NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS

STUDIES OF PRIMIDONE

(CAS NO. 125-33-7)

IN F344/N RATS AND B6C3F$_1$ MICE

(FEED STUDIES)

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

September 2000

NTP TR 476

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National Toxicology Program

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; 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 described in this Technical Report were performed under the direction of the NIEHS and 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 Food and Drug Administration (FDA) Good Laboratory Practice Regulations, and all aspects of the chronic studies were subjected to retrospective quality assurance audits before being presented for public review.

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.

Listings of all published NTP reports and ongoing studies are available from NTP Central Data Management, NIEHS, P.O. Box 12233, MD E1-02, Research Triangle Park, NC 27709 (919-541-3419). The Abstracts and other study information for 2-year studies are also available at the NTP's World Wide Web site: http://ntp-server.niehs.nih.gov.

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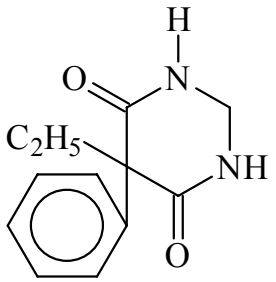
ABSTRACT



PRIMIDONE

CAS No. 125-33-7

Chemical Formula: $C_{12}H_{14}N_2O_2$ Molecular Weight: 218.28

Synonyms: 5-Aethyl-5-phenyl-hexahydropyrimidin-4,6-dion; 2-deoxyphenobarbital; 2-desoxyphenobarbital; desoxyphenobarbitone; 5-ethyldihydro-5-phenyl-4,6 (1H,5H)-pyrimidinedione; 5-ethylhexahydro-4,6-dioxo-5-phenylphrimidine; 5-ethylhexahydro-5-phenylpyrimidine-4,6-dione; 5-ethyl-5-phenylhexahydropyrimidine-4,6-dione

Trade names: Cyral; Hexadiona; Hexamidine; Lepimidin; Lepsiral; Majsolin; Midone; Milepsin; Misodine; Misolyne; Mizodin; Mizolin; Mylepsin; Mylepsinum; Mysedon; Mysoline; Prilepsin; Primacione; Primaclone; Primacone; Primakton; Primadon; Prysoline; Pyrimidone; ROE 101; Sertan

Primidone is used alone or with other anticonvulsants in the control of grand mal, psychomotor, and focal epileptic seizures. It may control grand mal seizures refractory to other anticonvulsant therapy. Primidone was nominated by the National Cancer Institute for 2-year toxicology and carcinogenicity studies due to its human use as an anticonvulsant. Male and female F344/N rats and B6C3F$_1$ mice received primidone (greater than 99% pure) in feed for 14 days, 14 weeks, or 2 years. Genetic toxicology studies were conducted in *Salmonella typhimurium*, cultured Chinese hamster ovary cells, and mouse bone marrow cells.

14-Day Study in Rats

Five male and five female rats were exposed to 0, 1,250, 2,500, 5,000, 10,000 or 20,000 ppm primidone (equivalent to average daily doses of approximately 120, 240, 500, 970, or 1,100 mg primidone/kg body weight to males and 120, 240, 500, or 900 mg/kg to females) in feed for 14 days. All 20,000 ppm females died before the end of the study as did one 10,000 ppm male and two 20,000 ppm males. The mean body weights of 10,000 ppm males and females and 20,000 ppm males were significantly less than those of the controls. Feed consumption by all exposed rats was generally similar to that by the controls. Males and females in the 10,000 and 20,000 ppm groups were observed to have eye discharge, ataxia, and abnormal posture and were thin and lethargic.

14-Day Study in Mice

Five male and five female mice were exposed to 0, 625, 1,250, 2,500, 5,000 or 10,000 ppm primidone (equivalent to average daily doses of approximately 100, 200, 400, or 800 mg/kg body weight to males and 100, 250, 500, or 900 mg/kg to females) in feed for 14 days. All mice in the 10,000 ppm groups and one male and one female mouse in the 5,000 ppm groups died on day 3 of the study. The mean body weights of mice in the 625, 1,250, 2,500, and

5,000 ppm groups were similar to those of the controls. Feed consumption by all exposed mice was generally similar to that by the controls. Males and females in the 10,000 ppm groups were observed to have abnormal posture, ataxia, and lethargy.

14-Week Study in Rats

Groups of 10 male and 10 female rats were exposed to 0, 300, 600, 1,300, 2,500, or 5,000 ppm primidone (equivalent to average daily doses of approximately 20, 40, 100, 200, or 400 mg/kg) in feed for 14 weeks. All rats survived to the end of the study. The mean body weights of male and female rats in the 2,500 and 5,000 ppm groups were significantly less than those of the controls. Feed consumption by all exposed rats was generally similar to that by the controls.

A minimal to mild exposure-related thrombocytosis occurred on day 22 and at week 14 in all exposed groups of male rats and in females in the 1,300 ppm or greater groups. A minimal decrease in hemoglobin concentration occurred in 2,500 and 5,000 ppm male and female rats on day 22 and at week 14.

The incidences of centrilobular hepatocyte hypertrophy in male rats exposed to 600 ppm or greater and in female rats exposed to 1,300 ppm or greater were significantly greater than those in the controls. The severity of chronic nephropathy in male rats exposed to 1,300 ppm or greater increased with increasing exposure concentration.

14-Week Study in Mice

Groups of 10 male and 10 female mice were exposed to 0, 300, 600, 1,300, 2,500, or 5,000 ppm primidone (equivalent to average daily doses of approximately 50, 100, 200, 400, or 1,000 mg/kg to males and 60, 120, 220, 440, or 1,100 mg/kg to females) in feed for 14 weeks. Three male and two female mice in the 5,000 ppm group died during week 1 of the study. The final mean body weights of all exposed groups were similar to those of the controls. Feed consumption by male mice in the 5,000 ppm group was slightly greater than that by the controls; this may have been due to feed spillage. Male and female mice in the 5,000 ppm groups were ataxic and lethargic.

Compared to controls, the estrous cycle lengths of females exposed to 1,300, 2,500, or 5,000 ppm were significantly longer. The liver weights of male and female mice exposed to 600 ppm or greater were significantly greater than those of the controls. The incidences of centrilobular hepatocyte hypertrophy in all exposed males and in females exposed to 600 ppm or greater and the incidences of cytoplasmic alteration of the adrenal gland and hematopoietic cell proliferation of the spleen in 2,500 and 5,000 ppm males and in 5,000 ppm females were significantly greater than in the controls.

2-Year Study in Rats

Groups of 50 male and 50 female F344/N rats were exposed to 0, 600, 1,300, or 2,500 ppm primidone (equivalent to average daily doses of approximately 25, 50, or 100 mg/kg) in feed for 2 years.

Survival, Body Weights, and Feed Consumption

Survival of the 1,300 and 2,500 ppm males was significantly less than that of the controls. The mean body weights of males and females in the 2,500 ppm groups were less than those of the controls, beginning at week 29 for males and week 17 for females; the mean body weights of 1,300 ppm males and females were less than those of the controls during the second year of the study. Feed consumption by all exposed groups of rats was generally similar to that by the controls.

Pathology Findings

Male rats exposed to primidone had increased incidences of thyroid gland follicular cell neoplasms (adenoma and/or carcinoma). All exposed groups of male rats had follicular cell adenomas or carcinomas (combined) at incidences above the historical control range, with the highest incidence in the 1,300 ppm group.

Hepatocyte cytoplasmic vacuolation and centrilobular hypertrophy were associated with primidone exposure in male and female rats. These changes were more severe in females than in males and the incidences in all exposed groups of females were significantly greater than those in the controls. Females in the 2,500 ppm group had an increased incidence of hepatocellular eosinophilic foci.

In 2,500 ppm males, the incidence of renal tubule hyperplasia was greater than that in the controls in the standard evaluation. Additional hyperplasias were found in the extended evaluation, and the incidences in exposed groups of males were significantly greater than that in the controls. In the extended evaluation, the incidence of renal tubule adenoma in 2,500 ppm males was significantly increased. The incidence of adenoma or carcinoma (combined) in 2,500 ppm males in the combined standard and extended evaluations were marginally increased over those in the controls. Male rats had an exposure-related increase in the severity of chronic nephropathy, which probably accounted for the reduced survival in the 1,300 and 2,500 ppm groups. The incidences of kidney cysts were increased in 1,300 and 2,500 ppm males. Hyperparathyroidism, secondary to the loss of renal function, was present in many exposed male rats. The incidences of parathyroid gland hyperplasia in all groups of exposed males were significantly greater than that in the controls.

2-Year Study in Mice

Groups of 50 male and 50 female mice were exposed to dietary levels of 0, 300, 600, or 1,300 ppm primidone (equivalent to average daily doses of approximately 30, 65, or 150 mg/kg to males and 25, 50, or 100 mg/kg to females) in feed for 2 years.

Survival, Body Weights, Feed Consumption, and Clinical Findings

Survival of the 1,300 ppm males was significantly less than that of the controls. During the second year of the study, the mean body weights of 1,300 ppm male and female mice were less than those of the controls. The final mean body weights of 600 ppm males and females were less than those of the controls. Feed consumption by all exposed groups of mice was similar to that by the controls. During the latter part of the study, a treatment-related increase in the number of animals with swelling of the abdominal area was observed; necropsy revealed that the swelling was due to liver nodules/masses.

Pathology Findings

The liver was a target organ in both male and female mice. The incidences and multiplicities of hepatocellular neoplasms (hepatocellular adenoma, hepatocellular carcinoma, and hepatoblastoma) in all exposed groups of males and females (except hepatoblastoma in females) were significantly greater than those in the controls. The incidences of hepatocellular adenoma or carcinoma (combined) and hepatocellular adenoma, hepatocellular carcinoma, or hepatoblastoma (combined) in all exposed groups exceeded the historical control ranges in 2-year NTP studies. The incidences of centrilobular hepatocyte hypertrophy were increased in exposed groups of males and females, and the severities increased with increasing exposure concentration. The incidences of cytoplasmic vacuolization were increased in all exposed groups of females and in 300 ppm males. Incidences of eosinophilic focus in all exposed groups of females were significantly greater than those in the controls.

Proliferative changes occurred in the thyroid gland in an exposure-related manner in male and female mice. Incidences of follicular cell hyperplasia were increased in all exposed groups of males and in 600 and 1,300 ppm females, but incidences of follicular cell adenomas were increased only in male mice.

Genetic Toxicology

Primidone was mutagenic in *Salmonella typhimurium* strain TA1535 in the absence of S9 activation only; no mutagenicity was detected in strain TA98, TA100, or TA1537, with or without S9. Primidone did not induce sister chromatid exchanges or chromosomal aberrations in cultured Chinese hamster ovary cells, with or without S9. The single *in vivo* study with primidone, a mouse bone marrow micronucleus test, also gave negative results.

CONCLUSIONS

Under the conditions of these 2-year feed studies, there was *equivocal evidence of carcinogenic activity** of primidone in male F344/N rats based on a marginal increase in thyroid gland follicular cell neoplasms, primarily adenomas, and a marginal increase in renal tubule neoplasms. There was *no evidence of carcinogenic activity* of primidone in female F344/N rats exposed to 600, 1,300, or 2,500 ppm. There was *clear evidence of carcinogenic activity* of primidone in male $B6C3F_1$ mice based on the increased incidences of hepatocellular neoplasms, and the increased incidence of thyroid gland follicular cell adenomas was also considered to be chemical related. There was *clear evidence of carcinogenic activity* of primidone in female $B6C3F_1$ mice based on the increased incidences of hepatocellular neoplasms.

Exposure of rats to primidone resulted in increased incidences of hepatocyte cytoplasmic vacuolization and centrilobular hypertrophy in males and females and eosinophilic foci in females. The increased severity of nephropathy and increased incidence of renal tubule hyperplasia in male rats were related to primidone exposure. Exposure of male mice to primidone resulted in hepatocyte centrilobular hypertrophy and thyroid gland follicular cell hyperplasia. Exposure of female mice to primidone resulted in hepatocyte centrilobular hypertrophy and cytoplasmic vacuolization, eosinophilic focus, and thyroid gland follicular cell hyperplasia.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 11. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 13.

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Primidone

	Male F344/N Rats	Female F344/N Rats	Male B6C3F$_1$ Mice	Female B6C3F$_1$ Mice
Concentrations in feed	0, 600, 1,300, or 2,500 ppm	0, 600, 1,300, or 2,500 ppm	0, 300, 600, or 1,300 ppm	0, 300, 600, or 1,300 ppm
Body weights	1,300 and 2,500 ppm groups less than the control group	1,300 and 2,500 ppm groups less than the control group	600 and 1,300 ppm groups less than the control group	600 and 1,300 ppm groups less than the control group
2-Year survival rates	13/50, 7/50, 4/50, 0/50	24/50, 27/50, 31/50, 28/50	35/50, 34/50, 31/50, 19/50	41/50, 42/50, 44/49, 39/50
Nonneoplastic effects	Liver: hepatocyte cytoplasmic vacuolization (26/50, 28/50, 33/50, 43/50); hepatocyte centrilobular hypertrophy (0/50, 14/50, 33/50, 40/50) Kidney: severity of nephropathy (2.2, 2.9, 3.4, 3.8); renal tubule hyperplasia (1/50, 2/50, 4/50, 10/50)	Liver: hepatocyte cytoplasmic vacuolization (25/50, 44/50, 46/50, 44/50); hepatocyte centrilobular hypertrophy (1/50, 36/50, 38/50, 35/50); eosinophilic focus (2/50, 0/50, 1/50, 18/50)	Liver: hepatocyte centrilobular hypertrophy (3/50, 30/50, 21/50, 18/50) Thyroid gland: follicular cell hyperplasia (8/49, 20/48, 31/50, 42/50)	Liver: hepatocyte centrilobular hypertrophy (1/50, 11/50, 11/49, 21/50); hepatocyte cytoplasmic vacuolization (3/50, 35/50, 39/49, 28/50); eosinophilic focus (8/50, 23/50, 24/49, 17/50) Thyroid gland: follicular cell hyperplasia (13/50, 12/48, 28/48, 49/50)
Neoplastic effects	None	None	Liver: hepatocellular adenoma (22/50, 41/50, 39/50, 32/50); hepatocellular carcinoma (12/50, 31/50, 35/50, 38/50); hepatocellular adenoma or carcinoma (31/50, 48/50, 47/50, 46/50); hepatoblastoma (0/50, 17/50, 26/50, 7/50); hepatocellular carcinoma or hepatoblastoma (12/50, 39/50, 40/50, 39/50); hepatocellular adenoma, hepatocellular carcinoma, or hepatoblastoma (31/50, 49/50, 49/50, 46/50) Thyroid gland: follicular cell adenoma (0/49, 3/48, 3/50, 6/50)	Liver: hepatocellular adenoma (15/50, 42/50, 45/49, 47/50); hepatocellular carcinoma (3/50, 11/50, 19/49, 38/50); hepatocellular adenoma or carcinoma (16/50, 42/50, 45/49, 50/50); hepatoblastoma (1/50, 4/50, 4/49, 4/50); hepatocellular carcinoma or hepatoblastoma (4/50, 12/50, 20/49, 39/50); hepatocellular adenoma, hepatocellular carcinoma, or hepatoblastoma (16/50, 42/50, 46/49, 50/50)
Uncertain findings	Thyroid gland: follicular cell adenoma (1/50, 1/50, 6/49, 3/49); follicular cell adenoma or carcinoma (2/50, 4/50, 7/49, 4/49) Kidney: renal tubule adenoma or carcinoma (standard and extended evaluations combined - 4/50, 2/50, 4/50, 7/50)	None	None	None
Level of evidence of carcinogenic activity	Equivocal evidence	No evidence	Clear evidence	Clear evidence

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Primidone

Genetic toxicology	
Salmonella typhimurium gene mutations:	Positive in strain TA1535 without S9; negative in strains TA98, TA100, and TA1537 with and without S9
Sister chromatid exchanges	
Cultured Chinese hamster ovary cells *in vitro*:	Negative with and without S9
Chromosomal aberrations	
Cultured Chinese hamster ovary cells *in vitro*:	Negative with and without S9
Micronucleated erythrocytes	
Mouse bone marrow *in vivo*:	Negative

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 primidone on 12 December 1996 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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* Did not attend

SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

On 12 December 1996, the draft Technical Report on the toxicology and carcinogenicity studies of primidone 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.K. Dunnick, NIEHS, introduced the toxicology and carcinogenesis studies of primidone by discussing the uses of the chemical and the rationale for study, describing the experimental design, reporting on survival and body weight effects, and commenting on compound-related neoplastic lesions in male and female mice and nonneoplastic lesions in male and female rats and mice. The proposed conclusions for the 2-year studies in mice and rats were *equivocal evidence of carcinogenic activity* in male rats, *no evidence of carcinogenic activity* in female rats, *clear evidence of carcinogenic activity* in male mice, and *clear evidence of carcinogenic activity* in female mice.

Dr. Goldsworthy, a principal reviewer, agreed in principle with the proposed conclusions. He said the poor survival in 1,300 and 2,500 ppm male rats, as well as decreased weight gain, made the decision between *equivocal evidence* and *some evidence* unclear in male rats, even though the incidences of thyroid gland follicular cell and renal tubule neoplasms were above the historical control range. Dr. Goldsworthy asked whether it might have been appropriate with the male rat data to use the survival-adjusted "Poly-3" quantal response employed in the chloroprene study. Dr. J.K. Haseman, NIEHS, reported that the new "Poly-K" methods will be used routinely with the technical reports for the next review meeting. This and other newer methods have an advantage over current methods in that they do not require an assumption regarding whether a tumor is fatal or incidental. Dr. Goldsworthy thought that there was an overemphasis in the Introduction and Discussion sections on relating all of the neoplasm responses to a primary metabolite, phenobarbital, and that some discussion should be given to possible carcinogenic activity of primidone and the other primary metabolite, phenylethylmalonamide.

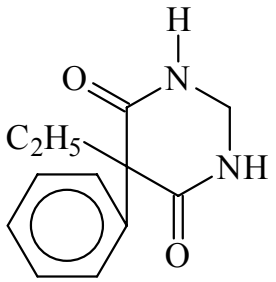
Dr. Ryan, the second principal reviewer, agreed with the proposed conclusions. She liked the section dealing with plasma concentrations of primidone and phenobarbital and questioned whether markedly different plasma level patterns between rats and mice might explain differences in response between the species. Dr. Ryan noted the widespread human usage as an anticonvulsant and asked why some of these toxicology studies would not have been done as part of the FDA approval process. Dr. Dunnick said that primidone was developed in the 1950s and nominated because there were no long-term toxicology and carcinogenicity studies reported in the literature.

Dr. LeBoeuf, the third principal reviewer, agreed with the proposed conclusions. He commented that the pharmacokinetics and toxicokinetics, although limited in scope, were extremely useful for cross comparisons to studies with phenobarbital and, further, that this type of data should be collected routinely to aid in interpretation of other bioassays. Dr. LeBoeuf said that the confirmation of an absence of *Helicobacter* in this study was comforting with regard to interpretation of the neoplasm results in mice.

There was some discussion about the neoplasm-promoting activity of primidone/phenobarbital. Dr. J. Rice, International Agency for Research on Cancer, noted the markedly increased incidences of hepatoblastomas in exposed mice and said that agents capable of promoting hepatocarcinogenic effects in certain strains of mice, and especially in male mice, invariably generate a significant fraction of hepatoblastomas. This was consistently seen with phenobarbital. These neoplasms are highly malignant, metastasize readily, and are often lethal.

Dr. Goldsworthy moved that the Technical Report on primidone be accepted with revisions discussed and the conclusions as written. Dr. LeBoeuf seconded the motion, which was accepted unanimously with eight votes.

INTRODUCTION



PRIMIDONE

CAS No. 125-33-7

Chemical Formula: $C_{12}H_{14}N_2O_2$ Molecular Weight: 218.28

Synonyms: 5-Aethyl-5-phenyl-hexahydropyrimidin-4,6-dion; 2-deoxyphenobarbital; 2-desoxyphenobarbital; desoxyphenobarbitone; 5-ethyldihydro-5-phenyl-4,6 (1H,5H)-pyrimidinedione; 5-ethylhexahydro-4,6-dioxo-5-phenylphrimidine; 5-ethylhexahydro-5-phenylpyrimidine-4,6-dione; 5-ethyl-5-phenylhexahydropyrimidine-4,6-dione

Trade names: Cyral; Hexadiona; Hexamidine; Lepimidin; Lepsiral; Majsolin; Midone; Milepsin; Misodine; Misolyne; Mizodin; Mizolin; Mylepsin; Mylepsinum; Mysedon; Mysoline; Prilepsin; Primacione; Primaclone; Primacone; Primakton; Primadon; Prysoline; Pyrimidone; ROE 101; Sertan

CHEMICAL AND PHYSICAL PROPERTIES

Primidone, a desoxybarbiturate, was synthesized in 1949 by Bogue and Carrington (1953). It was first reported to be clinically effective as an anticonvulsant by Handley and Stewart (1952). Primidone is a white crystalline substance with a molecular weight of 218.28. It differs from phenobarbital by reduction of the carbonyl group at position 2 of the pyrimidine ring. The compound is tasteless and essentially neutral. It is sparingly soluble in water (0.6 g/L at 37° C) and in most organic solvents with the exception of propylene glycol (20.0 g/L at 37° C) (Bogue and Carrington, 1953; Gallagher and Baumel, 1972).

PRODUCTION, USE, AND HUMAN EXPOSURE

Methods of synthesis include electrolytic reduction of phenobarbital, catalytic desulfuration of the corresponding 2-thiobarbituric acid, and ring closure of phenylethylmalonamide synthesized from benzyl chloride. The resulting mixture is then cooled and the precipitate product crystallized from ethanol:water (Sittig, 1979). Approximately 1,800,000 pounds (820,000 kg) of primidone were produced in the United States in 1982 (USITC, 1983). Approximately 10,000 pounds (4,500 kg) of primidone were imported in 1981 and 90,000 pounds (41,000 kg) in 1982 and 1983 (USITC, 1982, 1983, 1984).

It is estimated that 50 million people worldwide have epilepsy, and the annual incidence ranges from 20 to 70 cases per 100,000 (Shorvon, 1990; Brodie and Dichter, 1996). There are approximately 2 million cases of epilepsy in the United States (Hauser and Kurland, 1975; Mattson *et al.*, 1985). Treatment with an antiepileptic drug usually begins when the patient has had more than one unprovoked seizure within a year (Brodie and Dichter, 1996). Various drugs used in reducing the frequency of partial seizures include carbamazepine, phenytoin, valproic acid, phenobarbital, and primidone (Brodie and Dichter, 1996).

The starting oral dose of primidone for treatment of partial or generalized tonic-clonic seizures is 10 mg/kg per day, with a maintenance oral dose of 2 to 30 mg/kg per day. The target therapeutic plasma drug concentration is 5 to 12 μg/mL (PDR, 1996; Brodie and Dichter, 1996).

Phenobarbital (a major metabolite of primidone) was introduced as an antiepileptic drug in 1912 (Watanabe *et al.*, 1977). Target therapeutic plasma concentrations for phenobarbital are 10 to 40 μg/mL (Brodie and Dichter, 1996).

ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION

Experimental Animals

Phenylethylmalonamide (PEMA) and phenobarbital have been identified as the major metabolites of primidone in most species of (Gallagher *et al.*, 1972; Pisani *et al.*, 1984; Martines *et al.*, 1990; Sato *et al.*, 1992; Figure 1), mice (McElhatton *et al.*, 1977), rabbits (Fujimoto *et al.*, 1968; Hunt and Miller, 1978), dogs (Frey *et al.*, 1979; Yeary, 1980; Frey and Löscher, 1985), and rats (Baumel *et al.*, 1973).

Baumel *et al.* (1972, 1973) have shown that primidone possesses independent anticonvulsant activity, and that primidone and phenobarbital are more effective anticonvulsants than PEMA. Moriyama *et al.* (1994) have reported the pharmacokinetic parameters of primidone and its major metabolites in the rat (Table 1). The plasma half-life of primidone in the mouse has been described (Leal *et al.*, 1979; Table 2). In all species, primidone has an elimination half-life (6 to 10 hours) that is considerably shorter than the elimination half-life for phenobarbital (3 to 4 days) (Eadie *et al.*, 1981).

The plasma levels of primidone and/or phenobarbital in the F344/N rat and $B6C3F_1$ mouse in the current studies are described in Appendixes H and N.

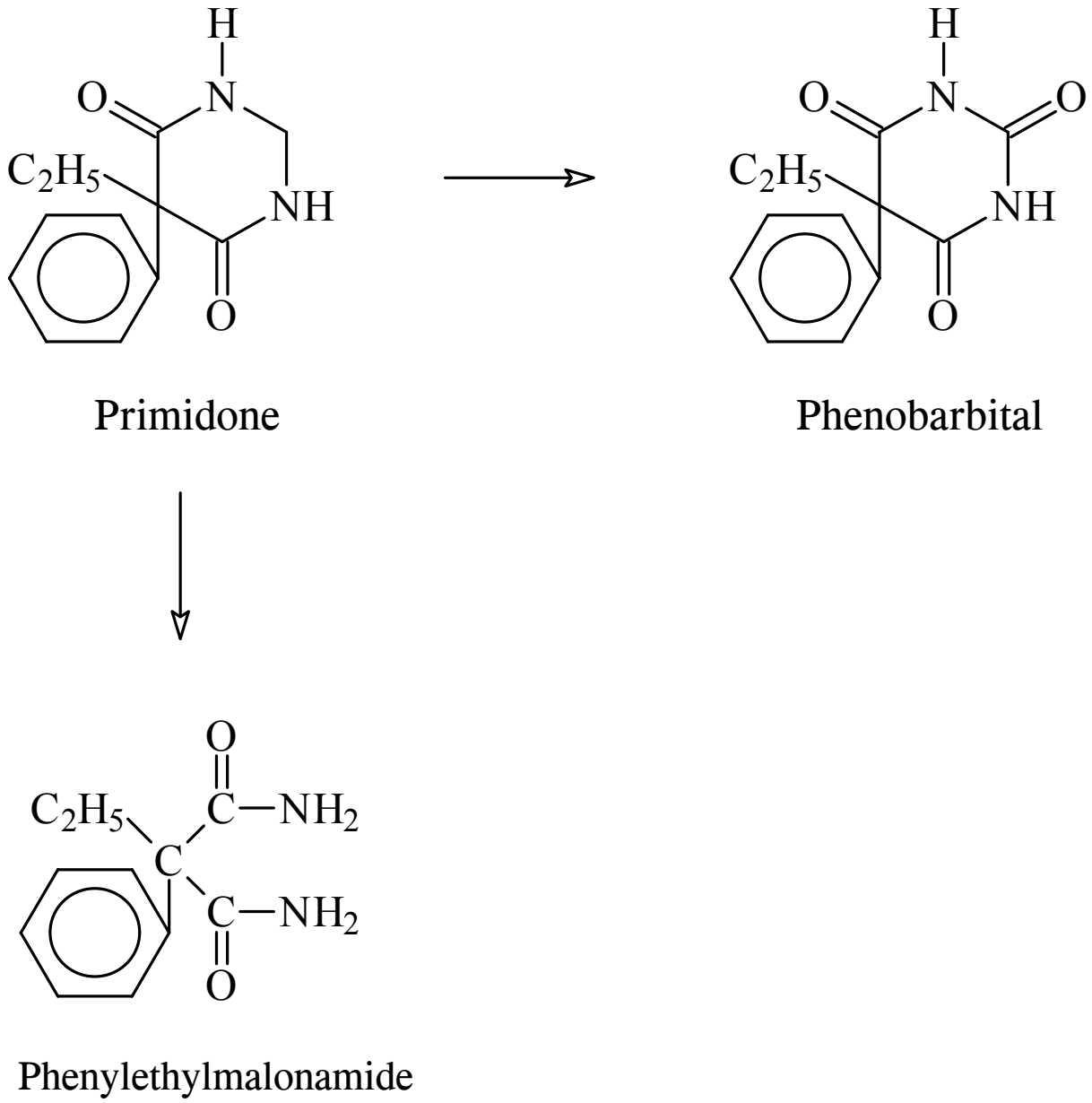


FIGURE 1
Metabolites of Primidone (Baumel *et al.*, 1972)

TABLE 1
Pharmacokinetic Parameters of the Plasma Concentration of Primidone (PRM), Phenylethylmalonamide (PEMA), and Phenobarbital (PB) After Oral Administration of PRM in Rats[a]

	K_a (hour^{-1})	T_{max} (hour)	C_{max} (μg/mL)	$T_{½}$ (hour)	AUC[b] (μg·hour/mL)
PRM	1.17 ± 0.26	1.36 ± 0.14	18.15 ± 1.62	1.64 ± 0.45	76.28 ± 1.35
PEMA		5.70 ± 0.31	8.11 ± 0.45	4.29 ± 0.21	111.12 ± 4.70
PB		6.55 ± 0.47	9.64 ± 0.42	4.96 ± 0.29	148.18 ± 8.01

[a] Data from Moriyama *et al*. (1994). PRM at a dose of 50 mg/kg was administered orally. Each value indicates the mean ± standard error for six rats.
[b] AUC values were calculated from 0 to 12 hours in PRM and 0 to 24 hours in PEMA and PRM after oral administration.

TABLE 2
Apparent Half-life in Mouse Plasma of Primidone and its Metabolites[a]

Drug	Half-life (hour)
Primidone	2.23
Phenobarbital	4.26
Phenylethylmalonamide	2.32

[a] Data from Leal *et al*. (1979). Each compound was delivered transesophageally as a single 50 mg/kg dose. Each value represents the mean for five mice.

Humans

Primidone is metabolized primarily to PEMA by ring scission and by oxidation to phenobarbital by hepatic enzyme activity (Gallagher *et al*., 1972; Pisani *et al*., 1984; Martines *et al*., 1990; Sato *et al*., 1992; Figure 1). Phenobarbital accumulates due to its prolonged serum half-life, and levels of phenobarbital equivalent to those obtained with treatment by phenobarbital alone are present in patients on a primidone dosage (Booker, 1972a).

A summary of pharmacokinetic data of primidone in humans is presented in Table 3 (Martines *et al*., 1990). The plasma half-life of primidone is estimated at 6.2 hours and that of phenobarbital at 84 hours. Analysis of the plasma concentration-time curve for primidone suggests the presence of two distinct absorption phases (Matzke *et al*., 1981).

TABLE 3
Parameters Describing the Disposition of Primidone and its Metabolites in Young and Elderly Study Groups[a]

	Young (n=8)	Elderly (n=10)	P value[b]
Primidone terminal elimination rate constant (h^{-1})	0.0510 ± 0.0184	0.0655 ± 0.0244	NS
Primidone half-life (h)	14.7 ± 3.5	12.1 ± 4.6	NS
Primidone volume of distribution (1 kg^{-1})*	0.69 ± 0.18	0.56 ± 0.14	NS
Primidone AUC (0, 12 h) (mg L^{-1} h)**[c]	112 ± 33	110 ± 28	NS
Primidone total clearance (mL h^{-1} kg^{-1})*	33.2 ± 7.2	34.8 ± 9.0	NS
Phenobarbitone AUC (0, 12 h) (mg L^{-1} h)	78.7 ± 44.5	111.6 ± 51.0	NS
PEMA[d] AUC (0, 12 h) (mg L^{-1} h)**	33.7 ± 22.0	57.1 ± 20.7	<0.05
Phenobarbitone AUC/Primidone AUC	0.71 ± 0.33	1.10 ± 0.63	NS
PEMA AUC/Primidone AUC	0.29± 0.15	0.54 ± 0.21	<0.01
Renal clearance of unchanged primidone (mL h^{-1} kg^{-1})	15.3 ± 6.7	11.3 ± 4.8	NS
Renal clearance of unchanged phenobarbitone (mL h^{-1} kg^{-1})	1.0 ± 0.2	0.8 ± 0.3	NS
Renal clearance of PEMA (mL h^{-1} kg^{-1})	26.4 ± 8.0	18.3 ± 6.6	<0.05
Proportion of dose recovered in urine as unchanged primidone (%)+	45.9 ± 16.5	36.1 ± 22.7	NS
Proportion of dose recovered in urine as phenobarbitone (%)+	2.0 ± 0.8	2.1 ± 0.9	NS
Proportion of dose recovered in urine as unconjugated *p*-OH-phenobarbitone (%)	2.3 ± 2.1	1.5 ± 0.6	NS
Proportion of dose recovered in urine as total (unconjugated + conjugated) *p*-OH-phenobarbitone (%)	4.3 ± 4.1	3.5 ± 1.8	NS
Proportion of dose recovered in urine as PEMA (%)+	21.2 ± 8.6	27.1 ± 8.8	NS

* Assuming complete oral availability
** Normalized for a dose of 500 mg per day
\+ No conjugates of these compounds were detected.
[a] Data from Martines *et al*. (1990). Elderly patients were 70 to 81 years and young patients were 18 to 26 years.
[b] NS=Not significant
[c] AUC=Area under the curve
[d] PEMA=Phenylethylmalonamide

TOXICITY

Experimental Animals

In the rat, the oral LD_{50} is 1,500 mg/kg (Bogue and Carrinton, 1953) and the intraperitoneal LD_{50} is 240 mg/kg (Chernobrovin *et al*., 1991). In the mouse, the oral LD_{50} is 280 mg/kg (Sullivan and McElhatton, 1975) and the intraperitoneal LD_{50} is 332 mg/kg (Kozhevnikov *et al*., 1981).

Carl *et al*. (1987a) hypothesized that chronic primidone treatment leads to folate depletion through interference with folate metabolism. When rats were treated chronically with primidone (100 mg/kg per 12 hours, *per os*) for up to 8 weeks, there was an effect on folate-dependent metabolism in the liver as measured by an increase in the activity of the major one-carbon generating enzyme 5,10-hydroxymethyltransferase. The authors were not able to identify the primary site for interference with folate metabolism, but suggested that primidone interferes with the synthesis of folylpolyglutamates.

Carl *et al*. (1987b) found that when primidone was given to rats (orally, 100 mg/kg, twice per day) for a week, pentaglutamate derivatives of folates (the major form in rat liver) were decreased in the liver, and total liver and plasma folate concentrations were decreased by 30%. Primidone had no effect on brain folate concentrations, at least within 8 weeks of

treatment. Primidone has also been shown to cause folate depletion in clinical situations (Chanarin, 1979; Rosenberg *et al.*, 1979; Reynolds, 1981).

Primidone given to rats was protective against seizures induced by hexafluorodiethylether (Carl and Smith, 1988). Primidone has also been shown to cause changes in hepatic function and morphology in dogs receiving the drug for 6 months at 55 to 165 mg/kg per day. Histologic findings included hepatocellular hypertrophy attributable to hyperplasia of the smooth endoplasmic reticulum. Single-cell necrosis and multifocal lipidosis were observed. Electron microscopy of the liver showed dilated bile canaliculi and damaged sinusoidal epithelium (Bunch *et al.*, 1985).

It has long been known that phenobarbital, a metabolite of primidone, induces the expression of drug- and steroid-metabolizing enzymes, particularly P450 2A, 2B, and 2C, as well as aldehyde dehydrogenase, epoxide hydrolase, UDP-glucuronyl transferase, and several glutathione S-transferases (Imaoko *et al.*, 1989; Waxman and Azaroff, 1992; Honkakoski *et al.*, 1996).

Humans

Epileptic patients normally require long-term therapy with anticonvulsant drugs. With prolonged use, sporadic side effects reported include folic acid deficiency, induction of hepatic microsomal enzyme systems and hepatotoxic effects, rash, agranulocytosis, thrombocytopenia, lupus-like syndrome, and other nonspecific effects such as fatigue, listlessness, depression, psychosis, decreased libido, and impotence (Mattson *et al.*, 1985; Braide and Davies, 1987; Brodie and Dichter, 1996). Primidone may have a sedative effect, but tolerance to the primidone sedative effect appears to develop even though serum levels of the drug/metabolites remain fairly constant. This tolerance is thought to represent a change in responsiveness rather than a change in metabolism or absorption of the drug (Booker, 1972b).

