc													X			X									
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
Leukemia monuc			X																						
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
Leukemia monuc			X																						
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+			
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
Intestine small, ileum	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+		+			
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+					
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia monuc			X	X															X						
Lacrimal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
Larynx	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+					
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatoclr aden														X											
Hepatoclr carc				X																					
Leukemia monuc		X	X	X	X	X			X		X		X	X		X	X		X						
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
Alv bron aden																									
Alv bron carc																		X							
Leukemia monuc		X	X	X		X								X		X	X		X						
Lung, bronchus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
Squam cel carc							X																		
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
Carcinoma, metastatic, lung, mediastinal							X																		
Leukemia monuc																									
Leukemia monuc, thoracic						X																			
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
Leukemia monuc			X	X		X			X		X			X		X	X								
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
Leukemia monuc		X	X	X	X	X			X		X			X		X									
Mammary gland	+	+	M	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
Mesentery	+					+																			
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
Leukemia monuc									X																

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Fumonisin B_1: 5 ppm

Carcass ID Number	258	270	271	272	273	316	319	322	323	324	356	357	385	406	407	Total Tissues/ Tumors
Adrenal gland	+					+	M									22
Leukemia monuc																3
Pheochrom bgn, medulla	X															4
Blood vessel	+	+				+	+									23
Blood vessel, aorta	+	+				+	+									23
Bone	+					+	+									23
Bone, femur	+					+	+									23
Bone, sternum	+					+	+									23
Bone marrow	+					+	+									23
Leukemia monuc							X									12
Brain	+					+	+	+								24
Brain, cerebellum	+					+	+	+								24
Brain, cerebrum	+					+	+	+								24
Coagulating gland	+					+	M									22
Epididymis	+					+	+									23
Esophagus	+					+	+									22
Eye	+					+	+									24
Leukemia monuc, retrobulbar																1
Harderian gland	+					+	+									23
Leukemia monuc																1
Heart	+					+	+									23
Leukemia monuc							X									3
Intestine large	+					+	+									23
Intestine large, cecum	+					+	+									23
Leukemia monuc																1
Intestine large, colon	+					+	+									23
Leukemia monuc																1
Intestine large, rectum	+					+	+									23
Intestine small	+					+	+									24
Intestine small, duodenum	+					+	+									23
Intestine small, ileum	+					+	+									23
Intestine small, jejunum	+					+	+									21
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Leukemia monuc							X									4
Lacrimal gland	+					+	+									23
Larynx	+					+	+									21
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Hepatoclr aden			X													2
Hepatoclr carc																1
Leukemia monuc	X			X	X		X		X		X		X		X	20
Lung	+					+	+		+							24
Alv bron aden									X							1
Alv bron carc																1
Leukemia monuc							X									9
Lung, bronchus	+					+	+		+							24
Squam cel carc																1
Lymph node	+					+	+						+			24
Carcinoma, metastatic, lung, mediastinal																1
Leukemia monuc	X												X			2
Leukemia monuc, thoracic																1
Lymph node, mandibular	+					+	+									23
Leukemia monuc	X					X	X									11
Lymph node, mesenteric	+					+	+									23
Leukemia monuc	X						X									11
Mammary gland	+					+	+									20
Mesentery				+												3
Nose	+					+	+									23
Leukemia monuc																1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Fumonisin B_1: 5 ppm

Carcass ID Number	0 5 5	0 6 6	0 6 8	0 7 6	0 7 8	0 8 1	0 8 3	0 8 8	0 9 9	1 1 2	1 2 0	1 2 7	1 3 1	1 3 8	1 5 6	1 6 6	1 7 9	1 8 5	1 9 3	2 0 4	2 1 8	2 1 9	2 2 0	2 2 1	2 2 8
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			+		
Carcinoma															X										
Leukemia monuc														X											
Parathyroid gland	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+					
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
Peripheral nerve, sciatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
Pituitary gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Adenoma, pars distalis					X	X	X				X	X	X		X	X	X	X		X	X				
Carcinoma, pars distalis																									
Leukemia monuc			X								X					X									
Preputial gland	+	+	M	+	M	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+		+			
Adenoma								X														X			
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				+	
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
Skeletal muscle, thigh	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+		+	
Fibroma, subcut tiss																						X			
Keratoacanthma, multiple																			X						
Lipoma, subcut tiss															X										
Trichoepithel																								X	
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
Spinal cord, thoracic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			+		
Leukemia monuc		X	X	X	X	X			X		X		X	X	X	X	X		X						
Liposarc																									
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
Papilloma squa																	X								
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, bilateral, interstit cell				X		X	X		X	X				X				X	X		X		X	X	
Adenoma, interstit cell								X								X	X			X		X			X
Thymus	M	+	M	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+					
Leukemia monuc		X		X		X										X	X								
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
Adenoma, c cell					X	X																			
Carcinoma, c cell								X																	
Carcinoma, follicular cel																									
Tongue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
Zymbal's gland	+	M	+	+	+	M	+	+	+	+	M	+	+	M	+	+	+	+	+	+					
Carcinoma																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Fumonisin B_1: 5 ppm

Carcass ID Number	258	270	271	272	273	316	319	322	323	324	356	357	385	406	407	Total Tissues/ Tumors
Pancreas	+					+	+									24
Carcinoma	X															2
Leukemia monuc																1
Parathyroid gland	+					+	+									21
Peripheral nerve	+					+	+									23
Peripheral nerve, sciatic	+					+	+									23
Pituitary gland	+	+		+		+	+	+			+		+			28
Adenoma, pars distalis	X	X		X		X					X		X			18
Carcinoma, pars distalis								X								1
Leukemia monuc																3
Preputial gland	+					+	M									19
Adenoma																2
Prostate	+					+	M									22
Salivary glands	+					+	+									23
Seminal vesicle	+					+	M									23
Skeletal muscle	+					+	+									23
Skeletal muscle, thigh	+					+	+									23
Skin	+			+		+	+								+	27
Fibroma, subcut tiss				X											X	3
Keratoacanthma, multiple																1
Lipoma, subcut tiss																1
Trichoepithel																1
Spinal cord	+					+	+									23
Spinal cord, thoracic	+					+	+									23
Spleen	+			+	+	+	+		+				+		+	29
Leukemia monuc	X			X	X	X	X						X		X	20
Liposarc															X	1
Stomach	+					+	+									23
Stomach, forestomach	+					+	+									23
Papilloma squa																1
Stomach, glandular	+					+	+									23
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+		+	39
Adenoma, bilateral, interstit cell	X	X	X	X	X		X	X	X	X	X	X	X		X	24
Adenoma, interstit cell																6
Thymus	+					+	+									19
Leukemia monuc							X									6
Thyroid gland	+			+		+	+									24
Adenoma, c cell																2
Carcinoma, c cell																1
Carcinoma, follicular cel				X												1
Tongue	+					+	+									23
Trachea	+					+	+									23
Urinary bladder	+					+	M									22
Zymbal's gland	+			+		+	M									19
Carcinoma				X												1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Fumonisin B_1: 15 ppm

Carcass ID Number	034	036	037	046	050	051	054	059	080	117	126	147	150	167	186	187	190	192	194	199	222	223	224	225	257
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				+	+
Leukemia monuc			X										X			X									X
Pheochrom bgn, medulla						X									X	X			X						
Pheochrom mal, medulla																								X	
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+
Blood vessel, aorta	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+
Sarcoma, synovial tiss						X																			
Bone, femur	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+
Bone, sternum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+
Leukemia monuc			X						X		X		X			X		X	X	X					X
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+
Leukemia monuc													X					X	X						
Brain, cerebellum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+
Brain, cerebrum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+
Astrocyto mal															X										
Coagulating gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+					+
Leukemia monuc													X												
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				+
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+
Carcinoma															X										
Leukemia monuc																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+
Leukemia monuc											X		X			X		X	X						
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+
Leukemia monuc																			X						
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+
Leukemia monuc			X																						
Intestine small, ileum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+
Leukemia monuc													X												
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+					+
Leukemia monuc													X												
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia monuc			X								X		X					X							
Lacrimal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+					+
Leukemia monuc													X												
Larynx	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, thyroid gland									X																
Hepatoclr aden																									
Hepatoclr carc																									
Leukemia monuc			X						X		X		X			X		X	X	X					X
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+
Carcinoma, metastatic, thyroid gland									X																
Leukemia monuc			X								X		X			X		X		X					X
Lung, bronchus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+
Leukemia monuc, axillary													X												
Leukemia monuc, deep cervical													X												
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+
Leukemia monuc											X		X			X		X	X	X					

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Fumonisin B_1: 15 ppm

Carcass ID Number	259	279	280	281	282	305	329	330	351	352	378	379	380	381	388	408	409	410	411	412	413	454	455	Total Tissues/ Tumors
Adrenal gland	+					+												+						25
Leukemia monuc						X																		5
Pheochrom bgn, medulla						X												X						6
Pheochrom mal, medulla																								1
Blood vessel	+					+																		23
Blood vessel, aorta	+					+																		23
Bone	+					+																		23
Sarcoma, synovial tiss																								1
Bone, femur	+					+																		23
Bone, sternum	+					+																		23
Bone marrow	+					+																		23
Leukemia monuc						X																		10
Brain	+					+																		23
Leukemia monuc						X																		4
Brain, cerebellum	+					+																		23
Brain, cerebrum	+					+																		23
Astrocyto mal																								1
Coagulating gland	+					+																		23
Epididymis	+					+																		22
Leukemia monuc																								1
Esophagus	+					+																		23
Eye	+	+				+													+					26
Harderian gland	+					+																		23
Carcinoma																								1
Leukemia monuc						X																		1
Heart	+					+															+			24
Leukemia monuc						X																		6
Intestine large	+					+																		23
Intestine large, cecum	+					+																		23
Leukemia monuc																								1
Intestine large, colon	+					+																		23
Intestine large, rectum	+					+																		23
Intestine small	+					+																		23
Intestine small, duodenum	+					+																		23
Leukemia monuc																								1
Intestine small, ileum	+					+																		22
Leukemia monuc																								1
Intestine small, jejunum	+					A																		21
Leukemia monuc																								1
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia monuc						X								X					X	X			X	9
Lacrimal gland	+					+																		22
Leukemia monuc																								1
Larynx	+					+																		22
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma, metastatic, thyroid gland																								1
Hepatoclr aden		X	X																					2
Hepatoclr carc	X																							1
Leukemia monuc						X			X					X	X	X			X	X			X	17
Lung	+					+																		23
Carcinoma, metastatic, thyroid gland																								1
Leukemia monuc						X																		8
Lung, bronchus	+					+																		23
Lymph node	+					+									M	+	+			+		+		27
Leukemia monuc, axillary																								1
Leukemia monuc, deep cervical																								1
Lymph node, mandibular	+					+											+			+		+		26
Leukemia monuc																				X				7

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Fumonisin B_1: 15 ppm

Carcass ID Number	034	036	037	046	050	051	054	059	080	117	126	147	150	167	186	187	190	192	194	199	222	223	224	225	257
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+
Leukemia monuc			X						X		X		X			X		X		X					
Mammary gland	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	M	+	+	+				+
Carcinoma																									
Mesentery																+									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				+
Adenoma, acinar cell														X							X				
Carcinoma																					X				X
Leukemia monuc			X										X												
Parathyroid gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+					+
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+
Peripheral nerve, sciatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+
Pituitary gland	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+				+
Adenoma, pars distalis	X			X	X			X	X	X		X		X		X					X				X
Leukemia monuc													X												
Preputial gland	+	+	+	M	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+					+
Adenoma	X																								
Carcinoma		X																							
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				+	+
Fibrosarc																								X	
Skeletal muscle, thigh	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+
Adenoma, sebaceous gland																			X						
Fibroma, subcut tiss																									X
Hemangioma, subcut tiss																			X						
Keratoacanthma																									
Lipoma, subcut tiss																									
Sarcoma, subcut tiss																	X								
Trichoepithel																									
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+
Spinal cord, thoracic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+
Leukemia monuc																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+
Leukemia monuc			X						X		X		X			X	X	X	X	X					X
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+
Leukemia monuc													X												
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, bilateral, interstit cell															X	X	X	X		X		X	X	X	
Adenoma, interstit cell		X									X								X		X				X
Thymus	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+					+
Leukemia monuc			X								X		X			X									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+
Adenoma, c cell		X																							
Carcinoma, c cell									X																
Leukemia monuc													X												
Tissue NOS																							+		+
Chordoma																									X
Tongue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+
Leukemia monuc													X												
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+
Zymbal's gland	+	+	+	+	M	M	+	+	+	+	M	+	+	+	+	+	+	+	+	M					M
Carcinoma							X																		

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Fumonisin B$_1$: 15 ppm

Carcass ID Number	259	279	280	281	282	305	329	330	351	352	378	379	380	381	388	408	409	410	411	412	413	454	455	Total Tissues/ Tumors
Lymph node, mesenteric	+					+																		23
Leukemia monuc						X																		8
Mammary gland	+		+		+	+		+				M												24
Carcinoma	X																							1
Mesentery																+	+							3
Nose	+					+																		23
Pancreas	+			+		+																		25
Adenoma, acinar cell																								2
Carcinoma																								2
Leukemia monuc																								2
Parathyroid gland	+					+																		22
Peripheral nerve	+					+																		23
Peripheral nerve, sciatic	+					+																		23
Pituitary gland	+	+			+	+		+		+		+	+			+			+	+	+		+	33
Adenoma, pars distalis	X	X			X			X		X		X	X			X			X	X	X		X	23
Leukemia monuc																								1
Preputial gland	+					+																		20
Adenoma																								1
Carcinoma																								1
Prostate	+					+																		23
Salivary glands	+					+																M		23
Seminal vesicle	+					+					+													24
Skeletal muscle	+					+																		24
Fibrosarc																								1
Skeletal muscle, thigh	+					+																		24
Skin	+			+	+	+						+		+								+		28
Adenoma, sebaceous gland																								1
Fibroma, subcut tiss																						X		2
Hemangioma, subcut tiss																								1
Keratoacanthma				X	X							X												3
Lipoma, subcut tiss												X												1
Sarcoma, subcut tiss																								1
Trichoepithel														X										1
Spinal cord	+					+																		23
Spinal cord, thoracic	+					+																		23
Leukemia monuc						X																		1
Spleen	+	+		+		+			+		+			+	+		+		+	+			+	33
Leukemia monuc		X		X		X			X		X			X	X				X	X			X	20
Stomach	+					+																		23
Stomach, forestomach	+					+																		23
Leukemia monuc																								1
Stomach, glandular	+					+																		23
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+		46
Adenoma, bilateral, interstit cell	X	X				X	X	X	X	X				X	X		X		X	X				20
Adenoma, interstit cell			X	X	X						X	X	X			X		X				X		14
Thymus	+					+														M				21
Leukemia monuc						X																		5
Thyroid gland	+	+		+		+					M													25
Adenoma, c cell		X		X		X																		4
Carcinoma, c cell	X																							2
Leukemia monuc																								1
Tissue NOS																								2
Chordoma																								1
Tongue	+					+							M											23
Leukemia monuc																								1
Trachea	+					+																		23
Urinary bladder	+					+																		23
Zymbal's gland	M					+																		17
Carcinoma																								1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Fumonisin B_1: 50 ppm

Carcass ID Number	0 0 6	0 1 4	0 1 5	0 1 6	0 3 2	0 4 7	0 4 8	0 7 2	0 8 4	0 9 3	0 9 4	0 9 8	1 0 6	1 1 3	1 2 4	1 2 8	1 3 0	1 3 4	1 4 4	1 5 3	1 7 1	1 7 4	1 8 1	1 8 2	1 8 4
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, cortex							X																		
Leukemia monuc								X																	
Pheochrom bgn, medulla																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Blood vessel, aorta	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bone, femur	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bone, sternum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia monuc								X			X	X	X		X	X									X
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia monuc											X														
Brain, cerebellum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Brain, cerebrum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Oligodendr mal																									
Coagulating gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ear																									
Keratoacanthma																									
Epididymis	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Eye	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia monuc											X	X													
Schwannoma mal																	X								
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	M	M	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+
Intestine large, colon	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelio mal										X															
Intestine small, ileum	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	A	+
Intestine small, jejunum	A	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+
Carcinoma					X																				
Sarcoma																			X						
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, bilateral, renal tubule																									
Adenoma, renal tubule																									
Carcinoma, bilateral, renal tubule																									
Carcinoma, renal tubule																								X	
Leukemia monuc											X	X	X												
Nephroblastoma	X																								
Lacrimal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia monuc											X														
Larynx	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia monuc								X			X	X	X		X	X									X
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alv bron aden																									
Carcinoma, metastatic, kidney																								X	
Leukemia monuc								X			X	X	X		X	X									X
Lung, bronchus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squam cel carc							X																		
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia monuc											X	X	X		X										X

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Fumonisin B_1: 50 ppm

Carcass ID Number	189	196	198	200	210	211	212	268	274	275	276	277	307	325	333	334	370	414	415	456	457	458	459	Total Tissues/ Tumors
Adrenal gland	+	+	+	+									+									+		31
Adenoma, cortex																								1
Leukemia monuc	X		X																					3
Pheochrom bgn, medulla	X		X																			X		3
Blood vessel	+	+	+	+									+											30
Blood vessel, aorta	+	+	+	+									+											30
Bone	+	+	+	+									+											30
Bone, femur	+	+	+	+									+											29
Bone, sternum	+	+	+	+									+											30
Bone marrow	+	+	+	+									+											30
Leukemia monuc	X		X										X											10
Brain	+	+	+	+									+	+										31
Leukemia monuc	X																							2
Brain, cerebellum	+	+	+	+									+	+										31
Brain, cerebrum	+	+	+	+									+	+										31
Oligodendr mal													X											1
Coagulating gland	+	+	+	+									+											29
Ear						+																		1
Keratoacanthma						X																		1
Epididymis	+	+	+	+									+											28
Esophagus	+	+	+	+									+											30
Eye	+	+	+	+			+	+				+	+		+	+					+			35
Harderian gland	+	+	+	+									+											30
Heart	+	+	+	+									+											30
Leukemia monuc	X																							3
Schwannoma mal																								1
Intestine large	+	+	+	+									+											30
Intestine large, cecum	+	+	+	+									+											25
Intestine large, colon	+	+	+	+									+											28
Intestine large, rectum	+	+	+	+									+											30
Intestine small	+	+	+	+									+											30
Intestine small, duodenum	+	+	+	+									+											30
Mesothelio mal																								1
Intestine small, ileum	+	+	+	+									+											26
Intestine small, jejunum	+	+	+	+									+											26
Carcinoma																								1
Sarcoma																								1
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma, bilateral, renal tubule																				X				1
Adenoma, renal tubule																	X							1
Carcinoma, bilateral, renal tubule									X															1
Carcinoma, renal tubule							X	X		X											X	X		6
Leukemia monuc	X																							4
Nephroblastoma																								1
Lacrimal gland	+	+	+	+									+											30
Leukemia monuc																								1
Larynx	+	+	+	+									+											29
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia monuc	X		X							X	X		X	X	X				X	X	X		X	18
Lung	+	+	+	+					+		+		+											32
Alv bron aden			X																					1
Carcinoma, metastatic, kidney									X															2
Leukemia monuc	X										X													9
Lung, bronchus	+	+	+	+					+		+													31
Squam cel carc																								1
Lymph node	+	+	+	+				+					+			+			+					33
Lymph node, mandibular	+	+	+	+									+			+			+					32
Leukemia monuc	X		X										X											8

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Fumonisin B_1: 50 ppm

Carcass ID Number	0 0 6	0 1 4	0 1 5	0 1 6	0 3 2	0 4 7	0 4 8	0 7 2	0 8 4	0 9 3	0 9 4	0 9 8	1 0 6	1 1 3	1 2 4	1 2 8	1 3 0	1 3 4	1 4 3	1 5 3	1 7 1	1 7 4	1 8 1	1 8 2	1 8 4
Lymph node, mesenteric	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia monuc								X			X	X	X		X	X									
Mammary gland	+	+	+	+	M	+	M	M	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+
Mesentery																									
Fibroma																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma								X																	X
Adenoma, acinar cell														X									X		
Leukemia monuc											X														
Mesothelio mal										X															
Parathyroid gland	+	+	+	+	+	M	M	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve, sciatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Adenoma, pars distalis						X	X		X			X			X			X			X		X	X	X
Adenoma, pars intermed														X											
Leukemia monuc								X																	
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Adenoma				X														X							
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Leukemia monuc																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia monuc											X														
Seminal vesicle	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle, thigh	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cel aden																									
Fibroma, subcut tiss																X									
Hemangioma																									X
Histio sarc, subcut tiss																	X								
Lipoma, subcut tiss																									
Papilloma squa, tail																									X
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord, thoracic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia monuc								X			X	X	X		X	X									X
Mesothelio mal										X															
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia monuc											X														
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelio mal										X															
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, bilateral, interstit cell										X	X		X	X			X		X		X	X			
Adenoma, interstit cell							X					X			X	X		X						X	X
Mesothelio mal										X															
Thymus	M	+	+	+	+	+	+	+	M	+	+	+	M	+	+	M	+	+	+	M	M	+	+	+	+
Leukemia monuc								X			X	X													
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+
Adenoma, c cell		X									X														
Carcinoma, c cell																									
Leukemia monuc											X														
Tissue NOS										+															
Mesothelio mal, scrotal										X															

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Fumonisin B_1: 50 ppm

Carcass ID Number	189	196	198	200	210	211	212	268	274	275	276	277	307	325	333	334	370	414	415	456	457	458	459	Total Tissues/ Tumors
Lymph node, mesenteric	+	+	+	+				+					+											30
Leukemia monuc	X		X					X																9
Mammary gland	+	M	+	+									+											24
Mesentery			+			+	+															+		4
Fibroma																						X		1
Nose	+	+	+	+									+											29
Pancreas	+	+	+	+									+											30
Adenoma																								2
Adenoma, acinar cell																								2
Leukemia monuc																								1
Mesothelio mal																								1
Parathyroid gland	+	+	+	+									+											26
Peripheral nerve	+	+	+	+									+											30
Peripheral nerve, sciatic	+	+	+	+									+											30
Pituitary gland	M	+	+	+	+								+	+					+			+	+	33
Adenoma, pars distalis		X	X	X	X									X					X			X	X	18
Adenoma, pars intermed																								1
Leukemia monuc																								1
Preputial gland	+	+	+	+									+				+							30
Adenoma																								2
Prostate	+	+	+	+	M								+											30
Adenoma				X																				1
Leukemia monuc			X										X											2
Salivary glands	+	+	+	+									+											30
Leukemia monuc																								1
Seminal vesicle	+	+	+	+									+								+			30
Skeletal muscle	+	+	+	+									+											30
Skeletal muscle, thigh	+	+	+	+									+											30
Skin	+	+	+	+								+	+						+					32
Basal cel aden													X											1
Fibroma, subcut tiss												X												2
Hemangioma																								1
Histio sarc, subcut tiss																								1
Lipoma, subcut tiss																			X					1
Papilloma squa, tail																								1
Spinal cord	+	+	+	+									+											30
Spinal cord, thoracic	+	+	+	+									+											30
Spleen	+	+	+	+					+	+		+	+	+	+		+		+	+	+	+	+	41
Leukemia monuc	X		X						X	X			X	X	X				X	X	X		X	18
Mesothelio mal																								1
Stomach	+	+	+	+									+											30
Stomach, forestomach	+	+	+	+									+											30
Leukemia monuc																								1
Stomach, glandular	+	+	+	+									+											30
Mesothelio mal																								1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+		+	+	+	+	46
Adenoma, bilateral, interstit cell		X				X		X	X	X	X	X	X		X	X		X		X	X		X	22
Adenoma, interstit cell	X		X	X	X		X															X		13
Mesothelio mal														X										2
Thymus	+	+	+	+									+											24
Leukemia monuc													X											4
Thyroid gland	+	+	+	+		+					+		+											31
Adenoma, c cell																								2
Carcinoma, c cell						X					X													2
Leukemia monuc																								1
Tissue NOS																								1
Mesothelio mal, scrotal																								1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Fumonisin B_1: 50 ppm

Carcass ID Number	006	014	015	016	032	047	048	072	084	093	094	098	106	113	124	128	130	134	144	153	171	174	181	182	184
Tongue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ureter								M																	
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia monuc												X													
Mesothelio mal										X															
Zymbal's gland	M	+	M	M	+	+	+	+	+	+	M	+	M	+	M	+	+	+	+	M	+	M	+	+	+
Carcinoma												X													

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Fumonisin B_1: 50 ppm

Carcass ID Number	189	196	198	200	210	211	212	268	274	275	276	277	307	325	333	334	370	414	415	456	457	458	459	Total Tissues/ Tumors
Tongue	+	+	+	+									+											30
Trachea	+	+	+	+									+											30
Ureter																								0
Urinary bladder	+	+	+	+									+											30
Leukemia monuc			X																					2
Mesothelio mal																								1
Zymbal's gland	+	+	+	M									+											21
Carcinoma																								1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Fumonisin B_1: 150 ppm

Carcass ID Number	020	021	022	023	033	060	069	085	086	104	115	132	140	168	178	183	195	205	215	216	217	265	269	283	284
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, cortex									X																
Carcinoma, cortex														X											
Leukemia monuc												X					X	X							
Pheochrom bgn, bilateral, medulla																									
Pheochrom bgn, medulla								X				X							X						X
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Blood vessel, aorta	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bone, femur	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bone, sternum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia monuc						X		X				X				X	X	X				X			
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia monuc, medulla						X																			
Brain, cerebellum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Brain, cerebrum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Coagulating gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelio mal													X												
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia monuc						X		X				X					X								
Intestine large	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, renal tubule																									
Carcinoma, renal tubule										X										X			X		X
Leukemia monuc												X					X								
Mesothelio mal													X												
Lacrimal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fib histiocyt, metastatic, skin											X														
Hepatoclr aden																									
Histio sarc, metastatic, skin																X									
Leukemia monuc						X		X				X				X	X	X				X			
Mesothelio mal													X												
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, adrenal gland														X											
Carcinoma, metastatic, kidney										X										X					
Fib histiocyt, metastatic, skin											X														
Histio sarc, metastatic, skin																X									
Leukemia monuc						X		X				X					X	X							
Lung, bronchus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squam cel carc							X																		
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, kidney										X															
Carcinoma, metastatic, kidney, mediastinal																									
Carcinoma, metastatic, kidney, renal																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Fumonisin B_1: 150 ppm

Carcass ID Number	285	286	306	309	318	331	353	354	355	366	382	383	384	416	417	418	419	420	421	422	460	461	462	Total Tissues/ Tumors
Adrenal gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma, cortex													X											2
Carcinoma, cortex																								1
Leukemia monuc																						X		4
Pheochrom bgn, bilateral, medulla				X														X						2
Pheochrom bgn, medulla							X	X																6
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Blood vessel, aorta	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Bone, femur	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Bone, sternum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia monuc			X						X									X						10
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia monuc, medulla																								1
Brain, cerebellum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	47
Brain, cerebrum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Coagulating gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	47
Mesothelio mal				X																X				3
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia monuc																								4
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma, renal tubule												X		X				X			X	X		5
Carcinoma, renal tubule									X	X					X	X	X						X	10
Leukemia monuc			X																					3
Mesothelio mal																								1
Lacrimal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Larynx	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Fib histiocyt, metastatic, skin																								1
Hepatoclr aden																			X					1
Histio sarc, metastatic, skin																								1
Leukemia monuc			X			X			X									X				X		12
Mesothelio mal																								1
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma, metastatic, adrenal gland																								1
Carcinoma, metastatic, kidney															X	X								4
Fib histiocyt, metastatic, skin																								1
Histio sarc, metastatic, skin																								1
Leukemia monuc			X			X																		7
Lung, bronchus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Squam cel carc																								1
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma, metastatic, kidney																								1
Carcinoma, metastatic, kidney, mediastinal															X									1
Carcinoma, metastatic, kidney, renal															X									1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Fumonisin B_1: 150 ppm

Carcass ID Number	020	021	022	023	033	060	069	085	086	104	115	132	140	168	178	183	195	205	215	216	217	265	269	283	284
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia monuc						X		X				X			X	X	X					X			
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia monuc						X						X					X	X				X			
Mammary gland	+	+	+	+	+	M	+	+	M	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma																							X		
Mesentery																									
Carcinoma, metastatic, kidney																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma										X															
Adenoma, acinar cell																					X				
Adenoma, duct												X													
Carcinoma																		X							
Carcinoma, metastatic, kidney																									
Histio sarc, metastatic, skin																X									
Leukemia monuc												X										X			
Mesothelio mal													X												
Mixd tumor bgn																									
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve, sciatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, pars distalis		X					X				X						X	X	X	X		X		X	
Carcinoma, pars distalis																									
Leukemia monuc																									
Preputial gland	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																	X								
Carcinoma									X																
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																				X					
Histio sarc, metastatic, skin																X									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelio mal													X												
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelio mal, abdominal													X												
Skeletal muscle, thigh	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cel aden															X										
Fib histiocyt, subcut tiss											X														
Histio sarc															X										
Histio sarc, subcut tiss																X									
Keratoacanthma								X																	
Lipoma, subcut tiss																								X	
Trichoepithel																									
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord, thoracic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, kidney																									
Histio sarc, metastatic, skin																X									
Leukemia monuc						X		X				X			X	X	X	X				X			
Mesothelio mal													X												
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia monuc												X													
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Fumonisin B_1: 150 ppm

Carcass ID Number	285	286	306	309	318	331	353	354	355	366	382	383	384	416	417	418	419	420	421	422	460	461	462	Total Tissues/ Tumors
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia monuc			X															X				X		10
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia monuc			X																			X		7
Mammary gland	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	42
Fibroadenoma	X																			X		X		4
Mesentery		+			+											+							+	4
Carcinoma, metastatic, kidney																X								1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma																				X			X	3
Adenoma, acinar cell								X																2
Adenoma, duct																								1
Carcinoma												X										X		3
Carcinoma, metastatic, kidney																X								1
Histio sarc, metastatic, skin																								1
Leukemia monuc																								2
Mesothelio mal																								1
Mixd tumor bgn																X								1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Peripheral nerve, sciatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pituitary gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	45
Adenoma, pars distalis	X	X	X	X	X		X	X				X	X		X		X		X	X	X		X	24
Carcinoma, pars distalis										X														1
Leukemia monuc																		X						1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	44
Adenoma				X																				2
Carcinoma																								1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma																								1
Histio sarc, metastatic, skin																								1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Mesothelio mal																								1
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Mesothelio mal, abdominal																								1
Skeletal muscle, thigh	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Basal cel aden														X	X									3
Fib histiocyt, subcut tiss																								1
Histio sarc																								1
Histio sarc, subcut tiss																								1
Keratoacanthma																								1
Lipoma, subcut tiss																								1
Trichoepithel														X										1
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spinal cord, thoracic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma, metastatic, kidney																X								1
Histio sarc, metastatic, skin																								1
Leukemia monuc			X			X			X								X	X		X		X	X	16
Mesothelio mal																								1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia monuc																								1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Fumonisin B_1: 150 ppm

Carcass ID Number	020	021	022	023	033	060	069	085	086	104	115	132	140	160	178	183	195	205	215	216	217	265	269	283	284
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, bilateral, interstit cell									X	X	X		X			X	X				X		X	X	X
Adenoma, interstit cell														X	X			X	X						
Mesothelio mal													X												
Thymus	+	+	+	+	M	+	+	+	+	M	+	+	+	+	M	+	+	M	+	M	+	+	+	+	+
Leukemia monuc												X					X								
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, c cell																		X						X	
Adenoma, multiple, c cell												X													
Tissue NOS														+											
Tongue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelio mal													X												
Zymbal's gland	+	M	+	+	+	+	M	M	+	+	M	+	+	M	+	+	+	M	+	+	+	M	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Fumonisin B_1: 150 ppm

Carcass ID Number	285	286	306	309	318	331	353	354	355	366	382	383	384	416	417	418	419	420	421	422	460	461	462	Total Tissues/ Tumors
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma, bilateral, interstit cell	X		X	X	X	X		X	X		X	X	X		X	X	X	X	X				X	26
Adenoma, interstit cell		X					X			X				X						X	X	X		11
Mesothelio mal				X													X			X				4
Thymus	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	41
Leukemia monuc			X																					3
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma, c cell		X				X	X						X	X			X		X		X			10
Adenoma, multiple, c cell																								1
Tissue NOS																								1
Tongue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Mesothelio mal																								1
Zymbal's gland	+	+	+	+	M	M	M	M	M	M	+	+	M	+	+	+	+	+	+	+	+	M	+	33

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of Fumonisin B_1

	0 ppm	5 ppm	15 ppm	50 ppm	150 ppm
Adrenal Medulla: Benign Pheochromocytoma					
Overall rate[a]	11/47 (23%)	4/22 (18%)	6/25 (24%)	3/31 (10%)	8/47 (17%)
Adjusted rate[b]	29.6%	26.5%	34.8%	16.7%	20.7%
Terminal rate[c]	6/18 (33%)	0/0	1/2 (50%)	1/3 (33%)	5/25 (20%)
First incidence (days)	631	607	523	720	629
Poly-3 test[d]	P=0.2116N	P=0.5841N	P=0.4284	P=0.2203N	P=0.3071N
Kidney (Renal Tubule): Adenoma					
Overall rate	0/48 (0%)	0/40 (0%)	0/48 (0%)	2/48 (4%)	5/48 (10%)
Adjusted rate	0.0%	0.0%	0.0%	5.7%	12.9%
Terminal rate	0/18 (0%)	0/17 (0%)	0/25 (0%)	2/20 (10%)	5/25 (20%)
First incidence (days)	—[e]	—	—	740 (T)	740 (T)
Poly-3 test	P=0.0004	—[f]	—	P=0.2293	P=0.0314
Kidney (Renal Tubule): Carcinoma					
Overall rate	0/48 (0%)	0/40 (0%)	0/48 (0%)	7/48 (15%)	10/48 (21%)
Adjusted rate	0.0%	0.0%	0.0%	20.0%	25.4%
Terminal rate	0/18 (0%)	0/17 (0%)	0/25 (0%)	6/20 (30%)	8/25 (32%)
First incidence (days)	—	—	—	680	594
Poly-3 test	P=0.0001	—	—	P=0.0059	P=0.0008
Kidney (Renal Tubule): Adenoma or Carcinoma					
Overall rate	0/48 (0%)	0/40 (0%)	0/48 (0%)	9/48 (19%)	15/48 (31%)
Adjusted rate	0.0%	0.0%	0.0%	25.7%	38.1%
Terminal rate	0/18 (0%)	0/17 (0%)	0/25 (0%)	8/20 (40%)	13/25 (52%)
First incidence (days)	—	—	—	680	594
Poly-3 test	P=0.0001	—	—	P=0.0011	P=0.0001
Liver: Adenoma					
Overall rate	0/48 (0%)	2/40 (5%)	2/48 (4%)	0/48 (0%)	1/48 (2%)
Adjusted rate	0.0%	6.2%	5.2%	0.0%	2.6%
Terminal rate	0/18 (0%)	1/17 (6%)	2/25 (8%)	0/20 (0%)	1/25 (4%)
First incidence (days)	—	677	740 (T)	—	740 (T)
Poly-3 test	P=0.5375N	P=0.1993	P=0.2412	—	P=0.5050
Liver: Adenoma or Carcinoma					
Overall rate	0/48 (0%)	3/40 (8%)	3/48 (6%)	0/48 (0%)	1/48 (2%)
Adjusted rate	0.0%	9.2%	7.7%	0.0%	2.6%
Terminal rate	0/18 (0%)	1/17 (6%)	2/25 (8%)	0/20 (0%)	1/25 (4%)
First incidence (days)	—	607	685	—	740 (T)
Poly-3 test	P=0.3391N	P=0.0905	P=0.1223	—	P=0.5050
Mammary Gland: Fibroadenoma					
Overall rate	2/40 (5%)	0/20 (0%)	0/24 (0%)	0/24 (0%)	4/42 (10%)
Adjusted rate	6.5%	0.0%	0.0%	0.0%	11.5%
Terminal rate	1/15 (7%)	0/0	0/4 (0%)	0/2 (0%)	4/23 (17%)
First incidence (days)	705	—	—	—	740 (T)
Poly-3 test	P=0.0838	P=0.4520N	P=0.4128N	P=0.4151N	P=0.3607

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of Fumonisin B_1

	0 ppm	5 ppm	15 ppm	50 ppm	150 ppm
Pancreas: Adenoma					
Overall rate	6/47 (13%)	0/24 (0%)	2/25 (8%)	4/30 (13%)	6/48 (13%)
Adjusted rate	16.2%	0.0%	12.5%	21.9%	15.1%
Terminal rate	1/18 (6%)	0/1 (0%)	1/2 (50%)	0/2 (0%)	4/25 (16%)
First incidence (days)	633	—	666	606	594
Poly-3 test	P=0.4038	P=0.1273N	P=0.5543N	P=0.4737	P=0.6106N
Pancreas: Carcinoma					
Overall rate	3/47 (6%)	2/24 (8%)	2/25 (8%)	0/30 (0%)	3/48 (6%)
Adjusted rate	8.4%	12.2%	12.7%	0.0%	7.7%
Terminal rate	2/18 (11%)	0/1 (0%)	1/2 (50%)	0/2 (0%)	2/25 (8%)
First incidence (days)	729	656	727	—	673
Poly-3 test	P=0.4837N	P=0.5033	P=0.4891	P=0.2751N	P=0.6477N
Pancreas: Adenoma or Carcinoma					
Overall rate	9/47 (19%)	2/24 (8%)	3/25 (12%)	4/30 (13%)	9/48 (19%)
Adjusted rate	24.2%	12.2%	18.7%	21.9%	22.6%
Terminal rate	3/18 (17%)	0/1 (0%)	1/2 (50%)	0/2 (0%)	6/25 (24%)
First incidence (days)	633	656	666	606	594
Poly-3 test	P=0.4464	P=0.2963N	P=0.5005N	P=0.5191N	P=0.5853N
Pituitary Gland (Pars Distalis): Adenoma					
Overall rate	30/43 (70%)	18/28 (64%)	23/33 (70%)	18/33 (55%)	24/45 (53%)
Adjusted rate	80.0%	73.2%	77.5%	72.5%	60.6%
Terminal rate	13/17 (77%)	5/6 (83%)	12/12 (100%)	5/7 (71%)	15/24 (63%)
First incidence (days)	284	561	454	477	319
Poly-3 test	P=0.0320N	P=0.4394N	P=0.6001N	P=0.2336N	P=0.0661N
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma					
Overall rate	30/43 (70%)	19/28 (68%)	23/33 (70%)	18/33 (55%)	25/45 (56%)
Adjusted rate	80.0%	77.2%	77.5%	72.5%	63.0%
Terminal rate	13/17 (77%)	6/6 (100%)	12/12 (100%)	5/7 (71%)	15/24 (63%)
First incidence (days)	284	561	454	477	319
Poly-3 test	P=0.0434N	P=0.5999N	P=0.6001N	P=0.2336N	P=0.1016N
Skin: Basal Cell Adenoma					
Overall rate	3/48 (6%)	0/27 (0%)	0/28 (0%)	1/32 (3%)	3/48 (6%)
Adjusted rate	8.1%	0.0%	0.0%	5.3%	7.7%
Terminal rate	0/18 (0%)	0/4 (0%)	0/5 (0%)	0/4 (0%)	2/25 (8%)
First incidence (days)	560	—	—	715	697
Poly-3 test	P=0.3408	P=0.2777N	P=0.2808N	P=0.5442N	P=0.6624N
Skin: Squamous Cell Papilloma or Keratoacanthoma					
Overall rate	3/48 (6%)	1/27 (4%)	3/28 (11%)	1/32 (3%)	1/48 (2%)
Adjusted rate	8.2%	5.3%	16.0%	5.2%	2.5%
Terminal rate	1/18 (6%)	0/4 (0%)	3/5 (60%)	0/4 (0%)	0/25 (0%)
First incidence (days)	631	687	740 (T)	673	629
Poly-3 test	P=0.1615N	P=0.5760N	P=0.3146	P=0.5384N	P=0.2984N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of Fumonisin B_1

	0 ppm	5 ppm	15 ppm	50 ppm	150 ppm
Skin: Squamous Cell Papilloma, Keratoacanthoma, Trichoepithelioma, or Basal Cell Adenoma					
Overall rate	6/48 (13%)	2/27 (7%)	4/28 (14%)	2/32 (6%)	4/48 (8%)
Adjusted rate	15.9%	10.5%	21.4%	10.4%	10.1%
Terminal rate	1/18 (6%)	1/4 (25%)	4/5 (80%)	0/4 (0%)	2/25 (8%)
First incidence (days)	560	687	740 (T)	673	629
Poly-3 test	P=0.2892N	P=0.4700N	P=0.4165	P=0.4158N	P=0.3716N
Skin (Subcutaneous Tissue): Fibroma					
Overall rate	3/48 (6%)	3/27 (11%)	2/28 (7%)	2/32 (6%)	0/48 (0%)
Adjusted rate	8.3%	15.9%	10.7%	10.4%	0.0%
Terminal rate	1/18 (6%)	3/4 (75%)	1/5 (20%)	1/4 (25%)	0/25 (0%)
First incidence (days)	645	740 (T)	727	615	—
Poly-3 test	P=0.0365N	P=0.3202	P=0.5560	P=0.6047	P=0.1146N
Skin (Subcutaneous Tissue): Fibroma, Fibrous Histiocytoma, Histiocytic Sarcoma, or Sarcoma					
Overall rate	4/48 (8%)	3/27 (11%)	3/28 (11%)	3/32 (9%)	3/48 (6%)
Adjusted rate	10.9%	15.9%	15.9%	15.3%	7.6%
Terminal rate	1/18 (6%)	3/4 (75%)	1/5 (20%)	1/4 (25%)	0/25 (0%)
First incidence (days)	645	740 (T)	720	615	655
Poly-3 test	P=0.2682N	P=0.4332	P=0.4339	P=0.5007	P=0.4863N
Testis: Adenoma					
Overall rate	33/48 (69%)	30/39 (77%)	34/46 (74%)	35/46 (76%)	37/48 (77%)
Adjusted rate	80.9%	85.6%	86.4%	89.6%	89.2%
Terminal rate	15/18 (83%)	16/16 (100%)	23/23 (100%)	15/18 (83%)	24/25 (96%)
First incidence (days)	600	582	442	519	594
Poly-3 test	P=0.1518	P=0.2412	P=0.1901	P=0.2334	P=0.0984
Thyroid Gland (C-cell): Adenoma					
Overall rate	9/48 (19%)	2/24 (8%)	4/25 (16%)	2/31 (7%)	11/48 (23%)
Adjusted rate	24.4%	11.9%	24.0%	10.2%	27.9%
Terminal rate	5/18 (28%)	0/1 (0%)	2/2 (100%)	1/4 (25%)	9/25 (36%)
First incidence (days)	635	561	442	284	669
Poly-3 test	P=0.2150	P=0.2730N	P=0.6082	P=0.1839N	P=0.4135
All Organs: Mononuclear Cell Leukemia					
Overall rate	24/48 (50%)	22/40 (55%)	21/48 (44%)	20/48 (42%)	16/48 (33%)
Adjusted rate	59.2%	59.3%	50.5%	52.6%	39.0%
Terminal rate	9/18 (50%)	6/17 (35%)	10/25 (40%)	10/20 (50%)	7/25 (28%)
First incidence (days)	390	550	461	580	533
Poly-3 test	P=0.0369N	P=0.4932	P=0.3653N	P=0.3532N	P=0.0775N
All Organs: Benign Neoplasms					
Overall rate	45/48 (94%)	36/40 (90%)	45/48 (94%)	44/48 (92%)	43/48 (90%)
Adjusted rate	99.3%	94.2%	97.2%	98.0%	98.2%
Terminal rate	17/18 (94%)	16/17 (94%)	25/25 (100%)	19/20 (95%)	25/25 (100%)
First incidence (days)	61	561	442	284	319
Poly-3 test	P=0.3807	P=0.4184N	P=0.7592N	P=0.5916N	P=0.7033

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of Fumonisin B_1

	0 ppm	5 ppm	15 ppm	50 ppm	150 ppm
All Organs: Malignant Neoplasms					
Overall rate	30/48 (63%)	26/40 (65%)	28/48 (58%)	30/48 (63%)	30/48 (63%)
Adjusted rate	72.0%	67.7%	63.4%	71.8%	69.0%
Terminal rate	11/18 (61%)	7/17 (41%)	12/25 (48%)	13/20 (65%)	13/25 (52%)
First incidence (days)	390	550	442	238	533
Poly-3 test	P=0.4515	P=0.5501N	P=0.3735N	P=0.5860N	P=0.5879
All Organs: Benign or Malignant Neoplasms					
Overall rate	46/48 (96%)	38/40 (95%)	48/48 (100%)	46/48 (96%)	44/48 (92%)
Adjusted rate	99.7%	96.6%	100.0%	98.5%	99.1%
Terminal rate	17/18 (94%)	16/17 (94%)	25/25 (100%)	19/20 (95%)	25/25 (100%)
First incidence (days)	61	550	442	238	319
Poly-3 test	P=0.5095	P=0.6422N	P=0.4594	P=0.6167N	P=0.6343

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined microscopically
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence is the P value associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. For all tissues except the kidney, liver, and testis, only the pairwise comparisons between the 150 ppm group and control group are unbiased; overall rates and all other pairwise comparisons may not be valid. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in an exposure group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group
[f] Value of statistic cannot be computed.

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of Fumonisin B_1[a]

	0 ppm	5 ppm	15 ppm	50 ppm	150 ppm
Disposition Summary					
6-Week evaluation	4	4	4	4	4
10-Week evaluation	4	4	4	4	4
14-Week evaluation	4	4	4	4	4
26-Week evaluation	4	4	4	4	4
Animals initially in 2-year study	48	40	48	48	48
Early deaths					
Removed from study	2			2	
Moribund	24	19	19	19	21
Natural deaths	6	4	4	9	2
Survivors					
Terminal sacrifice	16	17	25	18	25
Animals examined microscopically	64	56	64	64	64
6-Week Evaluation					
Kidney	(4)	(4)	(4)	(4)	(4)
Apoptosis, cortex, renal tubule			4 (100%)	4 (100%)	4 (100%)
Cyst, medulla	1 (25%)				
Cytoplas alter, cortex, renal tubule	1 (25%)				
Liver	(4)	(4)	(4)	(4)	(4)
Fatty change, centrilobular		1 (25%)			
Inflammation, chronic		1 (25%)			
10-Week Evaluation					
Kidney	(4)	(4)	(4)	(4)	(4)
Apoptosis, cortex, renal tubule			4 (100%)	4 (100%)	4 (100%)
Cyst, medulla					1 (25%)
Inflammation, chronic, pelvis	1 (25%)	2 (50%)			
Nephropathy	1 (25%)	1 (25%)	1 (25%)	1 (25%)	
Liver	(4)	(4)	(4)	(4)	(4)
Angiectasis, focal, sinusoid					1 (25%)
Hyperplasia, bile duct					1 (25%)
Necrosis, focal		1 (25%)			
Mesentery				(1)	
Necrosis, focal, fat				1 (100%)	
14-Week Evaluation					
Kidney	(4)	(4)	(4)	(4)	(4)
Apoptosis, cortex, renal tubule			4 (100%)	4 (100%)	4 (100%)
Cyst, medulla				1 (25%)	
Cytoplas alter, cortex, renal tubule	2 (50%)				
Nephropathy		3 (75%)	1 (25%)	1 (25%)	2 (50%)
Liver	(4)	(4)	(4)	(4)	(4)
Hyperplasia, bile duct		2 (50%)	1 (25%)	1 (25%)	
Inflammation, chronic			1 (25%)	1 (25%)	
Necrosis, multifocal			1 (25%)		
Testes		(1)			
Hemorrhage		1 (100%)			

[a] Number of animals examined microscopically at the site and the number of animals with lesion

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of Fumonisin B_1

	0 ppm	5 ppm	15 ppm	50 ppm	150 ppm
26-Week Evaluation					
Intestine large					(1)
Hemorrhage, focal, cecum, submucosa					1 (100%)
Kidney	(4)	(4)	(4)	(4)	(4)
Apoptosis, cortex, renal tubule		1 (25%)		4 (100%)	4 (100%)
Mineralization	2 (50%)				1 (25%)
Nephropathy	4 (100%)	3 (75%)	1 (25%)	3 (75%)	4 (100%)
Liver	(4)	(4)	(4)	(4)	(4)
Devel malfor			1 (4%)		
Fatty change, centrilobular	4 (100%)	4 (100%)		4 (100%)	4 (100%)
Hyperplasia, bile duct	1 (25%)	2 (50%)	3 (75%)	4 (100%)	2 (50%)
Inflammation, chronic	4 (100%)	3 (75%)	3 (75%)	3 (75%)	2 (50%)
Necrosis, focal	1 (25%)			1 (25%)	
Necrosis, multifocal			1 (25%)		
Vacuoliz cyto, focal	2 (50%)		1 (25%)	1 (25%)	1 (25%)
2-Year Study					
Adrenal gland	(47)	(22)	(25)	(31)	(47)
Angiectasis, bilateral, cortex					1 (2%)
Angiectasis, cortex				1 (3%)	
Hema cell prol, cortex				1 (3%)	1 (2%)
Hyperplasia, focal, bilateral, cortex					1 (2%)
Hyperplasia, focal, bilateral, medulla	1 (2%)	1 (5%)	1 (4%)	2 (6%)	
Hyperplasia, focal, cortex	5 (11%)	1 (5%)	1 (4%)	1 (3%)	1 (2%)
Hyperplasia, focal, medulla	7 (15%)	3 (14%)	2 (8%)	3 (10%)	5 (11%)
Infiltrat cell, lymphocytic	1 (2%)				
Vacuoliz cyto, diffuse, bilateral, cortex	1 (2%)			1 (3%)	
Vacuoliz cyto, diffuse, cortex	2 (4%)		1 (4%)		1 (2%)
Vacuoliz cyto, focal, bilateral, cortex	1 (2%)				1 (2%)
Vacuoliz cyto, focal, cortex	11 (23%)	4 (18%)		5 (17%)	8 (17%)
Blood vessel	(47)	(23)	(23)	(30)	(47)
Inflammation, chronic, mesent artery		1 (4%)			
Bone	(48)	(23)	(23)	(30)	(48)
Degen, epiphysis					1 (2%)
Degen, joint, cartilage		1 (4%)			
Hyperostosis, turbinate	1 (2%)				
Inflammation, chronic, joint				1 (3%)	
Bone, femur	(48)	(23)	(23)	(29)	(48)
Hyperplasia, cartilage, epiphysis			2 (9%)		
Bone marrow	(47)	(23)	(23)	(30)	(48)
Angiectasis					1 (2%)
Atrophy				1 (3%)	
Depletion	1 (2%)		3 (13%)	2 (7%)	3 (6%)
Hyperplasia	7 (15%)	3 (13%)	3 (13%)	7 (23%)	12 (25%)
Myelofibrosis	1 (2%)				
Brain	(48)	(24)	(23)	(31)	(48)
Compression, hypothalamus	11 (23%)	7 (29%)	6 (26%)	8 (26%)	4 (8%)
Hemorrhage, hypothalamus				1 (3%)	
Hemorrhage, ventricle				1 (3%)	
Necrosis, hippocampus, neuron					1 (2%)
Brain, cerebrum	(48)	(24)	(23)	(31)	(48)
Compression		1 (4%)			
Hemorrhage				1 (3%)	

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of Fumonisin B_1

	0 ppm		5 ppm		15 ppm		50 ppm		150 ppm	
2-Year Study (continued)										
Coagulating gland	(48)		(22)		(23)		(29)		(48)	
Atrophy	9	(19%)	2	(9%)	2	(9%)	1	(3%)	3	(6%)
Atrophy, bilateral	14	(29%)	4	(18%)	8	(35%)	6	(21%)	16	(33%)
Degen, bilateral					1	(4%)				
Infiltrat cell, lymphocytic									1	(2%)
Inflammation, acute							1	(3%)		
Inflammation, chronic active			1	(5%)						
Epididymis	(48)		(23)		(22)		(28)		(47)	
Atrophy									1	(2%)
Atrophy, bilateral	2	(4%)			3	(14%)	1	(4%)		
Degen, mucoid, bilateral, epithelium	2	(4%)	1	(4%)	1	(5%)			2	(4%)
Degen, mucoid, epithelium	6	(13%)			1	(5%)	1	(4%)	6	(13%)
Hyperplasia, epithelium			1	(4%)						
Inflammation, chronic	1	(2%)							1	(2%)
Esophagus	(48)		(22)		(23)		(30)		(48)	
Inflammation, chronic, muscularis							1	(3%)		
Eye	(47)		(24)		(26)		(35)		(48)	
Atrophy, bilateral, retina	32	(68%)	7	(29%)	14	(54%)	20	(57%)	27	(56%)
Atrophy, retina	5	(11%)	5	(21%)	3	(12%)	3	(9%)	5	(10%)
Cataract, bilateral, lens	21	(45%)	4	(17%)	7	(27%)	13	(37%)	15	(31%)
Cataract, lens	4	(9%)	1	(4%)	2	(9%)	3	(9%)	3	(6%)
Degen, optic nerve									1	(2%)
Inflammation, acute, cornea					1	(4%)				
Inflammation, acute, iris			1	(4%)						
Inflammation, chronic, cornea	1	(2%)								
Necrosis, optic nerve	1	(2%)								
Harderian gland	(48)		(23)		(23)		(30)		(48)	
Atrophy, focal	2	(4%)								
Hyperplasia, focal							1	(3%)		
Infiltrat cell, lymphocytic	15	(31%)	4	(17%)	5	(22%)	11	(37%)	18	(38%)
Infiltrat cell, lymphocytic, bilateral	9	(19%)	3	(13%)	1	(4%)	2	(7%)	5	(10%)
Inflammation, chronic							2	(7%)	1	(2%)
Heart	(48)		(23)		(24)		(30)		(48)	
Cardiomyopathy	42	(89%)	15	(65%)	14	(58%)	23	(77%)	37	(77%)
Inflammation, chronic, coron artery			1	(4%)						
Inflammation, chronic, epicardium			1	(4%)						
Inflammation, chronic, pericardium			1	(4%)						
Inflammation, chronic, valve			1	(4%)					3	(6%)
Thrombus, atrium	1	(2%)	2	(9%)	1	(4%)			1	(2%)
Intestine large, cecum	(45)		(23)		(23)		(25)		(47)	
Parasite meta									1	(2%)
Intestine large, colon	(47)		(23)		(23)		(28)		(47)	
Hyperplasia, lymphoid					1	(4%)				
Parasite meta									1	(2%)
Ulcer			1	(4%)						
Intestine large, rectum	(48)		(23)		(23)		(30)		(47)	
Hemorrhage							1	(3%)		
Hyperplasia, focal, epithelium							1	(3%)		
Parasite meta									1	(2%)
Intestine small, ileum	(45)		(23)		(22)		(26)		(47)	
Hyperplasia, lymphoid					1	(5%)				

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of Fumonisin B_1

	0 ppm	5 ppm	15 ppm	50 ppm	150 ppm
2-Year Study (continued)					
Kidney	(48)	(40)	(48)	(48)	(48)
Acc hyaline d, bilateral, renal tubule	1 (2%)			1 (2%)	1 (2%)
Cyst	2 (4%)	1 (3%)		3 (6%)	7 (15%)
Cyst, bilateral					1 (2%)
Cytoplas alter, bilateral, renal tubule					1 (2%)
Hydronephrosis	1 (2%)				
Hyperplasia, focal, renal tubule	2 (4%)	1 (3%)	4 (8%)	14 (29%)	8 (17%)
Inflammation, acute, bilateral, pelvis				1 (2%)	
Inflammation, chronic, artery			1 (2%)	1 (2%)	
Inflammation, chronic, artery, pelvis		1 (3%)			
Inflammation, chronic, bilateral, artery	1 (2%)	1 (3%)	1 (2%)		
Mineralization	1 (2%)		1 (2%)	1 (2%)	1 (2%)
Mineralization, bilateral		1 (3%)			
Nephropathy			1 (2%)	4 (8%)	3 (6%)
Nephropathy, bilateral	44 (92%)	38 (95%)	43 (90%)	34 (71%)	39 (81%)
Pigment, bilateral, renal tubule	13 (27%)	8 (20%)	8 (17%)	2 (4%)	6 (13%)
Pigment, renal tubule		1 (3%)		1 (2%)	1 (2%)
Lacrimal gland	(47)	(23)	(22)	(30)	(48)
Atrophy, diffuse		1 (4%)			
Atrophy, focal		2 (9%)	1 (5%)	4 (13%)	1 (2%)
Cyst					1 (2%)
Hyperplasia, duct					1 (2%)
Infiltrat cell, lymphocytic	11 (23%)	11 (48%)	5 (23%)	9 (30%)	20 (42%)
Larynx	(46)	(21)	(22)	(29)	(46)
Cyst	2 (4%)	2 (10%)	2 (9%)		2 (4%)
Inflammation, chronic	1 (2%)	2 (10%)		1 (3%)	3 (7%)
Inflammation, chronic active	2 (4%)	1 (5%)			
Liver	(48)	(40)	(48)	(48)	(48)
Angiectasis, focal	1 (2%)	1 (3%)		1 (2%)	
Basoph focus	3 (6%)	11 (28%)	7 (15%)	9 (19%)	23 (48%)
Clear cl focus	5 (10%)	10 (25%)	14 (29%)	6 (13%)	10 (21%)
Congestion		1 (3%)	1 (2%)	1 (2%)	
Degen, cystic, focal	6 (13%)	4 (10%)	5 (10%)	3 (6%)	2 (4%)
Degen, cystic, focal, hepatocyte			1 (2%)		
Eosin focus	5 (10%)	6 (15%)	10 (21%)	5 (10%)	10 (21%)
Hdn	3 (6%)	3 (8%)	2 (4%)	3 (6%)	5 (10%)
Hema cell prol			1 (2%)	1 (2%)	
Hemorrhage	1 (2%)				
Hyperplasia, bile duct	38 (79%)	35 (88%)	45 (94%)	42 (88%)	43 (90%)
Inflammation, chronic	2 (4%)	4 (10%)	2 (4%)	1 (2%)	4 (8%)
Mixed cl focus	5 (10%)	6 (15%)	5 (10%)	4 (8%)	9 (19%)
Necrosis	4 (8%)		1 (2%)	5 (10%)	1 (2%)
Pigment					1 (2%)
Tension lipoid	3 (6%)	5 (13%)	7 (15%)	7 (15%)	7 (15%)
Thrombus, vein			1 (2%)		
Vacuoliz cyto, hepatocyte	13 (27%)	8 (20%)	12 (25%)	9 (19%)	13 (27%)
Lung	(48)	(24)	(23)	(32)	(48)
Congestion					1 (2%)
Foreign body			1 (4%)		
Hyperplasia, focal, alveolar epith		1 (4%)		2 (6%)	1 (2%)
Infiltrat cell, histiocytic		1 (4%)	1 (4%)	1 (3%)	1 (2%)
Infiltrat cell, lymphocytic					1 (2%)
Inflammation, chronic, interstitium	1 (2%)		1 (4%)	2 (6%)	1 (2%)
Lung, bronchus	(48)	(24)	(23)	(31)	(48)
Inflammation, chronic active			1 (4%)		

Table A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of Fumonisin B_1

	0 ppm		5 ppm		15 ppm		50 ppm		150 ppm	
2-Year Study (continued)										
Lymph node	(48)		(24)		(27)		(33)		(48)	
Degen, cystic, deep cervical					1	(4%)				
Degen, cystic, mediastinal			1	(4%)						
Degen, cystic, renal			1	(4%)						
Lymph node, mandibular	(48)		(23)		(26)		(32)		(48)	
Degen, cystic	6	(13%)			2	(8%)	3	(9%)	6	(13%)
Hemorrhage	1	(2%)					3	(9%)	1	(2%)
Hyperplasia, lymphoid	5	(10%)	4	(17%)			5	(16%)	10	(21%)
Infiltrat cell, histiocytic	1	(2%)	1	(4%)			2	(6%)		
Lymph node, mesenteric	(47)		(23)		(23)		(30)		(48)	
Atrophy	1	(2%)			1	(4%)	1	(3%)		
Degen, cystic	3	(6%)	1	(4%)	1	(4%)	1	(3%)	3	(6%)
Hemorrhage	1	(2%)	1	(4%)	2	(9%)	3	(10%)	1	(2%)
Hyperplasia, lymphoid			1	(4%)			2	(7%)		
Infiltrat cell, histiocytic	27	(57%)	9	(39%)	11	(48%)	15	(50%)	27	(56%)
Inflammation, chronic									1	(2%)
Mammary gland	(40)		(20)		(24)		(24)		(42)	
Cyst	11	(28%)	3	(15%)	3	(13%)	5	(21%)	4	(10%)
Galactocele	5	(13%)	3	(15%)	7	(29%)			8	(19%)
Hyperplasia, epithelium					1	(4%)	1	(4%)		
Hyperplasia, focal, epithelium									1	(2%)
Mesentery	(4)		(3)		(3)		(4)		(4)	
Accessory spln			1	(33%)						
Inflammation, chronic, artery			1	(33%)						
Necrosis, fat	3	(75%)	1	(33%)	3	(100%)	3	(75%)	3	(75%)
Nose	(48)		(23)		(23)		(29)		(48)	
Cytoplas alter, olfactory epi	20	(42%)	7	(30%)	10	(43%)	6	(21%)	18	(38%)
Foreign body	2	(4%)	3	(13%)	1	(4%)	1	(3%)	3	(6%)
Inflammation, acute					1	(4%)	1	(3%)	1	(2%)
Inflammation, acute, nasolacrim dct	1	(2%)	1	(4%)	1	(4%)	2	(7%)	1	(2%)
Inflammation, chronic	1	(2%)	2	(9%)	1	(4%)	1	(3%)		
Inflammation, chronic active	1	(2%)	2	(9%)	1	(4%)	2	(7%)	2	(4%)
Inflammation, chronic active, nasolacrim dct	5	(10%)	4	(17%)			3	(10%)	10	(21%)
Inflammation, chronic, nasolacrim dct	7	(15%)	2	(9%)	4	(17%)			4	(8%)
Pancreas	(47)		(24)		(25)		(30)		(48)	
Atrophy, diffuse, acinar cell	2	(4%)	1	(4%)	2	(8%)	1	(3%)	1	(2%)
Atrophy, focal, acinar cell	20	(43%)	8	(33%)	9	(36%)	13	(43%)	28	(58%)
Basoph focus, acinar cell					1	(4%)			2	(4%)
Hyperplasia, focal			1	(4%)	1	(4%)			1	(2%)
Hyperplasia, focal, acinar cell	1	(2%)							1	(2%)
Hyperplasia, focal, duct	1	(2%)								
Infiltrat cell, lymphocytic							1	(3%)	2	(4%)
Inflammation, chronic, artery	1	(2%)	1	(4%)	1	(4%)			2	(4%)
Necrosis, focal			1	(4%)						
Parathyroid gland	(46)		(21)		(22)		(26)		(47)	
Hyperplasia, focal									1	(2%)
Pigment									1	(2%)
Pituitary gland	(43)		(28)		(33)		(33)		(45)	
Angiectasis, pars distalis							1	(3%)	1	(2%)
Atypical cells, pars nervosa									1	(2%)
Cyst, pars distalis									2	(4%)
Cyst, pars intermed	1	(2%)							1	(2%)
Cyst, pars nervosa									1	(2%)
Cyst, Rathke's cleft									1	(2%)
Hemorrhage	1	(2%)					1	(3%)		
Hemorrhage, pars distalis							1	(3%)		
Hyperplasia, focal, pars distalis	3	(7%)	1	(4%)	2	(6%)	1	(3%)	7	(16%)
Hypertrophy, focal, pars distalis			1	(4%)	2	(6%)			1	(2%)

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of Fumonisin B_1

	0 ppm		5 ppm		15 ppm		50 ppm		150 ppm	
2-Year Study (continued)										
Preputial gland	(43)		(19)		(20)		(30)		(44)	
Foreign body									1	(2%)
Hyperplasia, focal	3	(7%)								
Inflammation, acute	1	(2%)								
Inflammation, chronic	18	(42%)	6	(32%)	9	(45%)	15	(50%)	13	(30%)
Inflammation, chronic active					1	(5%)			4	(9%)
Inflammation, chronic active, bilateral			2	(11%)			2	(7%)	2	(5%)
Inflammation, chronic, bilateral	7	(16%)	3	(16%)	6	(30%)	5	(17%)	9	(20%)
Prostate	(48)		(22)		(23)		(30)		(48)	
Atrophy	10	(21%)	4	(18%)	5	(22%)	6	(20%)	12	(25%)
Cyst			1	(5%)						
Cytoplas alter, epithelium									1	(2%)
Fibrosis					1	(4%)				
Hyperplasia, focal, epithelium	1	(2%)					3	(10%)	3	(6%)
Inflammation, acute	7	(15%)	3	(14%)	2	(9%)	7	(23%)	6	(13%)
Inflammation, chronic	3	(6%)			3	(13%)	2	(7%)	2	(4%)
Inflammation, chronic active	11	(23%)	8	(36%)	4	(17%)	3	(10%)	10	(21%)
Salivary glands	(48)		(23)		(23)		(30)		(48)	
Atrophy, diffuse, parotid gland	2	(4%)	1	(4%)	3	(13%)	1	(3%)	4	(8%)
Cyst			1	(4%)						
Cytoplas alter, focal, submandibul gland	1	(2%)							1	(2%)
Infiltrat cell, lymphocytic									1	(2%)
Inflammation, chronic, submandibul gland									1	(2%)
Seminal vesicle	(48)		(23)		(24)		(30)		(48)	
Atrophy	8	(17%)	1	(4%)	2	(8%)	1	(3%)	5	(10%)
Atrophy, bilateral	19	(40%)	11	(48%)	13	(54%)	10	(33%)	18	(38%)
Skeletal muscle, thigh	(48)		(23)		(24)		(30)		(48)	
Degen			1	(4%)			1	(3%)	1	(2%)
Hemorrhage					1	(4%)				
Skin	(48)		(27)		(28)		(32)		(48)	
Atrophy, hair follicle									1	(2%)
Inflammation, chronic	1	(2%)					1	(3%)		
Spinal cord, thoracic	(47)		(23)		(23)		(30)		(48)	
Hemorrhage	1	(2%)								
Spleen	(48)		(29)		(33)		(41)		(48)	
Atrophy, lymph follic	1	(2%)			2	(6%)	1	(2%)		
Congestion	2	(4%)	1	(3%)	1	(3%)	1	(2%)	3	(6%)
Depletion, focal	1	(2%)					2	(5%)		
Fibrosis, focal	1	(2%)	2	(7%)			3	(7%)	2	(4%)
Hema cell prol	5	(10%)	4	(14%)	3	(9%)	5	(12%)	6	(13%)
Infarct, focal					1	(3%)				
Inflammation, chronic active							1	(2%)		
Inflammation, chronic, capsule	1	(2%)			1	(3%)				
Pigment	4	(8%)			4	(12%)	3	(7%)	2	(4%)
Stomach, forestomach	(48)		(23)		(23)		(30)		(48)	
Edema	2	(4%)					1	(3%)	1	(2%)
Erosion, focal	1	(2%)								
Hyperplasia, epithelium	8	(17%)	3	(13%)	4	(17%)	3	(10%)	4	(8%)
Inflammation, acute							1	(3%)		
Inflammation, chronic	4	(8%)	2	(9%)	2	(9%)	5	(17%)	1	(2%)
Inflammation, chronic active	1	(2%)							1	(2%)
Ulcer	1	(2%)					2	(7%)	2	(4%)

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of Fumonisin B_1

	0 ppm		5 ppm		15 ppm		50 ppm		150 ppm	
2-Year Study (continued)										
Stomach, glandular	(48)		(23)		(23)		(30)		(48)	
Cyst	3	(6%)	2	(9%)						
Edema			1	(4%)					1	(2%)
Erosion					1	(4%)				
Erosion, focal	1	(2%)			2	(9%)				
Inflammation, acute	1	(2%)								
Inflammation, chronic	1	(2%)	1	(4%)	1	(4%)	1	(3%)		
Necrosis	1	(2%)							1	(2%)
Testes	(48)		(39)		(46)		(46)		(48)	
Atrophy, bilateral, germinal epith	3	(6%)			2	(4%)				
Atrophy, germinal epith	6	(13%)	1	(3%)	10	(22%)	6	(13%)	9	(19%)
Granloma sperm	1	(2%)								
Hyperplasia, focal, bilateral, interstit cell	2	(4%)	2	(5%)			1	(2%)		
Hyperplasia, focal, interstit cell	4	(8%)	6	(15%)	10	(22%)	5	(11%)	2	(4%)
Inflammation, chronic, artery	1	(2%)								
Mineralization			1	(3%)	1	(2%)			1	(2%)
Thymus	(37)		(19)		(21)		(24)		(41)	
Atrophy	13	(35%)	5	(26%)	9	(43%)	8	(33%)	19	(46%)
Cyst	1	(3%)							1	(2%)
Hemorrhage	2	(5%)					3	(13%)	4	(10%)
Hyperplasia, lymphoid					1	(5%)				
Thyroid gland	(48)		(24)		(25)		(31)		(48)	
Cyst, follicle							2	(6%)		
Hyperplasia, focal, c cell	10	(21%)	6	(25%)	5	(20%)	3	(10%)	9	(19%)
Inflammation, chronic	1	(2%)								
Ultimobra cyst	2	(4%)	1	(4%)					1	(2%)
Tissue NOS	(2)				(2)		(1)		(1)	
Cyst	1	(50%)								
Inflammation, chronic					1	(50%)				
Inflammation, chronic, mediastinum									1	(100%)
Tongue	(48)		(23)		(23)		(30)		(48)	
Inflammation, chronic					1	(4%)			1	(2%)
Inflammation, chronic, artery			1	(4%)						
Trachea	(48)		(23)		(23)		(30)		(48)	
Inflammation, chronic			1	(4%)					1	(2%)
Urinary bladder	(47)		(22)		(23)		(30)		(48)	
Dilatation							1	(3%)		
Hyperplasia, transit epithe			1	(5%)						
Infiltrat cell, lymphocytic	2	(4%)	2	(9%)					1	(2%)
Inflammation, acute							2	(7%)		
Inflammation, chronic			1	(5%)						