Chronic anticonvulsant therapy has been associated with folate deficiency, and has been seen with primidone as well as some of the other antiepileptic drugs (e.g., phenytoin and phenobarbital). The mechanism of anticonvulsant-induced folate depletion is unknown. The involvement of these drugs in folate depletion has led to speculation that the folate depletion may be required for anticonvulsant action, but this concept has not been proven. Folate deficiency may cause megaloblastic anemia (Carl *et al.*, 1987a).

In the clinical situation, massive crystalluria has been reported, and the crystals identified as primidone. One case report describes a child that had been on a combination of primidone (250 mg, twice per day) and phenytoin (150 mg/day). One week prior to admission, a routine phenobarbital concentration was less than 4 μg/mL plasma (normal 15 to 40 μg/mL) and a routine phenytoin concentration was 2.5 μg/mL (normal 10 to 20 μg/mL). On admission, the primidone blood concentration was 150 μg/mL (normal 6 to 10 μg/mL), the phenobarbital level was 8.5 μg/mL, and the phenytoin concentration was 33 μg/mL. Kidney damage secondary to the crystalluria was not reported (Turner, 1980).

REPRODUCTIVE TOXICITY AND TERATOGENICITY

Experimental animals

Because of the suggested association between teratogenic effects in epilepsy and drug treatment, a number of animal studies have been carried out. Sullivan and McElhatton (1975) evaluated the teratogenic potential of primidone in albino ICI mice. Primidone was administered either in feed at doses of 500, 1,250, 2,000, or 2,500 mg primidone/kg feed on gestation days 6 through 16, or by gavage at 100, 150, 200, or 250 mg/kg body weight on gestation days 12 through 16. Maternal toxicity (ataxia and low pregnancy rate) was observed in mice fed 200 or 2,500 mg/kg. Dietary administration induced a dose-related increase in the incidence of cleft palates in fetuses. The percentages of fetuses with palatal defects in the feed controls were 0%; 500 mg/kg, 1.6%; 1,250 mg/kg, 3.7%; 2,000 mg/kg, 5.3%; and 2,500 mg/kg, 15.1%. Oral administration induced submucosal cleft palates in 12 of 16 fetuses at 100 mg/kg and full-length cleft palates in 8 of 11 at 150 mg/kg and 6 of 15 at 200 mg/kg. Except for an increase in cutaneous hemorrhages, no other drug-related malformations were observed.

McElhatton *et al.* (1977) administered doses of 0, 25, 50, 100, or 150 mg primidone/kg body weight by

gavage to groups of 9 to 13 ICI albino mice on gestation days 6 through 16. Primidone induced full-length clefts and submucosal and abnormally shaped palatal bones in the fetuses. The numbers of fetuses noted with palatal defects in the treated groups were 16 of 84 (25 mg/kg), 18 of 117 (50 mg/kg), 19 of 102 (100 mg/kg), and 17 of 92 (150 mg/kg), compared to 0 of 85 in the controls.

Oral administration of primidone at 30, 90, or 180 mg/kg body weight to groups of 19 CD-1 mice on gestation days 6 through 16 induced a variety of abnormalities in the fetuses. These included cleft palates (90 and 170 mg/kg), enlarged cerebral ventricles (all doses), club foot (30 and 180 mg/kg), open eyes (180 mg/kg), and hemorrhage in the subarachnoid space (90 mg/kg). In addition, there was an increase in advance fetal resorptions (19.4%) at the 90 mg/kg level when compared to either the vehicle (8.1%) or untreated controls (11.8%). The overall incidence of fetuses with major defects in all treated groups regardless of dose was 4.8% compared to 1.3% in the untreated controls (Sullivan and McElhatton, 1975).

Rao *et al.* (1986) reported that daily dosing of male Swiss mice with primidone at 4.4, 8.8, or 13.1 mg/mouse for 5 consecutive days caused a significant dose-dependent increase in the incidence of sperm-head abnormalities.

The teratogenic effects of primidone may be due to alterations in folic acid metabolism (Carl *et al.*, 1987b).

Folate-deficient epithelial tissues are at increased risk for DNA damage, probably due to the role that folate plays in DNA synthesis, repair and methylation (Blount and Ames, 1995). Recent studies in plants have shown that methylation of DNA is one way of controlling gene activity, and turns off genes during normal development (Ronemus *et al.*, 1996).

Humans

There have been a number of epidemiological surveys in various parts of the world reporting increases in the incidence of congenital malformation in the children of women with epilepsy (Elshove and van Eck, 1971; Spiedel and Meadow, 1972; Fedrick, 1973; Monson *et al.*, 1973; Annegers *et al.*, 1974; Rating *et al.*, 1982), but a cause and effect relationship between exposure to the drug and an adverse effect has not been established. It has not been possible to determine whether the increased malformation rate is due to the disease or to the drugs used in its treatment. Some studies have suggested that the incidence of malformations is higher in epileptics receiving drug treatment during pregnancy (Janz and Fuchs, 1964; Spiedel and Meadow, 1972; Monson *et al.*, 1973; Lindhout *et al.*, 1992).

Primidone has been found in cord blood and in breast milk (Martinez and Snyder, 1973; Nau *et al.*, 1980).

CARCINOGENICITY

Experimental Animals

There have been no previous carcinogenicity studies of primidone in rodents. However, carcinogenicity studies of phenobarbital, a metabolite of primidone, have been reported and are summarized below.

When phenobarbital is given alone to certain strains of rodents without prior exposure to an initiator, it eventually elicits a low to moderate yield of hepatocellular neoplasms, presumably by promotion of naturally ("spontaneously") initiated cells (IARC, 1976, 1987; Feldman *et al.*, 1981; Ward, 1983). Many of these early studies of phenobarbital alone did not differentiate between liver tumor types. Other studies have shown that phenobarbital (500 ppm in drinking water) given to C3H/HeNCr mice at 12 months of age significantly increased the number of gross tumors or microscopic foci and adenomas or carcinomas in the liver (Ward *et al.*, 1988a).

Phenobarbital sodium, administered to CFA mice for 109 weeks at a concentration of 500 mg/kg in feed, increased the incidence of liver tumors: liver tumors occurred in 24/30 exposed males and 21/28 exposed females, compared with 11/45 control males and 10/44 control females (Thorpe and Walker, 1973). In C3H mice exposed to 500 mg/kg phenobarbital in feed for 12 months, the incidence of liver tumors was 16/17 in exposed males and 10/16 exposed females, compared with 7/17 in control males and 1/16 in control females (Peraino *et al.*, 1973a,b). In CF1 mice receiving 0.05% phenobarbital in drinking water for life (maximum duration, 120 weeks), the incidence of liver tumors was 77/98 in treated males and 45/73

in treated females compared with 12/44 untreated males and 0/47 untreated females (Ponomarkov *et al.*, 1976). When phenobarbital was administered to Wistar rats for their lifespan at 500 mg/L in drinking water, 13/36 treated males and 9/34 treated females had liver tumors, compared to none in 36 male and 35 female control rats (Rossi *et al.*, 1977). (These studies did not classify the liver tumors according to the classifications used today.) In contrast, phenobarbital fed to male Fischer rats at 500 ppm for 1 week followed by 1,000 ppm for 103 weeks resulted in foci of nodular hyperplasia in 11/33 rats and parenchymal cell damage in all treated rats, but no evidence for phenobarbital-induced neoplasms (Butler, 1978). Additional studies in CD-1 and B6C3F$_1$ mice administered 10, 75, or 150 mg phenobarbital per kg body weight daily resulted in dose-related increases in the incidences of hepatocellular adenomas and carcinomas, with a predominant eosinophilic phenotypic appearance (McClain, 1993). Hepatoblastomas were also observed in treated B6C3F$_1$ males, and a few hepatocellular carcinomas and hepatoblastomas metastasized to the lung. A clear stepwise progression of lesions was observed in phenobarbital-treated mice from focal areas of altered hepatocytes to focal hyperplasia, adenomas, carcinomas, and metastases. With few exceptions, the carcinomas were found within adenomas, strongly indicating that these arise from adenomas.

Phenobarbital is thought to exert its carcinogenic activity (or "tumor promoting activity") in part by the induction of DNA synthesis in rodents initiated with a genotoxic carcinogen (Klaunig, 1993). Phenobarbital "promotes" liver tumors in mice after initiation by diethylnitrosamine (Klaunig, 1993) or N-nitrosodiethylamine (Rice *et al.*, 1992, 1994; Weghorst *et al.*, 1993/1994) as well as N-nitrosodimethylamine and N-ethoyl-N-nitrosourea (IARC, 1987). Phenobarbital "promotes" liver tumors in rats after initiation by tamoxifen (Carthew *et al.*, 1995) or 2-acetylaminofluorene (Peraino *et al.*, 1971, 1973b, 1980) as well as N-nitrosodiethylamine, 2-methyl-N,N-dimethyl-4-aminoazobenzene, benzo[α]pyrene, cycasin, N-hydroxy-N-formyl- or -acetylaminobiphenyl, N-nitroso-N-(4-hydroxybutyl)butylamine, or N-nitrosomorpholine (IARC, 1987). Phenobarbital has also been shown to "promote" liver tumors in a nonhuman primate (Patas monkey) after initiation with diethylnitrosamine (Palmer *et al.*, 1984). The liver tumor promoting effects of phenobarbital on hepatocellular carcinogenesis in the rodent are markedly dependent on the underlying genotype of the strain; DBA/2 and C3H mice are sensitive to phenobarbital-induced hepatocarcinogenesis, C57BL/6 are resistant and Syrian golden hamsters are generally resistant (Rice *et al.*, 1992).

In a study comparing the responsiveness of three strains of rats to phenobarbital induction of liver enzymes, it was found that the DA and F344/NCr rats showed markedly increased induction of enzymes in comparison to the Zucker rat (Lubet *et al.*, 1992). Phenobarbital promotes hepatocarcinogenesis in more than a single rodent species and in nonhuman primates.

In a study comparing the roles of Aroclor-1254, dichlorodiphenyltrichloroethane, and phenobarbital on the promotion of liver tumors in D2B6F$_1$ mice receiving N-nitrosodiethylamine as the inducing agent, phenobarbital was the most effective agent in stimulating the evolution of hepatocellular neoplasms to hepatoblastomas (Diwan *et al.*, 1994).

Phenobarbital fed to rats at 500 ppm has been shown to induce hepatic P4502B1 by 40 fold. Phenobarbital induces this enzyme in the mouse and Patas monkey but not in the Syrian hamster (Rice *et al.*, 1992), suggesting that induction of this enzyme may be predictive of susceptibility to liver tumor promotion among species. Other studies have suggested that the phenobarbital-induced liver monoxygenase system may potentiate the formation of reactive oxygen in neoplastic liver nodules (Scholz *et al.*, 1990).

It has been hypothesized that exposure to phenobarbital causes chronic cytotoxicity that may result in increased cell turnover, which leads to increased susceptibility to cancer. However, several chronic hepatotoxins (e.g., butylated hydroxytoluene, diallylphthalate, acetaminophen) are not carcinogenic in mice or rats. In order to further understand the mechanisms in phenobarbital liver carcinogenicity in the mouse, phenobarbital was given to male B6C3F$_1$ mice in drinking water at 500 ppm for 40 weeks. This treatment regimen was evaluated for its effects on histopathological lesions and cell turnover. It was found that phenobarbital caused increases in liver/body weight ratios and centrilobular cytomegaly, but

not thymidine kinase activity or DNA synthesis as measured by tritiated thymidine autoradiography or bromodeoxyuridine immunohistochemistry. Thus, in these studies there were no consistent chronic effects on cell turnover (as measured by label index and thymidine kinase activity) that correlated with the carcinogenic or tumor-promoting capability of phenobarbital (Ward *et al.*, 1988b).

Humans

There have been a number of studies to investigate the possible influence of anticonvulsant treatment on cancer risk. Olsen *et al.* (1993) reported that, in a nested case-control study of 104 lung cancers and 18 bladder cancers in patients taking a variety of anticonvulsant drugs (including phenobarbital, phenytoin, primidone, ospolate, carbamazepine, oxazolidine, etosuximide and other drugs) and 322 cancer-free controls, there was no indication that anticonvulsant treatment was associated with these cancers. There was some suggestion that phenobarbital treatment reduced the incidence of bladder cancer. [In a previous study done by the same group in Denmark, an association was reported between anticonvulsant drug therapy and an increase in lung cancer and a decrease in bladder cancer (Olsen *et al.*, 1989), but this was not confirmed in the 1991 study.] Olsen *et al.* (1995) also found that antiepileptic treatment was not associated with an increased risk for hepatobiliary cancer.

GENETIC TOXICITY

Primidone was mutagenic in *Salmonella typhimurium* strain TA1535 when tested in the absence of S9 exogenous metabolic activation; no mutagenic activity was detected in the presence of S9, or in any of the other tester strains employed, with or without S9 (Mortelmans *et al.*, 1986). No increase in the frequency of sex-linked recessive lethal mutations was noted in male *Drosophila melanogaster* treated as larvae by feeding on solutions of 6 to 12 mM primidone (Zolotareva *et al.*, 1979). No increases in sister chromatid exchanges or chromosomal aberrations were induced in cultured Chinese hamster ovary cells after primidone exposure with and without S9 activation (Riedel and Obe, 1984), and chromosomal aberrations were not induced in human peripheral lymphocytes treated *in vitro* in the absence of S9 (Stenchever and Allen, 1973; Bishun *et al.*, 1975). In two independent tests, primidone did not induce dominant lethal mutations in germ cells of male mice treated by single intraperitoneal injection (maximum doses of 90 or 400 mg/kg, respectively) (Epstein *et al.*, 1972; Zolotareva *et al.*, 1979). No induction of chromosomal aberrations was reported in bone marrow cells of male mice treated with up to 400 mg/kg primidone by intraperitoneal injection (Zolotareva *et al.*, 1979). There is one report of increased frequencies of micronucleated polychromatic erythrocytes in bone marrow of mice administered 13.11 mg primidone (approximately 500 mg/kg) twice at an interval of 24 hours (Rao *et al.*, 1986); however, this study had protocol deficiencies that make the interpretation of the data questionable. Chromosomal effects from primidone (somatic or germinal) *in vivo* have been suggested by Buckel (1975, 1976); these reports are abstracts that contain no data, statistics, or methods. The current NTP studies and other published reports do not support these claims of *in vivo* mammalian chromosomal effects.

In summary, the genetic toxicity data for primidone are limited in scope and amount, but suggest that the mutagenic action of the chemical is highly specific: clear demonstration of the mutagenic activity of primidone was limited to a single report of mutation induction in *S. typhimurium* strain TA1535 in the absence of S9 metabolic activation only (Mortelmans *et al.*, 1986).

A greater amount of mutagenicity test data exists for phenobarbital, a major metabolite of primidone. The activity profile of this drug is similar to that of the parent compound. *In vitro* studies gave isolated positive results with weak mutagenic activity demonstrated in *S. typhimurium* strain TA1535 in the presence of S9 (Zeiger and Haworth, 1985), induction of aneuploidy observed in *Saccharomyces cerevisiae* without S9 activation (Albertini *et al.*, 1985), and weak activity demonstrated in the cultured Chinese hamster ovary cell chromosomal aberrations assay (Gulati *et al.*, 1985). Negative results were reported in tests for induction of DNA single strand breaks in hamster V79 cells (Swenberg *et al.*, 1976), sister chromatid exchanges and chromosomal aberrations in Chinese hamster ovary cells (Riedel and Obe, 1984) and human fetal fibroblasts (Stenchever and

Jarvis, 1971), with and without S9. No initiation of unscheduled DNA synthesis, indicative of DNA damage, was detected in rat cell cultures treated with phenobarbital (Ide *et al.*, 1981; Althaus *et al.*, 1982).

In vivo, no induction of DNA single strand breaks was noted in NMRI mice administered 0.1% phenobarbital in drinking water for 5 days (Schwarz *et al.*, 1979) or Sprague-Dawley rats given 0.05% phenobarbital in feed for 5 weeks (Brambilla *et al.*, 1986).

The frequency of micronucleated erythrocytes in mouse bone marrow was not increased after two intraperitoneal injections of 116 mg/kg phenobarbital (King *et al.*, 1979). Two laboratories reported positive results with phenobarbital in cytogenetic tests conducted *in vivo* with mice (Nandan and Rao, 1981, 1982, 1983) and human epilepsy patients (Kulkarni *et al.*, 1984); however, both investigations contained unusual protocols and the results require independent confirmation.

STUDY RATIONALE

Primidone was nominated by the National Cancer Institute for study because there were no previous toxicity or carcinogenicity studies reported in the literature. The chemical was administered in the feed because the drug is given orally in the clinical situation.

MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF PRIMIDONE

Primidone was obtained from Siegfried, LTD (Zofingen, Switzerland) in one lot (G041889). Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory, Research Triangle Institute (Research Triangle Park, NC) (Appendix J). Reports on analyses performed in support of the primidone studies are on file at the NIEHS.

The chemical, a white crystalline powder, was identified as primidone by melting point, infrared, ultraviolet/visible, nuclear magnetic resonance spectroscopy, and low- and high-resolution mass spectrometry. The purity of lot G041889 was determined by Karl Fischer water analysis, thin-layer chromatography, and high-performance liquid chromatography. Karl Fischer water analysis indicated 0.27% ± 0.01% water. Thin-layer chromatography by two systems indicated a major product spot and no impurities. High-performance liquid chromatography revealed a major peak and one impurity with an area of 0.06% by one system or 0.32% by a second system relative to the major peak area. The overall purity was determined to be greater than 99%.

Accelerated stability studies of the bulk chemical were performed by the analytical chemistry laboratory using high-performance liquid chromatography. These studies indicated that primidone was stable as a bulk chemical for 2 weeks when stored protected from light at 22° to 27° C. To ensure stability, the bulk chemical was stored at room temperature protected from light in plastic bags in metal containers.

Stability was monitored over the course of the 14-day, 14-week, and 2-year studies using high-performance liquid chromatography. No degradation of the bulk chemical was detected.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

The dose formulations were prepared once during the 14-day studies, five times during the 14-week studies, and approximately every 6 weeks during the 2-year studies by mixing primidone with feed (Table J1). Homogeneity and stability studies of the 300 and 5,000 ppm dose formulations for the 14-week studies and of 300 and 2,500 ppm dose formulations for the 2-year studies were performed by the study laboratory using high-performance liquid chromatography. Homogeneity was confirmed, and the stability of the dose formulations was confirmed for at least 28 days at –14° to –19° C when stored in sealed glass bottles. The study laboratory confirmed stability for dose formulations stored in plastic containers at 5° C for at least 35 days.

Periodic analyses of the dose formulations of primidone were conducted at the study laboratory using high-performance liquid chromatography. For the 14-week studies, dose formulations were analyzed three times during the studies (Table J3). During the 2-year studies, dose formulations were analyzed approximately every 8 weeks (Table J4). Of the dose formulations analyzed and used during the 14-day studies, all formulations were within 10% of the target. Of the dose formulations analyzed and used during the 14-week studies, all formulations were within 10% of the target concentration; all animal room samples for rats and 14 of 15 animal room samples for mice were within 10% of the target concentration. Of the dose formulations analyzed and used during the 2-year studies, 57 of 58 dose formulations for rats and 37 of 39 dose formulations for mice were within 10% of the target concentration; all animal room samples for rats and 9 of 12 animal room samples for mice were also within 10% of the target concentration. One dose formulation that was 111% of the target concentration was fed to mice; all dose formulations given to rats were within 10% of the target concentration.

14-DAY STUDIES

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Taconic Farms (Germantown, NY). On receipt, the rats and mice were 4 weeks old. Animals were quarantined for 11 or 12 days and were 42 or 43 days old on the first day of the studies. Groups of five male and five female rats were fed diets containing 0, 1,250, 2,500, 5,000, 10,000, or 20,000 ppm primidone. Groups of five male and five female mice were fed diets containing 0, 625, 1,250, 2,500, 5,000, or 10,000 ppm primidone. Feed and water were available *ad libitum*. Rats were housed five per cage and mice were housed individually. Clinical findings were recorded twice daily for rats and mice. Feed consumption was recorded twice weekly for rats and weekly for mice by cage. The animals were weighed initially, weekly, and at the end of the studies. Details of the study design and animal maintenance are summarized in Table 4.

14-WEEK STUDIES

The 14-week studies were conducted to evaluate the cumulative toxic effects of repeated exposure to primidone and to determine the appropriate exposure concentrations to be used in the 2-year studies.

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Simonsen Laboratories (Gilroy, CA). On receipt, the rats and mice were 4 weeks old. Animals were quarantined for 11 or 12 days and were 40 to 42 days old on the first day of the studies. Before the studies began, five male and five female rats and mice were randomly selected for parasite evaluation and gross observation for evidence of disease. At the end of the studies, serologic analyses were performed on five male and five female control rats and mice using the protocols of the NTP Sentinel Animal Program (Appendix M).

Groups of 20 male and 20 female rats and 10 male and 10 female mice were fed diets containing 0, 300, 600, 1,300, 2,500, or 5,000 ppm primidone. Ten male and ten female rats were designated as special study animals for hematology and clinical chemistry evaluations. Feed and water were available *ad libitum*. Rats were housed five per cage and mice were housed individually. Clinical findings were recorded weekly for rats and mice. Feed consumption was recorded twice weekly for rats and weekly for mice by cage. The animals were weighed initially, weekly, and at the end of the studies. Details of the study design and animal maintenance are summarized in Table 4.

At all time points, rats were anesthetized with CO_2 or a CO_2/O_2 mixture for blood collection. Blood for hematology was collected in tubes containing potassium EDTA as the anticoagulant. Blood for serum analyses was collected in containers without anticoagulant, allowed to clot at room temperature, and centrifuged to separate serum. Hematology determinations, including erythrocyte and leukocyte counts, hemoglobin concentration, hematocrit, mean cell volume, mean cell hemoglobin, and mean cell hemoglobin concentration, were performed on a Serono-Baker System 9000 hematology analyzer (Baker Instruments, Allentown, PA). Differential leukocyte counts and morphologic evaluation of blood cells were performed by light microscopic examination of blood films stained with Wright-Giemsa. Reticulocyte counts were performed by light microscopy, using smears prepared from blood stained by incubating equal volumes of whole blood and new methylene blue for at least 20 minutes. A Miller disc was used for reticulocyte quantitation. All clinical chemistry evaluations were performed on a Hitachi 704® chemistry analyzer (Boehringer Mannheim, Indianapolis, IN) using reagents obtained from the manufacturer. Reagents for sorbitol dehydrogenase and total bile salts analyses were obtained from Sigma Diagnostics (St. Louis, MO). The parameters measured are listed in Table 4.

At the end of the 14-week studies, samples were collected for sperm motility and vaginal cytology evaluations on rats and mice exposed to 0, 1,300, 2,500, or 5,000 ppm. The parameters evaluated are listed in Table 4. Methods used were those described in the NTP's sperm morphology and vaginal cytology evaluations protocol (NTP, 1987). For 12 consecutive days prior to scheduled terminal sacrifice, the vaginal vaults of the females were moistened with saline, if necessary, and samples of vaginal fluid and cells were stained. Relative numbers of leukocytes, nucleated epithelial cells, and large squamous epithelial cells were determined and used to ascertain estrous cycle stage (i.e., diestrus, proestrus, estrus, and metestrus). Male animals were evaluated for sperm count and motility. The left testis and left epididymis were isolated and weighed. The tail of the

epididymis (cauda epididymis) was then removed from the epididymal body (corpus epididymis) and weighed. Test yolk (rats) or modified Tyrode's buffer (mice) was applied to slides and a small incision was made at the distal border of the cauda epididymis. The sperm effluxing from the incision were dispersed in the buffer on the slides, and the numbers of motile and nonmotile spermatozoa were counted for five fields per slide by two observers. Following completion of sperm motility estimates, each left cauda epididymis was placed in buffered saline solution. Caudae were finely minced, and the tissue was incubated in the saline solution and then heat fixed at 65° C. Sperm density was then determined microscopically with the aid of a hemacytometer. To quantify spermatogenesis, the testicular spermatid head count was determined by removing the tunica albuginea and homogenizing the left testis in phosphate-buffered saline containing 10% dimethyl sulfoxide. Homogenization-resistant spermatid nuclei were counted with a hemacytometer.

A necropsy was performed on all core study animals. The heart, right kidney, liver, lung, right testis, thymus, and thyroid gland were weighed. Tissues for microscopic examination were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned to a thickness of 4 to 6 μm, and stained with hematoxylin and eosin. A complete histopathologic examination was performed on 0 and 5,000 ppm rats and mice. Table 4 lists the tissues and organs routinely examined.

2-Year Studies

Study Design

Groups of 50 male and 50 female rats were fed diets containing 0, 600, 1,300, or 2,500 ppm primidone for 104 weeks. Groups of 50 male and 50 female mice were fed diets containing 0, 300, 600, or 1,300 ppm primidone for 104 to 105 weeks.

Source and Specification of Animals

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Taconic Farms (Germantown, NY) for use in the 2-year studies. Rats and mice were quarantined for 9 or 13 days before the beginning of the studies. Five male and five female rats and mice were randomly selected for parasite evaluation and gross observation of disease. Rats were 41 or 42 days old and mice 38 or 39 days old at the beginning of the studies. The health of the animals was monitored during the studies according to the protocols of the NTP Sentinel Animal Program (Appendix M).

Animal Maintenance

Rats and female mice were housed five per cage and male mice were housed individually. Feed and water were available *ad libitum*. Feed consumption was measured over a 7-day period during study weeks 1 and 4, then once every 4 weeks thereafter by cage. Cages for rats and female mice were changed twice weekly; cages for male mice were changed weekly. Further details of animal maintenance are given in Table 4. Information on feed composition and contaminants is provided in Appendix L.

Clinical Examinations and Pathology

All animals were observed twice daily. Clinical findings were recorded initially and then monthly thereafter; body weights were recorded initially, then monthly, and at the end of the studies.

On the last 2 days of the 2-year studies, blood was collected from the retroorbital sinus of three anesthetized female rats in each group or via cardiac puncture of three male and female mice per group. There were not sufficient numbers of male rats alive at the end of the study for determination of plasma concentrations of primidone and phenobarbital. Blood samples were collected at five time points (8:30 a.m., 2:30 p.m., 8:00 p.m., 10:00 p.m., and 8:30 a.m.) for the determination of plasma concentrations of primidone and/or phenobarbital. Feed was available *ad libitum* during the collection period. The plasma was stored at –20° C or lower until analysis. Plasma samples were analyzed using a procedure for the analysis of concentrations of primidone and phenobarbital developed during the single-dose toxicokinetic studies (Appendix N). Plasma was separated via centrifugation and was analyzed using high-performance liquid chromatography. The average plasma concentrations of primidone and phenobarbital and standard deviations were calculated. The logarithms of these values were plotted as a function of time. Results of analyses of plasma concentrations of primidone and/or phenobarbital at the end of the 2-year studies are given in Appendix H.

Complete necropsies and microscopic examinations were performed on all rats and mice. 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 paraffin, sectioned to a thickness of 5 to 6 μm, and stained with hematoxylin and eosin for microscopic examination. For extended evaluation of renal tubule proliferative lesions in male rats, kidneys were step-sectioned at 1 mm intervals to obtain a maximum of four additional sections per kidney. For all paired organs (e.g., adrenal gland, kidney, ovary), samples from each organ were examined. Tissues examined microscopically are listed in Table 4.

Microscopic evaluations were completed by the study laboratory pathologist, and the pathology data were entered into the Toxicology Data Management System. The microscopic slides, paraffin blocks, and residual wet tissues were sent to the NTP Archives for inventory, slide/block match, and wet tissue audit. The slides, individual animal data records, and pathology tables were evaluated by an independent quality assessment laboratory. 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 reviewed the adrenal gland cortex and medulla of male and female rats, bone marrow of female rats, heart of male rats, kidney of male rats, liver, ovary of female mice, pancreatic islets of male and female mice, pituitary gland (pars distalis) of female mice, spleen of male rats and male and female mice, thyroid gland of male rats and male and female mice, and uterus of female mice.

The quality assessment report and the reviewed slides were submitted to the NTP Pathology Working Group (PWG) chairperson, who reviewed the selected tissues and addressed any inconsistencies in the diagnosis 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 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).

TABLE 4
Experimental Design and Materials and Methods in the Feed Studies of Primidone

14-Day Studies	14-Week Studies	2-Year Studies
Study Laboratory		
Battelle Columbus Laboratories (Columbus, OH)	Battelle Columbus Laboratories (Columbus, OH)	Battelle Columbus Laboratories (Columbus, OH)
Strain and Species		
Rats: F344/N Mice: $B6C3F_1$	Rats: F344/N Mice: $B6C3F_1$	Rats: F344/N Mice: $B6C3F_1$
Animal Source		
Taconic Farms (Germantown, NY)	Simonsen Laboratories, Inc. (Gilroy, CA)	Taconic Farms (Germantown, NY)
Time Held Before Studies		
Rats: 11 days Mice: 12 days	Rats: 11 days Mice: 12 days	Rats: 13 days Mice: 9 days
Average Age When Studies Began		
Rats: 42 days Mice: 43 days	Rats: 40 days (males) or 41 days (females) Mice: 41 days (males) or 42 days (females)	Rats: 41 days (males) or 42 days (females) Mice: 38 days (males) or 39 days (females)
Date of First Dose		
Rats: 17 September 1990 Mice: 18 September 1990	Rats: 17 December 1990 (males) 18 December 1990 (females) Mice: 11 December 1990 (males) 12 December 1990 (females)	Rats: 6 April 1992 (males) 7 April 1992 (females) Mice: 16 April 1992 (males) 17 April 1992 (females)
Duration of Dosing		
14 days (7 days/week)	92 days (core study animals) 22 days (special study rats) (7 days/week)	Rats: 104 weeks (7 days/week) Mice: 104-105 weeks (7 days/week)
Date of Last Dose		
Rats: 1 October 1990 Mice: 2 October 1990	Rats: 18 March 1991 (males) 19 March 1991 (females) Mice: 12 March 1991 (males) 13 March 1991 (females)	Rats: 29 March 1994 (males 29-31 March 1994 (females) Mice: 11–12 April 1994 (males) 13–15 April 1994 (females)
Necropsy Dates		
Rats: 1 October 1990 Mice: 2 October 1990	Rats: 18 March 1991 (males) 19 March 1991 (females) Mice: 12 March 1991 (males) 13 March 1991 (females)	Rats: 29 March 1994 (males) 29-31 March 1994 (females) Mice: 11–12 April 1994 (males) 13–15 April 1994 (females)
Average Age at Necropsy		
8 weeks	19 weeks	110 weeks
Size of Study Groups		
5 males and 5 females	Rats: 20 males and 20 females Mice: 10 males and 10 females	50 males and 50 females
Method of Distribution		
Animals were distributed randomly into groups of approximately equal initial mean body weights.	Same as 14-day studies	Same as 14-day studies
Animals per Cage		
Rats: 5 Mice: 1	Rats: 5 Mice: 1	Rats: 5 Mice: 1 (males) or 5 (females)

TABLE 4
Experimental Design and Materials and Methods in the Feed Studies of Primidone

14-Day Studies	14-Week Studies	2-Year Studies
Method of Animal Identification		
Tail tattoo	Tail tattoo	Tail tattoo
Diet		
NIH-07 open formula meal diet (Zeigler Brothers, Inc., Gardners, PA), available *ad libitum*	Same as 14-day studies	Same as 14-day studies
Water		
Tap water (City of Columbus municipal supply) via automatic watering system (Edstrom Industries, Inc., Waterford, WI), available *ad libitum*	Same as 14-day studies	Same as 14-day studies
Cages		
Polycarbonate (Lab Products, Inc., Maywood, NJ), changed twice per week in rat studies and changed weekly in mice studies	Same as 14-day studies	Same as 14-day studies, except female mouse cages changed twice per week
Bedding		
Sani-Chips (P.J. Murphy Forest Products Corp., Montville, NJ), changed twice per week in rat studies and weekly in mice studies	Same as 14-day studies	Same as 14-day studies, except female mouse bedding changed twice per week
Cage Filters		
DuPont 2024 spun-bonded polyester (Snow Filtration Co., Cincinnati, OH), changed every other week	Same as 14-day studies	Same as 14-day studies
Animal Room Environment		
Temperature: 21.1°–23.3° C Relative humidity: 52%–65% Room fluorescent light: 12 hours/day Room air changes: 10/hour	Temperature: 21.1°–23.9° C (rats) or 21.1°–25.0° C (mice) Relative humidity: 40%–62% (rats) or 20%–97% (mice) Room fluorescent light: 12 hours/day Room air changes: 10/hour	Temperature: 20.6°–25.6° C (rats) or 19.4°–25.0° C (mice) Relative humidity: 31%–62% (rats) or 30%–63% (mice) Room fluorescent light: 12 hours/day Room air changes: 10/hour
Doses		
Rats: 0, 1,250, 2,500, 5,000, 10,000, or 20,000 ppm in feed, available *ad libitum*. Mice: 0, 625, 1,250, 2,500, 5,000, or 10,000 ppm in feed, available *ad libitum*	0, 300, 600, 1,300, 2,500, or 5,000 ppm in feed, available *ad libitum*	Rats: 0, 600, 1,300, or 2,500 ppm in feed, available *ad libitum* Mice: 0, 300, 600, or 1,300 ppm in feed, available *ad libitum*
Type and Frequency of Observation		
Observed twice daily; animals were weighed initially, weekly, and at the end of the studies; clinical findings were recorded twice daily. Feed consumption was recorded twice weekly for rats and weekly for mice by cage.	Observed twice daily; animals were weighed initially, weekly, and at the end of the studies; clinical findings were recorded weekly. Feed consumption was recorded twice weekly for rats and weekly for mice by cage.	Observed twice daily; animals were weighed initially, weekly for 13 weeks, monthly thereafter, and at the end of the studies; clinical findings were recorded initially and then monthly thereafter. Feed consumption was recorded over a 7-day period during study weeks 1 and 4, then once every 4 weeks thereafter.

TABLE 4
Experimental Design and Materials and Methods in the Feed Studies of Primidone

14-Day Studies	14-Week Studies	2-Year Studies
Method of Sacrifice		
Anesthetization with carbon dioxide followed by exsanguination by cardiac puncture	Same as 14-day studies	Same as 14-day studies
Necropsy		
None	Necropsy performed on all core study animals. Organs weighed were heart, right kidney, liver, lung, right testis, thymus, and thyroid gland.	Necropsy performed on all animals.
Clinical Pathology		
None	Blood was collected from the retroorbital sinus of special study rats on study days 4 and 22 and of core study rats surviving to the end of the study for hematology and clinical chemistry. ***Hematology:*** hematocrit, hemoglobin concentration, erythrocyte, reticulocyte, and nucleated erythrocyte counts, mean cell volume, mean cell hemoglobin, mean cell hemoglobin concentration, platelet count, and total leukocyte count and differentials. ***Clinical chemistry:*** urea nitrogen, creatinine, total protein, albumin, alanine aminotransferase, alkaline phosphatase, creatine kinase, sorbitol dehydrogenase, and bile salts.	None
Histopathology		
None	Complete histopathology was performed on 0, and 5,000 ppm rats and mice. In addition to gross lesions and tissue masses, the following tissues were examined: adrenal gland, brain, clitoral gland, esophagus, femur, gallbladder (mice), harderian gland (mice), heart, large intestine (cecum, colon, rectum), small intestine (duodenum, jejunum, ileum), kidney, liver, lung, lymph nodes (mandibular and mesenteric), mammary gland with adjacent skin, nasal cavity and turbinates, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, spleen, stomach (forestomach and glandular), testes with epididymis and seminal vesicle, thymus, thyroid gland, trachea, urinary bladder, and uterus. In rats, the liver and kidney (males) were examined to a no-effect-level. In mice, the adrenal gland, liver, and spleen were examined to a no-effect-level.	Complete histopathology was performed on all rats and mice. In addition to gross lesions and tissue masses, the following tissues were examined: adrenal gland, brain, clitoral gland, esophagus, femur, gallbladder (mice), heart, large intestine (cecum, colon, rectum), small intestine (duodenum, jejunum, ileum), kidney, liver, lungs, lymph nodes (mandibular and mesenteric), mammary gland with adjacent skin, nasal cavity and turbinates, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, spleen, stomach (forestomach and glandular), testes with epididymis and seminal vesicle, thymus, thyroid gland, trachea, urinary bladder, and uterus.