APPENDIX B
SUMMARY OF LESIONS IN FEMALE RATS IN THE 2-YEAR FEED STUDY OF FUMONISIN B_1

Table B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of Fumonisin B_1[a]

	0 ppm	5 ppm	15 ppm	50 ppm	100 ppm
Disposition Summary					
6-Week evaluation	4	4	4	4	4
10-Week evaluation	4	4	4	4	4
14-Week evaluation	4	4	4	4	4
26-Week evaluation	4	4	4	4	4
Animals initially in 2-year study	48	40	48	48	48
Early deaths					
Removed from study	1	2		2	
Moribund	20	15	23	16	16
Natural deaths	2	1	1		3
Survivors					
Terminal sacrifice	25	22	24	30	29
Animals examined microscopically	64	56	64	64	64

Tissues Examined at 6 Weeks with No Neoplasms Observed
Kidney
Liver

Tissues Examined at 10 Weeks with No Neoplasms Observed
Kidney
Liver
Mesentery
Ovary

Tissues Examined at 14 Weeks with No Neoplasms Observed
Intestine large
Kidney
Liver
Ovary
Uterus

Tissues Examined at 26 Weeks with No Neoplasms Observed
Kidney
Liver
Ovary
Uterus

2-Year Study

	0 ppm	5 ppm	15 ppm	50 ppm	100 ppm
Adrenal gland	(48)	(20)	(24)	(19)	(47)
Adenoma, cortex	1 (2%)				1 (2%)
Leukemia monuc	5 (10%)	2 (10%)	8 (33%)	2 (11%)	6 (13%)
Osteosarc, metastatic, bone	1 (2%)				
Pheochrom bgn, medulla	2 (4%)		1 (4%)	1 (5%)	2 (4%)
Bone	(48)	(18)	(24)	(18)	(48)
Sarcoma, maxilla				1 (6%)	

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of Fumonisin B_1

	0 ppm		5 ppm		15 ppm		50 ppm		100 ppm	
2-Year Study (continued)										
Bone, femur	(48)		(18)		(24)		(18)		(48)	
Osteosarc	1	(2%)								
Bone marrow	(46)		(18)		(23)		(18)		(48)	
Leukemia monuc	6	(13%)	6	(33%)	10	(43%)	5	(28%)	10	(21%)
Brain	(48)		(18)		(24)		(18)		(48)	
Carcinoma, metastatic, pituitary gland									1	(2%)
Leukemia monuc			1	(6%)	1	(4%)			1	(2%)
Brain, cerebrum	(48)		(18)		(24)		(18)		(48)	
Astrocyto mal	1	(2%)								
Meningioma mal									1	(2%)
Clitoral gland	(41)		(19)		(25)		(22)		(40)	
Adenoma	9	(22%)	2	(11%)	7	(28%)	6	(27%)	8	(20%)
Adenoma, bilateral	1	(2%)			2	(8%)			2	(5%)
Carcinoma	1	(2%)							1	(3%)
Leukemia monuc	1	(2%)	1	(5%)	1	(4%)				
Esophagus	(48)		(18)		(23)		(17)		(48)	
Leukemia monuc					1	(4%)				
Osteosarc, metastatic, bone	1	(2%)								
Harderian gland	(48)		(18)		(24)		(18)		(48)	
Leukemia monuc					1	(4%)			1	(2%)
Heart	(48)		(18)		(24)		(18)		(48)	
Alv bron carc, metastatic, lung									1	(2%)
Leukemia monuc	3	(6%)	1	(6%)	6	(25%)	2	(11%)	5	(10%)
Mesothelio mal, metastatic, unc pri site	1	(2%)								
Intestine large, cecum	(47)		(16)		(24)		(16)		(47)	
Leukemia monuc					1	(4%)				
Intestine large, colon	(47)		(18)		(24)		(18)		(47)	
Leukemia monuc					1	(4%)				
Intestine large, rectum	(47)		(18)		(24)		(18)		(48)	
Histio sarc, metastatic, skin									1	(2%)
Leukemia monuc					1	(4%)				
Schwannoma mal, metastatic, uterus					1	(4%)				
Intestine small, duodenum	(47)		(18)		(24)		(18)		(48)	
Leiomyosar							1	(6%)		
Leukemia monuc					1	(4%)				
Intestine small, ileum	(44)		(18)		(24)		(18)		(46)	
Leukemia monuc					2	(8%)				
Intestine small, jejunum	(47)		(18)		(24)		(18)		(46)	
Leukemia monuc					1	(4%)				
Kidney	(48)		(40)		(48)		(48)		(48)	
Adenoma, renal tubule							1	(2%)		
Carcinoma, renal tubule									1	(2%)
Leukemia monuc	2	(4%)	1	(3%)	6	(13%)	3	(6%)	5	(10%)
Lacrimal gland	(47)		(22)		(26)		(19)		(48)	
Leukemia monuc	2	(4%)			3	(12%)			6	(13%)
Liver	(48)		(40)		(48)		(48)		(48)	
Hepatoclr aden					1	(2%)				
Histio sarc, metastatic, skin									1	(2%)
Leukemia monuc	12	(25%)	13	(33%)	15	(31%)	8	(17%)	16	(33%)
Lung	(47)		(40)		(48)		(48)		(48)	
Alv bron aden			1	(3%)			1	(2%)	2	(4%)
Alv bron carc									1	(2%)
Histio sarc, metastatic, skin									1	(2%)
Leukemia monuc	8	(17%)	10	(25%)	11	(23%)	6	(13%)	6	(13%)
Osteosarc, metastatic, bone	1	(2%)								

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of Fumonisin B_1

	0 ppm	5 ppm	15 ppm	50 ppm	100 ppm
2-Year Study (continued)					
Lung, bronchus	(47)	(40)	(48)	(48)	(48)
Carcinoma			1 (2%)		
Lymph node	(48)	(20)	(25)	(18)	(48)
Leukemia monuc	1 (2%)			1 (6%)	
Leukemia monuc, inguinal		1 (5%)			
Leukemia monuc, pancreatic			1 (4%)		
Leukemia monuc, renal	1 (2%)				
Leukemia monuc, thoracic				1 (6%)	
Lymph node, mandibular	(48)	(17)	(24)	(17)	(48)
Leukemia monuc	9 (19%)	5 (29%)	8 (33%)	4 (24%)	10 (21%)
Lymph node, mesenteric	(48)	(19)	(25)	(18)	(48)
Leukemia monuc	8 (17%)	5 (26%)	10 (40%)	4 (22%)	7 (15%)
Mammary gland	(47)	(28)	(33)	(30)	(48)
Adenoma	1 (2%)		1 (3%)		
Carcinoma	2 (4%)	3 (11%)	3 (9%)		3 (6%)
Carcinoma, multiple			1 (3%)		
Fibroadenoma	15 (32%)	11 (39%)	12 (36%)	11 (37%)	8 (17%)
Fibroadenoma, multiple	3 (6%)	2 (7%)	4 (12%)	5 (17%)	3 (6%)
Fibroma	1 (2%)				
Leukemia monuc		1 (4%)	1 (3%)		
Mesentery	(2)	(5)	(5)	(3)	(2)
Leukemia monuc	1 (50%)	1 (20%)	1 (20%)		
Ovary	(47)	(19)	(25)	(22)	(47)
Gra cl tum bgn	2 (4%)				
Leukemia monuc	1 (2%)	1 (5%)	3 (12%)		
Pancreas	(48)	(18)	(24)	(18)	(48)
Leukemia monuc	1 (2%)	1 (6%)	6 (25%)	1 (6%)	
Pituitary gland	(47)	(30)	(35)	(34)	(48)
Adenoma, pars distalis	32 (68%)	20 (67%)	25 (71%)	23 (68%)	29 (60%)
Adenoma, pars intermed				1 (3%)	
Carcinoma, pars distalis					1 (2%)
Leukemia monuc	1 (2%)	3 (10%)	4 (11%)	2 (6%)	
Salivary glands	(48)	(18)	(25)	(18)	(48)
Leukemia monuc		1 (6%)	2 (8%)		
Skeletal muscle	(48)	(18)	(24)	(18)	(48)
Histio sarc, metastatic, skin					1 (2%)
Skeletal muscle, thigh	(48)	(18)	(24)	(18)	(48)
Osteosarc, metastatic, bone	1 (2%)				
Skin	(48)	(18)	(27)	(21)	(48)
Fibroma, subcut tiss	1 (2%)		1 (4%)		2 (4%)
Histio sarc, subcut tiss					1 (2%)
Keratoacanthma			1 (4%)		
Lipoma, subcut tiss	1 (2%)			2 (10%)	
Liposarc, subcut tiss				1 (5%)	
Melanoma mal, subcut tiss, head					1 (2%)
Schwannoma mal, subcut tiss	1 (2%)				
Squam cel carc				1 (5%)	
Spleen	(48)	(25)	(30)	(21)	(48)
Histio sarc, metastatic, skin					1 (2%)
Leukemia monuc	13 (27%)	12 (48%)	15 (50%)	8 (38%)	16 (33%)
Stomach, forestomach	(48)	(17)	(24)	(18)	(48)
Leukemia monuc	1 (2%)	1 (6%)	2 (8%)		1 (2%)
Stomach, glandular	(48)	(18)	(24)	(18)	(48)
Leukemia monuc		1 (6%)	3 (13%)		1 (2%)

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of Fumonisin B_1

	0 ppm		5 ppm		15 ppm		50 ppm		100 ppm	
2-Year Study (continued)										
Thymus	(41)		(15)		(22)		(18)		(40)	
Leukemia monuc	4	(10%)	4	(27%)	9	(41%)	2	(11%)	7	(18%)
Thyroid gland	(48)		(18)		(25)		(19)		(48)	
Adenoma, c cell	2	(4%)			3	(12%)			6	(13%)
Adenoma, multiple, c cell	1	(2%)								
Carcinoma, c cell	1	(2%)			1	(4%)	1	(5%)	1	(2%)
Leukemia monuc			1	(6%)	2	(8%)				
Tongue	(48)		(18)		(24)		(20)		(48)	
Papilloma squa							2	(10%)		
Trachea	(48)		(18)		(24)		(18)		(48)	
Leukemia monuc					1	(4%)				
Urinary bladder	(45)		(17)		(24)		(18)		(47)	
Leukemia monuc	1	(2%)	1	(6%)	6	(25%)				
Papilloma, transit epithe									1	(2%)
Schwannoma mal, metastatic, uterus					1	(4%)				
Uterus	(47)		(23)		(30)		(23)		(48)	
Carcinoma, endometrium									1	(2%)
Deciduoma bgn	1	(2%)								
Leiomyosar	1	(2%)								
Leukemia monuc	1	(2%)	1	(4%)	3	(10%)				
Leukemia monuc, cervix							1	(4%)		
Polyp stromal, endometrium	10	(21%)	4	(17%)	5	(17%)	3	(13%)	7	(15%)
Sarc stromal									1	(2%)
Sarcoma, cervix			1	(4%)						
Schwannoma mal					1	(3%)				
Vagina	(47)		(17)		(25)		(18)		(47)	
Leukemia monuc	1	(2%)	1	(6%)	3	(12%)	2	(11%)	1	(2%)
Liposarc									1	(2%)
Papilloma squa	1	(2%)								
Polyp					1	(4%)				
Schwannoma mal, metastatic, uterus					1	(4%)				
Zymbal's gland	(34)		(15)		(18)		(14)		(38)	
Adenoma							1	(7%)		
Carcinoma			1	(7%)						

	0 ppm	5 ppm	15 ppm	50 ppm	100 ppm
Neoplasm Summary					
Total animals with primary neoplasms[b]					
2-Year study	43	32	44	43	46
Total primary neoplasms					
2-Year study	175	121	221	114	184
Total animals with benign neoplasms					
2-Year study	41	26	37	38	42
Total benign neoplasms					
2-Year study	84	40	64	57	71
Total animals with malignant neoplasms					
2-Year study	18	17	22	14	25
Total malignant neoplasms					
2-Year study	91	81	157	57	113
Total animals with metastatic neoplasms					
2-Year study	2		1		3
Total metastatic neoplasms					
2-Year study	5		3		7

[a] Number of animals examined microscopically at the site and the number of animals with neoplasm
[b] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Fumonisin B_1: 0 ppm

Carcass ID Number	007	017	053	057	075	079	101	105	108	110	122	141	175	176	206	208	233	234	235	236	254	262	263	287	288
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, cortex																							X		
Leukemia monuc																						X			
Osteosarc, metastatic, bone																									
Pheochrom bgn, medulla										X															
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Blood vessel, aorta	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bone, femur	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarc																									
Bone, sternum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Leukemia monuc									X		X		X												
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Brain, cerebellum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Brain, cerebrum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocyto mal																									
Clitoral gland	+	+	+	+	+	M	+	+	+	M	+	M	+	+	+	+	+	+	+	+	M	M	+	+	+
Adenoma				X				X					X		X			X		X					
Adenoma, bilateral																									
Carcinoma																									
Leukemia monuc																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarc, metastatic, bone																									
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia monuc									X																
Mesothelio mal, metastatic, unc pri site				X																					
Intestine large	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	M	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia monuc											X														
Lacrimal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Leukemia monuc																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia monuc				X					X	X	X		X									X			
Lung	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia monuc									X	X	X		X									X			
Osteosarc, metastatic, bone																									
Lung, bronchus	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia monuc																									
Leukemia monuc, renal																									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia monuc									X		X		X									X			
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia monuc									X		X		X									X			

+: Tissue examined microscopically
A: Autolysis precludes examination
M: Missing tissue
I: Insufficient tissue
X: Lesion present
Blank: Not examined

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Fumonisin B_1: 0 ppm

Carcass ID Number	289	304	320	342	343	347	371	372	396	397	423	424	425	426	427	428	429	430	449	450	463	464	465	Total Tissues/ Tumors
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma, cortex																								1
Leukemia monuc		X						X		X						X								5
Osteosarc, metastatic, bone																			X					1
Pheochrom bgn, medulla										X														2
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	47
Blood vessel, aorta	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	47
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Bone, femur	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Osteosarc																			X					1
Bone, sternum	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	47
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	46
Leukemia monuc		X				X										X								6
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Brain, cerebellum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	47
Brain, cerebrum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Astrocyto mal																X								1
Clitoral gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	41
Adenoma					X						X									X				9
Adenoma, bilateral							X																	1
Carcinoma								X																1
Leukemia monuc						X																		1
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Osteosarc, metastatic, bone																			X					1
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia monuc						X										X								3
Mesothelio mal, metastatic, unc pri site																								1
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	A	+	+	+	+	44
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia monuc						X																		2
Lacrimal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Leukemia monuc		X			X																			2
Larynx	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia monuc		X			X	X		X		X						X								12
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Leukemia monuc		X				X		X																8
Osteosarc, metastatic, bone																			X					1
Lung, bronchus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia monuc					X																			1
Leukemia monuc, renal						X																		1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia monuc		X			X	X		X								X								9
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia monuc		X			X	X		X																8

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Fumonisin B_1: 0 ppm

Carcass ID Number	0 0 7	0 1 7	0 5 3	0 5 7	0 7 5	0 7 9	1 0 1	1 0 5	1 0 8	1 1 0	1 2 2	1 4 1	1 7 5	1 7 6	2 0 6	2 0 8	2 3 3	2 3 4	2 3 5	2 3 6	2 5 4	2 6 2	2 6 3	2 8 7	2 8 8
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma																					X				
Fibroadenoma		X										X	X			X	X			X		X	X	X	X
Fibroadenoma, multiple														X											
Fibroma																									
Mesentery				+					+																
Leukemia monuc									X																
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Gra cl tum bgn																	X								
Leukemia monuc																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia monuc																									
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve, sciatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Adenoma, pars distalis				X		X	X			X		X	X	X		X		X		X	X			X	X
Leukemia monuc																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle, thigh	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarc, metastatic, bone																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma, subcut tiss								X																	
Lipoma, subcut tiss																									
Schwannoma mal, subcut tiss						X																			
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord, thoracic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia monuc				X					X	X	X		X									X			
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia monuc																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+
Leukemia monuc									X				X									X			
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, c cell																									
Adenoma, multiple, c cell																									
Carcinoma, c cell																									X
Tongue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+
Leukemia monuc																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Deciduoma bgn																									
Leiomyosar																					X				
Leukemia monuc																									
Polyp stromal, endometrium			X			X											X				X				
Vagina	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Leukemia monuc																									
Papilloma squa																									X
Zymbal's gland	+	+	+	+	M	+	M	+	+	+	+	+	+	M	M	M	+	+	+	+	M	+	M	+	+

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Fumonisin B_1: 0 ppm

Carcass ID Number	289	304	320	342	343	347	371	372	396	397	423	424	425	426	427	428	429	430	449	450	463	464	465	Total Tissues/ Tumors
Mammary gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma	X																							1
Carcinoma			X																					2
Fibroadenoma										X						X	X	X		X				15
Fibroadenoma, multiple								X															X	3
Fibroma						X																		1
Mesentery																								2
Leukemia monuc																								1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Gra cl tum bgn														X										2
Leukemia monuc						X																		1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia monuc		X																						1
Parathyroid gland	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	44
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	47
Peripheral nerve, sciatic	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	47
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma, pars distalis	X	X	X	X	X	X		X	X	X	X		X	X	X	X	X		X	X		X	X	32
Leukemia monuc						X																		1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Skeletal muscle, thigh	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Osteosarc, metastatic, bone																			X					1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Fibroma, subcut tiss																								1
Lipoma, subcut tiss													X											1
Schwannoma mal, subcut tiss																								1
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spinal cord, thoracic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia monuc		X			X	X		X	X	X						X								13
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia monuc						X																		1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thymus	+	M	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	41
Leukemia monuc						X																		4
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma, c cell								X									X							2
Adenoma, multiple, c cell														X										1
Carcinoma, c cell																								1
Tongue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Leukemia monuc						X																		1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Deciduoma bgn		X																						1
Leiomyosar																								1
Leukemia monuc						X																		1
Polyp stromal, endometrium	X							X	X					X		X		X						10
Vagina	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Leukemia monuc						X																		1
Papilloma squa																								1
Zymbal's gland	+	+	M	+	+	M	+	+	+	M	M	M	+	M	+	M	+	+	+	+	+	+	+	34

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Fumonisin B_1: 5 ppm

Carcass ID Number	008	009	038	039	041	044	052	061	062	100	103	109	135	159	163	169	203	244	245	246	247	248	290	291	308
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								+
Leukemia monuc										X	X														
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								+
Blood vessel, aorta	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								+
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								+
Bone, femur	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								+
Bone, sternum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								+
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								+
Leukemia monuc			X					X		X	X			X											X
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								+
Leukemia monuc											X														
Brain, cerebellum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								+
Brain, cerebrum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								+
Clitoral gland	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+								+
Adenoma																									
Leukemia monuc											X														
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								+
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								+
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								+
Leukemia monuc											X														
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								+
Intestine large, cecum	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								+
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia monuc											X														
Lacrimal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+						+		+
Larynx	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+								+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia monuc			X					X		X	X			X											X
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alv bron aden																									
Leukemia monuc			X					X			X			X											
Lung, bronchus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								+
Leukemia monuc, inguinal																									
Lymph node, mandibular	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								+
Leukemia monuc			X							X	X			X											X
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								+
Leukemia monuc								X		X	X			X											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			+
Carcinoma					X										X					X					
Fibroadenoma							X		X		X	X	X		X			X			X	X			
Fibroadenoma, multiple																X									
Leukemia monuc											X														
Mesentery			+					+			+								+						
Leukemia monuc											X														
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+							+
Leukemia monuc											X														
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								+
Leukemia monuc											X														

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Fumonisin B_1: 5 ppm

Carcass ID Number	335	336	337	338	363	364	365	394	395	400	401	431	432	433	434	Total Tissues/ Tumors
Adrenal gland		+	+													20
Leukemia monuc																2
Blood vessel																18
Blood vessel, aorta																18
Bone																18
Bone, femur																18
Bone, sternum																18
Bone marrow																18
Leukemia monuc																6
Brain																18
Leukemia monuc																1
Brain, cerebellum																18
Brain, cerebrum																18
Clitoral gland		+	+		+											19
Adenoma			X		X											2
Leukemia monuc																1
Esophagus																18
Eye					+		+	+								21
Harderian gland																18
Heart																18
Leukemia monuc																1
Intestine large																18
Intestine large, cecum																16
Intestine large, colon																18
Intestine large, rectum																18
Intestine small																18
Intestine small, duodenum																18
Intestine small, ileum																18
Intestine small, jejunum																18
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Leukemia monuc																1
Lacrimal gland				M						+	+	+				22
Larynx																17
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Leukemia monuc	X	X					X	X	X					X	X	13
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Alv bron aden												X				1
Leukemia monuc	X	X						X	X					X	X	10
Lung, bronchus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Lymph node		+													+	20
Leukemia monuc, inguinal															X	1
Lymph node, mandibular																17
Leukemia monuc																5
Lymph node, mesenteric		+														19
Leukemia monuc		X														5
Mammary gland	+	+		+		+	+									28
Carcinoma																3
Fibroadenoma		X		X												11
Fibroadenoma, multiple						X										2
Leukemia monuc																1
Mesentery														+		5
Leukemia monuc																1
Nose																18
Ovary																19
Leukemia monuc																1
Pancreas																18
Leukemia monuc																1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Fumonisin B_1: 5 ppm

Carcass ID Number	008	009	038	039	041	044	052	061	062	100	103	109	135	159	163	169	203	244	245	246	247	248	290	291	308
Parathyroid gland	+	+	+	+	+	+	M	+	+	M	+	M	+	+	+	+	+								+
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								+
Peripheral nerve, sciatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								+
Pituitary gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+
Adenoma, pars distalis				X	X		X		X				X		X	X	X	X		X	X	X	X		X
Leukemia monuc			X					X			X														
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								+
Leukemia monuc											X														
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								+
Skeletal muscle, thigh	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								+
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								+
Spinal cord, thoracic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				+				+
Leukemia monuc			X					X		X	X			X											X
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								+
Stomach, forestomach	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								+
Leukemia monuc											X														
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								+
Leukemia monuc											X														
Thymus	+	M	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+								+
Leukemia monuc			X					X		X	X														
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								+
Leukemia monuc											X														
Tongue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								+
Urinary bladder	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+								+
Leukemia monuc											X														
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+			+
Leukemia monuc											X														
Polyp stromal, endometrium																X						X			
Sarcoma, cervix												X													
Vagina	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+								+
Leukemia monuc											X														
Zymbal's gland	+	M	+	+	M	+	+	+	+	+	M	+	+	+	M	+	+								+
Carcinoma																									

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Fumonisin B_1: 5 ppm

Carcass ID Number	335	336	337	338	363	364	365	394	395	400	401	431	432	433	434	Total Tissues/ Tumors
Parathyroid gland																15
Peripheral nerve																18
Peripheral nerve, sciatic																18
Pituitary gland	+	+	+	+		+			+					+		30
Adenoma, pars distalis	X	X	X	X		X								X		20
Leukemia monuc																3
Salivary glands																18
Leukemia monuc																1
Skeletal muscle																18
Skeletal muscle, thigh																18
Skin																18
Spinal cord																18
Spinal cord, thoracic																18
Spleen	+	+						+	+					+	+	25
Leukemia monuc	X	X						X	X					X	X	12
Stomach																18
Stomach, forestomach																17
Leukemia monuc																1
Stomach, glandular																18
Leukemia monuc																1
Thymus																15
Leukemia monuc																4
Thyroid gland																18
Leukemia monuc																1
Tongue																18
Trachea																18
Urinary bladder																17
Leukemia monuc																1
Uterus		+						+						+	+	23
Leukemia monuc																1
Polyp stromal, endometrium								X							X	4
Sarcoma, cervix																1
Vagina																17
Leukemia monuc																1
Zymbal's gland									+							15
Carcinoma									X							1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Fumonisin B_1: 15 ppm

Carcass ID Number	027	040	042	043	049	065	070	077	082	092	111	118	121	143	149	152	155	168	177	180	249	250	251	252	264
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+
Leukemia monuc					X						X		X		X	X				X					
Pheochrom bgn, medulla																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+					+
Blood vessel, aorta	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+					+
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+
Bone, femur	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+
Bone, sternum	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+
Bone marrow	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+
Leukemia monuc					X						X		X		X	X	X			X					
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+
Leukemia monuc					X																				
Brain, cerebellum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+
Brain, cerebrum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+
Clitoral gland	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+		+			+
Adenoma				X		X														X		X			X
Adenoma, bilateral																			X						
Leukemia monuc					X																				
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+					+
Leukemia monuc					X																				
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+
Leukemia monuc					X																				
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+
Leukemia monuc					X						X		X		X	X	X								
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+
Leukemia monuc					X																				
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+
Leukemia monuc					X																				
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+
Leukemia monuc					X																				
Schwannoma mal, metastatic, uterus						X																			
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+
Leukemia monuc					X																				
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+
Leukemia monuc					X								X												
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+
Leukemia monuc					X																				
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia monuc					X										X	X	X			X					
Lacrimal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+			+
Leukemia monuc											X					X									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatoclr aden																									
Leukemia monuc					X						X		X		X	X	X			X					
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia monuc					X						X		X		X	X	X			X					
Lung, bronchus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+
Leukemia monuc, pancreatic																X									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+
Leukemia monuc					X						X		X		X	X	X								
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+
Leukemia monuc					X						X		X		X	X	X			X					

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Fumonisin B_1: 15 ppm

Carcass ID Number	266	292	293	294	315	344	345	358	359	367	389	390	391	402	435	436	437	438	466	467	468	469	470	Total Tissues/ Tumors
Adrenal gland	+				+					+														24
Leukemia monuc	X									X														8
Pheochrom bgn, medulla	X																							1
Blood vessel	+				+					+														23
Blood vessel, aorta	+				+					+														23
Bone	+				+					+														24
Bone, femur	+				+					+														24
Bone, sternum	+				+					+														23
Bone marrow	+				+					+														23
Leukemia monuc	X				X					X														10
Brain	+				+					+														24
Leukemia monuc																								1
Brain, cerebellum	+				+					+														24
Brain, cerebrum	+				+					+														24
Clitoral gland	M		+		M			+		+								+			+			25
Adenoma																		X			X			7
Adenoma, bilateral			X																					2
Leukemia monuc																								1
Esophagus	+				+					+														23
Leukemia monuc																								1
Eye	+				+			+	+	+	+		+				+		+		+		+	32
Harderian gland	+				+					+														24
Leukemia monuc																								1
Heart	+				+					+														24
Leukemia monuc																								6
Intestine large	+				+					+														24
Intestine large, cecum	+				+					+														24
Leukemia monuc																								1
Intestine large, colon	+				+					+														24
Leukemia monuc																								1
Intestine large, rectum	+				+					+														24
Leukemia monuc																								1
Schwannoma mal, metastatic, uterus																								1
Intestine small	+				+					+														24
Intestine small, duodenum	+				+					+														24
Leukemia monuc																								1
Intestine small, ileum	+				+					+														24
Leukemia monuc																								2
Intestine small, jejunum	+				+					+														24
Leukemia monuc																								1
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia monuc																				X				6
Lacrimal gland	+				+					+										+				26
Leukemia monuc																				X				3
Larynx	+				+					+														24
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hepatoclr aden																		X						1
Leukemia monuc	X				X		X		X	X								X	X	X				15
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia monuc	X				X													X		X				11
Lung, bronchus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma																			X					1
Lymph node	+				+					+										+				25
Leukemia monuc, pancreatic																								1
Lymph node, mandibular	+				+					+														24
Leukemia monuc	X				X																			8
Lymph node, mesenteric	+				+					+										+				25
Leukemia monuc					X					X										X				10

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Fumonisin B_1: 15 ppm

Carcass ID Number	0 2 7	0 4 0	0 4 2	0 4 3	0 4 9	0 6 5	0 7 0	0 7 7	0 8 2	0 9 2	1 1 1	1 1 8	1 2 1	1 4 3	1 4 9	1 5 2	1 5 5	1 6 8	1 7 0	1 8 0	2 4 9	2 5 0	2 5 1	2 5 2	2 6 4
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			+	+
Adenoma												X													
Carcinoma	X								X									X							
Carcinoma, multiple												X													
Fibroadenoma			X								X			X	X	X			X		X			X	
Fibroadenoma, multiple																									
Leukemia monuc																	X								
Mesentery																+									
Leukemia monuc																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+
Leukemia monuc					X											X	X								
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+
Leukemia monuc					X						X				X	X	X								
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+
Peripheral nerve, sciatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, pars distalis				X		X	X		X	X		X		X	X			X	X	X	X	X	X	X	X
Leukemia monuc					X								X			X	X								
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+
Leukemia monuc					X						X														
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+
Skeletal muscle, thigh	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+
Fibroma, subcut tiss																									
Keratoacanthma																									
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+
Spinal cord, thoracic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+
Leukemia monuc					X						X		X		X	X	X			X					
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+
Leukemia monuc					X												X								
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+
Leukemia monuc					X											X	X								
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+					+
Leukemia monuc					X						X		X		X	X	X			X					
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+
Adenoma, c cell		X				X																			
Carcinoma, c cell																									
Leukemia monuc					X												X								
Tongue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+
Leukemia monuc					X																				
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+
Leukemia monuc					X						X				X	X	X								
Schwannoma mal, metastatic, uterus						X																			
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			+		+
Leukemia monuc					X												X			X					
Polyp stromal, endometrium		X																							
Schwannoma mal						X																			
Vagina	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+
Leukemia monuc					X											X	X								
Polyp																				X					
Schwannoma mal, metastatic, uterus						X																			
Zymbal's gland	+	+	+	+	+	+	+	M	+	M	+	+	+	+	M	+	M	+	M	+					+

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Fumonisin B_1: 15 ppm

Carcass ID Number	266	292	293	294	315	344	345	358	359	367	389	390	391	402	435	436	437	438	466	467	468	469	470	Total Tissues/ Tumors
Mammary gland	+	+			M		+			+	+	+	+	+					+			+		33
Adenoma																								1
Carcinoma																								3
Carcinoma, multiple																								1
Fibroadenoma	X						X						X									X		12
Fibroadenoma, multiple		X									X	X							X					4
Leukemia monuc																								1
Mesentery		+								+							+			+				5
Leukemia monuc																				X				1
Nose	+				+					+														24
Ovary	+				+					+						+								25
Leukemia monuc																								3
Pancreas	+				+					+														24
Leukemia monuc	X																							6
Parathyroid gland	+				+					+														24
Peripheral nerve	+				+					+														24
Peripheral nerve, sciatic	+				+					+														24
Pituitary gland	+	+	+		M	+	+			+				M						+	+	+	+	35
Adenoma, pars distalis		X	X			X	X			X										X	X	X	X	25
Leukemia monuc																								4
Salivary glands	+				+					+										+				25
Leukemia monuc																								2
Skeletal muscle	+				+					+														24
Skeletal muscle, thigh	+				+					+														24
Skin	+				+	+				+					+								+	27
Fibroma, subcut tiss						X																		1
Keratoacanthma																							X	1
Spinal cord	+				+					+														24
Spinal cord, thoracic	+				+					+														24
Spleen	+			+	+		+	+	+	+								+		+				30
Leukemia monuc	X			X	X		X		X	X								X		X				15
Stomach	+				+					+														24
Stomach, forestomach	+				+					+														24
Leukemia monuc																								2
Stomach, glandular	+				+					+														24
Leukemia monuc																								3
Thymus	+				M					M										+				22
Leukemia monuc	X																			X				9
Thyroid gland	+		+		+					+														25
Adenoma, c cell	X																							3
Carcinoma, c cell			X																					1
Leukemia monuc																								2
Tongue	+				+					+														24
Trachea	+				+					+														24
Leukemia monuc																								1
Urinary bladder	+				+					+														24
Leukemia monuc	X																							6
Schwannoma mal, metastatic, uterus																								1
Uterus	+		+		+			+		+						+		+	+					30
Leukemia monuc																								3
Polyp stromal, endometrium	X		X					X								X								5
Schwannoma mal																								1
Vagina	+				+					+										+				25
Leukemia monuc																								3
Polyp																								1
Schwannoma mal, metastatic, uterus																								1
Zymbal's gland	M				+					+														18

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Fumonisin B_1: 50 ppm

Carcass ID Number	010	011	018	031	058	089	090	095	129	136	145	157	173	207	226	227	229	230	231	232	253	255	295	296	297
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+			+				+	+			
Leukemia monuc													X												
Pheochrom bgn, medulla																	X								
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+							+	+			
Blood vessel, aorta	+	+	+	+	+	+	+	+	+	+	+	+	+	+							+	+			
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+							+	+			
Sarcoma, maxilla							X																		
Bone, femur	+	+	+	+	+	+	+	+	+	+	+	+	+	+							+	+			
Bone, sternum	+	+	+	+	+	+	+	+	+	+	+	+	+	+							+	+			
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+							+	+			
Leukemia monuc								X		X			X								X				
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+							+	+			
Brain, cerebellum	+	+	+	+	+	+	+	+	+	+	+	+	+	+							+	+			
Brain, cerebrum	+	+	+	+	+	+	+	+	+	+	+	+	+	+							+	+			
Clitoral gland	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+						+	+			+
Adenoma											X	X			X										X
Esophagus	+	+	+	+	+	+	+	+	+	+	+	I	+	+							+	+			
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+							+	+			
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+							+	+			
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+							+	+			
Leukemia monuc													X												
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+							+	+			
Intestine large, cecum	M	M	+	+	+	+	+	+	+	+	+	+	+	+							+	+			
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+							+	+			
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+							+	+			
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+							+	+			
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+							+	+			
Leiomyosar									X																
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+							+	+			
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+							+	+			
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, renal tubule														X											
Leukemia monuc																								X	
Lacrimal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+							+	+			+
Larynx	+	+	+	+	M	+	+	+	+	+	+	+	+	+							+	+			
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia monuc								X		X			X						X		X			X	
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alv bron aden																		X							
Leukemia monuc								X		X			X								X			X	
Lung, bronchus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+							+	+			
Leukemia monuc													X												
Leukemia monuc, thoracic													X												
Lymph node, mandibular	+	+	+	+	+	+	+	M	+	+	+	+	+	+							+	+			
Leukemia monuc										X			X								X				
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+							+	+			
Leukemia monuc								X		X			X												
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+				+	+	+			
Fibroadenoma					X	X			X											X	X				
Fibroadenoma, multiple																						X			
Mesentery	+																						+		
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+							+	+			
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+							+	+			
Oviduct	+																								
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+							+	+			
Leukemia monuc													X												
Parathyroid gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+							+	+			

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Fumonisin B_1: 50 ppm

Carcass ID Number	298	299	300	313	339	340	341	348	349	350	373	374	375	376	439	440	441	442	471	472	473	474	475	Total Tissues/ Tumors
Adrenal gland				+						+														19
Leukemia monuc				X																				2
Pheochrom bgn, medulla																								1
Blood vessel				+						+														18
Blood vessel, aorta				+						+														18
Bone				+						+														18
Sarcoma, maxilla																								1
Bone, femur				+						+														18
Bone, sternum				+						+														18
Bone marrow				+						+														18
Leukemia monuc				X																				5
Brain				+						+														18
Brain, cerebellum				+						+														18
Brain, cerebrum				+						+														18
Clitoral gland				+			+	+		+		+											+	22
Adenoma							X					X												6
Esophagus				+						+														17
Eye				+						+					+	+	+	+	+			+	+	25
Harderian gland				+						+														18
Heart				+						+														18
Leukemia monuc				X																				2
Intestine large				+						+														18
Intestine large, cecum				+						+														16
Intestine large, colon				+						+														18
Intestine large, rectum				+						+														18
Intestine small				+						+														18
Intestine small, duodenum				+						+														18
Leiomyosar																								1
Intestine small, ileum				+						+														18
Intestine small, jejunum				+						+														18
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma, renal tubule																								1
Leukemia monuc				X				X																3
Lacrimal gland				+						+														19
Larynx				+						+														17
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia monuc				X				X																8
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Alv bron aden																								1
Leukemia monuc				X																				6
Lung, bronchus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node				+						+														18
Leukemia monuc																								1
Leukemia monuc, thoracic																								1
Lymph node, mandibular				+						+														17
Leukemia monuc				X																				4
Lymph node, mesenteric				+						+														18
Leukemia monuc				X																				4
Mammary gland			+	+	+			+		+	+	+				+	+	+				+	+	30
Fibroadenoma					X						X	X				X		X				X		11
Fibroadenoma, multiple			X					X									X						X	5
Mesentery														+										3
Nose				+						+														18
Ovary		+		+	+	+				+					+									22
Oviduct																								1
Pancreas				+						+														18
Leukemia monuc																								1
Parathyroid gland				+						+														17

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Fumonisin B_1: 50 ppm

Carcass ID Number	0 1 0	0 1 1	0 1 8	0 3 1	0 5 8	0 8 9	0 9 0	0 9 5	1 2 9	1 3 6	1 4 5	1 5 7	1 7 3	2 0 7	2 2 6	2 2 7	2 2 9	2 3 0	2 3 1	2 3 2	2 5 3	2 5 5	2 9 5	2 9 6	2 9 7
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	M	+	+							+	+			
Peripheral nerve, sciatic	+	+	+	+	+	+	+	+	+	+	+	M	+	+							+	+			
Pituitary gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+		+		+	+	+	+		+
Adenoma, pars distalis				X						X	X			X	X	X		X		X	X	X	X		
Adenoma, pars intermed																									
Leukemia monuc													X												
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+							+	+			
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+							+	+			
Skeletal muscle, thigh	+	+	+	+	+	+	+	+	+	+	+	+	+	+							+	+			
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+							+	+			
Lipoma, subcut tiss																									
Liposarc, subcut tiss																									
Squam cel carc											X														
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+							+	+			
Spinal cord, thoracic	+	+	+	+	+	+	+	+	+	+	+	+	+	+							+	+			
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+		+	+		+	
Leukemia monuc								X		X			X						X		X			X	
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+							+	+			
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+							+	+			
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+							+	+			
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+							+	+			
Leukemia monuc													X								X				
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+							+	+			+
Carcinoma, c cell																									X
Tongue	+	+	+	+	+	+	+	+	+	+	+	+	+	+							+	+			
Papilloma squa																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+							+	+			
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+							+	+			
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+			+				+	+	+		
Leukemia monuc, cervix													X												
Polyp stromal, endometrium											X						X								
Vagina	+	+	+	+	+	+	+	+	+	+	+	+	+	+							+	+			
Leukemia monuc								X																	
Zymbal's gland	M	+	M	+	+	M	+	+	+	+	+	+	M	+							+	+			
Adenoma									X																

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Fumonisin B_1: 50 ppm

Carcass ID Number	298	299	300	313	339	340	341	348	349	350	373	374	375	376	439	440	441	442	471	472	473	474	475	Total Tissues/ Tumors
Peripheral nerve				+						+														17
Peripheral nerve, sciatic				+						+														17
Pituitary gland	+			+	+	+	+		+	+	+		+		+				+		+	+		34
Adenoma, pars distalis	X			X	X	X	X		X	X			X		X				X		X	X		23
Adenoma, pars intermed											X													1
Leukemia monuc				X																				2
Salivary glands				+						+														18
Skeletal muscle				+						+														18
Skeletal muscle, thigh				+						+														18
Skin				+						+			+			+	+							21
Lipoma, subcut tiss																X	X							2
Liposarc, subcut tiss													X											1
Squam cel carc																								1
Spinal cord				+						+														18
Spinal cord, thoracic				+						+														18
Spleen				+						+											+			21
Leukemia monuc				X																	X			8
Stomach				+						+														18
Stomach, forestomach				+						+														18
Stomach, glandular				+						+														18
Thymus				+						+														18
Leukemia monuc																								2
Thyroid gland				+						+														19
Carcinoma, c cell																								1
Tongue				+		+				+				+										20
Papilloma squa						X								X										2
Trachea				+						+														18
Urinary bladder				+						+														18
Uterus				+						+	+			+				+						23
Leukemia monuc, cervix																								1
Polyp stromal, endometrium											X													3
Vagina				+						+														18
Leukemia monuc				X																				2
Zymbal's gland				+						+														14
Adenoma																								1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Fumonisin B_1: 100 ppm

Carcass ID Number	035	045	067	096	097	119	142	151	161	162	164	165	188	197	202	209	237	238	239	240	241	242	243	261	301
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, cortex																									
Leukemia monuc								X		X		X			X									X	
Pheochrom bgn, medulla											X							X							
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+
Blood vessel, aorta	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bone, femur	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bone, sternum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia monuc		X	X					X		X	X	X			X									X	
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pituitary gland													X												
Leukemia monuc										X															
Brain, cerebellum	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Brain, cerebrum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Meningioma mal																X									
Clitoral gland	M	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+
Adenoma											X					X	X			X				X	
Adenoma, bilateral																						X			
Carcinoma																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia monuc								X																	
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alv bron carc, metastatic, lung															X										
Leukemia monuc		X	X					X		X														X	
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histio sarc, metastatic, skin														X											
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, renal tubule																									
Leukemia monuc		X						X				X												X	
Lacrimal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia monuc			X									X													
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histio sarc, metastatic, skin														X											
Leukemia monuc		X	X					X		X	X	X			X								X	X	
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alv bron aden																									
Alv bron carc															X										
Histio sarc, metastatic, skin														X											
Leukemia monuc			X					X		X		X												X	
Lung, bronchus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia monuc		X	X					X		X		X											X	X	
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia monuc		X	X					X		X		X			X									X	

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Fumonisin B_1: 100 ppm

Carcass ID Number	302	303	314	317	346	360	361	362	392	393	398	399	443	444	445	446	447	448	476	477	478	479	480	Total Tissues/ Tumors
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	47
Adenoma, cortex																			X					1
Leukemia monuc				X																				6
Pheochrom bgn, medulla																								2
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Blood vessel, aorta	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Bone, femur	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Bone, sternum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia monuc				X																	X			10
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma, metastatic, pituitary gland																								1
Leukemia monuc																								1
Brain, cerebellum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Brain, cerebrum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Meningioma mal																								1
Clitoral gland	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	M	+	+	+	+	40
Adenoma			X	X																			X	8
Adenoma, bilateral																		X						2
Carcinoma					X																			1
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia monuc																								1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Alv bron carc, metastatic, lung																								1
Leukemia monuc																								5
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Histio sarc, metastatic, skin																								1
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma, renal tubule													X											1
Leukemia monuc				X																				5
Lacrimal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia monuc				X		X															X		X	6
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Histio sarc, metastatic, skin																								1
Leukemia monuc				X		X			X						X				X		X		X	16
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Alv bron aden		X												X										2
Alv bron carc																								1
Histio sarc, metastatic, skin																								1
Leukemia monuc				X																				6
Lung, bronchus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia monuc						X			X												X			10
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia monuc																								7

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Fumonisin B_1: 100 ppm

Carcass ID Number	035	045	067	096	097	119	142	151	161	162	164	165	188	197	202	209	237	238	239	240	241	242	243	261	301
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																		X							
Fibroadenoma								X													X				
Fibroadenoma, multiple																							X		
Mesentery																	+								
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve, sciatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, pars distalis	X		X	X	X	X			X	X					X		X	X	X	X	X	X			X
Carcinoma, pars distalis													X												
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histio sarc, metastatic, skin														X											
Skeletal muscle, thigh	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma, subcut tiss																			X						
Histio sarc, subcut tiss														X											
Melanoma mal, subcut tiss, head															X										
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord, thoracic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histio sarc, metastatic, skin														X											
Leukemia monuc		X	X					X		X	X	X			X								X	X	
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia monuc										X															
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia monuc										X															
Thymus	+	+	+	+	+	+	+	+	M	+	+	M	+	M	+	+	+	+	+	+	M	+	+	+	M
Leukemia monuc		X	X					X		X														X	
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, c cell							X			X		X													
Carcinoma, c cell																									
Tongue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma, transit epithe									X																
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, endometrium																									
Polyp stromal, endometrium		X						X				X							X	X					
Sarc stromal																									
Vagina	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Leukemia monuc																								X	
Liposarc													X												
Zymbal's gland	+	+	+	+	M	M	+	+	+	+	M	+	+	M	M	M	+	+	+	M	+	+	+	+	+

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Fumonisin B_1: 100 ppm

Carcass ID Number	3 0 2	3 0 3	3 1 4	3 1 7	3 4 6	3 6 0	3 6 1	3 6 2	3 9 2	3 9 3	3 9 8	3 9 9	4 4 3	4 4 4	4 4 5	4 4 6	4 4 7	4 4 8	4 7 6	4 7 7	4 7 8	4 7 9	4 8 0	Total Tissues/ Tumors
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma										X							X							3
Fibroadenoma			X						X			X			X		X		X					8
Fibroadenoma, multiple																				X		X		3
Mesentery	+																							2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Ovary	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	45
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Peripheral nerve, sciatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma, pars distalis	X	X	X	X		X			X	X	X	X	X				X	X			X	X		29
Carcinoma, pars distalis																								1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Histio sarc, metastatic, skin																								1
Skeletal muscle, thigh	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Fibroma, subcut tiss														X										2
Histio sarc, subcut tiss																								1
Melanoma mal, subcut tiss, head																								1
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spinal cord, thoracic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Histio sarc, metastatic, skin																								1
Leukemia monuc				X		X			X						X				X		X		X	16
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia monuc																								1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia monuc																								1
Thymus	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	40
Leukemia monuc																					X		X	7
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma, c cell						X														X		X		6
Carcinoma, c cell																X								1
Tongue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Papilloma, transit epithe																								1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma, endometrium										X														1
Polyp stromal, endometrium										X	X													7
Sarc stromal																							X	1
Vagina	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Leukemia monuc																								1
Liposarc																								1
Zymbal's gland	+	M	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	38

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Feed Study of Fumonisin B_1

	0 ppm	5 ppm	15 ppm	50 ppm	100 ppm
Clitoral Gland: Adenoma					
Overall rate[a]	10/41 (24%)	2/19 (11%)	9/25 (36%)	6/22 (27%)	10/40 (25%)
Adjusted rate[b]	27.8%	17.8%	48.9%	37.0%	27.6%
Terminal rate[c]	5/24 (21%)	2/5 (40%)	4/5 (80%)	4/7 (57%)	5/24 (21%)
First incidence (days)	574	740 (T)	509	642	659
Poly-3 test[d]	P=0.5089N	P=0.3240N	P=0.0967	P=0.3948	P=0.5840
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma					
Overall rate	0/47 (0%)	1/40 (3%)	0/48 (0%)	1/48 (2%)	3/48 (6%)
Adjusted rate	0.0%	3.2%	0.0%	2.5%	7.1%
Terminal rate	0/26 (0%)	1/24 (4%)	0/24 (0%)	1/32 (3%)	2/29 (7%)
First incidence (days)	—[e]	740 (T)	—	740 (T)	680
Poly-3 test	P=0.0340	P=0.4534	—[f]	P=0.5032	P=0.1218
Mammary Gland: Fibroadenoma					
Overall rate	18/47 (38%)	13/28 (46%)	16/33 (49%)	16/30 (53%)	11/48 (23%)
Adjusted rate	43.6%	59.8%	61.8%	67.2%	26.0%
Terminal rate	10/25 (40%)	6/12 (50%)	9/10 (90%)	11/14 (79%)	9/29 (31%)
First incidence (days)	321	498	509	539	673
Poly-3 test	P=0.0112N	P=0.2318	P=0.0914	P=0.0841	P=0.0803N
Mammary Gland: Carcinoma					
Overall rate	2/47 (4%)	3/28 (11%)	4/33 (12%)	0/30 (0%)	3/48 (6%)
Adjusted rate	5.0%	15.1%	15.8%	0.0%	7.2%
Terminal rate	0/25 (0%)	1/12 (8%)	0/10 (0%)	0/14 (0%)	3/29 (10%)
First incidence (days)	706	509	406	—	740 (T)
Poly-3 test	P=0.3600N	P=0.2319	P=0.1487	P=0.3613N	P=0.5147
Mammary Gland: Adenoma or Carcinoma					
Overall rate	3/47 (6%)	3/28 (11%)	4/33 (12%)	0/30 (0%)	3/48 (6%)
Adjusted rate	7.6%	15.1%	15.8%	0.0%	7.2%
Terminal rate	1/25 (4%)	1/12 (8%)	0/10 (0%)	0/14 (0%)	3/29 (10%)
First incidence (days)	706	509	406	—	740 (T)
Poly-3 test	P=0.2642N	P=0.3579	P=0.2561	P=0.2286N	P=0.6481N
Mammary Gland: Fibroadenoma, Adenoma, or Carcinoma					
Overall rate	21/47 (45%)	15/28 (54%)	20/33 (61%)	16/30 (53%)	13/48 (27%)
Adjusted rate	50.5%	66.9%	71.9%	67.2%	30.7%
Terminal rate	11/25 (44%)	7/12 (58%)	9/10 (90%)	11/14 (79%)	11/29 (38%)
First incidence (days)	321	498	406	539	673
Poly-3 test	P=0.0032N	P=0.2285	P=0.0436	P=0.2078	P=0.0578N
Pituitary Gland (Pars Distalis): Adenoma					
Overall rate	32/47 (68%)	20/30 (67%)	25/35 (71%)	23/34 (68%)	29/48 (60%)
Adjusted rate	75.6%	78.6%	83.3%	80.4%	63.6%
Terminal rate	19/26 (73%)	11/15 (73%)	12/12 (100%)	15/19 (79%)	19/29 (66%)
First incidence (days)	574	460	509	400	477
Poly-3 test	P=0.0761N	P=0.5933N	P=0.2375	P=0.5455	P=0.2003N

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Feed Study of Fumonisin B_1

	0 ppm	5 ppm	15 ppm	50 ppm	100 ppm
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma					
Overall rate	32/47 (68%)	20/30 (67%)	25/35 (71%)	23/34 (68%)	30/48 (63%)
Adjusted rate	75.6%	78.6%	83.3%	80.4%	65.4%
Terminal rate	19/26 (73%)	11/15 (73%)	12/12 (100%)	15/19 (79%)	19/29 (66%)
First incidence (days)	574	460	509	400	477
Poly-3 test	P=0.1126N	P=0.5933N	P=0.2375	P=0.5455	P=0.2550N
Skin (Subcutaneous Tissue): Fibroma, Fibrous Histiocytoma, Histiocytic Sarcoma, or Sarcoma					
Overall rate	1/48 (2%)	0/18 (0%)	1/27 (4%)	0/21 (0%)	3/48 (6%)
Adjusted rate	2.4%	0.0%	5.8%	0.0%	7.1%
Terminal rate	0/26 (0%)	0/2 (0%)	1/3 (33%)	0/5 (0%)	2/29 (7%)
First incidence (days)	587	—	740 (T)	—	671
Poly-3 test	P=0.1878	P=0.7444N	P=0.5497	P=0.6956N	P=0.3074
Thyroid Gland (C-cell): Adenoma					
Overall rate	3/48 (6%)	0/18 (0%)	3/25 (12%)	0/19 (0%)	6/48 (13%)
Adjusted rate	7.4%	0.0%	17.9%	0.0%	14.1%
Terminal rate	3/26 (12%)	0/2 (0%)	0/1 (0%)	0/3 (0%)	3/29 (10%)
First incidence (days)	740 (T)	—	453	—	659
Poly-3 test	P=0.1990	P=0.4401N	P=0.2428	P=0.3896N	P=0.2559
Thyroid Gland (C-cell): Adenoma or Carcinoma					
Overall rate	4/48 (8%)	0/18 (0%)	4/25 (16%)	1/19 (5%)	7/48 (15%)
Adjusted rate	9.9%	0.0%	23.9%	9.0%	16.4%
Terminal rate	4/26 (15%)	0/2 (0%)	1/1 (100%)	1/3 (33%)	4/29 (14%)
First incidence (days)	740 (T)	—	453	740 (T)	659
Poly-3 test	P=0.2383	P=0.3563N	P=0.1684	P=0.6243N	P=0.2771
Uterus: Stromal Polyp					
Overall rate	10/47 (21%)	4/23 (17%)	5/30 (17%)	3/23 (13%)	7/48 (15%)
Adjusted rate	24.6%	28.3%	23.6%	19.4%	16.2%
Terminal rate	7/26 (27%)	3/7 (43%)	3/6 (50%)	2/7 (29%)	4/29 (14%)
First incidence (days)	537	659	453	649	477
Poly-3 test	P=0.1723N	P=0.5979	P=0.6056N	P=0.4175N	P=0.2645N
Uterus: Stromal Polyp, Stromal Sarcoma, or Carcinoma					
Overall rate	10/47 (21%)	4/23 (17%)	5/30 (17%)	3/23 (13%)	8/48 (17%)
Adjusted rate	24.6%	28.3%	23.6%	19.4%	18.5%
Terminal rate	7/26 (27%)	3/7 (43%)	3/6 (50%)	2/7 (29%)	5/29 (17%)
First incidence (days)	537	659	453	649	477
Poly-3 test	P=0.2631N	P=0.5979	P=0.6056N	P=0.4175N	P=0.3614N
All Organs: Mononuclear Cell Leukemia					
Overall rate	13/48 (27%)	13/40 (33%)	16/48 (33%)	9/48 (19%)	16/48 (33%)
Adjusted rate	30.6%	39.0%	38.8%	21.8%	35.9%
Terminal rate	6/26 (23%)	7/24 (29%)	6/24 (25%)	4/32 (13%)	7/29 (24%)
First incidence (days)	574	468	495	580	477
Poly-3 test	P=0.4956N	P=0.3354	P=0.2612	P=0.2350N	P=0.3542

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Feed Study of Fumonisin B_1

	0 ppm	5 ppm	15 ppm	50 ppm	100 ppm
All Organs: Benign Neoplasms					
Overall rate	41/48 (85%)	26/40 (65%)	37/48 (77%)	38/48 (79%)	42/48 (88%)
Adjusted rate	89.9%	73.5%	81.9%	86.2%	88.5%
Terminal rate	22/26 (85%)	15/24 (63%)	19/24 (79%)	26/32 (81%)	25/29 (86%)
First incidence (days)	321	460	453	400	477
Poly-3 test	P=0.1454	P=0.0282N	P=0.2859N	P=0.3275N	P=0.6053
All Organs: Malignant Neoplasms					
Overall rate	18/48 (38%)	17/40 (43%)	22/48 (46%)	14/48 (29%)	25/48 (52%)
Adjusted rate	41.6%	49.0%	50.3%	33.0%	55.3%
Terminal rate	7/26 (27%)	8/24 (33%)	7/24 (29%)	6/32 (19%)	13/29 (45%)
First incidence (days)	574	468	406	580	477
Poly-3 test	P=0.2318	P=0.3806	P=0.2439	P=0.2508N	P=0.1168
All Organs: Benign or Malignant Neoplasms					
Overall rate	43/48 (90%)	32/40 (80%)	44/48 (92%)	43/48 (90%)	46/48 (96%)
Adjusted rate	92.5%	85.5%	92.8%	95.0%	95.8%
Terminal rate	22/26 (85%)	17/24 (71%)	21/24 (88%)	28/32 (88%)	27/29 (93%)
First incidence (days)	321	460	406	400	477
Poly-3 test	P=0.0788	P=0.1774N	P=0.4964	P=0.5927	P=0.2681

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined microscopically
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence is the P value associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. For all tissues except the lung, only the pairwise comparisons between the 100 ppm group and control group are unbiased; overall rates and all other pairwise comparisons may not be valid. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in an exposure group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group
[f] Value of statistic cannot be computed.

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of Fumonisin B_1[a]

	0 ppm	5 ppm	15 ppm	50 ppm	100 ppm
Disposition Summary					
6-Week evaluation	4	4	4	4	4
10-Week evaluation	4	4	4	4	4
14-Week evaluation	4	4	4	4	4
26-Week evaluation	4	4	4	4	4
Animals initially in 2-year study	48	40	48	48	48
Early deaths					
Removed from study	1	2		2	
Moribund	20	15	23	16	16
Natural deaths	2	1	1		3
Survivors					
Terminal sacrifice	25	22	24	30	29
Animals examined microscopically	64	56	64	64	64
6-Week Evaluation					
Kidney	(4)	(4)	(4)	(4)	(4)
Mineralization	4 (100%)	4 (100%)	4 (100%)	4 (100%)	4 (100%)
Liver	(4)	(4)	(4)	(4)	(4)
Hyperplasia, bile duct	2 (50%)				
Inflammation, chronic		1 (25%)		2 (50%)	1 (25%)
Vacuoliz cyto, focal	1 (25%)				
10-Week Evaluation					
Kidney	(4)	(4)	(4)	(4)	(4)
Mineralization	4 (100%)	4 (100%)	4 (100%)	4 (100%)	4 (100%)
Liver	(4)	(4)	(4)	(4)	(4)
Develop malfor	1 (25%)	1 (25%)			
Hyperplasia, bile duct		3 (75%)		1 (25%)	1 (25%)
Inflammation, chronic		1 (25%)		1 (25%)	
Vacuoliz cyto, focal				1 (25%)	
Mesentery	(1)			(1)	
Necrosis, focal, fat	1 (100%)			1 (100%)	
Ovary					(1)
Cyst					1 (100%)
14-Week Evaluation					
Intestine large				(1)	
Hemorrhage, focal, cecum, submucosa				1 (100%)	
Kidney	(4)	(4)	(4)	(4)	(4)
Mineralization	4 (100%)	4 (100%)	4 (100%)	4 (100%)	4 (100%)
Liver	(4)	(4)	(4)	(4)	(4)
Hyperplasia, bile duct			1 (25%)	1 (25%)	
Inflammation, chronic	1 (25%)	2 (50%)	3 (75%)	2 (50%)	2 (50%)
Vacuoliz cyto, focal					1 (25%)
Ovary	(1)				(1)
Cyst	1 (100%)				1 (100%)
Uterus	(1)	(1)	(1)	(1)	
Dilatation	1 (100%)	1 (100%)	1 (100%)	1 (100%)	
Inflammation, chronic		1 (100%)			

[a] Number of animals examined microscopically at the site and the number of animals with lesion

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of Fumonisin B_1

	0 ppm	5 ppm	15 ppm	50 ppm	100 ppm
26-Week Evaluation					
Kidney	(4)	(4)	(4)	(4)	(4)
Mineralization	4 (100%)	4 (100%)	4 (100%)	4 (100%)	4 (100%)
Nephropathy					1 (25%)
Liver	(4)	(4)	(4)	(4)	(4)
Develop malfor			1 (25%)		1 (25%)
Hyperplasia, bile duct	1 (25%)	3 (75%)	4 (100%)	3 (75%)	1 (25%)
Infiltrate cell, mixed cell, focal, serosa			2 (50%)		
Inflammation, chronic	2 (50%)	2 (50%)	2 (50%)	4 (100%)	3 (75%)
Vacuolz cyto, focal					1 (25%)
Uterus		(1)			(1)
Dilatation		1 (100%)			1 (100%)
Inflammation, chronic					1 (100%)

Tissues Examined with No Lesions Observed
Ovary

	0 ppm	5 ppm	15 ppm	50 ppm	100 ppm
2-Year Study					
Adrenal gland	(48)	(20)	(24)	(19)	(47)
Angiectasis, bilateral, cortex	16 (33%)	1 (5%)	2 (8%)	2 (11%)	16 (34%)
Angiectasis, cortex	1 (2%)			1 (5%)	1 (2%)
Cyst, cortex				1 (5%)	
Hema cell prol					1 (2%)
Hyperplasia, focal, cortex	2 (4%)			2 (11%)	4 (9%)
Hyperplasia, focal, medulla	2 (4%)		1 (4%)	1 (5%)	4 (9%)
Hypertrophy, focal, cortex					1 (2%)
Infiltrat cell, lymphocytic					1 (2%)
Infiltrat cell, lymphocytic, bilateral					1 (2%)
Inflammation, chronic, cortex		1 (5%)			
Necrosis, cortex	1 (2%)				
Pigment, bilateral, cortex	1 (2%)		1 (4%)		
Vacuoliz cyto, diffuse, bilateral, cortex		2 (10%)			
Vacuoliz cyto, diffuse, cortex		1 (5%)			
Vacuoliz cyto, focal, bilateral, cortex	3 (6%)			1 (5%)	1 (2%)
Vacuoliz cyto, focal, cortex	2 (4%)	4 (20%)	3 (13%)	1 (5%)	6 (13%)
Bone	(48)	(18)	(24)	(18)	(48)
Cyst, mandible			1 (4%)		
Hyperostosis, turbinate	6 (13%)	1 (6%)	2 (8%)		5 (10%)
Inflammation, chronic, joint					1 (2%)
Bone, femur	(48)	(18)	(24)	(18)	(48)
Hyperostosis	19 (40%)	7 (39%)	9 (38%)	5 (28%)	22 (46%)
Bone, sternum	(47)	(18)	(23)	(18)	(48)
Hyperostosis	19 (40%)	7 (39%)	8 (35%)	5 (28%)	22 (46%)
Bone marrow	(46)	(18)	(23)	(18)	(48)
Depletion	1 (2%)	1 (6%)	1 (4%)	1 (6%)	1 (2%)
Hyperplasia	11 (24%)	6 (33%)	4 (17%)	3 (17%)	8 (17%)
Myelofibrosis	1 (2%)	2 (11%)			1 (2%)
Brain	(48)	(18)	(24)	(18)	(48)
Compression, hypothalamus	9 (19%)	4 (22%)	8 (33%)	3 (17%)	8 (17%)
Hydrocephalus	1 (2%)			1 (6%)	

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of Fumonisin B_1

	0 ppm		5 ppm		15 ppm		50 ppm		100 ppm	
2-Year Study (continued)										
Clitoral gland	(41)		(19)		(25)		(22)		(40)	
Cyst			1	(5%)			2	(9%)	2	(5%)
Hyperplasia, focal	1	(2%)	1	(5%)	1	(4%)	1	(5%)	3	(8%)
Inflammation, acute									1	(3%)
Inflammation, acute, bilateral									1	(3%)
Inflammation, chronic	4	(10%)	1	(5%)					6	(15%)
Inflammation, chronic active	1	(2%)			2	(8%)	1	(5%)		
Inflammation, chronic active, bilateral	1	(2%)								
Eye	(48)		(21)		(32)		(25)		(48)	
Atrophy, bilateral, retina	22	(46%)	7	(33%)	20	(63%)	18	(72%)	27	(56%)
Atrophy, retina	5	(10%)	5	(24%)	2	(6%)	1	(4%)	9	(19%)
Cataract, bilateral, lens	13	(27%)	5	(24%)	10	(31%)	8	(32%)	18	(38%)
Cataract, lens	3	(6%)	1	(5%)	1	(3%)	1	(4%)	1	(2%)
Inflammation, chronic, bilateral, cornea									1	(2%)
Inflammation, chronic, cornea	1	(2%)					1	(4%)		
Harderian gland	(48)		(18)		(24)		(18)		(48)	
Atrophy, focal					1	(4%)	1	(6%)		
Hyperplasia, focal									1	(2%)
Infiltrat cell, lymphocytic	19	(40%)	5	(28%)	8	(33%)	6	(33%)	15	(31%)
Infiltrat cell, lymphocytic, bilateral	9	(19%)	7	(39%)	6	(25%)	4	(22%)	17	(35%)
Inflammation, chronic	2	(4%)	1	(6%)						
Inflammation, chronic, bilateral	3	(6%)	2	(11%)	3	(13%)	2	(11%)	4	(8%)
Heart	(48)		(18)		(24)		(18)		(48)	
Cardiomyopathy	38	(79%)	8	(44%)	11	(46%)	8	(44%)	35	(73%)
Cardiomyopathy, multifocal									1	(2%)
Inflammation, chronic, valve	1	(2%)								
Mineralization			1	(6%)						
Thrombus, atrium			1	(6%)						
Intestine small, ileum	(44)		(18)		(24)		(18)		(46)	
Inflammation, chronic	1	(2%)								
Kidney	(48)		(40)		(48)		(48)		(48)	
Acc hyaline d, bilateral, renal tubule	1	(2%)	1	(3%)	1	(2%)	1	(2%)	1	(2%)
Cyst			3	(8%)					1	(2%)
Hydronephrosis, bilateral			1	(3%)						
Hyperplasia, focal, bilateral, renal tubule									1	(2%)
Hyperplasia, focal, pelvis, transit epithe	1	(2%)								
Hyperplasia, focal, renal tubule			1	(3%)	1	(2%)	2	(4%)	2	(4%)
Hyperplasia, pelvis, transit epithe	1	(2%)			1	(2%)				
Infarct	1	(2%)								
Infarct, chronic							1	(2%)		
Infiltrat cell, lymphocytic							1	(2%)		
Inflammation, acute, pelvis							1	(2%)		
Inflammation, chronic, artery	1	(2%)			1	(2%)				
Inflammation, chronic, bilateral, artery							1	(2%)		
Inflammation, chronic, pelvis							1	(2%)		
Mineralization			2	(5%)	1	(2%)	2	(4%)	3	(6%)
Mineralization, bilateral	48	(100%)	37	(93%)	46	(96%)	42	(88%)	42	(88%)
Necrosis, bilateral, renal tubule			1	(3%)						
Nephropathy			2	(5%)	1	(2%)				
Nephropathy, bilateral	41	(85%)	20	(50%)	34	(71%)	23	(48%)	35	(73%)
Pigment, bilateral, renal tubule	6	(13%)	16	(40%)	6	(13%)	4	(8%)	1	(2%)
Pigment, renal tubule			1	(3%)	1	(2%)			2	(4%)
Lacrimal gland	(47)		(22)		(26)		(19)		(48)	
Atrophy, focal	1	(2%)			1	(4%)			1	(2%)
Cytoplas alter	1	(2%)	1	(5%)						
Infiltrat cell, lymphocytic	26	(55%)	14	(64%)	10	(38%)	12	(63%)	23	(48%)
Proliferation, focal, duct	1	(2%)								

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of Fumonisin B_1

	0 ppm	5 ppm	15 ppm	50 ppm	100 ppm
2-Year Study (continued)					
Larynx	(46)	(17)	(24)	(17)	(47)
Foreign body		1 (6%)			
Hyperplasia, epithelium	1 (2%)				
Inflammation, acute	1 (2%)		1 (4%)		
Inflammation, chronic	5 (11%)	3 (18%)	1 (4%)	3 (18%)	
Inflammation, chronic active	3 (7%)				1 (2%)
Liver	(48)	(40)	(48)	(48)	(48)
Angiectasis, focal	1 (2%)	1 (3%)	2 (4%)		1 (2%)
Basoph focus	35 (73%)	26 (65%)	31 (65%)	37 (77%)	40 (83%)
Basoph focus, multiple			1 (2%)	1 (2%)	
Clear cl focus	4 (8%)	5 (13%)	6 (13%)	6 (13%)	5 (10%)
Eosin focus	7 (15%)	3 (8%)	11 (23%)	11 (23%)	4 (8%)
Hdn	5 (10%)	6 (15%)	6 (13%)	3 (6%)	8 (17%)
Hema cell prol	3 (6%)	3 (8%)	1 (2%)	1 (2%)	
Hyperplasia, bile duct	20 (42%)	20 (50%)	23 (48%)	21 (44%)	21 (44%)
Hyperplasia, nodular, focal, hepatocyte				1 (2%)	
Inflammation, chronic	17 (35%)	17 (43%)	18 (38%)	28 (58%)	26 (54%)
Mixed cl focus	19 (40%)	12 (30%)	11 (23%)	17 (35%)	16 (33%)
Necrosis		1 (3%)	1 (2%)		2 (4%)
Pigment	1 (2%)				
Tension lipoid	13 (27%)	8 (20%)	18 (38%)	16 (33%)	15 (31%)
Vacuoliz cyto, hepatocyte	7 (15%)	7 (18%)	7 (15%)	6 (13%)	12 (25%)
Lung	(47)	(40)	(48)	(48)	(48)
Congestion		1 (3%)			
Foreign body	1 (2%)				
Hyperplasia, focal, alveolar epith		2 (5%)	1 (2%)	2 (4%)	2 (4%)
Infiltrat cell, histiocytic	2 (4%)	2 (5%)	4 (8%)	2 (4%)	2 (4%)
Inflammation, chronic active, interstitium	1 (2%)				
Inflammation, chronic, interstitium	1 (2%)	3 (8%)	2 (4%)	1 (2%)	1 (2%)
Inflammation, granulomatous	1 (2%)				
Metapl, osseous	1 (2%)		1 (2%)	1 (2%)	
Lymph node	(48)	(20)	(25)	(18)	(48)
Hyperplasia, lymphoid, deep cervical				1 (6%)	
Lymph node, mandibular	(48)	(17)	(24)	(17)	(48)
Atrophy		1 (6%)			
Degen, cystic	2 (4%)	1 (6%)	2 (8%)	2 (12%)	2 (4%)
Hemorrhage	1 (2%)		1 (4%)		
Hyperplasia, lymphoid	7 (15%)	1 (6%)	5 (21%)	3 (18%)	4 (8%)
Lymph node, mesenteric	(48)	(19)	(25)	(18)	(48)
Atrophy		1 (5%)			
Degen, cystic	1 (2%)	2 (11%)		1 (6%)	
Hemorrhage	3 (6%)	1 (5%)		2 (11%)	2 (4%)
Hyperplasia, lymphoid		1 (5%)	1 (4%)		1 (2%)
Infiltrat cell, histiocytic	37 (77%)	11 (58%)	16 (64%)	12 (67%)	32 (67%)
Mammary gland	(47)	(28)	(33)	(30)	(48)
Cyst	12 (26%)	4 (14%)	6 (18%)	4 (13%)	12 (25%)
Galactocele	10 (21%)	4 (14%)	4 (12%)	5 (17%)	11 (23%)
Hyperplasia, epithelium				1 (3%)	2 (4%)
Hyperplasia, focal, epithelium	2 (4%)	1 (4%)			
Mesentery	(2)	(5)	(5)	(3)	(2)
Necrosis, fat	1 (50%)	4 (80%)	4 (80%)	3 (100%)	2 (100%)