TABLE 4
Experimental Design and Materials and Methods in the Feed Studies of Primidone

14-Day Studies	14-Week Studies	2-Year Studies
Sperm Motility and Vaginal Cytology		
None	At the end of the studies, sperm samples were collected from all male animals in the 0, 1,300, 2,500, and 5,000 ppm groups for sperm motility evaluations. The parameters evaluated included spermatid heads, spermatid count, motility, and concentration. The left cauda, left epididymis, and left testis were weighed. Vaginal samples were collected for up to 12 consecutive days prior to the end of the studies from all females exposed to 0, 1,300, 2,500, or 5,000 ppm for vaginal cytology evaluations. The parameters evaluated included relative frequency of estrous stages and estrous cycle length.	None
Determinations of Primidone and Phenobarbital in Plasma		
None	None	On the last 2 days of the studies, blood was collected from the retroorbital sinus of three female rats or by cardiac puncture from three male and three female mice from each group at five time points (8:30 a.m., 2:30 p.m., 8:00 p.m., 10:00 p.m., and 8:30 a.m.) for the determination of plasma concentrations of primidone and/or phenobarbital.

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 or missing 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 incidences of neoplasms or nonneoplastic lesions are presented in Tables A1, A5, B1, B5, C1, C5, D1, and D5 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 most neoplasms (Tables A3, B3, C3, and D3) and all nonneoplastic lesions are given as the numbers of animals affected at each site examined microscopically. However, when macroscopic examination was required to detect neoplasms in certain tissues (e.g., harderian gland, intestine, mammary gland, and skin) before microscopic evaluation, or when neoplasms had multiple potential sites of occurrence (e.g., leukemia or lymphoma), the denominators consist of the number of animals on which a necropsy was performed. Tables A3, B3, C3, and D3 also give the survival-adjusted neoplasm rate for each group and each site-specific neoplasm, i.e., the Kaplan-Meier estimate of the neoplasm incidence that would have been observed at the end of the study in the absence of mortality from all other competing risks (Kaplan and Meier, 1958).

Analysis of Neoplasm Incidences

The majority of neoplasms in these studies were considered to be incidental to the cause of death or not rapidly lethal. Thus, the primary statistical method used was logistic regression analysis, which assumed that the diagnosed neoplasms were discovered as the result of death from an unrelated cause and thus did not affect the risk of death. In this approach, neoplasm prevalence was modeled as a logistic function of chemical exposure and time. Both linear and quadratic terms in time were incorporated initially, and the quadratic term was eliminated if the fit of the model was not significantly enhanced. The neoplasm incidences of exposed and control groups were compared on the basis of the likelihood score test for the regression coefficient of dose. This method of adjusting for intercurrent mortality is the prevalence analysis of Dinse and Lagakos (1983), further described and illustrated by Dinse and Haseman (1986). When neoplasms are incidental, this comparison of the time-specific neoplasm prevalences also provides a comparison of the time-specific neoplasm incidences (McKnight and Crowley, 1984).

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

Tests of significance included pairwise comparisons of each exposed group with controls and a test for an overall dose-related trend. Continuity-corrected tests were used in the analysis of neoplasm incidence, and reported P values are one sided. The procedures described in the preceding paragraphs were also used to evaluate selected nonneoplastic lesions. For further discussion of these statistical methods, refer to Haseman (1984).

Analysis of Nonneoplastic Lesion Incidences

Because all nonneoplastic lesions in this study were considered to be incidental to the cause of death or not rapidly lethal, the primary statistical analysis used was a logistic regression analysis in which non-neoplastic lesion prevalence was modeled as a logistic function of chemical exposure and time.

Analysis of Continuous Variables

Two approaches were employed to assess the significance of pairwise comparisons between exposed and control groups in the analysis of continuous variables. Organ and body weight data, which historically have approximately normal distributions, were analyzed with the parametric multiple comparison procedures of Dunnett (1955) and Williams (1971, 1972). Hematology, clinical chemistry, spermatid, and epididymal spermatozoal data, which have typically skewed distributions, were analyzed using the nonparametric multiple comparison methods of Shirley (1977) and Dunn (1964). Jonckheere's test (Jonckheere, 1954) was used to assess the significance of the dose-related trends and to determine whether a trend-sensitive test (Williams' or Shirley's test) was more appropriate for pairwise comparisons than a test that does not assume a monotonic dose-related trend (Dunnett's or Dunn's test). Prior to statistical analysis, extreme values identified by the outlier test of Dixon and Massey (1951) were examined by NTP personnel, and implausible values were eliminated from the analysis. Average severity values were analyzed for significance with the Mann-Whitney U test (Hollander and Wolfe, 1973). Because vaginal cytology data are proportions (the proportion of the observation period that an animal was in a given estrous stage), an arcsine transformation was used to bring the data into closer conformance with a normality assumption. Treatment effects were investigated by applying a multivariate analysis of variance (Morrison, 1976) to the transformed data to test for simultaneous equality of measurements across exposure concentrations.

Historical Control Data

Although the concurrent control group is always the first and most appropriate control group used for evaluation, historical control data can be helpful in the overall assessment of neoplasm incidence in certain instances. Consequently, neoplasm incidences from the NTP historical control database, which is updated yearly, are included in the NTP reports for neoplasms appearing to show compound-related effects.

QUALITY ASSURANCE METHODS

The 14-week and 2-year studies were conducted in compliance with Food and Drug Administration Good Laboratory Practice Regulations (21 CFR, Part 58). In addition, as records from the 2-year studies were submitted to the NTP Archives, these studies were audited retrospectively by an independent quality assurance contractor. 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 NIEHS. The audit findings were reviewed and assessed by NTP staff, so all comments had been resolved or were otherwise addressed during the preparation of this Technical Report.

GENETIC TOXICOLOGY

The genetic toxicity of primidone was assessed by testing the ability of the chemical to induce mutations in various strains of *Salmonella typhimurium*, sister chromatid exchanges and chromosomal aberrations in cultured Chinese hamster ovary cells, and increases in the frequency of micronucleated polychromatic bone marrow erythrocytes in mice. The protocols for these studies and the results are given in Appendix E.

The genetic toxicity studies of primidone are part of a larger effort by the NTP to develop a database that would permit the evaluation of carcinogenicity in experimental animals from the molecular structure and the effect of the chemical in short-term *in vitro* and *in vivo* genetic toxicity tests. These genetic toxicity tests were originally developed to clarify mechanisms of chemical-induced DNA damage growing out of the earlier electrophilicity/mutagenicity relationship proposed by Miller and Miller (1977) and the somatic mutation theory of cancer (Straus, 1981; Crawford, 1985). Therefore, the information obtained from these tests applies only to mutagenic carcinogens.

There is a strong correlation between a chemical's potential electrophilicity (structural alert to DNA reactivity), mutagenicity in *Salmonella*, and carcinogenicity in rodents. The combination of electrophilicity and *Salmonella* mutagenicity is highly correlated with the induction of carcinogenicity in rats and mice and/or at multiple tissue sites (Ashby and Tennant, 1991). Other *in vitro* genetic toxicity tests correlate less well with rodent carcinogenicity (Tennant *et al.*, 1987; Zeiger *et al.*, 1990), although these other tests can provide information on the types of DNA and chromosome effects that can be induced by the chemical being investigated. Data from NTP studies show that a positive response in *Salmonella* is the most predictive *in vitro* test for rodent carcinogenicity (89% of the *Salmonella* mutagens are rodent carcinogens), and that there is no complementarity among the *in vitro* genetic toxicity tests. That is, no battery of tests that included the *Salmonella* test improved the predictivity of the *Salmonella* test alone. The predictivity for carcinogenicity of a positive response in bone marrow chromosome aberration or micronucleus tests appears to be less than the *Salmonella* test (Shelby *et al.*, 1993; Shelby and Witt, 1995). Positive responses in long-term peripheral blood micronucleus tests have not been formally evaluated for their predictivity for rodent carcinogenicity. But, because of the theoretical and observed associations between induced genetic damage and adverse effects in somatic and germ cells, the determination of *in vivo* genetic effects is important to the overall understanding of the risks associated with exposure to a particular chemical.

RESULTS

RATS

14-DAY STUDY

One 10,000 ppm male, two 20,000 ppm males, and all 20,000 ppm females died before the end of the study (Table 5). The final mean body weights and mean body weight gains of 10,000 ppm males and females and of 20,000 ppm males were significantly lower than those of the controls; the final mean body weight of 20,000 ppm males was less than the initial mean body weight. Feed consumption by the 20,000 ppm males was less than that by the controls. Feed consumption by all other exposed groups was generally similar to that by the controls. Dietary levels of 1,250, 2,500, 5,000, 10,000, or 20,000 ppm primidone resulted in average daily doses of approximately 120, 240, 500, 970, or 1,100 mg primidone/kg body weight to males and 120, 240, 500, or 900 mg/kg to females. The average daily dose for 20,000 ppm females was not calculated due to high mortality. Males and females in the 10,000 and 20,000 ppm groups were observed to have eye discharge, ataxia, and abnormal posture and were thin and lethargic.

TABLE 5
Survival, Body Weights, and Feed Consumption of Rats in the 14-Day Feed Study of Primidone

Dose (ppm)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)	Feed Consumption[c]	
		Initial	Final	Change		Day 7	Day 14
Male							
0	5/5	136 ± 7	211 ± 5	75 ± 4		16.3	16.8
1,250	5/5	133 ± 7	208 ± 8	75 ± 1	99	15.4	17.4
2,500	5/5	138 ± 7	212 ± 9	74 ± 3	100	15.9	17.1
5,000	5/5	137 ± 8	207 ± 9	70 ± 3	98	15.9	17.9
10,000	4/5[d]	133 ± 9	175 ± 7**	46 ± 4**	83	15.1	14.9
20,000	3/5[e]	139 ± 7	123 ± 9**	−25 ± 4**	58	6.8	7.6
Female							
0	5/5	103 ± 3	140 ± 4	36 ± 2		11.3	12.1
1,250	5/5	101 ± 2	135 ± 2	34 ± 2	97	10.4	11.4
2,500	5/5	104 ± 2	137 ± 2	32 ± 2	98	11.2	11.5
5,000	5/5	105 ± 2	138 ± 3	34 ± 1	99	12.2	12.0
10,000	5/5	104 ± 2	125 ± 2**	20 ± 2**	89	9.4	11.3
20,000	0/5[f]	103 ± 3	—	—	—	4.4	—

** Significantly different (P≤0.01) from the control group by Williams' or Dunnett's test
[a] Number of animals surviving at 14 days/number initially in group. Subsequent calculations are based on animals surviving to the end of the study.
[b] Weights and weight changes are given as mean ± standard error. No data were calculated for groups with 100% mortality.
[c] Feed consumption is expressed as grams of feed consumed per animal per day.
[d] Day of death: 9
[e] Day of death: 9, 12
[f] Day of death: 5, 6, 9

14-WEEK STUDY

All rats survived to the end of the study (Table 6). The final mean body weights and mean body weight gains of male and female rats in the 2,500 and 5,000 ppm groups were significantly lower than those of the controls. Feed consumption by all exposed rats was generally similar to that by the controls. Dietary concentrations of 300, 600, 1,300, 2,500, or 5,000 ppm primidone resulted in average daily doses of approximately 20, 40, 100, 200, or 400 mg/kg to males and females. Clinical findings that may have been related to primidone exposure included nasal and/or eye discharge.

TABLE 6
Survival, Body Weights, and Feed Consumption of Rats in the 14-Week Feed Study of Primidone

Dose (ppm)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)	Feed Consumption[c]	
		Initial	Final	Change		Week 1	Week 14
Male							
0	10/10	110 ± 3	348 ± 6	238 ± 4		14.4	17.4
300	10/10	113 ± 3	363 ± 8	251 ± 7	104	15.2	17.5
600	10/10	112 ± 3	358 ± 2	246 ± 3	103	14.9	17.6
1,300	10/10	112 ± 3	356 ± 4	244 ± 3	103	15.0	15.6
2,500	10/10	112 ± 3	325 ± 8*	213 ± 7**	93	14.4	20.2
5,000	10/10	112 ± 3	321 ± 2**	204 ± 5**	92	15.4	18.5
Female							
0	10/10	101 ± 2	201 ± 3	99 ± 4		11.4	10.4
300	10/10	100 ± 2	198 ± 3	97 ± 2	99	11.6	10.7
600	10/10	102 ± 2	197 ± 4	95 ± 3	98	11.5	10.7
1,300	10/10	101 ± 2	194 ± 3	93 ± 2	97	12.0	9.8
2,500	10/10	101 ± 2	187 ± 3**	86 ± 3**	93	12.4	10.1
5,000	10/10	102 ± 2	188 ± 2**	86 ± 3**	94	12.4	9.4

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Number of animals surviving at 14 weeks/number initially in group.
[b] Weights and weight changes are given as mean ± standard error. Final mean body weights and mean body weight changes of 2,500 and 5,000 ppm males are based on five animals per group due to dehydration in some animals.
[c] Feed consumption is expressed as grams of feed consumed per animal per day.

The hematology and clinical chemistry data for rats in the 14-week study are listed in Table G1. A minimal to mild exposure-related thrombocytosis, evidenced by increased platelet counts, occurred on day 22 and at week 14 in all exposed groups of male rats and in females exposed to 1,300 ppm or greater. A minimal decrease in hemoglobin concentration, suggesting an anemic tendency, occurred in 2,500 and 5,000 ppm male and female rats on day 22 and at week 14. There were, however, no alterations of other markers of anemia (hematocrit values or erythrocyte counts) to support the decreases in hemoglobin. A minimal to mild hyperproteinemia (increased total protein concentration) occurred on day 22 and at week 14 in male rats exposed to 600 ppm or greater and 2,500 and 5,000 ppm female rats. In the male rats, albumin concentrations also were increased at week 14 in the 600 ppm or greater groups. There were minimal to mild decreases of alkaline phosphatase activity in the 1,300 ppm females and 2,500 ppm or greater male and female rats on day 22 and in the 1,300 ppm or greater males and all exposed groups of females at

week 14. Changes in other hematological and clinical chemistry variables did not appear to be exposure related and were not considered toxicologically relevant.

No significant differences in sperm motility or vaginal cytology parameters between exposed groups and control groups were observed (Table I1).

The liver weights of males exposed to 600 ppm or greater and females exposed to 300 ppm or greater were significantly greater than those of the controls (Table F1).

The incidences of centrilobular hepatocyte hypertrophy in male rats exposed to 600 ppm or greater and in female rats exposed to 1,300 ppm or greater were significantly greater than those in the controls (Table 7). Hepatocytes most closely associated with central veins were enlarged, with a gradual decrease in size closer to the portal triad. This enlargement was due exclusively to an increase in cell cytoplasm which tended to stain intensely eosinophilic, suggesting an increased size or number of organelles. There was chemical-related hepatocellular hypertrophy at exposure concentrations of 600 ppm or greater, but the morphology at the 5,000 ppm concentration included vacuolization. The severity of chronic nephropathy of the kidney in male rats exposed to 1,300 ppm or greater increased with increasing exposure concentration (Table 7). Exposed males also exhibited dilation of one or more of the renal cortical tubules (principally in the distal nephron), which were filled with an eosinophilic proteinaceous fluid (hyaline casts), which is an indication of increased severity of nephropathy. The severity grading scheme for nephropathy in this 14-week study was somewhat unusual in that the background incidence of chronic nephropathy in control males was graded as minimal, rather than not graded. This made all severities for this lesion higher than usually observed for 14-week studies. A post-PWG review of the kidney step sections showed little difference in the severity of nephropathy between the 600, 1,300, and 2,500 ppm groups.

Exposure Concentration Selection Rationale: Based on lower mean body weights, increased liver weights, and severity of nephropathy at 5,000 ppm, the highest primidone exposure concentration for the 2-year feed study in rats was set at 2,500 ppm.

TABLE 7
Incidences of Selected Nonneoplastic Lesions in Rats in the 14-Week Feed Study of Primidone

	0 ppm	300 ppm	600 ppm	1,300 ppm	2,500 ppm	5,000 ppm
Male						
Liver[a]	10	10	10	10	10	10
Hepatocyte Centrilobular, Hypertrophy[b]	0	0	10** (1.0)[c]	10** (2.1)	10** (3.0)	10** (3.0)
Kidney	10	10	10	10	10	10
Nephropathy	9 (1.0)	10 (1.0)	10 (1.2)	10 (1.3)	10 (1.9)**	10 (3.0)**
Female						
Liver	10	10	10	10	10	10
Hepatocyte Centrilobular, Hypertrophy	0	0	1 (1.0)	10** (2.0)	10** (3.0)	10** (3.0)

** Significantly different (P≤0.01) from the control group by the Fisher exact test (incidences) or the Mann-Whitney U test (severity of nephropathy)
[a] Number of animals with organ/tissue 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

2-YEAR STUDY

Survival

Estimates of 2-year survival probabilities for male and female rats are shown in Table 8 and in the Kaplan-Meier survival curves (Figure 2). Survival of the 1,300 and 2,500 ppm males was significantly lower than that of the controls; survival of all other exposed groups was similar to that of the controls.

Body Weights, Feed and Compound Consumption, and Clinical Findings

The mean body weights of males and females in the 2,500 ppm groups were lower than those of the controls beginning at week 29 for males and week 17 for females; the mean body weights of 1,300 ppm males and females were lower than those of the controls during the second year of the study (Tables 9 and 10 and Figure 3). Feed consumption by all exposed groups of rats was generally similar to that by the controls (Tables K1 and K2). Dietary levels of 600, 1,300, or 2,500 ppm primidone resulted in average daily doses of approximately 25, 50, or 100 mg/kg to males and females. Male rats in the 1,300 and 2,500 ppm groups were observed to be lethargic during the second year of the study; no other clinical findings related to primidone exposure were observed.

TABLE 8
Survival of Rats in the 2-Year Feed Study of Primidone

	0 ppm	600 ppm	1,300 ppm	2,500 ppm
Male				
Animals initially in study	50	50	50	50
Moribund	33	33	39	36
Natural deaths	4	10	7	14
Animals surviving to study termination	13	7	4	0
Percent probability of survival at end of study[a]	26	14	8	0
Mean survival (days)[b]	639	645	631	558
Survival analysis[c]	P<0.001	P=0.324	P=0.016	P<0.001
Female				
Animals initially in study	50	50	50	50
Moribund	21	18	14	19
Natural deaths	5	5	5	3
Animals surviving to study termination	24	27	31	28[d]
Percent probability of survival at end of study	48	54	62	56
Mean survival (days)	673	650	684	672
Survival analysis	P=0.450N	P=0.968N	P=0.219N	P=0.597N

[a] Kaplan-Meier determinations
[b] Mean of all deaths (uncensored, censored, and terminal sacrifice)
[c] 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**.
[d] Includes one animal that died during the last week of the study

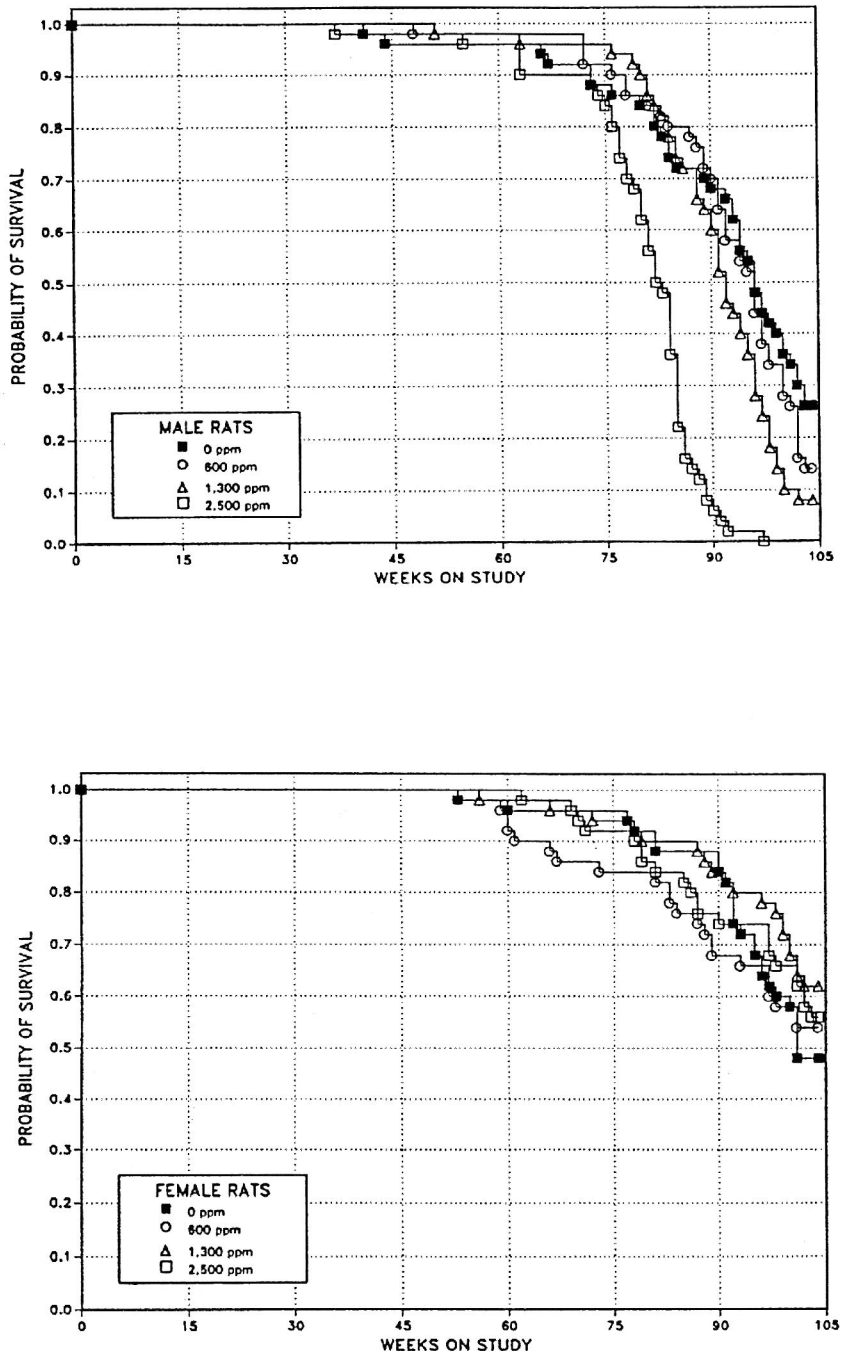


Figure 2
Kaplan-Meier Survival Curves for Male and Female Rats Exposed to Primidone in Feed for 2 Years

TABLE 9
Mean Body Weights and Survival of Male Rats in the 2-Year Feed Study of Primidone

Weeks on Study	0 ppm Av. Wt. (g)	0 ppm No. of Survivors	600 ppm Av. Wt. (g)	600 ppm Wt. (% of controls)	600 ppm No. of Survivors	1,300 ppm Av. Wt. (g)	1,300 ppm Wt. (% of controls)	1,300 ppm No. of Survivors	2,500 ppm Av. Wt. (g)	2,500 ppm Wt. (% of controls)	2,500 ppm No. of Survivors
1	151	50	151	100	50	150	100	50	150	99	50
2	191	50	192	100	50	191	100	50	190	99	50
3	222	50	227	102	50	223	100	50	227	102	50
4	256	50	258	101	50	256	100	50	258	101	50
5	271	50	276	102	50	276	102	50	278	103	50
6	294	50	299	102	50	299	102	50	296	101	50
7	308	50	309	100	50	306	99	50	305	99	50
8	327	50	330	101	50	329	101	50	324	99	50
9	336	50	342	102	50	337	100	50	329	98	50
10	344	50	351	102	50	349	101	50	339	99	50
11	350	50	359	103	50	355	101	50	348	99	50
12	363	50	369	102	50	364	100	50	358	99	50
13	372	50	378	102	50	376	101	50	369	99	50
17	395	50	401	101	50	398	101	50	386	98	50
21	421	50	424	101	50	423	100	50	405	96	50
25	440	50	442	100	50	438	100	50	418	95	50
29	459	50	456	99	50	450	98	50	432	94	50
33	471	50	467	99	50	458	97	50	440	94	50
37	480	50	474	99	50	466	97	50	441	92	50
41	490	50	485	99	50	476	97	50	454	93	49
45	493	48	489	99	50	479	97	50	458	93	49
49	506	48	498	98	49	488	96	50	455	90	49
53	514	48	508	99	49	488	95	49	464	90	49
57	517	48	510	99	49	496	96	49	471	91	48
60	518	48	509	98	49	494	95	49	468	90	48
65	521	48	515	99	49	500	96	48	468	90	45
69	521	46	505	97	49	493	95	48	460	88	45
73	522	45	510	98	46	492	94	48	459	88	44
77	521	43	505	97	45	485	93	47	444	85	40
81	513	42	503	98	43	481	94	44	443	86	29
85	510	37	500	98	40	471	93	39	390	77	18
89	498	36	479	96	38	469	94	33			
93	485	33	477	98	29	445	92	23			
97	483	24	462	96	22	432	89	14			
101	468	18	444	95	14						
Mean for weeks											
1-13	291		295	101		293	101		290	100	
14-52	462		460	100		453	98		432	94	
53-101	507		494	97		479	94		452	89	

TABLE 10
Mean Body Weights and Survival of Female Rats in the 2-Year Feed Study of Primidone

Weeks on Study	0 ppm Av. Wt. (g)	0 ppm No. of Survivors	600 ppm Av. Wt. (g)	600 ppm Wt. (% of controls)	600 ppm No. of Survivors	1,300 ppm Av. Wt. (g)	1,300 ppm Wt. (% of controls)	1,300 ppm No. of Survivors	2,500 ppm Av. Wt. (g)	2,500 ppm Wt. (% of controls)	2,500 ppm No. of Survivors
1	118	50	118	99	50	117	99	50	118	99	50
2	133	50	133	100	50	135	102	50	135	101	50
3	143	50	143	100	50	146	102	50	145	101	50
4	160	50	158	99	50	159	99	50	157	98	50
5	167	50	166	99	50	166	99	50	165	99	50
6	176	50	173	98	50	175	99	50	172	97	50
7	185	50	183	99	50	182	98	50	178	96	50
8	186	50	184	99	50	182	98	50	182	98	50
9	190	50	186	98	50	187	99	50	184	97	50
10	194	50	192	99	50	191	98	50	189	97	50
11	200	50	197	98	50	193	96	50	192	96	50
12	204	50	199	98	50	197	96	50	195	95	50
13	207	50	201	97	50	199	96	50	198	96	50
17	219	50	212	97	50	210	96	50	206	94	50
21	229	50	223	97	50	219	96	50	212	93	50
25	236	50	230	98	50	225	95	50	218	92	50
29	247	50	242	98	50	237	96	50	225	91	50
33	255	50	252	99	50	243	95	50	233	91	50
37	265	50	259	98	50	252	95	50	238	90	50
41	273	50	268	98	50	258	95	50	244	89	50
45	280	50	274	98	50	268	96	50	251	90	50
49	294	50	284	97	50	278	94	50	260	88	50
53	301	50	288	96	50	284	94	50	266	89	50
57	308	49	296	96	49	291	94	49	276	90	50
60	317	48	304	96	47	300	95	49	281	89	50
65	322	48	309	96	45	304	94	49	291	90	49
69	328	48	317	97	43	310	95	48	295	90	48
73	339	48	326	96	43	319	94	47	302	89	46
77	341	48	328	96	42	322	95	47	304	89	46
81	342	45	328	96	42	325	95	45	310	91	42
85	350	44	330	94	38	327	93	45	308	88	42
89	347	44	329	95	36	330	95	43	314	90	38
93	358	37	340	95	34	338	94	40	320	89	37
97	363	32	347	96	33	338	93	39	315	87	37
101	361	29	348	96	29	337	93	34	317	88	33
Mean for weeks											
1-13	174		172	99		171	98		170	98	
14-52	255		249	98		243	95		232	91	
53-101	337		322	96		317	94		300	89	

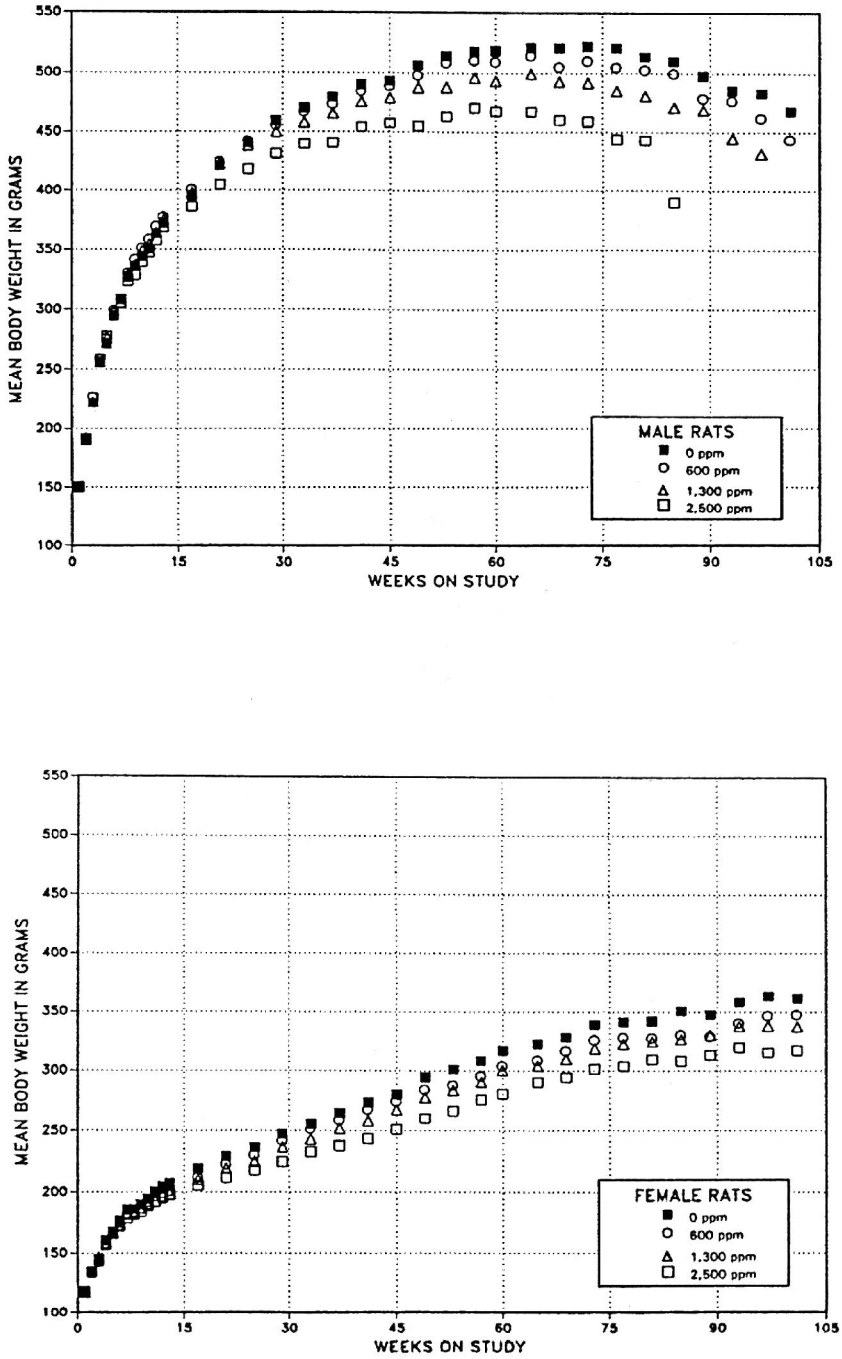


Figure 3
Growth Curves for Male and Female Rats Exposed to Primidone in Feed for 2 Years

Determinations of Primidone and Phenobarbital in Plasma

On the last 2 days of the study, blood was collected from the retroorbital sinus of three female rats at five time points for the determination of plasma concentrations of primidone and phenobarbital. The plasma concentrations of primidone and phenobarbital and their standard deviations are given in Tables H1 and H2. For the female rats, peak primidone and phenobarbital plasma concentrations increased with increasing exposure concentration. The peak concentrations were observed from 8:00 p.m. until 10:00 p.m.

Pathology and Statistical Analyses

This section describes the statistically significant or biologically noteworthy changes in the incidences of neoplasms and/or nonneoplastic lesions of the thyroid gland, liver, kidney (with parathyroid gland, bone, forestomach, glandular stomach, and lung), and testis and the incidences of mononuclear cell leukemia. Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, statistical analyses of primary neoplasms that occurred with an incidence of at least 5% in at least one animal group, and historical incidences for the neoplasms mentioned in this section are presented in Appendix A for male rats and Appendix B for female rats.

Thyroid Gland: Male rats exposed to primidone had increased incidences of follicular cell neoplasms (adenoma and/or carcinoma) (Tables 11 and A3). All exposed groups of male rats had follicular cell adenomas or carcinomas (combined) at incidences above the historical control range (Table A4), with the highest incidence in the 1,300 ppm group; however, there was no significant trend or pairwise effect. One follicular cell carcinoma was observed in a control female. In some cases, these neoplasms have been attributed to increased liver metabolism of thyroxin, secondary to a chemical-induced increase in microsomal glucuronidation activity. Usually, however, increased metabolism of thyroxin leads to diffuse thyroid follicular cell hyperplasia as well as neoplasia (Capen, 1996). In this study, only the neoplasms were present; diffuse follicular cell hyperplasia occurred only rarely. The reason for the lack of a significant increase in the incidence of hyperplasia was not apparent. Follicular cell adenomas were well-differentiated and well-circumscribed masses that compressed the adjacent parenchyma. They were composed of variably sized follicles and/or cystic spaces with papillary fronds projecting into the lumen. The cells were more basophilic than normal, but otherwise resembled normal follicular epithelial cells. Follicular cell carcinomas were more varied in appearance than adenomas and showed some invasion into surrounding parenchyma or into the fibrous capsule. In some areas the cells were arranged in solid sheets, as well as in follicles and cysts.