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of Fumonisin B_1

	0 ppm		5 ppm		15 ppm		50 ppm		100 ppm	
2-Year Study (continued)										
Nose	(47)		(18)		(24)		(18)		(48)	
Cytoplas alter, olfactory epi	24	(51%)	7	(39%)	13	(54%)	4	(22%)	19	(40%)
Foreign body	1	(2%)							1	(2%)
Inflammation, acute							1	(6%)		
Inflammation, acute, nasolacrim dct	2	(4%)	1	(6%)					2	(4%)
Inflammation, chronic							1	(6%)	1	(2%)
Inflammation, chronic active	3	(6%)			1	(4%)			1	(2%)
Inflammation, chronic active, nasolacrim dct	8	(17%)	4	(22%)	5	(21%)	5	(28%)	11	(23%)
Inflammation, chronic, nasolacrim dct	4	(9%)	2	(11%)	5	(21%)	1	(6%)	5	(10%)
Metapl, olfactory epi			1	(6%)						
Ovary	(47)		(19)		(25)		(22)		(47)	
Cyst, bilateral, periovarn tiss									1	(2%)
Cyst, follicle	1	(2%)	1	(5%)	2	(8%)	1	(5%)	2	(4%)
Cyst, periovarn tiss	1	(2%)	2	(11%)			2	(9%)	1	(2%)
Hyperplasia, rete ovarii			1	(5%)	2	(8%)				
Inflammation, chronic, bilateral							1	(5%)		
Oviduct							(1)			
Cyst							1	(100%)		
Pancreas	(48)		(18)		(24)		(18)		(48)	
Atrophy, diffuse, acinar cell	1	(2%)					1	(6%)	1	(2%)
Atrophy, focal, acinar cell	15	(31%)	5	(28%)	6	(25%)	5	(28%)	24	(50%)
Hyperplasia, focal					1	(4%)				
Hyperplasia, focal, acinar cell	2	(4%)	1	(6%)						
Infiltrat cell, lymphocytic	1	(2%)	1	(6%)	1	(4%)	1	(6%)		
Inflammation, chronic	1	(2%)								
Inflammation, chronic, artery									1	(2%)
Pituitary gland	(47)		(30)		(35)		(34)		(48)	
Angiectasis, pars distalis	2	(4%)	1	(3%)						
Atypical cells, pars nervosa							1	(3%)		
Cyst, pars distalis	6	(13%)	7	(23%)	3	(9%)	4	(12%)	5	(10%)
Hyperplasia, focal, pars distalis			2	(7%)					4	(8%)
Hypertrophy, focal, pars distalis	1	(2%)							1	(2%)
Inflammation, chronic, pars distalis							1	(3%)		
Salivary glands	(48)		(18)		(25)		(18)		(48)	
Atrophy			1	(6%)						
Atrophy, parotid gland	3	(6%)			3	(12%)	2	(11%)	2	(4%)
Atrophy, submandibul gland	1	(2%)								
Cytoplas alter, focal	1	(2%)								
Cytoplas alter, focal, parotid gland									1	(2%)
Hyperplasia, focal, parotid gland			1	(6%)						
Mineralization, parotid gland	1	(2%)								
Skeletal muscle, thigh	(48)		(18)		(24)		(18)		(48)	
Atrophy	1	(2%)								
Degen					2	(8%)				
Inflammation, chronic									1	(2%)
Mineralization			1	(6%)						
Skin	(48)		(18)		(27)		(21)		(48)	
Cyst epith inc					2	(7%)	1	(5%)		
Hyperplasia, epidermis					1	(4%)			1	(2%)
Inflammation, chronic			1	(6%)	2	(7%)	1	(5%)		
Inflammation, chronic active	1	(2%)	1	(6%)						
Ulcer			1	(6%)						

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of Fumonisin B_1

	0 ppm	5 ppm	15 ppm	50 ppm	100 ppm
2-Year Study (continued)					
Spleen	(48)	(25)	(30)	(21)	(48)
Atrophy, lymph follic		1 (4%)			1 (2%)
Cyst, capsule				1 (5%)	
Hema cell prol	11 (23%)	5 (20%)	7 (23%)	4 (19%)	7 (15%)
Hyperplasia, focal, lymph follic		1 (4%)			
Inflammation, chronic					1 (2%)
Pigment	16 (33%)	4 (16%)	5 (17%)	4 (19%)	19 (40%)
Stomach, forestomach	(48)	(17)	(24)	(18)	(48)
Edema			1 (4%)		
Erosion, focal		1 (6%)	1 (4%)	1 (6%)	
Hyperplasia, epithelium	4 (8%)	3 (18%)	2 (8%)	4 (22%)	3 (6%)
Inflammation, chronic	2 (4%)	3 (18%)	2 (8%)	3 (17%)	
Ulcer	1 (2%)				
Stomach, glandular	(48)	(18)	(24)	(18)	(48)
Cyst	9 (19%)	7 (39%)	7 (29%)	1 (6%)	6 (13%)
Erosion, focal		2 (11%)	1 (4%)		
Fibrosis					1 (2%)
Inflammation, chronic, serosa	1 (2%)				
Thymus	(41)	(15)	(22)	(18)	(40)
Atrophy	10 (24%)	2 (13%)		1 (6%)	2 (5%)
Cyst	2 (5%)		1 (5%)	3 (17%)	2 (5%)
Ect parathyr					1 (3%)
Hemorrhage		1 (7%)	1 (5%)		
Hyperplasia, lymphoid			3 (14%)		
Thyroid gland	(48)	(18)	(25)	(19)	(48)
Cyst, follicle	1 (2%)				
Hyperplasia, diffuse, c cell	1 (2%)		1 (4%)		
Hyperplasia, focal, c cell	6 (13%)	5 (28%)	5 (20%)	1 (5%)	11 (23%)
Hyperplasia, follicle	1 (2%)				1 (2%)
Tongue	(48)	(18)	(24)	(20)	(48)
Infiltrat cell, mast cell					1 (2%)
Inflammation, chronic, artery	1 (2%)				
Mineralization		1 (6%)			
Trachea	(48)	(18)	(24)	(18)	(48)
Hyperplasia, epithelium	1 (2%)	1 (6%)			
Inflammation, chronic	4 (8%)			1 (6%)	
Inflammation, chronic active	1 (2%)				
Urinary bladder	(45)	(17)	(24)	(18)	(47)
Infiltrat cell, lymphocytic	1 (2%)	1 (6%)			3 (6%)
Uterus	(47)	(23)	(30)	(23)	(48)
Atrophy		1 (4%)			
Cyst, endometrium	4 (9%)	1 (4%)	1 (3%)	2 (9%)	2 (4%)
Fibrosis				1 (4%)	
Hemorrhage	2 (4%)				
Hemorrhage, endometrium					1 (2%)
Hydrometra	3 (6%)	4 (17%)	1 (3%)	3 (13%)	3 (6%)
Hydrometra, bilateral				1 (4%)	
Hyperplasia, cervix, epithelium		1 (4%)			
Hypertrophy, cervix				1 (4%)	1 (2%)
Inflammation, chronic active, endometrium		1 (4%)		1 (4%)	
Inflammation, chronic, endometrium	1 (2%)				
Necrosis, endometrium			1 (3%)		
Prolapse	1 (2%)	1 (4%)			1 (2%)

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of Fumonisin B_1

	0 ppm	5 ppm	15 ppm	50 ppm	100 ppm
2-Year Study (continued)					
Vagina	(47)	(17)	(25)	(18)	(47)
Fibrosis, focal					1 (2%)
Hyperplasia, epithelium					1 (2%)
Inflammation, acute			1 (4%)		1 (2%)
Inflammation, chronic active				1 (6%)	
Inflammation, chronic, muscularis			1 (4%)		

APPENDIX C
SUMMARY OF LESIONS IN MALE MICE IN THE 2-YEAR FEED STUDY OF FUMONISIN B_1

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of Fumonisin B_1[a]

	0 ppm		5 ppm		15 ppm		80 ppm		150 ppm	
Disposition Summary										
3-Week evaluation	4		4		4		4		4	
7-Week evaluation	4		4		4		4		4	
9-Week evaluation	4		4		4		4		4	
24-Week evaluation	4		4		4		4		4	
Animals initially in 2-year study	48		48		48		48		48	
Early deaths										
Removed from study			1							
Moribund	4		3		1		5		4	
Natural deaths	3		5		2		6		2	
Survivors										
Terminal sacrifice	41		39		45		37		42	
Animals examined microscopically	64		64		64		64		64	

Tissues Examined at 3 Weeks with No Neoplasms Observed
Kidney
Liver

Tissues Examined at 7 Weeks with No Neoplasms Observed
Kidney
Liver
Preputial gland
Seminal vesicle

Tissues Examined at 9 and 24 Weeks with No Neoplasms Observed
Kidney
Liver
Preputial gland

2-Year Study

	0 ppm		5 ppm		15 ppm		80 ppm		150 ppm	
Adrenal gland	(46)		(8)		(1)		(9)		(48)	
Lymph mal	1	(2%)							1	(2%)
Pheochrom bgn	1	(2%)								
Blood vessel, aorta	(46)		(9)		(3)		(11)		(48)	
Lymph mal			1	(11%)			1	(9%)		
Bone, femur	(48)		(9)		(2)		(11)		(48)	
Histio sarc							1	(9%)		
Lymph mal	1	(2%)					1	(9%)	2	(4%)
Bone, sternum	(47)		(9)		(2)		(11)		(48)	
Histio sarc							1	(9%)		
Lymph mal	1	(2%)	1	(11%)			1	(9%)	1	(2%)
Bone marrow	(47)		(9)		(2)		(11)		(47)	
Hemangiosarc, metastatic, spleen							1	(9%)		
Histio sarc					1	(50%)	2	(18%)	1	(2%)
Lymph mal	1	(2%)	1	(11%)			1	(9%)	2	(4%)
Brain, cerebellum	(47)		(8)		(2)		(8)		(46)	
Lymph mal			1	(13%)						

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of Fumonisin B_1

	0 ppm		5 ppm		15 ppm		80 ppm		150 ppm	
2-Year Study (continued)										
Brain, cerebrum	(47)		(9)		(2)		(10)		(48)	
Lymph mal			1	(11%)						
Coagulating gland	(46)		(7)		(1)		(10)		(47)	
Lymph mal	1	(2%)					1	(10%)	1	(2%)
Ear	(45)		(5)		(2)		(9)		(48)	
Lymph mal	1	(2%)								
Epididymis	(48)		(8)		(2)		(8)		(48)	
Adenoma, interstit cell					1	(50%)				
Histio sarc							1	(13%)		
Lymph mal	2	(4%)					1	(13%)	1	(2%)
Eye	(44)		(6)		(1)		(7)		(45)	
Lymph mal	1	(2%)								
Gallbladder	(40)		(3)		(1)		(7)		(42)	
Lymph mal	1	(3%)					1	(14%)		
Harderian gland	(46)		(8)		(1)		(9)		(44)	
Adenoma	1	(2%)							5	(11%)
Carcinoma			1	(13%)						
Lymph mal	1	(2%)					1	(11%)	2	(5%)
Heart	(48)		(9)		(3)		(11)		(48)	
Lymph mal			1	(11%)			1	(9%)		
Intestine large, cecum	(46)		(5)		(1)		(6)		(46)	
Lymph mal									1	(2%)
Intestine large, colon	(46)		(6)		(1)		(8)		(46)	
Lymph mal	1	(2%)							1	(2%)
Intestine large, rectum	(45)		(8)		(1)		(7)		(47)	
Lymph mal	1	(2%)								
Intestine small, ileum	(46)		(6)		(1)		(7)		(46)	
Lymph mal							1	(14%)	1	(2%)
Kidney	(47)		(48)		(45)		(47)		(48)	
Histio sarc							1	(2%)		
Lymph mal	1	(2%)	2	(4%)			2	(4%)	3	(6%)
Lacrimal gland	(44)		(8)		(2)		(8)		(47)	
Lymph mal	2	(5%)							1	(2%)
Liver	(47)		(47)		(48)		(48)		(48)	
Hemangiosarc			1	(2%)			1	(2%)		
Hepatoclr aden	9	(19%)	7	(15%)	7	(15%)	6	(13%)	8	(17%)
Hepatoclr carc	4	(9%)	3	(6%)	4	(8%)	3	(6%)	2	(4%)
Histio sarc					1	(2%)	2	(4%)	1	(2%)
Ito cl tm mal			1	(2%)						
Lymph mal	1	(2%)	1	(2%)			1	(2%)	4	(8%)
Lung	(48)		(9)		(2)		(11)		(48)	
Adenocarc, multiple									1	(2%)
Alv bron aden	6	(13%)							6	(13%)
Histio sarc					1	(50%)	2	(18%)	1	(2%)
Lymph mal	3	(6%)	1	(11%)			1	(9%)	2	(4%)
Lymph node	(48)		(9)		(3)		(15)		(48)	
Lymph mal, inguinal							1	(7%)		
Lymph node, mandibular	(46)		(8)		(2)		(10)		(48)	
Fibrosarc, metastatic, skin	1	(2%)								
Histio sarc									1	(2%)
Lymph mal	3	(7%)					1	(10%)	3	(6%)
Lymph node, mesenteric	(48)		(7)		(3)		(15)		(45)	
Histio sarc					1	(33%)	2	(13%)	1	(2%)
Lymph mal	4	(8%)			1	(33%)	5	(33%)	5	(11%)

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of Fumonisin B_1

	0 ppm		5 ppm		15 ppm		80 ppm		150 ppm	
2-Year Study (continued)										
Mammary gland	(4)		(2)				(1)		(10)	
Lymph mal	1	(25%)							1	(10%)
Nose	(48)		(9)		(1)		(11)		(48)	
Histio sarc							1	(9%)		
Lymph mal	2	(4%)	1	(11%)			1	(9%)	4	(8%)
Pancreas	(47)		(8)		(1)		(10)		(47)	
Lymph mal	1	(2%)					1	(10%)	2	(4%)
Peripheral nerve	(46)		(8)		(3)		(11)		(46)	
Lymph mal	1	(2%)							1	(2%)
Preputial gland	(46)		(9)		(4)		(17)		(46)	
Lymph mal	1	(2%)					1	(6%)	1	(2%)
Prostate	(46)		(8)				(10)		(47)	
Lymph mal	2	(4%)					1	(10%)		
Salivary glands	(48)		(11)		(1)		(10)		(48)	
Fibrosarc, metastatic, skin	2	(4%)								
Lymph mal	2	(4%)	1	(9%)			1	(10%)	5	(10%)
Seminal vesicle	(46)		(8)		(1)		(9)		(47)	
Lymph mal	1	(2%)					1	(11%)		
Skeletal muscle	(47)		(9)		(2)		(12)		(48)	
Fibrosarc							1	(8%)		
Fibrosarc, metastatic, thoracic, skin									1	(2%)
Skin	(48)		(11)		(7)		(14)		(47)	
Fib histiocyt			1	(9%)						
Fibroma							1	(7%)		
Fibrosarc	5	(10%)	1	(9%)	5	(71%)	4	(29%)	5	(11%)
Hemangioma			1	(9%)						
Lymph mal							1	(7%)	1	(2%)
Sarcoma	1	(2%)								
Squam cel carc			1	(9%)						
Spleen	(47)		(8)		(1)		(13)		(48)	
Hemangiosarc							1	(8%)		
Histio sarc							2	(15%)	1	(2%)
Lymph mal	2	(4%)					3	(23%)	6	(13%)
Stomach, forestomach	(47)		(7)		(1)		(11)		(48)	
Lymph mal	1	(2%)					1	(9%)		
Papilloma squa	1	(2%)					1	(9%)		
Stomach, glandular	(45)		(7)		(2)		(10)		(45)	
Adenocarc					1	(50%)				
Lymph mal	1	(2%)								
Testes	(48)		(9)		(1)		(12)		(48)	
Histio sarc							1	(8%)		
Thymus	(33)		(6)		(2)		(7)		(26)	
Lymph mal			1	(17%)			1	(14%)	2	(8%)
Thyroid gland	(44)		(7)		(1)		(7)		(46)	
Lymph mal							1	(14%)		
Trachea	(40)		(7)		(1)		(9)		(43)	
Lymph mal							1	(11%)		
Urinary bladder	(46)		(9)				(10)		(46)	
Lymph mal	3	(7%)					1	(10%)	4	(9%)
Zymbal's gland	(31)		(5)		(2)		(8)		(34)	
Lymph mal							1	(13%)		

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of Fumonisin B_1

	0 ppm	5 ppm	15 ppm	80 ppm	150 ppm
Neoplasm Summary					
Total animals with primary neoplasms[b]					
2-Year study	24	16	16	21	27
Total primary neoplasms					
2-Year study	73	30	23	71	91
Total animals with benign neoplasms					
2-Year study	15	8	8	8	17
Total benign neoplasms					
2-Year study	18	8	8	8	19
Total animals with malignant neoplasms					
2-Year study	13	10	11	16	16
Total malignant neoplasms					
2-Year study	55	22	15	63	72
Total animals with metastatic neoplasms					
2-Year study	2			1	1
Total metastatic neoplasms					
2-Year study	3			1	1

[a] Number of animals examined microscopically at the site and the number of animals with neoplasm
[b] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Fumonisin B_1: 0 ppm

Carcass ID Number	0 0 6	0 2 6	0 3 5	0 4 5	0 6 9	0 7 3	0 8 0	1 0 2	1 0 3	1 0 4	1 0 5	1 0 6	1 0 7	1 0 8	1 6 6	1 6 7	1 6 8	1 6 9	2 0 1	2 0 2	2 0 3	2 0 4	2 4 0	2 4 1	2 4 2
Adrenal gland	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph mal																									
Pheochrom bgn							X																		
Blood vessel	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Blood vessel, aorta	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bone, femur	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph mal																									
Bone, sternum	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph mal																									
Bone marrow	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph mal																									
Brain	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Brain, cerebellum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Brain, cerebrum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Coagulating gland	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph mal																									
Ear	M	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph mal																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph mal																							X		
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Eye	A	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph mal																									
Gallbladder	A	+	+	A	M	M	+	+	+	+	+	+	+	I	+	+	M	+	+	M	+	+	+	+	+
Lymph mal																									
Harderian gland	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								X	
Lymph mal																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph mal																					X				
Intestine large, rectum	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph mal																									
Intestine small	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Intestine small, ileum	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Kidney	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph mal																									
Lacrimal gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Lymph mal																					X				
Larynx	M	+	+	M	+	M	M	M	M	+	M	M	+	+	+	+	+	M	+	+	+	+	M	+	+
Liver	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatoclr aden				X		X		X		X									X						
Hepatoclr carc						X						X													
Lymph mal																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alv bron aden					X			X			X													X	
Lymph mal																							X		
Lung, bronchus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, deep cervical																									

+: Tissue examined microscopically
A: Autolysis precludes examination
M: Missing tissue
I: Insufficient tissue
X: Lesion present
Blank: Not examined

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Fumonisin B_1: 0 ppm

Carcass ID Number	243	298	299	300	301	302	303	304	389	390	391	392	393	394	395	396	433	434	435	436	437	438	439	Total Tissues/ Tumors
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	46
Lymph mal								X																1
Pheochrom bgn																								1
Blood vessel	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Blood vessel, aorta	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Bone, femur	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph mal								X																1
Bone, sternum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph mal								X																1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph mal								X																1
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Brain, cerebellum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Brain, cerebrum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Coagulating gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Lymph mal								X																1
Ear	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Lymph mal								X																1
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph mal								X																2
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	44
Lymph mal								X																1
Gallbladder	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Lymph mal								X																1
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	46
Adenoma																								1
Lymph mal								X																1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Lymph mal																								1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	45
Lymph mal								X																1
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph mal								X																1
Lacrimal gland	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Lymph mal								X																2
Larynx	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	34
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Hepatoclr aden	X				X	X																X		9
Hepatoclr carc							X				X													4
Lymph mal								X																1
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Alv bron aden					X							X												6
Lymph mal		X						X																3
Lung, bronchus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, deep cervical																								0

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Fumonisin B_1: 0 ppm

Carcass ID Number	006	026	035	045	069	073	080	102	103	104	105	106	107	108	166	167	168	169	201	202	203	204	240	241	242
Lymph node, mandibular	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarc, metastatic, skin					X																				
Lymph mal																					X			X	
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph mal																					X		X	X	
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	+	M
Lymph mal																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph mal																					X				
Pancreas	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph mal																									
Parathyroid gland	M	M	+	+	M	M	M	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph mal																									
Pituitary gland	I	+	M	+	M	M	M	+	+	+	+	+	+	M	+	I	M	+	+	+	+	I	+	+	+
Preputial gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Lymph mal																									
Prostate	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph mal																							X		
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarc, metastatic, skin			X		X																				
Lymph mal																					X				
Seminal vesicle	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph mal																									
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarc			X		X		X													X				X	
Sarcoma						X																			
Spinal cord	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord, thoracic	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph mal																					X				
Stomach	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph mal																									
Papilloma squa																									
Stomach, glandular	A	+	+	+	+	A	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph mal																									
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	A	+	M	M	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	M	+
Thyroid gland	A	+	+	+	M	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Tongue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	A	+	+	+	M	A	M	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+
Urinary bladder	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph mal																					X			X	
Zymbal's gland	M	M	+	M	+	M	M	+	M	+	M	+	+	M	+	M	M	+	M	+	+	+	M	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Fumonisin B_1: 0 ppm

Carcass ID Number	243	298	299	300	301	302	303	304	389	390	391	392	393	394	395	396	433	434	435	436	437	438	439	Total Tissues/ Tumors
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	46
Fibrosarc, metastatic, skin																								1
Lymph mal								X																3
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph mal								X																4
Mammary gland	+	M	M	M	M	M	M	+	M	+	M	M	M	M	M	M	M	M	M	M	M	M	M	4
Lymph mal								X																1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph mal								X																2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph mal								X																1
Parathyroid gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	39
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	46
Lymph mal								X																1
Pituitary gland	+	M	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	M	I	+	I	+	+	33
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Lymph mal								X																1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Lymph mal								X																2
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Fibrosarc, metastatic, skin																								2
Lymph mal								X																2
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Lymph mal								X																1
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	47
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Fibrosarc																								5
Sarcoma																								1
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Spinal cord, thoracic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph mal								X																2
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph mal								X																1
Papilloma squa															X									1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Lymph mal								X																1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thymus	+	+	+	+	+	M	M	M	+	+	M	M	+	M	M	+	+	+	+	+	+	M	+	33
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Tongue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Trachea	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	40
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Lymph mal								X																3
Zymbal's gland	M	+	M	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	31

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Fumonisin B_1: 5 ppm

Carcass ID Number	008	014	018	024	027	038	068	093	114	115	116	117	118	174	175	176	177	209	210	211	212	234	250	251	252
Adrenal gland	+	A	+	+	+	+	+	+														+			
Blood vessel	+	+	+	+	+	+	+	+														+			
Blood vessel, aorta	+	+	+	+	+	+	+	+														+			
Lymph mal		X																							
Bone	+	+	+	+	+	+	+	+														+			
Bone, femur	+	+	+	+	+	+	+	+														+			
Bone, sternum	+	+	+	+	+	+	+	+														+			
Lymph mal		X																							
Bone marrow	+	+	+	+	+	+	+	+														+			
Lymph mal		X																							
Brain	+	+	+	+	+	+	+	+														+			
Brain, cerebellum	+	+	+	+	+	+	+	+														M			
Lymph mal		X																							
Brain, cerebrum	+	+	+	+	+	+	+	+														+			
Lymph mal		X																							
Coagulating gland	+	A	+	M	+	+	+	+														+			
Ear	M	+	M	M	M	+	+	+														+			
Epididymis	+	A	+	+	+	+	+	+														+			
Esophagus	+	A	+	+	+	+	M	+														+			
Eye	+	A	+	+	A	A	+	+														+			
Gallbladder	+	A	+	M	M	A	+	M														A			
Harderian gland	+	A	+	+	+	+	+	+														+			
Carcinoma																						X			
Heart	+	+	+	+	+	+	+	+														+			
Lymph mal		X																							
Intestine large	+	A	+	+	+	+	+	+														+			
Intestine large, cecum	+	A	+	+	A	A	+	+														A			
Intestine large, colon	+	A	+	+	A	A	+	+														+			
Intestine large, rectum	+	A	+	+	+	+	+	+														+			
Intestine small	+	A	+	+	A	A	+	+														+			
Intestine small, duodenum	+	A	+	+	A	A	+	+														A			
Intestine small, ileum	+	A	+	+	A	A	+	+														+			
Intestine small, jejunum	+	A	+	+	A	A	+	+														A			
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph mal		X																							
Lacrimal gland	+	A	+	+	+	+	+	+														+			
Larynx	+	A	+	+	+	M	+	M														M			
Liver	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarc																									
Hepatoclr aden							X																		
Hepatoclr carc								X						X											
Ito cl tm mal																									
Lymph mal																									
Lung	+	+	+	+	+	+	+	+														+			
Lymph mal		X																							
Lung, bronchus	+	+	+	+	+	+	+	+														+			
Lymph node	+	A	+	+	+	+	+	+														+			
Lymph node, deep cervical																									
Lymph node, mandibular	+	A	+	+	M	+	+	+														+			
Lymph node, mesenteric	+	A	M	+	+	M	+	+														+			
Mammary gland	M	A	M	+	M	M	M	M														+			
Mesentery																									
Nose	+	+	+	+	+	+	+	+														+			
Lymph mal		X																							
Pancreas	+	A	+	+	+	+	+	+														+			

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Fumonisin B_1: 5 ppm

Carcass ID Number	253	254	255	256	257	305	306	307	308	383	384	385	386	387	388	440	441	442	443	444	445	446	447	Total Tissues/ Tumors
Adrenal gland																								8
Blood vessel																								9
Blood vessel, aorta																								9
Lymph mal																								1
Bone																								9
Bone, femur																								9
Bone, sternum																								9
Lymph mal																								1
Bone marrow																								9
Lymph mal																								1
Brain																								9
Brain, cerebellum																								8
Lymph mal																								1
Brain, cerebrum																								9
Lymph mal																								1
Coagulating gland																								7
Ear																								5
Epididymis																								8
Esophagus																								7
Eye																								6
Gallbladder																								3
Harderian gland																								8
Carcinoma																								1
Heart																								9
Lymph mal																								1
Intestine large																								8
Intestine large, cecum																								5
Intestine large, colon																								6
Intestine large, rectum																								8
Intestine small																								6
Intestine small, duodenum																								5
Intestine small, ileum																								6
Intestine small, jejunum																								5
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph mal																					X			2
Lacrimal gland																								8
Larynx																								5
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Hemangiosarc									X															1
Hepatoclr aden		X						X	X				X	X				X						7
Hepatoclr carc														X										3
Ito cl tm mal																X								1
Lymph mal																					X			1
Lung																								9
Lymph mal																								1
Lung, bronchus																								9
Lymph node		+																						9
Lymph node, deep cervical																								0
Lymph node, mandibular		+																						8
Lymph node, mesenteric		+																						7
Mammary gland																								2
Mesentery						+																		1
Nose																								9
Lymph mal																								1
Pancreas																								8

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Fumonisin B_1: 5 ppm

Carcass ID Number	008	014	018	024	027	038	068	093	114	115	116	117	118	174	175	176	177	209	210	211	212	234	250	251	252
Parathyroid gland	+	A	M	M	M	M	+	M														+			
Peripheral nerve	+	+	+	+	+	+	+	M														+			
Pituitary gland	M	A	M	+	+	M	M	+														+			
Preputial gland	+	A	+	+	+	+	+	+														+	+		
Prostate	+	A	+	+	+	+	+	+														+			
Salivary glands	+	+	+	+	+	+	+	+								+						+			
Lymph mal																									
Seminal vesicle	+	A	+	+	+	+	+	+														+			
Skeletal muscle	+	+	+	+	+	+	+	+														+			
Skin	+	A	+	+	+	+	+	+				+										+			
Fib histiocyt																						X			
Fibrosarc												X													
Hemangioma					X																				
Squam cel carc				X																					
Spinal cord	+	A	+	+	+	+	+	+														+			
Spinal cord, thoracic	+	A	+	+	+	+	+	+														+			
Spleen	+	A	+	+	+	+	+	+														+			
Stomach	+	A	+	+	+	A	+	+														+			
Stomach, forestomach	+	A	+	+	+	A	+	+														+			
Stomach, glandular	+	A	+	+	+	A	+	+														+			
Testes	+	A	+	+	+	+	+	+														+			
Thymus	+	+	+	M	M	M	+	+														+			
Lymph mal		X																							
Thyroid gland	+	A	M	+	+	+	+	+														+			
Tongue	+	+	+	+	+	+	+	+														+			
Trachea	+	A	M	+	+	+	+	+														+			
Urinary bladder	+	A	+	+	+	+	+	+				+										+			
Zymbal's gland	M	M	+	M	M	+	+	+														+			

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Fumonisin B_1: 5 ppm

Carcass ID Number	253	254	255	256	257	305	306	307	308	383	384	385	386	387	388	440	441	442	443	444	445	446	447	Total Tissues/ Tumors
Parathyroid gland																								3
Peripheral nerve																								8
Pituitary gland																								4
Preputial gland																								9
Prostate																								8
Salivary glands																					+			11
Lymph mal																					X			1
Seminal vesicle																								8
Skeletal muscle																								9
Skin						+		+																11
Fib histiocyt																								1
Fibrosarc																								1
Hemangioma																								1
Squam cel carc																								1
Spinal cord																								8
Spinal cord, thoracic																								8
Spleen																								8
Stomach																								7
Stomach, forestomach																								7
Stomach, glandular																								7
Testes					+																			9
Thymus																								6
Lymph mal																								1
Thyroid gland																								7
Tongue																								9
Trachea																								7
Urinary bladder																								9
Zymbal's gland																								5

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Fumonisin B_1: 15 ppm

Carcass ID Number	058	077	084	119	120	121	122	123	124	125	126	178	179	180	213	214	215	216	258	259	260	261	262	263	264
Adrenal gland	A	+	A																						
Blood vessel	+	+	+																						
Blood vessel, aorta	+	+	+																						
Bone	A	+	+																						
Bone, femur	A	+	+																						
Bone, sternum	A	+	+																						
Bone marrow	A	+	+																						
Histio sarc			X																						
Brain	A	+	+																						
Brain, cerebellum	A	+	+																						
Brain, cerebrum	A	+	+																						
Coagulating gland	A	+	A																						
Ear	+	+	M																						
Epididymis	A	+	A									+													
Adenoma, interstit cell												X													
Esophagus	A	+	+																						
Eye	A	+	A																						
Gallbladder	A	+	A																						
Harderian gland	A	+	A																						
Heart	+	+	+																						
Intestine large	A	+	A																						
Intestine large, cecum	A	+	A																						
Intestine large, colon	A	+	A																						
Intestine large, rectum	A	+	A																						
Intestine small	A	+	A							+															
Intestine small, duodenum	A	+	A																						
Intestine small, ileum	A	+	A																						
Intestine small, jejunum	A	+	A							+															
Kidney	A	+	A	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lacrimal gland	A	+	+																						
Larynx	A	M	+																						
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatoclr aden		X											X										X		
Hepatoclr carc																							X		
Histio sarc			X																						
Lung	A	+	+																						
Histio sarc			X																						
Lung, bronchus	A	+	+																						
Lymph node	A	+	+																						
Lymph node, deep cervical																									
Lymph node, mandibular	A	+	+																						
Lymph node, mesenteric	A	+	+																						
Histio sarc			X																						
Lymph mal																									
Mammary gland	A	M	M																						
Nose	A	+	A																						
Pancreas	A	+	A																						
Parathyroid gland	A	+	M																						
Peripheral nerve	+	+	+																						
Pituitary gland	+	+	M																						
Preputial gland	A	+	A																				+		
Prostate	A	M	A																						
Salivary glands	A	+	A																						
Seminal vesicle	A	+	A																						
Skeletal muscle	+	+	A																						
Skin	A	+	A																						+
Fibrosarc		X																							X

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Fumonisin B_1: 15 ppm

Carcass ID Number	265	309	310	311	312	313	314	315	363	364	365	366	367	368	369	370	448	449	450	451	452	453	454	Total Tissues/ Tumors
Adrenal gland																								1
Blood vessel																								3
Blood vessel, aorta																								3
Bone																								2
Bone, femur																								2
Bone, sternum																								2
Bone marrow																								2
Histio sarc																								1
Brain																								2
Brain, cerebellum																								2
Brain, cerebrum																								2
Coagulating gland																								1
Ear																								2
Epididymis																								2
Adenoma, interstit cell																								1
Esophagus																								2
Eye																								1
Gallbladder																								1
Harderian gland																								1
Heart																								3
Intestine large																								1
Intestine large, cecum																								1
Intestine large, colon																								1
Intestine large, rectum																								1
Intestine small																								2
Intestine small, duodenum																								1
Intestine small, ileum																								1
Intestine small, jejunum																								2
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Lacrimal gland																								2
Larynx																								1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hepatoclr aden	X												X		X			X						7
Hepatoclr carc																		X	X			X		4
Histio sarc																								1
Lung																								2
Histio sarc																								1
Lung, bronchus																								2
Lymph node																+								3
Lymph node, deep cervical																								0
Lymph node, mandibular																								2
Lymph node, mesenteric																+								3
Histio sarc																								1
Lymph mal																X								1
Mammary gland																								0
Nose																								1
Pancreas																								1
Parathyroid gland																								1
Peripheral nerve																								3
Pituitary gland																								2
Preputial gland	+											+												4
Prostate																								0
Salivary glands																								1
Seminal vesicle																								1
Skeletal muscle																								2
Skin			+	+	+		+															+		7
Fibrosarc				X			X															X		5

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Fumonisin B_1: 15 ppm

Carcass ID Number	058	077	084	119	120	121	122	123	124	125	126	178	179	180	213	214	215	216	258	259	260	261	262	263	264
Spinal cord	A	+	+																						
Spinal cord, thoracic	A	+	+																						
Spleen	A	+	A																						
Stomach	+	+	A																						
Stomach, forestomach	A	+	A																						
Stomach, glandular	+	+	A																						
Adenocarc	X																								
Testes	A	+	A																						
Thymus	M	+	+																						
Thyroid gland	A	+	M																						
Tongue	+	+	M																						
Trachea	A	+	M																						
Urinary bladder	A	M	A																						
Zymbal's gland	+	+	M																						

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Fumonisin B_1: 15 ppm

Carcass ID Number	265	309	310	311	312	313	314	315	363	364	365	366	367	368	369	370	448	449	450	451	452	453	454	Total Tissues/ Tumors
Spinal cord																								2
Spinal cord, thoracic																								2
Spleen																								1
Stomach																								2
Stomach, forestomach																								1
Stomach, glandular																								2
Adenocarc																								1
Testes																								1
Thymus																								2
Thyroid gland																								1
Tongue																								2
Trachea																								1
Urinary bladder																								0
Zymbal's gland																								2

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Fumonisin B_1: 80 ppm

Carcass ID Number	007	013	015	016	017	054	060	078	081	082	094	095	096	097	098	099	100	101	162	163	164	165	198	199	200
Adrenal gland	+	M	+	I	+	+	+	+	+	+	+														
Blood vessel	+	+	+	+	+	+	+	+	+	+	+														
Blood vessel, aorta	+	+	+	+	+	+	+	+	+	+	+														
Lymph mal		X																							
Bone	+	+	+	+	+	+	+	+	+	+	+														
Bone, femur	+	+	+	+	+	+	+	+	+	+	+														
Histio sarc											X														
Lymph mal		X																							
Bone, sternum	+	+	+	+	+	+	+	+	+	+	+														
Histio sarc											X														
Lymph mal		X																							
Bone marrow	+	+	+	+	+	+	+	+	+	+	+														
Hemangiosarc, metastatic, spleen						X																			
Histio sarc										X	X														
Lymph mal		X																							
Brain	+	A	+	+	+	+	+	+	+	+	+														
Brain, cerebellum	+	A	+	+	+	+	+	M	I	+	+														
Brain, cerebrum	+	A	+	+	+	+	+	+	+	+	+														
Coagulating gland	+	+	+	+	+	+	+	+	+	A	+														
Lymph mal		X																							
Ear	+	+	+	M	M	+	+	+	+	+	+														
Epididymis	+	+	+	+	+	+	+	M	M	A	+														
Histio sarc											X														
Lymph mal		X																							
Esophagus	+	+	+	+	+	+	+	+	+	+	+														
Eye	+	A	A	+	+	+	+	+	+	A	A														
Gallbladder	+	+	A	+	+	M	+	+	+	A	M														
Lymph mal		X																							
Harderian gland	+	+	A	+	+	+	+	+	+	A	+														
Lymph mal		X																							
Heart	+	+	+	+	+	+	+	+	+	+	+														
Lymph mal		X																							
Intestine large	+	A	A	+	+	+	+	+	+	A	+														
Intestine large, cecum	A	A	A	+	+	+	+	+	+	A	A														
Intestine large, colon	+	A	A	+	+	+	+	+	+	A	+														
Intestine large, rectum	A	A	A	+	+	+	+	+	+	M	+														
Intestine small	A	A	A	+	+	+	+	+	+	A	A									+					
Intestine small, duodenum	A	A	A	+	+	+	+	M	+	A	A														
Intestine small, ileum	A	A	A	+	+	+	+	+	+	A	A									+					
Lymph mal																				X					
Intestine small, jejunum	A	A	A	+	+	+	+	+	+	A	A														
Kidney	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histio sarc											X														
Lymph mal		X																		X					
Lacrimal gland	+	M	+	+	+	+	+	M	+	A	+														
Larynx	M	M	+	+	+	M	+	M	+	M	+														
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarc			X																						
Hepatoclr aden						X								X											
Hepatoclr carc													X												
Histio sarc										X	X														
Lymph mal		X																							
Lung	+	+	+	+	+	+	+	+	+	+	+														
Histio sarc										X	X														
Lymph mal		X																							
Lung, bronchus	+	+	+	+	+	+	+	+	+	+	+														
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+		+						+					
Lymph mal, inguinal		X																							

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Fumonisin B_1: 80 ppm

Carcass ID Number	235	236	237	238	239	316	317	318	319	320	321	322	323	379	380	381	382	455	456	457	458	459	460	Total Tissues/ Tumors
Adrenal gland																								9
Blood vessel																								11
Blood vessel, aorta																								11
Lymph mal																								1
Bone																								11
Bone, femur																								11
Histio sarc																								1
Lymph mal																								1
Bone, sternum																								11
Histio sarc																								1
Lymph mal																								1
Bone marrow																								11
Hemangiosarc, metastatic, spleen																								1
Histio sarc																								2
Lymph mal																								1
Brain																								10
Brain, cerebellum																								8
Brain, cerebrum																								10
Coagulating gland																								10
Lymph mal																								1
Ear																								9
Epididymis																								8
Histio sarc																								1
Lymph mal																								1
Esophagus																								11
Eye																								7
Gallbladder																								7
Lymph mal																								1
Harderian gland																								9
Lymph mal																								1
Heart																								11
Lymph mal																								1
Intestine large																								8
Intestine large, cecum																								6
Intestine large, colon																								8
Intestine large, rectum																								7
Intestine small																								7
Intestine small, duodenum																								5
Intestine small, ileum																								7
Lymph mal																								1
Intestine small, jejunum																								6
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Histio sarc																								1
Lymph mal																								2
Lacrimal gland																								8
Larynx																								6
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hemangiosarc																								1
Hepatoclr aden							X						X			X							X	6
Hepatoclr carc			X												X									3
Histio sarc																								2
Lymph mal																								1
Lung																								11
Histio sarc																								2
Lymph mal																								1
Lung, bronchus																								11
Lymph node															+									15
Lymph mal, inguinal																								1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Fumonisin B_1: 80 ppm

Carcass ID Number	007	013	015	016	017	054	060	078	081	082	094	095	096	097	098	099	100	101	162	163	164	165	198	199	200
Lymph node, mandibular	M	+	+	+	+	+	+	+	+	+	+														
Lymph mal		X																							
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+		+						+					
Histio sarc										X	X														
Lymph mal		X										X		X						X					
Mammary gland	M	M	A	M	M	M	M	+	M	M	M														
Nose	+	+	+	+	+	+	+	+	+	+	+														
Histio sarc											X														
Lymph mal		X																							
Pancreas	+	+	+	+	+	+	+	+	+	A	+														
Lymph mal		X																							
Parathyroid gland	M	M	+	M	M	+	+	+	M	M	+														
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+														
Pituitary gland	+	M	I	M	M	M	+	+	+	M	M														
Preputial gland	+	+	+	+	+	+	+	+	+	+	+											+	+	+	
Lymph mal		X																							
Prostate	+	+	+	+	+	+	+	+	+	A	+														
Lymph mal		X																							
Salivary glands	+	+	+	+	+	+	+	+	+	A	+														
Lymph mal		X																							
Seminal vesicle	A	+	+	+	+	+	+	+	+	A	+														
Lymph mal		X																							
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+												+		
Fibrosarc																							X		
Skin	+	+	+	+	+	+	+	+	+	+	+														
Fibroma																									
Fibrosarc							X	X	X																
Lymph mal		X																							
Spinal cord	+	+	+	+	+	+	+	+	+	A	+														
Spinal cord, thoracic	+	+	+	+	+	+	+	+	+	A	+														
Spleen	+	+	+	+	+	+	+	+	+	+	+	+		+											
Hemangiosarc						X																			
Histio sarc										X	X														
Lymph mal		X										X		X											
Stomach	+	+	+	+	+	+	+	+	+	+	+														
Stomach, forestomach	+	+	+	+	+	+	+	+	+	A	+														
Lymph mal		X																							
Papilloma squa																									
Stomach, glandular	A	+	+	+	+	+	+	+	+	+	+														
Testes	+	+	+	+	+	+	+	+	+	+	+														
Histio sarc											X														
Thymus	M	+	+	+	+	+	M	+	+	M	M														
Lymph mal		X																							
Thyroid gland	M	+	+	M	+	+	+	+	M	M	+														
Lymph mal		X																							
Tongue	+	+	+	+	+	+	+	+	+	+	+														
Trachea	M	+	+	+	+	+	+	+	+	M	+														
Lymph mal		X																							
Urinary bladder	+	+	+	+	+	+	+	+	+	A	+														
Lymph mal		X																							
Zymbal's gland	+	+	M	+	M	+	+	+	M	+	+														
Lymph mal		X																							

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Fumonisin B_1: 80 ppm

Carcass ID Number	235	236	237	238	239	316	317	318	319	320	321	322	323	379	380	381	382	455	456	457	458	459	460	Total Tissues/ Tumors
Lymph node, mandibular																								10
Lymph mal																								1
Lymph node, mesenteric															+									15
Histio sarc																								2
Lymph mal															X									5
Mammary gland																								1
Nose																								11
Histio sarc																								1
Lymph mal																								1
Pancreas																								10
Lymph mal																								1
Parathyroid gland																								5
Peripheral nerve																								11
Pituitary gland																								4
Preputial gland	+														+					+				17
Lymph mal																								1
Prostate																								10
Lymph mal																								1
Salivary glands																								10
Lymph mal																								1
Seminal vesicle																								9
Lymph mal																								1
Skeletal muscle																								12
Fibrosarc																								1
Skin				+							+		+											14
Fibroma				X																				1
Fibrosarc													X											4
Lymph mal																								1
Spinal cord																								10
Spinal cord, thoracic																								10
Spleen																								13
Hemangiosarc																								1
Histio sarc																								2
Lymph mal																								3
Stomach																	+							12
Stomach, forestomach																	+							11
Lymph mal																								1
Papilloma squa																	X							1
Stomach, glandular																								10
Testes		+																						12
Histio sarc																								1
Thymus																								7
Lymph mal																								1
Thyroid gland																								7
Lymph mal																								1
Tongue																								11
Trachea																								9
Lymph mal																								1
Urinary bladder																								10
Lymph mal																								1
Zymbal's gland																								8
Lymph mal																								1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Fumonisin B_1: 150 ppm

Carcass ID Number	046	061	083	085	087	109	110	111	112	113	170	171	172	173	205	206	207	208	244	245	246	247	248	249	324
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph mal	X																								
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Blood vessel, aorta	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bone, femur	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph mal												X	X												
Bone, sternum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph mal												X													
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+
Histio sarc			X																						
Lymph mal												X	X												
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Brain, cerebellum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Brain, cerebrum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Coagulating gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph mal																									
Ear	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph mal																									
Esophagus	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Eye	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Gallbladder	+	M	A	M	+	+	I	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Harderian gland	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	I	+
Adenoma														X				X		X		X			
Lymph mal														X											
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph mal																									
Intestine large, colon	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph mal																									
Intestine large, rectum	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph mal													X												
Intestine small, jejunum	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph mal												X		X											
Lacrimal gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph mal												X													
Larynx	+	+	M	+	+	+	M	M	M	M	M	M	+	+	+	M	+	M	+	+	+	+	M	+	I
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatoclr aden															X	X	X								
Hepatoclr carc				X			X																		
Histio sarc			X																						
Lymph mal	X					X						X													
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarc, multiple																			X						
Alv bron aden														X					X						
Histio sarc			X																						
Lymph mal												X													
Lung, bronchus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histio sarc			X																						
Lymph mal													X	X											

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Fumonisin B_1: 150 ppm

Carcass ID Number	325	326	327	328	329	330	331	371	372	373	374	375	376	377	378	432	463	464	465	466	467	468	469	Total Tissues/ Tumors
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph mal																								1
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Blood vessel, aorta	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Bone, femur	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph mal																								2
Bone, sternum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph mal																								1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Histio sarc																								1
Lymph mal																								2
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Brain, cerebellum	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	46
Brain, cerebrum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Coagulating gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph mal						X																		1
Ear	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph mal						X																		1
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	45
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	42
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	44
Adenoma					X																			5
Lymph mal																						X		2
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Lymph mal						X																		1
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Lymph mal																						X		1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Lymph mal																								1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph mal						X																		3
Lacrimal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph mal																								1
Larynx	+	+	M	+	I	I	+	+	M	M	+	+	M	+	+	I	M	M	M	M	+	+	+	26
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hepatoclr aden		X		X						X						X						X		8
Hepatoclr carc																								2
Histio sarc																								1
Lymph mal						X																		4
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenocarc, multiple																								1
Alv bron aden						X	X								X	X								6
Histio sarc																								1
Lymph mal						X																		2
Lung, bronchus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Histio sarc																								1
Lymph mal						X																		3

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Fumonisin B_1: 150 ppm

Carcass ID Number	046	061	083	085	087	109	110	111	112	113	170	171	172	173	205	206	207	208	244	245	246	247	248	249	324
Lymph node, mesenteric	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+
Histio sarc			X																						
Lymph mal						X							X	X											
Mammary gland	+	M	M	M	M	M	M	M	I	M	M	M	M	M	M	+	I	M	M	M	M	M	M	M	M
Lymph mal																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph mal	X												X	X											
Pancreas	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph mal																									
Parathyroid gland	+	+	M	M	+	+	+	+	M	M	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+
Peripheral nerve	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph mal																									
Pituitary gland	M	+	M	+	+	M	M	M	+	M	+	+	M	+	+	+	+	+	+	I	M	I	I	+	I
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph mal	X																								
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph mal												X	X	X											
Seminal vesicle	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarc, metastatic, skin, thoracic																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarc		X			X															X					
Lymph mal																									
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord, thoracic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histio sarc			X																						
Lymph mal	X					X							X	X											
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	M	M	M	M	+	M	+	M	+	+	+	+	I	M	+	+	I	M	+	M	+	I	M	+
Lymph mal																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Urinary bladder	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph mal						X							X												
Zymbal's gland	+	+	M	+	+	+	M	+	M	M	+	+	+	+	+	+	+	M	M	+	+	+	M	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Fumonisin B_1: 150 ppm

	325	326	327	328	329	330	331	371	372	373	374	375	376	377	378	432	463	464	465	466	467	468	469	Total Tissues/ Tumors
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Histio sarc																								1
Lymph mal						X																X		5
Mammary gland	M	M	M	+	M	+	M	M	M	M	+	M	+	M	+	M	+	+	M	M	M	M	+	10
Lymph mal						X																		1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph mal						X																		4
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph mal						X																X		2
Parathyroid gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	39
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Lymph mal						X																		1
Pituitary gland	M	M	I	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	M	I	+	+	29
Preputial gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	46
Lymph mal																								1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	47
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph mal						X																X		5
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Fibrosarc, metastatic, skin, thoracic	X																							1
Skin	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	47
Fibrosarc	X															X								5
Lymph mal						X																		1
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spinal cord, thoracic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Histio sarc																								1
Lymph mal						X																X		6
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, glandular	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thymus	M	+	+	M	+	+	+	+	+	M	+	M	M	M	+	M	+	+	+	M	M	+	+	26
Lymph mal						X																X		2
Thyroid gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	46
Tongue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Trachea	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	43
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Lymph mal						X																X		4
Zymbal's gland	+	+	+	M	+	+	+	I	+	M	+	M	M	+	+	+	+	M	+	M	+	+	+	34

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Feed Study of Fumonisin B_1

	0 ppm	5 ppm	15 ppm	80 ppm	150 ppm
Harderian Gland: Adenoma					
Overall rate[a]	1/46 (2%)	0/8 (0%)	0/1 (0%)	0/9 (0%)	5/44 (11%)
Adjusted rate[b]	2.3%	0.0%	0.0%	0.0%	11.7%
Terminal rate[c]	1/40 (3%)	0/1 (0%)	0/0	0/0	5/40 (13%)
First incidence (days)	740 (T)	—[e]	—	—	740 (T)
Poly-3 test[d]	P=0.0466	P=0.8706N	P=0.9995N	P=0.8645N	P=0.0994
Harderian Gland: Adenoma or Carcinoma					
Overall rate	1/46 (2%)	1/8 (13%)	0/1 (0%)	0/9 (0%)	5/44 (11%)
Adjusted rate	2.3%	29.7%	0.0%	0.0%	11.7%
Terminal rate	1/40 (3%)	0/1 (0%)	0/0	0/0	5/40 (13%)
First incidence (days)	740 (T)	725	—	—	740 (T)
Poly-3 test	P=0.0894	P=0.2609	P=0.9995N	P=0.8645N	P=0.0994
Liver: Hepatocellular Adenoma					
Overall rate	9/47 (19%)	7/47 (15%)	7/48 (15%)	6/48 (13%)	8/48 (17%)
Adjusted rate	20.1%	16.4%	14.8%	14.2%	17.1%
Terminal rate	7/41 (17%)	6/40 (15%)	6/45 (13%)	5/37 (14%)	7/42 (17%)
First incidence (days)	563	667	668	585	738
Poly-3 test	P=0.4980N	P=0.4166N	P=0.3479N	P=0.3318N	P=0.4637N
Liver: Hepatocellular Carcinoma					
Overall rate	4/47 (9%)	3/47 (6%)	4/48 (8%)	3/48 (6%)	2/48 (4%)
Adjusted rate	9.0%	7.1%	8.5%	7.2%	4.3%
Terminal rate	3/41 (7%)	2/40 (5%)	4/45 (9%)	3/37 (8%)	1/42 (2%)
First incidence (days)	685	708	740 (T)	740 (T)	691
Poly-3 test	P=0.2398N	P=0.5107N	P=0.6092N	P=0.5330N	P=0.3116N
Liver: Hepatocellular Adenoma or Carcinoma					
Overall rate	12/47 (26%)	9/47 (19%)	9/48 (19%)	9/48 (19%)	10/48 (21%)
Adjusted rate	26.8%	21.1%	19.0%	21.3%	21.3%
Terminal rate	10/41 (24%)	7/40 (18%)	8/45 (18%)	8/37 (22%)	8/42 (19%)
First incidence (days)	563	667	668	585	691
Poly-3 test	P=0.4662N	P=0.3341N	P=0.2629N	P=0.3675N	P=0.3591N
Lung: Alveolar/Bronchiolar Adenoma					
Overall rate	6/48 (13%)	0/9 (0%)	0/2 (0%)	0/11 (0%)	6/48 (13%)
Adjusted rate	13.5%	0.0%	0.0%	0.0%	12.9%
Terminal rate	5/41 (12%)	0/1 (0%)	0/0	0/0	5/42 (12%)
First incidence (days)	654	—	—	—	738
Poly-3 test	P=0.5535	P=0.4831N	P=0.7506N	P=0.4687N	P=0.5848N
Skin: Fibrosarcoma					
Overall rate	5/48 (10%)	1/11 (9%)	5/7 (71%)	4/14 (29%)	5/47 (11%)
Adjusted rate	11.0%	15.8%	71.4%	46.7%	10.8%
Terminal rate	2/41 (5%)	1/4 (25%)	4/6 (67%)	1/3 (33%)	2/41 (5%)
First incidence (days)	447	740 (T)	668	643	638
Poly-3 test	P=0.2186N	P=0.6405	P=0.0001	P=0.0329	P=0.6198N

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Feed Study of Fumonisin B_1

	0 ppm	5 ppm	15 ppm	80 ppm	150 ppm
Skin (Subcutaneous Tissue): Fibrosarcoma or Sarcoma					
Overall rate	6/48 (13%)	1/11 (9%)	5/7 (71%)	4/14 (29%)	5/47 (11%)
Adjusted rate	13.1%	15.8%	71.4%	46.7%	10.8%
Terminal rate	2/41 (5%)	1/4 (25%)	4/6 (67%)	1/3 (33%)	2/41 (5%)
First incidence (days)	447	740 (T)	668	643	638
Poly-3 test	P=0.1576N	P=0.6822	P=0.0003	P=0.0526	P=0.4919N
All Organs: Malignant Lymphoma					
Overall rate	5/48 (10%)	2/48 (4%)	1/48 (2%)	5/48 (10%)	7/48 (15%)
Adjusted rate	11.3%	4.6%	2.1%	11.7%	14.8%
Terminal rate	5/41 (12%)	1/40 (3%)	1/45 (2%)	4/37 (11%)	6/42 (14%)
First incidence (days)	740 (T)	291	740 (T)	282	584
Poly-3 test	P=0.0400	P=0.2139N	P=0.0871N	P=0.6093	P=0.4279
All Organs: Benign Neoplasms					
Overall rate	15/48 (31%)	8/48 (17%)	8/48 (17%)	8/48 (17%)	17/48 (35%)
Adjusted rate	33.0%	18.4%	16.9%	19.0%	36.4%
Terminal rate	11/41 (27%)	6/40 (15%)	7/45 (16%)	7/37 (19%)	16/42 (38%)
First incidence (days)	563	440	668	585	738
Poly-3 test	P=0.0779	P=0.0813N	P=0.0583N	P=0.1045N	P=0.4518
All Organs: Malignant Neoplasms					
Overall rate	13/48 (27%)	10/48 (21%)	11/48 (23%)	16/48 (33%)	16/48 (33%)
Adjusted rate	28.5%	22.5%	22.9%	35.4%	33.3%
Terminal rate	9/41 (22%)	6/40 (15%)	8/45 (18%)	8/37 (22%)	10/42 (24%)
First incidence (days)	447	291	624	282	584
Poly-3 test	P=0.0992	P=0.3220N	P=0.3529N	P=0.3164	P=0.3895
All Organs: Benign or Malignant Neoplasms					
Overall rate	24/48 (50%)	16/48 (33%)	16/48 (33%)	21/48 (44%)	27/48 (56%)
Adjusted rate	52.0%	35.2%	33.3%	46.5%	56.3%
Terminal rate	19/41 (46%)	10/40 (25%)	13/45 (29%)	13/37 (35%)	21/42 (50%)
First incidence (days)	447	291	624	282	584
Poly-3 test	P=0.0352	P=0.0672N	P=0.0514N	P=0.3765N	P=0.4172

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined microscopically
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence is the P value associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. For all tissues except the liver, only the pairwise comparisons between the 150 ppm group and control group are unbiased; overall rates and all other pairwise comparisons may not be valid. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in an exposure group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group

TABLE C4
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of Fumonisin B_1[a]

	0 ppm	5 ppm	15 ppm	80 ppm	150 ppm
Disposition Summary					
3-Week evaluation	4	4	4	4	4
7-Week evaluation	4	4	4	4	4
9-Week evaluation	4	4	4	4	4
24-Week evaluation	4	4	4	4	4
Animals initially in 2-year study	48	48	48	48	48
Early deaths					
Removed from study		1			
Moribund	4	3	1	5	4
Natural deaths	3	5	2	6	2
Survivors					
Terminal sacrifice	41	39	45	37	42
Animals examined microscopically	64	64	64	64	64
3-Week Evaluation					
Kidney	(4)	(4)	(4)	(4)	(4)
Inflammation, subacute, unilateral	1 (25%)				
Liver	(4)	(4)	(4)	(4)	(4)
Inflammation, subacute, multifocal	1 (25%)				
7-Week Evaluation					
Preputial gland		(1)		(1)	(1)
Cyst, focal				1 (100%)	
Cyst, multifocal		1 (100%)			1 (100%)
Tissues Examined with No Lesions Observed					
Kidney					
Liver					
Seminal vesicle					
9-Week Evaluation					
Kidney	(4)	(4)	(4)	(4)	(4)
Fatty change, multifocal, bilateral, renal tubule		1 (25%)			
Inflammation, unilateral, perirenal tiss			1 (25%)		
Vacuoliz cyto, multifocal, bilateral, renal tubule			1 (25%)		
Liver	(4)	(4)	(4)	(4)	(4)
Inflammation, granulomatous, focal				1 (25%)	
Preputial gland		(1)			(1)
Cyst, focal		1 (100%)			1 (100%)

[a] Number of animals examined microscopically at the site and the number of animals with lesion

TABLE C4
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of Fumonisin B_1

	0 ppm		5 ppm		15 ppm		80 ppm		150 ppm	
24-Week Evaluation										
Kidney	(4)		(4)		(4)		(4)		(4)	
Fatty change, multifocal, bilateral, renal tubule	1	(25%)			2	(50%)				
Inflammation, subacute, focal, unilateral					1	(25%)				
Vacuoliz cyto, multifocal, bilateral, renal tubule	2	(50%)	4	(100%)	1	(25%)				
Preputial gland	(1)				(1)		(1)			
Cyst, focal	1	(100%)								
Cyst, multifocal					1	(100%)	1	(100%)		

Tissues Examined with No Lesions Observed
Liver

	0 ppm		5 ppm		15 ppm		80 ppm		150 ppm	
2-Year Study										
Adrenal gland	(46)		(8)		(1)		(9)		(48)	
Hyperplasia, bilateral, cortex, spindle cell	29	(63%)	2	(25%)	1	(100%)	3	(33%)	27	(56%)
Hyperplasia, unilateral, cortex, spindle cell	12	(26%)	2	(25%)			3	(33%)	18	(38%)
Hyperplasia, unilateral, medulla									2	(4%)
Blood vessel, aorta	(46)		(9)		(3)		(11)		(48)	
Mineralization, focal									1	(2%)
Bone, femur	(48)		(9)		(2)		(11)		(48)	
Proliferation, focal									1	(2%)
Bone, sternum	(47)		(9)		(2)		(11)		(48)	
Proliferation, focal									2	(4%)
Proliferation, multifocal									1	(2%)
Bone marrow	(47)		(9)		(2)		(11)		(47)	
Hyperplasia, diffuse	21	(45%)	3	(33%)	1	(50%)	4	(36%)	25	(53%)
Hyperplasia, multifocal			2	(22%)					2	(4%)
Brain, cerebellum	(47)		(8)		(2)		(8)		(46)	
Mineralization, multifocal	1	(2%)								
Brain, cerebrum	(47)		(9)		(2)		(10)		(48)	
Cyst, focal			1	(11%)						
Mineralization, focal							1	(10%)		
Mineralization, multifocal	8	(17%)	1	(11%)	1	(50%)			17	(35%)
Coagulating gland	(46)		(7)		(1)		(10)		(47)	
Inflammation, chronic, focal	2	(4%)								
Inflammation, subacute, focal	1	(2%)								
Epididymis	(48)		(8)		(2)		(8)		(48)	
Inflammation, chronic, focal	1	(2%)								
Inflammation, chronic, focal, bilateral	1	(2%)							1	(2%)
Inflammation, chronic, focal, unilateral	1	(2%)	1	(13%)					1	(2%)
Inflammation, subacute, focal, unilateral	1	(2%)					1	(13%)	1	(2%)
Mineralization, focal, unilateral	1	(2%)								
Esophagus	(47)		(7)		(2)		(11)		(45)	
Hyperkeratosis, diffuse			1	(14%)						
Hyperkeratosis, multifocal			1	(14%)						
Inflammation, subacute, focal	1	(2%)								
Eye	(44)		(6)		(1)		(7)		(45)	
Hyperplasia, melanocyte, focal, unilateral			1	(17%)						

TABLE C4
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of Fumonisin B_1

	0 ppm	5 ppm	15 ppm	80 ppm	150 ppm
2-Year Study (continued)					
Gallbladder	(40)	(3)	(1)	(7)	(42)
Edema, multifocal					1 (2%)
Fibrosis, diffuse					1 (2%)
Harderian gland	(46)	(8)	(1)	(9)	(44)
Degen, focal	1 (2%)				
Hyperplasia	1 (2%)				1 (2%)
Inflammation, chronic	3 (7%)	1 (13%)			7 (16%)
Inflammation, subacute	3 (7%)			3 (33%)	3 (7%)
Heart	(48)	(9)	(3)	(11)	(48)
Cardiomyopathy, diffuse					1 (2%)
Intestine large, cecum	(46)	(5)	(1)	(6)	(46)
Hyperplasia, lymphoid, focal	3 (7%)				2 (4%)
Intestine large, colon	(46)	(6)	(1)	(8)	(46)
Hyperplasia, lymphoid, focal	2 (4%)				2 (4%)
Intestine large, rectum	(45)	(8)	(1)	(7)	(47)
Cyst, multifocal, anus, mucosa		1 (13%)			
Hyperplasia, lymphoid, focal					1 (2%)
Inflammation, chronic, multifocal, anus		1 (13%)			
Intestine small, ileum	(46)	(6)	(1)	(7)	(46)
Hyperplasia, lymphoid, focal	1 (2%)	1 (17%)			3 (7%)
Intestine small, jejunum	(46)	(5)	(2)	(6)	(46)
Cyst, focal			1 (50%)		
Kidney	(47)	(48)	(45)	(47)	(48)
Cyst	1 (2%)	5 (10%)	3 (7%)	5 (11%)	1 (2%)
Degen, focal, cortex, renal tubule			1 (2%)	4 (9%)	1 (2%)
Degen, multifocal, cortex, renal tubule		2 (4%)		1 (2%)	
Dilatation, diffuse,, right, pelvis				1 (2%)	
Glmsclerosis, diffuse		1 (2%)			1 (2%)
Glmsclerosis, multifocal	14 (30%)	19 (40%)	22 (49%)	14 (30%)	13 (27%)
Hyperplasia, focal, cortex, renal tubule	6 (13%)	2 (4%)	4 (9%)	1 (2%)	8 (17%)
Hyperplasia, lymphoid, focal				1 (2%)	
Hyperplasia, multifocal, cortex, renal tubule	14 (30%)	14 (29%)	21 (47%)	7 (15%)	4 (8%)
Infarct				1 (2%)	
Inflammation, chronic, focal	7 (15%)	1 (2%)	6 (13%)	6 (13%)	6 (13%)
Inflammation, chronic, focal, pelvis					2 (4%)
Inflammation, chronic, multifocal	12 (26%)	18 (38%)	18 (40%)	20 (43%)	6 (13%)
Inflammation, focal		1 (2%)			
Inflammation, multifocal	1 (2%)				
Inflammation, subacute, focal			1 (2%)		
Inflammation, subacute, multifocal	5 (11%)	5 (10%)	9 (20%)	3 (6%)	5 (10%)
Mineralization, multifocal, renal tubule		1 (2%)	3 (7%)		
Nephropathy, chronic, multifocal		1 (2%)			3 (6%)
Proliferation, focal, renal tubule			2 (4%)	2 (4%)	
Proliferation, multifocal, renal tubule		2 (4%)	4 (9%)		
Lacrimal gland	(44)	(8)	(2)	(8)	(47)
Hyperplasia, focal, duct					1 (2%)
Hyperplasia, multifocal, duct	1 (2%)				
Inflammation, chronic, focal	6 (14%)				5 (11%)
Inflammation, chronic, multifocal	1 (2%)				1 (2%)
Inflammation, subacute, focal	2 (5%)	1 (13%)			1 (2%)

TABLE C4
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of Fumonisin B_1

	0 ppm		5 ppm		15 ppm		80 ppm		150 ppm	
2-Year Study (continued)										
Liver	(47)		(47)		(48)		(48)		(48)	
Amyloid dep, multifocal							1	(2%)		
Apoptosis, hepatocyte									3	(6%)
Basoph focus	2	(4%)	1	(2%)			2	(4%)	2	(4%)
Clear cl focus	1	(2%)							1	(2%)
Cyst, focal					1	(2%)				
Cyst, multifocal	1	(2%)							1	(2%)
Eosin focus									1	(2%)
Granuloma	5	(11%)	5	(11%)	3	(6%)	6	(13%)	18	(38%)
Hypertrophy, diffuse, hepatocyte	10	(21%)	3	(6%)	16	(33%)	24	(50%)	30	(63%)
Hypertrophy, focal, hepatocyte			6	(13%)	8	(17%)	1	(2%)		
Infiltrat cell, lymphocytic, multifocal	2	(4%)	3	(6%)	3	(6%)	5	(10%)	8	(17%)
Mineralization, multifocal			1	(2%)			1	(2%)		
Necrosis, multifocal	1	(2%)	1	(2%)			4	(8%)	14	(29%)
Pigment, multifocal							2	(4%)	18	(38%)
Tension lipoid	3	(6%)	5	(11%)	4	(8%)	3	(6%)	9	(19%)
Vacuoliz cyto, centrilobular	7	(15%)	12	(26%)	21	(44%)	9	(19%)	9	(19%)
Vacuoliz cyto, diffuse					1	(2%)				
Lung	(48)		(9)		(2)		(11)		(48)	
Degen, cystic, alveolar epith	1	(2%)								
Hyperplasia, focal, alveolar epith	1	(2%)					1	(9%)	1	(2%)
Inflammation, chronic, multifocal	7	(15%)							12	(25%)
Inflammation, subacute, focal	2	(4%)	1	(11%)						
Inflammation, subacute, multifocal	2	(4%)							3	(6%)
Inflammation, subacute, multifocal, perivascular			1	(11%)						
Lymph node, mandibular	(46)		(8)		(2)		(10)		(48)	
Hyperplasia, lymphoid	6	(13%)							11	(23%)
Inflammation, focal									1	(2%)
Pigment, hemosiderin, multifocal			1	(13%)						
Pigment, multifocal	8	(17%)	2	(25%)	1	(50%)			8	(17%)
Lymph node, mesenteric	(48)		(7)		(3)		(15)		(45)	
Angiectasis			1	(14%)						
Cyst, multifocal									1	(2%)
Deplet lymph, multifocal	2	(4%)								
Hemorrhage, focal	1	(2%)	1	(14%)						
Hemorrhage, multifocal	5	(10%)	1	(14%)					1	(2%)
Hyperplasia, lymphoid	7	(15%)	1	(14%)					18	(40%)
Hyperplasia, mononuclear cl, multifocal					1	(33%)				
Pigment, multifocal	6	(13%)							1	(2%)
Mesentery			(1)							
Granuloma, focal			1	(100%)						
Nose	(48)		(9)		(1)		(11)		(48)	
Cytoplas alter, olfactory epi									1	(2%)
Exudate, focal, nasolacrim dct	2	(4%)								
Inflammation, chronic, focal	1	(2%)							2	(4%)
Inflammation, chronic, multifocal							1	(9%)	3	(6%)
Inflammation, subacute, focal	2	(4%)								
Inflammation, subacute, multifocal	2	(4%)							3	(6%)
Proliferation, multifocal							1	(9%)		
Pancreas	(47)		(8)		(1)		(10)		(47)	
Atrophy, focal, acinar cell									1	(2%)
Cyst, focal									1	(2%)
Inflammation, chronic, focal									1	(2%)
Inflammation, subacute, focal							1	(10%)		
Parathyroid gland	(39)		(3)		(1)		(5)		(39)	
Cyst, focal	1	(3%)							1	(3%)