TABLE 11
Incidences of Neoplasms and Nonneoplastic Lesions of the Thyroid Gland in Rats in the 2-Year Feed Study of Primidone

	0 ppm	600 ppm	1,300 ppm	2,500 ppm
Male				
Number Examined Microscopically	50	50	49	49
Follicle, Cyst[a]	1 (2.0)[b]	3 (2.3)	1 (3.0)	6 (2.8)
Follicular Cell, Hyperplasia	2 (1.5)	1 (2.0)	2 (2.0)	1 (1.0)
Follicular Cell Adenoma[c]				
Overall rate[d]	1/50 (2%)	1/50 (2%)	6/49 (12%)	3/49 (6%)
Adjusted rate[e]	5.0%	4.5%	21.7%	10.7%
Terminal rate[f]	0/13 (0%)	0/7 (0%)	0/4 (0%)	0/0 (0%)
First incidence (days)	697	673	354	529
Logistic regression test[g]	P=0.227	P=0.754	P=0.047	P=0.280
Follicular Cell Carcinoma[h]				
Overall rate	1/50 (2%)	3/50 (6%)	1/49 (2%)	1/49 (2%)
Adjusted rate	7.7%	20.6%	5.6%	5.6%
Terminal rate	1/13 (8%)	1/7 (14%)	0/4 (0%)	0/0 (0%)
First incidence (days)	723 (T)	641	667	589
Logistic regression test	P=0.461	P=0.281	P=0.662	P=0.583
Follicular Cell Adenoma or Carcinoma[i]				
Overall rate	2/50 (4%)	4/50 (8%)	7/49 (14%)	4/49 (8%)
Adjusted rate	12.3%	24.2%	26.1%	15.7%
Terminal rate	1/13 (8%)	1/7 (14%)	0/4 (0%)	0/0 (0%)
First incidence (days)	697	641	354	529
Logistic regression test	P=0.266	P=0.309	P=0.076	P=0.207
Female				
Number Examined Microscopically	49	50	50	50
Follicular Cell, Hyperplasia	0	0	1 (2.0)	0
Follicular Cell Carcinoma	1	0	0	0

(T)Terminal sacrifice
[a] Number of animals with lesion
[b] Average severity of lesions in affected animals: 1=minimal; 2=mild; 3=moderate; 4=marked
[c] Historical incidence for 2-year NTP feed studies with untreated control groups (mean ± standard deviation): 11/1,295 (0.9% ± 1.2%); range, 0%-4%
[d] Number of animals with neoplasm per number of animals with thyroid gland examined microscopically
[e] Kaplan-Meier estimated neoplasm incidence after adjustment for intercurrent mortality
[f] Observed incidence in animals surviving until the end of the study
[g] In the control column are the P values associated with the trend test. In the exposed group columns are the P values corresponding to the pairwise comparisons between the controls and that exposed group. The logistic regression test regards neoplasms in animals dying prior to terminal kill as nonfatal.
[h] Historical incidence: 11/1,295 (0.9% ± 1.2%); range, 0%-4%
[i] Historical incidence: 22/1,295 (1.7% ± 1.6%); range, 0%-6%

Liver: Hepatocyte cytoplasmic vacuolation and centrilobular hypertrophy were associated with primidone exposure in male and female rats (Tables 12, A5, and B5). These changes were more severe in females than males and the incidences in all exposed groups of females were significantly greater than those in the controls. Vacuolation was often observed within the enlarged cells. Females in the 2,500 ppm group had an increased incidence of hepatocellular eosinophilic foci. Male rats in the 600 and 1,300 ppm groups had marginal increases in the incidences of eosinophilic foci. The lesions consisted of areas of hepatocytes with distinct cytoplasmic eosinophilia, although some of the cells had clear cytoplasm or pale granular cytoplasm. The foci retained features of the normal liver lobule.

TABLE 12
Incidences of Selected Nonneoplastic Lesions of the Liver of Rats in the 2-Year Feed Study of Primidone

	0 ppm	600 ppm	1,300 ppm	2,500 ppm
Male				
Number Examined Microscopically	50	50	50	50
Eosinophilic Focus[a]	1	6	5	2
Hepatocyte, Centrilobular Hypertrophy	0	14** (1.4)[b]	33** (2.0)	40** (2.4)
Hepatocyte, Vacuolization Cytoplasmic	26 (1.6)	28 (1.7)	33 (2.0)	43** (2.3)
Female				
Number Examined Microscopically	50	50	50	50
Eosinophilic Focus	2	0	1	18**
Hepatocyte, Centrilobular Hypertrophy	1 (2.0)	36** (1.0)	38** (2.1)	35** (3.0)
Hepatocyte, Vacuolization Cytoplasmic	25 (1.8)	44** (2.0)	46** (1.8)	44** (2.1)

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

Kidney (with parathyroid gland, bone, forestomach, glandular stomach, and lung): The incidence of renal tubule hyperplasia in 2,500 ppm males was greater than that in the controls in the standard evaluation (Table 13). Additional hyperplasias were found in the extended evaluation, and the incidences in all groups of exposed males were significantly greater than that in the controls. The incidences of renal tubule adenoma or carcinoma (combined) in exposed groups of male rats were similar to those in the controls at the standard evaluation. In the extended evaluation, the incidence of renal tubule adenoma in 2,500 ppm males was significantly greater than in the controls. The incidence of adenoma or carcinoma (combined) in 2,500 ppm males in the combined standard and extended evaluations was marginally increased over that in the controls. Male rats had an exposure-related increase in the severity of chronic nephropathy. In 2,500 ppm male rats, nephropathy was considered severe in most animals, with marked fibrosis, loss of nephrons, and mineralization. Chronic nephropathy was responsible for the decreased survival of 1,300 and 2,500 ppm male rats. The incidences of cysts were increased in 1,300 and 2,500 ppm males.

Hyperparathyroidism, secondary to the loss of renal function, was present in many exposed male rats. The incidences of parathyroid gland hyperplasia in all groups of exposed males were significantly greater than that in the controls (2/45, 16/41, 26/46, 40/49). The incidences of bone fibrous osteodystrophy (0/50,

TABLE 13
Incidences of Neoplasms and Nonneoplastic Lesions of the Kidney of Male Rats in the 2-Year Feed Study of Primidone

	0 ppm	600 ppm	1,300 ppm	2,500 ppm
Single Section (Standard Evaluation)				
Number Examined Microscopically	50	50	50	50
Cyst[a]	2 (3.0)[b]	2 (3.0)	12** (2.3)	9* (2.8)
Nephropathy, Chronic	49 (2.2)	48 (2.9)	50 (3.4)	50 (3.8)
Renal Tubule, Hyperplasia	1 (1.0)	2 (3.0)	4 (2.3)	10* (2.5)
Renal Tubule, Adenoma or Carcinoma[c]	2	1	1	2
Step Sections (Extended Evaluation)				
Renal Tubule, Hyperplasia	4	11*	22**	27**
Renal Tubule, Adenoma				
Overall rate[d]	2/50 (4%)	1/50 (2%)	4/50 (8%)	5/50 (10%)
Adjusted rate[e]	13.8%	4.5%	20.9%	54.9%
Terminal rate[f]	1/13 (8%)	0/7 (0%)	0/4 (0%)	0/0 (0%)
First incidence (days)	715	673	613	585
Logistic regression test[g]	P=0.012	P=0.557N	P=0.264	P=0.030
Single Sections and Step Sections (Combined)				
Renal Tubule, Hyperplasia	5	13*	26**	37**
Renal Tubule, Adenoma				
Overall rate	4/50 (8%)	2/50 (4%)	4/50 (8%)	6/50 (12%)
Adjusted rate	23.2%	8.0%	20.9%	56.0%
Terminal rate	2/13 (15%)	0/7 (0%)	0/4 (0%)	0/0 (0%)
First incidence (days)	619	654	613	529
Logistic regression test	P=0.056	P=0.355N	P=0.563	P=0.098
Renal Tubule, Carcinoma	0	0	0	1
Renal Tubule, Adenoma or Carcinoma				
Overall rate	4/50 (8%)	2/50 (4%)	4/50 (8%)	7/50 (14%)
Adjusted rate	23.2%	8.0%	20.9%	62.3%
Terminal rate	2/13 (15%)	0/7 (0%)	0/4 (0%)	0/0 (0%)
First incidence (days)	619	654	613	529
Logistic regression test	P=0.025	P=0.355N	P=0.563	P=0.050

* Significantly different ($P \leq 0.05$) from the control group by the logistic regression test
** $P \leq 0.01$
[a] Number of animals with lesion
[b] Average severity of lesions in affected animals: 1=minimal; 2=mild; 3=moderate; 4=marked
[c] Historical incidence in 2-year NTP feed studies with untreated controls (mean ± standard deviation): 12/1,301 (0.9% ± 1.5%); range, 0%-6%
[d] Number of animals with neoplasm per number of animals with kidney examined microscopically
[e] Kaplan-Meier estimated neoplasm incidence after adjustment for intercurrent mortality
[f] Observed incidence in animals surviving until the end of the study
[g] In the control column are the P values associated with the trend test. In the exposed group columns are the P values corresponding to the pairwise comparisons between the controls and that exposed group. The logistic regression test regards neoplasms in animals dying prior to terminal kill as nonfatal. A lower incidence in an exposure group is indicated by **N**.

10/50, 26/50, 37/50) and incidences of mineralization of the forestomach (0 ppm, 0/50; 600 ppm, 3/50; 1,300 ppm, 3/50; 2,500 ppm, 12/49), glandular stomach (0/50, 6/50, 15/50, 36/49), and lung interstitium (0/50, 3/50, 7/50, 25/50) in 2,500 ppm males were significantly greater than those in the controls (Table A5). These lesions were considered to be related to chronic nephropathy.

Mononuclear Cell Leukemia: The incidence of mononuclear cell leukemia in 2,500 ppm females was marginally increased relative to the controls (13/50, 13/50, 13/50, 22/50; Table B3). The incidence in the 2,500 ppm group was well within the historical control range (14% to 52%; Table B4), and this slight increase was not considered to be chemical related.

Testis: There was a significant increase in the incidences of testicular interstitial cell adenoma in the 2,500 ppm males due primarily to an earlier onset of this neoplasm (41/50, 44/50, 42/50, 43/48; Table A3). Testicular adenoma is a common neoplasm that generally occurs in nearly 100% of animals surviving to at least 18 months. In this study, 98% (42/43) of 2,500 ppm males surviving beyond day 440 had testicular interstitial cell adenoma compared with 85% (41/48) of the controls. This slight increase was not considered chemical related.

MICE

14-DAY STUDY

All male and female mice in the 10,000 ppm groups and one male and one female mouse in the 5,000 ppm groups died on day 3 of the study (Table 14). The final mean body weights and mean body weight gains of mice in the 625, 1,250, 2,500, and 5,000 ppm groups were similar to those of the controls. Feed consumption by exposed and control mice was generally similar. Dietary levels of 625, 1,250, 2,500, or 5,000 ppm primidone resulted in average daily doses of approximately 100, 200, 400, or 800 mg/kg to males and 100, 250, 500, or 900 mg/kg to females. The average daily dose for 10,000 ppm male and female groups was not calculated due to high mortality. Male and female mice in the 10,000 ppm groups were observed to have abnormal posture, ataxia, and lethargy.

TABLE 14
Survival, Body Weights, and Feed Consumption of Mice in the 14-Day Feed Study of Primidone

Dose (ppm)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)	Feed Consumption[c]	
		Initial	Final	Change		Day 7	Day 14
Male							
0	5/5	22.5 ± 0.5	23.6 ± 0.4	1.1 ± 0.4		3.8	4.3
625	5/5	22.5 ± 0.6	24.0 ± 0.5	1.5 ± 0.2	102	4.0	3.7
1,250	5/5	23.0 ± 0.4	23.9 ± 0.4	0.9 ± 0.2	102	3.7	4.1
2,500	5/5	23.0 ± 0.5	24.2 ± 0.4	1.2 ± 0.3	103	4.8	4.4
5,000	4/5[d]	22.9 ± 0.5	24.7 ± 0.5	1.4 ± 0.2	105	3.8	3.7
10,000	0/5[d]	23.3 ± 0.4	—	—	—	—	—
Female							
0	5/5	18.1 ± 0.4	18.8 ± 0.4	0.8 ± 0.3		3.8	4.7
625	5/5	17.9 ± 0.2	18.3 ± 0.3	0.4 ± 0.3	97	2.8	3.4
1,250	5/5	17.9 ± 0.4	18.8 ± 0.4	0.9 ± 0.4	100	3.4	3.9
2,500	5/5	18.0 ± 0.4	19.1 ± 0.4	1.1 ± 0.2	102	2.7	5.2
5,000	4/5[d]	18.6 ± 0.3	19.6 ± 0.4	0.8 ± 0.3	104	3.3	3.6
10,000	0/5[d]	18.4 ± 0.3	—	—	—	—	—

[a] Number of animals surviving at 14 days/number initially in group. Subsequent calculations are based on animals surviving to the end of the study.
[b] Weights and weight changes are given as mean ± standard error. No final mean body weights were calculated for groups with 100% mortality. Differences from the control group are not significant by Williams' or Dunnett's test.
[c] Feed consumption is expressed as grams of feed consumed per animal per day.
[d] Day of death: 3

14-WEEK STUDY

Three male and two female mice in the 5,000 ppm groups died during week 1 of the study (Table 15). The final mean body weights of all exposed groups were similar to those of the controls. Feed consumption by male mice in the 5,000 ppm group was slightly greater than that by the controls; this may have been due to feed spillage. Dietary levels of 300, 600, 1,300, 2,500, or 5,000 ppm primidone resulted in average daily doses of approximately 50, 100, 200, 400, or 1,000 mg primidone/kg body weight to males and 60, 120, 220, 440, or 1,100 mg/kg to females. Male and female mice in the 5,000 ppm groups displayed signs of ataxia and lethargy.

The estrous cycle lengths of females exposed to 1,300, 2,500, or 5,000 ppm were significantly longer than that of the controls (Table H2). No differences in sperm motility were observed.

The liver weights of male and female mice exposed to 600 ppm or greater were significantly greater than those of the controls (Table F2).

TABLE 15
Survival, Body Weights, and Feed Consumption of Mice in the 14-Week Feed Study of Primidone

Dose (ppm)	Survival[a]	Mean Body Weight[b] (g) Initial	Final	Change	Final Weight Relative to Controls (%)	Feed Consumption[c] Week 2	Week 14
Male							
0	10/10	19.8 ± 0.3	31.3 ± 0.8	11.5 ± 0.6		3.6	4.8
300	10/10	20.0 ± 0.4	31.2 ± 0.8	11.2 ± 0.9	100	3.5	4.5
600	10/10	20.2 ± 0.3	31.6 ± 1.3	11.5 ± 1.1	101	3.2	5.0
1,300	10/10	20.3 ± 0.4	31.7 ± 0.6	11.4 ± 0.4	101	3.0	4.8
2,500	10/10	20.1 ± 0.3	31.7 ± 0.8	11.6 ± 0.7	101	3.5	4.9
5,000	7/10[d]	20.4 ± 0.3	29.1 ± 0.7	8.8 ± 0.8	93	3.5	6.8
Female							
0	10/10	17.6 ± 0.3	27.4 ± 0.5	9.8 ± 0.4		4.1	6.9
300	10/10	17.7 ± 0.2	28.5 ± 0.5	10.8 ± 0.4	104	3.3	5.5
600	10/10	17.4 ± 0.4	29.7 ± 0.7	12.3 ± 0.6*	108	3.4	5.7
1,300	10/10	17.4 ± 0.2	28.6 ± 1.1	11.1 ± 1.0	104	2.7	5.0
2,500	10/10	17.7 ± 0.3	28.7 ± 0.5	10.9 ± 0.4	105	3.1	5.0
5,000	8/10[d]	17.9 ± 0.2	26.7 ± 0.7	8.7 ± 0.5	98	3.3	6.7

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
[a] Number of animals surviving at 14 weeks/number initially in group. Subsequent calculations are based on animals surviving to the end of the study.
[b] Weights and weight changes are given as mean ± standard error.
[c] Feed consumption is expressed as grams of feed consumed per animal per day.
[d] Week of death: 1

The incidences of hepatocyte centrilobular hypertrophy of the liver in all exposed males and in females exposed to 600 ppm or greater were significantly greater than in the controls (Table 16). Hepatocytes most closely associated with central veins were enlarged, with a gradual decrease in size the closer to the portal triad. The enlargement was due almost exclusively to an increase in cell cytoplasm. The cytoplasm of enlarged hepatocytes tended to stain more intensely eosinophilic, suggesting an increased size and/or number of organelles. The incidences of cytoplasmic alteration of the adrenal cortex in males exposed to 2,500 or 5,000 ppm and in 5,000 ppm females were significantly greater than in the controls (Table 16). Enlargement of adrenal cortical cells was due to an increase in cell cytoplasm, with the zona fasciculata cells being principally affected. The cause and significance of the adrenal gland change was not determined. The incidences of hematopoietic cell proliferation of the spleen in 2,500 and 5,000 ppm males and in 5,000 ppm females were significantly greater than in the controls (Table 16).

Exposure Concentration Selection Rationale: Based on reduced survival, adrenal cortical cytoplasmic alteration, and increased severity of hepatocellular centrilobular hypertrophy at higher feed concentrations in the 14-week studies, primidone exposure concentrations selected for the 2-year feed study in mice were 300, 600, and 1,300 ppm.

TABLE 16
Incidences of Selected Nonneoplastic Lesions in Mice in the 14-Week Feed Study of Primidone

	0 ppm	300 ppm	600 ppm	1,300 ppm	2,500 ppm	5,000 ppm
Male						
Liver[a]	10	10	10	10	10	7[c]
Hepatocyte Centrilobular, Hypertrophy[b]	0	10** (1.0)[d]	10** (1.0)	10** (2.0)	10** (3.0)	7** (3.0)
Adrenal Gland	10	—[e]	—	10	10	7[c]
Cytoplasmic Alteration	0			0	9** (1.0)	7** (1.9)
Spleen	10	—	—	10	10	7[c]
Hematopoietic Cell Proliferation	0			0	5* (1.0)	7** (1.1)
Female						
Liver	10	10	10	10	10	8[c]
Hepatocyte Centrilobular, Hypertrophy	0	0	10** (1.0)	10** (2.0)	10** (3.0)	8** (3.0)
Adrenal Gland	10	—	—	—	10	8[c]
Cytoplasmic Alteration	0				0	8** (1.0)
Spleen	10	—	1	10	10	8[c]
Hematopoietic Cell Proliferation	1 (1.0)		1 (1.0)	2 (1.0)	4 (1.5)	8** (1.1)

* 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/tissue examined microscopically
[b] Number of animals with lesion
[c] Does not include animals dying during week 1
[d] Average severity grade of lesions in affected animals: 1=minimal; 2=mild; 3=moderate; 4=marked
[e] Tissue not examined at this exposure concentration

2-Year Study

Survival

Estimates of 2-year survival probabilities for male and female mice are shown in Table 17 and in the Kaplan-Meier survival curves (Figure 4). Survival of the 1,300 ppm males was significantly lower than that of the controls; survival of all other groups of mice was similar to that of the controls.

Body Weights, Feed and Compound Consumption, and Clinical Findings

During the second year of the study, the mean body weights of 1,300 ppm male and female mice were less than those of the controls (Tables 18 and 19, Figure 5). The final mean body weights of 600 ppm males and females were less than those of the controls. Feed consumption by all exposed groups of mice was similar to that by the controls (Tables K3 and K4). Dietary concentrations of 300, 600, or 1,300 ppm primidone resulted in average daily doses of approximately 30, 65, or 150 mg/kg to males and 25, 50, or 100 mg/kg to females. During the latter part of the study, a treatment-related increase in the number of animals with swelling of the abdominal area was observed; necropsy revealed that the swelling was due to liver nodules/masses. No other clinical findings related to primidone exposure were observed.

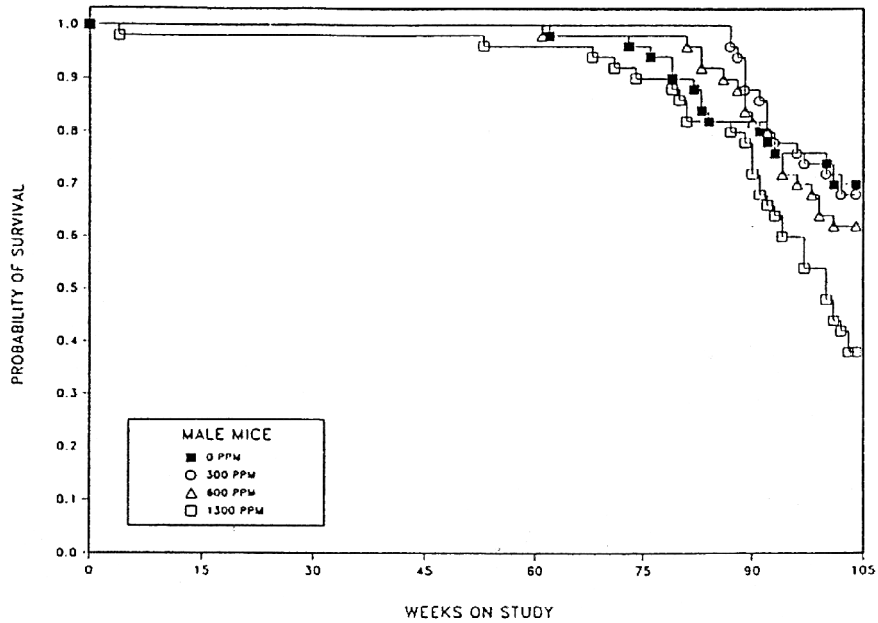
Determinations of Primidone and Phenobarbital in Plasma

During the last 2 days of the study, blood was collected by cardiac puncture from three male and three female mice from each group at five time points for the determination of plasma concentrations of phenobarbital. The plasma concentrations of phenobarbital and their standard deviations are given in Tables H3 and H4. For exposed females, the only primidone plasma concentration value not below the limit of detection (0.5 μg/mL) was 1.72 μg/mL in the 1,300 ppm group. Phenobarbital plasma concentrations increased with increasing exposure concentration for male and female mice; peak plasma concentrations were observed from 10:00 p.m. until 8:30 a.m.

TABLE 17
Survival of Mice in the 2-Year Feed Study of Primidone

	0 ppm	300 ppm	600 ppm	1,300 ppm
Male				
Animals initially in study	50	50	50	50
Moribund	6	7	6	17
Natural deaths	9	9	13	14
Animals surviving to study termination	35	34[d]	31	19
Percent probability of survival at end of study[a]	70	68	62	38
Mean survival (days)[b]	686	701	688	651
Survival analysis[c]	P<0.001	P=1.000N	P=0.611	P=0.005
Female				
Animals initially in study	50	50	50	50
Missing[e]	0	0	1	0
Moribund	7	1	3	8
Natural deaths	2	7	2	3
Animals surviving to study termination	41	42	44	39
Percent probability of survival at end of study	82	84	90	78
Mean survival (days)	704	722	716	712
Survival analysis	P=0.642	P=0.864N	P=0.359N	P=0.884

[a] Kaplan-Meier determinations
[b] Mean of all deaths (uncensored, censored, and terminal sacrifice)
[c] 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**.
[d] Includes one animal that died during the last week of the study
[e] Censored from the survival analyses



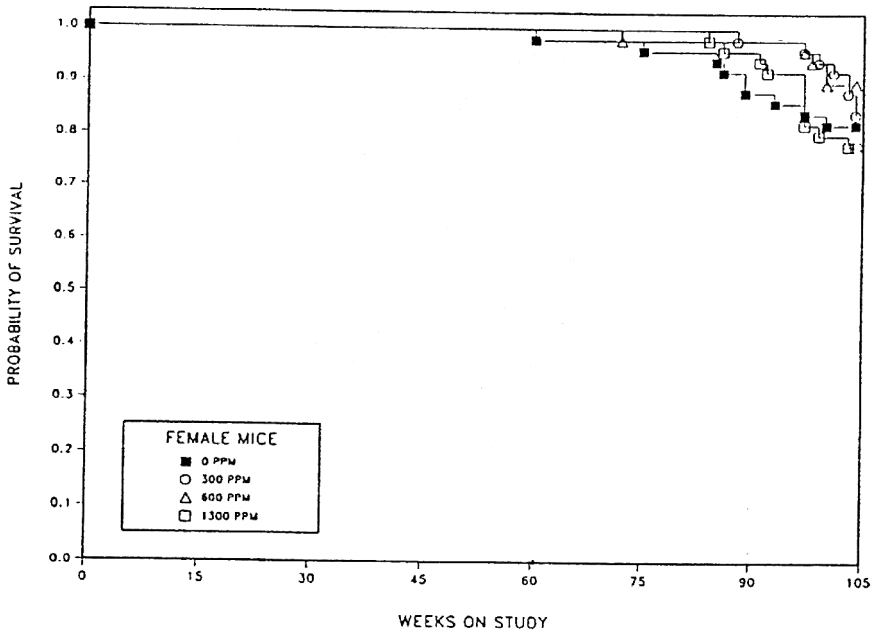


Figure 4
Kaplan-Meier Survival Curves for Male and Female Mice Exposed to Primidone in Feed for 2 Years

TABLE 18
Mean Body Weights and Survival of Male Mice in the 2-Year Feed Study of Primidone

Weeks on Study	0 ppm Av. Wt. (g)	0 ppm No. of Survivors	300 ppm Av. Wt. (g)	300 ppm Wt. (% of controls)	300 ppm No. of Survivors	600 ppm Av. Wt. (g)	600 ppm Wt. (% of controls)	600 ppm No. of Survivors	1,300 ppm Av. Wt. (g)	1,300 ppm Wt. (% of controls)	1,300 ppm No. of Survivors
1	22.4	50	22.0	98	50	22.0	98	50	21.9	98	50
2	23.8	50	23.8	100	50	23.7	100	50	23.6	99	50
3	25.4	50	25.7	101	50	25.6	101	50	25.7	101	50
4	27.3	50	27.3	100	50	27.0	99	50	27.6	101	49
5	28.0	50	28.7	103	50	28.6	102	50	28.6	102	49
6	29.8	50	30.3	102	50	30.1	101	50	29.8	100	49
7	30.9	50	31.9	103	50	31.4	102	50	30.7	99	49
8	31.9	50	33.0	103	50	32.1	101	50	31.4	98	49
9	32.6	50	33.8	104	50	32.9	101	50	32.5	100	49
10	33.9	50	35.2	104	50	34.5	102	50	33.8	100	49
11	35.2	50	35.9	102	50	35.2	100	50	34.3	97	49
12	36.3	50	36.5	101	50	35.9	99	50	34.8	96	49
13	37.8	50	38.0	101	50	36.9	98	50	36.3	96	49
17	42.3	50	42.2	100	50	41.2	97	50	39.1	92	49
21	44.5	50	45.3	102	50	43.7	98	50	41.8	94	49
25	46.0	50	46.6	101	50	45.4	99	50	43.7	95	49
29	47.2	50	47.2	100	50	46.1	98	50	44.3	94	49
33	47.5	50	48.3	102	50	47.3	100	50	45.2	95	49
36	47.8	50	48.4	101	50	47.6	100	50	45.4	95	49
41	49.9	50	49.6	99	50	48.5	97	50	46.8	94	49
45	49.2	50	49.1	100	50	48.2	98	50	47.5	97	49
49	50.4	50	51.3	102	50	50.8	101	50	49.5	98	49
53	50.3	50	51.4	102	50	51.0	101	50	48.8	97	49
57	50.5	50	52.3	104	50	51.8	103	50	49.3	98	48
61	49.7	50	51.3	103	50	50.7	102	50	48.3	97	48
65	50.7	49	52.0	103	50	52.2	103	49	48.4	96	48
69	49.9	49	51.7	104	50	51.5	103	49	46.4	93	47
73	50.3	49	52.1	104	50	52.4	104	49	45.3	90	46
77	49.7	47	51.5	104	50	50.7	102	49	43.4	87	45
81	50.2	45	51.8	103	50	49.5	99	49	41.8	83	43
84	50.8	41	52.2	103	50	48.9	96	46	41.9	83	41
88	51.2	41	52.0	102	47	46.9	92	44	40.7	80	40
93	49.6	39	50.7	102	40	44.1	89	39	39.5	80	33
97	49.1	38	51.1	104	37	43.9	89	35	38.3	78	30
101	48.9	37	48.3	99	36	43.0	88	32	37.9	78	24
Mean for weeks											
1-13	30.4		30.9	102		30.5	100		30.1	99	
14-52	47.2		47.6	101		46.5	99		44.8	95	
53-101	50.1		51.4	103		49.0	98		43.8	87	

TABLE 19
Mean Body Weights and Survival of Female Mice in the 2-Year Feed Study of Primidone

Weeks on Study	0 ppm Av. Wt. (g)	0 ppm No. of Survivors	300 ppm Av. Wt. (g)	300 ppm Wt. (% of controls)	300 ppm No. of Survivors	600 ppm Av. Wt. (g)	600 ppm Wt. (% of controls)	600 ppm No. of Survivors	1,300 ppm Av. Wt. (g)	1,300 ppm Wt. (% of controls)	1,300 ppm No. of Survivors
1	18.1	50	18.1	100	50	18.1	100	50	18.0	99	50
2	19.0	50	19.0	100	50	18.8	99	50	19.0	100	50
3	19.9	50	20.5	103	50	20.4	103	50	20.2	102	50
4	21.4	50	22.0	103	50	21.5	101	50	21.6	101	50
5	22.8	50	23.3	102	50	23.0	101	50	23.3	102	50
6	24.0	50	24.4	102	50	24.3	101	50	24.2	101	50
7	25.4	50	26.7	105	50	26.0	102	50	25.9	102	50
8	25.9	50	27.8	107	50	27.0	104	50	26.5	102	50
9	27.8	50	29.1	105	50	28.6	103	50	28.2	101	50
10	29.0	50	29.5	102	50	29.5	102	50	28.9	100	50
11	28.3	50	31.5	111	50	30.3	107	50	29.5	104	50
12	31.5	50	33.5	106	50	31.8	101	50	31.0	98	50
13	32.9	50	34.3	104	50	33.0	100	50	32.2	98	50
17	37.7	50	39.9	106	50	37.9	101	50	37.1	98	50
21	40.7	50	42.7	105	50	40.2	99	50	39.4	97	50
25	43.3	50	45.5	105	50	42.5	98	50	41.8	97	50
29	43.4	50	47.2	109	50	43.9	101	50	43.0	99	50
33	45.2	50	48.3	107	50	44.8	99	50	43.1	95	50
36	46.7	50	49.6	106	50	46.0	99	50	44.5	95	50
41	49.1	50	51.5	105	50	48.2	98	50	46.3	94	50
45	51.1	50	53.4	105	50	49.8	98	50	47.7	93	50
49	53.4	50	55.3	104	50	52.4	98	50	49.7	93	50
53	54.7	50	55.7	102	50	53.2	97	50	50.4	92	50
57	55.6	50	57.2	103	50	54.5	98	50	51.7	93	50
61	55.8	49	57.1	102	50	54.8	98	50	52.2	94	50
65	56.2	49	57.5	102	50	54.8	98	50	51.8	92	50
69	57.4	49	58.8	102	50	55.8	97	50	53.1	93	50
73	59.0	49	60.0	102	50	57.0	97	49	54.5	92	50
77	58.1	48	59.8	103	50	56.2	97	49	53.5	92	50
81	59.3	48	61.2	103	50	57.8	98	48	53.9	91	50
84	60.6	48	62.7	104	50	59.3	98	48	54.1	89	49
88	60.3	46	63.1	105	49	59.7	99	48	52.2	87	48
93	60.7	44	63.7	105	49	58.7	97	48	49.0	81	46
97	61.6	43	64.7	105	48	58.7	95	48	47.6	77	46
101	61.3	41	61.6	101	47	57.6	94	44	46.0	75	40
Mean for weeks											
1-13	25.1		26.1	104		25.6	102		25.3	101	
14-52	45.6		48.2	106		45.1	99		43.6	96	
53-101	58.5		60.2	103		56.8	97		51.5	88	

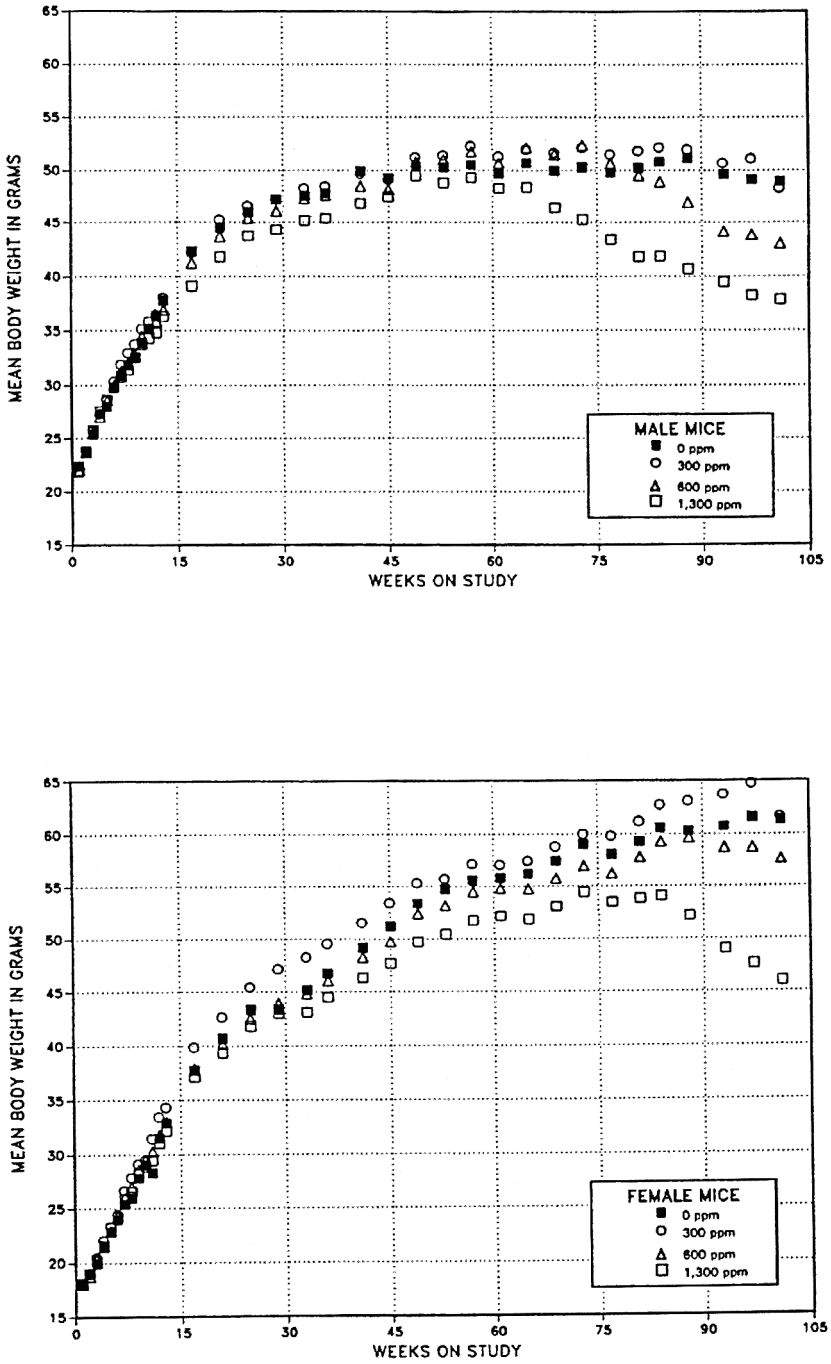


Figure 5
Growth Curves for Male and Female Mice Exposed to Primidone in Feed for 2 Years

Pathology and Statistical Analyses

This section describes the statistically significant or biologically noteworthy changes in the incidences of neoplasms and/or nonneoplastic lesions of the liver, thyroid gland, spleen, and pancreatic islets. Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, statistical analyses of primary neoplasms that occurred with an incidence of at least 5% in at least one animal group, and historical incidences for the neoplasms mentioned in this section are presented in Appendix C for male mice and Appendix D for female mice.