TABLE C4
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of Fumonisin B_1

	0 ppm		5 ppm		15 ppm		80 ppm		150 ppm	
2-Year Study (continued)										
Preputial gland	(46)		(9)		(4)		(17)		(46)	
Abscess, focal	1	(2%)							1	(2%)
Cyst, focal, right					1	(25%)				
Cyst, multifocal	9	(20%)	4	(44%)	2	(50%)	9	(53%)	18	(39%)
Cyst, multifocal, bilateral	9	(20%)	1	(11%)			2	(12%)	6	(13%)
Hyperplasia, diffuse, bilateral	1	(2%)								
Hyperplasia, diffuse, unilateral	1	(2%)								
Hypertrophy, diffuse, bilateral	1	(2%)								
Inflammation, chronic					2	(50%)	2	(12%)	2	(4%)
Inflammation, subacute	2	(4%)	1	(11%)					1	(2%)
Prostate	(46)		(8)				(10)		(47)	
Inflammation, chronic	7	(15%)	2	(25%)			1	(10%)	7	(15%)
Inflammation, subacute	4	(9%)								
Salivary glands	(48)		(11)		(1)		(10)		(48)	
Cyst, focal			1	(9%)						
Inflammation, chronic	19	(40%)	1	(9%)			2	(20%)	22	(46%)
Inflammation, subacute	4	(8%)	2	(18%)			3	(30%)	1	(2%)
Seminal vesicle	(46)		(8)		(1)		(9)		(47)	
Inflammation, chronic, focal	1	(2%)	1	(13%)						
Inflammation, subacute, multifocal	1	(2%)								
Skeletal muscle	(47)		(9)		(2)		(12)		(48)	
Degen	4	(9%)							3	(6%)
Skin	(48)		(11)		(7)		(14)		(47)	
Hyperkeratosis, focal	1	(2%)								
Hyperplasia, focal	1	(2%)								
Hyperplasia, focal, sebaceous gland	1	(2%)								
Hyperplasia, lymphoid, focal	1	(2%)								
Hyperplasia, multifocal, dermis	1	(2%)								
Inflammation, chronic	1	(2%)	2	(18%)	3	(43%)	1	(7%)	4	(9%)
Necrosis, focal	1	(2%)								
Spinal cord, thoracic	(47)		(8)		(2)		(10)		(48)	
Atrophy, focal									1	(2%)
Cyst, focal	1	(2%)								
Spleen	(47)		(8)		(1)		(13)		(48)	
Congestion, multifocal	1	(2%)								
Cyst, focal	1	(2%)								
Deplet lymph, multifocal							1	(8%)	1	(2%)
Edema, multifocal			1	(13%)						
Hema cell prol	1	(2%)	2	(25%)			1	(8%)	2	(4%)
Hemorrhage, multifocal			1	(13%)					1	(2%)
Hyperplasia, lymphoid	14	(30%)	1	(13%)	1	(100%)	2	(15%)	15	(31%)
Stomach, forestomach	(47)		(7)		(1)		(11)		(48)	
Hyperkeratosis, diffuse	1	(2%)	1	(14%)						
Hyperplasia, diffuse	1	(2%)	1	(14%)						
Necrosis, focal	1	(2%)								
Stomach, glandular	(45)		(7)		(2)		(10)		(45)	
Hyperplasia, focal	1	(2%)								
Testes	(48)		(9)		(1)		(12)		(48)	
Atrophy, unilateral, seminif tub	1	(2%)								
Degen, diffuse, bilateral, seminif tub	1	(2%)								
Degen, diffuse, unilateral, seminif tub			1	(11%)						
Degen, focal, unilateral, seminif tub	1	(2%)								
Degen, multifocal, bilateral, seminif tub	1	(2%)								
Degen, multifocal, unilateral, seminif tub	1	(2%)					1	(8%)		
Inflammation, subacute, multifocal, bilateral			1	(11%)						
Mineralization, multifocal, unilateral			1	(11%)			2	(16%)	1	(2%)

TABLE C4
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of Fumonisin B_1

	0 ppm	5 ppm	15 ppm	80 ppm	150 ppm
2-Year Study (continued)					
Thymus	(33)	(6)	(2)	(7)	(26)
Atrophy	1 (3%)			1 (14%)	
Cyst		1 (17%)		1 (14%)	
Hyperplasia, lymphoid					1 (4%)
Thyroid gland	(44)	(7)	(1)	(7)	(46)
Cyst	2 (5%)				6 (13%)
Urinary bladder	(46)	(9)		(10)	(46)
Dilatation		1 (11%)		1 (10%)	
Inflammation, chronic	17 (37%)	3 (33%)		2 (20%)	22 (48%)
Inflammation, subacute	1 (2%)				1 (2%)

APPENDIX D
SUMMARY OF LESIONS IN FEMALE MICE IN THE 2-YEAR FEED STUDY OF FUMONISIN B_1

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of Fumonisin B_1[a]

	0 ppm	5 ppm	15 ppm	50 ppm	80 ppm
Disposition Summary					
3-Week evaluation	4	4	4	4	4
7-Week evaluation	4	4	4	4	4
9-Week evaluation	4	4	4	4	4
24-Week evaluation	4	4	4	4	4
Animals initially in 2-year study	48	48	48	48	48
Early deaths					
Removed from study	4				
Moribund	7	3	2	3	6
Natural deaths	1	1		6	14
Survivors					
Terminal sacrifice	35	44	46	39	28
Missing	1				
Animals examined microscopically	63	64	64	64	64

Tissues Examined at 3 Weeks with No Neoplasms Observed
Kidney
Liver

Tissues Examined at 7 Weeks with No Neoplasms Observed
Eye
Heart
Kidney
Liver

Tissues Examined at 9 Weeks with No Neoplasms Observed
Intestine small
Kidney
Liver

Tissues Examined at 24 Weeks with No Neoplasms Observed
Kidney
Liver
Ovary
Oviduct
Thymus
Uterus

2-Year Study

	0 ppm	5 ppm	15 ppm	50 ppm	80 ppm
Adrenal gland	(45)	(3)	(3)	(9)	(40)
Histio sarc			1 (33%)		
Histio sarc, metastatic, spleen					1 (3%)
Lymph mal				3 (33%)	
Blood vessel, aorta	(43)	(4)	(2)	(7)	(48)
Lymph mal				1 (14%)	
Bone, femur	(47)	(3)	(2)	(8)	(47)
Lymph mal					1 (2%)

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of Fumonisin B_1

	0 ppm	5 ppm	15 ppm	50 ppm	80 ppm
2-Year Study (continued)					
Bone marrow	(47)	(4)	(2)	(8)	(45)
Histio sarc	1 (2%)				
Lymph mal	2 (4%)			1 (13%)	1 (2%)
Brain, cerebellum	(45)	(4)	(2)	(9)	(42)
Lymph mal	1 (2%)			1 (11%)	
Meningioma mal					1 (2%)
Brain, cerebrum	(47)	(4)	(2)	(9)	(47)
Lymph mal				1 (11%)	
Meningioma mal					2 (4%)
Clitoral gland	(34)	(3)		(2)	(34)
Adenoma	1 (3%)				
Lymph mal	1 (3%)			1 (50%)	3 (9%)
Ear	(46)	(3)	(2)	(6)	(41)
Lymph mal				1 (17%)	
Esophagus	(46)	(4)	(2)	(8)	(46)
Lymph mal	1 (2%)			3 (38%)	1 (2%)
Eye	(45)	(3)	(2)	(4)	(36)
Lymph mal				1 (25%)	
Gallbladder	(42)	(3)	(2)	(5)	(26)
Lymph mal	2 (5%)			1 (20%)	2 (8%)
Harderian gland	(46)	(5)	(3)	(8)	(44)
Adenoma	4 (9%)	1 (20%)	1 (33%)	2 (25%)	
Carcinoma	1 (2%)				
Histio sarc	1 (2%)				
Lymph mal	7 (15%)			3 (38%)	3 (7%)
Heart	(47)	(4)	(2)	(9)	(47)
Lymph mal	2 (4%)			2 (22%)	
Intestine large, cecum	(47)	(3)	(2)	(6)	(35)
Lymph mal	2 (4%)			1 (17%)	4 (11%)
Intestine large, colon	(47)	(4)	(2)	(5)	(36)
Lymph mal	1 (2%)				2 (6%)
Intestine large, rectum	(47)	(4)	(2)	(6)	(34)
Lymph mal	1 (2%)				
Intestine small, duodenum	(47)	(3)	(2)	(5)	(34)
Lymph mal	2 (4%)				
Intestine small, ileum	(47)	(3)	(2)	(6)	(35)
Lymph mal				1 (17%)	2 (6%)
Intestine small, jejunum	(47)	(3)	(3)	(5)	(35)
Lymph mal			1 (33%)		
Kidney	(47)	(48)	(48)	(48)	(42)
Histio sarc	2 (4%)		1 (2%)		
Histio sarc, metastatic, spleen					1 (2%)
Lymph mal	13 (28%)	8 (17%)	4 (8%)	7 (15%)	13 (31%)
Lacrimal gland	(46)	(4)	(1)	(7)	(40)
Lymph mal	14 (30%)			4 (57%)	9 (23%)
Liver	(47)	(48)	(48)	(47)	(45)
Hemangiosarc	1 (2%)				2 (4%)
Hepatoclr aden	5 (11%)	3 (6%)	1 (2%)	16 (34%)	31 (69%)
Hepatoclr carc				10 (21%)	9 (20%)
Histio sarc	2 (4%)		1 (2%)		
Histio sarc, metastatic, spleen	1 (2%)			1 (2%)	1 (2%)
Lymph mal	16 (34%)	6 (13%)	4 (8%)	7 (15%)	7 (16%)

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of Fumonisin B_1

	0 ppm		5 ppm		15 ppm		50 ppm		80 ppm	
2-Year Study (continued)										
Lung	(47)		(4)		(2)		(9)		(47)	
Adenocarc, metastatic, mammary gland	1	(2%)								
Alv bron aden	2	(4%)					1	(11%)		
Hepatoclr carc, metastatic, liver									2	(4%)
Histio sarc	2	(4%)								
Histio sarc, metastatic, spleen	1	(2%)					1	(11%)		
Lymph mal	15	(32%)					5	(56%)	11	(23%)
Lymph mal hist									1	(2%)
Squam cel carc, metastatic, skin			1	(25%)						
Lymph node	(47)		(6)		(7)		(11)		(45)	
Lymph mal, lumbar	2	(4%)					1	(9%)		
Lymph mal, renal	2	(4%)			1	(14%)			1	(2%)
Squam cel carc, metastatic, axillary, skin			1	(17%)						
Lymph node, deep cervical			(1)						(1)	
Lymph mal									1	(100%)
Squam cel carc, metastatic, skin			1	(100%)						
Lymph node, mandibular	(46)		(5)		(3)		(8)		(44)	
Lymph mal	13	(28%)	1	(20%)			4	(50%)	10	(23%)
Lymph mal hist									1	(2%)
Squam cel carc, metastatic, skin			1	(20%)						
Lymph node, mesenteric	(47)		(5)		(5)		(8)		(39)	
Histio sarc	1	(2%)			1	(20%)				
Histio sarc, metastatic, spleen	1	(2%)								
Lymph mal	17	(36%)	1	(20%)	2	(40%)	3	(38%)	10	(26%)
Lymph mal hist									1	(3%)
Mammary gland	(46)		(2)		(2)		(9)		(38)	
Adenocarc	1	(2%)			1	(50%)	1	(11%)		
Adenocarc, inguinal							1	(11%)		
Lymph mal	5	(11%)					3	(33%)	4	(11%)
Nose	(47)		(4)		(2)		(9)		(48)	
Adenoma, glands									1	(2%)
Lymph mal	5	(11%)					3	(33%)	4	(8%)
Ovary	(46)		(15)		(15)		(22)		(42)	
Hemangioma							1	(5%)		
Histio sarc	1	(2%)								
Histio sarc, metastatic, spleen									1	(2%)
Lymph mal	9	(20%)					5	(23%)	11	(26%)
Lymph mal hist									1	(2%)
Pancreas	(47)		(5)		(2)		(8)		(39)	
Histio sarc, metastatic, spleen	1	(2%)							1	(3%)
Lymph mal	6	(13%)					2	(25%)	4	(10%)
Salivary glands	(47)		(4)		(2)		(8)		(47)	
Lymph mal	14	(30%)					4	(50%)	12	(26%)
Lymph mal hist									1	(2%)
Skeletal muscle	(47)		(4)		(2)		(9)		(48)	
Lymph mal									1	(2%)
Skin	(47)		(4)		(1)		(9)		(42)	
Carc adenosqua	1	(2%)								
Fibrosarc	1	(2%)	1	(25%)						
Lymph mal							2	(22%)		
Papilloma									1	(2%)
Squam cel carc			1	(25%)						
Spinal cord, thoracic	(47)		(4)		(2)		(8)		(46)	
Lymph mal	1	(2%)					1	(13%)		

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of Fumonisin B_1

	0 ppm	5 ppm	15 ppm	50 ppm	80 ppm
2-Year Study (continued)					
Spleen	(47)	(10)	(13)	(17)	(42)
Hemangiosarc					1 (2%)
Hemangiosarc, metastatic, liver					1 (2%)
Histio sarc	2 (4%)		1 (8%)	1 (6%)	1 (2%)
Lymph mal	17 (36%)	5 (50%)	9 (69%)	9 (53%)	12 (29%)
Stomach, forestomach	(46)	(4)	(2)	(9)	(43)
Lymph mal	1 (2%)			2 (22%)	
Stomach, glandular	(46)	(4)	(2)	(6)	(39)
Lymph mal	1 (2%)			1 (17%)	1 (3%)
Thymus	(37)	(4)	(2)	(5)	(34)
Lymph mal	7 (19%)			2 (40%)	6 (18%)
Thyroid gland	(46)	(3)	(1)	(7)	(41)
Adenoma	1 (2%)			1 (14%)	1 (2%)
Tongue	(47)	(4)	(2)	(9)	(46)
Lymph mal	2 (4%)			1 (11%)	
Trachea	(43)	(3)	(1)	(5)	(38)
Lymph mal					1 (3%)
Urinary bladder	(45)	(4)	(2)	(8)	(35)
Histio sarc	2 (4%)				
Lymph mal	13 (29%)			4 (50%)	10 (29%)
Uterus	(47)	(38)	(32)	(38)	(42)
Hemangioma	1 (2%)				
Hemangiosarc		1 (3%)			
Histio sarc	2 (4%)			1 (3%)	
Histio sarc, metastatic, spleen					1 (2%)
Leiomyoma	1 (2%)				
Lymph mal	2 (4%)			4 (11%)	
Polyp			1 (3%)	1 (3%)	
Sarc stromal		1 (3%)			1 (2%)
Vagina	(47)	(3)	(2)	(8)	(38)
Histio sarc	2 (4%)				
Histio sarc, metastatic, spleen					1 (3%)
Lymph mal	3 (6%)			4 (50%)	2 (5%)
Neoplasm Summary					
Total animals with primary neoplasms[b]					
2-Year study	32	16	13	30	44
Total primary neoplasms					
2-Year study	238	29	30	135	205
Total animals with benign neoplasms					
2-Year study	13	4	3	21	31
Total benign neoplasms					
2-Year study	15	4	3	22	34
Total animals with malignant neoplasms					
2-Year study	28	13	12	19	24
Total malignant neoplasms					
2-Year study	223	25	27	113	171
Total animals with metastatic neoplasms					
2-Year study	2	1		1	4
Total metastatic neoplasms					
2-Year study	5	4		2	10

[a] Number of animals examined microscopically at the site and the number of animals with neoplasm
[b] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Fumonisin B_1: 0 ppm

Carcass ID Number	028	044	056	063	064	065	066	067	076	079	141	142	143	144	145	146	147	148	186	187	188	197	220	221	222
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Blood vessel	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Blood vessel, aorta	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bone, femur	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bone, sternum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histio sarc																						X			
Lymph mal																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Brain, cerebellum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph mal																									
Brain, cerebrum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Clitoral gland	M	+	+	+	+	+	+	M	+	M	+	+	M	+	+	M	+	+	+	+	M	+	+	+	+
Adenoma			X																						
Lymph mal																									
Ear	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph mal																									
Eye	A	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph mal																									
Harderian gland	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma					X						X			X		X									
Carcinoma														X											
Histio sarc																						X			
Lymph mal																	X								X
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph mal																									
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph mal										X															
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph mal																									
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph mal																									
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph mal																			X						
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histio sarc	X																					X			
Lymph mal											X						X		X		X				X
Lacrimal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph mal											X		X				X		X		X			X	X
Larynx	+	+	+	+	+	M	+	+	+	+	M	M	+	+	M	+	+	+	M	M	M	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarc																							X		
Hepatoclr aden																		X			X				
Histio sarc	X																					X			
Histio sarc, metastatic, spleen								X																	
Lymph mal										X	X		X		X		X				X			X	X

+: Tissue examined microscopically
A: Autolysis precludes examination
M: Missing tissue
I: Insufficient tissue
X: Lesion present
Blank: Not examined

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Fumonisin B_1: 0 ppm

Carcass ID Number	275	276	277	278	279	280	332	333	334	335	336	337	362	420	421	422	423	470	471	472	473	474	Total Tissues/ Tumors
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	45
Blood vessel	M	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	43
Blood vessel, aorta	M	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	43
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Bone, femur	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Bone, sternum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Histio sarc																							1
Lymph mal					X	X																	2
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Brain, cerebellum	+	+	+	+	+	+	+	+	+	I	I	+	+	+	+	+	+	+	+	+	+	+	45
Lymph mal			X																				1
Brain, cerebrum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Clitoral gland	+	M	+	+	M	+	M	M	+	+	+	+	+	+	+	+	M	M	+	+	M	+	34
Adenoma																							1
Lymph mal																X							1
Ear	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Lymph mal																X							1
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Gallbladder	+	M	+	+	M	+	+	+	+	+	I	+	+	+	+	+	+	I	+	+	+	+	42
Lymph mal																	X		X				2
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Adenoma																							4
Carcinoma																							1
Histio sarc																							1
Lymph mal			X		X	X		X											X				7
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph mal			X			X																	2
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph mal																					X		2
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph mal																					X		1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph mal																			X				1
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph mal								X															2
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Histio sarc																							2
Lymph mal			X		X	X			X							X	X		X		X		13
Lacrimal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	46
Lymph mal			X			X		X	X							X			X		X		14
Larynx	M	+	M	+	+	+	+	+	M	M	+	+	+	I	+	+	+	M	M	M	+	I	31
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Hemangiosarc																							1
Hepatoclr aden					X				X							X							5
Histio sarc																							2
Histio sarc, metastatic, spleen																							1
Lymph mal			X		X	X		X								X	X		X		X		16

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Fumonisin B_1: 0 ppm

Carcass ID Number	028	044	056	063	064	065	066	067	076	079	141	142	143	144	145	146	147	148	186	187	188	197	220	221	222
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarc, metastatic, mammary gland		X																							
Alv bron aden			X											X											
Histio sarc	X																					X			
Histio sarc, metastatic, spleen								X																	
Lymph mal											X		X				X		X		X				X
Lung, bronchus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph mal, lumbar													X												X
Lymph mal, renal										X						X									
Lymph node, mandibular	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph mal											X		X				X		X					X	X
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histio sarc																						X			
Histio sarc, metastatic, spleen								X																	
Lymph mal										X	X		X			X	X		X						X
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarc		X																							
Lymph mal																								X	
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph mal																	X								
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histio sarc	X																								
Lymph mal																			X						
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histio sarc, metastatic, spleen								X																	
Lymph mal																	X				X				
Parathyroid gland	M	+	M	+	+	+	+	+	+	+	+	M	+	+	M	M	M	+	+	+	+	+	+	M	+
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Pituitary gland	M	+	+	+	+	+	M	+	+	+	+	+	M	+	M	I	M	I	+	+	+	M	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph mal											X						X		X		X			X	
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carc adenosqua			X																						
Fibrosarc																									
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord, thoracic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph mal																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histio sarc								X														X			
Lymph mal										X	X		X				X				X			X	X
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+
Lymph mal											X														
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+
Lymph mal																									
Thymus	M	+	+	+	+	+	+	M	+	+	+	+	M	M	+	+	+	+	+	M	+	M	M	M	+
Lymph mal																X									X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Adenoma																									

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Fumonisin B_1: 0 ppm

Carcass ID Number	275	276	277	278	279	280	332	333	334	335	336	337	362	420	421	422	423	470	471	472	473	474	Total Tissues/ Tumors
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenocarc, metastatic, mammary gland																							1
Alv bron aden																							2
Histio sarc																							2
Histio sarc, metastatic, spleen																							1
Lymph mal			X			X	X	X	X							X	X		X		X		15
Lung, bronchus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph mal, lumbar																							2
Lymph mal, renal																							2
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Lymph mal			X			X		X	X								X		X		X		13
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Histio sarc																							1
Histio sarc, metastatic, spleen																							1
Lymph mal			X		X	X	X	X	X							X	X		X		X		17
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	46
Adenocarc																							1
Lymph mal			X					X	X								X						5
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph mal			X			X		X													X		5
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	46
Histio sarc																							1
Lymph mal			X		X	X	X		X								X		X		X		9
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Histio sarc, metastatic, spleen																							1
Lymph mal			X			X													X		X		6
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	M	+	37
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	45
Pituitary gland	+	I	+	+	+	I	M	M	+	+	M	M	I	M	+	M	M	+	+	+	+	+	29
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph mal			X		X	X		X	X							X	X		X		X		14
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Carc adenosqua																							1
Fibrosarc													X										1
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Spinal cord, thoracic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph mal			X																				1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Histio sarc																							2
Lymph mal			X		X	X	X	X	X							X	X		X		X		17
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Lymph mal																							1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Lymph mal						X																	1
Thymus	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	37
Lymph mal					X	X		X											X		X		7
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Adenoma				X																			1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Fumonisin B_1: 0 ppm

Carcass ID Number	028	044	056	063	064	065	066	067	076	079	141	142	143	144	145	146	147	148	186	187	188	197	220	221	222
Tongue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph mal																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	M	+	M	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+
Histio sarc	X																					X			
Lymph mal											X		X						X		X				X
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma									X																
Histio sarc	X																					X			
Leiomyoma																							X		
Lymph mal											X														
Vagina	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histio sarc																						X			X
Lymph mal																									
Zymbal's gland	M	+	+	+	+	+	+	M	M	+	+	+	+	M	+	M	+	M	+	+	+	+	M	M	+

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Fumonisin B_1: 0 ppm

Carcass ID Number	275	276	277	278	279	280	332	333	334	335	336	337	362	420	421	422	423	470	471	472	473	474	Total Tissues/ Tumors
Tongue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph mal								X													X		2
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	45
Histio sarc																							2
Lymph mal			X			X	X	X	X								X		X		X		13
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Hemangioma																							1
Histio sarc																							2
Leiomyoma																							1
Lymph mal			X																				2
Vagina	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Histio sarc																							2
Lymph mal						X		X											X				3
Zymbal's gland	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	M	+	35

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Fumonisin B_1: 5 ppm

Carcass ID Number	036	040	072	133	134	135	136	137	138	139	140	183	184	185	226	227	228	229	271	272	273	274	296	338	339
Adrenal gland	+	+	I																				+		
Blood vessel	+	+	+																				+		
Blood vessel, aorta	+	+	+																				+		
Bone	+	+	+																				+		
Bone, femur	+	M	+																				+		
Bone, sternum	+	+	+																				+		
Bone marrow	+	+	+																				+		
Brain	+	+	+																				+		
Brain, cerebellum	+	+	+																				+		
Brain, cerebrum	+	+	+																				+		
Clitoral gland	M	+	+																				+		
Ear	M	+	+																				+		
Esophagus	+	+	+																				+		
Eye	+	+	A																				+		
Gallbladder	+	+	A																				+		
Harderian gland	+	+	+																				+		
Adenoma																									
Heart	+	+	+																				+		
Intestine large	+	+	+																				+		
Intestine large, cecum	+	+	A																				+		
Intestine large, colon	+	+	+																				+		
Intestine large, rectum	+	+	+																				+		
Intestine small	+	+	A																				+		
Intestine small, duodenum	+	+	A																				+		
Intestine small, ileum	+	+	A																				+		
Intestine small, jejunum	+	+	A																				+		
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph mal				X									X							X		X			
Lacrimal gland	+	+	+																				+		
Larynx	M	M	M																				M		
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatoclr aden																	X								
Lymph mal																				X		X			
Lung	+	+	+																				+		
Squam cel carc, metastatic, skin	X																								
Lung, bronchus	+	+	+																				+		
Lymph node	+	+	+																	+			+		
Squam cel carc, metastatic, skin, axillary	X																								
Lymph node, deep cervical	+																								
Squam cel carc, metastatic, skin	X																								
Lymph node, mandibular	+	+	+																	+			+		
Lymph mal																				X					
Squam cel carc, metastatic, skin	X																								
Lymph node, mesenteric	+	+	+																				+		
Lymph mal																									
Mammary gland	M	M	+																				+		
Nose	+	+	+																				+		
Ovary	+	+	+		I						+			+		+	+					+	+	+	
Pancreas	+	+	+																				+		
Parathyroid gland	M	+	+																				M		
Peripheral nerve	+	+	+																				+		
Pituitary gland	M	+	M																				+		
Salivary glands	+	+	+																				+		
Skeletal muscle	+	+	+																				+		

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Fumonisin B_1: 5 ppm

Carcass ID Number	340	341	342	343	344	403	404	405	406	407	408	424	425	426	427	476	477	478	479	480	481	482	483	Total Tissues/ Tumors
Adrenal gland																								3
Blood vessel																								4
Blood vessel, aorta																								4
Bone																								4
Bone, femur																								3
Bone, sternum																								4
Bone marrow																								4
Brain																								4
Brain, cerebellum																								4
Brain, cerebrum																								4
Clitoral gland																								3
Ear																								3
Esophagus																								4
Eye																								3
Gallbladder																								3
Harderian gland																						+		5
Adenoma																						X		1
Heart																								4
Intestine large																								4
Intestine large, cecum																								3
Intestine large, colon																								4
Intestine large, rectum																								4
Intestine small																								3
Intestine small, duodenum																								3
Intestine small, ileum																								3
Intestine small, jejunum																								3
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph mal	X				X						X							X						8
Lacrimal gland																								4
Larynx																								0
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hepatoclr aden							X											X						3
Lymph mal	X				X						X							X						6
Lung																								4
Squam cel carc, metastatic, skin																								1
Lung, bronchus																								4
Lymph node											+													6
Squam cel carc, metastatic, skin, axillary																								1
Lymph node, deep cervical																								1
Squam cel carc, metastatic, skin																								1
Lymph node, mandibular																								5
Lymph mal																								1
Squam cel carc, metastatic, skin																								1
Lymph node, mesenteric											+													5
Lymph mal											X													1
Mammary gland																								2
Nose																								4
Ovary						+						+					+		+				+	15
Pancreas																+								5
Parathyroid gland																								2
Peripheral nerve																								4
Pituitary gland																								2
Salivary glands																								4
Skeletal muscle																								4

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Fumonisin B_1: 5 ppm

Carcass ID Number	036	040	072	133	134	135	136	137	138	139	140	183	184	185	226	227	228	229	271	272	273	274	296	338	339
Skin	+	+	+																				+		
Fibrosarc																							X		
Squam cel carc	X																								
Spinal cord	+	+	+																				+		
Spinal cord, thoracic	+	+	+																				+		
Spleen	+	+	+				+													+			+		
Lymph mal							X													X					
Stomach	+	+	+																				+		
Stomach, forestomach	+	+	+																				+		
Stomach, glandular	+	+	+																				+		
Thymus	+	+	+																				+		
Thyroid gland	+	+	+																				M		
Tongue	+	+	+																				+		
Trachea	+	+	+																				M		
Urinary bladder	+	+	+																				+		
Uterus	+	+	+		+	+	+		+	+	+	+	+	+		+		+	+	+	+	+	+	+	+
Hemangiosarc			X																						
Sarc stromal																									
Vagina	+	+	M																				+		
Zymbal's gland	M	+	M																				+		

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Fumonisin B_1: 5 ppm

	3	3	3	3	3	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	Total
Carcass ID Number	4	4	4	4	4	0	0	0	0	0	0	2	2	2	2	7	7	7	7	8	8	8	8	Tissues/
	0	1	2	3	4	3	4	5	6	7	8	4	5	6	7	6	7	8	9	0	1	2	3	Tumors
Skin																								4
Fibrosarc																								1
Squam cel carc																								1
Spinal cord																								4
Spinal cord, thoracic																								4
Spleen	+										+							+			+			10
Lymph mal	X										X							X						5
Stomach																								4
Stomach, forestomach																								4
Stomach, glandular																								4
Thymus																								4
Thyroid gland																								3
Tongue																								4
Trachea																								3
Urinary bladder																								4
Uterus	+		+	+	+		+	+		+	+	+			+	+		+	+	+	+	+	+	38
Hemangiosarc																								1
Sarc stromal																X								1
Vagina																								3
Zymbal’s gland																								2

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Fumonisin B_1: 15 ppm

Carcass ID Number	043	092	155	156	157	158	159	160	161	193	194	195	196	223	224	225	288	289	290	291	292	293	294	295	345
Adrenal gland	+	+												+											
Histio sarc														X											
Blood vessel	+	+																							
Blood vessel, aorta	+	+																							
Bone	+	+																							
Bone, femur	+	+																							
Bone, sternum	+	+																							
Bone marrow	+	+																							
Brain	+	+																							
Brain, cerebellum	+	+																							
Brain, cerebrum	+	+																							
Clitoral gland	M	M																							
Ear	+	+																							
Esophagus	+	+																							
Eye	+	+																							
Gallbladder	+	+																							
Harderian gland	+	+		+																					
Adenoma				X																					
Heart	+	+																							
Intestine large	+	+																							
Intestine large, cecum	+	+																							
Intestine large, colon	+	+																							
Intestine large, rectum	+	+																							
Intestine small	+	+																							
Intestine small, duodenum	+	+																							
Intestine small, ileum	+	+																							
Intestine small, jejunum	+	+																							
Lymph mal																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histio sarc														X											
Lymph mal				X			X								X					X					
Lacrimal gland	+	M																							
Larynx	+	+																							
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatoclr aden																									
Histio sarc														X											
Lymph mal				X		X									X					X					
Lung	+	+																							
Lung, bronchus	+	+																							
Lymph node	+	+												+	+				+						
Lymph mal, renal															X										
Lymph node, mandibular	+	+																	+						
Lymph node, mesenteric	+	+												+											
Histio sarc														X											
Lymph mal																									
Mammary gland	+	+																							
Adenocarc	X																								
Nose	+	+																							
Ovary	+	M							+				+			+					+	+			
Pancreas	+	+																							
Parathyroid gland	M	+																							
Peripheral nerve	+	+																							
Pituitary gland	+	M																							
Salivary glands	+	+																							
Skeletal muscle	+	+																							

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Fumonisin B_1: 15 ppm

Carcass ID Number	346	347	348	349	350	351	352	412	413	414	415	416	417	418	419	484	485	486	487	488	489	490	491	Total Tissues/ Tumors
Adrenal gland																								3
Histio sarc																								1
Blood vessel																								2
Blood vessel, aorta																								2
Bone																								2
Bone, femur																								2
Bone, sternum																								2
Bone marrow																								2
Brain																								2
Brain, cerebellum																								2
Brain, cerebrum																								2
Clitoral gland																								0
Ear																								2
Esophagus																								2
Eye																								2
Gallbladder																								2
Harderian gland																								3
Adenoma																								1
Heart																								2
Intestine large																								2
Intestine large, cecum																								2
Intestine large, colon																								2
Intestine large, rectum																								2
Intestine small		+																						3
Intestine small, duodenum																								2
Intestine small, ileum																								2
Intestine small, jejunum		+																						3
Lymph mal		X																						1
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Histio sarc																								1
Lymph mal																								4
Lacrimal gland																								1
Larynx																								2
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hepatoclr aden			X																					1
Histio sarc																								1
Lymph mal																								4
Lung																								2
Lung, bronchus																								2
Lymph node		+	+																					7
Lymph mal, renal																								1
Lymph node, mandibular																								3
Lymph node, mesenteric		+	+																					5
Histio sarc																								1
Lymph mal		X	X																					2
Mammary gland																								2
Adenocarc																								1
Nose																								2
Ovary				+	+	+	+		+			+				+				+			+	15
Pancreas																								2
Parathyroid gland																								1
Peripheral nerve																								2
Pituitary gland																								1
Salivary glands																								2
Skeletal muscle																								2

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Fumonisin B_1: 15 ppm

Carcass ID Number	043	092	155	156	157	158	159	160	161	193	194	195	196	223	224	225	288	289	290	291	292	293	294	295	345
Skin	M	+																							
Spinal cord	+	+																							
Spinal cord, thoracic	+	+																							
Spleen	+	+		+		+	+							+	+					+			+		
Histio sarc														X											
Lymph mal				X		X	X								X					X			X		
Stomach	+	+																							
Stomach, forestomach	+	+																							
Stomach, glandular	+	+																							
Thymus	+	+																							
Thyroid gland	M	+																							
Tongue	+	+																							
Trachea	M	+																							
Urinary bladder	+	+																							
Uterus	+	+	+	+					+		+	+			+	+		+		+	+	+	+		+
Polyp																									
Vagina	+	+																							
Zymbal's gland	+	+																							

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Fumonisin B_1: 15 ppm

Carcass ID Number	3	3	3	3	3	3	3	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	Total
	4	4	4	4	5	5	5	1	1	1	1	1	1	1	1	8	8	8	8	8	8	9	9	Tissues/
	6	7	8	9	0	1	2	2	3	4	5	6	7	8	9	4	5	6	7	8	9	0	1	Tumors
Skin																								1
Spinal cord																								2
Spinal cord, thoracic																								2
Spleen		+		+																	+	+		13
Histio sarc																								1
Lymph mal		X		X																	X			9
Stomach																								2
Stomach, forestomach																								2
Stomach, glandular																								2
Thymus																								2
Thyroid gland																								1
Tongue																								2
Trachea																								1
Urinary bladder																								2
Uterus	+		+	+		+	+	+	+	+		+	+	+		+	+	+		+	+	+		32
Polyp								X																1
Vagina																								2
Zymbal's gland																								2

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Fumonisin B_1: 50 ppm

Carcass ID Number	034	037	039	053	071	075	086	088	149	150	151	152	153	154	189	190	191	192	230	231	232	233	281	282	283
Adrenal gland	+	+	+	+	+	+	+	+																	
Lymph mal	X		X			X																			
Blood vessel	+	+	+	A	M	+	+	+																	
Blood vessel, aorta	+	+	+	A	M	+	+	+																	
Lymph mal						X																			
Bone	+	+	+	A	+	+	+	+																	
Bone, femur	+	+	+	A	+	+	+	+																	
Bone, sternum	+	+	+	A	+	+	+	+																	
Bone marrow	+	+	+	A	+	+	+	+																	
Lymph mal	X																								
Brain	+	+	+	+	+	+	+	+																	
Brain, cerebellum	+	+	+	+	+	+	+	+																	
Lymph mal	X																								
Brain, cerebrum	+	+	+	+	+	+	+	+																	
Lymph mal	X																								
Clitoral gland	+	M	A	M	M	M	+	M																	
Lymph mal	X																								
Ear	M	M	M	+	+	+	+	+																	
Lymph mal																									
Esophagus	+	+	+	M	+	+	+	+																	
Lymph mal						X	X																		
Eye	+	+	A	A	A	I	A	+																	
Lymph mal	X																								
Gallbladder	+	+	A	A	A	+	M	+																	
Lymph mal						X																			
Harderian gland	+	M	+	+	+	+	+	+																	
Adenoma					X		X																		
Lymph mal	X						X																		
Heart	+	+	+	+	+	+	+	+																	
Lymph mal	X					X																			
Intestine large	+	+	A	A	+	+	A	+																	
Intestine large, cecum	+	+	A	A	+	+	A	+																	
Lymph mal						X																			
Intestine large, colon	+	+	A	A	+	M	A	+																	
Intestine large, rectum	+	+	A	A	+	+	A	+																	
Intestine small	+	+	A	A	+	+	A	+																	
Intestine small, duodenum	+	+	A	A	+	+	A	A																	
Intestine small, ileum	+	+	A	A	+	+	A	+																	
Lymph mal						X																			
Intestine small, jejunum	+	+	A	A	+	+	A	A																	
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph mal	X		X			X																			
Lacrimal gland	+	+	+	A	M	+	+	+																	
Lymph mal	X					X	X																		
Larynx	+	M	M	+	+	+	M	+																	
Liver	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatoclr aden							X	X	X	X	X	X	X						X	X	X	X			
Hepatoclr carc					X			X			X		X								X	X			
Histio sarc, metastatic, spleen		X																							
Lymph mal	X		X			X																			
Lung	+	+	+	+	+	+	+	+																	
Alv bron aden																									
Histio sarc, metastatic, spleen		X																							
Lymph mal	X		X			X	X																		
Lung, bronchus	+	+	+	+	+	+	+	+																	

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Fumonisin B_1: 50 ppm

Carcass ID Number	284	285	286	287	297	353	354	355	356	357	358	397	398	399	400	401	402	492	493	494	495	496	497	Total Tissues/ Tumors
Adrenal gland					+																			9
Lymph mal																								3
Blood vessel					+																			7
Blood vessel, aorta					+																			7
Lymph mal																								1
Bone					+																			8
Bone, femur					+																			8
Bone, sternum					+																			8
Bone marrow					+																			8
Lymph mal																								1
Brain					+																			9
Brain, cerebellum					+																			9
Lymph mal																								1
Brain, cerebrum					+																			9
Lymph mal																								1
Clitoral gland					M																			2
Lymph mal																								1
Ear					+																			6
Lymph mal					X																			1
Esophagus					+																			8
Lymph mal					X																			3
Eye					+																			4
Lymph mal																								1
Gallbladder					+																			5
Lymph mal																								1
Harderian gland					+																			8
Adenoma																								2
Lymph mal					X																			3
Heart					+																			9
Lymph mal																								2
Intestine large					+																			6
Intestine large, cecum					+																			6
Lymph mal																								1
Intestine large, colon					+																			5
Intestine large, rectum					+																			6
Intestine small					+																			6
Intestine small, duodenum					+																			5
Intestine small, ileum					+																			6
Lymph mal																								1
Intestine small, jejunum					+																			5
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph mal					X		X					X											X	7
Lacrimal gland					+																			7
Lymph mal					X																			4
Larynx					+																			6
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Hepatoclr aden											X					X				X		X	X	16
Hepatoclr carc								X										X		X			X	10
Histio sarc, metastatic, spleen																								1
Lymph mal					X		X		X														X	7
Lung					+																			9
Alv bron aden					X																			1
Histio sarc, metastatic, spleen																								1
Lymph mal					X																			5
Lung, bronchus					+																			9

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Fumonisin B_1: 50 ppm

Carcass ID Number	034	037	039	053	071	075	086	088	149	150	151	152	153	154	189	190	191	192	230	231	232	233	281	282	283
Lymph node	+	+	+	+	+	+	+	+					+												
Lymph mal, lumbar																									
Lymph node, mandibular	+	M	+	+	+	+	+	+																	
Lymph mal			X			X	X																		
Lymph node, mesenteric	+	+	+	A	+	+	A	+					+												
Lymph mal			X			X																			
Mammary gland	+	+	+	M	+	+	+	+					+												
Adenocarc													X												
Adenocarc, inguinal								X																	
Lymph mal	X		X																						
Mesentery																									
Nose	+	+	+	+	+	+	+	+																	
Lymph mal			X			X																			
Ovary	+	+	+	M	+	+	+	+	+	+		+	+			M		+		+				+	+
Hemangioma																									
Lymph mal	X		X			X	X																		
Pancreas	+	+	+	+	+	+	A	+																	
Lymph mal						X																			
Parathyroid gland	M	+	M	M	+	M	+	+																	
Peripheral nerve	+	+	+	+	+	+	+	+																	
Pituitary gland	+	M	I	M	+	M	M	I																	
Salivary glands	+	+	+	A	+	+	+	+																	
Lymph mal	X					X	X																			
Skeletal muscle	+	+	+	+	+	+	+	+																	
Skin	+	+	+	+	+	+	+	+																	
Lymph mal	X		X																						
Spinal cord	+	+	+	+	+	+	A	+																	
Spinal cord, thoracic	+	+	+	+	+	+	A	+																	
Lymph mal	X																								
Spleen	+	+	+	A	+	+	+	+			+	+	+												
Histio sarc		X																							
Lymph mal	X		X			X	X																		
Stomach	+	+	+	+	+	+	+	+																	
Stomach, forestomach	+	+	+	+	+	+	+	+																	
Lymph mal			X																						
Stomach, glandular	+	+	A	A	+	+	A	+																	
Lymph mal						X																			
Thymus	+	M	M	+	M	+	A	+																	
Lymph mal						X																			
Thyroid gland	+	+	+	M	+	+	A	+																+	
Adenoma																								X	
Tongue	+	+	+	+	+	+	+	+																	
Lymph mal	X																								
Trachea	+	+	A	M	+	+	A	+																	
Urinary bladder	+	+	+	+	+	+	A	+																	
Lymph mal	X		X			X																			
Uterus	+	+	+	+	+	+	+	+	+			+	+	+	+	+		+		+				+	+
Histio sarc																									
Lymph mal	X		X			X																			
Polyp				X																					
Vagina	+	+	+	A	+	+	+	+																	
Lymph mal	X		X			X																			
Zymbal's gland	M	M	M	+	+	M	+	M																	

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Fumonisin B_1: 50 ppm

Carcass ID Number	2 8 4	2 8 5	2 8 6	2 8 7	2 9 7	3 5 3	3 5 4	3 5 5	3 5 6	3 5 7	3 5 8	3 9 7	3 9 8	3 9 9	4 0 0	4 0 1	4 0 2	4 9 2	4 9 3	4 9 4	4 9 5	4 9 6	4 9 7	Total Tissues/ Tumors
Lymph node					+		+																	11
Lymph mal, lumbar							X																	1
Lymph node, mandibular					+																			8
Lymph mal					X																			4
Lymph node, mesenteric					+																			8
Lymph mal					X																			3
Mammary gland					+																			9
Adenocarc																								1
Adenocarc, inguinal																								1
Lymph mal					X																			3
Mesentery												+												1
Nose					+																			9
Lymph mal					X																			3
Ovary			+		+	+	+					+		+	+									22
Hemangioma															X									1
Lymph mal					X																			5
Pancreas					+																			8
Lymph mal					X																			2
Parathyroid gland					M																			4
Peripheral nerve					+																			9
Pituitary gland					I																			2
Salivary glands					+																			8
Lymph mal					X																			4
Skeletal muscle					+																			9
Skin					+																			9
Lymph mal																								2
Spinal cord					+																			8
Spinal cord, thoracic					+																			8
Lymph mal																								1
Spleen			+	+	+		+		+			+											+	17
Histio sarc																								1
Lymph mal					X		X		X			X											X	9
Stomach					+																			9
Stomach, forestomach					+																			9
Lymph mal					X																			2
Stomach, glandular					+																			6
Lymph mal																								1
Thymus					+																			5
Lymph mal					X																			2
Thyroid gland					M																			7
Adenoma																								1
Tongue					+																			9
Lymph mal																								1
Trachea					M																			5
Urinary bladder					+																			8
Lymph mal					X																			4
Uterus		+	+	+	+	+	+	+	+			+	+	+	+	+	+	+	+	+	+	+	+	38
Histio sarc																				X				1
Lymph mal					X																			4
Polyp																								1
Vagina					+																			8
Lymph mal					X																			4
Zymbal's gland					M																			3

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Fumonisin B_1: 80 ppm

Carcass ID Number	019	025	029	030	031	032	033	041	042	047	052	055	057	059	062	070	074	089	090	091	127	128	129	130	131
Adrenal gland	A	+	+	+	+	+	+	M	+	+	A	+	+	M	+	M	+	+	+	+	+	+	+	+	+
Histio sarc, metastatic, spleen													X												
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Blood vessel, aorta	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bone, femur	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Lymph mal																									
Bone, sternum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bone marrow	A	+	+	+	+	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Lymph mal																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Brain, cerebellum	+	+	+	+	+	+	+	A	+	+	+	+	+	A	M	+	+	+	+	+	+	+	+	+	+
Meningioma mal												X													
Brain, cerebrum	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Meningioma mal												X			X										
Clitoral gland	M	M	+	M	+	M	+	A	+	+	M	+	M	+	A	+	M	+	+	+	+	+	+	M	+
Lymph mal																									X
Ear	M	M	+	M	M	M	+	A	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Lymph mal																									X
Eye	A	A	+	A	A	A	+	A	+	+	A	+	+	A	A	A	A	A	+	+	+	+	+	+	+
Gallbladder	M	A	M	M	A	A	A	A	M	M	M	+	I	A	A	A	M	M	+	+	+	+	I	+	+
Lymph mal																									
Harderian gland	A	+	+	+	+	+	+	+	+	+	A	+	+	A	+	A	+	+	+	+	+	+	+	+	+
Lymph mal																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	A	A	+	+	A	+	A	A	+	+	A	+	+	A	A	A	A	A	+	+	+	+	+	+	+
Intestine large, cecum	A	A	+	A	A	A	A	A	+	+	A	+	+	A	A	A	A	A	+	+	+	+	+	+	+
Lymph mal																									
Intestine large, colon	A	A	+	+	A	A	A	A	+	+	A	+	+	A	A	A	A	A	+	+	+	+	+	+	+
Lymph mal																									
Intestine large, rectum	A	A	+	A	A	+	A	A	+	+	A	+	+	A	A	A	A	A	+	+	+	+	+	+	+
Intestine small	A	A	+	A	A	A	A	A	+	+	A	+	+	A	A	A	A	A	+	+	+	+	+	+	+
Intestine small, duodenum	A	A	+	A	A	A	A	A	+	+	A	+	+	A	A	A	A	A	+	+	+	+	M	+	+
Intestine small, ileum	A	A	+	A	A	A	A	A	+	+	A	+	+	A	A	A	A	A	+	+	+	+	+	+	+
Lymph mal																									
Intestine small, jejunum	A	A	+	A	A	A	A	A	+	+	A	+	+	A	A	A	A	A	+	+	+	+	+	+	+
Kidney	A	+	+	+	A	+	A	A	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Histio sarc, metastatic, spleen													X												
Lymph mal																				X					X
Lacrimal gland	M	+	M	+	+	+	+	M	+	+	A	+	+	+	+	M	+	+	+	+	+	+	I	+	+
Lymph mal																									X
Larynx	A	+	+	+	+	M	+	A	M	+	+	M	M	A	+	A	M	+	+	M	+	+	M	+	+
Liver	A	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarc										X															
Hepatoclr aden		X		X	X	X				X	X	X		X					X	X	X	X	X	X	X
Hepatoclr carc			X						X							X	X	X		X					
Histio sarc, metastatic, spleen													X												
Lymph mal																									
Lung	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatoclr carc, metastatic, liver			X						X																
Lymph mal																									X
Lymph mal hist																X									
Lung, bronchus	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	A	+	+	+	+	+	+	M	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph mal, renal																									X
Lymph node, deep cervical																									+
Lymph mal																									X

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Fumonisin B_1: 80 ppm

Carcass ID Number	1 3 2	1 8 1	1 8 2	2 1 7	2 1 8	2 1 9	2 6 6	2 6 7	2 6 8	2 6 9	2 7 0	3 5 9	3 6 0	3 6 1	4 0 9	4 1 0	4 1 1	4 6 1	4 6 2	4 7 5	4 9 8	4 9 9	5 0 0	Total Tissues/ Tumors
Adrenal gland	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	40
Histio sarc, metastatic, spleen																								1
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Blood vessel, aorta	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Bone, femur	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph mal				X																				1
Bone, sternum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Lymph mal				X																				1
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Brain, cerebellum	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	I	+	+	+	+	+	+	+	42
Meningioma mal																								1
Brain, cerebrum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Meningioma mal																								2
Clitoral gland	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	M	+	34
Lymph mal					X												X							3
Ear	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Lymph mal																								1
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	36
Gallbladder	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	I	+	M	26
Lymph mal	X																			X				2
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Lymph mal				X	X																	X		3
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	47
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	37
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	35
Lymph mal			X														X				X	X		4
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	36
Lymph mal																	X		X					2
Intestine large, rectum	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	34
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	35
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	34
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	35
Lymph mal																				X	X			2
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	35
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Histio sarc, metastatic, spleen																								1
Lymph mal	X		X	X	X			X								X	X		X	X	X	X		13
Lacrimal gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	40
Lymph mal	X			X	X			X								X	X		X	X				9
Larynx	+	M	+	+	+	+	M	M	+	+	+	M	+	+	M	+	+	M	+	M	M	M	+	28
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Hemangiosarc													X											2
Hepatoclr aden		X	X	X	X	X	X		X	X		X		X	X	X	X	X		X			X	31
Hepatoclr carc													X						X		X			9
Histio sarc, metastatic, spleen																								1
Lymph mal	X			X	X												X		X	X	X			7
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Hepatoclr carc, metastatic, liver																								2
Lymph mal	X			X	X			X								X	X		X	X	X	X		11
Lymph mal hist																								1
Lung, bronchus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Lymph mal, renal																								1
Lymph node, deep cervical																								1
Lymph mal																								1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Fumonisin B_1: 80 ppm

Carcass ID Number	019	025	029	030	031	032	033	041	042	047	052	055	057	059	062	070	074	089	090	091	127	128	129	130	131
Lymph node, mandibular	A	+	+	+	+	+	+	M	+	+	A	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Lymph mal																									X
Lymph mal hist																X									
Lymph node, mesenteric	M	+	+	+	M	+	A	M	+	+	M	+	+	A	A	+	A	+	+	+	+	M	+	+	+
Lymph mal																									X
Lymph mal hist																X									
Mammary gland	M	+	+	M	+	+	A	M	M	+	+	+	+	+	A	M	A	+	+	+	+	+	+	+	+
Lymph mal																									X
Mesentery																				+					
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, glands														X											
Lymph mal																									
Ovary	A	+	+	+	+	+	A	A	+	+	A	+	+	A	+	+	M	+	+	+	+	+	+	+	+
Histio sarc, metastatic, spleen													X												
Lymph mal																				X					X
Lymph mal hist																X									
Pancreas	M	+	+	+	A	+	A	A	+	+	A	+	+	A	+	A	A	A	+	+	+	+	+	+	+
Histio sarc, metastatic, spleen													X												
Lymph mal																									
Parathyroid gland	M	+	M	+	M	+	A	M	+	+	+	+	M	A	M	+	+	+	+	+	+	M	+	+	M
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Pituitary gland	M	M	+	M	+	+	+	M	M	+	+	M	M	A	+	+	+	+	M	+	M	M	+	+	+
Salivary glands	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph mal																				X					X
Lymph mal hist																X									
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph mal																									X
Skin	A	+	+	+	A	+	A	A	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+
Papilloma																									
Spinal cord	+	+	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Spinal cord, thoracic	+	+	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Spleen	A	+	+	+	A	+	A	A	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarc																									
Hemangiosarc, metastatic, liver										X															
Histio sarc													X												
Lymph mal																									X
Stomach	+	+	+	A	+	+	+	+	+	+	A	+	+	A	+	A	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	A	+	+	+	+	+	+	A	+	+	A	+	A	+	+	+	+	+	+	+	+	+
Stomach, glandular	A	+	+	A	A	+	A	A	+	+	A	+	+	A	A	A	+	+	+	+	+	+	+	+	+
Lymph mal																									
Thymus	+	+	M	+	+	+	M	M	+	M	M	+	M	M	+	M	M	M	+	M	+	+	+	+	+
Lymph mal																									X
Thyroid gland	A	+	+	+	A	+	A	M	+	+	A	+	+	A	A	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Tongue	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+
Trachea	A	+	+	M	A	+	A	A	+	M	A	+	+	A	A	+	A	+	+	+	+	+	+	+	+
Lymph mal																									
Urinary bladder	A	M	+	+	A	+	A	A	+	+	A	+	+	A	A	A	M	+	+	+	+	+	+	+	+
Lymph mal																				X					X
Uterus	A	+	+	+	+	+	A	A	+	+	+	+	+	+	A	A	M	+	+	+	+	+	+	+	+
Histio sarc, metastatic, spleen													X												
Sarc stromal																									
Vagina	A	+	+	+	I	+	A	+	+	+	A	+	+	+	A	A	M	+	+	+	+	M	+	+	+
Histio sarc, metastatic, spleen													X												
Lymph mal																									X
Zymbal's gland	M	M	+	M	M	M	+	M	+	+	+	+	+	+	+	M	M	+	+	M	M	+	+	+	+

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Fumonisin B_1: 80 ppm

Carcass ID Number	132	181	182	217	218	219	266	267	268	269	270	359	360	361	409	410	411	461	462	475	498	499	500	Total Tissues/ Tumors
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Lymph mal	X		X	X	X			X								X	X			X	X			10
Lymph mal hist																								1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	39
Lymph mal	X		X	X				X								X	X		X		X	X		10
Lymph mal hist																								1
Mammary gland	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	38
Lymph mal			X		X												X							4
Mesentery																								1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma, glands																								1
Lymph mal			X		X			X											X					4
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Histio sarc, metastatic, spleen																								1
Lymph mal	X		X		X			X								X			X	X	X	X		11
Lymph mal hist																								1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	39
Histio sarc, metastatic, spleen																								1
Lymph mal	X			X				X												X				4
Parathyroid gland	+	+	+	+	+	+	+	+	I	+	+	M	+	+	+	+	+	+	M	M	+	+	+	34
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	46
Pituitary gland	+	+	M	I	+	+	+	I	+	+	+	+	+	+	M	M	+	+	I	+	+	M	I	29
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph mal	X		X	X	X			X								X	X			X	X	X		12
Lymph mal hist																								1
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph mal																								1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Papilloma												X												1
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Spinal cord, thoracic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Hemangiosarc													X											1
Hemangiosarc, metastatic, liver																								1
Histio sarc																								1
Lymph mal	X		X	X	X			X								X	X		X	X	X	X		12
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	43
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	39
Lymph mal	X																							1
Thymus	M	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	34
Lymph mal				X															X	X	X	X		6
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Adenoma									X															1
Tongue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	38
Lymph mal								X																1
Urinary bladder	+	+	M	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	M	35
Lymph mal	X			X	X			X									X		X	X	X			10
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Histio sarc, metastatic, spleen																								1
Sarc stromal						X																		1
Vagina	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	I	+	38
Histio sarc, metastatic, spleen																								1
Lymph mal	X																							2
Zymbal's gland	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	M	+	M	+	M	M	M	M	30

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Feed Study of Fumonisin B_1

	0 ppm	5 ppm	15 ppm	50 ppm	80 ppm
Harderian Gland: Adenoma					
Overall rate[a]	4/46 (9%)	1/5 (20%)	1/3 (33%)	2/8 (25%)	0/44 (0%)
Adjusted rate[b]	9.3%	30.7%	42.1%	35.9%	0.0%
Terminal rate[c]	4/39 (10%)	1/1 (100%)	1/1 (100%)	0/0	0/28 (0%)
First incidence (days)	630	740 (T)	740 (T)	636	—[e]
Poly-3 test[d]	P=0.0839N	P=0.4035	P=0.3148	P=0.1546	P=0.0914N
Harderian Gland: Adenoma or Carcinoma					
Overall rate	4/46 (9%)	1/5 (20%)	1/3 (33%)	2/8 (25%)	0/44 (0%)
Adjusted rate	9.3%	30.7%	42.1%	35.9%	0.0%
Terminal rate	4/39 (10%)	1/1 (100%)	1/1 (100%)	0/0	0/28 (0%)
First incidence (days)	630	740 (T)	740 (T)	—	—
Poly-3 test	P=0.0839N	P=0.4035	P=0.3148	P=0.1546	P=0.0914N
Liver: Hepatocellular Adenoma					
Overall rate	5/47 (11%)	3/48 (6%)	1/48 (2%)	16/47 (34%)	31/45 (69%)
Adjusted rate	11.7%	6.5%	2.1%	36.3%	73.7%
Terminal rate	5/39 (13%)	3/44 (7%)	1/46 (2%)	14/39 (36%)	21/28 (75%)
First incidence (days)	740 (T)	740 (T)	740 (T)	703	391
Poly-3 test	P=0.0001	P=0.3314N	P=0.0862N	P=0.0047	P=0.0001
Liver: Hepatocellular Carcinoma					
Overall rate	0/47 (0%)	0/48 (0%)	0/48 (0%)	10/47 (21%)	9/45 (20%)
Adjusted rate	0.0%	0.0%	0.0%	22.5%	23.1%
Terminal rate	0/39 (0%)	0/44 (0%)	0/46 (0%)	8/39 (21%)	3/28 (11%)
First incidence (days)	—	—	—	636	437
Poly-3 test	P=0.0001	—[f]	—	P=0.0007	P=0.0007
Liver: Hepatocellular Adenoma or Carcinoma					
Overall rate	5/47 (11%)	3/48 (6%)	1/48 (2%)	19/47 (40%)	39/45 (87%)
Adjusted rate	11.7%	6.5%	2.1%	42.7%	88.3%
Terminal rate	5/39 (13%)	3/44 (7%)	1/46 (2%)	16/39 (41%)	24/28 (86%)
First incidence (days)	740 (T)	740 (T)	740 (T)	636	391
Poly-3 test	P=0.0001	P=0.3314N	P=0.0862N	P=0.0005	P=0.0001
All Organs: Malignant Lymphoma					
Overall rate	20/47 (43%)	9/48 (19%)	10/48 (21%)	9/48 (19%)	13/48 (27%)
Adjusted rate	46.6%	19.5%	21.1%	19.5%	34.6%
Terminal rate	19/39 (49%)	9/44 (21%)	10/46 (22%)	4/39 (10%)	12/28 (43%)
First incidence (days)	668	740 (T)	740 (T)	481	722
Poly-3 test	P=0.4117N	P=0.0070N	P=0.0115N	P=0.0070N	P=0.2316N
All Organs: Benign Neoplasms					
Overall rate	13/47 (28%)	4/48 (8%)	3/48 (6%)	21/48 (44%)	31/48 (65%)
Adjusted rate	29.7%	8.6%	6.3%	46.1%	72.5%
Terminal rate	11/39 (28%)	4/44 (9%)	3/46 (7%)	16/39 (41%)	21/28 (75%)
First incidence (days)	619	740 (T)	740 (T)	572	391
Poly-3 test	P=0.0001	P=0.0114N	P=0.0036N	P=0.0691	P=0.0001

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Feed Study of Fumonisin B_1

	0 ppm	5 ppm	15 ppm	50 ppm	80 ppm
All Organs: Malignant Neoplasms					
Overall rate	28/47 (60%)	13/48 (27%)	12/48 (25%)	19/48 (40%)	25/48 (52%)
Adjusted rate	62.0%	27.5%	25.0%	40.0%	60.2%
Terminal rate	21/39 (54%)	10/44 (23%)	11/46 (24%)	11/39 (28%)	15/28 (54%)
First incidence (days)	436	475	555	454	437
Poly-3 test	P=0.0796	P=0.0009N	P=0.0003N	P=0.0405N	P=0.5742
All Organs: Benign or Malignant Neoplasms					
Overall rate	32/47 (68%)	16/48 (33%)	13/48 (27%)	30/48 (63%)	44/48 (92%)
Adjusted rate	69.8%	33.8%	27.1%	62.5%	96.3%
Terminal rate	24/39 (62%)	13/44 (30%)	12/46 (26%)	21/39 (54%)	27/28 (96%)
First incidence (days)	436	475	555	454	391
Poly-3 test	P=0.0001	P=0.0005N	P=0.0001N	P=0.3621N	P=0.0002

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined microscopically
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence is the P value associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. For all tissues except the liver, only the pairwise comparisons between the 80 ppm group and control group are unbiased; overall rates and all other pairwise comparisons may not be valid. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in an exposure group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group
[f] Value of statistic cannot be computed.

TABLE D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of Fumonisin B_1[a]

	0 ppm	5 ppm	15 ppm	50 ppm	80 ppm
Disposition Summary					
3-Week evaluation	4	4	4	4	4
7-Week evaluation	4	4	4	4	4
9-Week evaluation	4	4	4	4	4
24-Week evaluation	4	4	4	4	4
Animals initially in 2-year study	48	48	48	48	48
Early deaths					
Removed from study	4				
Moribund	7	3	2	3	6
Natural deaths	1	1		6	14
Survivors					
Terminal sacrifice	35	44	46	39	28
Missing	1				
Animals examined microscopically	63	64	64	64	64

3-Week Evaluation

	0 ppm	5 ppm	15 ppm	50 ppm	80 ppm
Liver	(4)	(4)	(4)	(4)	(4)
Apoptosis, centrilobular					4 (100%)
Cytoplas alter, centrilobular				2 (50%)	4 (100%)
Hyperplasia, centrilobular, Kupffer cell					2 (50%)
Hypertrophy, centrilobular				2 (50%)	4 (100%)
Necrosis, centrilobular					1 (25%)
Vacuoliz cyto, centrilobular				1 (25%)	
Vacuoliz cyto, portal					4 (100%)

Tissues Examined with No Lesions Observed

Kidney

7-Week Evaluation

	0 ppm	5 ppm	15 ppm	50 ppm	80 ppm
Liver	(4)	(4)	(4)	(4)	(4)
Apoptosis, centrilobular					4 (100%)
Cytoplas alter, centrilobular			2 (50%)	3 (75%)	4 (100%)
Hyperplasia, centrilobular, Kupffer cell					2 (50%)
Hypertrophy, centrilobular				2 (50%)	4 (100%)
Necrosis, centrilobular					2 (50%)
Pigment, centrilobular					4 (100%)
Vacuoliz, cyto, centrilobular		2 (50%)		2 (50%)	1 (25%)

Tissues Examined with No Lesions Observed

Eye
Heart
Kidney

[a] Number of animals examined microscopically at the site and the number of animals with lesion

TABLE D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of Fumonisin B_1

	0 ppm	5 ppm	15 ppm	50 ppm	80 ppm
9-Week Evaluation					
Intestine small	(1)				
Diverticulum, ileum	1 (100%)				
Kidney	(4)	(4)	(4)	(4)	(4)
Hypertrophy, multifocal, bilateral, renal tubule	1 (25%)				
Inflammation, focal, unilateral		1 (25%)			
Mineralization, focal, unilateral				1 (25%)	
Liver	(4)	(4)	(4)	(4)	(4)
Apoptosis, centrilobular			4 (100%)		
Cytoplas alter, centrilobular			3 (75%)		
Cytoplas alter, diffuse		1 (25%)	1 (25%)	4 (100%)	
Hyperplasia, diffuse, Kupffer cell					4 (100%)
Hypertrophy, centrilobular		1 (25%)	3 (75%)		
Necrosis, focal					1 (25%)
Necrosis, centrilobular			4 (100%)		
Pigment, centrilobular			4 (100%)		
Vacuoliz cyto, centrilobular		1 (25%)			1 (25%)
24-Week Evaluation					
Kidney	(4)	(4)	(4)	(4)	(4)
Inflammation, focal, unilateral	1 (25%)				1 (25%)
Inflammation, multifocal, unilateral				1 (25%)	
Liver	(4)	(4)	(4)	(4)	(4)
Apoptosis, centrilobular	4 (100%)				1 (25%)
Cytoplas alter, centrilobular					4 (100%)
Cytoplas alter, diffuse			1 (25%)	4 (25%)	
Granuloma, multifocal	3 (75%)				4 (100%)
Hypertrophy, centrilobular	1 (25%)		1 (25%)		4 (100%)
Inflammation, multifocal				1 (25%)	
Pigment, centrilobular	4 (100%)				4 (100%)
Thymus	(1)				
Cyst, focal	1 (100%)				
Uterus		(1)			
Endometriosis, multifocal		1 (100%)			
Tissues Examined with No Lesions Observed					
Ovary					
Oviduct					
2-Year Study					
Adrenal gland	(45)	(3)	(3)	(9)	(40)
Amyloid dep, multifocal					1 (3%)
Hemorrhage, multifocal, bilateral				1 (11%)	
Hyperplasia, bilateral, cortex, spindle cell	38 (84%)	2 (67%)	2 (67%)	8 (89%)	37 (93%)
Hyperplasia, bilateral, medulla					2 (5%)
Hyperplasia, unilateral, cortex, spindle cell	6 (13%)	1 (33%)			3 (8%)
Pigment, focal, unilateral	1 (2%)				1 (3%)
Pigment, multifocal, bilateral					2 (5%)

TABLE D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of Fumonisin B_1

	0 ppm	5 ppm	15 ppm	50 ppm	80 ppm
2-Year Study (continued)					
Bone, femur	(47)	(3)	(2)	(8)	(47)
Hyperplasia, diffuse	1 (2%)				
Proliferation, focal	5 (11%)	1 (33%)			3 (6%)
Proliferation, multifocal	10 (21%)				5 (11%)
Bone, sternum	(47)	(4)	(2)	(8)	(48)
Proliferation, focal	1 (2%)				7 (15%)
Proliferation, multifocal	27 (57%)	1 (25%)	2 (100%)		11 (23%)
Bone marrow	(47)	(4)	(2)	(8)	(45)
Hyperplasia, diffuse	25 (53%)	3 (75%)	2 (100%)	2 (25%)	28 (62%)
Hyperplasia, multifocal	1 (2%)				
Pigment					1 (2%)
Brain, cerebrum	(47)	(4)	(2)	(9)	(47)
Cyst epith inc	1 (2%)				
Edema, focal		1 (25%)			
Edema, multifocal					1 (2%)
Inflammation, chronic, artery, meninges		1 (25%)			
Mineralization, focal	2 (4%)				
Mineralization, multifocal	11 (23%)		1 (50%)		7 (15%)
Necrosis, focal		1 (25%)			
Necrosis, multifocal					1 (2%)
Clitoral gland	(34)	(3)		(2)	(34)
Cyst	1 (3%)				
Cyst, bilateral					1 (3%)
Cyst, multifocal	10 (29%)	2 (67%)			13 (38%)
Cyst, multifocal, bilateral					1 (3%)
Dilatation	1 (3%)				
Dilatation, multifocal	1 (3%)				
Inflammation, chronic, focal	1 (3%)				1 (3%)
Inflammation, chronic, multifocal	1 (3%)				
Inflammation, subacute, multifocal	1 (3%)				
Ear	(46)	(3)	(2)	(6)	(41)
Inflammation, chronic, focal					1 (2%)
Esophagus	(46)	(4)	(2)	(8)	(46)
Hyperkeratosis, diffuse		2 (50%)			
Eye	(45)	(3)	(2)	(4)	(36)
Hyperplasia, melanocyte, diffuse					1 (3%)
Inflammation, chronic, diffuse, unilateral, cornea	1 (2%)				
Harderian gland	(46)	(5)	(3)	(8)	(44)
Degen, focal	1 (2%)				
Inflammation, chronic	6 (13%)		1 (33%)	1 (13%)	4 (9%)
Inflammation, subacute	2 (4%)	1 (20%)			3 (7%)
Regeneration, focal	1 (2%)				
Heart	(47)	(4)	(2)	(9)	(47)
Cardiomyopathy, multifocal	1 (2%)	1 (25%)			
Congestion, atrium					1 (2%)
Degen, multifocal		1 (25%)		1 (11%)	1 (2%)
Inflammation, subacute, multifocal				1 (11%)	
Thrombus, focal					1 (2%)
Thrombus, focal, ventricl rgt	1 (2%)				
Thrombus, ventricl lft				1 (11%)	
Intestine large, rectum	(47)	(4)	(2)	(6)	(34)
Hyperplasia, lymphoid, focal	1 (2%)				
Intestine small, ileum	(47)	(3)	(2)	(6)	(35)
Hyperplasia, lymphoid					1 (3%)
Hyperplasia, lymphoid, focal	2 (4%)				

TABLE D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of Fumonisin B_1

	0 ppm		5 ppm		15 ppm		50 ppm		80 ppm	
2-Year Study (continued)										
Intestine small, jejunum	(47)		(3)		(3)		(5)		(35)	
Hyperplasia, lymphoid, focal	1	(2%)								
Kidney	(47)		(48)		(48)		(48)		(42)	
Amyloid dep, glomerulus	1	(2%)								
Amyloid dep, multifocal									1	(2%)
Cyst	1	(2%)			1	(2%)	1	(2%)	2	(5%)
Degen, multifocal, cortex, renal tubule			1	(2%)						
Dilatation, diffuse, pelvis							2	(4%)	2	(5%)
Glmsclerosis, multifocal	15	(32%)	18	(38%)	19	(40%)	20	(42%)	19	(45%)
Hyperplasia, focal, cortex, renal tubule			3	(6%)					1	(2%)
Hyperplasia, lymphoid, focal					1	(2%)				
Hyperplasia, lymphoid, multifocal					3	(6%)				
Hyperplasia, multifocal, cortex, renal tubule			2	(4%)	1	(2%)	2	(4%)		
Hypertrophy, focal, cortex, renal tubule	1	(2%)								
Inflammation, chronic	1	(2%)							1	(2%)
Inflammation, chronic, focal	5	(11%)	2	(4%)	4	(8%)	9	(19%)	2	(5%)
Inflammation, chronic, multifocal	3	(6%)	16	(33%)	12	(25%)	15	(31%)	4	(10%)
Inflammation, subacute, focal	2	(4%)	3	(6%)	2	(4%)	1	(2%)	1	(2%)
Inflammation, subacute, multifocal	5	(11%)	5	(10%)	4	(8%)	6	(13%)	6	(14%)
Metapl, osseous, focal					1	(2%)				
Mineralization, focal, renal tubule							1	(2%)		
Mineralization, renal tubule							1	(2%)		
Necrosis, multifocal	1	(2%)								
Nephropathy, chronic, multifocal									2	(5%)
Proliferation, focal, renal tubule			1	(2%)			2	(4%)		
Proliferation, multifocal, renal tubule					1	(2%)				
Regeneration, focal, cortex, renal tubule	1	(2%)								
Lacrimal gland	(46)		(4)		(1)		(7)		(40)	
Atrophy, focal	1	(2%)								
Cytoplas alter							1	(14%)		
Focal cell ch	1	(2%)								
Inflammation, chronic	1	(2%)							1	(3%)
Inflammation, chronic, focal	5	(11%)	1	(25%)					2	(5%)
Inflammation, chronic, multifocal	2	(4%)							2	(5%)
Inflammation, subacute, focal	3	(7%)							2	(5%)
Necrosis, multifocal									1	(3%)
Liver	(47)		(48)		(48)		(47)		(45)	
Apoptosis, hepatocyte							7	(15%)	14	(31%)
Basoph focus	2	(4%)	1	(2%)	2	(4%)	2	(4%)	2	(4%)
Cyst, focal	1	(2%)			1	(2%)	1	(2%)		
Cyst, multifocal							1	(2%)		
Ectasia, focal									1	(2%)
Eosin focus			1	(2%)			3	(6%)	4	(9%)
Fatty change, focal									2	(4%)
Fatty change, multifocal									1	(2%)
Granuloma							1	(2%)		
Granuloma, multifocal	3	(6%)	14	(29%)	9	(19%)	36	(77%)	24	(53%)
Hemorrhage, multifocal									1	(2%)
Hypertrophy, diffuse, hepatocyte							27	(57%)	31	(69%)
Infiltrat cell, lymphocytic, focal					2	(4%)				
Infiltrat cell, lymphocytic, multifocal	18	(38%)	17	(35%)	14	(29%)	21	(45%)	6	(13%)
Mixed cl focus							1	(2%)	5	(11%)
Necrosis, focal	2	(4%)	1	(2%)			1	(2%)		
Necrosis, multifocal	1	(2%)	1	(2%)	1	(2%)	29	(62%)	26	(58%)
Necrosis, multifocal, centrilobular	1	(2%)								

TABLE D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of Fumonisin B_1

	0 ppm		5 ppm		15 ppm		50 ppm		80 ppm	
2-Year Study (continued)										
Liver (continued)	(47)		(48)		(48)		(47)		(45)	
Pigment, multifocal			4	(8%)	3	(6%)	38	(81%)	35	(77%)
Tension lipoid	3	(6%)	5	(10%)	4	(8%)	4	(9%)	1	(2%)
Vacuoliz cyto, centrilobular	2	(4%)	4	(8%)	5	(10%)	2	(4%)		
Vacuoliz cyto, diffuse	2	(4%)	6	(13%)	2	(4%)	19	(40%)	2	(4%)
Vacuoliz cyto, focal	1	(2%)							1	(2%)
Vacuoliz cyto, multifocal	2	(4%)	1	(2%)	1	(2%)	2	(4%)	12	(27%)
Vacuoliz cyto, periportal	1	(2%)					2	(4%)		
Lung	(47)		(4)		(2)		(9)		(47)	
Congestion, diffuse									2	(4%)
Edema, diffuse									1	(2%)
Inflammation, chronic									1	(2%)
Inflammation, chronic, focal	2	(4%)								
Inflammation, chronic, multifocal	5	(11%)							5	(11%)
Inflammation, multifocal	1	(2%)								
Inflammation, subacute, focal	1	(2%)								
Inflammation, subacute, multifocal	2	(4%)							5	(11%)
Inflammation, subacute, multifocal, interstitim, perivascular	1	(2%)								
Necrosis, focal							1	(11%)		
Lymph node, mandibular	(46)		(5)		(3)		(8)		(44)	
Cyst, multifocal					1	(33%)				
Deplet lymph, diffuse									1	(2%)
Hyperplasia, lymphoid	6	(13%)							4	(9%)
Pigment, multifocal	3	(7%)					2	(25%)	3	(7%)
Lymph node, mesenteric	(47)		(5)		(5)		(8)		(39)	
Cyst, diffuse							1	(13%)		
Hemorrhage, multifocal									1	(3%)
Hyperplasia, lymphoid	4	(9%)							4	(10%)
Hyperplasia, lymphoid, diffuse	1	(2%)								
Pigment	1	(2%)								
Pigment, multifocal	3	(6%)	1	(20%)					2	(5%)
Mammary gland	(46)		(2)		(2)		(9)		(38)	
Dilatation, multifocal, duct	1	(2%)								
Edema, diffuse	1	(2%)								
Mesentery							(1)		(1)	
Necrosis, focal									1	(100%)
Necrosis, focal, fat							1	(100%)		
Nose	(47)		(4)		(2)		(9)		(48)	
Cytoplas alter, olfactory epi									1	(2%)
Inflammation, acute, multifocal	1	(2%)								
Inflammation, chronic, multifocal	1	(2%)								
Inflammation, subacute, focal	1	(2%)								
Inflammation, subacute, multifocal	4	(9%)							1	(2%)
Proliferation, focal	1	(2%)							1	(2%)
Proliferation, multifocal	4	(9%)								
Ovary	(46)		(15)		(15)		(22)		(42)	
Cyst	24	(52%)	11	(73%)	14	(93%)	15	(68%)	11	(26%)
Cyst, bilateral			1	(7%)						
Hematocyst	1	(2%)								
Hemorrhage, multifocal, right	1	(2%)								
Metapl, squamous, focal, right							1	(5%)		
Mineralization, multifocal							1	(5%)		
Pigment, multifocal	3	(7%)	1	(7%)			1	(5%)	5	(12%)
Pigment, multifocal, bilateral	12	(26%)							10	(24%)
Thrombus, focal, right					1	(7%)				

TABLE D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of Fumonisin B_1

	0 ppm		5 ppm		15 ppm		50 ppm		80 ppm	
2-Year Study (continued)										
Pancreas	(47)		(5)		(2)		(8)		(39)	
Atrophy, diffuse, acinar cell	1	(2%)							1	(3%)
Atrophy, multifocal, acinar cell			1	(20%)			1	(13%)		
Cyst, multifocal			1	(20%)						
Inflammation, subacute, focal	1	(2%)								
Inflammation, subacute, multifocal	1	(2%)								
Parathyroid gland	(37)		(2)		(1)		(4)		(34)	
Cyst, focal	1	(3%)								
Hyperplasia, focal			1	(50%)						
Pituitary gland	(29)		(2)		(1)		(2)		(29)	
Cyst, focal	1	(3%)								
Salivary glands	(47)		(4)		(2)		(8)		(47)	
Inflammation, chronic	12	(26%)			1	(50%)			6	(13%)
Inflammation, subacute	6	(13%)			1	(50%)			6	(13%)
Skeletal muscle	(47)		(4)		(2)		(9)		(48)	
Degen									2	(4%)
Inflammation, subacute, focal									2	(4%)
Skin	(47)		(4)		(1)		(9)		(42)	
Edema, diffuse							1	(11%)		
Hyperplasia, focal, vulva									1	(2%)
Spinal cord, thoracic	(47)		(4)		(2)		(8)		(46)	
Degen, multifocal			1	(25%)						
Inflammation, chronic, multifocal	1	(2%)								
Necrosis, multifocal			1	(25%)						
Spleen	(47)		(10)		(13)		(17)		(42)	
Amyloid dep, multifocal									1	(2%)
Congestion	1	(2%)								
Congestion, multifocal									1	(2%)
Hema cell prol	2	(4%)	2	(20%)			4	(24%)	8	(19%)
Hyperplasia, erythrocyte, multifocal	1	(2%)								
Hyperplasia, lymphoid	14	(30%)	2	(20%)	3	(23%)	5	(29%)	4	(10%)
Stomach, forestomach	(46)		(4)		(2)		(9)		(43)	
Edema, diffuse							1	(11%)		
Hyperkeratosis, diffuse			1	(25%)					1	(2%)
Hyperplasia, diffuse			1	(25%)					1	(2%)
Hyperplasia, focal	1	(2%)								
Inflammation									1	(2%)
Inflammation, proliferative, chronic, diffuse									1	(2%)
Inflammation, subacute, focal							1	(11%)		
Inflammation, subacute, multifocal			1	(25%)						
Proliferation, chronic, focal									1	(2%)
Ulcer									1	(2%)
Stomach, glandular	(46)		(4)		(2)		(6)		(39)	
Mineralization, focal							1	(17%)	1	(3%)
Necrosis, focal									1	(3%)
Thymus	(37)		(4)		(2)		(5)		(34)	
Atrophy	2	(5%)	2	(50%)			1	(20%)	3	(9%)
Cyst									2	(6%)
Hemorrhage, multifocal							1	(20%)		
Hyperplasia, lymphoid	1	(3%)								
Thyroid gland	(46)		(3)		(1)		(7)		(41)	
Cyst	2	(4%)							4	(10%)
Hyperplasia, multifocal	1	(2%)								

TABLE D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of Fumonisin B_1

	0 ppm	5 ppm	15 ppm	50 ppm	80 ppm
2-Year Study (continued)					
Tongue	(47)	(4)	(2)	(9)	(46)
Granuloma, focal	1 (2%)				
Hyperkeratosis, focal					1 (2%)
Inflammation, chronic, focal	1 (2%)				
Inflammation, chronic, multifocal, artery		1 (25%)			
Inflammation, subacute, multifocal					1 (2%)
Urinary bladder	(45)	(4)	(2)	(8)	(35)
Hyperplasia, multifocal, mucosa		1 (25%)			
Hyperplasia, papillary, multifocal, mucosa					1 (3%)
Inflammation, chronic	9 (20%)		1 (50%)	2 (25%)	6 (17%)
Inflammation, chronic, focal	1 (2%)				
Inflammation, subacute	3 (7%)				2 (6%)
Uterus	(47)	(38)	(32)	(38)	(42)
Cyst, endometrium	2 (4%)				3 (7%)
Cyst, focal	1 (2%)				
Cyst, focal, bilateral					1 (2%)
Cyst, focal, unilateral			1 (3%)		2 (5%)
Cyst, multifocal	5 (11%)	8 (21%)		3 (8%)	1 (2%)
Cyst, multifocal, bilateral	33 (70%)	18 (47%)	19 (59%)	18 (47%)	20 (48%)
Cyst, multifocal, endometrium					1 (2%)
Cyst, multifocal, unilateral	1 (2%)	3 (8%)	5 (16%)	2 (5%)	1 (2%)
Dilatation					1 (2%)
Dilatation, diffuse		1 (3%)		1 (3%)	
Dilatation, multifocal				1 (3%)	
Dilatation, diffuse, bilateral	2 (4%)	3 (8%)	6 (19%)	2 (5%)	1 (2%)
Dilatation, diffuse, unilateral	1 (2%)	4 (11%)	3 (9%)	2 (5%)	1 (2%)
Dilatation, multifocal, bilateral		1 (3%)	1 (3%)	6 (16%)	
Hemorrhage, multifocal		1 (3%)			
Inflammation, chronic, multifocal					1 (2%)
Mineralization, focal	1 (2%)				
Mineralization, multifocal					1 (2%)
Pigment, multifocal, bilateral					1 (2%)
Thrombus, multifocal		1 (3%)			1 (2%)

APPENDIX E
CELL PROLIFERATION STUDIES

TABLE E1
Liver Cell Cycle Data for Rats in the 28-Day Feed Study of Fumonisin B_1[a]

Cell Phase	0 ppm	99 ppm	163 ppm	234 ppm	484 ppm
n	10	10	10	10	10
Male					
G_0	99.461 ± 0.190	99.255 ± 0.125*	98.102 ± 0.286*	96.980 ± 0.382*	94.864 ± 0.681*
G_1	0.389 ± 0.133	0.548 ± 0.083*	1.503 ± 0.235*	2.523 ± 0.350*	1.991 ± 0.211*
G_2	0.056 ± 0.039	0.103 ± 0.038*	0.201 ± 0.043*	0.179 ± 0.020*	1.332 ± 0.206*
S	0.070 ± 0.028	0.085 ± 0.019	0.179 ± 0.040*	0.287 ± 0.042*	1.320 ± 0.266*
M	0.023 ± 0.011	0.010 ± 0.006	0.014 ± 0.010	0.032 ± 0.013	0.496 ± 0.156*
S + M	0.093 ± 0.034	0.094 ± 0.018	0.193 ± 0.042*	0.318 ± 0.049*	1.816 ± 0.404*
Female					
G_0	99.563 ± 0.101	99.455 ± 0.147	98.320 ± 0.493*	96.381 ± 0.472*	96.537 ± 0.276*
G_1	0.200 ± 0.054	0.372 ± 0.121	1.084 ± 0.314*	1.533 ± 0.165*	1.540 ± 0.115*
G_2	0.023 ± 0.008	0.027 ± 0.015	0.265 ± 0.108*	0.912 ± 0.145*	0.899 ± 0.120*
S	0.200 ± 0.049	0.136 ± 0.036	0.263 ± 0.076	0.860 ± 0.157*	0.742 ± 0.067*
M	0.014 ± 0.010	0.009 ± 0.006	0.068 ± 0.018*	0.314 ± 0.073*	0.282 ± 0.040*
S + M	0.214 ± 0.052	0.145 ± 0.035	0.331 ± 0.091	1.174 ± 0.224*	1.024 ± 0.093*

* Significantly different ($P \leq 0.05$) from the control group by a one-way analysis of variance with application of Holm's procedure
[a] Data are given as percentage of cells in each cycle (mean ± standard error); approximately 2,000 cells per slide were evaluated.

Table E2
Liver Cell Cycle Data for Mice in the 28-Day Feed Study of Fumonisin B_1[a]

Cell Phase	0 ppm	99 ppm	163 ppm	234 ppm	484 ppm
n	12	12	12	12	12
Male					
G_0	99.945 ± 0.020	99.907 ± 0.023	99.787 ± 0.055	99.834 ± 0.042	97.276 ± 0.235*
G_1	0.036 ± 0.017	0.066 ± 0.016	0.093 ± 0.021	0.089 ± 0.023	1.335 ± 0.164*
G_2	0.004 ± 0.004	0.004 ± 0.004	0.061 ± 0.022	0.015 ± 0.008	0.263 ± 0.066*
S	0.015 ± 0.006	0.016 ± 0.006	0.028 ± 0.013	0.032 ± 0.016	0.929 ± 0.083*
M	0	0.008 ± 0.005	0.031 ± 0.011	0.030 ± 0.012	0.197 ± 0.028*
S + M	0.015 ± 0.006	0.023 ± 0.009	0.058 ± 0.018	0.062 ± 0.024	1.126 ± 0.100*
Female					
G_0	99.815 ± 0.030	97.799 ± 0.292*	96.451 ± 0.362*	97.032 ± 0.199*	96.862 ± 0.205*
G_1	0.128 ± 0.019	1.116 ± 0.153*	2.121 ± 0.228*	1.672 ± 0.089*	1.882 ± 0.178*
G_2	0.019 ± 0.008	0.262 ± 0.065*	0.407 ± 0.109*	0.226 ± 0.058*	0.166 ± 0.037
S	0.038 ± 0.012	0.640 ± 0.089*	0.942 ± 0.115*	1.036 ± 0.130*	1.072 ± 0.043*
M	0	0.183 ± 0.039*	0.079 ± 0.023*	0.035 ± 0.018	0.019 ± 0.015
S + M	0.038 ± 0.012	0.823 ± 0.122*	1.021 ± 0.117*	1.071 ± 0.139*	1.090 ± 0.038*

* Significantly different ($P \leq 0.05$) from the control group by a one-way analysis of variance with application of Holm's procedure

a Data are given as percentage of cells in each cycle (mean ± standard error); approximately 2,000 cells per slide were evaluated.

TABLE E3
Percentages of PCNA-Labeled Kidney and Liver Cells in Active DNA Replication in Rats at the 6-, 10-, 14-, and 26-Week Evaluations in the Feed Study of Fumonisin B_1[a]

	0 ppm	5 ppm	15 ppm	50 ppm	150 ppm	Exposure Concentration Effect P Value[b]	Trend P Value[c]
n	4	4	4	4	4		
Male							
Kidney							
Week 6	1.202 ± 0.036	1.036 ± 0.176	1.012 ± 0.384	2.988 ± 0.279***	3.262 ± 0.166****	0.0001	0.0001
Week 10	0.952 ± 0.118	1.214 ± 0.098	1.810 ± 0.133*	2.821 ± 0.191**	2.690 ± 0.297*	0.0031	0.0047
Week 14	0.726 ± 0.141	1.012 ± 0.246	1.405 ± 0.195	2.607 ± 0.203**	2.798 ± 0.214***	0.0011	0.0001
Week 26	0.429 ± 0.051	1.000 ± 0.166	1.464 ± 0.152**	2.786 ± 0.159****	3.012 ± 0.230***	0.0001	0.0003
Liver							
Week 6	2.025 ± 0.270	2.850 ± 0.342	0.900 ± 0.074*	3.263 ± 0.488	3.038 ± 0.330	0.0006	0.0123
Week 10	1.950 ± 0.488	1.938 ± 0.043	0.813 ± 0.063	1.663 ± 0.215	1.863 ± 0.228	0.0001	0.5233
Week 14	1.813 ± 0.358	2.125 ± 0.307	1.188 ± 0.236	2.050 ± 0.201	1.863 ± 0.345	0.1775	0.6551
Week 26	0.838 ± 0.288	1.475 ± 0.278	0.938 ± 0.109	1.188 ± 0.125	0.900 ± 0.068	0.2248	0.4815
	0 ppm	**5 ppm**	**15 ppm**	**50 ppm**	**100 ppm**		
Female							
Kidney							
Week 6	0.619 ± 0.097	1.048 ± 0.085*	0.833 ± 0.168	0.976 ± 0.121	0.774 ± 0.068	0.0745	0.8776
Week 10	0.786 ± 0.131	0.536 ± 0.068	0.702 ± 0.083	0.690 ± 0.114	0.798 ± 0.079	0.2264	0.3554
Week 14	0.556 ± 0.092	0.464 ± 0.045	0.333 ± 0.034	0.810 ± 0.130	1.119 ± 0.221	0.0387	0.0324
Week 26	0.393 ± 0.076	0.262 ± 0.041	0.310 ± 0.014	0.464 ± 0.023	0.643 ± 0.057	0.0047	0.0020
Liver							
Week 6	0.525 ± 0.060	0.313 ± 0.120	1.400 ± 0.157**	0.563 ± 0.101	0.800 ± 0.074	0.0041	0.2829
Week 10	0.638 ± 0.116	0.488 ± 0.212	1.113 ± 0.101	0.763 ± 0.123	1.125 ± 0.443	0.1242	0.3742
Week 14	0.525 ± 0.116	0.863 ± 0.165	1.275 ± 0.078**	0.763 ± 0.109	0.863 ± 0.131	0.0150	0.8323
Week 26	0.450 ± 0.096	0.425 ± 0.095	0.663 ± 0.169	0.950 ± 0.046*	0.813 ± 0.185	0.0154	0.0610

* Significantly different ($P \leq 0.05$) from the control group by a one-way analysis of variance with application of Dunnett's test
** $P \leq 0.01$
*** $P \leq 0.001$
**** $P \leq 0.0001$
a Percentages (mean ± standard error) are the sum of the percentages of PCNA-labeled cells in each of the cell cycle phases G_1, G_2, S, and M.
b Test for overall exposure concentration effect (ANOVA)
c Tests for linear exposure concentration trends were conducted using orthogonal contrasts.

TABLE E4
Percentages of BrdU-Labeled Kidney and Liver Cells in Active DNA Replication in Rats at the 6-, 10-, 14-, and 26-Week Evaluations in the Feed Study of Fumonisin B_1[a]

	0 ppm	5 ppm	15 ppm	50 ppm	150 ppm	Exposure Concentration Effect P Value[b]	Trend P Value[c]
n	4	4	4	4	4		
Male							
Kidney							
Week 6	0.417 ± 0.074	0.131 ± 0.023	0.298 ± 0.053	1.119 ± 0.138*	0.869 ± 0.296	0.0017	0.0007
Week 10	0.238 ± 0.019	0.155 ± 0.030	0.440 ± 0.023	1.155 ± 0.125***	1.821 ± 0.268****	0.0001	0.0001
Week 14	0.131 ± 0.030	0.083 ± 0.023	0.155 ± 0.060	1.000 ± 0.112****	1.083 ± 0.068****	0.0001	0.0001
Week 26	0.048 ± 0.019	0.167 ± 0.031	0.131 ± 0.053	1.024 ± 0.111****	1.155 ± 0.141****	0.0001	0.0001
Liver							
Week 6	0.063 ± 0.024	0.288 ± 0.120	0.038 ± 0.024	0.188 ± 0.031	0.188 ± 0.059	0.0759	0.4039
Week 10	0.250 ± 0.020	0.075 ± 0.014****	0.138 ± 0.031**	0.100 ± 0.020***	0.088 ± 0.013***	0.0002	0.0047N
Week 14	0.175 ± 0.032	0.213 ± 0.031	0.088 ± 0.031	0.125 ± 0.060	0.113 ± 0.031	0.2053	0.2230
Week 26	0.163 ± 0.024	0.263 ± 0.072	0.188 ± 0.038	0.175 ± 0.032	0.213 ± 0.043	0.5547	1.0000
	0 ppm	**5 ppm**	**15 ppm**	**50 ppm**	**100 ppm**		
Female							
Kidney							
Week 6	0.036 ± 0.023	0.060 ± 0.036	0.048 ± 0.019	0.119 ± 0.014	0.131 ± 0.081	0.4121	0.0685
Week 10	0.071 ± 0.041	0.071 ± 0.041	0.071 ± 0.031	0.071 ± 0.041	0.226 ± 0.030*	0.0345	0.0082
Week 14	0.036 ± 0.036	0.000 ± 0.000	0.071 ± 0.031	0.095 ± 0.019	0.298 ± 0.079**	0.0014	0.0001
Week 26	0.060 ± 0.045	0.012 ± 0.012	0.071 ± 0.024	0.179 ± 0.023	0.214 ± 0.057*	0.0056	0.0004
Liver							
Week 6	0.100 ± 0.071	0.063 ± 0.024	0.088 ± 0.031	0.150 ± 0.074	0.050 ± 0.020	0.6609	0.9135
Week 10	0.163 ± 0.043	0.113 ± 0.024	0.100 ± 0.020	0.200 ± 0.035	0.075 ± 0.014	0.0537	0.4818
Week 14	0.075 ± 0.032	0.163 ± 0.055	0.163 ± 0.080	0.238 ± 0.043	0.138 ± 0.024	0.3080	0.4198
Week 26	0.088 ± 0.013	0.050 ± 0.029	0.100 ± 0.020	0.138 ± 0.043	0.125 ± 0.043	0.3721	0.1169

* Significantly different ($P \leq 0.05$) from the control group by a one-way analysis of variance with application of Dunnett's test
** $P \leq 0.01$
*** $P \leq 0.001$
**** $P \leq 0.0001$
[a] Percentages (mean ± standard error) are the sum of the percentages of BrdU-labeled cells in each of the cell cycle phases G_1, G_2, S, and M.
[b] Test for overall exposure concentration effect (ANOVA)
[c] Tests for linear exposure concentration trends were conducted using orthogonal contrasts; a negative trend is indicated by **N**.

TABLE E5
Percentages of PCNA-Labeled Kidney and Liver Cells in Active DNA Replication in Mice at the 3-, 7-, 9-, and 24-Week Evaluations in the Feed Study of Fumonisin B_1[a]

	0 ppm	5 ppm	15 ppm	80 ppm	150 ppm	Exposure Concentration Effect P Value[b]	Trend P Value[c]
n	4	4	4	4	4		
Male							
Kidney							
Week 3	0.116 ± 0.070	0.058 ± 0.012	0.151 ± 0.044	0.244 ± 0.064	0.209 ± 0.059	0.0495	0.0905
Week 7	0.058 ± 0.012	0.012 ± 0.012	0.140 ± 0.054	0.012 ± 0.012	0.035 ± 0.022	0.0731	0.1849
Week 9	0.000 ± 0.000	0.000 ± 0.000	0.105 ± 0.061	0.058 ± 0.035	0.070 ± 0.045	—[d]	—
Week 24	0.047 ± 0.047	0.012 ± 0.012	0.035 ± 0.012	0.116 ± 0.013	0.116 ± 0.045	0.0198	0.0848
Liver							
Week 3	0.000 ± 0.000	0.075 ± 0.032	0.013 ± 0.013	0.163 ± 0.055	0.025 ± 0.025	—	—
Week 7	0.088 ± 0.088	0.013 ± 0.013	0.000 ± 0.000	0.025 ± 0.014	0.150 ± 0.089	—	—
Week 9	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.075 ± 0.032	0.013 ± 0.013	—	—
Week 24	0.000 ± 0.000	0.038 ± 0.024	0.125 ± 0.125	0.025 ± 0.025	0.013 ± 0.013	—	—
	0 ppm	**5 ppm**	**15 ppm**	**50 ppm**	**80 ppm**		
Female							
Kidney							
Week 3	0.035 ± 0.012	0.116 ± 0.048	0.070 ± 0.030	0.081 ± 0.040	0.291 ± 0.106	0.1910	0.1237
Week 7	0.174 ± 0.044	0.198 ± 0.040	0.058 ± 0.022	0.116 ± 0.101	0.093 ± 0.033	0.1011	0.2199
Week 9	0.047 ± 0.019	0.081 ± 0.040	0.419 ± 0.042***	0.337 ± 0.152	0.151 ± 0.052	0.0023	0.3100
Week 24	0.209 ± 0.067	0.279 ± 0.158	0.116 ± 0.030	0.140 ± 0.033	0.721 ± 0.288	0.3321	0.1968
Liver							
Week 3	0.050 ± 0.020	0.138 ± 0.107	0.163 ± 0.090	0.050 ± 0.035	1.363 ± 0.399	—	—
Week 7	0.238 ± 0.143	0.450 ± 0.106	0.013 ± 0.013	0.100 ± 0.054	0.388 ± 0.160	—	—
Week 9	0.063 ± 0.038	0.138 ± 0.080	0.688 ± 0.188	0.125 ± 0.125	0.175 ± 0.063	—	—
Week 24	0.313 ± 0.250	0.075 ± 0.032	0.000 ± 0.000	0.013 ± 0.013	0.188 ± 0.120	—	—

*** Significantly different ($P \leq 0.001$) from the control group by a one-way analysis of variance with application of Dunnett's test
[a] Percentages (mean ± standard error) are the sum of the percentages of PCNA-labeled cells in each of the cell cycle phases G_1, G_2, S, and M.
[b] Test for overall exposure concentration effect (ANOVA)
[c] Tests for linear exposure concentration trends were conducted using orthogonal contrasts.
[d] Data were not adequate to fit the statistical models.

TABLE E6
Percentages of BrdU-Labeled Kidney and Liver Cells in Active DNA Replication in Mice at the 3-, 7-, 9-, and 24-Week Evaluations in the Feed Study of Fumonisin B_1[a]

	0 ppm	5 ppm	15 ppm	80 ppm	150 ppm	Exposure Concentration Effect P Value[b]	Trend P Value[c]
n	4	4	4	4	4		
Male							
Kidney							
Week 3	0.000 ± 0.000	0.023 ± 0.013	0.116 ± 0.030	0.128 ± 0.012	0.070 ± 0.030	—[d]	—
Week 7	0.000 ± 0.000	0.047 ± 0.000	0.023 ± 0.023	0.023 ± 0.013	0.000 ± 0.000	—	—
Week 9	0.012 ± 0.012	0.023 ± 0.023	0.023 ± 0.023	0.058 ± 0.035	0.012 ± 0.012	0.7481	0.8307
Week 24	0.047 ± 0.019	0.023 ± 0.013	0.070 ± 0.040	0.047 ± 0.019	0.012 ± 0.012	0.3837	0.1714
Liver							
Week 3	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	—	—
Week 7	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	—	—
Week 9	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	—	—
Week 24	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	—	—
	0 ppm	**5 ppm**	**15 ppm**	**50 ppm**	**80 ppm**		
Female							
Kidney							
Week 3	0.058 ± 0.022	0.070 ± 0.040	0.023 ± 0.013	0.058 ± 0.035	0.128 ± 0.084	0.4786	0.4499
Week 7	0.047 ± 0.027	0.012 ± 0.012	0.058 ± 0.022	0.058 ± 0.012	0.163 ± 0.067	0.1392	0.1357
Week 9	0.023 ± 0.023	0.047 ± 0.019	0.151 ± 0.040	0.081 ± 0.029	0.035 ± 0.012	0.1519	0.5764
Week 24	0.081 ± 0.022	0.140 ± 0.033	0.081 ± 0.040	0.035 ± 0.035	0.186 ± 0.068	0.2855	0.4836
Liver							
Week 3	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.013 ± 0.013	0.000 ± 0.000	—	—
Week 7	0.013 ± 0.013	0.000 ± 0.000	0.000 ± 0.000	0.013 ± 0.013	0.000 ± 0.000	—	—
Week 9	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	—	—
Week 24	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	—	—

[a] Percentages (mean ± standard error) are the sum of the percentages of BrdU-labeled cells in each of the cell cycle phases G_1, G_2, S, and M.
[b] Test for overall exposure concentration effect (ANOVA)
[c] Tests for linear exposure concentration trends were conducted using orthogonal contrasts.
[d] Data were not adequate to fit the statistical models.

APPENDIX F
CLINICAL PATHOLOGY RESULTS

Table F1
Clinical Chemistry and Urinalysis Data for Rats in the 28-Day Feed Study of Fumonisin B_1[a]

	0 ppm	99 ppm	163 ppm	234 ppm	484 ppm
n					
Day 7	4	4	4	4	4
Day 14	4	4	4	4	4
Day 28	8	8	8	8	8
Core study	4	4	4	4	4
Male					
Clinical Chemistry					
Urea nitrogen (mg/dL)					
Day 28	14.8 ± 0.5	13.3 ± 0.8	12.8 ± 0.5	13.0 ± 0.3	16.7 ± 0.5
Core study	16.4 ± 0.3	15.0 ± 0.5	15.3 ± 0.4	15.2 ± 0.4	18.0 ± 0.8
Creatinine (mg/dL)					
Day 28	0.41 ± 0.01	0.46 ± 0.02	0.50 ± 0.04	0.53 ± 0.04**	0.63 ± 0.03****
Core study	0.56 ± 0.04	0.56 ± 0.06	0.55 ± 0.05[b]	0.69 ± 0.08	0.73 ± 0.03*[b]
Total protein (g/dL)					
Day 28	6.3 ± 0.1	6.3 ± 0.1	6.3 ± 0.1	6.9 ± 0.5	7.0 ± 0.3
Core study	6.6 ± 0.1	6.6 ± 0.1	6.6 ± 0.1	6.6 ± 0.1	7.0 ± 0.1*
Albumin (g/dL)					
Day 28	3.6 ± 0.1	3.5 ± 0.1	3.4 ± 0.1	3.7 ± 0.2	3.9 ± 0.2
Core study	3.6 ± 0.1	3.6 ± 0.1	3.6 ± 0.0	3.6 ± 0.1	3.9 ± 0.1
Cholesterol (mg/dL)					
Day 7	85 ± 5	92 ± 4	96 ± 5	103 ± 7	266 ± 30****
Day 14	88 ± 8	80 ± 7	83 ± 5	136 ± 13*	220 ± 18****
Day 28	48 ± 2	49 ± 1	54 ± 2	75 ± 8	225 ± 24****
Core study	60 ± 1	61 ± 2	60 ± 2	62 ± 3	212 ± 20****
Triglycerides (mg/dL)					
Day 7	82 ± 12	88 ± 4	83 ± 7	89 ± 11	175 ± 11****
Day 14	75 ± 12	100 ± 10	79 ± 4	133 ± 13**	163 ± 18****
Day 28	54 ± 3	66 ± 5	74 ± 5*	86 ± 7**	107 ± 7****
Core study	120 ± 17	122 ± 19	107 ± 18	101 ± 15	143 ± 9
Alanine aminotransferase (IU/L)					
Day 7	42 ± 2	42 ± 3	46 ± 2	61 ± 5	188 ± 46****[b]
Day 14	52 ± 14	40 ± 1	36 ± 5	83 ± 6	118 ± 15***
Day 28	35 ± 3	34 ± 1	48 ± 10	58 ± 7	156 ± 27****
Core study	24 ± 1	27 ± 1	34 ± 5	45 ± 4**	174 ± 29****
Alkaline phosphatase (IU/L)					
Day 7	360 ± 8	382 ± 11	388 ± 11	423 ± 3	846 ± 134****[b]
Day 14	379 ± 8[b]	346 ± 9	362 ± 12	336 ± 48	732 ± 81****
Day 28	259 ± 10	258 ± 8	284 ± 11	333 ± 19	623 ± 37****
Core study	266 ± 7	254 ± 8	260 ± 12	277 ± 14	577 ± 42****
Aspartate aminotransferase (IU/L)					
Day 28	75 ± 6	72 ± 3	94 ± 11	96 ± 8	248 ± 20****
Core study	50 ± 4	60 ± 4	65 ± 4*	69 ± 1**	238 ± 31****
Sorbitol dehydrogenase (IU/L)					
Day 28	16 ± 1	16 ± 1	14 ± 1	23 ± 2**[c]	21 ± 2*
Core study	16 ± 3	17 ± 3	15 ± 1	18 ± 3	18 ± 1
γ-Glutamyltransferase (IU/L)					
Day 28	0.4 ± 0.1	0.5 ± 0.1	0.4 ± 0.1	0.8 ± 0.2	5.8 ± 0.6****
Core study	0.8 ± 0.4	0.9 ± 0.3	1.2 ± 0.2	0.7 ± 0.2	5.0 ± 0.5****
Total bile acids (µmol/L)					
Day 7	17.4 ± 2.1	15.9 ± 1.0[d]	23.8 ± 1.6	29.2 ± 6.0	130.1 ± 66.4*[b]
Day 14	19.0 ± 2.6[b]	21.5 ± 6.5[d]	15.3[e]	52.6 ± 14.1[d]	117.2 ± 36.8***[d]
Day 28	10.3 ± 1.1	10.5 ± 1.3	20.0 ± 9.5	18.7 ± 2.7	72.4 ± 11.5****
Core study	18.2 ± 0.8	12.4 ± 1.4	12.7 ± 1.7	20.7 ± 1.6	115.7 ± 28.9****

TABLE F1
Clinical Chemistry and Urinalysis Data for Rats in the 28-Day Feed Study of Fumonisin B_1

	0 ppm	99 ppm	163 ppm	234 ppm	484 ppm
n					
Day 7	4	4	4	4	4
Day 14	4	4	4	4	4
Day 28	8	8	8	8	8
Core study	4	4	4	4	4
Male (continued)					
Urinalysis					
Creatinine (mg/dL)					
Day 7	80.83 ± 20.62	46.18 ± 3.24	51.60 ± 13.02	35.00 ± 6.41*	48.80 ± 6.21
Day 14	93.48 ± 7.84	56.90 ± 12.03*	57.48 ± 7.14**	47.33 ± 8.42**	54.70 ± 8.66*
Day 28	88.20 ± 9.78	77.56 ± 8.44	90.43 ± 9.04	59.75 ± 12.23	60.93 ± 5.83
Glucose (mg/dL)					
Day 7	23.45 ± 8.12	82.68 ± 16.94	82.63 ± 25.47	74.08 ± 42.44	24.85 ± 6.61
Day 14	34.13 ± 7.89	15.08 ± 2.84**	13.08 ± 1.97**	10.63 ± 2.45***	10.10 ± 1.22***
Day 28	35.29 ± 6.39	27.40 ± 5.84	23.94 ± 2.29	19.14 ± 5.24	25.11 ± 7.27
N-acetyl-β-D-glucosaminidase (IU/L)					
Day 7	60 ± 21[d]	52 ± 15	23 ± 2[b]	31 ± 4[b]	25 ± 6[b]
Day 14	34 ± 1[b]	36 ± 2	32 ± 3	32 ± 1[b]	30 ± 2
Day 28	45 ± 8	28 ± 3	34 ± 5[f]	31 ± 6[f]	35 ± 5[f]
Sphingosine (pmol/mL)					
Day 7	31.48 ± 7.19	76.15 ± 23.78	50.37 ± 13.24	41.48 ± 11.26	46.20 ± 13.73
Day 14	49.93 ± 1.95	176.21 ± 50.00	292.42 ± 68.27*[b]	225.74 ± 37.46	213.74 ± 43.33
Day 28	27.76 ± 3.13	166.38 ± 25.63*	346.15 ± 64.77*	152.76 ± 14.01*	171.90 ± 24.86*
Sphinganine (pmol/mL)					
Day 7	74.35 ± 45.59	320.24 ± 19.49	453.93 ± 136.30	365.62 ± 114.68	542.33 ± 211.84
Day 14	82.34 ± 20.80	805.32 ± 224.43	1,720.68 ± 327.04*[b]	1,583.51 ± 282.51*	1,579.41 ± 600.55*
Day 28	33.28 ± 3.53	880.46 ± 118.38*	2,137.35 ± 374.58*	1,103.07 ± 110.26*	1,326.02 ± 162.32*
Sphinganine/sphingosine ratio					
Day 7	2.29 ± 1.40	5.42 ± 1.51	8.70 ± 0.89*	9.13 ± 1.66*	10.04 ± 2.20*
Day 14	1.65 ± 0.41	4.56 ± 0.23	5.99 ± 0.29[b]	6.98 ± 0.20*	7.04 ± 2.02*
Day 28	1.35 ± 0.28	5.39 ± 0.18*	6.27 ± 0.11*	7.24 ± 0.26*	8.12 ± 0.59*
Female					
Clinical Chemistry					
Urea nitrogen (mg/dL)					
Day 28	15.7 ± 0.7	14.5 ± 1.4	15.2 ± 0.9	15.8 ± 0.7	17.1 ± 0.3
Core study	17.7 ± 0.4	18.4 ± 0.9	17.6 ± 0.5	17.6 ± 0.3	19.3 ± 0.9
Creatinine (mg/dL)					
Day 28	0.45 ± 0.02	0.45 ± 0.03	0.51 ± 0.01	0.51 ± 0.01	0.60 ± 0.02****
Core study	0.51 ± 0.04	0.54 ± 0.05	0.56 ± 0.04	0.59 ± 0.06*	0.65 ± 0.04***
Total protein (g/dL)					
Day 28	7.0 ± 0.4	6.7 ± 0.5	6.6 ± 0.0	7.3 ± 0.3	7.5 ± 0.3
Core study	6.5 ± 0.1	6.4 ± 0.0	6.7 ± 0.1	6.8 ± 0.1	7.1 ± 0.1**

TABLE F1
Clinical Chemistry and Urinalysis Data for Rats in the 28-Day Feed Study of Fumonisin B_1

	0 ppm	99 ppm	163 ppm	234 ppm	484 ppm
n					
Day 7	4	4	4	4	4
Day 14	4	4	4	4	4
Day 28	8	8	8	8	8
Core study	4	4	4	4	4
Female (continued)					
Clinical Chemistry (continued)					
Albumin (g/dL)					
Day 28	3.7 ± 0.2	3.6 ± 0.2	3.6 ± 0.1	4.0 ± 0.1	4.1 ± 0.2
Core study	3.7 ± 0.1	3.6 ± 0.1	3.7 ± 0.1	3.8 ± 0.0	3.9 ± 0.1
Cholesterol (mg/dL)					
Day 7	103 ± 8	95 ± 2	120 ± 6	195 ± 12****	272 ± 21****
Day 14	91 ± 3	97 ± 3	170 ± 14**	240 ± 19****	255 ± 34****
Day 28	117 ± 17	109 ± 17	130 ± 5	205 ± 22**	280 ± 32****
Core study	101 ± 4	106 ± 3	147 ± 9	189 ± 12**	244 ± 30***
Triglycerides (mg/dL)					
Day 7	62 ± 7	62 ± 11	60 ± 5	83 ± 11	82 ± 5
Day 14	45 ± 5	44 ± 2	68 ± 7*	94 ± 11****	128 ± 4****
Day 28	64 ± 6	60 ± 3	63 ± 4	74 ± 5	97 ± 8***
Core study	68 ± 9	80 ± 11	111 ± 12**	132 ± 11***	139 ± 13***
Alanine aminotransferase (IU/L)					
Day 7	35 ± 3	33 ± 2	38 ± 3	71 ± 3***	146 ± 12****
Day 14	30 ± 1	33 ± 0	50 ± 7	64 ± 9	165 ± 47***
Day 28	37 ± 5	35 ± 5	33 ± 2	59 ± 8	119 ± 22****
Core study	38 ± 3	43 ± 4	44 ± 9	59 ± 8	120 ± 14***
Alkaline phosphatase (IU/L)					
Day 7	287 ± 3	277 ± 11	278 ± 15	343 ± 4*	792 ± 27****
Day 14	234 ± 3	240 ± 6	265 ± 14	350 ± 23**	711 ± 48****
Day 28	196 ± 15	177 ± 14	177 ± 5	262 ± 16	529 ± 45****
Core study	166 ± 5	164 ± 7	177 ± 10	235 ± 9*	490 ± 36****
Aspartate aminotransferase (IU/L)					
Day 28	80 ± 5	71 ± 5	82 ± 4	119 ± 8**	194 ± 15****
Core study	73 ± 5	70 ± 5	70 ± 7	97 ± 9	201 ± 20****
Sorbitol dehydrogenase (IU/L)					
Day 28	14 ± 1	13 ± 2	19 ± 3	15 ± 2[c]	21 ± 2[c]
Core study	15 ± 3	16 ± 2	19 ± 3	18 ± 2	20 ± 2
γ-Glutamyltransferase (IU/L)					
Day 28	0.7 ± 0.2	0.6 ± 0.1	0.9 ± 0.2	1.5 ± 0.5	6.8 ± 1.1****
Core study	0.6 ± 0.2	0.9 ± 0.4	0.8 ± 0.1	1.7 ± 0.3*	10.8 ± 2.7****
Total bile acids (μmol/L)					
Day 7	16.1 ± 8.2[b]	18.6 ± 3.2[b]	26.3 ± 2.0	77.4 ± 8.9*	192.8 ± 27.0****
Day 14	13.3 ± 6.4[d]	14.9[e]	35.4 ± 1.2[d]	73.1 ± 13.4[d]	193.8 ± 42.0**
Day 28	11.3 ± 2.2	10.5 ± 1.6	19.0 ± 3.4	31.8 ± 4.5	110.9 ± 25.4****
Core study	13.7 ± 1.4	16.9 ± 2.3	29.9 ± 4.7**	47.0 ± 6.1****	109.8 ± 23.4****

TABLE F1
Clinical Chemistry and Urinalysis Data for Rats in the 28-Day Feed Study of Fumonisin B_1

	0 ppm	99 ppm	163 ppm	234 ppm	484 ppm
n					
Day 7	4	4	4	4	4
Day 14	4	4	4	4	4
Day 28	8	8	8	8	8
Core study	4	4	4	4	4
Female (continued)					
Urinalysis					
Creatinine (mg/dL)					
Day 7	34.38 ± 8.41	42.48 ± 14.28	42.13 ± 2.44	43.75 ± 10.09	44.85 ± 5.89
Day 14	37.33 ± 6.49	46.65 ± 1.86	45.93 ± 16.23	62.50 ± 12.41	48.83 ± 9.96
Day 28	55.83 ± 13.04	50.18 ± 10.13	42.69 ± 4.87	45.39 ± 4.74	45.53 ± 4.86
Glucose (mg/dL)					
Day 7	9.00 ± 1.93	10.20 ± 3.05	10.05 ± 0.52	13.88 ± 2.20	9.83 ± 0.74
Day 14	15.38 ± 5.09	11.45 ± 1.65	14.23 ± 7.59	10.75 ± 2.52	14.43 ± 3.97
Day 28	10.79 ± 2.30	11.54 ± 2.25	9.95 ± 1.90	12.94 ± 1.91	12.94 ± 1.60
N-acetyl-β-D-glucosaminidase (IU/L)					
Day 7	39 ± 15	26 ± 3	32 ± 4[b]	47 ± 9	38 ± 3
Day 14	35 ± 2	35 ± 2[b]	30 ± 2	32 ± 2[b]	29 ± 6
Day 28	32 ± 5	36 ± 4	27 ± 6	38 ± 3	35 ± 6[g]
Sphingosine (pmol/mL)					
Day 7	10.59 ± 1.62	38.24 ± 20.02*	139.55 ± 28.12*	237.10 ± 83.99*	204.79 ± 103.37*
Day 14	14.73 ± 2.41	39.83 ± 5.77*	68.07 ± 16.77*	142.68 ± 43.29*	107.71 ± 24.37*
Day 28	15.44 ± 3.87	20.55 ± 4.78	38.24 ± 9.48*	80.31 ± 21.19*	86.17 ± 10.03*
Sphinganine (pmol/mL)					
Day 7	18.39 ± 5.27	208.21 ± 68.31*	1,141.94 ± 223.65*	2,256.62 ± 1,141.94*	1,236.29 ± 131.84*
Day 14	39.12 ± 3.14	195.36 ± 15.84*	448.32 ± 95.07*	1,306.99 ± 331.51*	1,166.06 ± 302.75*
Day 28	22.11 ± 9.34	112.72 ± 24.61*	358.41 ± 87.42*	824.14 ± 204.25*	887.02 ± 149.43*
Sphinganine/sphingosine ratio					
Day 7	1.73 ± 0.39	7.49 ± 3.16*	8.20 ± 0.16*	8.92 ± 1.68*	9.34 ± 2.23*
Day 14	2.90 ± 0.59	5.15 ± 0.69*	7.05 ± 0.72*	9.63 ± 0.94*	10.58 ± 0.36*
Day 28	2.18 ± 1.31	5.67 ± 0.47	9.69 ± 0.87*	10.78 ± 0.98*	10.11 ± 0.76*

* Significantly different ($P \leq 0.05$) from the control group by Kleinbaum's procedure (clinical chemistry data) or a repeated measures analysis of variance (urinalysis data) with application of Holm's procedure
** $P \leq 0.01$
*** $P \leq 0.001$
**** $P \leq 0.0001$
[a] Mean ± standard error. Statistical tests were performed on unrounded data. Core study animals were evaluated on day 28; clinical pathology study animals were evaluated on days 7, 14, and 28.
[b] n=3
[c] n=7
[d] n=2
[e] n=1; no standard error calculated
[f] n=6
[g] n=5

Table F2
Hematology, Clinical Chemistry, Urinalysis, and Tissue Sphingolipid Data for Rats at the 6-, 10-, 14-, and 26-Week Evaluations and at 2 Years in the Feed Study of Fumonisin B_1[a]

	0 ppm	5 ppm	15 ppm	50 ppm	150 ppm
Male					
Hematology					
n					
Week 6	4	4	4	4	4
Week 10	4	4	4	4	4
Week 14	2	4	2	4	4
Week 26	4	3	3	4	4
Hematocrit (%)					
Week 6	45.5 ± 1.1	45.1 ± 1.1	47.3 ± 0.4	41.6 ± 3.0	45.9 ± 0.6
Week 10	45.7 ± 0.5	45.4 ± 1.0	47.4 ± 0.6	47.3 ± 0.8	45.8 ± 0.5
Week 14	45.0 ± 2.8	45.6 ± 0.8	46.7 ± 0.3	46.1 ± 0.3	46.2 ± 0.6
Week 26	46.6 ± 0.2	47.0 ± 0.4	45.7 ± 1.2	47.2 ± 0.5	45.9 ± 0.3
Hemoglobin (g/dL)					
Week 6	16.8 ± 0.5	16.9 ± 0.3	17.4 ± 0.2	15.7 ± 1.2	17.0 ± 0.3
Week 10	16.9 ± 0.1	16.7 ± 0.2	17.6 ± 0.3	17.5 ± 0.4	16.9 ± 0.2
Week 14	15.9 ± 0.9	16.7 ± 0.2	16.8 ± 0.0	16.8 ± 0.2	16.9 ± 0.2
Week 26	16.5 ± 0.1	16.4 ± 0.2[b]	16.0 ± 0.4	16.7 ± 0.2	16.2 ± 0.0
Erythrocytes (10^6/µL)					
Week 6	8.9 ± 0.2	8.9 ± 0.2	9.2 ± 0.1	8.2 ± 0.6	9.0 ± 0.1
Week 10	9.3 ± 0.1	9.2 ± 0.2	9.7 ± 0.1	9.6 ± 0.3	9.2 ± 0.1
Week 14	8.9 ± 0.5	9.1 ± 0.2	9.3 ± 0.0	9.0 ± 0.0	9.2 ± 0.1
Week 26	8.9 ± 0.1	9.0 ± 0.2	8.8 ± 0.3	9.0 ± 0.1	8.9 ± 0.1
Mean cell volume (fL)					
Week 6	51.2 ± 0.4	51.0 ± 0.3	51.4 ± 0.1	51.0 ± 0.2	50.9 ± 0.2
Week 10	49.3 ± 0.5	49.4 ± 0.5	49.1 ± 0.5	49.1 ± 0.6	49.6 ± 0.4
Week 14	50.4 ± 0.1	50.0 ± 0.1	50.1 ± 0.3	51.0 ± 0.5	50.1 ± 0.2
Week 26	52.3 ± 0.6	52.0 ± 0.6	52.2 ± 0.7	52.5 ± 0.5	51.9 ± 0.4
Mean cell hemoglobin (pg)					
Week 6	18.8 ± 0.1	19.1 ± 0.1	18.9 ± 0.2	19.3 ± 0.1	18.9 ± 0.1
Week 10	18.2 ± 0.1	18.2 ± 0.1	18.2 ± 0.1	18.2 ± 0.2	18.3 ± 0.1
Week 14	17.8 ± 0.0	18.3 ± 0.2	18.0 ± 0.0	18.6 ± 0.3	18.3 ± 0.2
Week 26	18.5 ± 0.2	18.4 ± 0.2	18.2 ± 0.4	18.6 ± 0.2	18.3 ± 0.1
Mean cell hemoglobin concentration (g/dL)					
Week 6	36.8 ± 0.1	37.5 ± 0.2	36.8 ± 0.3	37.7 ± 0.2**	37.1 ± 0.1
Week 10	36.9 ± 0.4	36.9 ± 0.4	37.2 ± 0.3	37.0 ± 0.5	36.9 ± 0.4
Week 14	35.4 ± 0.2	36.5 ± 0.4	36.0 ± 0.3	36.5 ± 0.2	36.5 ± 0.5
Week 26	35.4 ± 0.2	35.4 ± 0.2	34.9 ± 0.3	35.4 ± 0.2	35.2 ± 0.2
Platelets (10^3/µL)					
Week 6	517.8 ± 25.7	514.8 ± 29.9	408.0 ± 65.9	475.3 ± 33.5	548.5 ± 23.0
Week 10	505.5 ± 50.4	495.3 ± 49.8	487.5 ± 38.3	541.0 ± 43.7	567.0 ± 37.5
Week 14	767.0 ± 139.0	573.3 ± 10.3*	584.0 ± 14.0	601.5 ± 5.7	591.8 ± 23.2
Week 26	619.5 ± 24.4	657.8 ± 35.2[b]	666.0 ± 73.9	619.0 ± 4.3	653.3 ± 8.5
Leukocytes (10^3/µL)					
Week 6	4.4 ± 0.6	17.3 ± 10.9	4.4 ± 0.8	3.3 ± 1.2	3.7 ± 1.1
Week 10	4.9 ± 0.7	6.2 ± 0.7	5.2 ± 0.6	5.2 ± 1.0	5.0 ± 0.8
Week 14	8.8 ± 1.2	6.4 ± 0.7	6.1 ± 0.3	5.9 ± 0.4	6.8 ± 0.9
Week 26	6.3 ± 0.5	5.9 ± 0.2[b]	8.2 ± 1.5	6.3 ± 0.5	6.1 ± 0.2

Table F2
Hematology, Clinical Chemistry, Urinalysis, and Tissue Sphingolipid Data for Rats at the 6-, 10-, 14-, and 26-Week Evaluations and at 2 Years in the Feed Study of Fumonisin B_1

	0 ppm	5 ppm	15 ppm	50 ppm	150 ppm
Male (continued)					
Clinical Chemistry					
n	4	4	4	4	4
Urea nitrogen (mg/dL)					
Week 6	18.5 ± 0.5[c]	17.0 ± 0.0[c]	17.0 ± 0.0[c]	14.0 ± 1.0**[c]	18.5 ± 0.5[c]
Week 10	20.3 ± 1.3	17.8 ± 0.8	20.5 ± 0.6	20.3 ± 1.8	20.8 ± 1.6
Week 14	18.8 ± 2.9	16.0 ± 0.3	20.2 ± 2.5	17.2 ± 1.3	19.3 ± 1.5
Week 26	17.8 ± 0.7	16.8 ± 1.3	20.0 ± 2.3	18.6 ± 1.2	18.1 ± 0.6
Creatinine (mg/dL)					
Week 6	0.6 ± 0.1	0.6 ± 0.1	0.5 ± 0.0	0.7 ± 0.1	0.6 ± 0.0
Week 10	0.6 ± 0.1	0.6 ± 0.1	0.6 ± 0.0	0.6 ± 0.1	0.7 ± 0.1
Week 14	0.6 ± 0.0	0.6 ± 0.0	0.6 ± 0.0	0.6 ± 0.0	0.7 ± 0.0
Week 26	0.6 ± 0.0	0.5 ± 0.0	0.7 ± 0.2	0.6 ± 0.0	0.7 ± 0.0
Total protein (g/dL)					
Week 6	8.3 ± 0.6	8.2 ± 0.4	8.4 ± 0.5	8.9 ± 0.6	8.6 ± 0.4
Week 10	9.7 ± 0.2	9.4 ± 0.4	8.9 ± 0.5	9.7 ± 0.1	8.8 ± 0.6
Week 14	6.3 ± 0.3	6.8 ± 0.1	6.8 ± 0.1	6.7 ± 0.0	6.5 ± 0.2
Week 26	7.2 ± 0.1	7.0 ± 0.1	6.5 ± 0.2**	7.1 ± 0.2	7.1 ± 0.2
Albumin (g/dL)					
Week 6	3.9 ± 0.4	4.0 ± 0.3	3.9 ± 0.3	4.2 ± 0.4	4.0 ± 0.2
Week 10	5.1 ± 0.1	4.8 ± 0.2	4.8 ± 0.3	5.1 ± 0.1	4.6 ± 0.4
Week 14	3.5 ± 0.3	4.0 ± 0.1	3.9 ± 0.1	3.8 ± 0.1	3.6 ± 0.1
Week 26	3.8 ± 0.1	3.7 ± 0.1	3.7 ± 0.1	3.8 ± 0.0	3.8 ± 0.0
Cholesterol (mg/dL)					
Week 6	113 ± 6	96 ± 8	110 ± 3	89 ± 7*	112 ± 4
Week 10	98 ± 8	94 ± 4	100 ± 8	104 ± 7	89 ± 5
Week 14	74 ± 14	56 ± 5	63 ± 4	59 ± 3	58 ± 4
Week 26	82 ± 6	72 ± 3	73 ± 7	80 ± 7	70 ± 4
Triglycerides (mg/dL)					
Week 6	61 ± 11	62 ± 11	76 ± 16	60 ± 7	71 ± 16
Week 10	82 ± 20	85 ± 22	85 ± 11	115± 27	85 ± 14
Week 14	122 ± 56	49 ± 2*	75 ± 2	62 ± 3	73 ± 4
Week 26	96 ± 8	93 ± 4	84 ± 7	106 ± 9	98 ± 6
Alanine aminotransferase (IU/L)					
Week 6	52 ± 7	54 ± 8	52 ± 7	57 ± 5[c]	50 ± 8
Week 10	96 ± 12	79 ± 7	83 ± 10	87 ± 2	81 ± 5
Week 14	53 ± 9	61 ± 8	66 ± 17	49 ± 0	51 ± 3
Week 26	70 ± 6	60 ± 5	57 ± 3	65 ± 11	72 ± 17
Alkaline phosphatase (IU/L)					
Week 6	289 ± 17[c]	405 ± 25*[c]	303 ± 30[c]	356 ± 11[c]	331 ± 21[c]
Week 10	287 ± 18	232 ± 12*	244 ± 13	253 ± 11	252 ± 11
Week 14	111 ± 17	131 ± 2	124 ± 7	132 ± 6	132 ± 14
Week 26	83 ± 3	85 ± 4	77 ± 7	86 ± 4	79 ± 2
Creatine kinase (IU/L)					
Week 6	249 ± 43[c]	472 ± 48*[c]	236 ± 5[c]	502 ± 39*[c]	198 ± 6[c]
Week 10	475 ± 172	330 ± 100	804 ± 392	401 ± 145	855 ± 459[d]
Week 14	422 ± 73	371 ± 74	516 ± 225	388 ± 108	574 ± 195
Week 26	224 ± 33	189 ± 15	326 ± 83	274 ± 69	216 ± 22

TABLE F2
Hematology, Clinical Chemistry, Urinalysis, and Tissue Sphingolipid Data for Rats at the 6-, 10-, 14-, and 26-Week Evaluations and at 2 Years in the Feed Study of Fumonisin B_1

	0 ppm	5 ppm	15 ppm	50 ppm	150 ppm
Male (continued)					
Clinical Chemistry (continued)					
n	4	4	4	4	4
Sorbitol dehydrogenase (IU/L)					
Week 6	13 ± 2[c]	8 ± 3[c]	10 ± 1[c]	11 ± 3[c]	12 ± 3[c]
Week 10	14 ± 2[d]	12 ± 3	18 ± 1	13 ± 2	13 ± 3[d]
Week 14	21 ± 2	19 ± 2	23 ± 3	15 ± 3	17 ± 4
Week 26	15 ± 4	17 ± 1	11 ± 2	19 ± 2	19 ± 2
γ-glutamyltransferase (IU/L)					
Week 6	1.5 ± 0.5[c]	0.0[e]	0.0 ± 0.0*[c]	1.0 ± 0.0[c]	1.0 ± 0.0[c]
Week 10	0.0 ± 0.0[c]	0.0 ± 0.0[c]	0.0 ± 0.0[c]	0.0 ± 0.0[c]	1.0 ± 1.0[c]
Week 14	0.7 ± 0.2	0.4 ± 0.1	1.2 ± 0.3	0.7 ± 0.3	0.7 ± 0.1
Week 26	0.4 ± 0.1	0.3 ± 0.1	0.3 ± 0.1	0.7 ± 0.1	0.7 ± 0.4
Total bile acids (µmol/L)					
Week 6	11.7 ± 2.7	11.5 ± 2.6	9.0 ± 1.7	6.9 ± 0.8	8.8 ± 1.4
Week 10	10.1 ± 1.4	17.5 ± 9.2	9.8 ± 2.6	8.2 ± 1.3	8.0 ± 1.0
Week 14	27.6 ± 4.3	18.1 ± 3.7	15.5 ± 1.0	16.3 ± 4.0	19.0 ± 7.6
Week 26	18.0 ± 5.5	12.9 ± 0.3	30.2 ± 10.3	13.8 ± 3.0	22.2 ± 6.2
Urinalysis					
n	4	4	4	4	4
Creatinine (mg/dL)					
Week 6	91.8 ± 6.4	75.3 ± 11.4	99.3 ± 22.4	75.5 ± 8.2	71.8 ± 14.3
Week 10	134.3 ± 22.2	157.3 ± 21.3	145.0 ± 19.8	128.8 ± 11.8	105.5 ± 30.4
Week 14	115.3 ± 9.3	131.6 ± 15.9	134.1 ± 12.9	87.4 ± 9.4	77.9 ± 6.1**
Week 26	185.5 ± 17.6	170.6 ± 21.1	152.7 ± 20.8	127.5 ± 6.4*	142.9 ± 9.5
Protein/creatinine ratio					
Week 6	1.863 ± 0.276	2.247 ± 0.337	3.097 ± 0.550	1.966 ± 0.183	2.801 ± 0.335
Week 10	1.460 ± 0.245	1.342 ± 0.062	2.053 ± 0.257	1.204 ± 0.083	1.603 ± 0.118
Week 14	1.366 ± 0.315	1.727 ± 0.073	2.917 ± 0.140	1.729 ± 0.031	2.250 ± 0.070
Week 26	1.217 ± 0.118	1.233 ± 0.110	2.014 ± 0.110	1.191 ± 0.099	1.532 ± 0.228
Sphingosine (pmol/mL)					
Week 6	29.167 ± 4.739	38.019 ± 21.678	52.808 ± 8.506	126.239 ± 34.653*	165.017 ± 70.354*
Week 10	58.047 ± 17.588	93.381 ± 60.622	54.922 ± 11.535	143.259 ± 15.312	237.370 ± 27.261*
Week 14	40.785 ± 6.945	43.882 ± 6.965	90.782 ± 7.812*	136.151 ± 17.402*	209.541 ± 41.224*
Week 26	52.581 ± 11.406	110.742 ± 36.632	61.251 ± 11.893	169.748 ± 16.907*	193.798 ± 47.121*
Sphinganine (pmol/mL)					
Week 6	5.926 ± 5.926	0 ± 0	178.776 ± 52.155*	586.038 ± 177.872*	968.875 ± 328.900*
Week 10	13.177 ± 4.415	70.235 ± 20.080*	403.234 ± 47.073*	1,568.02 ± 329.36*	3,119.56 ± 514.36*
Week 14	16.916 ± 1.548	29.688 ± 8.025	953.149 ± 173.143*	1,645.73 ± 137.86*	2,669.07 ± 23.661*
Week 26	27.834 ± 6.959	894.983 ± 540.541*	367.352 ± 153.654*	2,435.34 ± 518.10*	4,617.82 ± 543.22*
Sphinganine/sphingosine ratio					
Week 6	0.149 ± 0.149	0 ± 0[d]	3.293 ± 0.625	4.581 ± 0.631	6.723 ± 1.065*
Week 10	0.210 ± 0.080	1.434 ± 0.511*	8.466 ± 2.350*	11.392 ± 3.096*	13.804 ± 2.946*
Week 14	0.435 ± 0.048	0.681 ± 0.129	10.948 ± 2.511*	12.367 ± 0.939*	14.551 ± 3.121*
Week 26	0.532 ± 0.088	5.497 ± 2.646*	5.264 ± 1.793*	14.541 ± 3.199*	26.375 ± 4.114*

TABLE F2
Hematology, Clinical Chemistry, Urinalysis, and Tissue Sphingolipid Data for Rats at the 6-, 10-, 14-, and 26-Week Evaluations and at 2 Years in the Feed Study of Fumonisin B_1

	0 ppm	5 ppm	15 ppm	50 ppm	150 ppm
Male (continued)					
Tissue Sphingolipid Analysis					
n	4	4	4	4	4
Kidney sphingosine (nmol/g)					
Week 6	2.323 ± 0.496	4.252 ± 1.115	7.509 ± 2.701	14.027 ± 5.059	11.686 ± 6.707
Week 10	2.786 ± 0.642	6.622 ± 1.135	7.765 ± 1.139	14.361 ± 1.714*	15.974 ± 2.914*
Week 14	1.929 ± 0.483	3.994 ± 0.448	5.362 ± 1.376*	6.708 ± 1.022*	8.704 ± 0.214*
Week 26	3.180 ± 1.396	5.877 ± 0.566	4.849 ± 1.967[d]	12.208 ± 1.726*	6.828 ± 2.235
2 Years	4.707 ± 1.242[f]	5.513 ± 1.257[g]	8.240 ± 2.282[f]	15.877 ± 4.337*[f]	16.134 ± 3.103*[h]
Kidney sphinganine (nmol/g)					
Week 6	1.432 ± 0.363	6.778 ± 1.607*	92.522 ± 51.368*	160.596 ± 56.495*	139.790 ± 73.051*
Week 10	2.669 ± 0.045	15.489 ± 1.819*	68.178 ± 5.061*	185.576 ± 31.918*	246.021 ± 37.690*
Week 14	3.842 ± 0.730	7.698 ± 1.621*	50.235 ± 9.585*	94.709 ± 16.438*	119.614 ± 30.644*
Week 26	3.977 ± 1.941	45.875 ± 20.413	53.487 ± 28.250[d]	111.360 ± 11.368*	146.902 ± 26.647*
2 Years	2.029 ± 0.542[f]	2.556 ± 0.540[g]	22.112 ± 5.710[f]	173.035 ± 19.555*[f]	241.310 ± 43.194*[h]
Kidney sphinganine/sphingosine ratio					
Week 6	0.617 ± 0.067	1.973 ± 0.521*	11.514 ± 2.623*	11.568 ± 0.160*	13.976 ± 1.795*
Week 10	1.217 ± 0.395	2.502 ± 0.386	9.730 ± 2.179*	12.638 ± 0.852*	16.023 ± 1.421*
Week 14	2.683 ± 1.099	1.898 ± 0.241	9.764 ± 0.962*	14.216 ± 1.223*	13.931 ± 3.733*
Week 26	3.025 ± 2.158	7.084 ± 2.857	17.388 ± 9.873[d]	9.651 ± 1.577	28.072 ± 10.473*
2 Years	0.724 ± 0.252[f]	0.580 ± 0.215[g]	3.191 ± 1.474[g]	15.692 ± 4.324*[f]	16.054 ± 1.901*[h]
Liver sphingosine (nmol/g)					
Week 6	3.443 ± 0.715	2.717 ± 0.302[c]	2.180 ± 0.432	2.572 ± 0.103[c]	3.563 ± 0.195[c]
Week 10	3.972 ± 0.956	3.361 ± 0.870[d]	3.082 ± 0.380	3.433 ± 0.303	3.666 ± 0.677
Week 14	2.837 ± 0.332	4.506 ± 1.104	3.069 ± 0.646	3.768 ± 0.208	3.312 ± 0.465
Week 26	2.279 ± 0.335	4.084 ± 0.559	2.911 ± 0.228[d]	4.210 ± 0.885	3.059 ± 0.282
Liver sphinganine (nmol/g)					
Week 6	0.982 ± 0.130	0.904 ± 0.305[c]	0.778 ± 0.189	0.591 ± 0.277[c]	1.581 ± 0.569[c]
Week 10	1.461 ± 0.397	1.230 ± 0.070[d]	1.336 ± 0.647	1.043 ± 0.161	2.767 ± 0.395
Week 14	1.584 ± 0.483	2.324 ± 0.521	1.069 ± 0.223	1.470 ± 0.465	2.831 ± 0.354
Week 26	0.693 ± 0.088	1.372 ± 0.566	0.505 ± 0.220	1.589 ± 0.561	1.771 ± 0.483
Liver sphinganine/sphingosine ratio					
Week 6	0.339 ± 0.032[d]	0.349 ± 0.151[c]	0.409 ± 0.093	0.226 ± 0.099[c]	0.437 ± 0.135[c]
Week 10	0.415 ± 0.099	0.404 ± 0.079[d]	0.414 ± 0.146	0.310 ± 0.053	0.786 ± 0.080
Week 14	0.528 ± 0.116	0.567 ± 0.113	0.368 ± 0.070	0.397 ± 0.122	0.908 ± 0.171
Week 26	0.312 ± 0.025	0.301 ± 0.100	0.180 ± 0.086	0.458 ± 0.161	0.620 ± 0.177

Table F2
Hematology, Clinical Chemistry, Urinalysis, and Tissue Sphingolipid Data for Rats at the 6-, 10-, 14-, and 26-Week Evaluations and at 2 Years in the Feed Study of Fumonisin B_1

	0 ppm	5 ppm	15 ppm	50 ppm	100 ppm
Female					
Hematology					
n					
Week 6	4	4	4	4	4
Week 10	4	3	4	4	4
Week 14	4	3	4	4	4
Week 26	4	2	4	4	4
Hematocrit (%)					
Week 6	40.6 ± 3.3	44.8 ± 0.4	45.7 ± 0.7	44.2 ± 1.7	41.9 ± 1.8
Week 10	45.0 ± 0.8	44.6 ± 0.5	45.4 ± 0.7	41.9 ± 3.2	45.2 ± 0.8
Week 14	45.1 ± 0.7	45.7 ± 0.5	45.7 ± 1.3	46.0 ± 0.4	45.6 ± 0.5
Week 26	46.6 ± 0.3	45.8 ± 0.7	46.7 ± 0.6	47.3 ± 0.7	47.5 ± 1.0
Hemoglobin (g/dL)					
Week 6	15.4 ± 1.2	16.9 ± 0.2	17.3 ± 0.3	16.7 ± 0.7	15.7 ± 0.8
Week 10	16.2 ± 0.2	16.0 ± 0.3	16.2 ± 0.3	15.0 ± 1.3	16.2 ± 0.3
Week 14	16.9 ± 0.2	17.0 ± 0.1	16.9 ± 0.4	17.5 ± 0.2	16.9 ± 0.2
Week 26	16.9 ± 0.0	16.4 ± 0.4	17.0 ± 0.2	16.9 ± 0.3	17.2 ± 0.2
Erythrocytes (10^6/µL)					
Week 6	7.8 ± 0.7	8.6 ± 0.0	8.8 ± 0.2	8.5 ± 0.3	8.0 ± 0.3
Week 10	8.5 ± 0.1	8.3 ± 0.1	8.5 ± 0.1	7.9 ± 0.6	8.4 ± 0.1
Week 14	8.5 ± 0.1	8.4 ± 0.1	8.6 ± 0.2	8.6 ± 0.1	8.5 ± 0.1
Week 26	8.5 ± 0.1	8.2 ± 0.2	8.5 ± 0.1	8.6 ± 0.1	8.6 ± 0.2
Mean cell volume (fL)					
Week 6	52.0 ± 0.4	52.0 ± 0.4	51.9 ± 0.3	52.1 ± 0.3	52.0 ± 0.2
Week 10	53.0 ± 0.4	53.5 ± 0.3	53.3 ± 0.2	53.0 ± 0.3	53.5 ± 0.2
Week 14	53.2 ± 0.6	54.1 ± 0.4	53.3 ± 0.5	53.3 ± 0.7	53.3 ± 0.5
Week 26	54.7 ± 0.1	55.6 ± 0.2	54.7 ± 0.3	55.2 ± 0.1	55.0 ± 0.4
Mean cell hemoglobin (pg)					
Week 6	19.8 ± 0.2	19.6 ± 0.2	19.6 ± 0.1	19.6 ± 0.2	19.5 ± 0.2
Week 10	19.1 ± 0.1	19.2 ± 0.0	19.0 ± 0.1	18.9 ± 0.2	19.2 ± 0.1
Week 14	20.0 ± 0.2	20.1 ± 0.1	19.8 ± 0.0	20.2 ± 0.4	19.8 ± 0.2
Week 26	19.9 ± 0.1	19.8 ± 0.2	19.9 ± 0.1	19.7 ± 0.2	19.9 ± 0.4
Mean cell hemoglobin concentration (g/dL)					
Week 6	38.1 ± 0.4	37.6 ± 0.0	37.8 ± 0.2	37.7 ± 0.3	37.4 ± 0.2
Week 10	36.0 ± 0.2	35.9 ± 0.3	35.8 ± 0.2	35.7 ± 0.5	35.9 ± 0.1
Week 14	37.5 ± 0.3	37.2 ± 0.3	37.1 ± 0.3	37.9 ± 0.5	37.2 ± 0.0
Week 26	36.3 ± 0.2	35.7 ± 0.4	36.5 ± 0.1	35.7 ± 0.4	36.2 ± 0.5
Platelets (10^3/µL)					
Week 6	480.5 ± 82.2	562.0 ± 62.6	561.5 ± 14.0	498.5 ± 49.2	403.3 ± 64.6
Week 10	614.3 ± 42.5	576.3 ± 58.2	516.8 ± 53.4	504.3 ± 93.3	596.0 ± 31.5
Week 14	617.5 ± 23.5	622.7 ± 24.2	612.3 ± 19.2	613.0 ± 14.0	572.5 ± 21.9
Week 26	605.8 ± 6.7	565.5 ± 21.5	574.0 ± 13.2	599.3 ± 11.1	616.8 ± 34.3
Leukocytes (10^3/µL)					
Week 6	4.5 ± 1.1	5.3 ± 0.6	3.7 ± 0.4	4.5 ± 1.1	5.1 ± 0.1
Week 10	4.4 ± 0.9	5.6 ± 0.2	5.0 ± 0.7	5.2 ± 0.8	5.8 ± 0.8
Week 14	4.4 ± 0.6	16.6 ± 7.0	5.0 ± 0.4	13.5 ± 6.6	5.0 ± 1.2
Week 26	3.6 ± 0.6	3.4 ± 1.0	3.8 ± 0.4	3.8 ± 0.7	4.2 ± 0.6