Liver: The liver was a target organ in male and female mice. An increase in the incidences of proliferative lesions as well as nonproliferative changes occurred in males and females. The incidences of hepatocellular neoplasms (hepatocellular adenoma, hepatocellular carcinoma, and hepatoblastoma) in all exposed groups (except hepatoblastoma in females) were significantly greater than those in the controls (Tables 20, C3, and D3). The incidences of hepatocellular adenoma or carcinoma (combined) and hepatocellular adenoma, hepatocellular carcinoma, or hepatoblastoma (combined) in all exposed groups exceeded the ranges in historical controls in 2-year NTP feed studies (Tables 20, C4a, and D4). Hepatocellular adenomas were generally round, compressive masses of well-differentiated, uniform-appearing hepatocytes. In contrast to foci of cellular alteration, adenomas lacked normal anatomic features of the liver lobule, such as bile ducts, ductlets, and portal triad areas. In other respects, adenomas resembled foci of cellular alteration. Hepatocellular carcinomas were less differentiated than adenomas and generally had a distinct trabecular or glandular pattern, at least in a portion of the mass. Areas of necrosis or loss of cells were common. The staining quality of cells typically varied from one area to another, as did the size and shape of the cells. Many hepatocellular carcinomas metastasized to the lung. Hepatoblastomas were distinguished from hepatocellular carcinomas by their elongated, basophilic cells that were often arranged radially around small blood vessels. These liver neoplasms also metastasized to the lung in several instances. Hepatoblastomas occurred in conjunction with adenomas and/or carcinomas in almost every instance.

The incidences of centrilobular hypertrophy of the hepatocytes were increased in exposed groups of males and females, and the severities increased with increasing exposure concentration (Tables 20, C5, and D5). The incidences of cytoplasmic vacuolization were increased in all exposed groups of females and in 300 ppm males. In 1,300 ppm mice, especially males, cytoplasmic and nuclear enlargement involved over half the distance from the central vein to the portal triad area in the most severely affected hepatic lobules. Incidences of eosinophilic focus in all exposed groups of females were significantly greater than those in the controls.

TABLE 20
Incidences of Neoplasms and Nonneoplastic Lesions of the Liver in Mice in the 2-Year Feed Study of Primidone

	0 ppm	300 ppm	600 ppm	1,300 ppm
Male				
Number Examined Microscopically	50	50	50	50
Hepatocyte, Centrilobular Hypertrophy[a]	3 (1.7)[b]	30** (2.0)	21** (2.0)	18** (2.1)
Hepatocyte, Vacuolization Cytoplasmic	1 (2.0)	8* (2.9)	3 (2.0)	2 (3.0)
Hepatocellular Adenoma				
Overall rate[c]	22/50 (44%)	41/50 (82%)	39/50 (78%)	32/50 (64%)
Adjusted rate[d]	59.2%	93.1%	92.6%	87.3%
Terminal rate[e]	20/35 (57%)	31/34 (91%)	28/31 (90%)	15/19 (79%)
First incidence (days)	551	603	566	368
Life table analysis[f]	P<0.001	P<0.001	P<0.001	P<0.001
Logistic regression test[f]	P=0.040	P<0.001	P<0.001	P=0.013
Hepatocellular Carcinoma				
Overall rate	12/50 (24%)	31/50 (62%)	35/50 (70%)	38/50 (76%)
Adjusted rate	29.1%	71.6%	81.1%	100.0%
Terminal rate	7/35 (20%)	22/34 (65%)	23/31 (74%)	19/19 (100%)
First incidence (days)	526	614	575	470
Life table analysis	P<0.001	P<0.001	P<0.001	P<0.001
Logistic regression test	P<0.001	P<0.001	P<0.001	P<0.001
Hepatoblastoma				
Overall rate	0/50 (0%)	17/50 (34%)	26/50 (52%)	7/50 (14%)
Adjusted rate	0.0%	39.9%	56.9%	23.4%
Terminal rate	0/35 (0%)	9/34 (26%)	12/31 (39%)	1/19 (5%)
First incidence (days)	—[g]	617	422	551
Life table analysis	P<0.043	P<0.001	P<0.001	P<0.003
Logistic regression test	P=0.271	P<0.001	P<0.001	P=0.009
Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma[h]				
Overall rate	31/50 (62%)	49/50 (98%)	49/50 (98%)	46/50 (92%)
Adjusted rate	73.5%	100.0%	100.0%	100.0%
Terminal rate	24/35 (69%)	34/34 (100%)	31/31 (100%)	19/19 (100%)
First incidence (days)	526	603	422	368
Life table analysis	P<0.001	P<0.001	P<0.001	P<0.001
Logistic regression test	P<0.001	P<0.001	P<0.001	P<0.001

TABLE 20
Incidences of Neoplasms and Nonneoplastic Lesions of the Liver in Mice in the 2-Year Feed Study of Primidone

	0 ppm	300 ppm	600 ppm	1,300 ppm
Female				
Number Examined Microscopically	50	50	49	50
Eosinophilic Focus	8	23**	24**	17*
Hepatocyte, Centrilobular Hypertrophy	1 (1.0)	11** (1.5)	11** (1.9)	21** (2.0)
Hepatocyte, Vacuolization Cytoplasmic	3 (2.3)	35** (2.9)	39** (2.9)	28** (2.6)
Hepatocellular Adenoma				
Overall rate	15/50 (30%)	42/50 (84%)	45/49 (92%)	47/50 (94%)
Adjusted rate	34.9%	91.3%	97.8%	97.9%
Terminal rate	13/41 (32%)	38/42 (90%)	43/44 (98%)	38/39 (97%)
First incidence (days)	673	701	680	583
Life table analysis	P<0.001	P<0.001	P<0.001	P<0.001
Logistic regression test	P<0.001	P<0.001	P<0.001	P<0.001
Hepatocellular Carcinoma				
Overall rate	3/50 (6%)	11/50 (22%)	19/49 (39%)	38/50 (76%)
Adjusted rate	7.1%	24.9%	42.2%	84.4%
Terminal rate	2/41 (5%)	9/42 (21%)	18/44 (41%)	32/39 (82%)
First incidence (days)	694	701	699	638
Life table analysis	P<0.001	P<0.029	P<0.001	P<0.001
Logistic regression test	P<0.001	P=0.032	P<0.001	P<0.001
Hepatocellular Adenoma or Carcinoma				
Overall rate	16/50 (32%)	42/50 (84%)	45/49 (92%)	50/50 (100%)
Adjusted rate	37.2%	91.3%	97.8%	100.0%
Terminal rate	14/41 (34%)	38/42 (90%)	43/44 (98%)	39/39 (100%)
First incidence (days)	673	701	680	583
Life table analysis	P<0.001	P<0.001	P<0.001	P<0.001
Logistic regression test	P<0.001	P<0.001	P<0.001	P<0.001
Hepatoblastoma	1	4	4	4
Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma[i]				
Overall rate	16/50 (32%)	42/50 (84%)	46/49 (94%)	50/50 (100%)
Adjusted rate	37.2%	91.3%	97.9%	100.0%
Terminal rate	14/41 (34%)	38/42 (90%)	43/44 (98%)	39/39 (100%)
First incidence (days)	673	701	677	583
Life table analysis	P<0.001	P<0.001	P<0.001	P<0.001
Logistic regression test	P<0.001	P<0.001	P<0.001	P<0.001

* Significantly different (P≤0.05) from the control group by the logistic regression test
** P≤0.01
[a] Number of animals with lesion
[b] Average severity 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] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[e] Observed incidence in animals surviving until the end of the study
[f] In the control column are the P values associated with the trend test. In the exposed group columns are the P values corresponding to the pairwise comparisons between the controls and that exposed group. The logistic regression test regards neoplasms in animals dying prior to terminal kill as nonfatal.
[g] Not applicable; no neoplasms in animal group
[h] Historical incidence for 2-year NTP feed studies with untreated controls (mean ± standard deviation): 596/1,465 (40.7% ± 14.5%); range, 10%-68%
[i] Historical incidence: 313/1,464 (21.4% ± 13.0%); range, 3%-56%

Thyroid Gland: Proliferative changes occurred in the thyroid gland in an exposure-related manner in male and female mice. Incidences of follicular cell hyperplasia were increased in all exposed groups of males and in 600 and 1,300 ppm females, but incidences of follicular cell adenomas were increased only in male mice (Tables 21, C3, C5, and D5). No thyroid gland carcinomas were observed. Hyperplastic follicles were enlarged and were lined by an increased number of cuboidal to columnar epithelial cells that were larger than normal. In some instances, the epithelial cells formed small projections toward the center of the follicle. Adenomas were considered to be on a continuum with focal hyperplasia, but adenomas were larger, showed cellular atypia, and compressed the surrounding thyroid parenchyma.

TABLE 21
Incidences of Neoplasms and Nonneoplastic Lesions of the Thyroid Gland in Mice in the 2-Year Feed Study of Primidone

	0 ppm	300 ppm	600 ppm	1,300 ppm
Male				
Number Examined Microscopically	49	48	50	50
Follicular Cell, Hyperplasia[a]	8 (1.1)[b]	20** (1.5)	31** (1.7)	42** (2.5)
Follicular Cell Adenoma[c]				
Overall rate[d]	0/49 (0%)	3/48 (6%)	3/50 (6%)	6/50 (12%)
Adjusted rate[e]	0.0%	9.1%	9.7%	25.3%
Terminal rate[f]	0/35 (0%)	3/33 (9%)	3/31 (10%)	3/19 (16%)
First incidence (days)	—[h]	726 (T)	726 (T)	674
Logistic regression test[g]	P=0.003	P=0.110	P=0.100	P=0.008
Female				
Number Examined Microscopically	50	48	48	50
Follicular Cell, Hyperplasia	13 (1.2)	12 (1.7)	28** (1.8)	49** (2.3)
Follicular Cell Adenoma	1	1	0	2

** Significantly different (P≤0.01) from the control group by the logistic regression test
(T)Terminal sacrifice
[a] Number of animals with lesion
[b] Average severity of lesions in affected animals: 1=minimal; 2=mild; 3=moderate; 4=marked
[c] Historical incidence in 2-year NTP feed studies with untreated controls (mean ± standard deviation): 22/1,455 (1.5% ± 1.5%); range, 0%-4%
[d] Number of animals with neoplasm per number of animals with thyroid gland examined microscopically
[e] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[f] Observed incidence in animals surviving until the end of the study
[g] In the control column is the P value associated with the trend test. In the exposed group columns are the P values corresponding to the pairwise comparisons between the controls and that exposed group. The logistic regression test regards neoplasms in animals dying prior to terminal kill as nonfatal.
[h] Not applicable; no neoplasms in animal group

Other Organs: In the spleen, the incidences of hematopoietic cell proliferation were increased in 600 ppm males and 1,300 ppm males and females compared to the controls (males: 0 ppm, 14/48; 300 ppm, 15/49; 600 ppm, 26/50; 1,300 ppm, 37/49; females: 14/50, 13/48, 13/49, 23/50; Tables C5 and D5). Incidences of hyperplasia of the pancreatic islets were significantly decreased in 600 and 1,300 ppm males and females (males: 32/45, 34/48, 18/49, 4/47; females: 15/50, 17/47, 6/49, 5/50).

GENETIC TOXICOLOGY

Primidone (33 to 10,000 μg/plate) induced mutations in *Salmonella typhimurium* strain TA1535 in trials conducted in the absence of exogenous metabolic activation (S9); no mutagenic response was detected in TA1535 with S9 (Mortelmans *et al.*, 1986; Table E1). Negative results were obtained in the *S. typhimurium* assay with strains TA98, TA100, and TA1537, with and without S9. No induction of sister chromatid exchanges (Table E2) or chromosomal aberrations (Table E3) was noted in cultured Chinese hamster ovary cells treated with concentrations of primidone ranging from 125 to 1,250 μg/mL, with or without S9. *In vivo*, no significant increase was observed in the frequency of micronucleated polychromatic erythrocytes in bone marrow of male mice treated with 87.5 to 350 mg primidone/kg body weight three times at 24-hour intervals in either of two trials (Table E4).

In summary, primidone induced gene mutations in *S. typhimurium* in the absence of S9 activation, but did not induce chromosomal damage in mammalian cells, *in vitro* or *in vivo*, even at doses associated with marked toxicity.

DISCUSSION AND CONCLUSIONS

Primidone was nominated for toxicity and carcinogenicity studies by the National Cancer Institute because of its high production and its use in the treatment of epilepsy in both adults and children. The International Agency for Research on Cancer had recommended to the National Cancer Institute that primidone be a high-priority chemical for carcinogenicity studies.

The recommended maintenance dose of primidone in the treatment of epilepsy is 10 to 25 mg/kg per day (given in divided doses). Clinically effective serum concentrations for primidone are between 5 and 12 μg/mL (PDR, 1996). A primary metabolite of primidone is phenobarbital, which is also used in the treatment of epilepsy. Effective clinical plasma concentrations for phenobarbital are between 5 and 40 μg/mL (PDR, 1996).

In the 14-day studies, concentrations of 1,250 to 20,000 ppm delivered approximately 120 to 1,100 mg primidone/kg body weight per day to rats and doses of 625 to 5,000 ppm delivered approximately 100 to 900 mg/kg to mice. In the 14-week studies, doses of 300 to 5,000 ppm delivered approximately 20 to 400 mg/kg to rats and 50 to 1,000 mg/kg to mice. In the 2-year studies, rats received 600 to 2,500 ppm and mice received 300 to 1,300 ppm in feed. These doses delivered approximately 25 to 150 mg/kg per day. At 2 years, the plasma concentrations of primidone (female rats) were generally within 1 to 8 μg/mL, and the plasma concentrations for phenobarbital (female rats and mice) were generally within 2 to 20 μg/mL. Peak concentrations of primidone and phenobarbital increased with increasing exposure concentration.

In the 14-day and 14-week studies, the principal chemical-related findings were toxicity to the kidney of rats and the liver of rats and mice. Exposure-related increases in liver weights occurred in rats and mice in the 14-week studies. In the 14-week studies, microscopic examination showed hepatocellular centrilobular hypertrophy in male rats exposed to 600 ppm or greater and in female rats exposed to 1,300, 2,500, or 5,000 ppm and chronic nephropathy in 2,500 and 5,000 ppm male rats. Based on these findings, the highest exposure concentration used in the 2-year study in rats was 2,500 ppm. An increased incidence of centrilobular hypertrophy was observed in all exposed groups of male and female mice. The morphologic appearance of the hepatocellular hypertrophy was typical of that seen in animals exposed to phenobarbital-type substances. Male mice in the 2,500 and 5,000 ppm groups and 5,000 ppm females also showed adrenal cortical cytoplasmic alteration and splenic hematopoietic cell proliferation. The highest exposure concentration was set at 1,300 ppm for the 2-year mouse study. At the end of the 14-week rat and mouse studies, results of the NTP sperm motility and/or vaginal cytology evaluations did not indicate any exposure-related changes in rats or male mice. There was an exposure-related increase in the estrous cycle length of female mice, but the estrous cycle was not affected in female rats. In the continuous breeding study in Swiss (CD-1®) mice, primidone was administered in feed at concentrations up to 2,000 ppm (approximately 350 mg/kg per day). Fertility and reproduction in F_0 animals were not affected, and mating, pregnancy, and fertility indices in F_1 mice were similar to those in the controls. Estrous cycle length was increased by approximately 7% in F_1 females exposed to 1,500 ppm (Appendix O).

It has been shown that rats treated with 100 mg/kg primidone, *per os*, twice daily, for up to 8 weeks, developed a folate deficiency (Carl *et al.*, 1987b). Additionally, a macrocytic, normochromatic anemia with leukopenia has been experimentally induced in folate deficient rats (Kodicek and Carpenter, 1950). In the 14-week study, 5,000 ppm primidone resulted in an average daily dose of 400 mg/kg in rats; thus, development of an anemia related to a primidone-induced folate deficiency could be hypothesized for rats in the 5,000 ppm group. There was, however, only minimal evidence (a minimal decrease of hemoglobin concentration) of an anemic tendency and no evidence of a macrocytosis. The lack of evidence indicating an anemia could be that, under the conditions of this 14-week study, there was little or no primidone-induced folate deficiency resulting in a

minimal to no anemic response. Additionally, dehydration could have masked a minimal anemia. In the 14-week study, rats in the 2,500 and 5,000 ppm groups had decreased mean body weight gains, suggesting decreased feed or water consumption or illness. There were minimal decreases of alkaline phosphatase activity in exposed groups of rats that would be consistent with decreased feed consumption. Circulating alkaline phosphatase in a normal rat is primarily of intestinal or bone origin (Righetti and Kaplan, 1971), and fasting or feed restriction causes decreases in serum alkaline phosphatase activity (Jenkins and Robinson, 1975). If feed consumption by rats was decreased, decreases in alkaline phosphatase activity might be related to loss of the normally circulating intestinal fraction. Also, mechanical difficulties with the automatic watering system caused inadequate water delivery to the 2,500 and 5,000 ppm male rats and resulted in dehydrated animals. There were increases in total protein and albumin concentrations in the exposed groups that would be consistent with dehydration (Kaneko, 1989). A relative erythrocytosis related to dehydration and hemoconcentration can occur in animals with a decreased plasma volume due to inadequate water intake or excessive water loss (e.g., diarrhea); thus, a relative erythrocytosis could mask the presence and/or the severity of an existing anemia.

In the 14-week study, thrombocytosis occurred in all exposed groups of male rats and in 1,300, 2,500, and 5,000 ppm female rats. These findings could be consistent with either physiologic thrombocytosis or a reactive thrombocytosis (Jain, 1986).

In the 2-year studies, survival was similar among exposed and control groups of female rats and mice. Male rats exposed to 1,300 or 2,500 ppm began to die near the end of the study, and this was attributed to kidney toxicity. Some early deaths were also seen in 1,300 ppm male mice; this was attributed to the toxic and carcinogenic effects in the liver. Mean body weights of 1,300 and 2,500 ppm male and female rats and 1,300 ppm male and female mice were lower than those of the controls during the second year of the study, but there was no evidence that these body weight effects masked the ability of the bioassay to detect a carcinogenic response.

In the 2-year rat study, exposure-related toxicity in the liver included cytoplasmic vacuolization and centrilobular hepatocyte hypertrophy. While these studies did not determine whether the exposure-related effects were due to primidone or its metabolites, the liver toxicity observed in rats exposed to primidone was similar to that previously observed in F344/N rats exposed to phenobarbital. For example, Butler (1978) gave 1,000 ppm sodium phenobarbital in drinking water to male F344/N rats for 103 weeks and found liver toxicity in treated rats but no evidence of treatment-induced neoplasms in the liver. The liver lesions were described as marked centrilobular cytomegaly of the parenchymal cells. Near the end of the study, focal nodules of hepatic parenchymal cells were seen, as well as areas of focal fatty degeneration and some evidence of cell necrosis. Biliary proliferation was prominent in all animals.

In the current studies there was no evidence for a treatment-related carcinogenic response in the liver of F344/N rats exposed to primidone. No hepatic neoplasms were seen in Sprague-Dawley rats receiving intraperitoneal injections of 2 mg/kg phenobarbital for life (Schmal and Habs, 1976). Liver neoplasms were seen in Wistar rats given 500 ppm phenobarbital in drinking water for their lifetime (Rossi *et al.*, 1977).

At 2 years, there was a marginal increase in the incidence of thyroid gland follicular cell adenoma or carcinoma (combined) in the 1,300 ppm male rats, and the incidences of these neoplasms were outside the historical range for 2-year NTP feed studies in all exposed groups of male rats. However, because this increase was not significant by the trend analysis and the incidence of follicular cell hyperplasia was not increased, this was considered equivocal evidence of carcinogenic activity. There was no increase in the incidence of follicular cell neoplasms in female rats. Thyroid gland proliferative effects have been related to exposure to phenobarbital (McClain *et al.*, 1988, 1989), but in the current study there was no evidence of thyroid gland follicular cell hyperplasia in exposed rats. Long-term changes in thyroid hormone levels are likely to predispose the rat to a higher incidence of proliferative lesions in the thyroid gland. The male rat has a higher circulating level of thyroid-stimulating hormone (TSH) than the female rat (Capen, 1996), and this might be one explanation why the thyroid gland neoplasms were seen in male but not female rats in the present study.

Phenobarbital is a prototype agent for induction of a variety of biotransformation systems including glutathione S-epoxide transferases, UDP-glucuronyl transferases, aldehyde dehydrogenases, and cytochrome P450 monoxygenases (Waxman and Azaroff, 1992; Ramsden *et al.*, 1993). UDP-glucuronosyl transferase inducers have been shown to lower plasma concentrations of tetraiodothyronine (T_4) by increasing its glucuronidation and elimination by the liver (Liu *et al.*, 1995). Plasma concentrations of triiodothyronine (T_3) may also be decreased (de Sandro *et al.*, 1991). Many xenobiotics that increase the incidence of thyroid gland neoplasms in rodents do so by increasing the peripheral metabolism of thyroid hormones through an induction of hepatic microsomal enzymes as has been reported for phenobarbital (Capen, 1994). Lowering thyroid hormone levels results in a compensatory increase in secretion of TSH, increased incidences of follicular cell hypertrophy and hyperplasia, and an increased incidence of follicular cell neoplasms in rodents (Barter and Klaassen, 1994; Capen, 1994).

The rodent may be more sensitive than other mammals to chemically induced changes in the thyroid gland because the rodent lacks a serum protein known as thyroxine-binding globulin that binds to thyroid hormones. Because rodents lack this protein, they quickly excrete thyroid hormones. In contrast, where thyroid globulin protein is present (in the human, monkey, and dog) (Döhler *et al.*, 1979; Capen, 1996), the protein would serve to modulate the effects of a chemical (e.g., phenobarbital) that induces enzymes that cause conjugation and excretion of the hormone. However, there is some evidence that long-term treatment of humans with phenobarbital (greater than 6 years) may result in altered serum T_3 and T_4 levels (Tanaka *et al.*, 1987).

Exposure to primidone for 2 years resulted in a marked increase in the severity of chronic nephropathy in male rats. In addition, increased incidences of parathyroid gland hyperplasia, mineralization of the forestomach and glandular stomach, fibrous osteodystrophy, and lung interstitium mineralization were seen in exposed male rats; these lesions were secondary to chronic nephropathy. The chemical-related increase in the severity of nephropathy in exposed males was a principal cause of decreased survival in these animals. The incidence of parathyroid gland hyperplasia as well as the mineralization observed in other organ systems are consistent with renal secondary hyperparathyroidism. Hyperparathyroidism accompanies severe nephropathy in rats because the progressive loss of renal function disrupts calcium and phosphorus homeostasis, leading to prolonged parathyroid gland stimulation. This has been observed in other NTP studies (e.g., coumarin; NTP, 1993a).

The NTP has found that examination of the entire kidney, by step-sectioning through residual tissue, may enable a more precise evaluation of the potential chemical-related induction of renal proliferative lesions than observations made from single sections, particularly when the proliferative lesions are small and identified only by microscopic examination (Eustis *et al.*, 1994). For primidone, this extended evaluation of the male rat kidney showed a marginal increase in neoplasms in the 2,500 ppm group when the results of the original and step-section evaluations were combined. The increased incidences of focal hyperplasia and the marginal increase in renal tubule neoplasms in the 2,500 ppm group were considered to be equivocal evidence of a carcinogenic effect. Chronic nephropathy may influence the induction, development, or progression of renal neoplasms in several ways, including a reduction in target cell population and/or increased number of cells in the replicative cycle due to chronic inflammation and continued degeneration and necrosis, alterations in vascularity as a result of fibrosis, or other alterations in microenvironment.

Kidney changes consistent with nephropathy were observed in both the 14-week and 2-year rat studies. The nephropathy in the 14-week study was much less severe than in the 2-year study. In the 14-week study, a "minimal" lesion was considered to be only a few regenerative tubules, while a grade of "mild" nephropathy (equivalent to grade 2) was four or more regenerative tubules, and "moderate" nephropathy included the presence of protein casts and/or glomerular lesions. These lesions progressed with continued exposure to primidone. At 2 years, the lesions were quite advanced, far exceeding the severity of the nephropathy in the 14-week study and resulting in compromised renal function, especially in the 1,300 and 2,500 ppm groups. In the 2-year study, nephropathy represented an entire spectrum of microscopic lesions including interstitial fibrosis, tubule degeneration and regeneration, protein casts, cyst formation, glomerular sclerosis, and eventual loss of nephrons.

These studies could not differentiate between the effects of primidone or its metabolites in the kidney. Phenobarbital, a metabolite of primidone, can induce hepatic, intestinal, and renal UDP-glucuronosyltransferase and cytochrome P450 enzyme activities (Koster *et al.*, 1986). Induction of these enzyme systems in the kidney may result in the accumulation of toxic metabolites and subsequent toxicity to the kidney (Nakagawa and Tayama, 1988; Imaoka *et al.*, 1989). Phenobarbital treatment has been shown to cause cell proliferation in the rat kidney, as measured by bromodeoxyuridine immunocytochemistry (Jones and Clarke, 1993); a phenobarbital-induced increase in cell proliferation may have contributed to the observed toxicity in the male rat kidney in this study. In the two long-term phenobarbital studies in male Wistar rats (Rossi *et al.*, 1977) or male F344/N rats (Butler, 1978), an increase in severity of nephropathy was not reported. However, the extent to which the kidney was examined for nonneoplastic lesions in these studies was not reported. Generally, female rats exhibit less renal toxicity than male rats after phenobarbital/chemical treatment. Age-dependent DNA modifications induced by endogenous electrophiles can be derived during normal metabolism of nutrients. DNA damage due to aging is sex, species, and tissue specific (Li *et al.*, 1992).

In male and female mice, there was clear evidence for carcinogenic activity in the liver, where the incidences of hepatocellular adenoma, hepatocellular carcinoma, and hepatoblastomas were increased (except hepatoblastoma in females). The incidence and multiplicity of hepatocellular neoplasms increased in an exposure-related manner. In addition, centrilobular hypertrophy and hepatocyte cytoplasmic vacuolization were increased. Thyroid gland follicular cell hyperplasia was seen in male and female mice. The incidence of thyroid gland follicular cell adenomas was increased in 1,300 ppm male mice. These effects may be due to phenobarbital-induced liver enzymes which can result in decreases in circulating T_3 and T_4 levels, followed by increases in TSH stimulation, but this was not measured in the current studies.

These studies could not determine the extent to which the mouse liver carcinogenic effects were due to the parent compound, the metabolites, or a combination of exposures to these chemicals. However, there is considerable literature on the carcinogenic effects of phenobarbital in mice (reviewed by IARC, 1976) since its introduction in 1912 as a sedative-hypnotic and anticonvulsant (McClain, 1990). Phenobarbital has been shown to cause liver neoplasms in several strains of mice including CF1 mice (Thorpe and Walker, 1973; Ponomarkov *et al.*, 1976) and C3H mice (Peraino *et al.*, 1973a). Those species or strains with high incidences of spontaneous liver neoplasms appear to be more sensitive than species with low neoplasm incidences (McClain, 1990); most rat strains have relatively low incidences of spontaneous liver neoplasms, and it has been shown that rats, as compared to mice, are relatively resistant to phenobarbital-induced liver neoplasms.

Hepatocellular adenomas, hepatocellular carcinomas, and hepatoblastomas represent a biological and morphological continuum in progression of proliferative lesions. It is probable that hepatoblastomas are composed of cells that are more primitive, rather than representing further progression to a more malignant state. Hepatoblastomas are considered to represent a phenotypic (and possibly genotypic) variant of a malignant liver neoplasm. Because the malignant potential of hepatoblastomas and hepatocellular carcinomas appears similar and hepatoblastomas are generally observed within hepatocellular neoplasms (mostly carcinomas), it is appropriate to combine the incidences of hepatoblastoma with those of adenoma and carcinoma when interpreting the carcinogenic potential of a chemical. Hepatoblastomas are rare and seen in relatively high numbers only after chemical administration [e.g., with oxazepam (NTP, 1993b, 1998), *o*-nitroanisole (NTP, 1993c), benzofuran (NTP, 1989), ethylene thiourea (NTP, 1992), 1-amino 2,4-dibromoanthraquinone (NTP, 1996), methylphenidate hydrochloride (NTP, 1995), and coumarin (NTP, 1993a)]. Liver cancer accounts for approximately 2% to 3% of all cancer deaths in the United States (Parker *et al.*, 1996). In children, hepatoblastomas account for approximately 70% of all liver cancers (Ding *et al.*, 1994).

To date, liver disease associated with *Helicobacter hepaticus* infection has been identified in male mice from nine 2-year bioassays. Using a polymerase chain reaction-based assay (Malarkey *et al.*, 1997); *H. hepaticus* was not identified in the livers of 20 mice evaluated from this study. Furthermore, histologic lesions consistent with those described for *H. hepaticus* were not identified in livers of mice in this study.

In NTP genetic toxicity studies, primidone did not induce chromosomal effects in a number of mammalian cell test systems (Appendix E). Primidone was mutagenic in *Salmonella* in the absence of S9, but no mutagenic activity was detected in the presence of S9. The metabolite phenobarbital has a longer half-life than the parent compound primidone, suggesting that the metabolite may have contributed to the carcinogenic effects observed, but these studies could not determine the extent to which the carcinogenic effects were due to parent compound, metabolite, or a combination of these exposures.

Phenobarbital has been used clinically for more than 80 years, and there is no conclusive evidence that it causes neoplasms in the clinical setting (Brodie and Dichter, 1996). The IARC has reviewed the data on phenobarbital and has found insufficient evidence to draw a conclusion that it is carcinogenic in humans, although the evidence for carcinogenicity in animals is clear (IARC, 1987). A recent review on the side effects of primidone did not report any evidence for cancer in humans for this or any other antiepileptic drug (Brodie and Dichter, 1996).

CONCLUSIONS

Under the conditions of these 2-year feed studies, there was *equivocal evidence of carcinogenic activity** of primidone in male F344/N rats based on a marginal increase in thyroid gland follicular cell neoplasms, primarily adenomas, and a marginal increase in renal tubule neoplasms. There was *no evidence of carcinogenic activity* of primidone in female F344/N rats exposed to 600, 1,300, or 2,500 ppm. There was *clear evidence of carcinogenic activity* of primidone in male $B6C3F_1$ mice based on the increased incidences of hepatocellular neoplasms, and the increased incidence of thyroid gland follicular cell adenomas was also considered to be chemical related. There was *clear evidence of carcinogenic activity* of primidone in female $B6C3F_1$ mice based on the increased incidences of hepatocellular neoplasms.

Exposure of rats to primidone resulted in increased incidences of hepatocyte cytoplasmic vacuolization and centrilobular hypertrophy in males and females and eosinophilic foci in females. The increased severity of nephropathy and increased incidence of renal tubule hyperplasia in male rats were related to primidone exposure. Exposure of male mice to primidone resulted in hepatocyte centrilobular hypertrophy and thyroid gland follicular cell hyperplasia. Exposure of female mice to primidone resulted in hepatocyte centrilobular hypertrophy and cytoplasmic vacuolization, eosinophilic focus, and thyroid gland follicular cell hyperplasia.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 11. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 13.