TABLE F2
Hematology, Clinical Chemistry, Urinalysis, and Tissue Sphingolipid Data for Rats at the 6-, 10-, 14-, and 26-Week Evaluations and at 2 Years in the Feed Study of Fumonisin B_1

	0 ppm	5 ppm	15 ppm	50 ppm	100 ppm
Female (continued)					
Clinical Chemistry					
n					
Week 6	4	4	4	2	4
Week 10	4	4	4	4	4
Week 14	4	4	4	4	4
Week 26	4	4	4	4	4
Urea nitrogen (mg/dL)					
Week 6	22.0 ± 0.0[c]	21.5 ± 0.5[c]	22.5 ± 0.5[c]	21.5 ± 0.5[c]	18.5 ± 1.5[c]
Week 10	20.8 ± 1.0	21.3 ± 1.0	19.8 ± 0.5	21.3 ± 0.9	22.5 ± 0.6
Week 14	18.5 ± 2.2	19.3 ± 2.1	16.4 ± 0.8	20.5 ± 2.9	17.1 ± 0.9
Week 26	17.7 ± 1.3	16.1 ± 0.9	17.8 ± 1.1	20.0 ± 0.8	–[i]
Creatinine (mg/dL)					
Week 6	0.6 ± 0.0	0.5 ± 0.0	0.6 ± 0.0	0.5 ± 0.1*[d]	0.6 ± 0.0
Week 10	0.6 ± 0.0	0.6 ± 0.0	0.6 ± 0.0	0.6 ± 0.0	0.6 ± 0.0
Week 14	0.5 ± 0.0	0.5 ± 0.0	0.5 ± 0.0	0.6 ± 0.0	0.6 ± 0.0
Week 26	0.6 ± 0.0	0.5 ± 0.0	0.6 ± 0.0	0.6 ± 0.1	0.7 ± 0.1
Protein (g/dL)					
Week 6	9.7 ± 1.1	8.2 ± 0.5*	9.2 ± 0.7	7.6 ± 0.9***	8.7 ± 0.6
Week 10	8.4 ± 0.3	8.8 ± 0.5	8.1 ± 0.6	9.0 ± 0.5	8.7 ± 0.4
Week 14	6.5 ± 0.1	6.7 ± 0.1	6.7 ± 0.1	6.8 ± 0.1	6.7 ± 0.2
Week 26	7.4 ± 0.3	7.1 ± 0.2	7.2 ± 0.2	7.4 ± 0.2	7.0 ± 0.2
Albumin (g/dL)					
Week 6	4.9 ± 0.6	4.2 ± 0.4*	4.6 ± 0.5	3.9 ± 0.5***	4.3 ± 0.4
Week 10	4.4 ± 0.2	4.9 ± 0.3	4.9 ± 0.2	4.9 ± 0.3	4.9 ± 0.2
Week 14	3.5 ± 0.1	3.6 ± 0.1	3.7 ± 0.1	3.7 ± 0.1	3.7 ± 0.2
Week 26	4.4 ± 0.1	4.0 ± 0.2	4.1 ± 0.1	4.3 ± 0.1	4.0 ± 0.1
Cholesterol (mg/dL)					
Week 6	95 ± 38	170 ± 20	88 ± 37	155 ± 20	140 ± 37
Week 10	136 ± 9	155 ± 13	144 ± 8	148 ± 11	153 ± 8
Week 14	100 ± 3	99 ± 5	97 ± 4	94 ± 4	94 ± 4
Week 26	134 ± 5	133 ± 9	142 ± 5	137 ± 1	135 ± 9
Triglycerides (mg/dL)					
Week 6	57 ± 3	59 ± 6	59 ± 7	55 ± 9[d]	71 ± 9
Week 10	37 ± 5	48 ± 4	40 ± 5	43 ± 6	50 ± 12
Week 14	53 ± 3	49 ± 2	48 ± 4	49 ± 9	42 ± 5
Week 26	62 ± 3	67 ± 6	69 ± 6	69 ± 9	56 ± 3
Alanine aminotransferase (IU/L)					
Week 6	57 ± 15	56 ± 15	60 ± 15	61 ± 16[d]	53 ± 11
Week 10	65 ± 5	71 ± 7	71 ± 6	70 ± 9	81 ± 21
Week 14	43 ± 7	38 ± 2	39 ± 2	40 ± 2	37 ± 1
Week 26	58 ± 8	72 ± 35	61 ± 10	70 ± 16	45 ± 2
Alkaline phosphatase (IU/L)					
Week 6	405 ± 27[c]	337 ± 47[c]	362 ± 8[c]	353 ± 13[c]	381 ± 2[c]
Week 10	167 ± 10	188 ± 17	178 ± 14	185 ± 12	192 ± 11
Week 14	105 ± 16	108 ± 8	91 ± 4	109 ± 13	101 ± 4
Week 26	59 ± 1	56 ± 1	60 ± 3	49 ± 3*	60 ± 2
Creatine kinase (IU/L)					
Week 6	290.5 ± 25.5[c]	473.5 ± 18.5[c]	236.0 ± 26.0[c]	389.5 ± 65.5[c]	372.5 ± 7.5[c]
Week 10	880.5 ± 446.2	812.5 ± 202.1	1,206.0 ± 601.4	596.8 ± 97.6	543.8 ± 85.7
Week 14	661.7 ± 257.3	332.9 ± 74.9	378.4 ± 75.4	377.0 ± 56.6	313.3 ± 38.0
Week 26	295.8 ± 55.3	258.5 ± 33.6	320.0 ± 43.5	317.0 ± 76.4	352.2 ± 79.9

TABLE F2
Hematology, Clinical Chemistry, Urinalysis, and Tissue Sphingolipid Data for Rats at the 6-, 10-, 14-, and 26-Week Evaluations and at 2 Years in the Feed Study of Fumonisin B_1

	0 ppm	5 ppm	15 ppm	50 ppm	100 ppm
Female (continued)					
Clinical Chemistry (continued)					
n					
Week 6	4	4	4	2	4
Week 10	4	4	4	4	4
Week 14	4	4	4	4	4
Week 26	4	4	4	4	4
Sorbitol dehydrogenase (IU/L)					
Week 6	16 ± 1[c]	12 ± 1[c]	17 ± 0[c]	14 ± 0[c]	16 ± 0[c]
Week 10	15 ± 1	15 ± 3	15 ± 2	15 ± 1	17 ± 1
Week 14	13 ± 2	15 ± 2	14 ± 1	16 ± 1	16 ± 0
Week 26	16 ± 2	17 ± 4	16 ± 2	17 ± 1	13 ± 1
γ-glutamyltransferase (IU/L)					
Week 6	1.0 ± 0.0[c]	0.0[e]	1.0 ± 0.0[c]	0.5 ± 0.5[c]	1.5 ± 0.5[c]
Week 14	0.6 ± 0.2	0.5 ± 0.2	1.0 ± 0.7	0.5 ± 0.2	0.2 ± 0.1
Week 26	0.4 ± 0.1	0.4 ± 0.2	0.4 ± 0.1	0.6 ± 0.2	0.9 ± 0.3
Total bile acids (µmol/L)					
Week 6	12.1 ± 1.3	14.8 ± 1.1	11.2 ± 1.5	13.3 ± 1.3	14.2 ± 4.2
Week 10	19.1 ± 5.3	35.3 ± 16.6	41.1 ± 25.1	32.4 ± 8.9	27.5 ± 9.7
Week 14	13.0 ± 1.8	31.4 ± 8.5	26.0 ± 11.7	32.1 ± 7.9	46.1 ± 20.8
Week 26	30.2 ± 10.9	42.3 ± 23.8	14.4 ± 1.3	30.4 ± 9.4	56.1 ± 26.7
Urinalysis					
n	4	4	4	4	4
Creatinine (mg/dL)					
Week 6	96.8 ± 18.4	68.5 ± 18.2	50.8 ± 7.8	60.3 ± 13.3	56.5 ± 10.4
Week 10	53.5 ± 11.9	65.5 ± 10.1	60.0 ± 7.0	62.3 ± 8.0	46.0 ± 5.0
Week 14	63.3 ± 8.7	50.9 ± 6.9	77.2 ± 15.9	63.1 ± 12.0	36.2 ± 5.5
Week 26	79.6 ± 14.2	67.1 ± 10.2	96.9 ± 15.1	87.7 ± 15.3	81.8 ± 12.0
Protein/creatinine ratio					
Week 6	0.153 ± 0.011	0.198 ± 0.028	0.198 ± 0.028	0.181 ± 0.037	0.182 ± 0.025
Week 10	0.187 ± 0.018	0.241 ± 0.017	0.175 ± 0.014	0.184 ± 0.008	0.191 ± 0.022
Week 14	0.275 ± 0.020	0.393 ± 0.048	0.273 ± 0.014	0.278 ± 0.007	0.278 ± 0.020
Week 26	0.233 ± 0.012	0.307 ± 0.012	0.239 ± 0.016	0.224 ± 0.013	0.259 ± 0.015
Sphingosine (pmol/mL)					
Week 6	6.954 ± 2.515	14.532 ± 3.926	17.141 ± 4.020	10.880 ± 3.742	15.726 ± 6.745
Week 10	4.901 ± 0.592	7.358 ± 1.629	8.013 ± 2.139	14.927 ± 4.327*	15.731 ± 1.852*
Week 14	9.245 ± 1.528	11.345 ± 4.206	13.150 ± 3.125	26.058 ± 5.131	19.157 ± 3.699*
Week 26	9.890 ± 2.299	9.207 ± 1.059	15.704 ± 2.728	32.271 ± 6.770	57.756 ± 13.682*
Sphinganine (pmol/mL)					
Week 6	3.148 ± 2.628[d]	4.391 ± 2.193	35.236 ± 35.236	26.285 ± 11.923[d]	84.600 ± 39.403[d]
Week 10	1.587 ± 0.576	3.764 ± 1.096	4.225 ± 0.869	58.767 ± 8.877*	137.068 ± 32.325*
Week 14	4.588 ± 1.674	1.848 ± 0.698	7.592 ± 1.852	103.666 ± 14.853*	201.132 ± 76.502*
Week 26	5.847 ± 1.236	7.342 ± 1.823	10.615 ± 2.212	209.394 ± 39.014*	664.289 ± 132.310*
Sphinganine/sphingosine ratio					
Week 6	0.391 ± 0.300	0.453 ± 0.261	1.855 ± 1.855	2.372 ± 0.730	6.283 ± 4.507
Week 10	0.328 ± 0.111	0.538 ± 0.100	0.589 ± 0.082	4.611 ± 1.085*	8.544 ± 1.167*
Week 14	0.457 ± 0.095	0.257 ± 0.095	0.582 ± 0.031	4.715 ± 1.290*	9.554 ± 1.757*
Week 26	0.605 ± 0.065	0.767 ± 0.094	0.673 ± 0.083	6.864 ± 0.736*	11.897 ± 0.726*

TABLE F2
Hematology, Clinical Chemistry, Urinalysis, and Tissue Sphingolipid Data for Rats at the 6-, 10-, 14-, and 26-Week Evaluations and at 2 Years in the Feed Study of Fumonisin B_1

	0 ppm	5 ppm	15 ppm	50 ppm	100 ppm
Female (continued)					
Tissue Sphingolipid Analysis					
n					
Week 6	4	4	4	2	4
Week 10	4	4	4	4	4
Week 14	4	4	4	4	4
Week 26	4	4	4	4	4
2 Years	5	5	5	5	5
Kidney sphingosine (nmol/g)					
Week 6	4.632 ± 0.793	4.231 ± 0.827	8.956 ± 3.668	16.627 ± 3.592*	14.835 ± 4.910*
Week 10	4.454 ± 0.754	4.386 ± 0.778	5.996 ± 1.097	14.692 ± 2.132*	13.649 ± 2.277*
Week 14	2.500 ± 0.127	2.341 ± 0.821	4.721 ± 0.932*	7.359 ± 1.559*	6.954 ± 1.660*
Week 26	3.191 ± 0.814	4.258 ± 0.993	5.207 ± 1.060	11.189 ± 1.512*[d]	10.514 ± 1.525*
2 Years	3.487 ± 0.996	5.727 ± 1.789	5.277 ± 1.664	9.495 ± 4.066	11.275 ± 2.398
Kidney sphinganine (nmol/g)					
Week 6	3.581 ± 1.624	2.713 ± 0.449	10.790 ± 6.014	74.234 ± 25.837*	190.620 ± 21.098*
Week 10	3.979 ± 0.488	2.163 ± 0.579	4.484 ± 0.283	79.939 ± 17.853	172.837 ± 31.446*
Week 14	1.545 ± 0.165	2.373 ± 0.742	7.323 ± 2.210*	49.236 ± 7.810*	120.807 ± 25.627*
Week 26	3.926 ± 0.568	4.295 ± 0.656	10.290 ± 2.310	87.141 ± 18.744[d]	198.381 ± 40.292*
2 Years	2.158 ± 0.321	2.914 ± 0.864	13.705 ± 7.743*	70.027 ± 36.057*	193.845 ± 57.413*
Kidney sphinganine/sphingosine ratio					
Week 6	0.707 ± 0.287	0.675 ± 0.106	1.001 ± 0.247	4.124 ± 0.677*	16.040 ± 3.844*
Week 10	1.015 ± 0.238	0.585 ± 0.197	0.805 ± 0.107	5.430 ± 0.919	12.517 ± 0.895*
Week 14	0.629 ± 0.086	1.518 ± 0.666	1.538 ± 0.232	7.624 ± 1.781*	18.121 ± 2.671*
Week 26	1.706 ± 0.622	1.182 ± 0.320	2.092 ± 0.420	7.647 ± 0.842*[d]	18.383 ± 1.877*
2 Years	0.787 ± 0.257	0.808 ± 0.320	2.139 ± 0.614	6.153 ± 1.812*	17.557 ± 3.367*
Liver sphingosine (nmol/g)					
Week 6	2.890 ± 0.134	3.354 ± 0.295	3.784 ± 0.044	4.162 ± 0.216	2.446 ± 0.228
Week 10	4.540 ± 0.548	5.424 ± 2.357	3.866 ± 0.694	4.110 ± 0.406	4.315 ± 0.922
Week 14	5.404 ± 1.328	5.287 ± 1.540	4.403 ± 0.571	6.625 ± 1.351	5.659 ± 1.169
Week 26	5.642 ± 0.721	7.564 ± 1.651	7.302 ± 1.406	7.926 ± 1.780	11.032 ± 4.583
Liver sphinganine (nmol/g)					
Week 6	0.489 ± 0.010	0.949 ± 0.193	2.011 ± 0.881	1.666 ± 0.202	2.393 ± 0.552
Week 10	1.520 ± 0.320	1.355 ± 0.308	1.705 ± 0.367	1.408 ± 0.167	3.913 ± 0.705
Week 14	1.798 ± 0.540	1.370 ± 0.398	1.727 ± 0.198	2.210 ± 0.590	4.563 ± 0.834
Week 26	1.536 ± 0.153	1.275 ± 0.257	1.635 ± 0.388	2.265 ± 0.469	3.751 ± 1.122
Liver sphinganine/sphingosine ratio					
Week 6	0.215 ± 0.054	0.303 ± 0.050	0.334 ± 0.151	0.262 ± 0.095	0.767 ± 0.138*
Week 10	0.324 ± 0.049	0.359 ± 0.104	0.454 ± 0.080	0.352 ± 0.055	0.975 ± 0.186*
Week 14	0.382 ± 0.141	0.255 ± 0.039	0.407 ± 0.067	0.385 ± 0.114	0.880 ± 0.156*
Week 26	0.287 ± 0.049	0.170 ± 0.019	0.241 ± 0.049	0.295 ± 0.035	0.499 ± 0.175

* Significantly different ($P \leq 0.05$) from the control group by a one-way analysis of variance with application of Dunnett's test
** $P \leq 0.01$
*** $P \leq 0.001$
[a] Mean ± standard error. Statistical tests were performed on unrounded data.
[b] n=4
[c] n=2
[d] n=3
[e] n=1; no standard error calculated
[f] n=6
[g] n=5
[h] n=7
[i] Data not reported

TABLE F3
Clinical Chemistry and Urinalysis Data for Mice in the 28-Day Feed Study of Fumonisin B_1[a]

	0 ppm	99 ppm	163 ppm	234 ppm	484 ppm
Male					
Clinical Chemistry					
n					
Day 7	4	4	4	4	4
Day 14	4	3	4	2	4
Day 28	7	6	8	7	6
Core study	3	3	3	3	3
Urea nitrogen (mg/dL)					
Core study	20.6 ± 0.7	22.1 ± 1.7	21.5 ± 0.9[b]	20.9 ± 0.7	19.7 ± 1.0
Creatinine (mg/dL)					
Core study	0.31 ± 0.03	0.29 ± 0.01	0.36 ± 0.02	0.36 ± 0.02	0.36 ± 0.02
Total protein (g/dL)					
Core study	5.9 ± 0.2	6.1 ± 0.3	6.1 ± 0.2	6.0 ± 0.3	6.2 ± 0.2
Albumin (g/dL)					
Core study	3.0 ± 0.1	3.2 ± 0.1	3.2 ± 0.1	3.1 ± 0.2	3.3 ± 0.1
Cholesterol (mg/dL)					
Day 7	136 ± 1	151 ± 3	142 ± 4	162 ± 8**	232 ± 13***
Day 14	148 ± 5	132 ± 2	165 ± 5	159 ± 7[c]	245 ± 17***
Day 28	130 ± 2[d]	126 ± 4	147 ± 4	160 ± 11**	233 ± 10***
Core study	138 ± 7	149 ± 9	160 ± 12	169 ± 12	253 ± 9****
Triglycerides (mg/dL)					
Day 7	49 ± 6	50 ± 6	59 ± 4	60 ± 6	78 ± 18
Day 14	66 ± 1	54 ± 2	50 ± 7	45 ± 8	87 ± 9
Day 28	43 ± 2[d]	47 ± 4	46 ± 3	51 ± 3	112 ± 12***
Core study	82 ± 2	86 ± 5	85 ± 5	77 ± 6	123 ± 12**
Alanine aminotransferase (IU/L)					
Day 7	29 ± 5	25 ± 3	19 ± 2	62 ± 31	634 ± 183***
Day 14	37 ± 14	28 ± 3	30 ± 5	25 ± 1	455 ± 88***[e]
Day 28	37 ± 9	40 ± 12	30 ± 6	122 ± 62	556 ± 232***[e]
Core study	67 ± 22	51 ± 7	36 ± 3	75 ± 23	384 ± 51*
Alkaline phosphatase (IU/L)					
Day 7	149 ± 3	211 ± 5	181 ± 5	228 ± 14	500 ± 95***
Day 14	135 ± 8	135 ± 5	152 ± 16	—[f]	621 ± 50***[e]
Day 28	121 ± 5	138 ± 7	—	—	579 ± 68***[b]
Core study	112 ± 3	122 ± 2*	136 ± 4*	145 ± 8*	426 ± 32**
Aspartate aminotransferase (IU/L)					
Core study	87 ± 17	71 ± 5	70 ± 6[b]	135 ± 62	214 ± 36
γ-Glutamyltransferase (IU/L)					
Core study	0.6[g]	0.4 ± 0.2[b]	0.2 ± 0.1[b]	0.7 ± 0.2[b]	0.6 ± 0.2
Total bile acids (µmol/L)					
Day 7	25.0 ± 2.3	25.5 ± 1.3	26.3 ± 3.5	25.8 ± 4.8[e]	275.3 ± 59.1***[e]
Day 14	15.2 ± 1.4	20.2 ± 2.4	16.2 ± 0.2[b]	—	179.4 ± 8.8***[b]
Day 28	14.0 ± 1.4	21.5 ± 0.6	—	—	207.3 ± 93.3***[b]
Core study	22.0 ± 1.4	20.5 ± 2.3	18.0 ± 1.0	26.0 ± 5.1	153.4 ± 5.7****

TABLE F3
Clinical Chemistry and Urinalysis Data for Mice in the 28-Day Feed Study of Fumonisin B_1

	0 ppm	99 ppm	163 ppm	234 ppm	484 ppm
Male (continued)					
Urinalysis					
n					
Day 7	4	4	4	4	4
Day 14	4	3	4	4	4
Day 28	8	6	8	7	6
Creatinine (mg/dL)					
Day 7	21.10 ± 3.28	23.73 ± 2.29	20.40 ± 4.27	18.68 ± 2.58	22.33 ± 1.52
Day 14	22.63 ± 3.06	23.70 ± 3.76	18.05 ± 2.93	15.08 ± 1.77	20.90 ± 2.12
Day 28	15.93 ± 2.25	14.25 ± 4.22	18.91 ± 2.65	17.54 ± 2.02	22.03 ± 2.56
Sphingosine (pmol/mL)					
Day 7	13.94 ± 1.30	11.97 ± 2.06	13.75 ± 1.84	8.20 ± 0.71*	6.06 ± 1.71**
Day 14	7.00 ± 3.58	9.80 ± 1.98	7.62 ± 3.52	5.36 ± 1.05	12.45 ± 4.21
Day 28	10.27 ± 2.99	18.70 ± 1.96	11.25 ± 1.89	11.44 ± 2.79	9.83 ± 2.89
Sphinganine (pmol/mL)					
Day 7	17.75 ± 2.48	59.65 ± 9.05*	46.13 ± 10.00	63.87 ± 9.72**	84.95 ± 15.30***
Day 14	9.84 ± 3.08	41.19 ± 12.61	38.52 ± 7.07	47.32 ± 3.92	100.30 ± 23.13***
Day 28	15.77 ± 2.56	42.78 ± 10.72	58.90 ± 5.68	57.68 ± 5.75	113.88 ± 36.23***
Sphinganine/sphingosine ratio					
Day 7	1.32 ± 0.26	5.45 ± 1.25	3.25 ± 0.30	8.03 ± 1.58*	15.92 ± 2.95****
Day 14	2.20 ± 0.89	4.87 ± 1.92	6.72 ± 1.46	9.56 ± 1.42	10.89 ± 4.17
Day 28	2.12 ± 0.48	2.33 ± 0.60	6.67 ± 1.37	9.33 ± 4.16	22.02 ± 12.20*
Female					
Clinical Chemistry					
n					
Day 7	4	4	3	4	4
Day 14	4	0	3	3	4
Day 28	8	4	8	7	8
Core study	3	3	3	3	3
Urea nitrogen (mg/dL)					
Core study	23.1 ± 0.7	18.1 ± 0.6*	16.3 ± 0.9**	16.6 ± 0.8**	19.0 ± 0.5*
Creatinine (mg/dL)					
Core study	0.30 ± 0.01	0.31 ± 0.01	0.30 ± 0.0	0.28 ± 0.01	0.28 ± 0.01
Total protein (g/dL)					
Core study	5.9 ± 0.1	6.0 ± 0.1	5.9 ± 0.1	6.0 ± 0.1	6.0 ± 0.3
Albumin (g/dL)					
Core study	3.3 ± 0.0	3.4 ± 0.1	3.4 ± 0.1	3.5 ± 0.1	3.4 ± 0.1

TABLE F3
Clinical Chemistry and Urinalysis Data for Mice in the 28-Day Feed Study of Fumonisin B_1

	0 ppm	99 ppm	163 ppm	234 ppm	484 ppm
Female (continued)					
Clinical Chemistry (continued)					
n					
Day 7	4	4	3	4	4
Day 14	4	0	3	3	4
Day 28	8	4	8	7	8
Core study	3	3	3	3	3
Cholesterol (mg/dL)					
Day 7	96 ± 3	165 ± 5***	175 ± 4***[c]	218 ± 5***	222 ± 3***
Day 14	98 ± 3	—	165 ± 5***[c]	199 ± 5***[c]	210 ± 5***
Day 28	87 ± 2	145 ± 11***	176 ± 7***	212 ± 5***	256 ± 10***
Core study	110 ± 11	173 ± 12****	197 ± 13****	228 ± 8****	259 ± 11****
Triglycerides (mg/dL)					
Day 7	58 ± 7	44 ± 1	62 ± 1	94 ± 1***	128 ± 9***
Day 14	43 ± 6	—	97 ± 7***[c]	98 ± 7***	124 ± 7***
Day 28	35 ± 2	84 ± 9***	97 ± 5***	115 ± 6***	162 ± 8***
Core study	63 ± 10	118 ± 6**	151 ± 19***	192 ± 4****	215 ± 10****
Alanine aminotransferase (IU/L)					
Day 7	64 ± 39	304 ± 118	247 ± 54	630 ± 115***	605 ± 91***
Day 14	29 ± 8	—	413 ± 84***	417 ± 98***	472 ± 43***
Day 28	28 ± 9	273 ± 66	596 ± 98***	419 ± 47***[h]	343 ± 33***
Core study	47 ± 3	170 ± 58	257 ± 26**	415 ± 59*	399 ± 44*
Alkaline phosphatase (IU/L)					
Day 7	163 ± 3	343 ± 45***	301 ± 33***	590 ± 26***	702 ± 16***
Day 14	174 ± 3	—	421 ± 16***	—	794 ± 12***
Day 28	164 ± 3	311 ± 15***	—	512 ± 11***[c]	793 ± 27***
Core study	176 ± 7	377 ± 38****	458 ± 31****	589 ± 19****	786 ± 16****
Aspartate aminotransferase (IU/L)					
Core study	113 ± 16	157 ± 30	208 ± 17	329 ± 59*	288 ± 53*
γ-Glutamyltransferase (IU/L)					
Core study	0.4 ± 0.2	0.5 ± 0.2[b]	0.7 ± 0.1	0.7 ± 0.1	0.6 ± 0.2
Total bile acids (µmol/L)					
Day 7	22.7 ± 0.8[e]	198.5 ± 79.3	175.8 ± 3.4[b]	420.6 ± 31.1***[e]	446.6 ± 61.4***
Day 14	19.1 ± 1.3[b]	—	184.1 ± 47.2***	—	543.4 ± 15.0***
Day 28	15.1 ± 1.3	118.4 ± 14.4[e]	—	—	359.9 ± 130.6***[e]
Core study	20.4 ± 2.0	103.6 ± 16.0*	139.7 ± 6.0****	228.4 ± 64.2	306.2 ± 50.0
Urinalysis					
n					
Day 7	3	4	3	4	3
Day 14	4	0	3	4	4
Day 28	8	3	8	7	7
Creatinine (mg/dL)					
Day 7	21.00 ± 6.63	18.75 ± 8.11	18.10 ± 4.90[c]	17.65 ± 3.51	21.63 ± 2.38
Day 14	23.33 ± 4.77[e]	–	15.90 ± 4.86[c]	22.05 ± 3.08	25.15 ± 3.11
Day 28	19.71 ± 2.60	5.37 ± 2.67***	13.63 ± 1.58	13.71 ± 2.28	21.97 ± 2.30[h]

TABLE F3
Clinical Chemistry and Urinalysis Data for Mice in the 28-Day Feed Study of Fumonisin B_1

	0 ppm	99 ppm	163 ppm	234 ppm	484 ppm
Female (continued)					
Urinalysis (continued)					
n					
Day 7	3	4	3	4	3
Day 14	4	0	3	4	4
Day 28	8	3	8	7	7
Sphingosine (pmol/mL)					
Day 7	4.04 ± 0.81	5.18 ± 1.06	6.16 ± 3.96	2.52 ± 0.32	16.87 ± 7.08
Day 14	5.30 ± 2.60	—	2.28 ± 0.47	8.21 ± 1.95	14.76 ± 11.33
Day 28	8.51 ± 2.21	4.13 ± 1.16	9.94 ± 1.95	7.48 ± 1.24	10.54 ± 0.90
Sphinganine (pmol/mL)					
Day 7	15.08 ± 5.23	22.03 ± 8.53[e]	9.76 ± 3.79	30.26 ± 13.19	14.83 ± 6.42
Day 14	5.08 ± 1.20	—	17.25 ± 5.29	12.65 ± 2.29	45.73 ± 35.39
Day 28	27.24 ± 7.49	22.33 ± 8.74	21.33 ± 2.56	19.49 ± 5.39	20.70 ± 1.75
Sphinganine/sphingosine ratio					
Day 7	3.94 ± 1.52	4.48 ± 1.59[e]	4.54 ± 3.33	12.61 ± 5.84	2.95 ± 2.57
Day 14	2.36 ± 0.96	—	9.11 ± 4.58	1.74 ± 0.37	3.10 ± 0.38
Day 28	4.40 ± 1.18	8.52 ± 5.93	2.56 ± 0.52	2.90 ± 0.98	2.14 ± 0.38

* Significantly different (P≤0.05) from the control group by Kleinbaum's procedure (clinical chemistry data) or a repeated measures analysis of variance (urinalysis data) with application of Holm's procedure
** P≤0.01
*** P≤0.001
****P≤0.0001
a Mean ± standard error. Statistical tests were performed on unrounded data. Core study animals were evaluated on day 28; clinical pathology study animals were evaluated on days 7, 14, and 28.
b n=2
c n=4
d n=8
e n=3
f Not examined for this exposure group
g n=1; no standard error calculated
h n=6

TABLE F4
Hematology, Clinical Chemistry, Urinalysis, and Tissue Sphingolipid Data for Mice at the 3-, 7-, 9-, and 24-Week Evaluations in the Feed Study of Fumonisin B_1[a]

	0 ppm	5 ppm	15 ppm	80 ppm	150 ppm
Male					
Hematology					
n					
Week 3	4	4	4	4	4
Week 7	4	4	4	4	4
Week 9	4	4	4	4	3
Week 24	4	4	4	4	4
Hematocrit (%)					
Week 3	41.2 ± 0.8	41.6 ± 1.0	42.8 ± 0.9	41.5 ± 0.7	39.9 ± 1.1
Week 7	50.7 ± 1.1	51.7 ± 0.3	50.7 ± 0.8	49.2 ± 0.6	52.3 ± 0.8
Week 9	50.2 ± 0.6	49.7 ± 0.2	49.2 ± 1.6	49.7 ± 1.4	50.3 ± 0.4
Week 24	48.7 ± 0.5	50.7 ± 1.3	47.6 ± 1.3	50.0 ± 0.4	50.4 ± 0.5
Hemoglobin (g/dL)					
Week 3	13.9 ± 0.3	14.1 ± 0.3	14.6 ± 0.4	13.7 ± 0.3	13.4 ± 0.5
Week 7	17.2 ± 0.4	17.7 ± 0.1	17.3 ± 0.4	16.8 ± 0.2	17.9 ± 0.3
Week 9	17.2 ± 0.2	16.9 ± 0.1	16.6 ± 0.6	17.1 ± 0.5	17.2 ± 0.2
Week 24	16.3 ± 0.2	17.0 ± 0.5	16.0 ± 0.5	16.8 ± 0.1	16.8 ± 0.4
Erythrocytes (10^6/µL)					
Week 3	8.6 ± 0.2	8.7 ± 0.2	8.8 ± 0.2	8.6 ± 0.2	8.3 ± 0.3
Week 7	10.4 ± 0.2	10.5 ± 0.1	10.4 ± 0.2	10.2 ± 0.1	10.7 ± 0.2
Week 9	10.2 ± 0.1	10.1 ± 0.0	10.0 ± 0.3	10.2 ± 0.3	10.1 ± 0.1
Week 24	10.1 ± 0.2	10.3 ± 0.3	9.7 ± 0.3	10.2 ± 0.1	10.2 ± 0.1
Mean cell volume (fL)					
Week 3	47.9 ± 0.2	47.9 ± 0.1	48.5 ± 0.1	48.5 ± 0.7	48.4 ± 0.4
Week 7	48.9 ± 0.3	49.3 ± 0.3	48.5 ± 0.2	48.3 ± 0.1	49.0 ± 0.1
Week 9	49.0 ± 0.3	49.1 ± 0.2	49.1 ± 0.2	48.9 ± 0.2	49.9 ± 0.3
Week 24	48.3 ± 0.7	49.3 ± 0.1	48.8 ± 0.3	48.9 ± 0.2	49.2 ± 0.2
Mean cell hemoglobin (pg)					
Week 3	16.1 ± 0.1	16.3 ± 0.0	16.5 ± 0.2	16.0 ± 0.1	16.2 ± 0.1
Week 7	16.6 ± 0.1	16.8 ± 0.1	16.6 ± 0.2	16.4 ± 0.0	16.7 ± 0.0
Week 9	16.8 ± 0.1	16.7 ± 0.1	16.6 ± 0.1	16.9 ± 0.1	17.0 ± 0.1
Week 24	16.2 ± 0.2	16.5 ± 0.1	16.4 ± 0.1	16.4 ± 0.1	16.4 ± 0.3
Mean cell hemoglobin concentration (g/dL)					
Week 3	33.7 ± 0.1	33.9 ± 0.0	34.1 ± 0.4	33.0 ± 0.4	33.5 ± 0.3
Week 7	34.0 ± 0.1	34.1 ± 0.1	34.2 ± 0.3	34.0 ± 0.1	34.1 ± 0.1
Week 9	34.3 ± 0.1	34.0 ± 0.2	33.8 ± 0.1	34.5 ± 0.2	34.1 ± 0.2
Week 24	33.6 ± 0.1	33.5 ± 0.1	33.6 ± 0.3	33.6 ± 0.2	33.3 ± 0.5
Platelets (10^3/µL)					
Week 3	586.8 ± 64.5	625.0 ± 62.6	742.3 ± 110.6	659.0 ± 29.6	628.3 ± 33.9
Week 7	1,063.0 ± 43.5	1,062.5 ± 11.6	1,008.5 ± 18.3	985.3 ± 57.5	858.0 ± 31.9**
Week 9	1,190.0 ± 66.6	978.5 ± 74.3	910.3 ± 37.4*	983.3 ± 36.5	963.7 ± 20.0
Week 24	964.3 ± 48.0	898.0 ± 46.2	971.5 ± 26.7	1,023.5 ± 27.5	933.0 ± 45.2
Leukocytes (10^3/µL)					
Week 3	7.2 ± 2.2	3.8 ± 0.5	8.1 ± 0.6	6.5 ± 1.0	6.0 ± 0.5
Week 7	7.8 ± 2.4	6.4 ± 1.2	7.4 ± 1.6	6.4 ± 1.5	4.1 ± 0.5
Week 9	7.7 ± 0.5	10.7 ± 3.1	8.2 ± 1.4	7.2 ± 1.3	4.5 ± 0.6
Week 24	6.7 ± 0.6	9.6 ± 0.9	11.1 ± 1.1**	6.5 ± 0.8	9.5 ± 0.7

TABLE F4
Hematology, Clinical Chemistry, Urinalysis, and Tissue Sphingolipid Data for Mice at the 3-, 7-, 9-, and 24-Week Evaluations in the Feed Study of Fumonisin B_1

	0 ppm	5 ppm	15 ppm	80 ppm	150 ppm
Male (continued)					
Clinical Chemistry					
n					
Week 3	4	4	4	4	4
Week 7	3	2	4	4	4
Week 9	4	4	4	4	3
Week 24	4	4	4	3	4
Creatinine (mg/dL)					
Week 3	0.3 ± 0.0	0.3 ± 0.0	0.3 ± 0.0	0.3 ± 0.0	0.3 ± 0.0
Week 7	0.5 ± 0.0	0.5 ± 0.0	0.5 ± 0.0	0.6 ± 0.0	0.6 ± 0.0
Week 9	0.4 ± 0.0	0.3 ± 0.1	0.3 ± 0.0	0.4 ± 0.0	0.4 ± 0.0
Week 24	0.3 ± 0.0	0.3 ± 0.0	0.3 ± 0.0	0.3 ± 0.0[b]	0.3 ± 0.0
Albumin (g/dL)					
Week 3	3.2 ± 0.1	3.3 ± 0.1	3.3 ± 0.1	1.8 ± 0.7	3.2 ± 0.0
Week 7	2.9 ± 0.1	—[c]	3.1 ± 0.0	3.1 ± 0.1	3.1 ± 0.1[d]
Week 9	2.9 ± 0.1	2.9 ± 0.1	3.0 ± 0.0	2.9 ± 0.1	3.0 ± 0.1
Week 24	3.0 ± 0.0	2.8 ± 0.1	2.8 ± 0.3	2.9 ± 0.0	2.9 ± 0.1
Cholesterol (mg/dL)					
Week 3	120 ± 7	141 ± 6	142 ± 2	116 ± 3	131 ± 10
Week 7	110 ± 4[b]	118 ± 5	121 ± 4	111 ± 5	120 ± 8
Week 9	124 ± 5	134 ± 12	113 ± 2	106 ± 7	119 ± 7
Week 24	104 ± 3	115 ± 8	110 ± 4	108 ± 6	130 ± 4*
Triglycerides (mg/dL)					
Week 3	61 ± 2	68 ± 4	59 ± 4	67 ± 4	59 ± 4
Week 7	51 ± 18[b]	66 ± 20	80 ± 3	82 ± 8	77 ± 4
Week 9	102 ± 19	68 ± 5	83 ± 5	96 ± 9	54 ± 4*
Week 24	74 ± 6	73 ± 5	83 ± 11	70 ± 4	75 ± 7
Alanine aminotransferase (IU/L)					
Week 3	134 ± 32	141 ± 36	149 ± 53	135 ± 27	83 ± 7
Week 7	62 ± 15	139 ± 28	60 ± 6	84 ± 24	83 ± 13
Week 9	105 ± 23	114 ± 30	54 ± 4	137 ± 55	324 ± 251
Week 24	73 ± 21	261 ± 143	100 ± 65	86 ± 29	97 ± 41
Alkaline phosphatase (IU/L)					
Week 3	208 ± 6	223 ± 14	210 ± 10	199 ± 4	260 ± 16*
Urinalysis					
n	4	4	4	4	4
Creatinine (mg/dL)					
Week 3	13.9 ± 2.7	16.0 ± 2.2	16.2 ± 2.0	14.4 ± 1.8	14.2 ± 3.5
Week 7	19.1 ± 7.0	18.9 ± 4.3	31.5 ± 8.0	17.3 ± 2.6	22.3 ± 5.9
Week 9	34.6 ± 10.6	35.5 ± 10.4	20.5 ± 6.3	26.2 ± 4.2	34.0 ± 7.8
Week 24	31.3 ± 5.4	25.8 ± 6.9	17.4 ± 2.8	25.4 ± 3.3	24.6 ± 6.5
Protein/creatinine ratio					
Week 3	26.406 ± 4.780	22.788 ± 2.268	22.955 ± 2.149	25.126 ± 2.760	26.423 ± 4.023
Week 7	27.615 ± 6.485	25.268 ± 6.149	15.907 ± 2.580	25.626 ± 4.733	21.046 ± 4.699
Week 9	17.06 ± 8.66	13.611 ± 3.734	17.010 ± 3.534	14.316 ± 1.696	11.785 ± 2.065
Week 24	12.913 ± 1.884	17.496 ± 5.614	18.194 ± 1.340	14.782 ± 1.838	15.219 ± 3.864

TABLE F4
Hematology, Clinical Chemistry, Urinalysis, and Tissue Sphingolipid Data for Mice at the 3-, 7-, 9-, and 24-Week Evaluations in the Feed Study of Fumonisin B_1

	0 ppm	5 ppm	15 ppm	80 ppm	150 ppm
Male (continued)					
Tissue Sphingolipid Analysis					
n					
Week 3	4	4	3	4	4
Week 7	4	4	4	4	4
Week 9	4	4	4	4	4
Liver sphingosine (nmol/g)					
Week 3	5.944 ± 1.378	6.783 ± 1.459	4.705 ± 1.492	5.302 ± 0.952	4.515 ± 2.446
Week 7	2.861 ± 0.591	3.234 ± 0.582	4.619 ± 0.947	6.656 ± 0.716*	3.902 ± 0.294
Week 9	2.868 ± 0.809	3.298 ± 0.680	2.507 ± 0.532	4.172 ± 1.810	4.456 ± 0.853
Liver sphinganine (nmol/g)					
Week 3	3.510 ± 1.140	4.250 ± 0.866	4.208 ± 1.387	4.216 ± 0.534	6.211 ± 3.884
Week 7	0.838 ± 0.257	2.283 ± 0.693	3.543 ± 0.544*	3.740 ± 0.506*	5.367 ± 0.632*
Week 9	0.905 ± 0.400	1.655 ± 0.228	1.029 ± 0.365	1.950 ± 0.438	5.444 ± 0.903*
Liver sphinganine/sphingosine ratio					
Week 3	0.642 ± 0.171	0.640 ± 0.050	0.987 ± 0.317	0.832 ± 0.087	1.345 ± 0.286
Week 7	0.335 ± 0.128	0.684 ± 0.113	0.807 ± 0.123	0.559 ± 0.026*	1.360 ± 0.061*
Week 9	0.338 ± 0.138	0.526 ± 0.068	0.585 ± 0.358	0.546 ± 0.191	1.246 ± 0.058

Table F4
Hematology, Clinical Chemistry, Urinalysis, and Tissue Sphingolipid Data for Mice at the 3-, 7-, 9-, and 24-Week Evaluations in the Feed Study of Fumonisin B_1

	0 ppm	5 ppm	15 ppm	50 ppm	80 ppm
Female					
Hematology					
n					
Week 3	4	4	4	4	3
Week 7	4	4	4	4	4
Week 9	4	4	4	4	4
Week 24	4	4	4	4	4
Hematocrit (%)					
Week 3	41.2 ± 0.5	47.7 ± 2.3*	40.8 ± 1.1	42.1 ± 1.0	43.1 ± 1 2
Week 7	50.0 ± 1.1	48.9 ± 0.3	49.9 ± 0.6	49.3 ± 0.7	46.3 ± 1.3*
Week 9	51.6 ± 0.4	51.3 ± 0.6	49.8 ± 0.7	50.9 ± 0.8	50.8 ± 0.7
Week 24	52.6 ± 0.4	53.9 ± 0.8	52.2 ± 1.6	51.8 ± 0.7	51.9 ± 0.6
Hemoglobin (g/dL)					
Week 3	14.1 ± 0.2	16.7 ± 0.8**	13.7 ± 0.3	14.4 ± 0.3	14.7 ± 0.3
Week 7	17.8 ± 0.3	17.2 ± 0.1	17.5 ± 0.2	17.2 ± 0.3	16.2 ± 0.4**
Week 9	17.8 ± 0.1	17.5 ± 0.2	16.9 ± 0.2	17.4 ± 0.4	17.5 ± 0.2
Week 24	17.9 ± 0.2	18.3 ± 0.3	17.7 ± 0.5	17.9 ± 0.3	17.5 ± 0.2
Erythrocytes (10^6/µL)					
Week 3	8.6 ± 0.1	9.8 ± 0.6	8.3 ± 0.2	8.7 ± 0.2	9.0 ± 0.2
Week 7	10.1 ± 0.2	10.0 ± 0.1	10.1 ± 0.1	10.0 ± 0.2	9.4 ± 0.3*
Week 9	10.6 ± 0.1	10.5 ± 0.1	10.2 ± 0.2	10.3 ± 0.2	10.4 ± 0.1
Week 24	10.8 ± 0.1	11.0 ± 0.2	10.6 ± 0.3	10.5 ± 0.2	10.4 ± 0.1
Mean cell volume (fL)					
Week 3	47.9 ± 0.2	49.0 ± 0.8	49.0 ± 0.5	48.3 ± 0.4	48.1 ± 0.5
Week 7	49.5 ± 0.2	48.9 ± 0.1	49.5 ± 0.0	49.2 ± 0.2	49.4 ± 0.3
Week 9	48.7 ± 0.2	48.8 ± 0.1	48.9 ± 0.4	49.2 ± 0.1	49.0 ± 0.1
Week 24	48.9 ± 0.5	49.1 ± 0.3	49.1 ± 0.0	49.5 ± 0.4	49.8 ± 0.6
Mean cell hemoglobin (pg)					
Week 3	16.4 ± 0.0	17.1 ± 0.3*	16.4 ± 0.2	16.5 ± 0.1	16.4 ± 0.2
Week 7	17.6 ± 0.1	17.2 ± 0.1**	17.4 ± 0.1	17.1 ± 0.1**	17.2 ± 0.1*
Week 9	16.8 ± 0.1	16.7 ± 0.1	16.5 ± 0.1	16.8 ± 0.1	16.9 ± 0.1
Week 24	16.7 ± 0.2	16.7 ± 0.3	16.6 ± 0.0	17.1 ± 0.1	16.8 ± 0.1
Mean cell hemoglobin concentration (g/dL)					
Week 3	34.2 ± 0.1	34.9 ± 0.2	33.5 ± 0.6	34.1 ± 0.2	34.0 ± 0.2
Week 7	35.6 ± 0.2	35.1 ± 0.1	35.1 ± 0.2	34.8 ± 0.1**	34.9 ± 0.1*
Week 9	34.5 ± 0.2	34.2 ± 0.1	33.8 ± 0.1*	34.2 ± 0.2	34.5 ± 0.1
Week 24	34.1 ± 0.2	34.0 ± 0.4	33.8 ± 0.0	34.6 ± 0.2	33.7 ± 0.2
Platelets (10^3/µL)					
Week 3	624.0 ± 9.7	923.3 ± 16.2***	581.3 ± 36.5	609.3 ± 38.4	528.3 ± 69.2
Week 7	851.5 ± 16.4	872.5 ± 6.8	820.3 ± 17.2	757.0 ± 9.6***	707.0 ± 16.6***
Week 9	853.8 ± 32.6	852.8 ± 31.9	816.3 ± 20.2	779.5 ± 46.0	858.5 ± 48.6
Week 24	903.3 ± 27.1	781.8 ± 67.3	751.8 ± 75.5	820.8 ± 5.9	830.8 ± 43.5
Leukocytes (10^3/µL)					
Week 3	6.3 ± 1.2	6.6 ± 0.9	7.0 ± 0.5	6.4 ± 0.1	5.1 ± 0.6
Week 7	8.0 ± 2.2	6.4 ± 0.9	6.3 ± 0.9	6.7 ± 0.6	7.2 ± 0.9
Week 9	6.7 ± 0.4	5.3 ± 0.5	6.3 ± 1.4	6.5 ± 0.7	6.1 ± 0.7
Week 24	5.8 ± 0.8	4.1 ± 0.5	3.6 ± 0.5	6.9 ± 0.7	3.2 ± 0.3*

Table F4
Hematology, Clinical Chemistry, Urinalysis, and Tissue Sphingolipid Data for Mice at the 3-, 7-, 9-, and 24-Week Evaluations in the Feed Study of Fumonisin B_1

	0 ppm	5 ppm	15 ppm	50 ppm	80 ppm
Female (continued)					
Clinical Chemistry					
n					
Week 3	4	4	4	4	3
Week 7	4	4	4	4	4
Week 9	1	4	4	2	4
Week 24	4	4	4	4	4
Creatinine (mg/dL)					
Week 3	0.5 ± 0.0	0.5 ± 0.1	0.5 ± 0.0	0.5 ± 0.0	0.5 ± 0.0
Week 7	0.5 ± 0.0	0.5 ± 0.0	0.5 ± 0.0	0.5 ± 0.0	0.5 ± 0.0
Week 9	0.3[e]	0.4 ± 0.0*	0.5 ± 0.0**	0.4 ± 0.1	0.4 ± 0.0*
Week 24	0.4 ± 0.0	0.4 ± 0.0	0.4 ± 0.0	0.3 ± 0.0**	0.4 ± 0.0
Albumin (g/dL)					
Week 3	3.3 ± 0.1	3.8 ± 0.0*[d]	3.5 ± 0.2	3.4 ± 0.1	3.6 ± 0.2
Week 7	3.6 ± 0.0	3.3 ± 0.1*[d]	3.7 ± 0.0[d]	3.5 ± 0.1	3.5 ± 0.1
Week 9	3.5[e]	3.6 ± 0.1	3.7 ± 0.1	3.6 ± 0.0	3.6 ± 0.0
Week 24	4.0 ± 0.1	4.1 ± 0.1	3.9 ± 0.1	4.0 ± 0.0	4.0 ± 0.0
Cholesterol (mg/dL)					
Week 3	84 ± 3	92 ± 4	112 ± 17	119 ± 7	144 ± 39
Week 7	91 ± 6	86 ± 6	93 ± 5	120 ± 5*	109 ± 5
Week 9	98[e]	99 ± 2	135 ± 7**	105 ± 7	102 ± 2
Week 24	111.7 ± 9.0	106 ± 4	91 ± 3*	99 ± 4	117 ± 3
Triglycerides (mg/dL)					
Week 3	68 ± 2	66 ± 6	74 ± 3	70 ± 3	71 ± 12
Week 7	65 ± 4	74 ± 11	59 ± 2	70 ± 2	67 ± 4
Week 9	77[e]	112 ± 6	68 ± 5	51 ± 1	125 ± 29
Week 24	73 ± 7	101 ± 4	92 ± 19	94 ± 11	80 ± 10
Alanine aminotransferase (IU/L)					
Week 3	290 ± 215	141 ± 47	113 ± 23	342 ± 247	411 ± 173
Week 7	38 ± 5	59 ± 10	75 ± 31	90 ± 42	99 ± 13
Week 9	54[e]	65 ± 15	139 ± 29	50 ± 6	105 ± 28
Week 24	219 ± 44	177 ± 55	111 ± 41	70 ± 20*	52 ± 6*
Alkaline phosphatase (IU/L)					
Week 7	172 ± 8	167 ± 8[d]	172 ± 9[d]	202 ± 8	186 ± 15
Urinalysis					
n	4	4	4	4	4
Creatinine (mg/dL)					
Week 3	34.6 ± 5.0	14.8 ± 7.7	11.0 ± 1.8	17.7 ± 5.3	6.5 ± 2.0**
Week 7	20.8 ± 5.1	25.2 ± 6.5	22.3 ± 4.0	20.4 ± 0.9	32.3 ± 3.6
Week 9	11.5 ± 6.0	17.0 ± 3.6	13.7 ± 2.9	21.3 ± 3.7	20.0 ± 7.7
Week 24	19.1 ± 10.3	19.9 ± 0.7	19.7 ± 3.1	12.5 ± 3.5	19.4 ± 6.1
Protein/creatinine ratio					
Week 3	8.359 ± 1.127	12.061 ± 2.327	9.183 ± 1.269	10.951 ± 1.307	12.322 ± 5.064
Week 7	10.476 ± 1.857	10.777 ± 0.391	4.946 ± 0.744	6.062 ± 0.586	3.390 ± 0.469
Week 9	7.547 ± 2.252	4.309 ± 0.271	2.849 ± 0.105	3.219 ± 0.299	5.741 ± 0.421
Week 24	3.949 ± 0.766	1.317 ± 0.147	3.085 ± 0.181	2.420 ± 0.193	1.908 ± 0.755

Table F4
Hematology, Clinical Chemistry, Urinalysis, and Tissue Sphingolipid Data for Mice at the 3-, 7-, 9-, and 24-Week Evaluations in the Feed Study of Fumonisin B_1

	0 ppm	5 ppm	15 ppm	50 ppm	80 ppm
Female (continued)					
Tissue Sphingolipid Analysis					
n	4	4	4	4	4
Liver sphingosine (nmol/g)					
Week 3	3.910 ± 0.466	3.662 ± 0.070	4.345 ± 0.940	3.047 ± 0.412	3.843 ± 0.526
Week 7	2.241 ± 0.376	3.016 ± 0.327	2.880 ± 0.724	2.800 ± 0.253	2.574 ± 0.390
Week 9	3.089 ± 0.172	4.097 ± 0.881	3.175 ± 0.158	5.791 ± 0.366	3.784 ± 0.675
Week 24	3.752 ± 0.479	3.438 ± 0.256	4.904 ± 0.726	4.349 ± 0.530	3.267 ± 0.772
Liver sphinganine (nmol/g)					
Week 3	1.700 ± 0.410	1.425 ± 0.268	2.684 ± 0.656	4.760 ± 0.856*	12.361 ± 3.688*
Week 7	5.015 ± 2.031	1.265 ± 0.222	2.035 ± 0.446	3.800 ± 2.170	4.536 ± 1.215
Week 9	0.805 ± 0.352	2.860 ± 0.679*	5.854 ± 0.699*	10.629 ± 0.618*	2.825 ± 0.309*
Week 24	1.757 ± 0.997	1.386 ± 0.462	2.045 ± 0.747	1.084 ± 0.134	1.268 ± 0.445
Liver sphinganine/sphingosine ratio					
Week 3	0.424 ± 0.067	0.391 ± 0.076	0.606 ± 0.026	1.543 ± 0.147*	3.275 ± 1.008*
Week 7	2.089 ± 0.527	0.438 ± 0.094	0.771 ± 0.194	1.258 ± 0.629	1.710 ± 0.242
Week 9	0.257 ± 0.104	0.721 ± 0.106*	1.862 ± 0.244*	1.859 ± 0.178*	2.925 ± 0.309*
Week 24	0.450 ± 0.192	0.394 ± 0.110	0.471 ± 0.186	0.257 ± 0.034	0.392 ± 0.110

* Significantly different ($P \leq 0.05$) from the control group by a one-way analysis of variance with application of Dunnett's test
** $P \leq 0.01$
*** $P \leq 0.001$
[a] Mean ± standard error. Statistical tests were performed on unrounded data.
[b] n=4
[c] Not measured at this time point
[d] n=3
[e] No standard error calculated

APPENDIX G
ORGAN WEIGHTS
AND ORGAN-WEIGHT-TO-BRAIN-WEIGHT
AND ORGAN-WEIGHT-TO-BODY-WEIGHT RATIOS

TABLE G1
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Core Study Rats in the 28-Day Feed Study of Fumonisin B_1[a]

	0 ppm	99 ppm	163 ppm	234 ppm	484 ppm
n	10	10	10	10	10
Male					
Final body wt	223 ± 2	218 ± 2	216 ± 2**	216 ± 2**	187 ± 1****
Brain					
Absolute	1.896 ± 0.038	1.917 ± 0.016	1.913 ± 0.019	1.927 ± 0.025	1.888 ± 0.023
Relative	8.524 ± 0.169	8.838 ± 0.172	8.875 ± 0.155	8.964 ± 0.172	10.096 ± 0.139****
Heart					
Absolute	0.891 ± 0.019	0.925 ± 0.039	0.918 ± 0.029	0.893 ± 0.032	0.735 ± 0.017***
Relative	4.002 ± 0.044	4.241 ± 0.133	4.255 ± 0.134	4.138 ± 0.106	3.929 ± 0.075
L. and R. Kidneys					
Absolute	1.874 ± 0.044	1.603 ± 0.038****	1.515 ± 0.024****	1.476 ± 0.033****	1.279 ± 0.028****
Relative	8.408 ± 0.082	7.364 ± 0.085****	7.025 ± 0.125****	6.846 ± 0.059****	6.836 ± 0.140****
Liver					
Absolute	8.802 ± 0.239	9.088 ± 0.312	8.848 ± 0.204	8.522 ± 0.267	6.216 ± 0.123****
Relative	39.492 ± 0.598	41.692 ± 0.749	40.950 ± 0.638	39.478 ± 0.722	33.227 ± 0.656****
L. and R. Testes					
Absolute	2.699 ± 0.033	2.768 ± 0.032	2.770 ± 0.042	2.732 ± 0.036	2.598 ± 0.047
Relative	12.133 ± 0.117	12.754 ± 0.207**	12.832 ± 0.155**	12.693 ± 0.155	13.875 ± 0.172****
Female					
Final body wt	148 ± 1	147 ± 1	143 ± 1**	136 ± 1****	131 ± 1****
Brain					
Absolute	1.805 ± 0.014	1.751 ± 0.035	1.830 ± 0.013	1.793 ± 0.016	1.780 ± 0.020
Relative	12.252 ± 0.191	11.944 ± 0.247	12.822 ± 0.137	13.202 ± 0.191**	13.630 ± 0.244****
Heart					
Absolute	0.659 ± 0.019	0.620 ± 0.020	0.647 ± 0.013	0.602 ± 0.016	0.617 ± 0.026
Relative	4.464 ± 0.109	4.220 ± 0.116	4.528 ± 0.073	4.424 ± 0.101	4.729 ± 0.226
L. and R. Kidneys					
Absolute	1.315 ± 0.025	1.160 ± 0.023****	1.155 ± 0.018****	1.076 ± 0.021****	1.042 ± 0.026****
Relative	8.907 ± 0.119	7.901 ± 0.112****	8.082 ± 0.079****	7.915 ± 0.110****	7.955 ± 0.122****
Liver					
Absolute	5.231 ± 0.112	5.203 ± 0.124	5.264 ± 0.114	4.581 ± 0.081***	4.641 ± 0.149***
Relative	35.452 ± 0.616	35.451 ± 0.713	36.815 ± 0.416	33.704 ± 0.538	35.435 ± 0.875

** Significantly different ($P \leq 0.01$) from the control group by a one-way analysis of variance with application of Holm's procedure
*** $P \leq 0.001$
**** $P \leq 0.0001$
[a] Organ weights (absolute weights) and body weights are given in grams; organ-weight-to-body-weight ratios (relative weights) are given as mg organ weight/g body weight (mean ± standard error).

TABLE G2
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Clinical Pathology Study Rats in the 28-Day Feed Study of Fumonisin B_1[a]

	0 ppm	99 ppm	163 ppm	234 ppm	484 ppm
n	8	8	8	8	8
Male					
Final body wt	198 ± 8	190 ± 3	185 ± 3	178 ± 7*	164 ± 4***
Brain					
Absolute	1.876 ± 0.019	1.860 ± 0.019	1.877 ± 0.011	1.828 ± 0.018	1.854 ± 0.016
Relative	9.576 ± 0.405	9.804 ± 0.179	10.166 ± 0.165	10.365 ± 0.350	11.354 ± 0.249***
Heart					
Absolute	0.867 ± 0.033	0.843 ± 0.021	0.879 ± 0.035	0.783 ± 0.049	0.790 ± 0.034
Relative	4.421 ± 0.252	4.446 ± 0.137	4.755 ± 0.191	4.415 ± 0.257	4.848 ± 0.260
L. and R. Kidneys					
Absolute	1.737 ± 0.059	1.459 ± 0.022****	1.380 ± 0.029****	1.272 ± 0.054****	1.210 ± 0.022****
Relative	8.791 ± 0.207	7.678 ± 0.092****	7.468 ± 0.141****	7.145 ± 0.105****	7.399 ± 0.125****
Liver					
Absolute	8.244 ± 0.312	8.153 ± 0.225	7.936 ± 0.208	7.230 ± 0.376*	6.089 ± 0.128****
Relative	41.746 ± 1.301	42.879 ± 0.871	42.915 ± 0.927	40.493 ± 0.819	37.194 ± 0.444**
L. and R. Testes					
Absolute	2.649 ± 0.063	2.630 ± 0.023	2.585 ± 0.040	2.382 ± 0.121	2.395 ± 0.092
Relative	13.433 ± 0.295	13.852 ± 0.153	13.989 ± 0.200	13.361 ± 0.416	14.604 ± 0.423
Female					
Final body wt	137 ± 3	136 ± 4	128 ± 3	127 ± 4	118 ± 3**
Brain					
Absolute	1.802 ± 0.016	1.750 ± 0.022	1.763 ± 0.025	1.749 ± 0.019	1.722 ± 0.017*
Relative	13.190 ± 0.253	12.919 ± 0.260	13.783 ± 0.375	13.845 ± 0.353	14.652 ± 0.285**
Heart					
Absolute	0.616 ± 0.018	0.617 ± 0.011	0.592 ± 0.025	0.560 ± 0.016	0.548 ± 0.020
Relative	4.500 ± 0.094	4.555 ± 0.093	4.610 ± 0.139	4.419 ± 0.096	4.649 ± 0.136
L. and R. Kidneys					
Absolute	1.301 ± 0.044	1.190 ± 0.100	1.039 ± 0.031**	1.071 ± 0.029**	0.937 ± 0.029***
Relative	9.489 ± 0.172	8.683 ± 0.484*	8.092 ± 0.162**	8.450 ± 0.170*	7.954 ± 0.179***
Liver					
Absolute	5.090 ± 0.150	5.152 ± 0.144	4.818 ± 0.176	4.689 ± 0.144	4.291 ± 0.093**
Relative	37.166 ± 0.784	37.968 ± 0.936	37.457 ± 0.775	36.966 ± 0.622	36.432 ± 0.404

* Significantly different ($P \le 0.05$) from the control group by a one-way analysis of variance with application of Holm's procedure
** $P \le 0.01$
*** $P \le 0.001$
**** $P \le 0.0001$
a Organ weights (absolute weights) and body weights are given in grams; organ-weight-to-body-weight ratios (relative weights) are given as mg organ weight/g body weight (mean ± standard error).

TABLE G3
Organ Weights and Organ-Weight-to-Brain-Weight and Organ-Weight-to-Body-Weight Ratios for Rats at the 6-Week Evaluation in the Feed Study of Fumonisin B_1[a]

	0 ppm	5 ppm	15 ppm	50 ppm	150 ppm
n	4	4	4	4	4
Male					
Necropsy body wt	218 ± 7	219 ± 8	225 ± 8	212 ± 7	213 ± 5
Brain					
Absolute	1.944 ± 0.031	1.946 ± 0.022	1.943 ± 0.015	1.946 ± 0.018	2.012 ± 0.010
Relative to body weight	8.94 ± 0.16	8.95 ± 0.43	8.65 ± 0.33	9.22 ± 0.27	9.45 ± 0.20
Heart					
Absolute	0.916 ± 0.042	0.953 ± 0.055	0.987 ± 0.022	1.102 ± 0.269	0.923 ± 0.083
Relative to brain weight	0.472 ± 0.025	0.490 ± 0.028	0.508 ± 0.014	0.569 ± 0.144	0.458 ± 0.040
Relative to body weight	4.22 ± 0.25	4.40 ± 0.40	4.39 ± 0.12	5.18 ± 1.21	4.34 ± 0.42
L. Kidney					
Absolute	0.932 ± 0.026	0.899 ± 0.030	0.887 ± 0.026	0.781 ± 0.031**	0.740 ± 0.027***
Relative to brain weight	0.480 ± 0.013	0.462 ± 0.019	0.457 ± 0.014	0.401 ± 0.017**	0.367 ± 0.013***
Relative to body weight	4.29 ± 0.12	4.12 ± 0.17	3.94 ± 0.06	3.69 ± 0.07**	3.46 ± 0.06***
R. Kidney					
Absolute	0.926 ± 0.029	0.910 ± 0.021	0.900 ± 0.017	0.780 ± 0.038**	0.746 ± 0.029**
Relative to brain weight	0.476 ± 0.014	0.468 ± 0.015	0.464 ± 0.012	0.401 ± 0.020**	0.371 ± 0.014***
Relative to body weight	4.26 ± 0.14	4.17 ± 0.08	4.00 ± 0.08	3.68 ± 0.08**	3.49 ± 0.06****
Liver					
Absolute	7.952 ± 0.335	8.277 ± 0.423	9.120 ± 0.339	8.190 ± 0.263	8.188 ± 0.447
Relative to brain weight	4.091 ± 0.149	4.257 ± 0.236	4.695 ± 0.187	4.208 ± 0.115	4.068 ± 0.215
Relative to body weight	36.55 ± 1.35	37.94 ± 1.96	40.46 ± 0.51	38.69 ± 0.41	38.33 ± 1.59
L. Testis					
Absolute	1.387 ± 0.031	1.397 ± 0.023	1.399 ± 0.044	1.389 ± 0.021	1.362 ± 0.023
Relative to brain weight	0.714 ± 0.008	0.718 ± 0.017	0.720 ± 0.021	0.714 ± 0.011	0.677 ± 0.013
Relative to body weight	6.38 ± 0.07	6.41 ± 0.16	6.21 ± 0.13	6.57 ± 0.13	6.39 ± 0.14
R. Testis					
Absolute	1.383 ± 0.032	1.345 ± 0.042	1.357 ± 0.022	1.380 ± 0.037	1.349 ± 0.007
Relative to brain weight	0.712 ± 0.018	0.692 ± 0.028	0.698 ± 0.007	0.709 ± 0.022	0.670 ± 0.005
Relative to body weight	6.36 ± 0.20	6.16 ± 0.13	6.05 ± 0.29	6.52 ± 0.14	6.33 ± 0.15

Table G3
Organ Weights and Organ-Weight-to-Brain-Weight and Organ-Weight-to-Body-Weight Ratios for Rats at the 6-Week Evaluation in the Feed Study of Fumonisin B_1

	0 ppm	5 ppm	15 ppm	50 ppm	100 ppm
n	4	4	4	4	4
Female					
Necropsy body wt	144 ± 2	146 ± 5	145 ± 4	146 ± 1	146 ± 6
Brain					
Absolute	1.833 ± 0.024	1.777 ± 0.050	1.836 ± 0.058	1.763 ± 0.017	1.875 ± 0.028
Relative to body weight	12.71 ± 0.33	12.21 ± 0.25	12.68 ± 0.22	12.11 ± 0.18	12.86 ± 0.35
Heart					
Absolute	0.634 ± 0.053	0.596 ± 0.021	0.612 ± 0.034	0.586 ± 0.013	0.642 ± 0.027
Relative to brain weight	0.346 ± 0.030	0.336 ± 0.010	0.333 ± 0.011	0.332 ± 0.008	0.342 ± 0.012
Relative to body weight	4.39 ± 0.39	4.09 ± 0.10	4.23 ± 0.20	4.02 ± 0.08	4.40 ± 0.20
L. Kidney					
Absolute	0.659 ± 0.020	0.638 ± 0.007	0.618 ± 0.021	0.602 ± 0.008	0.608 ± 0.043
Relative to brain weight	0.360 ± 0.012	0.360 ± 0.011	0.338 ± 0.016	0.342 ± 0.007	0.323 ± 0.018
Relative to body weight	4.56 ± 0.09	4.39 ± 0.13	4.29 ± 0.24	4.13 ± 0.05	4.14 ± 0.12
R. Kidney					
Absolute	0.624 ± 0.019	0.602 ± 0.016	0.609 ± 0.014	0.592 ± 0.016	0.602 ± 0.035
Relative to brain weight	0.340 ± 0.012	0.339 ± 0.007	0.333 ± 0.014	0.336 ± 0.008	0.321 ± 0.015
Relative to body weight	4.32 ± 0.08	4.14 ± 0.10	4.22 ± 0.21	4.07 ± 0.09	4.11 ± 0.08
Liver					
Absolute	5.253 ± 0.221	4.877 ± 0.214	4.793 ± 0.167	4.697 ± 0.163	5.212 ± 0.318
Relative to brain weight	2.869 ± 0.139	2.743 ± 0.073	2.616 ± 0.101	2.667 ± 0.114	2.774 ± 0.132
Relative to body weight	36.33 ± 1.02	33.44 ± 0.50	33.22 ± 1.63	32.25 ± 0.91	35.57 ± 1.02

** Significantly different ($P \leq 0.01$) from the control group by a one-way analysis of variance with application of Dunnett's test
*** $P \leq 0.001$
**** $P \leq 0.0001$
[a] Organ weights (absolute weights) and body weights are given in grams; organ-weight-to-brain-weight ratios (relative weights) are given as g organ weight/g brain weight (mean ± standard error); organ-weight-to-body-weight ratios (relative weights) are given as mg organ weight/g body weight (mean ± standard error).

TABLE G4
Organ Weights and Organ-Weight-to-Brain-Weight and Organ-Weight-to-Body-Weight Ratios for Rats at the 10-Week Evaluation in the Feed Study of Fumonisin B_1[a]

	0 ppm	5 ppm	15 ppm	50 ppm	150 ppm
n	4	4	4	4	4
Male					
Necropsy body wt	259 ± 8	273 ± 7	272 ± 13	281 ± 10	257 ± 10
Brain					
Absolute	1.983 ± 0.010	1.957 ± 0.005	2.000 ± 0.028	1.983 ± 0.036	1.953 ± 0.039
Relative to body weight	7.68 ± 0.29	7.19 ± 0.21	7.40 ± 0.30	7.08 ± 0.20	7.62 ± 0.19
Heart					
Absolute	0.969 ± 0.031	0.909 ± 0.076	1.018 ± 0.050	1.010 ± 0.064	0.980 ± 0.055
Relative to brain weight	0.489 ± 0.018	0.464 ± 0.038	0.509 ± 0.026	0.509 ± 0.032	0.501 ± 0.019
Relative to body weight	3.75 ± 0.15	3.34 ± 0.32	3.75 ± 0.15	3.59 ± 0.15	3.81 ± 0.11
L. Kidney					
Absolute	0.937 ± 0.022	0.940 ± 0.027	0.972 ± 0.023	0.824 ± 0.038	0.752 ± 0.033**
Relative to brain weight	0.473 ± 0.014	0.480 ± 0.013	0.486 ± 0.010	0.415 ± 0.013*	0.385 ± 0.014***
Relative to body weight	3.62 ± 0.07	3.45 ± 0.15	3.59 ± 0.09	2.94 ± 0.06***	2.93 ± 0.06***
R. Kidney					
Absolute	0.963 ± 0.030	0.903 ± 0.020	0.956 ± 0.063	0.860 ± 0.028	0.732 ± 0.042**
Relative to brain weight	0.486 ± 0.017	0.461 ± 0.009	0.478 ± 0.028	0.434 ± 0.008	0.375 ± 0.021**
Relative to body weight	3.72 ± 0.07	3.32 ± 0.15	3.51 ± 0.07	3.08 ± 0.13**	2.85 ± 0.09***
Liver					
Absolute	8.352 ± 0.445	9.001 ± 0.533	9.078 ± 0.809	9.236 ± 0.547	8.729 ± 0.711
Relative to brain weight	4.215 ± 0.243	4.598 ± 0.263	4.533 ± 0.380	4.652 ± 0.221	4.462 ± 0.316
Relative to body weight	32.17 ± 0.69	33.16 ± 2.67	33.22 ± 1.54	32.84 ± 0.78	33.82 ± 1.51
L. Testis					
Absolute	1.455 ± 0.029	1.403 ± 0.024	1.425 ± 0.009	1.371 ± 0.060	1.402 ± 0.037
Relative to brain weight	0.734 ± 0.018	0.717 ± 0.011	0.713 ± 0.006	0.691 ± 0.020	0.718 ± 0.009
Relative to body weight	5.62 ± 0.09	5.15 ± 0.18	5.28 ± 0.23	4.88 ± 0.08*	5.47 ± 0.18
R. Testis					
Absolute	1.368 ± 0.042	1.352 ± 0.034	1.396 ± 0.032	1.352 ± 0.037	1.378 ± 0.035
Relative to brain weight	0.690 ± 0.024	0.691 ± 0.016	0.698 ± 0.017	0.682 ± 0.018	0.706 ± 0.007
Relative to body weight	5.28 ± 0.06	4.96 ± 0.19	5.16 ± 0.19	4.83 ± 0.12	5.37 ± 0.09

TABLE G4
Organ Weights and Organ-Weight-to-Brain-Weight and Organ-Weight-to-Body-Weight Ratios for Rats at the 10-Week Evaluation in the Feed Study of Fumonisin B_1

	0 ppm	5 ppm	15 ppm	50 ppm	100 ppm
n	4	4	4	4	4
Female					
Necropsy body wt	163 ± 2	166 ± 5	161 ± 5	165 ± 4	162 ± 4
Brain					
Absolute	1.888 ± 0.032	1.788 ± 0.023	1.915 ± 0.005	1.882 ± 0.027	1.846 ± 0.043
Relative to body weight	11.58 ± 0.20	10.76 ± 0.27	11.90 ± 0.38	11.43 ± 0.24	11.37 ± 0.20
Heart					
Absolute	0.693 ± 0.051	0.698 ± 0.034	0.669 ± 0.025	0.630 ± 0.039	0.590 ± 0.026
Relative to brain weight	0.366 ± 0.023	0.390 ± 0.018	0.349 ± 0.013	0.335 ± 0.021	0.320 ± 0.014
Relative to body weight	4.24 ± 0.28	4.20 ± 0.18	4.14 ± 0.12	3.81 ± 0.15	3.63 ± 0.10
L. Kidney					
Absolute	0.641 ± 0.024	0.637 ± 0.005	0.608 ± 0.027	0.597 ± 0.026	0.569 ± 0.016
Relative to brain weight	0.340 ± 0.014	0.356 ± 0.006	0.317 ± 0.014	0.317 ± 0.010	0.308 ± 0.003
Relative to body weight	3.93 ± 0.13	3.84 ± 0.10	3.76 ± 0.13	3.63 ± 0.15	3.51 ± 0.09
R. Kidney					
Absolute	0.632 ± 0.029	0.635 ± 0.011	0.618 ± 0.026	0.603 ± 0.021	0.562 ± 0.024
Relative to brain weight	0.335 ± 0.014	0.356 ± 0.010	0.322 ± 0.013	0.320 ± 0.008	0.304 ± 0.006
Relative to body weight	3.88 ± 0.17	3.83 ± 0.16	3.82 ± 0.06	3.66 ± 0.14	3.46 ± 0.11
Liver					
Absolute	5.148 ± 0.266	4.941 ± 0.094	4.967 ± 0.198	5.169 ± 0.168	4.895 ± 0.213
Relative to brain weight	2.728 ± 0.140	2.765 ± 0.072	2.593 ± 0.098	2.747 ± 0.088	2.650 ± 0.074
Relative to body weight	31.59 ± 1.70	29.74 ± 0.84	30.75 ± 0.45	31.35 ± 0.46	30.17 ± 1.35

* Significantly different ($P \leq 0.05$) from the control group by a one-way analysis of variance with application of Dunnett's test
** $P \leq 0.01$
*** $P \leq 0.001$
[a] Organ weights (absolute weights) and body weights are given in grams; organ-weight-to-brain-weight ratios (relative weights) are given as g organ weight/g brain weight (mean ± standard error); organ-weight-to-body-weight ratios (relative weights) are given as mg organ weight/g body weight (mean ± standard error).

TABLE G5
Organ Weights and Organ-Weight-to-Brain-Weight and Organ-Weight-to-Body-Weight Ratios for Rats at the 14-Week Evaluation in the Feed Study of Fumonisin B_1[a]

	0 ppm	5 ppm	15 ppm	50 ppm	150 ppm
n	4	4	4	4	4
Male					
Necropsy body wt	328 ± 10	328 ± 4	338 ± 4	308 ± 4	308 ± 18
Brain					
Absolute	2.035 ± 0.015	1.962 ± 0.022	2.062 ± 0.044	2.049 ± 0.034	2.029 ± 0.038
Relative to body weight	6.21 ± 0.17	5.99 ± 0.13	6.10 ± 0.06	6.66 ± 0.15	6.65 ± 0.34
Heart					
Absolute	1.132 ± 0.033	1.077 ± 0.035	1.031 ± 0.049	1.038 ± 0.073	1.005 ± 0.056
Relative to brain weight	0.556 ± 0.015	0.549 ± 0.017	0.501 ± 0.026	0.508 ± 0.039	0.497 ± 0.034
Relative to body weight	3.45 ± 0.15	3.29 ± 0.13	3.06 ± 0.16	3.37 ± 0.20	3.31 ± 0.32
L. Kidney					
Absolute	1.114 ± 0.085	1.161 ± 0.032	1.080 ± 0.019	0.887 ± 0.031*	0.852 ± 0.050**
Relative to brain weight	0.547 ± 0.041	0.592 ± 0.021	0.524 ± 0.010	0.433 ± 0.013*	0.419 ± 0.021**
Relative to body weight	3.38 ± 0.19	3.54 ± 0.06	3.20 ± 0.06	2.89 ± 0.12*	2.77 ± 0.07**
R. Kidney					
Absolute	1.092 ± 0.067	1.179 ± 0.020	1.048 ± 0.016	0.877 ± 0.041*	0.818 ± 0.050**
Relative to brain weight	0.537 ± 0.033	0.601 ± 0.011	0.509 ± 0.008	0.427 ± 0.015**	0.402 ± 0.018***
Relative to body weight	3.32 ± 0.14	3.60 ± 0.09	3.10 ± 0.04	2.85 ± 0.16*	2.66 ± 0.10**
Liver					
Absolute	10.661 ± 0.667	10.241 ± 0.262	10.492 ± 0.202	9.618 ± 0.358	10.094 ± 0.412
Relative to brain weight	5.237 ± 0.317	5.225 ± 0.176	5.098 ± 0.158	4.693 ± 0.152	4.972 ± 0.163
Relative to body weight	32.36 ± 1.11	31.27 ± 0.72	31.10 ± 0.78	31.25 ± 1.04	32.90 ± 0.64
L. Testis					
Absolute	1.498 ± 0.063	1.479 ± 0.023	1.456 ± 0.022	1.480 ± 0.013	1.538 ± 0.126
Relative to brain weight	0.735 ± 0.026	0.754 ± 0.015	0.707 ± 0.006	0.723 ± 0.012	0.761 ± 0.073
Relative to body weight	4.57 ± 0.26	4.52 ± 0.06	4.31 ± 0.02	4.81 ± 0.04	5.13 ± 0.77
R. Testis					
Absolute	1.446 ± 0.044	1.473 ± 0.019	1.438 ± 0.032	1.433 ± 0.021	1.495 ± 0.056
Relative to brain weight	0.710 ± 0.019	0.751 ± 0.017	0.698 ± 0.022	0.700 ± 0.010	0.739 ± 0.039
Relative to body weight	4.40 ± 0.08	4.50 ± 0.03	4.26 ± 0.10	4.66 ± 0.09	4.94 ± 0.51

Table G5
Organ Weights and Organ-Weight-to-Brain-Weight and Organ-Weight-to-Body-Weight Ratios for Rats at the 14-Week Evaluation in the Feed Study of Fumonisin B_1

	0 ppm	5 ppm	15 ppm	50 ppm	100 ppm
n	4	4	4	4	4
Female					
Necropsy body wt	180 ± 8	181 ± 2	190 ± 3	174 ± 5	177 ± 7
Brain					
Absolute	1.888 ± 0.049[b]	1.899 ± 0.063	1.905 ± 0.020	1.809 ± 0.025	1.883 ± 0.032
Relative to body weight	10.59 ± 0.42	10.52 ± 0.41	10.06 ± 0.11	10.42 ± 0.44	10.67 ± 0.30
Heart					
Absolute	0.644 ± 0.028	0.699 ± 0.028	0.684 ± 0.013	0.666 ± 0.018	0.660 ± 0.036
Relative to brain weight	0.346 ± 0.011[b]	0.370 ± 0.024	0.359 ± 0.007	0.368 ± 0.012	0.350 ± 0.016
Relative to body weight	3.57 ± 0.11	3.87 ± 0.16	3.61 ± 0.09	3.82 ± 0.06	3.72 ± 0.10
L. Kidney					
Absolute	0.707 ± 0.051	0.668 ± 0.026	0.684 ± 0.060	0.607 ± 0.031	0.564 ± 0.056
Relative to brain weight	0.377 ± 0.029[b]	0.352 ± 0.012	0.358 ± 0.028	0.336 ± 0.021	0.299 ± 0.026
Relative to body weight	3.91 ± 0.17	3.70 ± 0.17	3.60 ± 0.25	3.48 ± 0.08	3.17 ± 0.21*
R. Kidney					
Absolute	0.695 ± 0.042	0.650 ± 0.026	0.659 ± 0.049	0.574 ± 0.032	0.549 ± 0.043
Relative to brain weight	0.368 ± 0.023[b]	0.342 ± 0.009	0.345 ± 0.022	0.318 ± 0.022	0.291 ± 0.020
Relative to body weight	3.84 ± 0.08	3.60 ± 0.17	3.47 ± 0.20	3.29 ± 0.10	3.09 ± 0.15**
Liver					
Absolute	5.371 ± 0.262	5.166 ± 0.226	5.505 ± 0.373	4.950 ± 0.289	4.978 ± 0.383
Relative to brain weight	0.898 ± 0.110[b]	2.734 ± 0.176	2.885 ± 0.165	2.742 ± 0.190	2.639 ± 0.178
Relative to body weight	29.80 ± 0.99	28.59 ± 1.13	28.98 ± 1.47	28.32 ± 0.85	28.00 ± 1.18

* Significantly different ($P \leq 0.05$) from the control group by a one-way analysis of variance with application of Dunnett's test
** $P \leq 0.01$
*** $P \leq 0.001$
[a] Organ weights (absolute weights) and body weights are given in grams; organ-weight-to-brain-weight ratios (relative weights) are given as g organ weight/g brain weight (mean ± standard error); organ-weight-to-body-weight ratios (relative weights) are given as mg organ weight/g body weight (mean ± standard error).
[b] n=3

TABLE G6
Organ Weights and Organ-Weight-to-Brain-Weight and Organ-Weight-to-Body-Weight Ratios for Rats at the 26-Week Evaluation in the Feed Study of Fumonisin B_1[a]

	0 ppm	5 ppm	15 ppm	50 ppm	150 ppm
n	4	4	4	4	4
Male					
Necropsy body wt	435 ± 15	415 ± 14	358 ± 28*	391 ± 13	404 ± 11
Brain					
Absolute	2.097 ± 0.062	2.194 ± 0.033	2.144 ± 0.083	2.137 ± 0.070	2.146 ± 0.059
Relative to body weight	4.85 ± 0.29	5.30 ± 0.11	6.06 ± 0.35**	5.47 ± 0.20	5.32 ± 0.14
Heart					
Absolute	1.277 ± 0.015	1.102 ± 0.074	1.111 ± 0.085	1.097 ± 0.067	1.184 ± 0.049
Relative to brain weight	0.610 ± 0.012	0.501 ± 0.028*	0.517 ± 0.023	0.517 ± 0.044	0.551 ± 0.012
Relative to body weight	2.95 ± 0.12	2.65 ± 0.09	3.12 ± 0.16	2.80 ± 0.14	2.93 ± 0.07
L. Kidney					
Absolute	1.366 ± 0.090	1.332 ± 0.033	1.092 ± 0.072*	1.076 ± 0.041**	0.937 ± 0.020***
Relative to brain weight	0.655 ± 0.056	0.607 ± 0.010	0.509 ± 0.027*	0.506 ± 0.031*	0.437 ± 0.010***
Relative to body weight	3.14 ± 0.18	3.21 ± 0.04	3.06 ± 0.08	2.75 ± 0.09*	2.32 ± 0.04****
R. Kidney					
Absolute	1.372 ± 0.069	1.276 ± 0.028	1.098 ± 0.096*	1.061 ± 0.028**	0.974 ± 0.035***
Relative to brain weight	0.658 ± 0.050	0.582 ± 0.010	0.511 ± 0.038*	0.498 ± 0.022**	0.454 ± 0.007***
Relative to body weight	3.15 ± 0.11	3.08 ± 0.05	3.06 ± 0.06	2.71 ± 0.07**	2.41 ± 0.05****
Liver					
Absolute	13.376 ± 0.369	12.316 ± 0.214	11.253 ± 1.237	11.605 ± 0.701	12.872 ± 0.584
Relative to brain weight	6.410 ± 0.375	5.617 ± 0.115	5.215 ± 0.459	5.458 ± 0.428	5.993 ± 0.169
Relative to body weight	30.78 ± 0.44	29.76 ± 0.82	31.16 ± 1.41	29.65 ± 1.43	31.87 ± 0.86
L. Testis					
Absolute	1.610 ± 0.047	1.576 ± 0.036	1.591 ± 0.069	1.568 ± 0.029	1.574 ± 0.041
Relative to brain weight	0.770 ± 0.037	0.718 ± 0.009	0.743 ± 0.021	0.735 ± 0.018	0.734 ± 0.022
Relative to body weight	3.71 ± 0.15	3.81 ± 0.08	4.49 ± 0.19**	4.01 ± 0.10	3.90 ± 0.09
R. Testis					
Absolute	1.555 ± 0.047	1.525 ± 0.074	1.484 ± 0.041	1.409 ± 0.063	1.518 ± 0.027
Relative to brain weight	0.745 ± 0.044	0.694 ± 0.024	0.693 ± 0.011	0.662 ± 0.037	0.708 ± 0.014
Relative to body weight	3.58 ± 0.04	3.68 ± 0.12	4.20 ± 0.24*	3.60 ± 0.12	3.77 ± 0.11

Table G6
Organ Weights and Organ-Weight-to-Brain-Weight and Organ-Weight-to-Body-Weight Ratios for Rats at the 26-Week Evaluation in the Feed Study of Fumonisin B_1

	0 ppm	5 ppm	15 ppm	50 ppm	100 ppm
n	4	4	4	4	4
Female					
Necropsy body wt	212 ± 7	212 ± 9	210 ± 10	199 ± 11	195 ± 11
Brain					
Absolute	2.005 ± 0.054	1.926 ± 0.055	1.909 ± 0.031	1.993 ± 0.029	1.917 ± 0.028
Relative to body weight	9.48 ± 0.16	9.12 ± 0.25	9.14 ± 0.48	10.10 ± 0.51	9.93 ± 0.53
Heart					
Absolute	0.756 ± 0.051	0.785 ± 0.042	0.740 ± 0.023	0.719 ± 0.036	0.692 ± 0.028
Relative to brain weight	0.376 ± 0.018	0.408 ± 0.022	0.389 ± 0.017	0.361 ± 0.016	0.361 ± 0.011
Relative to body weight	3.56 ± 0.14	3.71 ± 0.15	3.54 ± 0.17	3.62 ± 0.06	3.56 ± 0.08
L. Kidney					
Absolute	0.754 ± 0.017	0.778 ± 0.070	0.735 ± 0.028	0.700 ± 0.066	0.585 ± 0.036
Relative to brain weight	0.376 ± 0.005	0.402 ± 0.027	0.385 ± 0.015	0.351 ± 0.032	0.305 ± 0.019
Relative to body weight	3.56 ± 0.06	3.66 ± 0.24	3.51 ± 0.16	3.50 ± 0.20	3.01 ± 0.12
R. Kidney					
Absolute	0.774 ± 0.019	0.759 ± 0.055	0.729 ± 0.033	0.671 ± 0.054	0.589 ± 0.032*
Relative to brain weight	0.386 ± 0.007	0.393 ± 0.019	0.382 ± 0.019	0.336 ± 0.024	0.307 ± 0.016*
Relative to body weight	3.66 ± 0.06	3.58 ± 0.16	3.47 ± 0.10	3.36 ± 0.14	3.03 ± 0.14**
Liver					
Absolute	5.800 ± 0.171	6.323 ± 0.415	6.180 ± 0.483	5.930 ± 0.397	5.644 ± 0.326
Relative to brain weight	2.895 ± 0.082	3.276 ± 0.152	3.239 ± 0.256	2.971 ± 0.174	2.941 ± 0.148
Relative to body weight	27.41 ± 0.65	29.79 ± 0.91	29.29 ± 1.36	29.75 ± 0.67	28.95 ± 0.13

* Significantly different ($P \leq 0.05$) from the control group by a one-way analysis of variance with application of Dunnett's test
** $P \leq 0.01$
*** $P \leq 0.001$
**** $P \leq 0.0001$
[a] Organ weights (absolute weights) and body weights are given in grams; organ-weight-to-brain-weight ratios (relative weights) are given as g organ weight/g brain weight (mean ± standard error); organ-weight-to-body-weight ratios (relative weights) are given as mg organ weight/g body weight (mean ± standard error).

TABLE G7
Organ Weights and Organ-Weight-to-Brain-Weight and Organ-Weight-to-Body-Weight Ratios for Rats in the 2-Year Feed Study of Fumonisin B_1[a]

	0 ppm	5 ppm	15 ppm	50 ppm	150 ppm
Male					
n	16	17	25	18	26
Necropsy body wt	426 ± 12	455 ± 13	457 ± 11	458 ± 11	470 ± 10*
Brain					
Absolute	2.183 ± 0.031	2.228 ± 0.021	2.201 ± 0.045	2.195 ± 0.027	2.196 ± 0.019
Relative to body weight	5.178 ± 0.150	4.967 ± 0.153	4.902 ± 0.179	4.844 ± 0.146	4.717 ± 0.091*
Heart					
Absolute	1.355 ± 0.039	1.412 ± 0.045	1.408 ± 0.043	1.302 ± 0.041	1.346 ± 0.027
Relative to brain weight	0.623 ± 0.022	0.634 ± 0.020	0.646 ± 0.023	0.592 ± 0.014	0.614 ± 0.013
Relative to body weight	3.227 ± 0.155	3.162 ± 0.161	3.094 ± 0.080	2.883 ± 0.144	2.890 ± 0.074*
L. Kidney					
Absolute	1.658 ± 0.039	1.633 ± 0.051	1.608 ± 0.056	1.397 ± 0.035*	1.479 ± 0.073*[b]
Relative to brain weight	0.762 ± 0.021	0.733 ± 0.023	0.736 ± 0.027	0.637 ± 0.015*	0.671 ± 0.032*[b]
Relative to body weight	3.913 ± 0.089	3.641 ± 0.172	3.543 ± 0.111	3.067 ± 0.089*	3.126 ± 0.150*[b]
R. Kidney					
Absolute	1.704 ± 0.038	1.652 ± 0.053	1.620 ± 0.058	1.468 ± 0.067*[c]	1.506 ± 0.096[d]
Relative to brain weight	0.784 ± 0.023	0.742 ± 0.024	0.741 ± 0.028	0.668 ± 0 030*[c]	0.692 ± 0.047[d]
Relative to body weight	4.029 ± 0.109	3.687 ± 0.183	3.571 ± 0.116*	3.153 ± 0.122*[c]	3.228 ± 0.199*[d]
Liver					
Absolute	15.562 ± 0.780	13.822 ± 0.547	14.855 ± 0.750	14.141 ± 0.501	13.400 ± 0.350
Relative to brain weight	7.151 ± 0.387	6.208 ± 0.245*	6.789 ± 0.350	6.441 ± 0.217	6.109 ± 0.160*
Relative to body weight	37.074 ± 2.392	30.709 ± 1.470*	32.681 ± 1.578*	31.292 ± 1.559*	28.554 ± 0.497*
L. Testis					
Absolute	1.715 ± 0.280	1.639 ± 0.342	1.758 ± 0.262	1.953 ± 0.240[c]	2.030 ± 0.238
Relative to brain weight	0.779 ± 0.122	0.727 ± 0.143	0.816 ± 0.124	0.888 ± 0.111[c]	0.930 ± 0.110
Relative to body weight	4.090 ± 0.699	3.549 ± 0.708	3.845 ± 0.586	4.202 ± 0.494[c]	4.420 ± 0.540
R. Testis					
Absolute	1.990 ± 0.372	2.477 ± 0.351	1.975 ± 0.237	1.874 ± 0.310[c]	1.686 ± 0.202
Relative to brain weight	0.902 ± 0.164	1.114 ± 0.158	0.889 ± 0.104	0.845 ± 0.137[c]	0.764 ± 0.090
Relative to body weight	4.639 ± 0.870	5.382 ± 0.746	4.436 ± 0.608	4.162 ± 0.750[c]	3.601 ± 0.425

TABLE G7
Organ Weights and Organ-Weight-to-Brain-Weight and Organ-Weight-to-Body-Weight Ratios for Rats in the 2-Year Feed Study of Fumonisin B_1

	0 ppm	5 ppm	15 ppm	50 ppm	100 ppm
Female					
n	28	22	25	30	31
Necropsy body wt	335 ± 8	343 ± 9	344 ± 7	342 ± 8	340 ± 8
Brain					
Absolute	2.013 ± 0.015	1.993 ± 0.013	2.008 ± 0.014[d]	1.998 ± 0.014	2.002 ± 0.017
Relative to body weight	6.129 ± 0.204	5.891 ± 0.155	5.888 ± 0.128[d]	5.944 ± 0.159	5.985 ± 0.154
Heart					
Absolute	1.033 ± 0.018	1.050 ± 0.021	1.021 ± 0.019[d]	0.984 ± 0.015*	0.993 ± 0.018
Relative to brain weight	0.514 ± 0.010	0.527 ± 0.010	0.509 ± 0.011[d]	0.493 ± 0.007	0.496 ± 0.009
Relative to body weight	3.122 ± 0.085	3.108 ± 0.112	3.000 ± 0.099[d]	2.917 ± 0.073	2.970 ± 0.094
L. Kidney					
Absolute	1.210 ± 0.041	1.185 ± 0.032	1.088 ± 0.024*	0.978 ± 0.018*	0.968 ± 0.016*
Relative to brain weight	0.601 ± 0.020	0.595 ± 0.015	0.542 ± 0.012*[d]	0.490 ± 0.009*	0.484 ± 0.009*
Relative to body weight	3.643 ± 0.129	3.512 ± 0.144	3.184 ± 0.085*	2.893 ± 0.070*	2.887 ± 0.078*
R. Kidney					
Absolute	1.198 ± 0.035	1.221 ± 0.046	1.085 ± 0.021*	0.989 ± 0.016*	0.961 ± 0.017*
Relative to brain weight	0.596 ± 0.017	0.613 ± 0.023	0.541 ± 0.011*	0.495 ± 0.008*	0.480 ± 0.009*
Relative to body weight	3.604 ± 0.106	3.632 ± 0.199	3.174 ± 0.078*	2.924 ± 0.065*	2.868 ± 0.082*
Liver					
Absolute	10.643 ± 0.514	10.088 ± 0.570	9.981 ± 0.515	10.581 ± 0.559	9.928 ± 0.292
Relative to brain weight	5.304 ± 0.269	5.056 ± 0.285	5.016 ± 0.271[d]	5.303 ± 0.284	4.961 ± 0.141
Relative to body weight	32.042 ± 1.650	29.868 ± 2.000	29.185 ± 1.593	31.136 ± 1.594	29.533 ± 1.002

* Significantly different ($P \leq 0.05$) from the control group by a one-way analysis of variance with application of Dunnett's test

a Organ weights (absolute weights) and body weights are given in grams; organ-weight-to-brain-weight ratios (relative weights) are given as g organ weight/g brain weight (mean ± standard error); organ-weight-to-body-weight ratios (relative weights) are given as mg organ weight/g body weight (mean ± standard error).

b n=25

c n=16

d n=24

TABLE G8
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Core Study Mice in the 28-Day Feed Study of Fumonisin B_1[a]

	0 ppm	99 ppm	163 ppm	234 ppm	484 ppm
n	12	12	12	12	12
Male					
Final body wt	22.1 ± 0.4	22.3 ± 0.3	21.2 ± 0.2	21.6 ± 0.2	20.1 ± 0.3***
Brain					
Absolute	0.494 ± 0.005	0.485 ± 0.007	0.483 ± 0.008	0.477 ± 0.008	0.483 ± 0.007
Relative	22.425 ± 0.384	21.829 ± 0.452	22.808 ± 0.390	22.108 ± 0.402	23.991 ± 0.256*
Heart					
Absolute	0.138 ± 0.006	0.131 ± 0.005	0.128 ± 0.003	0.123 ± 0.006	0.122 ± 0.005
Relative	6.262 ± 0.270	5.867 ± 0.213	6.058 ± 0.184	5.691 ± 0.268	6.018 ± 0.228
L. and R. Kidneys					
Absolute	0.352 ± 0.012	0.360 ± 0.010	0.346 ± 0.008	0.327 ± 0.008	0.308 ± 0.008**
Relative	15.982 ± 0.509	16.170 ± 0.430	16.286 ± 0.325	15.103 ± 0.270	15.293 ± 0.299
Liver					
Absolute	1.000 ± 0.019	0.979 ± 0.011	0.927 ± 0.016*	0.931 ± 0.018*	0.877 ± 0.020****
Relative	45.360 ± 0.533	44.039 ± 0.608	43.734 ± 0.764	43.119 ± 0.758	43.543 ± 0.866
L. and R. Testes					
Absolute	0.195 ± 0.010	0.208 ± 0.004	0.202 ± 0.009	0.194 ± 0.007	0.200 ± 0.007
Relative	8.867 ± 0.453	9.367 ± 0.200	9.570 ± 0.446	8.966 ± 0.296	9.883 ± 0.277
Female					
Final body wt	15.7 ± 0.2	15.7 ± 0.1	16.2 ± 0.2	15.6 ± 0.1	15.4 ± 0.2
Brain					
Absolute	0.485 ± 0.004	0.483 ± 0.004	0.478 ± 0.010	0.489 ± 0.005	0.476 ± 0.005
Relative	31.007 ± 0.626	30.745 ± 0.235	29.504 ± 0.653	31.395 ± 0.353	31.020 ± 0.482
Heart					
Absolute	0.099 ± 0.003	0.099 ± 0.003	0.092 ± 0.005	0.097 ± 0.003	0.091 ± 0.003
Relative	6.338 ± 0.200	6.319 ± 0.157	5.693 ± 0.323	6.231 ± 0.236	5.940 ± 0.164
L. and R. Kidneys					
Absolute	0.248 ± 0.003	0.253 ± 0.005	0.248 ± 0.006	0.248 ± 0.006	0.226 ± 0.007*
Relative	15.866 ± 0.332	16.116 ± 0.301	15.286 ± 0.231	15.913 ± 0.343	14.690 ± 0.423
Liver					
Absolute	0.716 ± 0.021	0.670 ± 0.010	0.718 ± 0.017	0.745 ± 0.015	0.790 ± 0.013**
Relative	45.588 ± 0.836	42.629 ± 0.529	44.291 ± 0.952	47.862 ± 0.985	51.503 ± 0.917****

* Significantly different ($P \leq 0.05$) from the control group by a one-way analysis of variance with application of Holm's procedure
** $P \leq 0.01$
*** $P \leq 0.001$
**** $P \leq 0.0001$
a Organ weights (absolute weights) and body weights are given in grams; organ-weight-to-body-weight ratios (relative weights) are given as mg organ weight/g body weight (mean ± standard error).

TABLE G9
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Clinical Pathology Study Mice in the 28-Day Feed Study of Fumonisin B_1[a]

	0 ppm	99 ppm	163 ppm	234 ppm	484 ppm
Male					
n	8	6	8	6	6
Final body wt	20.3 ± 0.2	21.4 ± 0.3*	21.9 ± 0.3***	20.9 ± 0.4	19.1 ± 0.3*
Brain					
Absolute	0.488 ± 0.003	0.487 ± 0.009	0.482 ± 0.008	0.487 ± 0.006	0.486 ± 0.015
Relative	24.107 ± 0.316	22.776 ± 0.494	22.052 ± 0.295*	23.347 ± 0.578	25.535 ± 0.750
Heart					
Absolute	0.116 ± 0.003	0.121 ± 0.003	0.121 ± 0.005	0.130 ± 0.004	0.088 ± 0.007***
Relative	5.720 ± 0.127	5.640 ± 0.139	5.527 ± 0.152	6.240 ± 0.188	4.615 ± 0.419**
L. and R. Kidneys					
Absolute	0.303 ± 0.007	0.320 ± 0.004	0.320 ± 0.009	0.319 ± 0.016	0.275 ± 0.016
Relative	14.957 ± 0.292	14.996 ± 0.311	14.625 ± 0.409	15.254 ± 0.708	14.400 ± 0.680
Liver					
Absolute	0.759 ± 0.015	0.785 ± 0.034	0.853 ± 0.024*	0.757 ± 0.026	0.776 ± 0.023
Relative	37.475 ± 0.641	36.664 ± 1.297	39.021 ± 1.255	36.304 ± 1.298	40.838 ± 1.528
L. and R. Testes					
Absolute	0.201 ± 0.004	0.197 ± 0.008	0.196 ± 0.011	0.202 ± 0.010	0.169 ± 0.015
Relative	9.917 ± 0.158	9.221 ± 0.386	8.966 ± 0.509	9.682 ± 0.558	8.877 ± 0.769
Female					
n	8	3	8	7	8
Final body wt	15.3 ± 0.3	15.6 ± 0.4	15.5 ± 0.5	15.0 ± 0.6	14.8 ± 0.4
Brain					
Absolute	0.494 ± 0.007	0.496 ± 0.006	0.456 ± 0.015	0.485 ± 0.004	0.456 ± 0.016
Relative	32.364 ± 0.377	31.848 ± 0.674	29.438 ± 0.917	32.561 ± 1.041	30.866 ± 1.241
Heart					
Absolute	0.099 ± 0.003	0.095 ± 0.010	0.083 ± 0.004**	0.088 ± 0.003	0.074 ± 0.002****
Relative	6.451 ± 0.124	6.087 ± 0.446	5.324 ± 0.204**	5.928 ± 0.293	5.050 ± 0.282***
L. and R. Kidneys					
Absolute	0.241 ± 0.011	0.244 ± 0.011	0.205 ± 0.012	0.218 ± 0.009	0.204 ± 0.009
Relative	15.736 ± 0.567	15.611 ± 0.399	13.230 ± 0.722*	14.629 ± 0.601	13.795 ± 0.618
Liver					
Absolute	0.648 ± 0.023	0.549 ± 0.029	0.657 ± 0.026	0.629 ± 0.020	0.671 ± 0.022
Relative	42.357 ± 0.993	35.125 ± 0.914*	42.486 ± 1.910	41.981 ± 0.674	45.271 ± 1.040

* Significantly different ($P \leq 0.05$) from the control group by a one-way analysis of variance with application of Holm's procedure
** $P \leq 0.01$
*** $P \leq 0.001$
**** $P \leq 0.0001$
[a] Organ weights (absolute weights) and body weights are given in grams; organ-weight-to-body-weight ratios (relative weights) are given as mg organ weight/g body weight (mean ± standard error).

TABLE G10
Organ Weights and Organ-Weight-to-Brain-Weight and Organ-Weight-to-Body-Weight Ratios for Mice at the 3-Week Evaluation in the Feed Study of Fumonisin B_1[a]

	0 ppm	5 ppm	15 ppm	80 ppm	150 ppm
n	4	4	4	4	4
Male					
Necropsy body wt	19.9 ± 0.4	18.0 ± 0.5	20.0 ± 0.7	19.2 ± 0.5	18.7 ± 0.7
Brain					
Absolute	0.474 ± 0.011	0.447 ± 0.013	0.471 ± 0.008	0.464 ± 0.010	0.468 ± 0.010
Relative to body weight	23.86 ± 0.19	24.86 ± 0.99	23.58 ± 0.65	24.21 ± 0.19	25.14 ± 0.69
Heart					
Absolute	0.135 ± 0.019	0.119 ± 0.006	0.139 ± 0.016	0.109 ± 0.003	0.118 ± 0.013
Relative to brain weight	0.282 ± 0.032	0.267 ± 0.016	0.294 ± 0.029	0.235 ± 0.006	0.252 ± 0.028
Relative to body weight	6.73 ± 0.80	6.59 ± 0.22	6.89 ± 0.58	5.68 ± 0.14	6.29 ± 0.49
L. Kidney					
Absolute	0.166 ± 0.008	0.156 ± 0.009	0.154 ± 0.028	0.152 ± 0.003	0.152 ± 0.008
Relative to brain weight	0.349 ± 0.011	0.349 ± 0.024	0.326 ± 0.056	0.327 ± 0.007	0.324 ± 0.013
Relative to body weight	8.33 ± 0.27	8.62 ± 0.46	7.58 ± 1.18	7.91 ± 0.19	8.11 ± 0.22
R. Kidney					
Absolute	0.175 ± 0.010	0.157 ± 0.007	0.155 ± 0.027	0.159 ± 0.006	0.163 ± 0.008
Relative to brain weight	0.368 ± 0.017	0.353 ± 0.024	0.327 ± 0.056	0.344 ± 0.015	0.347 ± 0.014
Relative to body weight	8.78 ± 0.46	8.71 ± 0.37	7.60 ± 1.16	8.33 ± 0.42	8.69 ± 0.26
Liver					
Absolute	0.916 ± 0.039	0.831 ± 0.010	0.905 ± 0.064	0.830 ± 0.001	0.819 ± 0.018
Relative to brain weight	1.928 ± 0.045	1.866 ± 0.073	1.917 ± 0.102	1.790 ± 0.038	1.748 ± 0.002
Relative to body weight	46.03 ± 1.42	46.19 ± 1.10	45.09 ± 2.01	43.36 ± 1.19	43.94 ± 1.21
L. Testis					
Absolute	0.095 ± 0.004	0.089 ± 0.001	0.110 ± 0.013	0.090 ± 0.007	0.088 ± 0.004
Relative to brain weight	0.200 ± 0.005	0.200 ± 0.007	0.234 ± 0.029	0.194 ± 0.014	0.188 ± 0.006
Relative to body weight	4.76 ± 0.14	4.95 ± 0.15	5.57 ± 0.87	4.70 ± 0.35	4.72 ± 0.05
R. Testis					
Absolute	0.100 ± 0.004	0.093 ± 0.003	0.115 ± 0.015	0.089 ± 0.004	0.092 ± 0.006
Relative to brain weight	0.210 ± 0.006	0.208 ± 0.011	0.244 ± 0.032	0.191 ± 0.012	0.197 ± 0.012
Relative to body weight	5.01 ± 0.17	5.15 ± 0.22	5.81 ± 0.93	4.64 ± 0.33	4.92 ± 0.19

TABLE G10
Organ Weights and Organ-Weight-to-Brain-Weight and Organ-Weight-to-Body-Weight Ratios for Mice at the 3-Week Evaluation in the Feed Study of Fumonisin B_1

	0 ppm	5 ppm	15 ppm	50 ppm	80 ppm
n	4	4	4	4	4
Female					
Necropsy body wt	14.6 ± 0.3	14.5 ± 0.8	16.0 ± 0.4	15.2 ± 0.8	15.9 ± 0.4
Brain					
Absolute	0.477 ± 0.010	0.463 ± 0.007	0.462 ± 0.015	0.464 ± 0.022	0.493 ± 0.014
Relative to body weight	32.80 ± 1.05	32.32 ± 2.06	29.00 ± 1.26	30.94 ± 2.29	31.05 ± 1.03
Heart					
Absolute	0.098 ± 0.007	0.099 ± 0.004	0.104 ± 0.002	0.109 ± 0.004	0.107 ± 0.007
Relative to brain weight	0.206 ± 0.015	0.213 ± 0.010	0.226 ± 0.003	0.235 ± 0.013	0.217 ± 0.011
Relative to body weight	6.75 ± 0.44	6.88 ± 0.45	6.53 ± 0.22	7.19 ± 0.27	6.73 ± 0.44
L. Kidney					
Absolute	0.123 ± 0.009	0.114 ± 0.007	0.125 ± 0.002	0.118 ± 0.006	0.123 ± 0.010
Relative to brain weight	0.257 ± 0.018	0.247 ± 0.017	0.272 ± 0.010	0.256 ± 0.023	0.249 ± 0.017
Relative to body weight	8.40 ± 0.48	7.87 ± 0.11	7.85 ± 0.14	7.78 ± 0.25	7.69 ± 0.45
R. Kidney					
Absolute	0.127 ± 0.010	0.121 ± 0.008	0.124 ± 0.005	0.131 ± 0.009	0.134 ± 0.007
Relative to brain weight	0.268 ± 0.023	0.260 ± 0.018	0.268 ± 0.008	0.283 ± 0.025	0.272 ± 0.010
Relative to body weight	8.72 ± 0.56	8.34 ± 0.46	7.75 ± 0.32	8.60 ± 0.36	8.43 ± 0.31
Liver					
Absolute	0.647 ± 0.012	0.672 ± 0.049	0.692 ± 0.017	0.664 ± 0.041	0.731 ± 0.031
Relative to brain weight	1.358 ± 0.030	1.455 ± 0.120	1.500 ± 0.022	1.444 ± 0.131	1.487 ± 0.086
Relative to body weight	44.45 ± 0.46	46.30 ± 0.94	43.42 ± 1.38	43.82 ± 1.16	45.94 ± 1.52

[a] Organ weights (absolute weights) and body weights are given in grams; organ-weight-to-brain-weight ratios (relative weights) are given as g organ weight/g brain weight (mean ± standard error); organ-weight-to-body-weight ratios (relative weights) are given as mg organ weight/g body weight (mean ± standard error).

TABLE G11
Organ Weights and Organ-Weight-to-Brain-Weight and Organ-Weight-to-Body-Weight Ratios for Mice at the 7-Week Evaluation in the Feed Study of Fumonisin B_1[a]

	0 ppm	5 ppm	15 ppm	80 ppm	150 ppm
n	4	4	4	4	4
Male					
Necropsy body wt	22.4 ± 0.6	23.2 ± 0.4	22.6 ± 0.2	22.1 ± 0.1	23.4 ± 0.6
Brain					
Absolute	0.472 ± 0.005	0.469 ± 0.026	0.463 ± 0.005	0.481 ± 0.010	0.497 ± 0.010
Relative to body weight	21.15 ± 0.65	20.21 ± 0.86	20.47 ± 0.37	21.79 ± 0.44	21.26 ± 0.46
Heart					
Absolute	0.130 ± 0.003	0.152 ± 0.011	0.140 ± 0.007	0.127 ± 0.010	0.131 ± 0.005
Relative to brain weight	0.276 ± 0.009	0.323 ± 0.013	0.303 ± 0.012	0.265 ± 0.024	0.265 ± 0.014
Relative to body weight	5.84 ± 0.23	6.55 ± 0.44	6.20 ± 0.30	5.75 ± 0.43	5.62 ± 0.22
L. Kidney					
Absolute	0.169 ± 0.004	0.187 ± 0.021	0.180 ± 0.012	0.170 ± 0.005	0.186 ± 0.006
Relative to brain weight	0.357 ± 0.009	0.405 ± 0.051	0.388 ± 0.026	0.354 ± 0.016	0.374 ± 0.016
Relative to body weight	7.53 ± 0.05	8.14 ± 1.02	7.94 ± 0.52	7.70 ± 0.21	7.94 ± 0.21
R. Kidney					
Absolute	0.180 ± 0.008	0.224 ± 0.007	0.202 ± 0.013	0.176 ± 0.010	0.163 ± 0.018
Relative to brain weight	0.382 ± 0.019	0.480 ± 0.021	0.437 ± 0.028	0.366 ± 0.026	0.327 ± 0.032
Relative to body weight	8.05 ± 0.29	9.66 ± 0.29	8.94 ± 0.60	7.95 ± 0.43	6.93 ± 0.65
Liver					
Absolute	0.893 ± 0.037	0.943 ± 0.017	0.966 ± 0.025	0.915 ± 0.029	0.914 ± 0.038
Relative to brain weight	1.893 ± 0.091	2.029 ± 0.112	2.090 ± 0.070	1.904 ± 0.079	1.840 ± 0.052
Relative to body weight	39.88 ± 1.12	40.73 ± 0.59	42.73 ± 1.02	41.43 ± 1.34	39.08 ± 0.90
L. Testis					
Absolute	0.097 ± 0.006	0.108 ± 0.006	0.100 ± 0.002	0.099 ± 0.006	0.095 ± 0.012
Relative to brain weight	0.205 ± 0.012	0.230 ± 0.002	0.215 ± 0.007	0.207 ± 0.016	0.190 ± 0.020
Relative to body weight	4.34 ± 0.25	4.65 ± 0.20	4.40 ± 0.07	4.49 ± 0.25	4.03 ± 0.44
R. Testis					
Absolute	0.099 ± 0.007	0.121 ± 0.014	0.107 ± 0.017	0.099 ± 0.007	0.088 ± 0.015
Relative to brain weight	0.210 ± 0.014	0.263 ± 0.040	0.232 ± 0.037	0.206 ± 0.011	0.175 ± 0.026
Relative to body weight	4.44 ± 0.30	5.26 ± 0.66	4.74 ± 0.76	4.50 ± 0.32	3.72 ± 0.56

TABLE G11
Organ Weights and Organ-Weight-to-Brain-Weight and Organ-Weight-to-Body-Weight Ratios for Mice at the 7-Week Evaluation in the Feed Study of Fumonisin B_1

	0 ppm	5 ppm	15 ppm	50 ppm	80 ppm
n	4	4	4	4	4
Female					
Necropsy body wt	18.2 ± 0.5	17.4 ± 0.7	16.8 ± 0.4	17.7 ± 0.3	18.5 ± 1.0
Brain					
Absolute	0.487 ± 0.003	0.481 ± 0.018	0.491 ± 0.014	0.485 ± 0.009	0.456 ± 0.027
Relative to body weight	26.80 ± 0.70	27.63 ± 0.53	29.31 ± 0.30	27.45 ± 0.88	24.85 ± 2.06
Heart					
Absolute	0.124 ± 0.007	0.114 ± 0.009	0.102 ± 0.016	0.113 ± 0.004	0.107 ± 0.002
Relative to brain weight	0.254 ± 0.015	0.236 ± 0.010	0.205 ± 0.028	0.233 ± 0.006	0.238 ± 0.013
Relative to body weight	6.82 ± 0.56	6.53 ± 0.33	6.03 ± 0.87	6.41 ± 0.30	5.83 ± 0.28
L. Kidney					
Absolute	0.143 ± 0.010	0.126 ± 0.013	0.125 ± 0.005	0.139 ± 0.002	0.124 ± 0.016
Relative to brain weight	0.294 ± 0.018	0.261 ± 0.018	0.255 ± 0.015	0.287 ± 0.002	0.273 ± 0.035
Relative to body weight	7.87 ± 0.55	7.20 ± 0.50	7.45 ± 0.35	7.88 ± 0.23	6.67 ± 0.78
R. Kidney					
Absolute	0.145 ± 0.004	0.145 ± 0.017	0.133 ± 0.005	0.141 ± 0.006	0.138 ± 0.014
Relative to brain weight	0.297 ± 0.007	0.300 ± 0.027	0.271 ± 0.012	0.289 ± 0.008	0.306 ± 0.038
Relative to body weight	7.96 ± 0.32	8.28 ± 0.66	7.94 ± 0.32	7.96 ± 0.46	7.43 ± 0.54
Liver					
Absolute	0.699 ± 0.022	0.763 ± 0.054	0.660 ± 0.015	0.756 ± 0.012	0.757 ± 0.056
Relative to brain weight	1.436 ± 0.043	1.582 ± 0.055	1.349 ± 0.064	1.558 ± 0.025	1.689 ± 0.200
Relative to body weight	38.42 ± 0.99	43.72 ± 1.72	39.51 ± 1.72	42.74 ± 1.24	40.74 ± 1.19

[a] Organ weights (absolute weights) and body weights are given in grams; organ-weight-to-brain-weight ratios (relative weights) are given as g organ weight/g brain weight (mean ± standard error); organ-weight-to-body-weight ratios (relative weights) are given as mg organ weight/g body weight (mean ± standard error).

TABLE G12
Organ Weights and Organ-Weight-to-Brain-Weight and Organ-Weight-to-Body-Weight Ratios for Mice at the 9-Week Evaluation in the Feed Study of Fumonisin B_1[a]

	0 ppm	5 ppm	15 ppm	80 ppm	150 ppm
n	4	4	4	4	4
Male					
Necropsy body wt	22.6 ± 0.5	23.7 ± 0.8	23.6 ± 0.5	24.2 ± 0.0	23.6 ± 0.7
Brain					
Absolute	0.478 ± 0.004	0.470 ± 0.012	0.467 ± 0.013	0.470 ± 0.009	0.468 ± 0.012
Relative to body weight	21.16 ± 0.63	19.87 ± 0.59	19.84 ± 0.45	19.45 ± 0.36	19.82 ± 0.47
Heart					
Absolute	0.148 ± 0.006	0.154 ± 0.012	0.216 ± 0.075	0.150 ± 0.010	0.136 ± 0.012
Relative to brain weight	0.309 ± 0.015	0.327 ± 0.021	0.456 ± 0.151	0.319 ± 0.014	0.289 ± 0.023
Relative to body weight	6.52 ± 0.18	6.48 ± 0.34	9.16 ± 3.18	6.21 ± 0.39	5.71 ± 0.34
L. Kidney					
Absolute	0.163 ± 0.026	0.184 ± 0.004	0.187 ± 0.010	0.208 ± 0.009	0.195 ± 0.012
Relative to brain weight	0.342 ± 0.055	0.392 ± 0.010	0.400 ± 0.015	0.442 ± 0.013	0.417 ± 0.019
Relative to body weight	7.21 ± 1.12	7.80 ± 0.38	7.95 ± 0.34	8.60 ± 0.38	8.25 ± 0.31
R. Kidney					
Absolute	0.181 ± 0.003	0.201 ± 0.005	0.206 ± 0.010	0.210 ± 0.005	0.208 ± 0.014
Relative to brain weight	0.379 ± 0.006	0.428 ± 0.006	0.441 ± 0.012*	0.446 ± 0.012*	0.444 ± 0.025*
Relative to body weight	8.03 ± 0.26	8.52 ± 0.31	8.75 ± 0.34	8.67 ± 0.19	8.78 ± 0.44
Liver					
Absolute	0.978 ± 0.032	0.945 ± 0.035	0.940 ± 0.035	0.999 ± 0.020	0.973 ± 0.027
Relative to brain weight	2.048 ± 0.081	2.014 ± 0.074	2.014 ± 0.064	2.127 ± 0.066	2.079 ± 0.017
Relative to body weight	43.22 ± 1.17	39.90 ± 0.61*	39.89 ± 0.73*	41.32 ± 0.82	41.19 ± 0.81
L. Testis					
Absolute	0.094 ± 0.004	0.100 ± 0.005	0.114 ± 0.005*	0.111 ± 0.002	0.104 ± 0.006
Relative to brain weight	0.196 ± 0.008	0.213 ± 0.006	0.244 ± 0.011*	0.235 ± 0.006*	0.223 ± 0.016
Relative to body weight	4.14 ± 0.16	4.23 ± 0.21	4.83 ± 0.16	4.57 ± 0.08	4.40 ± 0.25
R. Testis					
Absolute	0.094 ± 0.003	0.104 ± 0.004	0.116 ± 0.006*	0.109 ± 0.003	0.105 ± 0.007
Relative to brain weight	0.196 ± 0.007	0.220 ± 0.005	0.247 ± 0.007**	0.231 ± 0.002*	0.225 ± 0.014
Relative to body weight	4.15 ± 0.12	4.38 ± 0.12	4.91 ± 0.24*	4.50 ± 0.12	4.45 ± 0.22

TABLE G12
Organ Weights and Organ-Weight-to-Brain-Weight and Organ-Weight-to-Body-Weight Ratios for Mice at the 9-Week Evaluation in the Feed Study of Fumonisin B_1

	0 ppm	5 ppm	15 ppm	50 ppm	80 ppm
n	4	4	4	4	4
Female					
Necropsy body wt	18.8 ± 0.7	18.9 ± 0.2	17.5 ± 0.4	17.9 ± 0.2	18.3 ± 0.6
Brain					
Absolute	0.493 ± 0.011	0.480 ± 0.020	0.481 ± 0.011	0.495 ± 0.022	0.485 ± 0.009
Relative to body weight	26.35 ± 1.13	25.45 ± 0.93	27.43 ± 0.02	27.71 ± 1.40	26.66 ± 0.99
Heart					
Absolute	0.111 ± 0.005	0.109 ± 0.003	0.121 ± 0.016	0.111 ± 0.006	0.133 ± 0.019
Relative to brain weight	0.226 ± 0.013	0.228 ± 0.011	0.251 ± 0.027	0.227 ± 0.018	0.273 ± 0.036
Relative to body weight	5.91 ± 0.19	5.77 ± 0.07	6.88 ± 0.76	6.23 ± 0.36	7.24 ± 0.89
L. Kidney					
Absolute	0.152 ± 0.009	0.143 ± 0.006	0.128 ± 0.012	0.142 ± 0.003	0.151 ± 0.006
Relative to brain weight	0.310 ± 0.022	0.297 ± 0.007	0.265 ± 0.020	0.288 ± 0.010	0.310 ± 0.011
Relative to body weight	8.10 ± 0.31	7.56 ± 0.25	7.26 ± 0.56	7.95 ± 0.19	8.28 ± 0.46
R. Kidney					
Absolute	0.147 ± 0.007	0.142 ± 0.008	0.136 ± 0.010	0.147 ± 0.004	0.153 ± 0.006
Relative to brain weight	0.299 ± 0.017	0.295 ± 0.006	0.283 ± 0.014	0.299 ± 0.020	0.316 ± 0.009
Relative to body weight	7.82 ± 0.15	7.53 ± 0.41	7.75 ± 0.39	8.21 ± 0.23	8.41 ± 0.33
Liver					
Absolute	0.767 ± 0.034	0.771 ± 0.027	0.612 ± 0.069*	0.732 ± 0.025	0.806 ± 0.027
Relative to brain weight	1.560 ± 0.084	1.611 ± 0.055	1.267 ± 0.120*	1.488 ± 0.078	1.663 ± 0.060
Relative to body weight	40.83 ± 0.78	40.88 ± 0.96	34.76 ± 3.32	40.96 ± 1.34	44.15 ± 0.06

* Significantly different (P≤0.05) from the control group by a one-way analysis of variance with application of Dunnett's test
** P≤0.01
[a] Organ weights (absolute weights) and body weights are given in grams; organ-weight-to-brain-weight ratios (relative weights) are given as g organ weight/g brain weight (mean ± standard error); organ-weight-to-body-weight ratios (relative weights) are given as mg organ weight/g body weight (mean ± standard error).

TABLE G13
Organ Weights and Organ-Weight-to-Brain-Weight and Organ-Weight-to-Body-Weight Ratios for Mice at the 24-Week Evaluation in the Feed Study of Fumonisin B_1[a]

	0 ppm	5 ppm	15 ppm	80 ppm	150 ppm
n	4	4	4	4	4
Male					
Necropsy body wt	28.8 ± 1.1	29.1 ± 1.5	29.4 ± 0.3	27.9 ± 0.8	27.6 ± 0.5
Brain					
Absolute	0.512 ± 0.009	0.487 ± 0.011	0.501 ± 0.014	0.508 ± 0.018	0.508 ± 0.020
Relative to body weight	17.80 ± 0.46	16.81 ± 0.49	17.07 ± 0.51	18.20 ± 0.22	18.45 ± 0.66
Heart					
Absolute	0.201 ± 0.024	0.177 ± 0.007	0.185 ± 0.018	0.177 ± 0.010	0.200 ± 0.032
Relative to brain weight	0.390 ± 0.041	0.365 ± 0.021	0.371 ± 0.045	0.389 ± 0.019	0.392 ± 0.059
Relative to body weight	6.93 ± 0.67	6.16 ± 0.49	6.28 ± 0.59	6.34 ± 0.33	7.21 ± 1.04
L. Kidney					
Absolute	0.226 ± 0.019	0.247 ± 0.010	0.235 ± 0.016	0.243 ± 0.011	0.214 ± 0.007
Relative to brain weight	0.440 ± 0.037	0.507 ± 0.010	0.470 ± 0.035	0.480 ± 0.015	0.422 ± 0.007
Relative to body weight	7.80 ± 0.51	8.51 ± 0.24	7.98 ± 0.50	8.72 ± 0.19	7.77 ± 0.18
R. Kidney					
Absolute	0.244 ± 0.016	0.237 ± 0.016[b]	0.263 ± 0.013	0.241 ± 0.011	0.239 ± 0.016
Relative to brain weight	0.477 ± 0.029	0.487 ± 0.017[b]	0.527 ± 0.035	0.474 ± 0.018	0.469 ± 0.017
Relative to body weight	8.46 ± 0.43	8.08 ± 0.17[b]	8.95 ± 0.36	8.62 ± 0.27	8.65 ± 0.49
Liver					
Absolute	1.286 ± 0.061	1.206 ± 0.115[b]	1.313 ± 0.066	1.187 ± 0.057	1.188 ± 0.066
Relative to brain weight	2.509 ± 0.089	2.472 ± 0.163[b]	2.629 ± 0.163	2.338 ± 0.062	2.333 ± 0.048
Relative to body weight	44.56 ± 0.80	40.97 ± 1.63[b]	44.67 ± 1.87	42.53 ± 1.02	43.09 ± 2.14
L. Testis					
Absolute	0.118 ± 0.004	0.122 ± 0.004	0.109 ± 0.007	0.114 ± 0.006	0.115 ± 0.004
Relative to brain weight	0.231 ± 0.009	0.250 ± 0.004	0.218 ± 0.015	0.224 ± 0.010	0.226 ± 0.006
Relative to body weight	4.13 ± 0.24	4.20 ± 0.09	3.72 ± 0.23	4.07 ± 0.19	4.16 ± 0.09
R. Testis					
Absolute	0.125 ± 0.004	0.123 ± 0.003	0.116 ± 0.010	0.124 ± 0.008	0.122 ± 0.004
Relative to brain weight	0.244 ± 0.007	0.253 ± 0.007	0.232 ± 0.021	0.244 ± 0.016	0.241 ± 0.007
Relative to body weight	4.34 ± 0.10	4.24 ± 0.17	3.95 ± 0.34	4.43 ± 0.25	4.44 ± 0.12

TABLE G13
Organ Weights and Organ-Weight-to-Brain-Weight and Organ-Weight-to-Body-Weight Ratios for Mice at the 24-Week Evaluation in the Feed Study of Fumonisin B_1

	0 ppm	5 ppm	15 ppm	50 ppm	80 ppm
n	4	4	4	4	4
Female					
Necropsy body wt	20.5 ± 0.6	21.0 ± 0.5	20.5 ± 0.6	19.9 ± 1.1	18.6 ± 1.2
Brain					
Absolute	0.513 ± 0.015	0.495 ± 0.011	0.480 ± 0.012	0.511 ± 0.014	0.505 ± 0.017
Relative to body weight	25.16 ± 1.08	23.58 ± 0.29	23.51 ± 0.64	25.75 ± 0.69	27.55 ± 2.06
Heart					
Absolute	0.140 ± 0.009	0.129 ± 0.006	0.135 ± 0.010	0.134 ± 0.010	0.127 ± 0.008
Relative to brain weight	0.272 ± 0.012	0.260 ± 0.015	0.280 ± 0.017	0.261 ± 0.017	0.252 ± 0.013
Relative to body weight	6.86 ± 0.58	6.13 ± 0.28	6.56 ± 0.35	6.70 ± 0.35	6.95 ± 0.62
L. Kidney					
Absolute	0.155 ± 0.005	0.141 ± 0.002	0.155 ± 0.009	0.145 ± 0.014	0.149 ± 0.005
Relative to brain weight	0.301 ± 0.006	0.285 ± 0.005	0.322 ± 0.018	0.282 ± 0.019	0.296 ± 0.012
Relative to body weight	7.57 ± 0.27	6.72 ± 0.17	7.54 ± 0.23	7.22 ± 0.30	8.18 ± 0.85
R. Kidney					
Absolute	0.166 ± 0.006	0.147 ± 0.003	0.158 ± 0.011	0.161 ± 0.005	0.161 ± 0.009
Relative to brain weight	0.324 ± 0.008	0.296 ± 0.005	0.327 ± 0.016	0.315 ± 0.007	0.319 ± 0.013
Relative to body weight	8.12 ± 0.25	6.98 ± 0.04	7.68 ± 0.32	8.10 ± 0.26	8.87 ± 1.05
Liver					
Absolute	0.834 ± 0.038	0.822 ± 0.028	0.829 ± 0.043	0.792 ± 0.059	0.802 ± 0.037
Relative to brain weight	1.630 ± 0.086	1.662 ± 0.052	1.727 ± 0.082	1.544 ± 0.073	1.587 ± 0.034
Relative to body weight	40.75 ± 0.90	39.14 ± 0.75	40.45 ± 0.95	39.60 ± 0.76	43.90 ± 4.21

[a] Organ weights (absolute weights) and body weights are given in grams; organ-weight-to-brain-weight ratios (relative weights) are given as g organ weight/g brain weight (mean ± standard error); organ-weight-to-body-weight ratios (relative weights) are given as mg organ weight/g body weight (mean ± standard error).

[b] n=3

TABLE G14
Organ Weights and Organ-Weight-to-Brain-Weight and Organ-Weight-to-Body-Weight Ratios for Mice in the 2-Year Feed Study of Fumonisin B_1[a]

	0 ppm	5 ppm	15 ppm	80 ppm	150 ppm
Male					
n	41	39	45	37	42
Necropsy body wt	32.1 ± 0.4	32.1 ± 0.3	31.9 ± 0.3	32.9 ± 0.3	31.6 ± 0.5
Brain					
Absolute	0.502 ± 0.004	0.488 ± 0.005	0.494 ± 0.008	0.502 ± 0.005	0.494 ± 0.005
Relative to body weight	15.705 ± 0.195	15.273 ± 0.211	15.520 ± 0.250	15.319 ± 0.176	15.795 ± 0.277
Heart					
Absolute	0.190 ± 0.004	0.190 ± 0.005	0.183 ± 0.004	0.191 ± 0.004	0.181 ± 0.003
Relative to brain weight	0.378 ± 0.007	0.390 ± 0.010	0.374 ± 0.009	0.382 ± 0.008	0.369 ± 0.008
Relative to body weight	5.923 ± 0.112	5.928 ± 0.146	5.761 ± 0.124	5.836 ± 0.117	5.815 ± 0.165
L. Kidney					
Absolute	0.270 ± 0.006	0.271 ± 0.005	0.260 ± 0.005	0.292 ± 0.006*	0.261 ± 0.006
Relative to brain weight	0.539 ± 0.012	0.558 ± 0.012	0.530 ± 0.011	0.581 ± 0.012*	0.531 ± 0.014
Relative to body weight	8.416 ± 0.146	8.454 ± 0.126	8.142 ± 0.117	8.853 ± 0.140*	8.288 ± 0.163
R. Kidney					
Absolute	0.284 ± 0.006	0.285 ± 0.007	0.275 ± 0.005	0.306 ± 0.006*	0.276 ± 0.006
Relative to brain weight	0.567 ± 0.012	0.586 ± 0.015	0.561 ± 0.012	0.609 ± 0.012*	0.560 ± 0.015
Relative to body weight	8.859 ± 0.167	8.859 ± 0.171	8.609 ± 0.126	9.282 ± 0.149	8.754 ± 0.176
Liver					
Absolute	1.508 ± 0.088	1.449 ± 0.087	1.382 ± 0.060	1.533 ± 0.086	1.434 ± 0.098
Relative to brain weight	3.015 ± 0.181	2.976 ± 0.177	2.818 ± 0.126	3.072 ± 0.185	2.922 ± 0.214
Relative to body weight	47.20 ± 2.95	45.30 ± 2.90	43.48 ± 2.00	46.82 ± 2.84	45.80 ± 3.49
L. Testis					
Absolute	0.098 ± 0.002	0.099 ± 0.002	0.100 ± 0.002	0.100 ± 0.001	0.099 ± 0.001
Relative to brain weight	0.197 ± 0.005	0.204 ± 0.004	0.205 ± 0.004	0.199 ± 0.003	0.201 ± 0.003
Relative to body weight	3.078 ± 0.073	3.103 ± 0.053	3.149 ± 0.043	3.040 ± 0.046	3.163 ± 0.044
R. Testis					
Absolute	0.101 ± 0.002	0.104 ± 0.001	0.102 ± 0.001	0.101 ± 0.001	0.102 ± 0.002
Relative to brain weight	0.201 ± 0.005	0.213 ± 0.003*	0.209 ± 0.004	0.203 ± 0.003	0.207 ± 0.003
Relative to body weight	3.146 ± 0.073	3.231 ± 0.041	3.208 ± 0.040	3.096 ± 0.045	3.254 ± 0.056

TABLE G14
Organ Weights and Organ-Weight-to-Brain-Weight and Organ-Weight-to-Body-Weight Ratios for Mice in the 2-Year Feed Study of Fumonisin B_1

	0 ppm	5 ppm	15 ppm	50 ppm	80 ppm
Female					
n	35	44	46	39	28
Necropsy body wt	27.4 ± 0.5	26.4 ± 0.3	26.3 ± 0.3	28.7 ± 0.6*	26.7 ± 0.6*
Brain					
Absolute	0.505 ± 0.005	0.510 ± 0.004[b]	0.506 ± 0.004[c]	0.514 ± 0.005	0.489 ± 0.006*
Relative to body weight	18.575 ± 0.315	19.426 ± 0.283[b]	19.350 ± 0.258[c]	18.087 ± 0.305	18.615 ± 0.459
Heart					
Absolute	0.145 ± 0.003	0.137 ± 0.002[b]	0.138 ± 0.003[c]	0.158 ± 0.007*	0.147 ± 0.005
Relative to brain weight	0.289 ± 0.007	0.270 ± 0.004[b]	0.274 ± 0.006[c]	0.307 ± 0.012	0.303 ± 0.012
Relative to body weight	5.345 ± 0.135	5.224 ± 0.086[b]	5.281 ± 0.106[c]	5.517 ± 0.204	5.555 ± 0.188
L. Kidney					
Absolute	0.198 ± 0.003	0.197 ± 0.004	0.190 ± 0.003	0.220 ± 0.005*	0.199 ± 0.005
Relative to brain weight	0.392 ± 0.007	0.385 ± 0.008[b]	0.378 ± 0.006[c]	0.428 ± 0.008*	0.407 ± 0.011
Relative to body weight	7.238 ± 0.118	7.452 ± 0.120	7.253 ± 0.109	7.723 ± 0.174*	7.476 ± 0.126
R. Kidney					
Absolute	0.208 ± 0.004	0.212 ± 0.005	0.203 ± 0.004	0.232 ± 0.006*	0.208 ± 0.004
Relative to brain weight	0.412 ± 0.008	0.417 ± 0.010[b]	0.403 ± 0.007[c]	0.451 ± 0.009*	0.428 ± 0.011
Relative to body weight	7.619 ± 0.139	8.056 ± 0.185	7.733 ± 0.128	8.126 ± 0.188*	7.873 ± 0.154
Liver					
Absolute	1.167 ± 0.028	1.214 ± 0.089	1.128 ± 0.038	1.632 ± 0.133*	3.258 ± 0.263*
Relative to brain weight	2.310 ± 0.055	2.382 ± 0.173	2.252 ± 0.078	3.154 ± 0.248*	6.727 ± 0.570*
Relative to body weight	42.70 ± 1.01	45.78 ± 3.07	42.95 ± 1.29	56.41 ± 4.24*	122.78 ± 9.72*

* Significantly different ($P \leq 0.05$) from the control group by a one-way analysis of variance with application of Dunnett's test

[a] Organ weights (absolute weights) and body weights are given in grams; organ-weight-to-brain-weight ratios (relative weights) are given as g organ weight/g brain weight (mean ± standard error); organ-weight-to-body-weight ratios (relative weights) are given as mg organ weight/g body weight (mean ± standard error).

[b] n=43

[c] n=45

APPENDIX H
CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

PROCUREMENT AND CHARACTERIZATION OF FUMONISIN B_1

Fumonisin B_1 was obtained from the Center for Food Safety and Applied Nutrition (CFSAN) (Food and Drug Administration, Washington, DC) in three lots (E12-27-1, E12-83, and E12-89). Lot E12-27-1 (a fumonisin B_1 free acid) was used during the 28-day studies, and lots E12-83 and E12-89 were used during the 2-year studies. Based on the purity analyses of lot E12-27-1, lots E12-83 and E12-89 were purified as an ammonium salt from cultures of *Fusarium proliferatum* at CFSAN. Identity and purity analyses were conducted by the study laboratory.

All lots of the compound were identified through structural confirmation as fumonisin B_1 by ^{1}H- and ^{13}C-nuclear magnetic resonance (NMR) spectroscopy. For the 2-year studies, both spectra were consistent with the literature reference (Bezuidenhout *et al*., 1988) of fumonisin B_1; the NMR spectra are presented in Figures H1 and H2. NMR analyses of lot E12-27-1 confirmed that the major component of lot E12-27-1 was the same as a South African fumonisin B_1 standard (PROMEC, C/93). Mass spectral analysis of all lots confirmed the presence of a compound with mass fragmentation characteristics of fumonisin B_1. The solubility of lot E12-27-1 in deionized water was determined to be approximately 20 mg/mL.

The purity of lots E12-27-1, E12-83, and E12-89 was determined by elemental analyses (lots E12-27-1 and E12-83), Karl Fischer water analysis, ^{1}H-NMR spectroscopy, and high-performance liquid chromatography (HPLC). Trace metals analyses for 39 elements were performed using inductively coupled plasma atomic emission spectrometry. For lot E12-27-1, HPLC was performed with a Rainin Microsorb C_8, 250 mm × 4.6 mm column following derivatization of fumonisin B_1 with (9-fluorenylmethyl) chloroformate and using fluorescence detection (Holcomb *et al*., 1993a). For lots E12-83 and E12-89, HPLC was performed with a Rainin Microsorb C_8, 250 mm × 4.6 mm column with 5µm film using evaporative light-scattering detection (ELSD) or ultraviolet detection (210 nm) (Wilkes *et al*., 1995).

The following elements were detected at concentrations above the limit of quantitation in lot E12-27-1: copper (4.9 ppm), zinc (15.9 ppm), silicon (368 ppm), calcium (125 ppm), magnesium (51.8 ppm), iron (25 ppm), nickel (6.2 ppm), tin (12.5 ppm), barium (0.6 ppm), and strontium (0.8 ppm). The following elements were detected at concentrations above the limit of quantitation in lot E12-83: tin (7.9 ppm), selenium (7.0 ppm), boron (6.0 ppm), zinc (5.0 ppm), silicon (3.2 ppm), magnesium (2.2 ppm), calcium (1.7 ppm), molybdenum (1.7 ppm), nickel (1.4 ppm), and copper (0.63 ppm). Karl Fischer water analysis indicated 0.10% water for lot E12-27-1, 0.00% water for lot E12-83, and 0.04% water for lot E12-89. HPLC using fluorescence detection indicated a purity of 92.0% ± 0.3% for lot E12-27-1, and HPLC using ELSD indicated a purity of 96.9% ± 0.6% for lot E12-83 and 97.6% ± 0.2% for lot E12-89. ^{1}H-NMR spectroscopy indicated a purity of 92% for lot E12-27-1 with pyridine detected as an impurity. HPLC with photodiode array detection was used to quantify pyridine in lots E12-27-1 and E12-83. HPLC indicated the presence of 0.51% pyridine in lot E12-27-1, and pyridine was not present at the 50 ppb limit of detection in lot E12-83. The overall purity was determined to be 92% for lot E12-27-1, greater than 96% for lot E12-83, and greater than 97% for lot E12-89. Lot E12-27-1 was used to prepare diets for the 28-day studies, and lots E12-83 and E12-89 were used to prepare diets for the 2-year studies.

Fumonisin B_1 was stored at room temperature in a dry and inert atmosphere; there was no apparent degradation of the fumonisin B_1 during the course of the study.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

The dose formulations were prepared once for the 28-day studies and as needed during the 2-year studies by mixing fumonisin B_1 with feed (Table H1). NIH-31 feed was obtained from Purina Corporation (St. Louis, MO). This feed is an open formulation that contains approximately 20% corn by weight. Samples of the corn for the NIH-31 diet were sent from Purina Corporation to the study laboratory for analysis of fumonisin B_1 content using HPLC/mass spectroscopy (Doerge *et al*., 1994; Churchwell *et al*., 1997; Newkirk *et al*., 1998). Only corn samples containing less than 60 ppb fumonisin B_1 were accepted. Premixes of fumonisin B_1 and feed were prepared by dissolving the fumonisin B_1 in deionized water and adding autoclaved-powdered feed using a Patterson-Kelley V-blender so that the water content did not exceed 10% by weight. The premixes were then blended with autoclaved-powdered feed to achieve the desired fumonisin B_1 dose formulations. During the 28-day and 2-year studies, the dose formulations were stored in stainless steel cans at 4° to 8° C; dose formulations for the 2-year studies were stored for up to 16 weeks.