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

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

	0 ppm	600 ppm	1,300 ppm	2,500 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	33	33	39	36
Natural deaths	4	10	7	14
Survivors				
Terminal sacrifice	13	7	4	
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine large, colon	(50)	(50)	(49)	(46)
Polyp adenomatous			1 (2%)	
Intestine small, duodenum	(50)	(50)	(50)	(47)
Intestine small, jejunum	(50)	(50)	(49)	(45)
Carcinoma	1 (2%)			
Leiomyosarcoma		1 (2%)		
Intestine small, ileum	(50)	(50)	(49)	(46)
Leiomyosarcoma	1 (2%)			
Liver	(50)	(50)	(50)	(50)
Fibrosarcoma, metastatic, spleen	1 (2%)			
Hepatocellular adenoma	1 (2%)			1 (2%)
Hepatocellular adenoma, multiple		1 (2%)	1 (2%)	
Mesentery	(11)	(6)	(9)	(3)
Fat, fibrosarcoma, metastatic, spleen	1 (9%)			
Oral mucosa	(1)			
Pharyngeal, squamous cell carcinoma	1 (100%)			
Pancreas	(50)	(50)	(50)	(49)
Salivary glands	(50)	(50)	(49)	(49)
Stomach, forestomach	(50)	(50)	(50)	(49)
Squamous cell papilloma			1 (2%)	
Stomach, glandular	(50)	(50)	(50)	(49)
Tongue			(1)	
Squamous cell papilloma			1 (100%)	
Tooth		(1)		
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Adrenal medulla	(50)	(50)	(50)	(49)
Pheochromocytoma malignant	1 (2%)	1 (2%)	1 (2%)	
Pheochromocytoma benign	16 (32%)	19 (38%)	19 (38%)	7 (14%)
Bilateral, pheochromocytoma benign	7 (14%)	9 (18%)	5 (10%)	5 (10%)
Islets, pancreatic	(50)	(50)	(50)	(49)
Adenoma	1 (2%)			
Carcinoma	1 (2%)			
Parathyroid gland	(45)	(41)	(46)	(49)
Pituitary gland	(49)	(50)	(48)	(49)
Pars distalis, adenoma	17 (35%)	12 (24%)	11 (23%)	4 (8%)
Pars intermedia, adenoma		1 (2%)	1 (2%)	1 (2%)

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

	0 ppm	600 ppm	1,300 ppm	2,500 ppm
Endocrine System (continued)				
Thyroid gland	(50)	(50)	(49)	(49)
Bilateral, C-cell, adenoma		1 (2%)		
C-cell, adenoma	7 (14%)	2 (4%)	7 (14%)	1 (2%)
C-cell, carcinoma	1 (2%)		1 (2%)	
Follicular cell, adenoma	1 (2%)	1 (2%)	6 (12%)	3 (6%)
Follicular cell, carcinoma	1 (2%)	3 (6%)	1 (2%)	1 (2%)
General Body System				
Peritoneum		(1)	(1)	(1)
Tissue NOS		(1)		
Genital System				
Coagulating gland	(2)	(1)		(1)
Epididymis	(50)	(50)	(50)	(48)
Preputial gland	(50)	(50)	(50)	(49)
Adenoma	2 (4%)	1 (2%)	2 (4%)	
Carcinoma	1 (2%)			
Prostate	(50)	(50)	(50)	(48)
Seminal vesicle	(50)	(50)	(50)	(48)
Testes	(50)	(50)	(50)	(48)
Bilateral, interstitial cell, adenoma	33 (66%)	33 (66%)	35 (70%)	34 (71%)
Interstitial cell, adenoma	8 (16%)	11 (22%)	7 (14%)	9 (19%)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Lymph node	(24)	(23)	(16)	(10)
Lymph node, mandibular	(50)	(50)	(48)	(49)
Lymph node, mesenteric	(50)	(50)	(50)	(48)
Spleen	(50)	(50)	(50)	(49)
Fibrosarcoma	3 (6%)	1 (2%)		
Thymus	(49)	(47)	(44)	(46)
Thymoma malignant	1 (2%)			
Integumentary System				
Mammary gland	(48)	(49)	(50)	(47)
Adenoma		1 (2%)		
Carcinoma	2 (4%)			
Fibroadenoma	3 (6%)	3 (6%)	3 (6%)	
Skin	(50)	(50)	(50)	(50)
Basal cell adenoma	1 (2%)			
Basal cell carcinoma	1 (2%)			
Basosquamous tumor benign		1 (2%)		
Keratoacanthoma	1 (2%)	1 (2%)		
Trichoepithelioma				1 (2%)
Pinna, melanoma malignant			1 (2%)	
Pinna, squamous cell papilloma		1 (2%)	1 (2%)	1 (2%)
Subcutaneous tissue, fibroma	3 (6%)	3 (6%)	3 (6%)	
Subcutaneous tissue, fibrosarcoma			2 (4%)	
Subcutaneous tissue, hemangiosarcoma			1 (2%)	
Subcutaneous tissue, pinna, melanoma benign	1 (2%)		1 (2%)	

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

	0 ppm	600 ppm	1,300 ppm	2,500 ppm
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Chordoma	1 (2%)			
Mandible, osteosarcoma	1 (2%)			
Tibia, osteosarcoma		1 (2%)		
Skeletal muscle	(1)			
Nervous System				
Brain	(50)	(50)	(49)	(49)
Astrocytoma malignant				2 (4%)
Peripheral nerve	(1)	(1)		
Spinal, schwannoma malignant	1 (100%)			
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	1 (2%)	1 (2%)		
Alveolar/bronchiolar carcinoma			1 (2%)	1 (2%)
Chordoma, metastatic, bone	1 (2%)			
Fibrosarcoma, metastatic, spleen	1 (2%)			
Hemangiosarcoma, metastatic, skin			1 (2%)	
Osteosarcoma, metastatic, bone	1 (2%)			
Squamous cell carcinoma			1 (2%)	
Nose	(50)	(50)	(50)	(50)
Special Senses System				
Zymbal's gland		(1)		
Carcinoma		1 (100%)		
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Fibrosarcoma, metastatic, spleen	1 (2%)			
Lipoma				1 (2%)
Osteosarcoma, metastatic, bone	1 (2%)			
Renal tubule, adenoma	2 (4%)	1 (2%)	1 (2%)	1 (2%)
Renal tubule, carcinoma				1 (2%)
Urinary bladder	(50)	(50)	(50)	(48)
Papilloma			1 (2%)	
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Leukemia mononuclear	35 (70%)	30 (60%)	24 (48%)	12 (24%)
Lymphoma malignant			1 (2%)	
Mesothelioma malignant	2 (4%)	3 (6%)	2 (4%)	1 (2%)

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

	0 ppm	600 ppm	1,300 ppm	2,500 ppm
Neoplasm Summary				
Total animals with primary neoplasms[c]	50	49	50	47
Total primary neoplasms	160	144	143	87
Total animals with benign neoplasms	49	49	49	44
Total benign neoplasms	105	103	107	69
Total animals with malignant neoplasms	41	35	29	15
Total malignant neoplasms	55	41	36	18
Total animals with metastatic neoplasms	3		1	
Total metastatic neoplasms	7		1	

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

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

Number of Days on Study	281	305	457	463	505	509	526	560	568	574	575	583	585	591	619	627	641	645	646	652	655	655	662	667	669
Carcass ID Number	014	044	043	013	017	005	034	011	010	024	020	007	009	022	032	004	015	029	042	050	038	048	016	001	036
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma				X																					
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma																				X					
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, spleen											X														
Hepatocellular adenoma																									
Mesentery								+		+	+			+										+	
Fat, fibrosarcoma, metastatic, spleen											X														
Oral mucosa				+																					
Pharyngeal, squamous cell carcinoma				X																					
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																									
Pheochromocytoma benign		X											X			X				X	X				
Bilateral, pheochromocytoma benign															X			X						X	
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma																									
Parathyroid gland	+	M	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma	X		X									X		X	X		X		X						
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma					X																				
C-cell, carcinoma																								X	
Follicular cell, adenoma																									
Follicular cell, carcinoma																									
General Body System																									
None																									

+: 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 Primidone: 0 ppm

Number of Days on Study	669	674	676	683	692	697	698	704	710	710	715	719	723	723	723	723	723	723	723	723	723	723	723	723	723	
Carcass ID Number	037	033	031	046	003	018	006	019	030	039	040	045	002	008	012	021	023	025	026	027	028	035	041	047	049	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, spleen																										1
Hepatocellular adenoma																					X					1
Mesentery						+	+		+								+	+				+				11
Fat, fibrosarcoma, metastatic, spleen																										1
Oral mucosa																										1
Pharyngeal, squamous cell carcinoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant											X															1
Pheochromocytoma benign		X	X							X	X	X	X		X						X	X	X		X	16
Bilateral, pheochromocytoma benign					X			X								X			X							7
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma				X																						1
Carcinoma															X											1
Parathyroid gland	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma		X		X		X				X		X				X			X	X	X		X			17
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma										X			X		X	X				X					X	7
C-cell, carcinoma																										1
Follicular cell, adenoma						X																				1
Follicular cell, carcinoma																	X									1
General Body System																										
None																										

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

Number of Days on Study	281	305	457	463	505	509	526	560	568	574	575	583	585	591	619	627	641	645	646	652	655	655	662	667	669
Carcass ID Number	014	044	043	013	017	005	034	011	010	024	020	007	009	022	032	004	015	029	042	050	038	048	016	001	036
Genital System																									
Coagulating gland																	+								
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																					X				
Carcinoma							X																		
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma				X		X	X	X	X	X						X	X			X	X	X	X		X
Interstitial cell, adenoma												X	X					X						X	
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node					+			+	+	+		+	+	+	+	+		+					+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma											X									X					
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymoma malignant																			X						
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+
Carcinoma																									
Fibroadenoma																X									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma																									
Basal cell carcinoma																									
Keratoacanthoma																									
Subcutaneous tissue, fibroma															X		X					X			
Subcutaneous tissue, pinna, melanoma benign																							X		
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Chordoma																	X								
Mandible, osteosarcoma																									
Skeletal muscle																							+		
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve		+																							
Spinal, schwannoma malignant		X																							
Spinal cord		+																							
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma												X													
Chordoma, metastatic, bone																	X								
Fibrosarcoma, metastatic, spleen											X														
Osteosarcoma, metastatic, bone																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

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

Number of Days on Study	669	674	676	683	692	697	698	704	710	710	715	719	723	723	723	723	723	723	723	723	723	723	723	723	723	
Carcass ID Number	037	033	031	046	003	018	006	019	030	039	040	045	002	008	012	021	023	025	026	027	028	035	041	047	049	Total Tissues/ Tumors
Genital System																										
Coagulating gland											+															2
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																									X	2
Carcinoma																										1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma	X		X	X	X	X	X	X	X		X		X	X	X	X	X	X			X	X	X	X	X	33
Interstitial cell, adenoma										X		X							X	X						8
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+			+	+	+	+	+						+								24
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma																	X									3
Thymus	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymoma malignant																										1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma								X								X										2
Fibroadenoma	X																		X							3
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell adenoma													X													1
Basal cell carcinoma																								X		1
Keratoacanthoma															X											1
Subcutaneous tissue, fibroma																										3
Subcutaneous tissue, pinna, melanoma benign																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Chordoma																										1
Mandible, osteosarcoma														X												1
Skeletal muscle																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve																										1
Spinal, schwannoma malignant																										1
Spinal cord																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										1
Chordoma, metastatic, bone																										1
Fibrosarcoma, metastatic, spleen																										1
Osteosarcoma, metastatic, bone														X												1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

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

Number of Days on Study	281	305	457	463	505	509	526	560	568	574	575	583	585	591	619	627	641	645	646	652	655	655	662	667	669
Carcass ID Number	014	044	043	013	017	005	034	011	010	024	020	007	009	022	032	004	015	029	042	050	038	048	016	001	036
Special Senses System																									
None																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, spleen											X														
Osteosarcoma, metastatic, bone																									
Renal tubule, adenoma															X										
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X			X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X
Mesothelioma malignant																									

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

Number of Days on Study	669	674	676	683	692	697	698	704	710	710	715	719	723	723	723	723	723	723	723	723	723	723	723	723	723	
Carcass ID Number	037	033	031	046	003	018	006	019	030	039	040	045	002	008	012	021	023	025	026	027	028	035	041	047	049	Total Tissues/ Tumors
Special Senses System																										
None																										
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, spleen																										1
Osteosarcoma, metastatic, bone														X												1
Renal tubule, adenoma																X										2
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X	X	X	X			X	X	X	X	X	X		X	X			X		X	X		X	X		35
Mesothelioma malignant																	X	X								2

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Primidone: 600 ppm

Number of Days on Study	330	502	502	503	526	542	544	562	579	583	609	610	619	619	627	634	635	635	641	641	642	652	654	661	669
Carcass ID Number	079	056	081	099	090	093	084	060	059	097	074	066	063	088	089	061	073	086	057	058	069	067	080	071	051
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma																									
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma, multiple																									
Mesentery						+	+													+					
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth						+																			
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant										X															
Pheochromocytoma benign								X		X			X	X	X		X		X	X			X		X
Bilateral, pheochromocytoma benign											X													X	
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	M	M	M	+	+	+	M	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma					X				X	X					X		X	X				X			
Pars intermedia, adenoma													X												
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, C-cell, adenoma										X															
C-cell, adenoma																									
Follicular cell, adenoma																									
Follicular cell, carcinoma																				X					
General Body System																									
Peritoneum							+																		
Tissue NOS									+																
Genital System																									
Coagulating gland																		+							
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma						X		X			X	X	X	X						X	X		X	X	X
Interstitial cell, adenoma		X	X	X			X			X					X	X		X	X						

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Primidone: 600 ppm

Number of Days on Study	669	669	670	673	674	674	683	683	694	697	697	703	709	709	710	712	712	715	723	723	723	723	723	723	723	
Carcass ID Number	055	072	075	095	096	098	065	094	068	070	085	091	062	087	083	054	092	076	052	053	064	077	078	082	010	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma												X														1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma, multiple														X												1
Mesentery														+						+					+	6
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth																										1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																										1
Pheochromocytoma benign			X	X			X		X						X		X	X	X			X				19
Bilateral, pheochromocytoma benign	X	X			X	X				X				X							X					9
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	41
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma		X			X		X	X					X													12
Pars intermedia, adenoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, C-cell, adenoma																										1
C-cell, adenoma																			X	X						2
Follicular cell, adenoma				X																						1
Follicular cell, carcinoma			X																		X					3
General Body System																										
Peritoneum																										1
Tissue NOS																										1
Genital System																										
Coagulating gland																										1
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma				X																						1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma			X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	33
Interstitial cell, adenoma	X				X																					11

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Primidone: 600 ppm

Number of Days on Study	330	502	502	503	526	542	544	562	579	583	609	610	619	619	627	634	635	635	641	641	642	652	654	661	669
Carcass ID Number	079	056	081	099	090	093	084	060	059	097	074	066	063	088	089	061	073	086	057	058	069	067	080	071	051
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node		+	+	+		+			+	+	+	+	+		+	+	+					+			+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																								X	
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Integumentary System																									
Mammary gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma										X															
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basosquamous tumor benign																									
Keratoacanthoma																									
Pinna, squamous cell papilloma								X																	
Subcutaneous tissue, fibroma												X							X		X				
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tibia, osteosarcoma																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve												+													
Spinal cord												+													
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma										X															
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye												+													
Zymbal's gland																				+					
Carcinoma																				X					
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																							X		
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X	X	X		X			X	X	X	X	X		X	X	X		X	X		X			X
Mesothelioma malignant							X						X												

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Primidone: 600 ppm

Number of Days on Study	669	669	670	673	674	674	683	683	694	697	697	703	709	709	710	712	712	715	723	723	723	723	723	723	723	
Carcass ID Number	055	072	075	095	096	098	065	094	068	070	085	091	062	087	083	054	092	076	052	053	064	077	078	082	010	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+						+	+		+		+	+	+	+		+									23
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma																										1
Thymus	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																										1
Fibroadenoma										X		X								X						3
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basosquamous tumor benign														X												1
Keratoacanthoma	X																									1
Pinna, squamous cell papilloma																										1
Subcutaneous tissue, fibroma																										3
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tibia, osteosarcoma								X																		1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve																										1
Spinal cord																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																										1
Zymbal's gland																										1
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X	X			X	X	X	X		X		X	X	X	X		X					X			X	30
Mesothelioma malignant																			X							3

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Primidone: 1,300 ppm

Number of Days on Study	354	437	529	551	558	561	562	572	576	583	585	589	589	599	612	613	613	619	627	627	631	632	635	635	641
Carcass ID Number	125	149	101	116	114	148	113	120	104	133	115	102	132	122	127	119	126	105	130	134	137	111	121	139	103
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
Polyp adenomatous													X												
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma, multiple																									
Mesentery			+								+					+			+	+					
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																									
Squamous cell papilloma																									
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant									X																
Pheochromocytoma benign			X		X				X									X			X	X	X	X	X
Bilateral, pheochromocytoma benign						X										X									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma		X							X	X										X					
Pars intermedia, adenoma																	X								
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma			X						X																
C-cell, carcinoma																						X			
Follicular cell, adenoma	X	X															X				X				
Follicular cell, carcinoma																									
General Body System																									
Peritoneum																			+						
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																X									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma				X	X	X		X	X			X	X	X	X		X	X			X	X	X		X
Interstitial cell, adenoma							X				X					X								X	

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Primidone: 1,300 ppm

Number of Days on Study	641	643	648	654	655	659	664	667	667	668	669	673	674	683	683	683	688	691	697	698	712	723	723	723	723	
Carcass ID Number	112	142	123	129	118	145	135	108	144	109	140	138	136	107	117	143	128	106	141	150	124	110	131	146	147	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Polyp adenomatous																										1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma, multiple																							X			1
Mesentery							+				+							+		+						9
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																							X			1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue							+																			1
Squamous cell papilloma							X																			1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																										1
Pheochromocytoma benign				X	X	X		X		X				X		X	X		X		X					19
Bilateral, pheochromocytoma benign											X												X		X	5
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	46
Pituitary gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pars distalis, adenoma											X	X	X	X							X		X		X	11
Pars intermedia, adenoma																										1
Thyroid gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell, adenoma	X											X						X	X	X						7
C-cell, carcinoma																										1
Follicular cell, adenoma							X									X										6
Follicular cell, carcinoma								X																		1
General Body System																										
Peritoneum																										1
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma							X																			2
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma	X	X	X	X	X	X	X		X	X	X		X			X	X	X	X	X	X	X		X	X	35
Interstitial cell, adenoma								X						X									X			7

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Primidone: 1,300 ppm

Number of Days on Study	354	437	529	551	558	561	562	572	576	583	585	589	589	599	612	613	613	619	627	627	631	632	635	635	641
Carcass ID Number	125	149	101	116	114	148	113	120	104	133	115	102	132	122	127	119	126	105	130	134	137	111	121	139	103
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+				+	+	+			+	+	+	+				+							+	
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pinna, melanoma malignant																									
Pinna, squamous cell papilloma																									
Subcutaneous tissue, fibroma																				X			X		
Subcutaneous tissue, fibrosarcoma									X															X	
Subcutaneous tissue, hemangiosarcoma			X																						
Subcutaneous tissue, pinna, melanoma benign																									X
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma				X																					
Hemangiosarcoma, metastatic, skin			X																						
Squamous cell carcinoma					X																				
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																							+		
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																	X								
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma																									
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X				X	X	X	X			X	X	X			X			X	X				X	X
Lymphoma malignant																									
Mesothelioma malignant																			X						

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Primidone: 1,300 ppm

Number of Days on Study	641	643	648	654	655	659	664	667	667	668	669	673	674	683	683	683	688	691	697	698	712	723	723	723	723	
Carcass ID Number	112	142	123	129	118	145	335	108	144	109	140	138	136	107	117	143	128	106	141	150	124	110	131	146	147	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node		+								+										+			+	+	+	16
Lymph node, mandibular	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	M	+	+	+	M	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	44
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroadenoma											X			X											X	3
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pinna, melanoma malignant						X																				1
Pinna, squamous cell papilloma																			X							1
Subcutaneous tissue, fibroma																			X							3
Subcutaneous tissue, fibrosarcoma																										2
Subcutaneous tissue, hemangiosarcoma																										1
Subcutaneous tissue, pinna, melanoma benign																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma																										1
Hemangiosarcoma, metastatic, skin																										1
Squamous cell carcinoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye											+															2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Papilloma															X											1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X			X	X		X		X			X				X					X	X	X	X	24
Lymphoma malignant																		X								1
Mesothelioma malignant																	X									2

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Primidone: 2,500 ppm

Number of Days on Study	254	380	436	437	437	505	517	522	529	532	533	537	538	542	544	548	556	559	560	561	561	562	569	572	573
Carcass ID Number	168	194	162	164	181	200	188	195	190	166	163	187	151	186	197	176	196	199	182	154	184	170	191	152	155
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Intestine large, colon	A	A	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	A	+	+	+	+	+	+	+	+	+	+	A	+	+	M	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	A	+	+	+	+	+	+	+	+	+	+	A	+	+	M	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	A	+	+	+	+	+	+	+	+	+	+	A	+	+	M	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	A	+	+	+	+	+	+	+	+	+	+	A	+	+	M	+	+	+	+	+	+	+	+	+
Intestine small, ileum	A	A	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Mesentery											+										+		+		
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign									X									X							
Bilateral, pheochromocytoma benign								X			X														
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Pars distalis, adenoma			X												X										
Pars intermedia, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
C-cell, adenoma																									
Follicular cell, adenoma									X																
Follicular cell, carcinoma																									
General Body System																									
Peritoneum											+														
Genital System																									
Coagulating gland																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma						X	X	X	X	X	X	X		X	X		X	X			X	X	X	X	X
Interstitial cell, adenoma				X															X	X					

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Primidone: 2,500 ppm

Number of Days on Study	581	583	583	585	585	585	588	589	589	589	589	589	589	589	596	599	599	603	610	619	619	626	632	641	674	
Carcass ID Number	183	174	189	159	171	172	160	153	161	165	167	169	180	198	177	173	175	179	156	185	193	192	158	178	157	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, jejunum	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma																									X	1
Mesentery																										3
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma benign				X			X				X								X				X			7
Bilateral, pheochromocytoma benign															X							X		X		5
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma											X								X							4
Pars intermedia, adenoma																									X	1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell, adenoma																				X						1
Follicular cell, adenoma		X				X																				3
Follicular cell, carcinoma												X														1
General Body System																										
Peritoneum																										1
Genital System																										
Coagulating gland																					+					1
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Bilateral, interstitial cell, adenoma			X	X		X	X	X		X	X	X		X	X	X		X		X	X	X	X	X	X	34
Interstitial cell, adenoma	X	X			X								X				X		X							9

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Primidone: 2,500 ppm

Number of Days on Study	254	380	436	437	437	505	517	522	529	532	533	537	538	542	544	548	556	559	560	561	561	562	569	572	573
Carcass ID Number	168	194	162	164	181	200	188	195	190	166	163	187	151	186	197	176	196	199	182	154	184	170	191	152	155
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node			+		+									+					+			+			+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Integumentary System																									
Mammary gland	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trichoepithelioma															X										
Pinna, squamous cell papilloma																						X			
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Astrocytoma malignant																									
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Special Senses System																									
None																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lipoma																		X							
Renal tubule, adenoma									X																
Renal tubule, carcinoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X	X		X									X					X						
Mesothelioma malignant											X														

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Primidone: 2,500 ppm

Number of Days on Study	581	583	583	585	585	585	588	589	589	589	589	589	589	589	596	599	599	603	610	619	619	626	632	641	674	
Carcass ID Number	183	174	189	159	171	172	160	153	161	165	167	169	180	198	177	173	175	179	156	185	193	192	158	178	157	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node						+					+									+					+	10
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	46
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trichoepithelioma																										1
Pinna, squamous cell papilloma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Astrocytoma malignant									X												X					2
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma									X																	1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																										
None																										
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lipoma																										1
Renal tubule, adenoma																										1
Renal tubule, carcinoma																			X							1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X				X			X			X								X				X	X	12
Mesothelioma malignant																										1

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

	0 ppm	600 ppm	1,300 ppm	2,500 ppm
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate[a]	23/50 (46%)	28/50 (56%)	24/50 (48%)	12/49 (24%)
Adjusted rate[b]	79.6%	83.3%	87.0%	85.0%
Terminal rate[c]	8/13 (62%)	3/7 (43%)	2/4 (50%)	0/0 (0%)
First incidence (days)	305	562	529	522
Life table test[d]	P<0.001	P=0.066	P=0.017	P<0.001
Logistic regression test[d]	P=0.231N	P=0.213	P=0.413	P=0.367N
Cochran-Armitage test[d]	P=0.006N			
Fisher exact test[d]		P=0.212	P=0.500	P=0.021N
Adrenal Medulla: Benign or Malignant Pheochromocytoma				
Overall rate	23/50 (46%)	28/50 (56%)	24/50 (48%)	12/49 (24%)
Adjusted rate	79.6%	83.3%	87.0%	85.0%
Terminal rate	8/13 (62%)	3/7 (43%)	2/4 (50%)	0/0 (0%)
First incidence (days)	305	562	529	522
Life table test	P<0.001	P=0.066	P=0.017	P<0.001
Logistic regression test	P=0.231N	P=0.213	P=0.413	P=0.367N
Cochran-Armitage test	P=0.006N			
Fisher exact test		P=0.212	P=0.500	P=0.021N
Kidney (Renal Tubule): Adenoma (Step Sections)				
Overall rate	2/50 (4%)	1/50 (2%)	4/50 (8%)	5/50 (10%)
Adjusted rate	13.8%	4.5%	20.9%	54.9%
Terminal rate	1/13 (8%)	0/7 (0%)	0/4 (0%)	0/0 (0%)
First incidence (days)	715	673	613	585
Life table test	P<0.001	P=0.650N	P=0.196	P<0.001
Logistic regression test	P=0.012	P=0.557N	P=0.264	P=0.030
Cochran-Armitage test	P=0.076			
Fisher exact test		P=0.500N	P=0.500	P=0.218
Kidney (Renal Tubule): Adenoma (Single and Step Sections)				
Overall rate	4/50 (8%)	2/50 (4%)	4/50 (8%)	6/50 (12%)
Adjusted rate	23.2%	8.0%	20.9%	56.0%
Terminal rate	2/13 (15%)	0/7 (0%)	0/4 (0%)	0/0 (0%)
First incidence (days)	619	654	613	529
Life table test	P<0.001	P=0.492N	P=0.304	P<0.001
Logistic regression test	P=0.056	P=0.355N	P=0.563	P=0.098
Cochran-Armitage test	P=0.185			
Fisher exact test		P=0.339N	P=0.643N	P=0.370
Kidney (Renal Tubule): Adenoma or Carcinoma (Step Sections)				
Overall rate	2/50 (4%)	1/50 (2%)	4/50 (8%)	5/50 (10%)
Adjusted rate	13.8%	4.5%	20.9%	54.9%
Terminal rate	1/13 (8%)	0/7 (0%)	0/4 (0%)	0/0 (0%)
First incidence (days)	715	673	613	585
Life table test	P<0.001	P=0.650N	P=0.196	P<0.001
Logistic regression test	P=0.010	P=0.557N	P=0.264	P=0.030
Cochran-Armitage test	P=0.076			
Fisher exact test		P=0.500N	P=0.500	P=0.218

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

	0 ppm	600 ppm	1,300 ppm	2,500 ppm
Kidney (Renal Tubule): Adenoma or Carcinoma (Single and Step Sections)				
Overall rate	4/50 (8%)	2/50 (4%)	4/50 (8%)	7/50 (14%)
Adjusted rate	23.2%	8.0%	20.9%	62.3%
Terminal rate	2/13 (15%)	0/7 (0%)	0/4 (0%)	0/0 (0%)
First incidence (days)	619	654	613	529
Life table test	P<0.001	P=0.492N	P=0.304	P<0.001
Logistic regression test	P=0.025	P=0.355N	P=0.563	P=0.050
Cochran-Armitage test	P=0.105			
Fisher exact test		P=0.339N	P=0.643N	P=0.262
Mammary Gland: Fibroadenoma				
Overall rate	3/50 (6%)	3/50 (6%)	3/50 (6%)	0/50 (0%)
Adjusted rate	13.8%	25.4%	35.8%	0.0%
Terminal rate	1/13 (8%)	1/7 (14%)	1/4 (25%)	0/0 (0%)
First incidence (days)	627	697	669	—[e]
Life table test	P=0.296	P=0.530	P=0.339	P=0.878N
Logistic regression test	P=0.632N	P=0.634	P=0.537	P=0.373N
Cochran-Armitage test	P=0.093N			
Fisher exact test		P=0.661N	P=0.661N	P=0.121N
Mammary Gland: Fibroadenoma or Adenoma				
Overall rate	3/50 (6%)	4/50 (8%)	3/50 (6%)	0/50 (0%)
Adjusted rate	13.8%	27.2%	35.8%	0.0%
Terminal rate	1/13 (8%)	1/7 (14%)	1/4 (25%)	0/0 (0%)
First incidence (days)	627	583	669	—
Life table test	P=0.396	P=0.379	P=0.339	P=0.878N
Logistic regression test	P=0.427N	P=0.492	P=0.537	P=0.373N
Cochran-Armitage test	P=0.076N			
Fisher exact test		P=0.500	P=0.661N	P=0.121N
Mammary Gland: Fibroadenoma, Adenoma, or Carcinoma				
Overall rate	5/50 (10%)	4/50 (8%)	3/50 (6%)	0/50 (0%)
Adjusted rate	25.4%	27.2%	35.8%	0.0%
Terminal rate	2/13 (15%)	1/7 (14%)	1/4 (25%)	0/0 (0%)
First incidence (days)	627	583	669	—
Life table test	P=0.573	P=0.601	P=0.495	P=0.878N
Logistic regression test	P=0.261N	P=0.524N	P=0.576N	P=0.362N
Cochran-Armitage test	P=0.022N			
Fisher exact test		P=0.500N	P=0.357N	P=0.028N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	17/49 (35%)	12/50 (24%)	11/48 (23%)	4/49 (8%)
Adjusted rate	61.1%	37.7%	73.5%	22.9%
Terminal rate	5/13 (38%)	0/7 (0%)	2/4 (50%)	0/0 (0%)
First incidence (days)	281	526	437	436
Life table test	P=0.318	P=0.391N	P=0.434	P=0.445
Logistic regression test	P=0.003N	P=0.172N	P=0.152N	P=0.003N
Cochran-Armitage test	P=0.001N			
Fisher exact test		P=0.172N	P=0.146N	P=0.001N

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

	0 ppm	600 ppm	1,300 ppm	2,500 ppm
Preputial Gland: Adenoma or Carcinoma				
Overall rate	3/50 (6%)	1/50 (2%)	2/50 (4%)	0/49 (0%)
Adjusted rate	12.8%	4.5%	8.0%	0.0%
Terminal rate	1/13 (8%)	0/7 (0%)	0/4 (0%)	0/0 (0%)
First incidence (days)	526	673	613	—
Life table test	P=0.468N	P=0.376N	P=0.653N	P=0.484N
Logistic regression test	P=0.134N	P=0.304N	P=0.501N	P=0.156N
Cochran-Armitage test	P=0.109N			
Fisher exact test		P=0.309N	P=0.500N	P=0.125N
Skin: Squamous Cell Papilloma, Keratoacanthoma, Trichoepithelioma, Benign Basosquamous Tumor, Basal Cell Adenoma, or Basal Cell Carcinoma				
Overall rate	3/50 (6%)	3/50 (6%)	1/50 (2%)	2/50 (4%)
Adjusted rate	23.1%	13.3%	14.3%	6.1%
Terminal rate	3/13 (23%)	0/7 (0%)	0/4 (0%)	0/0 (0%)
First incidence (days)	723 (T)	562	697	544
Life table test	P=0.158	P=0.496	P=0.716	P=0.182
Logistic regression test	P=0.605	P=0.645	P=0.704N	P=0.517
Cochran-Armitage test	P=0.330N			
Fisher exact test		P=0.661N	P=0.309N	P=0.500N
Skin (Subcutaneous Tissue): Fibroma				
Overall rate	3/50 (6%)	3/50 (6%)	3/50 (6%)	0/50 (0%)
Adjusted rate	8.8%	8.8%	19.9%	0.0%
Terminal rate	0/13 (0%)	0/7 (0%)	0/4 (0%)	0/0 (0%)
First incidence (days)	619	610	627	—
Life table test	P=0.610	P=0.645	P=0.504	P=0.723N
Logistic regression test	P=0.083N	P=0.661	P=0.655	P=0.163N
Cochran-Armitage test	P=0.093N			
Fisher exact test		P=0.661N	P=0.661N	P=0.121N
Skin (Subcutaneous Tissue): Fibroma or Fibrosarcoma				
Overall rate	3/50 (6%)	3/50 (6%)	5/50 (10%)	0/50 (0%)
Adjusted rate	8.8%	8.8%	24.7%	0.0%
Terminal rate	0/13 (0%)	0/7 (0%)	0/4 (0%)	0/0 (0%)
First incidence (days)	619	610	576	—
Life table test	P=0.400	P=0.645	P=0.231	P=0.723N
Logistic regression test	P=0.079N	P=0.661	P=0.356	P=0.163N
Cochran-Armitage test	P=0.143N			
Fisher exact test		P=0.661N	P=0.357	P=0.121N
Spleen: Fibrosarcoma				
Overall rate	3/50 (6%)	1/50 (2%)	0/50 (0%)	0/49 (0%)
Adjusted rate	12.9%	3.7%	0.0%	0.0%
Terminal rate	1/13 (8%)	0/7 (0%)	0/4 (0%)	0/0 (0%)
First incidence (days)	575	661	—	—
Life table test	P=0.147N	P=0.367N	P=0.210N	P=0.565N
Logistic regression test	P=0.045N	P=0.304N	P=0.124N	P=0.210N
Cochran-Armitage test	P=0.042N			
Fisher exact test		P=0.309N	P=0.121N	P=0.125N

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

	0 ppm	600 ppm	1,300 ppm	2,500 ppm
Testes: Adenoma				
Overall rate	41/50 (82%)	44/50 (88%)	42/50 (84%)	43/48 (90%)
Adjusted rate	100.0%	100.0%	100.0%	100.0%
Terminal rate	13/13 (100%)	7/7 (100%)	4/4 (100%)	0/0 (0%)
First incidence (days)	463	502	551	437
Life table test	P<0.001	P=0.070	P=0.003	P<0.001
Logistic regression test	P=0.009	P=0.387	P=0.559	P=0.009
Cochran-Armitage test	P=0.233			
Fisher exact test		P=0.288	P=0.500	P=0.217
Thyroid Gland (C-cell): Adenoma				
Overall rate	7/50 (14%)	3/50 (6%)	7/49 (14%)	1/49 (2%)
Adjusted rate	43.3%	30.3%	46.7%	16.7%
Terminal rate	5/13 (38%)	2/7 (29%)	0/4 (0%)	0/0 (0%)
First incidence (days)	505	583	529	619
Life table test	P=0.171	P=0.396N	P=0.114	P=0.589
Logistic regression test	P=0.365N	P=0.173N	P=0.510	P=0.546N
Cochran-Armitage test	P=0.066N			
Fisher exact test		P=0.159N	P=0.597	P=0.032N
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rate	8/50 (16%)	3/50 (6%)	8/49 (16%)	1/49 (2%)
Adjusted rate	45.4%	30.3%	48.5%	16.7%
Terminal rate	5/13 (38%)	2/7 (29%)	0/4 (0%)	0/0 (0%)
First incidence (days)	505	583	529	619
Life table test	P=0.177	P=0.279N	P=0.118	P=0.607
Logistic regression test	P=0.298N	P=0.108N	P=0.509	P=0.415N
Cochran-Armitage test	P=0.049N			
Fisher exact test		P=0.100N	P=0.590	P=0.017N
Thyroid Gland (Follicular Cell): Adenoma				
Overall rate	1/50 (2%)	1/50 (2%)	6/49 (12%)	3/49 (6%)
Adjusted rate	5.0%	4.5%	21.7%	10.7%
Terminal rate	0/13 (0%)	0/7 (0%)	0/4 (0%)	0/0 (0%)
First incidence (days)	697	673	354	529
Life table test	P=0.003	P=0.726	P=0.026	P=0.069
Logistic regression test	P=0.227	P=0.754	P=0.047	P=0.280
Cochran-Armitage test	P=0.136			
Fisher exact test		P=0.753N	P=0.053	P=0.301
Thyroid Gland (Follicular Cell): Carcinoma				
Overall rate	1/50 (2%)	3/50 (6%)	1/49 (2%)	1/49 (2%)
Adjusted rate	7.7%	20.6%	5.6%	5.6%
Terminal rate	1/13 (8%)	1/7 (14%)	0/4 (0%)	0/0 (0%)
First incidence (days)	723 (T)	641	667	589
Life table test	P=0.135	P=0.196	P=0.583	P=0.356
Logistic regression test	P=0.461	P=0.281	P=0.662	P=0.583
Cochran-Armitage test	P=0.438N			
Fisher exact test		P=0.309	P=0.747	P=0.747

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

	0 ppm	600 ppm	1,300 ppm	2,500 ppm
Thyroid Gland (Follicular Cell): Adenoma or Carcinoma				
Overall rate	2/50 (4%)	4/50 (8%)	7/49 (14%)	4/49 (8%)
Adjusted rate	12.3%	24.2%	26.1%	15.7%
Terminal rate	1/13 (8%)	1/7 (14%)	0/4 (0%)	0/0 (0%)
First incidence (days)	697	641	354	529
Life table test	P<0.001	P=0.225	P=0.024	P=0.023
Logistic regression test	P=0.266	P=0.309	P=0.076	P=0.207
Cochran-Armitage test	P=0.262			
Fisher exact test		P=0.339	P=0.075	P=0.329
All Organs: Mononuclear Cell Leukemia				
Overall rate	35/50 (70%)	30/50 (60%)	24/50 (48%)	12/50 (24%)
Adjusted rate	84.4%	79.3%	100.0%	100.0%
Terminal rate	7/13 (54%)	2/7 (29%)	4/4 (100%)	0/0 (0%)
First incidence (days)	505	502	354	380
Life table test	P=0.043	P=0.529	P=0.414	P=0.039
Logistic regression test	P<0.001N	P=0.059N	P=0.023N	P<0.001N
Cochran-Armitage test	P<0.001N			
Fisher exact test		P=0.201N	P=0.021N	P<0.001N
All Organs: Malignant Mesothelioma				
Overall rate	2/50 (4%)	3/50 (6%)	2/50 (4%)	1/50 (2%)
Adjusted rate	15.4%	18.4%	13.9%	2.5%
Terminal rate	2/13 (15%)	1/7 (14%)	0/4 (0%)	0/0 (0%)
First incidence (days)	723 (T)	544	627	533
Life table test	P=0.261	P=0.341	P=0.389	P=0.486
Logistic regression test	P=0.472N	P=0.499	P=0.555	P=0.739
Cochran-Armitage test	P=0.307N			
Fisher exact test		P=0.500	P=0.691N	P=0.500N
All Organs: Benign Neoplasms				
Overall rate	49/50 (98%)	49/50 (98%)	49/50 (98%)	44/50 (88%)
Adjusted rate	100.0%	100.0%	100.0%	100.0%
Terminal rate	13/13 (100%)	7/7 (100%)	4/4 (100%)	0/0 (0%)
First incidence (days)	281	502	354	436
Life table test	P<0.001	P=0.158	P=0.008	P<0.001
Logistic regression test	P=0.043N	P=0.666N	P=0.761N	P=0.127N
Cochran-Armitage test	P=0.009N			
Fisher exact test		P=0.753N	P=0.753N	P=0.056N
All Organs: Malignant Neoplasms				
Overall rate	41/50 (82%)	35/50 (70%)	29/50 (58%)	15/50 (30%)
Adjusted rate	90.6%	88.8%	100.0%	100.0%
Terminal rate	9/13 (69%)	4/7 (57%)	4/4 (100%)	0/0 (0%)
First incidence (days)	305	502	354	380
Life table test	P=0.026	P=0.518	P=0.392	P=0.032
Logistic regression test	P<0.001N	P=0.061N	P=0.008N	P<0.001N
Cochran-Armitage test	P<0.001N			
Fisher exact test		P=0.121N	P=0.008N	P<0.001N