Homogeneity studies of 100 and 500 ppm formulations for the 28-day studies and of the 5 and 150 ppm dose formulations for the 2-year studies, and stability studies of a 100 ppm formulation for the 28-day studies and of the 5 ppm dose formulation for the 2-year studies, were performed by the study laboratory using HPLC. HPLC was performed with a RP C_8, 25 cm × 4.6 mm column with 5 μ particle size using fluorescence detection (excitation 390 nm, emission 475 nm) and a solvent system of A) acetonitrile:1% aqueous acetic acid (30:70) and B) acetonitrile:1% aqueous acetic acid (70:30), 90:10 A:B initially, 80:20 for 3 minutes, 65:35 for 14 minutes, 45:55 for 1 minute, 30:70 for 2 minutes, and 100 % B for 5 minutes, at a flow rate of 1.5 mL/minute. Fumonisin B_1 contained in the diets was determined using established standard operating procedures, and consisted of extracting 50 g of feed with acetonitrile:water (1:1) followed by derivatization of fumonisin B_1 with (9-fluorenylmethyl) chloroformate and detection using HPLC-fluorescence techniques (Holcomb *et al*., 1993b). Homogeneity was confirmed; stability of the 100 ppm formulation was confirmed for up to 16 weeks for dose formulations stored in stainless steel cans at 2° to 6° C and for up to 14 days when stored at room temperature, open to air and light. Stability of the 5 ppm dose formulation was confirmed for up to 16 weeks for dose formulations stored in stainless steel cans at 4° to 8° C and for up to 30 days when stored at room temperature, open to air and light.

Prior to the start of the 28-day studies, the dose formulations were analyzed at the study laboratory with the HPLC system used for the homogeneity studies. The exposure concentrations for the 28-day studies were determined to be 99, 163, 234, and 484 ppm. Because single mixes of the dose formulations were made for the 28-day studies, the dose formulations were accepted as mixed. Dose formulations of fumonisin B_1 used in the 2-year studies were analyzed approximately every 1 to 4 weeks at the study laboratory with the HPLC system used for the homogeneity studies (Table H2). The acceptable deviations from the target concentrations were 5 ± 2 ppm, 15 ± 3 ppm, 50 ± 5 ppm, 80 ± 8 ppm, 100 ± 10 ppm, and 150 ± 15 ppm. During the 2-year studies, 96% (152/158) of the dose formulations for rats and 99% (149/151) of the dose formulations for mice were within the acceptable target concentration range. The dose formulations that were outside the acceptable range were used due to the limited availability of fumonisin B_1.

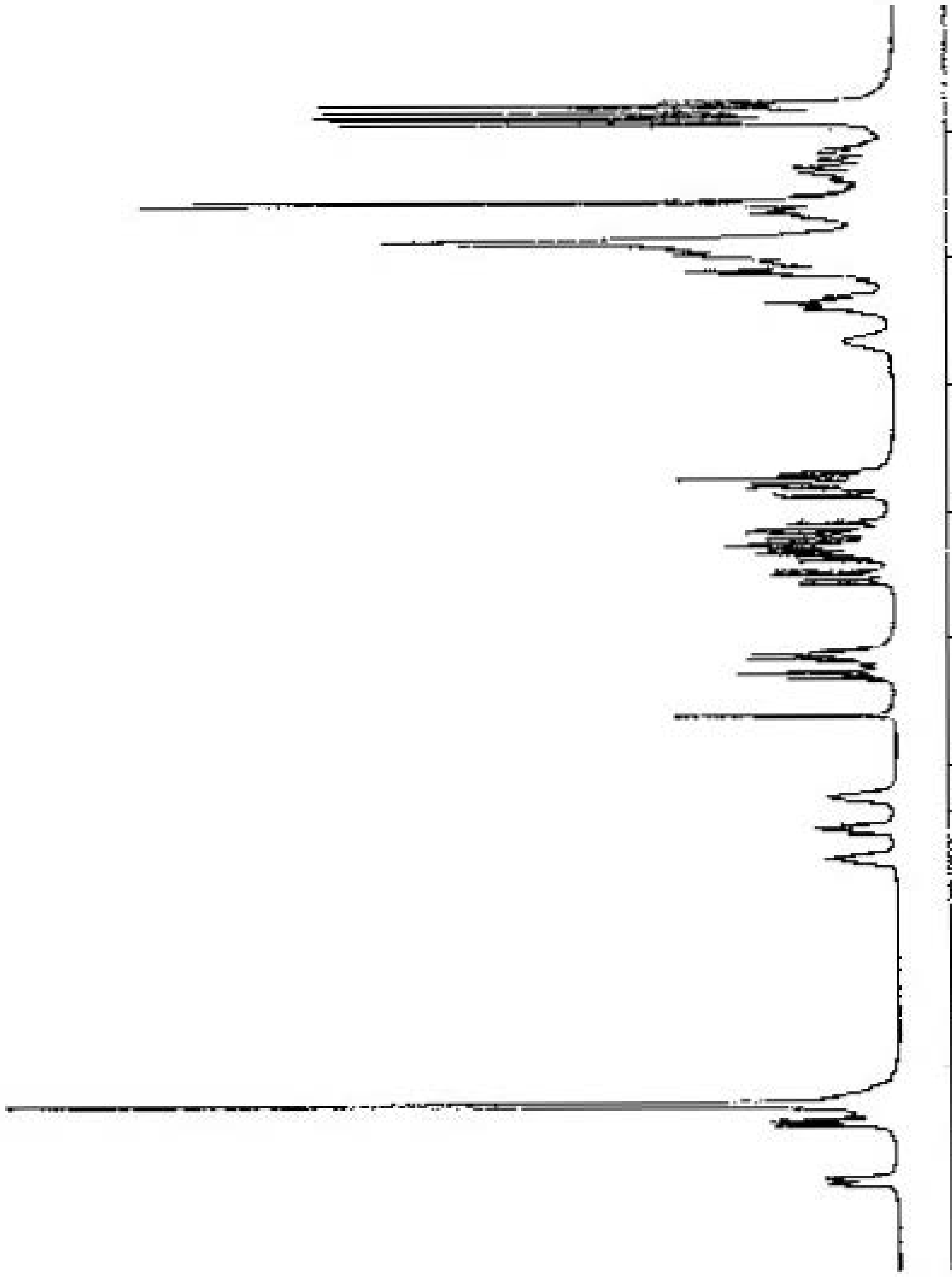

FIGURE H1
^{1}H-Nuclear Magnetic Resonance Spectrum of Fumonisin B_1

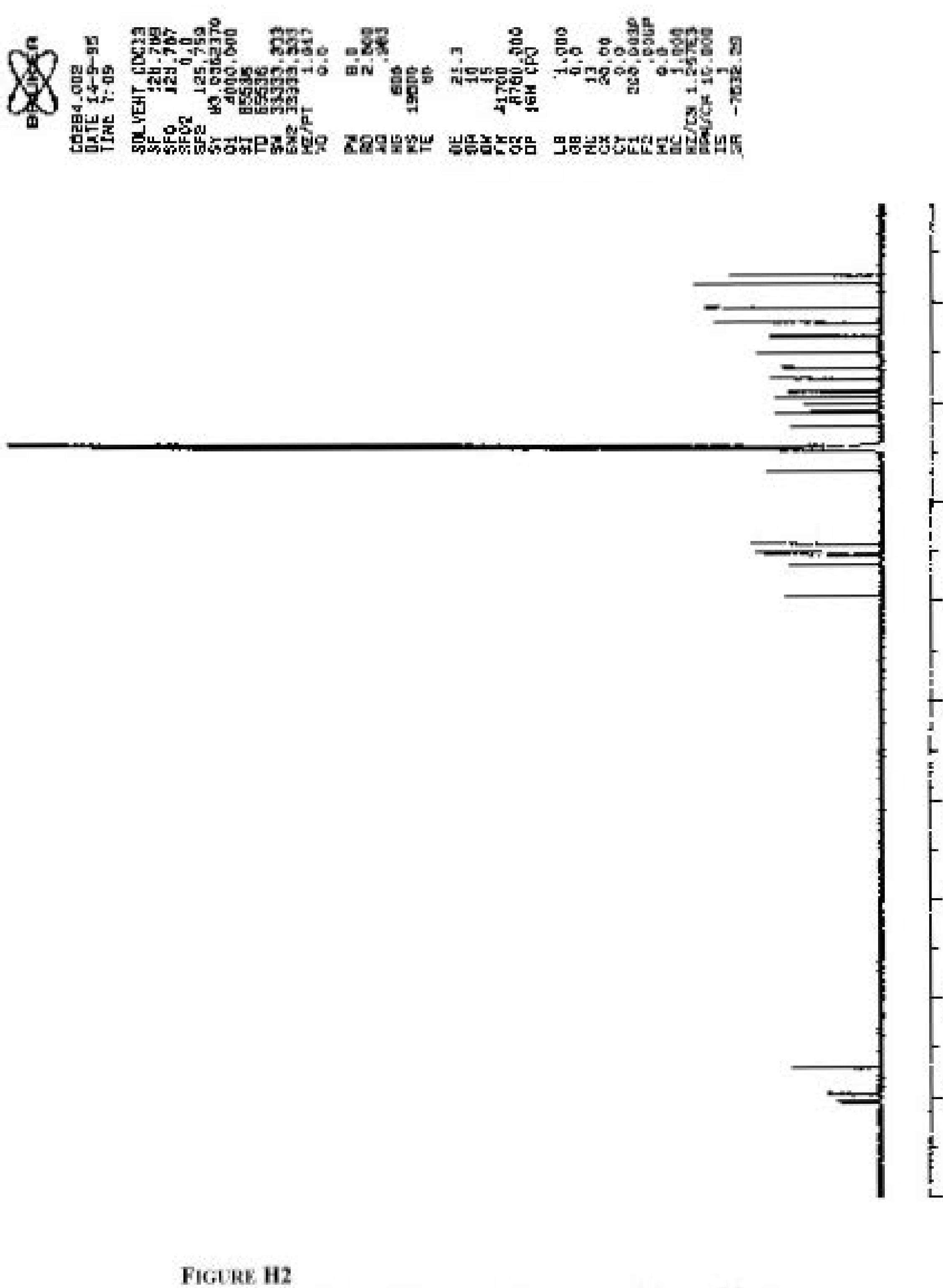

FIGURE H2
^{13}C-Nuclear Magnetic Resonance Spectrum of Fumonisin B_1

Table H1
Preparation and Storage of Dose Formulations in the Feed Studies of Fumonisin B_1

28-Day Studies	2-Year Studies
Preparation	
A premix of feed and fumonisin B_1 was prepared by dissolving the fumonisin B_1 in deionized water and adding autoclaved-powdered feed using a Patterson-Kelly V-blender until the water content did not exceed 10% by weight. The premixes were then blended with autoclaved-powdered feed to achieve the desired fumonisin B_1 dose formulations. Dose formulations were prepared once.	Same as 28-day studies. Dose formulations were prepared as needed.
Chemical Lot Number	
E12-27-1	E12-83 and E12-89
Maximum Storage Time	
4 Weeks	17 Weeks
Storage Conditions	
Stored in stainless steel cans at 2° to 8° C.	Same as 28-day studies
Study Laboratory	
National Center for Toxicological Research (Jefferson, AR)	National Center for Toxicological Research (Jefferson, AR)

Table H2
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 2-Year Feed Studies of Fumonisin B_1

Date Prepared	Date Analyzed	Target Concentration[a] (ppm)	Determined Concentration[b] (ppm)	Difference from Target (%)
Rats				
9 February 1995	19-24 February 1995	5	5.3	+6
		15	15.0	0
		50	47.2	−6
		100	109.0	+9
		150	149.7	0
28 March 1995	31 March or 3 April 1995	5	5.4	+8
		15	15.1	+1
		50	53.8	+8
12 April 1995	13-19 April 1995	5	5.2	+4
		15	14.7	−2
		50	53.2	+6
		100	102.3	+2
		150	149.7	0
19 April 1995	23-24 April 1995	5	5.2	+4
		15	14.4	−4
		50	48.7	−3
		100	99.2	−1
		150	155.8	+4
26 or 30 April 1995	2-5 May 1995	5	5.3	+6
		15	15.7	+5
		50	52.6	+5
		100	101.1	+1
		150	147.6	−2
15-17 May 1995	18-19 May or 1 June 1995	5	4.3	−14
		15	15.1	+1
		15	15.2	+1
		50	49.7	−1
		50	47.8	−4
9 or 14 June 1995	15-28 June or 7 July 1995	5	4.6	−8
		15	15.7	+5
		15	13.8	−8
		50	57.5	+15
		100	91.7	−8
		150	149.0	−1
27 June 1995	30 June or 7 July 1995	5	5.6	+12
		50	52.4	+5
		50	51.9	+4

Table H2
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 2-Year Feed Studies of Fumonisin B_1

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration (ppm)	Difference from Target (%)
Rats (continued)				
11 or 17 July 1995	14 or 21 July 1995	5	5.7	+14
		15	16.1	+7
		50	49.0	−2
		150	150.8	+1
1 August 1995	4 August 1995	15	16.1	+7
		100	105.0	+5
		150	156.0	+4
15 August 1995	22 August 1995	5	5.8	+16
		15	15.6	+4
		50	48.7	−3
5-6 September 1995	8-14 September 1995	5	5.8	+16
		15	14.3	−5
		50	46.2	−8
		100	111.9	+12
		150	164.3	+10
18 September 1995	22-29 September or 6 October 1995	5	6.2	+24
		15	15.3	+2
		50	51.5	+3
		100	101.6	+2
10 or 19 October 1995	20-27 October or 3 November 1995	5	6.7	+34
		15	14.0	−7
		15	16.1	+7
		50	48.5	−3
		100	93.0	−7
		150	154.4	+3
6 or 9 November 1995	9-21 November 1995	5	6.0	+20
		15	15.6	+4
		50	54.9	+10
21 November 1995	30 November or 4-8 December 1995	5	5.7	+14
		15	14.4	−4
		50	47.5	−5
		150	150.4	0
8 December 1995	13-21 December 1995	5	6.6	+32
		15	16.3	+9
		50	49.6	−1
		100	101.0	+1

TABLE H2
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 2-Year Feed Studies of Fumonisin B_1

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration (ppm)	Difference from Target (%)
Rats (continued)				
28-29 December 1995	8 or 16 January 1996	5	6.6	+32
		15	13.6	−9
		50	50.6	+1
		150	136.8	−9
8 January 1996	24 January 1996	100	100.0	0
15 or 17 January 1996	29-30 January 1996	5	6.5	+30
		15	13.7	−9
		50	52.7	+5
25 or 30 January 1996	16 or 20 February 1996	50	49.1	−2
		50	55.3	+11
		100	101.2	+1
		150	149.0	−1
13 February 1996	23 February or 4 March 1996	5	5.2	+4
		15	14.6	−3
		15	14.0	−7
23 February 1996	4 or 7 March 1996	5	4.9	−2
		15	14.3	−5
7 March 1996	18-22 March 1996	15	16.2	+8
		50	54.5	+9
		50	54.9	+10
		100	107.3	+7
		150	158.3	+6
19 March 1996	4 April 1996	5	5.8	+16
		15	15.8	+5
10 or 12 April 1996	19-25 April 1996	5	5.0	0
		15	14.6	−3
		50	49.0	−2
		100	112.1	+12
		150	144.0	−4
19 April 1996	3 or 13 May 1996	5	5.2	+4
		15	14.7	−2
		50	49.4	−1
8 May 1996	16 or 24 May 1996	50	57.5	+15
		50	51.6	+3
		100	91.5	−8
		150	136.8	−9

TABLE H2
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 2-Year Feed Studies of Fumonisin B_1

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration (ppm)	Difference from Target (%)
Rats (continued)				
21 May 1996	7 June 1996	5	5.7	+14
		15	14.5	−3
7 June 1996	13 or 18 June 1996	5	4.7	−6
		15	13.2	−12
		50	51.6	+3
18 June 1996	9 or 12 July 1996	50	50.9	+2
		100	107.5	+8
		150	147.3	−2
12, 16, or 19 July 1996	17-25 July or 1 August 1996	5	5.2	+4
		15	16.0	+7
		15	14.8	−1
		50	48.7	−3
		100	92.3	−8
		150	144.1	−4
26 July 1996	5 or 9 August 1996	5	4.4	−12
		50	49.2	−2
12 or 16 August 1996	16 August-11 September 1996	5	4.8	−4
		5	5.2	+4
		15	15.9	+6
		15	17.5	+17
		50	48.8	−2
		50	50.7	+1
		100	99.9	0
		150	143.2	−5
24 September 1996	1 or 4 October 1996	15	13.6	−9
		15	13.7	−9
		50	50.8	+2
4 October 1996	11 or 17 October 1996	100	97.4	−3
		150	161.3	+8
15 October 1996	25 or 29 October 1996	5	4.9	−2
		5	4.2	−16
		50	50.8	+2
5 November 1996	7 November 1996	15	14.3	−5
		15	13.5	−10

TABLE H2
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 2-Year Feed Studies of Fumonisin B_1

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration (ppm)	Difference from Target (%)
Rats (continued)				
13 or 18 November 1996	15-22 November 1996	5	5.3	+6
		5	4.6	−8
		50	47.6	−5
		100	94.9	−5
		150	146.1	−3
3 December 1996	12 December 1996	50	44.9	−10
10 or 12 December 1996	13-16 December 1996 or 17 January 1997	5	5.1	+2
		15	13.9	−7
		15	13.4	−11
		50	46.5	−7
		100	97.0	−3
		150	150.0	0
14 or 21 January 1997	17-31 January 1997	5	5.0	0
		15	13.8	−8
		15	14.3	−5
		50	48.7	−3
30 January 1997	11-12 February 1997	50	48.8	−2
		100	93.0	−7
		150	155.5	+4
4 February 1997	20 February 1997	5	4.9	−2
24 March 1997	1-14 April 1997	15	12.4	−17
		50	47.0	−6
		150	150.6	0

TABLE H2
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 2-Year Feed Studies of Fumonisin B_1

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration (ppm)	Difference from Target (%)
Mice				
9 February 1995	19 or 24 February 1995	5	5.3	+6
		15	15.0	0
		50	47.2	–6
		150	149.7	0
3 March 1995	7 March 1995	80	76.8	–4
28 March 1995	31 March or 3 April 1995	5	5.4	+8
		15	15.1	+1
		50	53.8	+8
12 April 1995	13-19 April 1995	5	5.2	+4
		15	14.7	–2
		50	53.2	+6
		150	149.7	0
19 April 1995	23-24 April 1995	5	5.2	+4
		15	14.4	–4
		50	48.7	–3
		150	155.8	+4
26 or 30 April 1995	2-9 May 1995	5	5.3	+6
		15	15.7	+5
		50	52.6	+5
		80	83.2	+4
		150	147.6	–2
15-17 May 1995	18-19 May or 1 June 1995	5	4.3	–14
		15	15.1	+1
		15	15.2	+1
		50	49.7	–1
		50	47.8	–4
9 or 14 June 1995	15-28 June or 7 July 1995	5	4.6	–8
		15	15.7	+5
		15	13.8	–8
		50	57.5	+15
		80	75.4	–6
		150	149.0	–1
27 June 1995	30 June or 7 July 1995	5	5.6	+12
		50	52.4	+5
		50	51.9	+4

TABLE H2
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 2-Year Feed Studies of Fumonisin B_1

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration (ppm)	Difference from Target (%)
Mice (continued)				
11 or 17 July 1995	14 or 21 July 1995	5	5.7	+14
		15	16.1	+7
		50	49.0	–2
		150	150.8	+1
1 August 1995	4 August 1995	15	16.1	+7
		150	156.0	+4
15 August 1995	22 August 1995	5	5.8	+16
		15	15.6	+4
		50	48.7	–3
30 August 1995	1 September 1995	80	88.0	+10
5-6 September 1995	8-14 September 1995	5	5.8	+16
		15	14.3	–5
		50	46.2	–8
		150	164.3	+10
18 September 1995	29 September or 6 October 1995	5	6.2	+24
		15	15.3	+2
		50	51.5	+3
		80	81.0	+1
10 or 19 October 1995	20-27 October 1995	5	6.7	+34
		15	14.0	–7
		15	16.1	+7
		50	48.5	–3
		80	76.3	–5
		150	154.4	+3
6 or 9 November 1995	9-21 November 1995	5	6.0	+20
		15	15.6	+4
		50	54.9	+10
21 or 27 November 1995	30 November or 4-8 December 1995	5	5.7	+14
		15	14.4	–4
		50	47.5	–5
		80	79.1	–1
		150	150.4	0
8 December 1995	19 or 21 December 1995	5	6.6	+32
		15	16.3	+9
		50	49.6	–1

TABLE H2
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 2-Year Feed Studies of Fumonisin B_1

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration (ppm)	Difference from Target (%)
Mice (continued)				
28-29 December 1995	8 or 16 January 1996	5	6.6	+32
		15	13.6	−9
		50	50.6	+1
		150	136.8	−9
15 or 17 January 1996	29-30 January 1996	5	6.5	+30
		15	13.7	−9
		50	52.7	+5
25 or 30 January 1996	9-20 February 1996	50	49.1	−2
		50	55.3	+11
		80	76.3	−5
		150	149.0	−1
13 February 1996	23 February or 4 March 1996	5	5.2	+4
		15	14.6	−3
		15	14.0	−7
23 February 1996	4 or 7 March 1996	5	4.9	−2
		15	14.3	−5
7 March 1996	19 or 22 March 1996	15	16.2	+8
		50	54.5	+9
		50	54.9	+10
		150	158.3	+6
19 March 1996	4 April 1996	5	5.8	+16
		15	15.8	+5
5 April 1996	12 April 1996	80	81.7	+2
10 or 12 April 1996	19 or 23 April 1996	5	5.0	0
		15	14.6	−3
		50	49.0	−2
		150	144.0	−4
19 April 1996	3 or 13 May 1996	5	5.2	+4
		15	14.7	−2
		50	49.4	−1
8 May 1996	16 or 24 May 1996	50	57.5	+15
		50	51.6	+3
		150	136.8	−9

TABLE H2
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 2-Year Feed Studies of Fumonisin B_1

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration (ppm)	Difference from Target (%)
Mice (continued)				
21 May 1996	3 or 7 June 1996	5	5.7	+14
		15	14.5	−3
		80	72.2	−10
7 June 1996	13 or 18 June 1996	5	4.7	−6
		15	13.2	−12
		50	51.6	+3
18 June 1996	9 or 12 July 1996	50	50.9	+2
		150	147.3	−2
12, 16, or 19 July 1996	17-25 July or 1 August 1996	5	5.2	+4
		15	16.0	+7
		15	14.8	−1
		50	48.7	−3
		150	144.1	−4
26 or 30 July 1996	5 or 9 August 1996	5	4.4	−12
		50	49.2	−2
		80	76.8	−4
12 or 16 August 1996	16 August-11 September 1996	5	4.8	−4
		5	5.2	+4
		15	15.9	+6
		15	17.5	+17
		50	48.8	−2
		50	50.7	+1
		150	143.2	−5
24 September 1996	1 or 4 October 1996	15	13.6	−9
		15	13.7	−9
		50	50.8	+2
4 October 1996	11 or 17 October 1996	80	86.7	+8
		150	161.3	+8
15 October 1996	25 or 29 October 1996	5	4.9	−2
		5	4.2	−16
		50	50.8	+2
5 November 1996	7 November 1996	15	14.3	−5
		15	13.5	−10

TABLE H2
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 2-Year Feed Studies of Fumonisin B_1

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration (ppm)	Difference from Target (%)
Mice (continued)				
13 or 18 November 1996	15-22 November 1996	5	5.3	+6
		5	4.6	−8
		50	47.6	−5
		80	72.3	−10
		150	146.1	−3
3 December 1996	12 December 1996	50	44.9	−10
10 or 12 December 1996	13-16 December 1996 or 17 January 1997	5	5.1	+2
		15	13.9	−7
		15	13.4	−11
		50	46.5	−7
		150	150.0	0
14, 16, or 21 January 1997	17-31 January 1997	5	5.0	0
		15	13.8	−8
		15	14.3	−5
		50	48.7	-3
		80	84.7	+6
30 January 1997	11-12 February 1997	50	48.8	−2
		150	155.5	+4
4 February 1997	20 February 1997	5	4.9	−2
24 March 1997	1-14 April 1997	15	12.4	−17
		50	47.0	−6
		80	77.6	−3
		150	150.6	0

[a] Acceptable target concentration ranges are 5 ± 2 ppm, 15 ± 3 ppm, 50 ± 5 ppm, 80 ± 8 ppm, 100 ± 10 ppm, and 150 ± 15 ppm.
[b] Results of triplicate analyses

APPENDIX I
FEED AND COMPOUND CONSUMPTION OF FUMONISIN B_1

TABLE I1
Feed and Compound Consumption by Male Rats at the 6-, 10-, 14-, and 26-Week Evaluations in the Feed Study of Fumonisin B_1

	0 ppm		5 ppm			15 ppm		
Week	Feed (g)[a]	Body Weight (g)	Feed (g)	Body Weight (g)	Dose (mg/kg)[b]	Feed (g)	Body Weight (g)	Dose (mg/kg)
2	20.47	121.51	20.00	121.27	0.82	21.22	116.52	2.73
3	18.15	151.49	16.93	150.43	0.56	20.55	148.49	2.08
4	17.06	184.56	19.27	183.79	0.52	16.26	187.80	1.30
5	18.69	209.51	19.71	214.56	0.46	16.85	213.46	1.18
6	17.64	234.51	16.64	229.14	0.36	16.74	229.18	1.10
7	17.57	254.49	18.43	247.59	0.37	18.10	240.05	1.13
8	16.21	264.83	17.56	264.19	0.33	17.83	261.18	1.02
9	17.87	280.41	18.02	279.47	0.32	16.96	273.53	0.93
10	19.19	307.30	17.75	291.43	0.30	19.36	296.81	0.98
11	19.39	319.09	19.27	305.18	0.32	19.12	313.33	0.92
12	20.13	330.71	18.14	321.33	0.28	17.54	312.26	0.84
13	20.19	346.31	18.27	331.95	0.28	22.16	323.66	1.03
14	19.98	355.28	21.88	339.27	0.32	16.98	320.97	0.79
16	20.14	356.01	18.45	341.39	0.27	18.13	329.00	0.83
20	21.92	406.86	19.23	387.43	0.25	18.67	341.98	0.82
24	21.99	435.87	19.99	412.54	0.24	18.95	365.66	0.78
26	22.33	447.60	20.79	430.43	0.24	17.05	364.43	0.70

TABLE I1
Feed and Compound Consumption by Male Rats at the 6-, 10-, 14-, and 26-Week Evaluations in the Feed Study of Fumonisin B_1

	50 ppm			150 ppm		
Week	Feed (g)	Body Weight (g)	Dose (mg/kg)	Feed (g)	Body Weight (g)	Dose (mg/kg)
2	22.48	120.73	9.31	21.77	119.34	27.36
3	16.86	153.41	5.50	18.34	147.54	18.64
4	18.41	179.53	5.13	17.49	178.98	14.66
5	17.15	208.47	4.11	19.28	204.36	14.15
6	16.76	226.16	3.71	17.47	219.17	11.95
7	18.05	241.53	3.74	16.77	235.46	10.68
8	17.81	253.88	3.51	16.31	252.12	9.70
9	17.37	270.54	3.21	16.87	271.29	9.33
10	15.97	271.20	2.95	16.59	282.10	8.82
11	16.54	285.98	2.89	18.14	295.20	9.22
12	17.45	300.04	2.91	18.91	309.85	9.15
13	18.46	311.94	2.96	18.40	318.58	8.66
14	18.73	321.40	2.91	18.62	324.10	8.62
16	18.76	322.12	2.91	18.47	328.54	8.43
20	19.99	362.34	2.76	20.50	376.18	8.17
24	21.71	388.90	2.79	21.48	403.34	7.99
26	20.28	407.45	2.49	19.93	418.23	7.15

[a] Grams of feed consumed per animal per day
[b] Milligrams of fumonisin B_1 consumed per kilogram body weight per day

TABLE I2
Feed and Compound Consumption by Female Rats at the 6-, 10-, 14-, and 26-Week Evaluations in the Feed Study of Fumonisin B_1

	0 ppm		5 ppm			15 ppm		
Week	Feed (g)[a]	Body Weight (g)	Feed (g)	Body Weight (g)	Dose (mg/kg)[b]	Feed (g)	Body Weight (g)	Dose (mg/kg)
2	16.00	109.33	15.42	108.68	0.71	15.38	106.77	2.16
3	13.25	124.13	13.07	122.79	0.53	13.03	122.48	1.60
4	12.87	136.36	13.36	135.91	0.49	12.71	134.91	1.41
5	12.35	146.29	12.79	147.21	0.43	12.54	144.80	1.30
6	12.60	153.97	12.76	154.06	0.41	12.06	152.40	1.19
7	12.89	161.37	12.73	160.75	0.40	12.33	160.26	1.15
8	13.24	168.41	13.43	168.63	0.40	13.02	169.87	1.15
9	13.04	173.48	12.54	173.07	0.36	12.33	173.98	1.06
10	13.33	178.44	13.92	177.66	0.39	12.63	181.90	1.04
11	14.06	181.73	13.50	180.71	0.37	13.76	185.48	1.11
12	13.43	186.15	13.17	186.25	0.35	13.10	189.60	1.04
13	12.93	191.26	13.66	190.33	0.36	13.17	195.21	1.01
14	13.80	193.05	12.81	197.65	0.32	12.63	191.75	0.99
16	13.30	194.75	13.76	194.38	0.35	12.89	197.67	0.98
20	15.69	209.34	13.93	211.80	0.33	14.58	207.14	1.06
24	14.18	219.95	13.85	220.78	0.31	13.38	215.62	0.93
26	13.56	223.00	14.78	225.33	0.33	13.30	220.50	0.90

TABLE I2
Feed and Compound Consumption by Female Rats at the 6-, 10-, 14-, and 26-Week Evaluations in the Feed Study of Fumonisin B_1

	50 ppm			100 ppm		
Week	Feed (g)	Body Weight (g)	Dose (mg/kg)	Feed (g)	Body Weight (g)	Dose (mg/kg)
2	14.86	106.93	6.95	14.91	108.68	13.72
3	12.48	122.83	5.08	12.86	121.54	10.58
4	12.32	135.04	4.56	12.72	133.85	9.50
5	12.59	144.72	4.35	12.79	144.91	8.83
6	12.10	150.40	4.02	12.12	150.09	8.07
7	12.25	157.93	3.88	12.15	157.28	7.72
8	13.17	164.87	3.99	12.42	164.43	7.55
9	12.51	169.05	3.70	12.37	168.60	7.34
10	13.32	176.29	3.78	13.78	173.58	7.94
11	13.25	175.51	3.77	13.62	175.44	7.76
12	13.75	179.14	3.84	12.79	180.49	7.09
13	13.20	182.85	3.61	12.82	183.14	7.00
14	12.95	184.38	3.51	11.50	184.40	6.24
16	13.22	185.37	3.57	12.69	185.87	6.83
20	16.20	197.32	4.11	14.93	194.81	7.66
24	15.33	207.84	3.69	15.12	203.63	7.43
26	15.39	211.15	3.64	15.15	206.85	7.32

[a] Grams of feed consumed per animal per day
[b] Milligrams of fumonisin B_1 consumed per kilogram body weight per day

TABLE I3
Feed and Compound Consumption by Male Mice at the 3-, 7-, 9-, and 24-Week Evaluations in the Feed Study of Fumonisin B_1

	0 ppm		5 ppm			15 ppm		
Week	Feed (g)[a]	Body Weight (g)	Feed (g)	Body Weight (g)	Dose (mg/kg)[b]	Feed (g)	Body Weight (g)	Dose (mg/kg)
2	3.66	21.32	3.66	21.68	0.84	3.88	21.76	2.68
3	3.12	22.66	3.36	23.22	0.72	3.22	22.96	2.11
4	3.87	24.10	3.51	24.20	0.72	3.37	23.57	2.15
5	3.93	24.93	3.68	25.50	0.72	3.77	25.02	2.26
6	3.80	25.14	3.71	25.81	0.72	3.55	25.17	2.12
7	4.07	26.11	3.42	25.48	0.67	3.55	25.56	2.08
8	4.38	25.21	3.54	25.24	0.70	3.85	25.61	2.25
9	1.81	27.48	4.54	27.43	0.83	3.98	25.33	2.36
10	4.23	27.78	5.04	28.95	0.87	3.26	24.18	2.02
11	3.62	28.43	3.66	30.13	0.61	4.30	28.75	2.24
12	4.05	30.73	3.32	29.43	0.56	3.05	28.00	1.63
16	4.17	30.74	3.70	30.29	0.61	3.71	28.96	1.92
20	3.83	30.60	3.95	32.28	0.61	3.78	30.65	1.85
24	3.64	30.83	3.76	32.32	0.58	3.51	31.41	1.68

TABLE I3
Feed and Compound Consumption by Male Mice at the 3-, 7-, 9-, and 24-Week Evaluations in the Feed Study of Fumonisin B_1

	80 ppm			150 ppm		
Week	Feed (g)	Body Weight (g)	Dose (mg/kg)	Feed (g)	Body Weight (g)	Dose (mg/kg)
2	3.99	21.71	14.72	3.84	21.37	26.99
3	3.67	23.46	12.51	3.40	23.34	21.87
4	3.71	24.03	12.36	3.57	23.93	22.37
5	3.55	24.88	11.43	3.64	24.37	22.41
6	3.76	25.30	11.89	3.69	25.00	22.12
7	3.94	25.98	12.15	3.49	25.30	20.68
8	4.58	25.88	14.17	3.51	24.96	21.09
9	4.11	26.25	12.53	3.79	26.00	21.89
10	3.59	25.48	11.27	3.29	25.08	19.66
11	3.98	27.18	11.71	3.77	27.55	20.51
12	3.14	27.13	9.26	3.57	27.75	19.29
16	3.80	28.41	10.71	4.56	28.97	23.61
20	4.25	30.30	11.23	4.53	31.14	21.82
24	4.03	30.54	10.56	3.89	30.68	19.03

[a] Grams of feed consumed per animal per day
[b] Milligrams of fumonisin B_1 consumed per kilogram body weight per day

TABLE I4
Feed and Compound Consumption by Female Mice at the 3-, 7-, 9-, and 24-Week Evaluations in the Feed Study of Fumonisin B_1

	0 ppm		5 ppm			15 ppm		
Week	Feed (g)[a]	Body Weight (g)	Feed (g)	Body Weight (g)	Dose (mg/kg)[b]	Feed (g)	Body Weight (g)	Dose (mg/kg)
2	3.11	17.06	3.04	16.94	0.90	3.04	17.14	2.66
3	3.75	17.85	3.08	17.81	0.86	2.81	17.43	2.42
4	4.92	19.43	2.95	18.83	0.78	3.19	19.00	2.52
5	4.16	19.61	2.70	18.76	0.72	3.02	19.19	2.36
6	3.12	19.77	3.01	19.53	0.77	3.09	19.57	2.37
7	3.33	20.07	3.02	19.51	0.77	3.89	19.68	2.96
8	4.12	20.24	2.90	19.46	0.75	2.90	19.56	2.22
9	4.13	19.81	3.51	20.73	0.85	4.72	20.85	3.40
10	3.71	21.00	3.62	21.53	0.84	4.00	20.43	2.94
11	3.32	20.60	3.02	20.90	0.72	3.30	20.13	2.46
12	3.25	20.18	3.43	21.03	0.82	3.50	20.80	2.53
16	3.55	21.03	3.60	22.15	0.81	3.56	21.33	2.50
20	3.73	22.13	3.61	22.76	0.79	4.21	22.66	2.79
24	3.56	23.48	3.37	23.38	0.72	3.45	23.73	2.18

TABLE I4
Feed and Compound Consumption by Female Mice at the 3-, 7-, 9-, and 24-Week Evaluations in the Feed Study of Fumonisin B_1

	50 ppm			80 ppm		
Week	Feed (g)	Body Weight (g)	Dose (mg/kg)	Feed (g)	Body Weight (g)	Dose (mg/kg)
2	3.12	16.93	9.21	2.79	16.58	13.48
3	3.23	18.11	8.90	3.27	18.31	14.30
4	3.12	19.04	8.20	2.73	18.54	11.78
5	3.02	19.10	7.90	3.24	19.46	13.30
6	3.13	19.50	8.03	2.94	19.76	11.92
7	2.82	18.83	7.49	2.98	20.03	11.89
8	3.26	19.15	8.52	3.35	19.54	13.73
9	3.13	20.64	7.57	3.23	20.26	12.75
10	3.28	21.08	7.77	3.47	22.10	12.54
11	3.33	21.60	7.70	2.49	20.78	9.58
12	3.18	21.68	7.33	3.38	21.50	12.57
16	3.81	22.34	8.52	3.48	22.00	12.65
20	4.01	23.09	8.69	3.94	22.76	13.85
24	3.55	24.50	7.25	3.54	24.41	11.59

[a] Grams of feed consumed per animal per day
[b] Milligrams of fumonisin B_1 consumed per kilogram body weight per day

TABLE I5
Feed and Compound Consumption by Male Rats in the 2-Year Feed Study of Fumonisin B_1

	0 ppm		5 ppm			15 ppm		
Week	Feed (g)[a]	Body Weight (g)	Feed (g)	Body Weight (g)	Dose (mg/kg)[b]	Feed (g)	Body Weight (g)	Dose (mg/kg)
2	19.15	130.45	19.19	133.46	0.72	19.00	131.81	2.16
3	18.40	165.58	18.45	166.32	0.55	18.07	164.96	1.64
4	19.37	197.70	19.92	199.39	0.50	19.17	197.23	1.46
5	20.34	225.08	20.42	226.30	0.45	19.79	222.88	1.33
6	19.78	246.27	19.39	247.37	0.39	19.96	243.79	1.23
7	20.13	268.54	19.14	267.65	0.36	19.34	263.14	1.10
8	19.33	282.22	20.16	284.35	0.35	19.44	278.58	1.05
9	19.91	299.23	19.50	300.36	0.32	19.83	294.63	1.01
10	20.19	313.78	20.09	314.06	0.32	20.13	307.43	0.98
11	19.32	327.53	21.15	326.15	0.32	20.72	318.61	0.98
12	20.95	338.14	19.28	336.83	0.29	20.73	328.74	0.95
16	21.01	363.43	21.34	361.48	0.30	20.98	351.18	0.90
20	21.24	392.53	21.12	389.87	0.27	21.51	381.59	0.85
24	21.12	409.38	20.95	408.64	0.26	21.26	402.21	0.79
28	19.96	419.77	19.81	421.14	0.24	20.43	416.38	0.74
32	19.93	434.95	19.59	433.71	0.23	20.02	432.03	0.70
36	19.28	450.20	19.53	448.53	0.22	19.46	446.89	0.65
40	19.84	461.11	19.41	460.45	0.21	19.25	458.65	0.63
44	20.00	469.09	19.95	470.38	0.21	19.91	467.54	0.64
48	20.21	479.82	20.69	478.82	0.22	20.90	477.98	0.66
52	21.64	488.91	21.35	489.74	0.22	21.60	488.10	0.66
56	21.15	495.99	21.65	497.62	0.22	21.65	497.58	0.65
60	21.11	502.18	20.70	503.84	0.21	21.35	505.25	0.63
64	21.26	508.47	20.94	509.92	0.21	21.37	513.54	0.62
68	21.96	514.79	21.29	514.68	0.21	21.64	516.13	0.63
72	21.73	520.42	20.93	518.09	0.20	22.55	516.06	0.66
76	22.39	525.19	20.84	521.43	0.20	22.70	520.43	0.65
80	22.94	529.42	20.82	524.23	0.20	23.33	520.57	0.67
84	22.45	519.97	21.16	521.13	0.20	23.56	516.16	0.68
88	22.88	510.89	21.08	510.50	0.21	23.72	510.59	0.70
92	22.67	513.41	23.63	507.28	0.23	23.18	507.80	0.68
96	23.20	509.57	23.59	506.59	0.23	22.89	498.76	0.69
100	23.91	481.77	24.45	496.19	0.25	23.19	492.73	0.71
104	24.28	470.56	26.28	486.23	0.27	23.26	489.99	0.71
106	23.47	453.92	26.90	477.67	0.28	23.35	481.07	0.73
Mean for weeks								
2-13	19.72	254.05	19.70	254.75	0.42	19.65	250.16	1.26
14-52	20.42	436.92	20.37	436.28	0.24	20.53	432.26	0.72
53-106	22.53	504.04	22.45	506.81	0.22	22.70	506.19	0.67

TABLE I5
Feed and Compound Consumption by Male Rats in the 2-Year Feed Study of Fumonisin B_1

Week	50 ppm Feed (g)	50 ppm Body Weight (g)	50 ppm Dose (mg/kg)	150 ppm Feed (g)	150 ppm Body Weight (g)	150 ppm Dose (mg/kg)
2	19.23	128.63	7.47	19.36	133.51	21.75
3	17.55	161.39	5.44	17.19	164.63	15.66
4	19.33	192.18	5.03	18.80	194.37	14.51
5	19.19	215.86	4.45	18.68	217.43	12.89
6	18.99	236.87	4.01	18.44	238.76	11.59
7	18.87	257.05	3.67	18.38	257.14	10.72
8	18.96	270.63	3.50	18.43	270.72	10.21
9	19.27	286.98	3.36	18.51	287.33	9.66
10	19.84	300.31	3.30	18.82	300.39	9.40
11	19.72	311.49	3.17	19.30	312.65	9.26
12	20.21	322.30	3.14	20.43	323.81	9.46
16	20.98	346.16	3.03	20.51	346.38	8.88
20	20.75	374.08	2.77	20.70	376.18	8.26
24	20.27	389.77	2.60	20.53	394.69	7.80
28	19.33	401.46	2.41	19.63	406.89	7.24
32	18.84	416.66	2.26	19.49	420.49	6.95
36	19.24	432.33	2.23	19.15	433.09	6.63
40	19.18	444.14	2.16	19.37	447.54	6.49
44	19.56	454.13	2.15	20.20	456.96	6.63
48	20.45	465.14	2.20	20.62	465.29	6.65
52	21.42	475.55	2.25	21.22	474.79	6.70
56	21.30	486.32	2.19	20.85	483.07	6.47
60	20.66	492.07	2.10	20.04	488.74	6.15
64	21.36	499.60	2.14	20.67	495.88	6.25
68	21.78	505.33	2.16	21.19	502.71	6.32
72	21.95	511.59	2.15	21.00	508.11	6.20
76	21.94	513.85	2.14	20.30	509.39	5.98
80	21.93	516.11	2.12	20.66	507.30	6.11
84	21.90	511.72	2.14	21.13	504.73	6.28
88	21.60	506.70	2.13	20.88	504.14	6.21
92	23.24	505.31	2.30	22.18	505.97	6.58
96	23.74	500.68	2.37	22.68	507.44	6.70
100	23.04	486.04	2.37	25.00	504.15	7.44
104	24.52	476.78	2.57	24.84	491.46	7.58
106	23.29	483.58	2.41	26.29	481.50	8.19
Mean for weeks						
2-13	19.20	243.97	4.23	18.76	245.52	12.28
14-52	20.00	419.94	2.41	20.14	422.23	7.22
53-106	22.30	499.69	2.24	21.98	499.61	6.60

[a] Grams of feed consumed per animal per day
[b] Milligrams of fumonisin B_1 consumed per kilogram body weight per day

TABLE I6
Feed and Compound Consumption by Female Rats in the 2-Year Feed Study of Fumonisin B_1

	0 ppm		5 ppm			15 ppm		
Week	Feed (g)[a]	Body Weight (g)	Feed (g)	Body Weight (g)	Dose (mg/kg)[b]	Feed (g)	Body Weight (g)	Dose (mg/kg)
2	17.28	106.71	16.44	105.60	0.78	16.66	107.36	2.33
3	14.97	124.34	15.43	123.73	0.62	14.73	123.44	1.79
4	14.58	137.20	14.61	136.55	0.53	13.88	136.31	1.53
5	14.81	148.79	14.42	146.49	0.49	14.55	146.70	1.49
6	13.66	157.57	13.71	155.22	0.44	13.48	155.34	1.30
7	13.49	164.53	12.81	161.66	0.40	13.15	161.20	1.22
8	13.82	170.56	14.08	168.15	0.42	13.70	168.45	1.22
9	13.04	176.17	12.82	174.15	0.37	12.75	171.98	1.11
10	13.68	181.14	13.36	179.15	0.37	13.11	177.23	1.11
11	13.59	185.89	13.83	183.52	0.38	13.47	181.04	1.12
12	14.11	191.92	13.81	188.26	0.37	13.62	188.96	1.08
16	14.47	200.95	14.85	199.71	0.37	14.78	198.19	1.12
20	13.94	211.58	14.96	212.70	0.35	14.78	209.88	1.06
24	13.77	221.60	14.63	222.09	0.33	14.20	219.53	0.97
28	13.94	230.54	14.42	231.52	0.31	14.72	229.79	0.96
32	13.88	238.72	14.71	240.50	0.31	14.13	238.11	0.89
36	13.87	245.42	14.51	248.15	0.29	13.93	245.46	0.85
40	13.94	250.90	14.06	253.62	0.28	13.78	250.56	0.82
44	14.14	256.21	14.43	258.43	0.28	14.02	256.96	0.82
48	15.31	264.52	15.19	265.87	0.29	14.96	265.67	0.84
52	16.23	274.13	16.63	277.68	0.30	15.96	276.73	0.87
56	15.66	284.46	16.76	288.42	0.29	15.81	288.04	0.82
60	15.65	295.59	16.10	299.27	0.27	15.80	299.97	0.79
64	15.92	305.64	16.54	309.47	0.27	16.41	310.15	0.79
68	16.28	315.80	16.81	318.66	0.26	16.58	320.11	0.78
72	16.55	324.55	16.90	330.45	0.26	16.91	328.95	0.77
76	17.10	330.92	18.03	337.74	0.27	16.98	336.77	0.76
80	17.53	336.29	18.27	344.22	0.27	18.04	341.83	0.79
84	17.51	340.46	18.66	345.68	0.27	17.83	343.86	0.78
88	18.12	342.04	18.27	349.22	0.26	17.54	340.10	0.77
92	18.48	350.20	18.46	351.40	0.26	17.28	341.88	0.76
96	18.40	351.95	20.19	361.68	0.28	18.52	348.02	0.80
100	17.49	347.89	19.71	353.65	0.28	18.29	357.47	0.77
104	18.40	342.70	20.84	355.17	0.29	18.71	358.87	0.78
106	19.62	356.39	20.33	360.23	0.28	18.74	362.04	0.78
Mean for weeks								
2-13	14.28	158.62	14.12	156.59	0.47	13.92	156.18	1.39
14-52	14.35	239.46	14.84	241.03	0.31	14.53	239.09	0.92
53-106	17.34	330.35	18.28	336.09	0.27	17.39	334.15	0.78

TABLE I6
Feed and Compound Consumption by Female Rats in the 2-Year Feed Study of Fumonisin B_1

Week	50 ppm Feed (g)[a]	50 ppm Body Weight (g)	50 ppm Dose (mg/kg)[b]	100 ppm Feed (g)	100 ppm Body Weight (g)	100 ppm Dose (mg/kg)
2	16.56	106.12	7.80	16.44	108.22	15.19
3	15.05	123.31	6.10	15.17	124.43	12.19
4	14.99	137.23	5.46	14.75	137.02	10.76
5	14.26	148.12	4.81	14.32	146.43	9.78
6	13.74	156.20	4.40	13.34	155.11	8.60
7	13.45	163.68	4.11	12.42	160.26	7.75
8	13.53	170.26	3.97	13.29	166.61	7.98
9	13.12	175.85	3.73	12.23	170.73	7.16
10	13.65	181.37	3.76	12.74	176.66	7.21
11	13.92	184.24	3.78	12.55	179.15	7.01
12	14.40	191.00	3.77	13.90	186.77	7.44
16	14.64	199.81	3.66	14.03	194.61	7.21
20	14.11	209.34	3.37	13.60	203.02	6.70
24	13.86	218.29	3.17	13.58	210.80	6.44
28	13.96	227.71	3.07	13.91	219.52	6.34
32	14.00	235.51	2.97	13.86	227.31	6.10
36	14.02	242.91	2.89	13.99	234.23	5.97
40	13.87	248.64	2.79	13.51	238.91	5.66
44	14.04	253.83	2.76	13.73	244.30	5.62
48	15.31	262.34	2.92	14.59	251.07	5.81
52	16.16	274.40	2.94	15.90	261.81	6.07
56	15.40	284.33	2.71	15.41	272.66	5.65
60	15.80	296.01	2.67	15.52	282.26	5.50
64	16.31	306.53	2.66	16.08	293.02	5.49
68	16.60	317.05	2.62	15.97	301.72	5.29
72	16.76	325.93	2.57	16.46	310.37	5.30
76	16.51	333.68	2.47	16.31	316.51	5.15
80	17.04	339.43	2.51	16.82	321.26	5.24
84	17.39	341.85	2.54	16.56	322.77	5.13
88	17.77	345.92	2.57	16.76	326.43	5.13
92	17.91	350.89	2.55	16.87	330.46	5.10
96	17.73	354.74	2.50	16.16	328.65	4.92
100	17.22	350.38	2.46	17.86	347.61	5.14
104	17.72	351.94	2.52	18.56	352.25	5.27
106	18.86	357.40	2.64	17.86	355.70	5.02
Mean for weeks						
2-13	14.24	157.94	4.70	13.74	155.58	9.19
14-52	14.40	237.28	3.05	14.07	228.56	6.19
53-106	17.07	332.58	2.57	16.66	318.69	5.24

[a] Grams of feed consumed per animal per day
[b] Milligrams of fumonisin B_1 consumed per kilogram body weight per day

TABLE I7
Feed and Compound Consumption by Male Mice in the 2-Year Feed Study of Fumonisin B_1

	0 ppm		5 ppm			15 ppm		
Week	Feed (g)[a]	Body Weight (g)	Feed (g)	Body Weight (g)	Dose (mg/kg)[b]	Feed (g)	Body Weight (g)	Dose (mg/kg)
2	3.85	21.79	3.78	21.55	0.88	3.76	21.68	2.60
3	3.67	23.26	3.68	23.05	0.80	3.49	22.97	2.28
4	3.41	23.94	3.44	23.74	0.72	3.35	23.54	2.13
5	3.65	24.54	3.49	24.67	0.71	3.49	24.31	2.16
6	3.57	25.31	3.72	25.68	0.72	3.48	25.19	2.07
7	3.70	26.11	3.69	26.48	0.70	3.65	25.46	2.15
8	3.54	26.04	3.78	26.79	0.70	3.67	26.09	2.11
9	3.90	26.88	3.50	26.89	0.65	3.74	26.45	2.12
10	3.71	26.79	3.67	27.34	0.67	3.55	26.73	1.99
11	3.78	27.43	3.50	27.62	0.63	3.84	27.05	2.13
12	3.81	27.80	3.43	27.47	0.62	3.73	27.19	2.06
16	3.76	28.78	3.51	28.80	0.61	3.69	28.35	1.95
20	3.61	29.67	3.59	29.61	0.61	3.77	29.55	1.91
24	3.59	30.36	3.48	30.26	0.57	3.60	30.11	1.79
28	3.54	31.26	3.57	31.44	0.57	3.50	30.98	1.69
32	3.48	31.88	3.65	32.31	0.56	3.40	31.56	1.62
36	3.49	32.40	3.48	32.67	0.53	3.37	32.10	1.58
40	3.66	32.64	3.66	32.66	0.56	3.33	31.96	1.56
44	3.44	32.52	3.53	32.92	0.54	3.21	31.94	1.51
48	3.44	32.82	3.54	33.14	0.53	3.37	32.19	1.57
52	3.67	33.28	3.64	33.52	0.54	3.35	32.33	1.55
56	3.62	32.87	3.90	33.52	0.58	3.50	32.46	1.62
60	3.20	32.18	3.45	33.59	0.51	3.41	32.08	1.59
64	3.23	32.51	3.28	33.45	0.49	3.37	32.33	1.57
68	3.37	32.57	3.58	34.08	0.53	3.36	32.69	1.54
72	3.47	33.40	3.51	34.56	0.51	3.52	33.06	1.60
76	3.67	33.79	3.59	34.74	0.52	3.42	32.66	1.57
80	3.76	33.65	3.39	33.56	0.50	3.64	33.26	1.64
84	3.81	33.65	3.61	33.57	0.54	3.52	32.93	1.60
88	3.76	33.48	3.55	33.37	0.53	3.43	32.65	1.57
92	3.77	34.29	3.69	34.25	0.54	3.40	33.60	1.52
96	3.58	33.87	3.56	33.87	0.53	3.28	33.60	1.46
100	3.36	33.30	3.68	34.60	0.53	3.28	33.11	1.49
104	3.42	32.96	3.61	34.35	0.53	3.04	32.09	1.42
106	3.51	33.08	3.78	33.64	0.56	3.35	32.53	1.54
Mean for weeks								
2-13	3.69	25.44	3.61	25.57	0.71	3.61	25.15	2.16
14-52	3.57	31.56	3.57	31.73	0.56	3.46	31.11	1.67
53-106	3.54	33.26	3.58	33.94	0.53	3.39	32.79	1.55

TABLE I7
Feed and Compound Consumption by Male Mice in the 2-Year Feed Study of Fumonisin B_1

	80 ppm			150 ppm		
Week	Feed (g)	Body Weight (g)	Dose (mg/kg)	Feed (g)	Body Weight (g)	Dose (mg/kg)
2	3.95	21.65	14.60	3.80	21.29	26.81
3	3.54	23.14	12.25	3.53	22.84	23.19
4	3.35	23.89	11.20	3.32	23.54	21.17
5	3.32	24.64	10.78	3.40	24.10	21.15
6	3.47	24.94	11.13	3.46	24.94	20.82
7	3.69	25.96	11.36	3.51	25.61	20.56
8	3.93	26.51	11.88	3.50	26.04	20.17
9	3.74	26.65	11.23	3.30	25.51	19.43
10	3.71	27.11	10.94	3.62	26.41	20.56
11	3.71	27.43	10.83	3.73	27.40	20.42
12	3.62	27.36	10.58	3.62	27.29	19.91
16	3.76	28.51	10.55	3.65	28.34	19.34
20	3.92	29.71	10.56	3.87	29.87	19.43
24	3.88	30.64	10.13	3.61	30.38	17.81
28	3.76	31.68	9.51	3.57	31.24	17.12
32	3.85	32.54	9.48	3.43	31.94	16.11
36	3.89	33.41	9.32	3.46	32.46	16.00
40	3.77	33.23	9.07	3.70	33.14	16.76
44	3.38	33.28	8.12	3.64	32.91	16.57
48	3.53	33.38	8.45	3.69	33.15	16.69
52	4.07	33.96	9.60	3.66	33.44	16.43
56	4.10	33.82	9.71	3.64	33.31	16.39
60	3.64	32.99	8.84	3.34	32.73	15.33
64	3.43	33.05	8.29	3.26	32.84	14.88
68	3.84	33.59	9.14	3.56	33.63	15.87
72	4.02	34.37	9.36	3.54	33.83	15.69
76	3.85	34.20	9.00	3.34	33.50	14.95
80	3.79	34.17	8.88	3.31	33.21	14.97
84	3.92	33.67	9.30	3.40	33.05	15.45
88	3.79	33.68	9.00	3.47	33.14	15.71
92	3.79	34.58	8.78	3.46	33.99	15.26
96	3.77	34.48	8.75	3.44	33.87	15.22
100	3.93	34.36	9.14	3.34	33.64	14.91
104	3.86	34.02	9.08	3.52	33.31	15.85
106	3.95	34.18	9.24	3.44	33.76	15.27
Mean for weeks						
2-13	3.64	25.39	11.53	3.53	25.00	21.29
14-52	3.78	32.03	9.48	3.63	31.69	17.23
53-106	3.83	33.94	9.04	3.43	33.42	15.41

[a] Grams of feed consumed per animal per day
[b] Milligrams of fumonisin B_1 consumed per kilogram body weight per day

TABLE I8
Feed and Compound Consumption by Female Mice in the 2-Year Feed Study of Fumonisin B_1

	0 ppm		5 ppm			15 ppm		
Week	Feed (g)[a]	Body Weight (g)	Feed (g)	Body Weight (g)	Dose (mg/kg)[b]	Feed (g)	Body Weight (g)	Dose (mg/kg)
2	3.32	17.17	3.43	17.28	0.99	3.83	17.13	3.36
3	3.26	17.68	3.30	17.53	0.94	2.98	17.48	2.56
4	3.38	17.98	3.13	18.07	0.87	3.25	18.12	2.69
5	3.10	18.57	3.03	18.39	0.82	3.24	18.50	2.63
6	3.21	19.13	3.15	18.98	0.83	3.27	18.83	2.60
7	3.10	19.06	3.07	19.22	0.80	3.16	19.09	2.48
8	3.20	19.27	3.26	19.33	0.84	3.16	19.42	2.44
9	3.37	19.66	3.17	19.26	0.82	3.43	19.60	2.63
10	3.39	19.73	3.23	19.46	0.83	3.49	20.07	2.61
11	3.29	20.32	3.31	19.89	0.83	3.39	20.28	2.51
12	3.23	20.39	3.26	20.04	0.81	3.14	20.25	2.32
16	3.36	21.23	3.32	21.02	0.79	3.44	21.26	2.43
20	3.46	21.79	3.49	21.71	0.80	3.59	22.00	2.45
24	3.38	22.64	3.27	22.32	0.73	3.34	22.39	2.24
28	3.36	23.54	3.35	23.11	0.72	3.39	23.45	2.17
32	3.40	24.43	3.32	24.09	0.69	3.31	24.32	2.04
36	3.40	24.61	3.38	24.75	0.68	3.32	24.55	2.03
40	3.48	24.81	3.42	24.60	0.70	3.29	24.68	2.00
44	3.38	24.70	3.31	24.40	0.68	3.16	24.49	1.93
48	3.36	24.87	3.48	24.84	0.70	3.32	24.86	2.01
52	3.53	25.38	3.56	25.44	0.70	3.47	25.37	2.05
56	3.47	25.14	3.60	25.06	0.72	3.38	25.11	2.02
60	3.17	25.42	3.32	25.26	0.66	3.46	25.48	2.04
64	3.08	25.75	3.21	25.61	0.63	3.28	25.86	1.90
68	3.30	25.99	3.36	25.90	0.65	3.39	25.98	1.96
72	3.48	26.37	3.39	26.18	0.65	3.38	26.17	1.94
76	3.68	26.53	3.51	26.57	0.66	3.41	26.55	1.93
80	3.82	26.33	3.52	26.42	0.67	3.65	26.74	2.05
84	3.77	26.40	3.38	26.38	0.64	3.70	26.44	2.10
88	3.75	26.63	3.49	26.46	0.66	3.50	26.61	1.97
92	4.00	27.92	3.54	27.61	0.64	3.38	27.42	1.85
96	3.64	27.68	3.42	27.78	0.62	3.32	27.29	1.83
100	3.47	27.85	3.47	27.48	0.63	3.33	27.66	1.81
104	3.67	27.77	3.61	27.46	0.66	3.04	27.41	1.66
106	3.84	28.12	3.61	27.96	0.64	3.13	27.26	1.72
Mean for weeks								
2-13	3.26	19.00	3.21	18.86	0.85	3.30	18.98	2.62
14-52	3.41	23.80	3.39	23.63	0.72	3.36	23.74	2.14
53-106	3.58	26.71	3.46	26.58	0.65	3.38	26.57	1.91

TABLE I8
Feed and Compound Consumption by Female Mice in the 2-Year Feed Study of Fumonisin B_1

	50 ppm			80 ppm		
Week	Feed (g)	Body Weight (g)	Dose (mg/kg)	Feed (g)	Body Weight (g)	Dose (mg/kg)
2	3.53	17.21	10.27	3.14	17.16	14.65
3	2.95	17.38	8.49	3.47	17.63	15.77
4	3.05	17.89	8.53	3.17	18.09	14.00
5	3.10	18.46	8.40	3.23	18.57	13.94
6	3.40	19.07	8.93	3.16	18.77	13.45
7	3.16	19.03	8.31	3.25	19.21	13.53
8	3.34	19.41	8.60	3.20	19.22	13.32
9	3.30	19.69	8.39	3.26	19.63	13.29
10	3.35	20.11	8.32	3.23	19.54	13.22
11	3.34	20.28	8.24	3.32	19.95	13.32
12	3.39	20.63	8.22	3.26	20.00	13.04
16	3.41	21.33	7.99	3.40	20.88	13.04
20	3.38	21.73	7.77	3.63	21.83	13.29
24	3.24	22.41	7.24	3.45	22.37	12.32
28	3.33	23.51	7.08	3.41	23.31	11.69
32	3.22	24.41	6.59	3.47	24.32	11.42
36	3.35	24.90	6.73	3.58	25.06	11.44
40	3.54	25.02	7.07	3.58	25.02	11.44
44	3.22	24.54	6.56	3.23	24.28	10.65
48	3.55	25.02	7.09	3.41	25.11	10.87
52	3.71	25.62	7.24	3.81	25.69	11.87
56	3.64	25.65	7.09	3.91	25.61	12.21
60	3.45	26.00	6.63	3.34	25.86	10.33
64	3.28	26.00	6.31	3.19	26.05	9.79
68	3.35	26.08	6.42	4.09	27.29	11.97
72	3.57	26.72	6.67	4.26	27.73	12.31
76	3.65	27.59	6.61	4.21	27.99	12.04
80	3.68	27.44	6.70	4.25	28.58	11.89
84	3.90	27.69	7.05	4.53	28.40	12.75
88	3.97	27.89	7.13	4.52	27.84	13.00
92	3.65	28.56	6.40	4.62	28.50	12.96
96	3.70	29.58	6.25	4.54	28.92	12.57
100	3.88	30.10	6.45	5.51	28.74	15.33
104	3.80	29.83	6.37	5.81	28.50	16.30
106	3.87	29.60	6.54	5.45	28.82	15.14
Mean for weeks						
2-13	3.26	19.01	8.61	3.24	18.89	13.78
14-52	3.40	23.85	7.14	3.50	23.79	11.80
53-106	3.67	27.77	6.62	4.45	27.77	12.76

[a] Grams of feed consumed per animal per day
[b] Milligrams of fumonisin B_1 consumed per kilogram body weight per day

APPENDIX J
INGREDIENTS, NUTRIENT COMPOSITION, AND CONTAMINANT LEVELS IN NIH-31 RAT AND MOUSE RATION

Table J1
Ingredients of NIH-31 Rat and Mouse Ration

Ingredients[a]	Percent by Weight
Ground #2 yellow shelled corn	21.0
Ground whole hard wheat	35.5
Ground whole oats	10.0
Soybean meal (49% protein)	5.0
Fish meal (60% protein)	9.0
Wheat middlings	10.0
Alfalfa meal (17% protein)	2.0
Corn gluten meal (60% protein)	2.0
Soy oil	1.5
Dried brewer's yeast	1.0
Dicalcium phosphate (food grade)	1.5
Ground limestone	0.5
Salt	0.5
Premixes (vitamin and mineral)	0.5

[a] Ingredients were ground to pass through a U.S. Standard Screen No. 16 before being mixed.

Table J2
Vitamins and Minerals in NIH-31 Rat and Mouse Ration[a]

	Amount	Source
Vitamins		
A	22,000,000 IU	Vitamin A palmitate or acetate
D_3	3,800,000 IU	D-activated animal sterol
K_3	20 g	Menadione activity
d-α-Tocopheryl acetate	15 g	
Choline	700 g	Choline chloride
Folic acid	1 g	
Niacin	20 g	
d-Pantothenic acid	25 g	*d*-Calcium pantothenate
Riboflavin	5 g	
Thiamine	65 g	Thiamine mononitrate
B_{12}	14 g	
Pyridoxine	2 g	Pyridoxine hydrochloride
Biotin	0.120 g	*d*-Biotin
Minerals		
Iron	60 g	Iron sulfate
Magnesium	400 g	Magnesium oxide
Manganese	100 g	Manganous oxide
Zinc	10 g	Zinc oxide
Copper	4 g	Copper sulfate
Iodine	1.5 g	Calcium iodate
Cobalt	0.4 g	Cobalt carbonate

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

TABLE J3
Nutrient Composition of NIH-31 Rat and Mouse Ration[a]

Nutrient	Mean ± Standard Deviation[b]
Crude protein (% by weight)	20.1 ± 1.75
Crude fat (% by weight)	3.55 ± 0.09
Dry matter (% by weight)	93.5 ± 4.14
Total energy (Kcal/g)	4.33 ± 0.21
Amino Acids (% of total diet)	
Alanine	0.98
Arginine	1.00
Aspartic acid	1.52
Cystine	0.24
Glutamic acid	3.51
Glycine	0.92
Histidine	0.58
Hydroxylysine	<0.01
Hydroxyproline	<0.01
Isoleucine	0.72
Leucine	1.44
Lysine, total	0.79
Methionine	0.37
Phenylalanine	0.79
Proline	1.30
Serine	0.81
Threonine	0.71
Tryptophan	0.29
Tyrosine	0.35
Valine	0.93
Vitamins	
Vitamin A (IU/g)	17.0 ± 14.43
Vitamin D_3 (IU/kg)	3,881.0 ± 538.0
Vitamin E (ppm)	53.5 ± 3.94
Thiamine, B_1 (ppm)	40.0 ± 0.98
Riboflavin, B_2 (ppm)	8.54 ± 0.71
Niacin (ppm)	122.3 ± 12.90
Pantothenate (ppm)	33.6 ± 9.90
Pyridoxine, B_6 (ppm)	11.4 ± 2.29
Folic acid (ppm)	2.48 ± 0.275
Biotin (ppm)	0.618 ± 0.305
Vitamin B_{12} (ppb)	43 ± 6
Choline (ppm)	3,379.7 ± 710.2

TABLE J3
Nutrient Composition of NIH-31 Rat and Mouse Ration

Nutrient	Mean ± Standard Deviation
Minerals	
Calcium (%)	1.43 ± 0.21
Phosphorus (%)	0.937 ± 0.015
Potassium (%)	0.690 ± 0.078
Chlorine (%)	0.600 ± 0.061
Fluorine (ppm)	16.0 ± 15.09
Selenium (ppm)	0.500 ± 0.026
Sodium (%)	0.380 ± 0.044
Magnesium (%)	0.247 ± 0.015
Iron (mg/kg)	260.0 ± 99.58
Manganese (ppm)	131.3 ± 1.16
Zinc (ppm)	92.3 ± 5.51
Copper (ppm)	11.7 ± 1.53
Iodine (ppm)	2.00 ± 3.46
Chromium (ppm)	4.07 ± 1.00
Cobalt (ppm)	0.273 ± 0.040
Molybdenum (ppm)	1.60 ± 0.44

[a] Post autoclaving
[b] Average of three diet production lots; amino acid measurements were from a single lot.

TABLE J4
Contaminant Levels in NIH-31 Rat and Mouse Ration[a]

	Mean ± Standard Deviation[b]
Contaminants	
Arsenic (µg/kg)[c]	216.3 ± 195.64
Cadmium (µg/kg)[c]	214.0 ± 145.43
Lead (mg/kg)[c]	0.190 ± 0.053
Mercury (ppm)	<0.05
Peroxides (MEQ/kg)[c]	9.12 ± 6.25
Aflatoxin (ppb)	<5.0
Pesticides (ppb)	
Heptachlor	<10.0
DDT, total[d]	<5.0
Dieldrin	<5.0
PCB	<10.0
Malathion	276.0
Lindane	<10.0

[a] Average of three diet production lots
[b] For values less than the limit of detection, the detection limit is given as the mean.
[c] Post autoclaving
[d] DDE+DDT+DDD

APPENDIX K
SENTINEL ANIMAL PROGRAM

SENTINEL ANIMAL PROGRAM

METHODS

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

Serum samples were collected from randomly selected rats and mice during the 2-year studies. Blood from each animal was collected and allowed to clot, and the serum was separated. The samples were processed appropriately and sent to the Surveillance/Diagnostic Program, Division of Microbiology, at NCTR for determination of antibody titers. The laboratory serology methods and viral agents for which testing was performed are tabulated below; the times at which blood was collected during the studies are also listed.

Method and Test	Time of Analysis
RATS	
ELISA	
H-1 (Toolan's H-1 virus)	6, 12, and 18 months, study termination
KRV (Kilham rat virus)	6, 12, and 18 months, study termination
Mycoplasma arthritidis	6, 12, and 18 months, study termination
Mycoplasma pulmonis	6, 12, and 18 months, study termination
PVM (pneumonia virus of mice)	6, 12, and 18 months, study termination
RCV/SDA (rat coronavirus/sialodacryoadenitis virus)	6, 12, and 18 months, study termination
Sendai	6, 12, and 18 months, study termination
MICE	
ELISA	
Ectromelia virus	6, 12, and 18 months, study termination
GDVII (mouse encephalomyelitis virus)	6, 12, and 18 months, study termination
LCM (lymphocytic choriomeningitis virus)	6, 12, and 18 months, study termination
MVM (minute virus of mice)	6, 12, and 18 months, study termination
MHV (mouse hepatitis virus)	6, 12, and 18 months, study termination
M. arthritidis	6, 12, and 18 months, study termination
M. pulmonis	6, 12, and 18 months, study termination
PVM	6, 12, and 18 months, study termination
Polyoma virus	6, 12, and 18 months, study termination
Reovirus 3	6, 12, and 18 months, study termination
Sendai	6, 12, and 18 months, study termination

RESULTS

All results were negative.

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