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

	0 ppm	600 ppm	1,300 ppm	2,500 ppm
All Organs: Benign or Malignant Neoplasms				
Overall rate	50/50 (100%)	49/50 (98%)	50/50 (100%)	47/50 (94%)
Adjusted rate	100.0%	100.0%	100.0%	100.0%
Terminal rate	13/13 (100%)	7/7 (100%)	4/4 (100%)	0/0 (0%)
First incidence (days)	281	502	354	380
Life table test	P<0.001	P=0.189	P=0.008	P<0.001
Logistic regression test	P=0.091N	P=0.248N	—[f]	P=0.172N
Cochran-Armitage test	P=0.046N			
Fisher exact test		P=0.500N	P=1.000N	P=0.121N

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, kidney, pituitary gland, preputial gland, spleen, testes, and thyroid gland; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence are the P values 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 life table test regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, 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
Historical Incidence of Thyroid Gland Follicular Cell Neoplasms in Untreated Male F344/N Rats[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Battelle Columbus Laboratories			
4,4'-Thiobis(6-*t*-butyl-*m*-cresol)	0/50	1/50	1/50
5,5-Diphenylhydantoin	0/49	1/49	1/49
Ethylene Thiourea	0/49	1/49	1/49
Polybrominated Biphenyls (Firemaster FF-1®)	1/49	0/49	1/49
Manganese (II) Sulfate Monohydrate	1/52	0/52	1/52
Triamterene	1/50	0/50	1/50
Tricresyl Phosphate	0/51	0/51	0/51
Overall Historical Incidence			
Total	11/1,295 (0.9%)	11/1,295 (0.9%)	22/1,295 (1.7%)
Standard deviation	1.2%	1.2%	1.6%
Range	0%-4%	0%-4%	0%-6%

[a] Data as of 12 May 1995

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of Primidone[a]

	0 ppm	600 ppm	1,300 ppm	2,500 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	33	33	39	36
Natural deaths	4	10	7	14
Survivors				
Terminal sacrifice	13	7	4	
Animals examined microscopically	50	50	50	50
Alimentary System				
Esophagus	(50)	(50)	(50)	(49)
Inflammation, chronic active			1 (2%)	
Ulcer			1 (2%)	
Intestine large, colon	(50)	(50)	(49)	(46)
Mineralization		1 (2%)		2 (4%)
Parasite metazoan		2 (4%)	1 (2%)	
Muscularis, mineralization				1 (2%)
Intestine large, rectum	(50)	(50)	(49)	(47)
Mineralization		1 (2%)		
Parasite metazoan	3 (6%)	3 (6%)	1 (2%)	2 (4%)
Intestine small, duodenum	(50)	(50)	(50)	(47)
Erosion		2 (4%)		
Inflammation, suppurative		2 (4%)		
Mineralization		1 (2%)		
Intestine small, jejunum	(50)	(50)	(49)	(45)
Ulcer			1 (2%)	
Liver	(50)	(50)	(50)	(50)
Basophilic focus	14 (28%)	9 (18%)	8 (16%)	6 (12%)
Clear cell focus			2 (4%)	1 (2%)
Eosinophilic focus	1 (2%)	6 (12%)	5 (10%)	2 (4%)
Hepatodiaphragmatic nodule	3 (6%)	2 (4%)	5 (10%)	3 (6%)
Inflammation, chronic	18 (36%)	19 (38%)	22 (44%)	24 (48%)
Mixed cell focus		2 (4%)		1 (2%)
Pigmentation, hemosiderin	19 (38%)	18 (36%)	15 (30%)	19 (38%)
Bile duct, hyperplasia	47 (94%)	50 (100%)	50 (100%)	44 (88%)
Hepatocyte, degeneration, cystic	16 (32%)	27 (54%)	27 (54%)	18 (36%)
Hepatocyte, necrosis	10 (20%)	12 (24%)	6 (12%)	10 (20%)
Hepatocyte, vacuolization cytoplasmic	26 (52%)	28 (56%)	33 (66%)	43 (86%)
Hepatocyte, centrilobular, degeneration		1 (2%)		
Hepatocyte, centrilobular, hypertrophy		14 (28%)	33 (66%)	40 (80%)
Portal vein, thrombosis	1 (2%)			
Mesentery	(11)	(6)	(9)	(3)
Angiectasis				1 (33%)
Hemorrhage			1 (11%)	
Inflammation, chronic active			1 (11%)	1 (33%)
Artery, inflammation, chronic active				1 (33%)
Artery, mineralization				1 (33%)
Artery, necrosis, fibrinoid				1 (33%)
Fat, inflammation, chronic active			1 (11%)	
Fat, mineralization			1 (11%)	
Fat, necrosis	6 (55%)	3 (50%)	4 (44%)	
Fat, pigmentation, hematoidin			1 (11%)	
Fat, pigmentation, hemosiderin	1 (9%)		1 (11%)	

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

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of Primidone

	0 ppm	600 ppm	1,300 ppm	2,500 ppm
Alimentary System (continued)				
Pancreas	(50)	(50)	(50)	(49)
Inflammation, chronic active		1 (2%)		
Acinus, atrophy	25 (50%)	14 (28%)	12 (24%)	8 (16%)
Acinus, hypertrophy				1 (2%)
Artery, inflammation, chronic active		1 (2%)		
Stomach, forestomach	(50)	(50)	(50)	(49)
Hyperplasia			1 (2%)	
Inflammation, chronic active				1 (2%)
Mineralization		3 (6%)	3 (6%)	12 (24%)
Perforation		2 (4%)	1 (2%)	
Epithelium, hyperplasia	4 (8%)	11 (22%)	19 (38%)	10 (20%)
Epithelium, inflammation, chronic active	2 (4%)	10 (20%)	14 (28%)	9 (18%)
Epithelium, ulcer	2 (4%)	7 (14%)	13 (26%)	8 (16%)
Stomach, glandular	(50)	(50)	(50)	(49)
Mineralization		6 (12%)	15 (30%)	36 (73%)
Epithelium, erosion	2 (4%)	1 (2%)		
Epithelium, inflammation, chronic active	2 (4%)	1 (2%)	1 (2%)	
Epithelium, necrosis		1 (2%)	2 (4%)	1 (2%)
Epithelium, ulcer	4 (8%)	1 (2%)		
Cardiovascular System				
Blood vessel	(50)	(50)	(50)	(50)
Inflammation, chronic active	1 (2%)			1 (2%)
Necrosis, fibrinoid				1 (2%)
Aorta, mineralization		5 (10%)	9 (18%)	31 (62%)
Heart	(50)	(50)	(50)	(50)
Cardiomyopathy, chronic	42 (84%)	45 (90%)	43 (86%)	48 (96%)
Mineralization		4 (8%)	8 (16%)	15 (30%)
Pigmentation, hemosiderin	1 (2%)			
Atrium, thrombosis	2 (4%)	3 (6%)		2 (4%)
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Accessory adrenal cortical nodule		2 (4%)	1 (2%)	
Atrophy			1 (2%)	
Degeneration, fatty	26 (52%)	18 (36%)	19 (38%)	12 (24%)
Hyperplasia	17 (34%)	4 (8%)	9 (18%)	6 (12%)
Hypertrophy	3 (6%)	2 (4%)		
Inflammation, chronic active	1 (2%)			
Mineralization				1 (2%)
Necrosis				1 (2%)
Thrombosis	1 (2%)			
Adrenal medulla	(50)	(50)	(50)	(49)
Hemorrhage		1 (2%)		
Hyperplasia	19 (38%)	22 (44%)	30 (60%)	29 (59%)
Necrosis	1 (2%)			
Parathyroid gland	(45)	(41)	(46)	(49)
Hyperplasia	2 (4%)	16 (39%)	26 (57%)	40 (82%)
Pituitary gland	(49)	(50)	(48)	(49)
Craniopharyngeal duct, cyst				1 (2%)
Pars distalis, cyst	1 (2%)	7 (14%)	2 (4%)	4 (8%)
Pars distalis, hyperplasia	17 (35%)	18 (36%)	16 (33%)	7 (14%)
Pars intermedia, cyst	1 (2%)	2 (4%)	1 (2%)	1 (2%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of Primidone

	0 ppm	600 ppm	1,300 ppm	2,500 ppm
Endocrine System (continued)				
Thyroid gland	(50)	(50)	(49)	(49)
C-cell, hyperplasia	11 (22%)	11 (22%)	5 (10%)	3 (6%)
Follicle, cyst	1 (2%)	3 (6%)	1 (2%)	6 (12%)
Follicle, hyperplasia, cystic			1 (2%)	
Follicular cell, hyperplasia	1 (2%)			1 (2%)
Follicular cell, hyperplasia, cystic	1 (2%)	1 (2%)	1 (2%)	
General Body System				
None				
Genital System				
Coagulating gland	(2)	(1)		(1)
Inflammation, chronic active	1 (50%)	1 (100%)		1 (100%)
Epididymis	(50)	(50)	(50)	(48)
Granuloma sperm		3 (6%)	3 (6%)	1 (2%)
Mineralization				4 (8%)
Necrosis				1 (2%)
Preputial gland	(50)	(50)	(50)	(49)
Cyst	2 (4%)	1 (2%)	3 (6%)	
Hyperplasia	5 (10%)	7 (14%)	3 (6%)	4 (8%)
Inflammation, chronic active	47 (94%)	47 (94%)	40 (80%)	45 (92%)
Prostate	(50)	(50)	(50)	(48)
Cyst			1 (2%)	
Inflammation, chronic active	37 (74%)	34 (68%)	34 (68%)	30 (63%)
Mineralization				2 (4%)
Seminal vesicle	(50)	(50)	(50)	(48)
Atrophy				2 (4%)
Mineralization		1 (2%)	2 (4%)	8 (17%)
Testes	(50)	(50)	(50)	(48)
Necrosis			1 (2%)	
Germinal epithelium, degeneration	2 (4%)	2 (4%)	2 (4%)	3 (6%)
Interstitial cell, hyperplasia	11 (22%)	11 (22%)	8 (16%)	11 (23%)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Atrophy	1 (2%)	1 (2%)		1 (2%)
Hyperplasia	38 (76%)	35 (70%)	28 (56%)	12 (24%)
Inflammation, suppurative		1 (2%)		
Myelofibrosis	2 (4%)	1 (2%)		1 (2%)
Lymph node	(24)	(23)	(16)	(10)
Lumbar, hyperplasia, lymphoid			1 (6%)	
Mediastinal, hyperplasia, plasma cell			1 (6%)	
Renal, ectasia			1 (6%)	3 (30%)
Renal, erythrophagocytosis				1 (10%)
Renal, pigmentation, hemosiderin				2 (20%)
Lymph node, mandibular	(50)	(50)	(48)	(49)
Ectasia		3 (6%)		

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of Primidone

	0 ppm	600 ppm	1,300 ppm	2,500 ppm
Hematopoietic System (continued)				
Lymph node, mesenteric	(50)	(50)	(50)	(48)
Ectasia	2 (4%)	2 (4%)	4 (8%)	2 (4%)
Fibrosis				1 (2%)
Spleen	(50)	(50)	(50)	(49)
Accessory spleen			1 (2%)	
Congestion	1 (2%)		1 (2%)	
Fibrosis	9 (18%)	19 (38%)	9 (18%)	12 (24%)
Hematopoietic cell proliferation		2 (4%)	6 (12%)	1 (2%)
Hyperplasia, lymphoid	1 (2%)			
Metaplasia, lipocyte		1 (2%)		
Necrosis			1 (2%)	1 (2%)
Thymus	(49)	(47)	(44)	(46)
Cyst		2 (4%)	1 (2%)	
Integumentary System				
Mammary gland	(48)	(49)	(50)	(47)
Cyst	1 (2%)	1 (2%)	2 (4%)	
Hyperplasia, cystic	28 (58%)	25 (51%)	16 (32%)	6 (13%)
Mineralization		1 (2%)		
Skin	(50)	(50)	(50)	(50)
Hyperkeratosis		1 (2%)		
Hyperplasia, basal cell				1 (2%)
Inflammation, chronic active	2 (4%)	1 (2%)	1 (2%)	
Inflammation, suppurative				1 (2%)
Epidermis, hyperplasia	1 (2%)	1 (2%)		
Pinna, ulcer				1 (2%)
Sebaceous gland, hyperplasia	1 (2%)			
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Fibrous osteodystrophy		10 (20%)	26 (52%)	37 (74%)
Necrosis			1 (2%)	
Osteopetrosis		2 (4%)		1 (2%)
Nervous System				
Brain	(50)	(50)	(49)	(49)
Hemorrhage	4 (8%)	2 (4%)	4 (8%)	1 (2%)
Inflammation, chronic active			1 (2%)	
Spinal cord	(1)	(1)		
Demyelination	1 (100%)			
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Inflammation, chronic active	2 (4%)		3 (6%)	3 (6%)
Metaplasia, osseous	1 (2%)	1 (2%)		2 (4%)
Alveolar epithelium, hyperplasia	6 (12%)	1 (2%)	2 (4%)	4 (8%)
Alveolus, hemorrhage			1 (2%)	
Alveolus, infiltration cellular, histiocyte	18 (36%)	18 (36%)	19 (38%)	15 (30%)
Alveolus, inflammation, suppurative			1 (2%)	4 (8%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of Primidone

	0 ppm	600 ppm	1,300 ppm	2,500 ppm
Respiratory System (continued)				
Lung (continued)	(50)	(50)	(50)	(50)
Artery, thrombosis		1 (2%)		
Artery, vein, mineralization	46 (92%)	42 (84%)	43 (86%)	45 (90%)
Interstitium, inflammation, chronic active				2 (4%)
Interstitium, mineralization		3 (6%)	7 (14%)	25 (50%)
Interstitium, alveolus, inflammation, suppurative				5 (10%)
Perivascular, infiltration cellular, lymphocyte	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Nose	(50)	(50)	(50)	(50)
Inflammation, chronic active	8 (16%)	12 (24%)	10 (20%)	9 (18%)
Inflammation, suppurative	6 (12%)	7 (14%)	3 (6%)	9 (18%)
Arteriole, venule, thrombosis	1 (2%)	2 (4%)		1 (2%)
Nasolacrimal duct, inflammation, suppurative			2 (4%)	2 (4%)
Respiratory epithelium, metaplasia, squamous				1 (2%)
Special Senses System				
Eye		(1)	(2)	
Anterior chamber, inflammation, suppurative			1 (50%)	
Lens, cataract			1 (50%)	
Retina, degeneration			2 (100%)	
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Cyst	2 (4%)	2 (4%)	12 (24%)	9 (18%)
Infarct	1 (2%)			
Inflammation, suppurative		1 (2%)		
Nephropathy, chronic	49 (98%)	48 (96%)	50 (100%)	50 (100%)
Papilla, hyperplasia, atypical	1 (2%)			
Renal tubule, hyperplasia	1 (2%)	2 (4%)	4 (8%)	10 (20%)
Urinary bladder	(50)	(50)	(50)	(48)
Hemorrhage	1 (2%)			1 (2%)
Inflammation, suppurative		1 (2%)		

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

TABLE B1 Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of Primidone 119

TABLE B2 Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Primidone 122

TABLE B3 Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Feed Study of Primidone 138

TABLE B4 Historical Incidence of Mononuclear Cell Leukemia in Untreated Female F344/N Rats 142

TABLE B5 Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of Primidone 143

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of Primidone[a]

	0 ppm	600 ppm	1,300 ppm	2,500 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	21	18	14	19
Natural deaths	5	5	5	3
Survivors				
Died last week of study				1
Terminal sacrifice	24	27	31	27
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine large, colon	(50)	(50)	(50)	(50)
Intestine large, cecum	(49)	(50)	(50)	(49)
Fibrosarcoma, metastatic, spleen				1 (2%)
Intestine small, duodenum	(49)	(50)	(50)	(50)
Intestine small, jejunum	(49)	(50)	(50)	(49)
Fibrosarcoma, metastatic, spleen				1 (2%)
Intestine small, ileum	(50)	(50)	(50)	(49)
Fibrosarcoma, metastatic, spleen				1 (2%)
Liver	(50)	(50)	(50)	(50)
Fibrosarcoma, metastatic, spleen				1 (2%)
Hepatocellular adenoma		1 (2%)		1 (2%)
Mesentery	(9)	(10)	(7)	(7)
Fibrosarcoma, metastatic, spleen				1 (14%)
Oral mucosa				(2)
Gingival, squamous cell carcinoma				1 (50%)
Pharyngeal, squamous cell carcinoma				1 (50%)
Pancreas	(49)	(50)	(50)	(50)
Fibrosarcoma, metastatic, spleen				1 (2%)
Salivary glands	(49)	(50)	(50)	(50)
Stomach, forestomach	(49)	(50)	(50)	(50)
Stomach, glandular	(49)	(50)	(50)	(50)
Carcinoid tumor benign	1 (2%)			
Carcinoid tumor malignant	1 (2%)			
Fibrosarcoma, metastatic, spleen				1 (2%)
Cardiovascular System				
Blood vessel	(49)	(50)	(50)	(50)
Heart	(49)	(50)	(50)	(50)
Schwannoma malignant				1 (2%)
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Adenoma	1 (2%)	2 (4%)		1 (2%)
Thymoma malignant, metastatic, thymus	1 (2%)			
Adrenal medulla	(50)	(50)	(49)	(50)
Pheochromocytoma benign	2 (4%)		2 (4%)	3 (6%)
Islets, pancreatic	(50)	(50)	(50)	(50)
Adenoma			1 (2%)	
Parathyroid gland	(38)	(44)	(42)	(39)

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

	0 ppm	600 ppm	1,300 ppm	2,500 ppm
Endocrine System (continued)				
Pituitary gland	(49)	(50)	(49)	(50)
Pars distalis, adenoma	16 (33%)	20 (40%)	13 (27%)	18 (36%)
Pars distalis, adenoma, multiple		1 (2%)	1 (2%)	2 (4%)
Pars distalis, carcinoma				1 (2%)
Thyroid gland	(49)	(50)	(50)	(50)
Bilateral, C-cell, adenoma			1 (2%)	
C-cell, adenoma	5 (10%)	2 (4%)	6 (12%)	4 (8%)
Follicular cell, carcinoma	1 (2%)			
General Body System				
None				
Genital System				
Clitoral gland	(49)	(49)	(50)	(50)
Adenoma	4 (8%)	1 (2%)	4 (8%)	1 (2%)
Carcinoma	1 (2%)		1 (2%)	2 (4%)
Ovary	(50)	(50)	(50)	(49)
Granulosa-theca tumor malignant		1 (2%)		
Uterus	(50)	(50)	(50)	(49)
Leiomyosarcoma			1 (2%)	
Polyp stromal	7 (14%)	7 (14%)	6 (12%)	7 (14%)
Polyp stromal, multiple	1 (2%)			
Sarcoma stromal		3 (6%)		3 (6%)
Vagina	(1)		(1)	(2)
Polyp	1 (100%)			2 (100%)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Lymph node	(11)	(7)	(8)	(12)
Thoracic, carcinoma, metastatic, mammary gland			1 (13%)	
Lymph node, mandibular	(49)	(50)	(50)	(50)
Lymph node, mesenteric	(50)	(50)	(50)	(49)
Spleen	(49)	(50)	(50)	(50)
Fibrosarcoma				1 (2%)
Thymus	(49)	(45)	(47)	(46)
Thymoma benign			1 (2%)	
Thymoma malignant	1 (2%)			
Integumentary System				
Mammary gland	(50)	(50)	(50)	(50)
Adenoma	2 (4%)			
Carcinoma	1 (2%)	2 (4%)	1 (2%)	
Fibroadenoma	13 (26%)	21 (42%)	14 (28%)	11 (22%)
Fibroadenoma, multiple	9 (18%)	4 (8%)	2 (4%)	1 (2%)
Skin	(50)	(50)	(50)	(50)
Basal cell carcinoma	1 (2%)			
Pinna, squamous cell papilloma			1 (2%)	

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

	0 ppm	600 ppm	1,300 ppm	2,500 ppm
Integumentary System (continued)				
Skin	(50)	(50)	(50)	(50)
Subcutaneous tissue, fibroma	1 (2%)	1 (2%)		1 (2%)
Subcutaneous tissue, fibrosarcoma	1 (2%)	1 (2%)	1 (2%)	2 (4%)
Subcutaneous tissue, liposarcoma		1 (2%)		
Subcutaneous tissue, sarcoma	1 (2%)			
Musculoskeletal System				
Skeletal muscle		(1)		(2)
Nervous System				
Brain	(50)	(50)	(50)	(50)
Astrocytoma malignant	1 (2%)		1 (2%)	
Carcinoma, metastatic, pituitary gland				1 (2%)
Spinal cord		(1)		(2)
Respiratory System				
Lung	(49)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma			1 (2%)	2 (4%)
Carcinoma, metastatic, mammary gland			1 (2%)	
Thymoma malignant, metastatic, thymus	1 (2%)			
Trachea	(49)	(50)	(50)	(50)
Special Senses System				
Zymbal's gland	(1)		(1)	
Carcinoma	1 (100%)		1 (100%)	
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Urinary bladder	(50)	(50)	(50)	(49)
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Leukemia mononuclear	13 (26%)	13 (26%)	13 (26%)	22 (44%)
Neoplasm Summary				
Total animals with primary neoplasms[c]	47	44	41	46
Total primary neoplasms	86	81	72	88
Total animals with benign neoplasms	39	35	35	33
Total benign neoplasms	63	60	53	54
Total animals with malignant neoplasms	21	20	17	28
Total malignant neoplasms	23	21	19	34
Total animals with metastatic neoplasms	1		1	2
Total metastatic neoplasms	2		2	8

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

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

Number of Days on Study	367	415	536	541	561	566	626	626	634	638	640	641	641	646	660	664	668	668	675	682	697	702	702	702	702
Carcass ID Number	237	204	235	210	234	212	208	231	247	244	248	214	245	230	201	216	219	225	203	211	202	221	236	238	241
Alimentary System																									
Esophagus	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery							+					+	+								+		+		
Pancreas	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoid tumor benign																									
Carcinoid tumor malignant														X											
Cardiovascular System																									
Blood vessel	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Thymoma malignant, metastatic, thymus													X												
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign															X										
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	M	M	+	+	+	M	M	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma				X		X				X	X	X								X			X		X
Thyroid gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																				X					
Follicular cell, carcinoma																									
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma															X										
Carcinoma																								X	
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal		X							X											X					
Polyp stromal, multiple													X												
Vagina														+											
Polyp														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 Primidone: 0 ppm

Number of Days on Study	703	722	722	722	723	723	723	723	723	723	723	723	723	723	723	724	724	724	724	724	724	724	724	724	724	
Carcass ID Number	218	213	224	228	205	206	207	209	222	223	227	239	243	246	249	215	217	220	226	229	232	233	240	242	250	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery	+			+							+													+		9
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoid tumor benign																				X						1
Carcinoid tumor malignant																										1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma												X														1
Thymoma malignant, metastatic, thymus																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign															X											2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	M	+	M	+	M	+	M	+	+	+	M	M	+	+	+	+	+	+	38
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	49
Pars distalis, adenoma					X	X			X			X					X	X	X		X					16
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell, adenoma				X						X		X											X			5
Follicular cell, carcinoma																						X				1
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma			X													X		X								4
Carcinoma																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal									X			X		X								X				7
Polyp stromal, multiple																										1
Vagina																										1
Polyp																										1

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

Number of Days on Study	367	415	536	541	561	566	626	626	634	638	640	641	644	646	660	664	668	668	675	682	697	702	702	702	702
Carcass ID Number	237	204	235	210	234	212	208	231	247	244	248	214	245	230	201	216	219	225	203	211	202	221	236	238	241
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node					+		+	+								+				+		+			
Lymph node, mandibular	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymoma malignant													X												
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma						X																			
Carcinoma																							X		
Fibroadenoma		X									X	X									X				X
Fibroadenoma, multiple															X		X		X			X		X	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma																								X	
Subcutaneous tissue, fibroma									X																
Subcutaneous tissue, fibrosarcoma															X										
Subcutaneous tissue, sarcoma	X																								
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant			X																						
Respiratory System																									
Lung	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymoma malignant, metastatic, thymus													X												
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye											+														
Zymbal's gland																						+			
Carcinoma																						X			
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X		X	X								X		X		X		X			

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

Number of Days on Study	703	722	722	722	723	723	723	723	723	723	723	723	723	723	723	724	724	724	724	724	724	724	724	724	724	724
Carcass ID Number	218	213	224	228	205	206	207	209	222	223	227	239	243	246	249	215	217	220	226	229	232	233	240	242	250	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+			+	+											+									+	11
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymoma malignant																										1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																			X							2
Carcinoma																										1
Fibroadenoma	X		X			X					X	X				X	X							X		13
Fibroadenoma, multiple					X			X												X			X			9
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell carcinoma																										1
Subcutaneous tissue, fibroma																										1
Subcutaneous tissue, fibrosarcoma																										1
Subcutaneous tissue, sarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma malignant																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymoma malignant, metastatic, thymus																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																										
Eye																										1
Zymbal's gland																										1
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear				X	X									X		X								X	X	13

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Primidone: 600 ppm

Number of Days on Study	367	410	415	419	426	456	466	511	567	578	578	584	605	612	618	618	645	675	675	675	682	702	702	722	722
Carcass ID Number	299	264	262	257	269	284	275	288	300	251	253	289	285	295	261	287	298	279	280	290	274	268	296	258	259
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma												X													
Mesentery						+	+		+	+	+			+			+							+	
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma		X							X		X			X	X	X	X			X				X	
Pars distalis, adenoma, multiple																						X			
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma										X				X											
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Adenoma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa-theca tumor malignant																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal														X			X	X		X					
Sarcoma stromal			X					X																	
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node				+		+	+		+				+	+							+				
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Primidone: 600 ppm

Number of Days on Study	722	723	723	723	723	723	723	723	723	723	723	723	723	724	724	724	724	724	724	724	724	724	724	724	724	
Carcass ID Number	292	254	255	256	266	267	270	271	272	278	283	294	297	252	260	263	265	273	276	277	281	282	286	291	293	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma																										1
Mesentery												+				+										10
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma	X	X																								2
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	M	44
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma		X			X	X			X			X			X			X	X	X	X	X				20
Pars distalis, adenoma, multiple																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma																										2
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma														X												1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa-theca tumor malignant									X																	1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal	X												X								X					7
Sarcoma stromal																				X						3
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																										7
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	M	+	M	+	+	+	M	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	45

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Primidone: 600 ppm

Number of Days on Study	367	410	415	419	426	456	466	511	567	578	578	584	605	612	618	618	645	675	675	675	682	702	702	722	722	
Carcass ID Number	299	264	262	257	269	284	275	288	300	251	253	289	285	295	261	287	298	279	280	290	274	268	296	258	259	
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Carcinoma	X																									
Fibroadenoma										X	X					X				X			X	X	X	
Fibroadenoma, multiple												X										X				
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Subcutaneous tissue, fibroma																										
Subcutaneous tissue, fibrosarcoma																		X								
Subcutaneous tissue, liposarcoma																				X						
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Skeletal muscle									+																	
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Spinal cord																									+	
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Special Senses System																										
Eye																										
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Leukemia mononuclear	X			X	X	X	X		X				X	X							X					

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Primidone: 600 ppm

Number of Days on Study	722	723	723	723	723	723	723	723	723	723	723	723	723	724	724	724	724	724	724	724	724	724	724	724	724	
Carcass ID Number	292	254	255	256	266	267	270	271	272	278	283	294	297	252	260	263	265	273	276	277	281	282	286	291	293	Total Tissues/ Tumors
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																						X				2
Fibroadenoma	X	X		X	X	X					X			X	X	X	X	X			X	X		X		21
Fibroadenoma, multiple																				X			X			4
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibroma											X															1
Subcutaneous tissue, fibrosarcoma																										1
Subcutaneous tissue, liposarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spinal cord																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nose	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																			+							1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear				X		X													X					X		13

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Primidone: 1,300 ppm

Number of Days on Study	389	456	501	543	550	603	610	618	634	644	668	682	690	693	695	696	703	707	709	722	722	722	722	722	722
Carcass ID Number	322	330	336	307	311	311	332	329	319	337	324	303	313	349	446	450	306	312	348	302	308	310	318	325	334
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery							+						+		+							+			
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign	X																								
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	+	M	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma				X	X					X				X	X		X	X		X	X				X
Pars distalis, adenoma, multiple																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, C-cell, adenoma																									
C-cell, adenoma																							X		
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma			X									X													
Carcinoma		X																							
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma																									X
Polyp stromal																				X					X
Vagina					+																				
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+								+				+		+		+					+			
Thoracic, carcinoma, metastatic, mammary gland	X																								
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Primidone: 1,300 ppm

Number of Days on Study	722	722	722	722	723	723	723	723	723	723	723	723	723	724	724	724	724	724	724	724	724	724	724	724	724	
Carcass ID Number	335	338	342	345	301	304	305	316	327	339	340	341	347	309	314	315	317	320	321	323	326	328	333	343	344	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery		+													+						+					7
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma benign						X																				2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																	X									1
Parathyroid gland	+	+	+	M	+	M	M	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	42
Pituitary gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma	X	X														X										13
Pars distalis, adenoma, multiple												X														1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, C-cell, adenoma		X																								1
C-cell, adenoma					X		X												X			X			X	6
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma						X					X															4
Carcinoma																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma																										1
Polyp stromal											X					X					X				X	6
Vagina																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node											+	+														8
Thoracic, carcinoma, metastatic, mammary gland																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Primidone: 1,300 ppm

Number of Days on Study	389	456	501	543	550	603	610	618	634	644	668	682	690	693	695	696	703	707	709	722	722	722	722	722	722
Carcass ID Number	322	330	336	307	311	311	332	329	319	337	324	303	313	349	446	450	306	312	348	302	308	310	318	325	334
Hematopoietic System (continued)																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymoma benign																					X				
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma	X																								
Fibroadenoma								X		X	X	X				X			X			X			
Fibroadenoma, multiple					X																				
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pinna, squamous cell papilloma																									
Subcutaneous tissue, fibrosarcoma						X																			
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant																									
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma											X														
Carcinoma, metastatic, mammary gland	X																								
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																									
Harderian gland																									
Zymbal's gland																									
Carcinoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X			X	X	X	X				X		X		X					X			

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Primidone: 1,300 ppm

Number of Days on Study	722	722	722	722	723	723	723	723	723	723	723	723	723	724	724	724	724	724	724	724	724	724	724	724	724	
Carcass ID Number	335	338	342	345	301	304	305	316	327	339	340	341	347	309	314	315	317	320	321	323	326	328	333	343	344	Total Tissues/ Tumors
Hematopoietic System (continued)																										
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	47
Thymoma benign																										1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Fibroadenoma	X			X		X		X								X	X		X							14
Fibroadenoma, multiple															X											2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pinna, squamous cell papilloma																X										1
Subcutaneous tissue, fibrosarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma malignant						X																				1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										1
Carcinoma, metastatic, mammary gland																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																								+	+	2
Harderian gland																								+		1
Zymbal's gland											+															1
Carcinoma											X															1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear											X	X		X	X											13

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Primidone: 2,500 ppm

Number of Days on Study	433	477	489	491	543	548	550	561	590	596	605	605	626	674	674	675	682	702	702	708	708	718	722	722	722
Carcass ID Number	355	380	399	363	392	359	365	357	370	378	372	397	364	367	386	356	368	384	391	366	369	382	362	373	374
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, spleen							X																		
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, spleen							X																		
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, spleen							X																		
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, spleen							X																		
Hepatocellular adenoma																					X				
Mesentery							+						+						+			+			
Fibrosarcoma, metastatic, spleen							X																		
Oral mucosa	+																				+				
Gingival, squamous cell carcinoma																					X				
Pharyngeal, squamous cell carcinoma	X																								
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, spleen							X																		
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, spleen							X																		
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant																						X			
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	M	+	+	+	+	+	M	+	M	+	M	+	+	+	+	+	+	+	+	M	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma				X		X								X	X		X	X		X	X				X
Pars distalis, adenoma, multiple																							X		
Pars distalis, carcinoma																						X			
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma				X																					
General Body System																									
None																									

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Primidone: 2,500 ppm

Number of Days on Study	722	723	723	723	723	723	723	723	723	723	723	723	723	723	724	724	724	724	724	724	724	724	724	724	724	
Carcass ID Number	400	351	352	353	360	376	379	381	387	389	390	394	396	398	354	358	361	371	375	377	383	385	388	393	395	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibrosarcoma, metastatic, spleen																										1
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibrosarcoma, metastatic, spleen																										1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibrosarcoma, metastatic, spleen																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, spleen																										1
Hepatocellular adenoma																										1
Mesentery				+		+		+																		7
Fibrosarcoma, metastatic, spleen																										1
Oral mucosa																										2
Gingival, squamous cell carcinoma																										1
Pharyngeal, squamous cell carcinoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, spleen																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, spleen																										1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma malignant																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma								X																		1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign	X					X				X																3
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	M	+	+	+	+	+	M	+	M	M	M	+	+	+	+	+	M	+	+	+	+	+	+	39
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma		X		X		X		X	X			X	X							X				X		18
Pars distalis, adenoma, multiple																			X							2
Pars distalis, carcinoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma					X	X					X															4
General Body System																										
None																										

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Primidone: 2,500 ppm

Number of Days on Study	433	477	489	491	543	548	550	561	590	596	605	605	626	674	674	675	682	702	702	708	708	718	722	722	722
Carcass ID Number	355	380	399	363	392	359	365	357	370	378	372	397	364	367	386	356	368	384	391	366	369	382	362	373	374
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma											X														
Carcinoma																X									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Polyp stromal			X								X						X			X					X
Sarcoma stromal								X																X	
Vagina										+															
Polyp										X															
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node										+		+	+		+						+	+			+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma							X																		
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma			X		X											X		X							X
Fibroadenoma, multiple																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, fibrosarcoma																			X						
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle												+			+										
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pituitary gland																						X			
Peripheral nerve		+																							
Spinal cord		+										+													
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X	X		X		X		X	X		X	X		X				X		X	X			X

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Primidone: 2,500 ppm

Number of Days on Study	722	723	723	723	723	723	723	723	723	723	723	723	723	723	724	724	724	724	724	724	724	724	724	724	724	
Carcass ID Number	400	351	352	353	360	376	379	381	387	389	390	394	396	398	354	358	361	371	375	377	383	385	388	393	395	Total Tissues/ Tumors
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Carcinoma					X																					2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Polyp stromal																X					X					7
Sarcoma stromal														X												3
Vagina														+												2
Polyp														X												2
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node								+	+			+			+										+	12
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma																										1
Thymus	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	46
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroadenoma					X					X			X						X	X				X		11
Fibroadenoma, multiple																X										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibroma										X																1
Subcutaneous tissue, fibrosarcoma									X																	2
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										2
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, pituitary gland																										1
Peripheral nerve																										1
Spinal cord																										2
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																	X			X						2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye			+			+																				2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear				X		X		X	X			X			X		X	X							X	22

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

	0 ppm	600 ppm	1,300 ppm	2,500 ppm
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate[a]	2/50 (4%)	0/50 (0%)	2/49 (4%)	3/50 (6%)
Adjusted rate[b]	6.8%	0.0%	5.2%	10.7%
Terminal rate[c]	1/24 (4%)	0/27 (0%)	1/31 (3%)	3/28 (11%)
First incidence (days)	660	—[e]	389	722 (T)
Life table test[d]	P=0.263	P=0.236N	P=0.635N	P=0.559
Logistic regression test[d]	P=0.226	P=0.251N	P=0.666	P=0.519
Cochran-Armitage test[d]	P=0.228			
Fisher exact test[d]		P=0.247N	P=0.684	P=0.500
Clitoral Gland: Adenoma				
Overall rate	4/49 (8%)	1/49 (2%)	4/50 (8%)	1/50 (2%)
Adjusted rate	14.9%	3.7%	10.7%	2.5%
Terminal rate	3/24 (13%)	1/27 (4%)	2/31 (6%)	0/28 (0%)
First incidence (days)	660	722 (T)	501	605
Life table test	P=0.196N	P=0.157N	P=0.529N	P=0.160N
Logistic regression test	P=0.221N	P=0.199N	P=0.631N	P=0.175N
Cochran-Armitage test	P=0.224N			
Fisher exact test		P=0.181N	P=0.631N	P=0.175N
Clitoral Gland: Adenoma or Carcinoma				
Overall rate	5/49 (10%)	1/49 (2%)	5/50 (10%)	3/50 (6%)
Adjusted rate	17.9%	3.7%	12.6%	8.7%
Terminal rate	3/24 (13%)	1/27 (4%)	2/31 (6%)	1/28 (4%)
First incidence (days)	660	722 (T)	456	605
Life table test	P=0.417N	P=0.093N	P=0.514N	P=0.309N
Logistic regression test	P=0.464N	P=0.118N	P=0.630	P=0.349N
Cochran-Armitage test	P=0.463N			
Fisher exact test		P=0.102N	P=0.617N	P=0.346N
Mammary Gland: Fibroadenoma				
Overall rate	22/50 (44%)	25/50 (50%)	16/50 (32%)	12/50 (24%)
Adjusted rate	61.7%	72.9%	40.9%	35.5%
Terminal rate	11/24 (46%)	18/27 (67%)	9/31 (29%)	8/28 (29%)
First incidence (days)	415	578	550	489
Life table test	P=0.003N	P=0.450	P=0.057N	P=0.017N
Logistic regression test	P=0.004N	P=0.209	P=0.128N	P=0.028N
Cochran-Armitage test	P=0.006N			
Fisher exact test		P=0.344	P=0.151N	P=0.028N
Mammary Gland: Fibroadenoma or Adenoma				
Overall rate	24/50 (48%)	25/50 (50%)	16/50 (32%)	12/50 (24%)
Adjusted rate	65.4%	72.9%	40.9%	35.5%
Terminal rate	12/24 (50%)	18/27 (67%)	9/31 (29%)	8/28 (29%)
First incidence (days)	415	578	550	489
Life table test	P=0.001N	P=0.548N	P=0.027N	P=0.007N
Logistic regression test	P=0.001N	P=0.350	P=0.065N	P=0.011N
Cochran-Armitage test	P=0.002N			
Fisher exact test		P=0.500	P=0.076N	P=0.011N

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

	0 ppm	600 ppm	1,300 ppm	2,500 ppm
Mammary Gland: Adenoma or Carcinoma				
Overall rate	3/50 (6%)	2/50 (4%)	1/50 (2%)	0/50 (0%)
Adjusted rate	9.5%	5.6%	2.0%	0.0%
Terminal rate	1/24 (4%)	1/27 (4%)	0/31 (0%)	0/28 (0%)
First incidence (days)	566	367	389	—
Life table test	P=0.053N	P=0.485N	P=0.271N	P=0.111N
Logistic regression test	P=0.068N	P=0.438N	P=0.335N	P=0.120N
Cochran-Armitage test	P=0.059N			
Fisher exact test		P=0.500N	P=0.309N	P=0.121N
Mammary Gland: Fibroadenoma, Adenoma, or Carcinoma				
Overall rate	25/50 (50%)	26/50 (52%)	17/50 (34%)	12/50 (24%)
Adjusted rate	66.7%	73.4%	42.0%	35.5%
Terminal rate	12/24 (50%)	18/27 (67%)	9/31 (29%)	8/28 (29%)
First incidence (days)	415	367	389	489
Life table test	P<0.001N	P=0.546N	P=0.030N	P=0.005N
Logistic regression test	P<0.001N	P=0.372	P=0.074N	P=0.006N
Cochran-Armitage test	P=0.001N			
Fisher exact test		P=0.500	P=0.078N	P=0.006N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	16/49 (33%)	21/50 (42%)	14/49 (29%)	20/50 (40%)
Adjusted rate	47.9%	56.7%	36.2%	54.5%
Terminal rate	8/23 (35%)	12/27 (44%)	7/30 (23%)	12/28 (43%)
First incidence (days)	541	410	543	491
Life table test	P=0.510N	P=0.281	P=0.223N	P=0.460
Logistic regression test	P=0.413	P=0.184	P=0.399N	P=0.289
Cochran-Armitage test	P=0.389			
Fisher exact test		P=0.226	P=0.413N	P=0.291
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma				
Overall rate	16/49 (33%)	21/50 (42%)	14/49 (29%)	21/50 (42%)
Adjusted rate	47.9%	56.7%	36.2%	56.0%
Terminal rate	8/23 (35%)	12/27 (44%)	7/30 (23%)	12/28 (43%)
First incidence (days)	541	410	543	491
Life table test	P=0.482	P=0.281	P=0.223N	P=0.394
Logistic regression test	P=0.330	P=0.184	P=0.399N	P=0.223
Cochran-Armitage test	P=0.307			
Fisher exact test		P=0.226	P=0.413N	P=0.226
Skin (Subcutaneous Tissue): Fibroma, Fibrosarcoma, or Sarcoma				
Overall rate	3/50 (6%)	2/50 (4%)	1/50 (2%)	3/50 (6%)
Adjusted rate	7.0%	6.6%	2.2%	10.0%
Terminal rate	0/24 (0%)	1/27 (4%)	0/31 (0%)	2/28 (7%)
First incidence (days)	367	675	603	702
Life table test	P=0.568N	P=0.513N	P=0.297N	P=0.633N
Logistic regression test	P=0.560	P=0.432N	P=0.339N	P=0.661N
Cochran-Armitage test	P=0.573			
Fisher exact test		P=0.500N	P=0.309N	P=0.661N

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

	0 ppm	600 ppm	1,300 ppm	2,500 ppm
Thyroid Gland (C-cell): Adenoma				
Overall rate	5/49 (10%)	2/50 (4%)	7/50 (14%)	4/50 (8%)
Adjusted rate	19.4%	5.1%	22.6%	12.6%
Terminal rate	4/24 (17%)	0/27 (0%)	7/31 (23%)	3/28 (11%)
First incidence (days)	682	578	722 (T)	491
Life table test	P=0.541N	P=0.210N	P=0.565	P=0.420N
Logistic regression test	P=0.535	P=0.227N	P=0.536	P=0.493N
Cochran-Armitage test	P=0.521			
Fisher exact test		P=0.210N	P=0.394	P=0.487N
Uterus: Stromal Polyp				
Overall rate	8/50 (16%)	7/50 (14%)	6/50 (12%)	7/50 (14%)
Adjusted rate	24.9%	21.1%	19.4%	19.9%
Terminal rate	4/24 (17%)	3/27 (11%)	6/31 (19%)	3/28 (11%)
First incidence (days)	415	612	722 (T)	489
Life table test	P=0.356N	P=0.488N	P=0.245N	P=0.433N
Logistic regression test	P=0.429N	P=0.517N	P=0.375N	P=0.498N
Cochran-Armitage test	P=0.439N			
Fisher exact test		P=0.500N	P=0.387N	P=0.500N
Uterus: Stromal Sarcoma				
Overall rate	0/50 (0%)	3/50 (6%)	0/50 (0%)	3/50 (6%)
Adjusted rate	0.0%	7.9%	0.0%	9.3%
Terminal rate	0/24 (0%)	1/27 (4%)	0/31 (0%)	2/28 (7%)
First incidence (days)	—	415	—	561
Life table test	P=0.192	P=0.123	—	P=0.137
Logistic regression test	P=0.149	P=0.178	—	P=0.121
Cochran-Armitage test	P=0.175			
Fisher exact test		P=0.121	—	P=0.121
Uterus: Stromal Polyp or Stromal Sarcoma				
Overall rate	8/50 (16%)	10/50 (20%)	6/50 (12%)	10/50 (20%)
Adjusted rate	24.9%	27.7%	19.4%	28.1%
Terminal rate	4/24 (17%)	4/27 (15%)	6/31 (19%)	5/28 (18%)
First incidence (days)	415	415	722 (T)	489
Life table test	P=0.529	P=0.414	P=0.245N	P=0.476
Logistic regression test	P=0.433	P=0.427	P=0.375N	P=0.399
Cochran-Armitage test	P=0.436			
Fisher exact test		P=0.398	P=0.387N	P=0.398
All Organs: Mononuclear Cell Leukemia				
Overall rate	13/50 (26%)	13/50 (26%)	13/50 (26%)	22/50 (44%)
Adjusted rate	38.3%	31.7%	31.3%	53.0%
Terminal rate	6/24 (25%)	4/27 (15%)	5/31 (16%)	10/28 (36%)
First incidence (days)	561	367	501	477
Life table test	P=0.068	P=0.574	P=0.415N	P=0.114
Logistic regression test	P=0.018	P=0.483N	P=0.582	P=0.047
Cochran-Armitage test	P=0.024			
Fisher exact test		P=0.590N	P=0.590N	P=0.046

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

	0 ppm	600 ppm	1,300 ppm	2,500 ppm
All Organs: Benign Neoplasms				
Overall rate	39/50 (78%)	35/50 (70%)	35/50 (70%)	33/50 (66%)
Adjusted rate	90.5%	87.2%	77.5%	79.8%
Terminal rate	20/24 (83%)	22/27 (81%)	21/31 (68%)	20/28 (71%)
First incidence (days)	415	410	389	489
Life table test	P=0.069N	P=0.240N	P=0.060N	P=0.083N
Logistic regression test	P=0.102N	P=0.439N	P=0.216N	P=0.134N
Cochran-Armitage test	P=0.134N			
Fisher exact test		P=0.247N	P=0.247N	P=0.133N
All Organs: Malignant Neoplasms				
Overall rate	21/50 (42%)	20/50 (40%)	17/50 (34%)	28/50 (56%)
Adjusted rate	52.1%	46.7%	39.1%	63.6%
Terminal rate	7/24 (29%)	7/27 (26%)	7/31 (23%)	13/28 (46%)
First incidence (days)	367	367	389	433
Life table test	P=0.213	P=0.508N	P=0.165N	P=0.258
Logistic regression test	P=0.059	P=0.351N	P=0.327N	P=0.114
Cochran-Armitage test	P=0.086			
Fisher exact test		P=0.500N	P=0.268N	P=0.115
All Organs: Benign or Malignant Neoplasms				
Overall rate	47/50 (94%)	44/50 (88%)	41/50 (82%)	46/50 (92%)
Adjusted rate	94.0%	89.7%	82.0%	92.0%
Terminal rate	21/24 (88%)	22/27 (81%)	22/31 (71%)	24/28 (86%)
First incidence (days)	367	367	389	433
Life table test	P=0.243N	P=0.352N	P=0.042N	P=0.288N
Logistic regression test	P=0.551	P=0.237N	P=0.129N	P=0.586N
Cochran-Armitage test	P=0.452N			
Fisher exact test		P=0.243N	P=0.061N	P=0.500N

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, clitoral gland, pituitary gland, and thyroid gland; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence are the P values 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 life table test regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in an exposure group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group

TABLE B4
Historical Incidence of Mononuclear Cell Leukemia in Untreated Female F344/N Rats[a]

Study	Incidence in Controls
Historical Incidence at Battelle Columbus Laboratories	
4,4′-Thiobis(6-*t*-butyl-*m*-cresol)	18/50
5,5-Diphenylhydantoin	13/50
Ethylene Thiourea	18/50
Polybrominated Biphenyls (Firemaster FF-1®)	14/50
Manganese (II) Sulfate Monohydrate	19/50
Triamterene	8/50
Tricresyl Phosphate	8/51
Overall Historical Incidence	
Total	355/1,301 (27.3%)
Standard deviation	9.0%
Range	14%-52%

[a] Data as of 12 May 1995. Includes data for lymphocytic, monocytic, mononuclear, and undifferentiated cell type leukemias

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of Primidone[a]

	0 ppm	600 ppm	1,300 ppm	2,500 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	21	18	14	19
Natural deaths	5	5	5	3
Survivors				
Died last week of study				1
Terminal sacrifice	24	27	31	27
Animals examined microscopically	50	50	50	50
Alimentary System				
Esophagus	(49)	(50)	(50)	(50)
Cyst			1 (2%)	
Intestine large, colon	(50)	(50)	(50)	(50)
Parasite metazoan	1 (2%)			
Intestine large, rectum	(49)	(50)	(50)	(50)
Parasite metazoan		2 (4%)	2 (4%)	3 (6%)
Intestine small, ileum	(50)	(50)	(50)	(49)
Inflammation, chronic active				1 (2%)
Liver	(50)	(50)	(50)	(50)
Angiectasis	2 (4%)		1 (2%)	3 (6%)
Basophilic focus	39 (78%)	35 (70%)	38 (76%)	10 (20%)
Clear cell focus	6 (12%)	5 (10%)		
Eosinophilic focus	2 (4%)		1 (2%)	18 (36%)
Hematopoietic cell proliferation		1 (2%)		
Hepatodiaphragmatic nodule	5 (10%)	13 (26%)	11 (22%)	5 (10%)
Inflammation, chronic	38 (76%)	38 (76%)	44 (88%)	34 (68%)
Mixed cell focus	5 (10%)		1 (2%)	6 (12%)
Pigmentation, hemosiderin	25 (50%)	14 (28%)	12 (24%)	19 (38%)
Bile duct, hyperplasia	30 (60%)	23 (46%)	35 (70%)	33 (66%)
Hepatocyte, degeneration	1 (2%)			
Hepatocyte, degeneration, cystic		1 (2%)		1 (2%)
Hepatocyte, necrosis	4 (8%)	1 (2%)	3 (6%)	4 (8%)
Hepatocyte, vacuolization cytoplasmic	25 (50%)	44 (88%)	46 (92%)	44 (88%)
Hepatocyte, centrilobular, degeneration		1 (2%)		1 (2%)
Hepatocyte, centrilobular, hypertrophy	1 (2%)	36 (72%)	38 (76%)	35 (70%)
Portal vein, thrombosis				1 (2%)
Mesentery	(9)	(10)	(7)	(7)
Accessory spleen	1 (11%)			
Fat, inflammation, chronic active		1 (10%)		
Fat, necrosis	7 (78%)	5 (50%)	5 (71%)	6 (86%)
Pancreas	(49)	(50)	(50)	(50)
Cyst	1 (2%)			
Inflammation, chronic active		1 (2%)	1 (2%)	
Acinus, atrophy	8 (16%)	7 (14%)	11 (22%)	11 (22%)
Salivary glands	(49)	(50)	(50)	(50)
Parotid gland, atrophy		1 (2%)		
Parotid gland, inflammation, chronic active		1 (2%)		
Stomach, forestomach	(49)	(50)	(50)	(50)
Hyperplasia, basal cell			1 (2%)	
Epithelium, hyperplasia	4 (8%)	4 (8%)	3 (6%)	4 (8%)
Epithelium, inflammation, chronic active	2 (4%)	2 (4%)	2 (4%)	2 (4%)
Epithelium, ulcer	2 (4%)	2 (4%)	2 (4%)	2 (4%)

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

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of Primidone

	0 ppm	600 ppm	1,300 ppm	2,500 ppm
Alimentary System (continued)				
Stomach, glandular	(49)	(50)	(50)	(50)
Epithelium, erosion		2 (4%)		1 (2%)
Epithelium, inflammation, chronic active		1 (2%)		
Epithelium, ulcer		1 (2%)		1 (2%)
Cardiovascular System				
Blood vessel	(49)	(50)	(50)	(50)
Inflammation, chronic active				1 (2%)
Heart	(49)	(50)	(50)	(50)
Cardiomyopathy, chronic	21 (43%)	29 (58%)	27 (54%)	21 (42%)
Atrium, thrombosis	1 (2%)			
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Accessory adrenal cortical nodule			1 (2%)	
Angiectasis			1 (2%)	
Atrophy			1 (2%)	
Degeneration, fatty	13 (26%)	11 (22%)	8 (16%)	6 (12%)
Hyperplasia	10 (20%)	8 (16%)	10 (20%)	8 (16%)
Hypertrophy	1 (2%)	1 (2%)	2 (4%)	3 (6%)
Inflammation, chronic active			1 (2%)	
Inflammation, granulomatous		1 (2%)		
Necrosis	1 (2%)			
Adrenal medulla	(50)	(50)	(49)	(50)
Hyperplasia	6 (12%)	5 (10%)	9 (18%)	7 (14%)
Pituitary gland	(49)	(50)	(49)	(50)
Angiectasis	1 (2%)			
Pars distalis, cyst	24 (49%)	24 (48%)	36 (73%)	28 (56%)
Pars distalis, hyperplasia	26 (53%)	25 (50%)	26 (53%)	21 (42%)
Pars intermedia, cyst		1 (2%)	1 (2%)	1 (2%)
Thyroid gland	(49)	(50)	(50)	(50)
C-cell, hyperplasia	14 (29%)	15 (30%)	11 (22%)	5 (10%)
Follicular cell, hyperplasia			1 (2%)	
General Body System				
None				
Genital System				
Clitoral gland	(49)	(49)	(50)	(50)
Cyst		2 (4%)	1 (2%)	2 (4%)
Hyperplasia	12 (24%)	5 (10%)	8 (16%)	10 (20%)
Inflammation, chronic active	4 (8%)	10 (20%)	2 (4%)	3 (6%)
Ovary	(50)	(50)	(50)	(49)
Atrophy		1 (2%)		1 (2%)
Cyst	3 (6%)	4 (8%)	2 (4%)	1 (2%)
Inflammation, chronic active				1 (2%)

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of Primidone

	0 ppm	600 ppm	1,300 ppm	2,500 ppm
Genital System (continued)				
Uterus	(50)	(50)	(50)	(49)
Angiectasis		1 (2%)		
Edema		1 (2%)		
Hemorrhage	1 (2%)	1 (2%)		
Hydrometra	2 (4%)			
Hyperplasia, cystic	2 (4%)		4 (8%)	3 (6%)
Inflammation, chronic active	1 (2%)			
Vagina	(1)		(1)	(2)
Cyst			1 (100%)	
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Atrophy		1 (2%)		
Hyperplasia	5 (10%)	10 (20%)	7 (14%)	7 (14%)
Hyperplasia, histiocytic		3 (6%)		
Hyperplasia, mast cell	1 (2%)			
Myelofibrosis	4 (8%)	1 (2%)	1 (2%)	1 (2%)
Lymph node	(11)	(7)	(8)	(12)
Mediastinal, hyperplasia, histiocytic	1 (9%)			
Mediastinal, necrosis	1 (9%)			
Lymph node, mandibular	(49)	(50)	(50)	(50)
Ectasia			1 (2%)	
Inflammation, chronic active			1 (2%)	
Lymph node, mesenteric	(50)	(50)	(50)	(49)
Ectasia			1 (2%)	3 (6%)
Spleen	(49)	(50)	(50)	(50)
Accessory spleen	2 (4%)			
Fibrosis	1 (2%)	1 (2%)	1 (2%)	
Hematopoietic cell proliferation	2 (4%)	3 (6%)	1 (2%)	2 (4%)
Hemorrhage			1 (2%)	
Necrosis	2 (4%)	1 (2%)	1 (2%)	
Thymus	(49)	(45)	(47)	(46)
Cyst		1 (2%)		
Integumentary System				
Mammary gland	(50)	(50)	(50)	(50)
Cyst	1 (2%)			1 (2%)
Hyperplasia, cystic	37 (74%)	44 (88%)	43 (86%)	37 (74%)
Inflammation, chronic active	1 (2%)			
Skin	(50)	(50)	(50)	(50)
Hyperkeratosis	1 (2%)		1 (2%)	
Inflammation, chronic active			2 (4%)	
Ulcer			1 (2%)	
Epidermis, hyperplasia	1 (2%)		2 (4%)	
Subcutaneous tissue, hemorrhage, acute				1 (2%)
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Osteopetrosis	2 (4%)	5 (10%)		1 (2%)
Skeletal muscle		(1)		(2)
Hemorrhage, acute				1 (50%)

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of Primidone

	0 ppm	600 ppm	1,300 ppm	2,500 ppm
Nervous System				
Brain	(50)	(50)	(50)	(50)
Hemorrhage	1 (2%)	3 (6%)	3 (6%)	1 (2%)
Hydrocephalus	1 (2%)		1 (2%)	
Spinal cord		(1)		(2)
Hemorrhage				1 (50%)
Respiratory System				
Lung	(49)	(50)	(50)	(50)
Inflammation, chronic active	1 (2%)	4 (8%)	1 (2%)	3 (6%)
Necrosis	1 (2%)			
Alveolar epithelium, hyperplasia	5 (10%)	5 (10%)	6 (12%)	2 (4%)
Alveolus, infiltration cellular, histiocyte	36 (73%)	44 (88%)	45 (90%)	46 (92%)
Artery, vein, mineralization	38 (78%)	39 (78%)	38 (76%)	44 (88%)
Interstitium, inflammation, chronic active				1 (2%)
Perivascular, infiltration cellular, lymphocyte	4 (8%)	1 (2%)	3 (6%)	5 (10%)
Nose	(50)	(49)	(50)	(50)
Inflammation, chronic active	2 (4%)		4 (8%)	5 (10%)
Inflammation, suppurative	1 (2%)	1 (2%)		1 (2%)
Nasolacrimal duct, inflammation, suppurative	2 (4%)	3 (6%)	3 (6%)	4 (8%)
Special Senses System				
Eye	(1)	(1)	(2)	(2)
Inflammation, chronic active			1 (50%)	
Anterior chamber, inflammation, suppurative				1 (50%)
Lens, cataract	1 (100%)	1 (100%)	1 (50%)	1 (50%)
Retina, degeneration	1 (100%)	1 (100%)	2 (100%)	1 (50%)
Harderian gland			(1)	
Inflammation, chronic active			1 (100%)	
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Cyst		1 (2%)		1 (2%)
Hydronephrosis				1 (2%)
Mineralization	12 (24%)	10 (20%)	5 (10%)	8 (16%)
Nephropathy, chronic	43 (86%)	43 (86%)	44 (88%)	43 (86%)
Urinary bladder	(50)	(50)	(50)	(49)
Inflammation, chronic active		1 (2%)		

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

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

	0 ppm	300 ppm	600 ppm	1,300 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	6	7	6	17
Natural deaths	9	9	13	14
Survivors				
Died last week of study		1		
Terminal sacrifice	35	33	31	19
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine large, rectum	(48)	(49)	(50)	(47)
Fibrous histiocytoma	1 (2%)			
Intestine small, jejunum	(46)	(49)	(50)	(47)
Histiocytic sarcoma				1 (2%)
Intestine small, ileum	(42)	(47)	(49)	(48)
Histiocytic sarcoma				1 (2%)
Liver	(50)	(50)	(50)	(50)
Hemangiosarcoma	2 (4%)	3 (6%)		
Hepatoblastoma		15 (30%)	21 (42%)	6 (12%)
Hepatoblastoma, multiple		2 (4%)	5 (10%)	1 (2%)
Hepatocellular carcinoma	10 (20%)	21 (42%)	13 (26%)	19 (38%)
Hepatocellular carcinoma, multiple	2 (4%)	10 (20%)	22 (44%)	19 (38%)
Hepatocellular adenoma	16 (32%)	12 (24%)	5 (10%)	10 (20%)
Hepatocellular adenoma, multiple	6 (12%)	29 (58%)	34 (68%)	22 (44%)
Histiocytic sarcoma				4 (8%)
Mast cell tumor malignant			1 (2%)	
Mesentery	(1)	(2)	(1)	(1)
Fat, histiocytic sarcoma				1 (100%)
Pancreas	(46)	(48)	(50)	(47)
Hemangioma	1 (2%)			
Hepatoblastoma, metastatic, liver			1 (2%)	
Stomach, forestomach	(50)	(49)	(50)	(49)
Squamous cell carcinoma				1 (2%)
Squamous cell papilloma				1 (2%)
Cardiovascular System				
None				
Endocrine System				
Adrenal cortex	(50)	(49)	(50)	(50)
Histiocytic sarcoma				1 (2%)
Capsule, adenoma	1 (2%)		1 (2%)	
Adrenal medulla	(50)	(49)	(50)	(50)
Pheochromocytoma benign		1 (2%)	1 (2%)	
Islets, pancreatic	(45)	(48)	(49)	(47)
Adenoma	1 (2%)			
Thyroid gland	(49)	(48)	(50)	(50)
Follicular cell, adenoma		3 (6%)	3 (6%)	6 (12%)

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

	0 ppm	300 ppm	600 ppm	1,300 ppm
General Body System				
None				
Genital System				
Epididymis	(50)	(50)	(50)	(50)
Hepatoblastoma, metastatic, liver			1 (2%)	
Prostate	(49)	(50)	(50)	(50)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Mast cell tumor malignant	1 (2%)			
Lymph node	(1)	(4)	(1)	(3)
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung		1 (25%)		
Lymph node, mesenteric	(48)	(48)	(49)	(42)
Histiocytic sarcoma				1 (2%)
Spleen	(48)	(49)	(50)	(49)
Hemangiosarcoma	2 (4%)			
Hepatoblastoma, metastatic, uncertain primary site		1 (2%)		
Histiocytic sarcoma				2 (4%)
Mast cell tumor malignant	1 (2%)			
Thymus	(42)	(40)	(42)	(34)
Integumentary System				
Skin	(50)	(50)	(50)	(50)
Subcutaneous tissue, fibrous histiocytoma	1 (2%)			
Subcutaneous tissue, histiocytic sarcoma	1 (2%)			1 (2%)
Subcutaneous tissue, mast cell tumor malignant	1 (2%)			
Musculoskeletal System				
Skeletal muscle			(1)	
Hepatoblastoma, metastatic, liver			1 (100%)	
Nervous System				
None				
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	6 (12%)	7 (14%)	5 (10%)	5 (10%)
Alveolar/bronchiolar adenoma, multiple	1 (2%)			1 (2%)
Alveolar/bronchiolar carcinoma	4 (8%)	1 (2%)	1 (2%)	3 (6%)
Alveolar/bronchiolar carcinoma, multiple		1 (2%)		
Carcinoma, metastatic, harderian gland		1 (2%)		
Hepatoblastoma, metastatic, liver		2 (4%)	11 (22%)	5 (10%)
Hepatocellular carcinoma, metastatic, liver	5 (10%)	5 (10%)	4 (8%)	5 (10%)

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

	0 ppm	300 ppm	600 ppm	1,300 ppm
Respiratory System (continued)				
Lung				
Histiocytic sarcoma				1 (2%)
Mast cell tumor malignant	1 (2%)			
Sarcoma, metastatic, uncertain primary site				1 (2%)
Mediastinum, hepatoblastoma, metastatic, liver			1 (2%)	
Special Senses System				
Harderian gland	(2)	(3)	(1)	(2)
Adenoma	2 (100%)	2 (67%)	1 (100%)	1 (50%)
Carcinoma		1 (33%)		
Urinary System				
Kidney	(50)	(49)	(50)	(50)
Alveolar/bronchiolar carcinoma, metastatic, lung	1 (2%)	1 (2%)		
Hepatoblastoma, metastatic, liver			1 (2%)	
Histiocytic sarcoma				1 (2%)
Renal tubule, carcinoma				1 (2%)
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Histiocytic sarcoma	1 (2%)			5 (10%)
Lymphoma malignant	7 (14%)	4 (8%)	2 (4%)	
Neoplasm Summary				
Total animals with primary neoplasms[c]	40	50	50	47
Total primary neoplasms	68	112	115	101
Total animals with benign neoplasms	26	42	39	36
Total benign neoplasms	34	54	50	46
Total animals with malignant neoplasms	22	42	42	42
Total malignant neoplasms	34	58	65	55
Total animals with metastatic neoplasms	5	9	14	11
Total metastatic neoplasms	6	11	20	11
Total animals with malignant neoplasms of uncertain primary site		1		1

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

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

Number of Days on Study	432	511	526	551	552	573	776	778	583	635	642	649	698	701	701	726	726	726	726	726	726	726	726	726	726
Carcass ID Number	050	027	013	029	048	025	039	030	035	008	017	041	018	009	015	003	007	011	012	019	021	023	026	031	044
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma														X											
Intestine large, cecum	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	M	+	A	+	+	M	A	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	A	+	+	+	A	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	M	+	A	+	M	+	A	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma					X		X																		
Hepatocellular carcinoma			X			X		X					X							X		X		X	
Hepatocellular carcinoma, multiple														X											
Hepatocellular adenoma				X											X			X	X					X	
Hepatocellular adenoma, multiple																					X				
Mesentery																									+
Pancreas	+	+	+	+	A	+	+	+	A	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, adenoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	A	A	+	+	+	A	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	M	+	+	M	M	+	M	+	M	M	M	M	M	M	+	+	M	+	+	M	+	M	+	M
Pituitary gland	M	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+
Thyroid gland	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

+: 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 Primidone: 0 ppm

Number of Days on Study	726	727	727	727	727	727	727	727	727	727	727	727	727	727	727	727	727	727	727	727	727	727	727	727	727	
Carcass ID Number	045	001	002	004	005	006	010	014	016	020	022	024	028	032	033	034	036	037	038	040	042	043	046	047	049	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Fibrous histiocytoma																										1
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, ileum	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										2
Hepatocellular carcinoma				X		X				X																10
Hepatocellular carcinoma, multiple							X																			2
Hepatocellular adenoma					X		X		X		X	X			X	X		X				X		X	X	16
Hepatocellular adenoma, multiple								X		X									X	X			X			6
Mesentery																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Hemangioma																					X					1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Capsule, adenoma																									X	1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Adenoma																							X			1
Parathyroid gland	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	M	+	+	31
Pituitary gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

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

Number of Days on Study	432	511	526	551	552	573	576	578	583	635	642	649	698	701	701	726	726	726	726	726	726	726	726	726	726
Carcass ID Number	050	027	013	029	048	025	039	030	035	008	017	041	018	009	015	003	007	011	012	019	021	023	026	031	044
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mast cell tumor malignant																								X	
Lymph node															+										
Lymph node, mandibular	M	+	M	M	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma							X												X						
Mast cell tumor malignant																								X	
Thymus	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrous histiocytoma														X											
Subcutaneous tissue, histiocytic sarcoma																									
Subcutaneous tissue, mast cell tumor malignant																								X	
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma									X						X							X			
Alveolar/bronchiolar adenoma, multiple																									
Alveolar/bronchiolar carcinoma								X																	
Hepatocellular carcinoma, metastatic, liver								X					X	X											
Mast cell tumor malignant																								X	
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland																						+			
Adenoma																						X			
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung								X																	
Urinary bladder	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Lymphoma malignant	X														X		X							X	

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

Number of Days on Study	726	727	727	727	727	727	727	727	727	727	727	727	727	727	727	727	727	727	727	727	727	727	727	727	727	
Carcass ID Number	045	001	002	004	005	006	010	014	016	020	022	024	028	032	033	034	036	037	038	040	042	043	046	047	049	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mast cell tumor malignant																										1
Lymph node																										1
Lymph node, mandibular	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	M	+	+	+	M	M	+	+	+	+	39
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hemangiosarcoma																										2
Mast cell tumor malignant																										1
Thymus	+	+	M	M	M	+	M	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	42
Integumentary System																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibrous histiocytoma																										1
Subcutaneous tissue, histiocytic sarcoma																		X								1
Subcutaneous tissue, mast cell tumor malignant																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma							X		X											X						6
Alveolar/bronchiolar adenoma, multiple																	X									1
Alveolar/bronchiolar carcinoma		X						X		X																4
Hepatocellular carcinoma, metastatic, liver							X			X																5
Mast cell tumor malignant																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Harderian gland																					+					2
Adenoma																					X					2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																		X								1
Lymphoma malignant				X		X								X												7

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Primidone: 300 ppm

Number of Days on Study	603	603	614	617	617	617	636	639	642	643	646	672	673	695	710	712	726	726	726	726	726	726	726	726	726
Carcass ID Number	058	090	091	056	066	096	075	081	080	097	051	088	055	083	057	089	054	059	062	063	067	068	069	071	072
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	M	+	+	M	+	+	M	A	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	M	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	M	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Hepatoblastoma				X		X					X	X		X	X	X			X	X					
Hepatoblastoma, multiple					X																				
Hepatocellular carcinoma			X		X			X	X	X		X	X	X					X			X			
Hepatocellular carcinoma, multiple							X										X				X				
Hepatocellular adenoma					X	X						X	X			X	X		X						
Hepatocellular adenoma, multiple		X	X				X				X				X			X		X	X		X	X	X
Mesentery											+								+						
Pancreas	+	M	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	+	M	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	I	+	+	M	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																		X							
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Primidone: 300 ppm

Number of Days on Study	726	726	726	726	726	726	726	726	726	727	727	727	727	727	727	727	727	727	727	727	727	727	727	727	727	
Carcass ID Number	077	078	082	087	092	093	094	095	100	052	053	060	061	064	065	070	073	074	076	079	084	085	086	098	099	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma							X					X												X		3
Hepatoblastoma											X			X	X		X				X			X		15
Hepatoblastoma, multiple							X																			2
Hepatocellular carcinoma						X			X		X			X		X	X	X	X		X	X			X	21
Hepatocellular carcinoma, multiple	X	X	X	X											X					X			X			10
Hepatocellular adenoma		X									X			X	X					X						12
Hepatocellular adenoma, multiple	X			X	X		X	X	X	X		X	X			X	X	X	X		X	X	X	X	X	29
Mesentery																										2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma benign																					X					1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	M	+	M	M	+	+	+	+	42
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Thyroid gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Follicular cell, adenoma																							X		X	3
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Primidone: 300 ppm

Number of Days on Study	603	603	614	617	617	617	636	639	642	643	646	672	673	695	710	712	726	726	726	726	726	726	726	726	726
Carcass ID Number	058	090	091	056	066	096	075	081	080	097	051	088	055	083	057	089	054	059	062	063	067	068	069	071	072
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+																								+
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung																									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	A	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatoblastoma, metastatic, uncertain primary site																	X								
Thymus	+	+	+	+	+	M	+	+	+	A	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma						X														X				X	
Alveolar/bronchiolar carcinoma																	X								
Alveolar/bronchiolar carcinoma, multiple																									
Carcinoma, metastatic, harderian gland											X														
Hepatoblastoma, metastatic, liver						X								X											
Hepatocellular carcinoma, metastatic, liver									X										X						
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland								+			+														
Adenoma								X																	
Carcinoma											X														
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung																									
Urinary bladder	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant	X																								

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Primidone: 300 ppm

Number of Days on Study	726	726	726	726	726	726	726	726	726	727	727	727	727	727	727	727	727	727	727	727	727	727	727	727	727	
Carcass ID Number	077	078	082	087	092	093	094	095	100	052	053	060	061	064	065	070	073	074	076	079	084	085	086	098	099	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node													+			+										4
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung																X										1
Lymph node, mandibular	+	+	+	M	+	M	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	43
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatoblastoma, metastatic, uncertain primary site																										1
Thymus	+	+	+	+	M	M	M	+	M	M	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	40
Integumentary System																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma											X				X				X		X					7
Alveolar/bronchiolar carcinoma																										1
Alveolar/bronchiolar carcinoma, multiple																X										1
Carcinoma, metastatic, harderian gland																										1
Hepatoblastoma, metastatic, liver																										2
Hepatocellular carcinoma, metastatic, liver	X		X													X										5
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																										
Harderian gland									+																	3
Adenoma									X																	2
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar carcinoma, metastatic, lung																X										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant												X	X					X								4

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Primidone: 600 ppm

Number of Days on Study	422	566	575	578	602	614	619	621	625	643	645	646	652	658	667	681	687	692	701	726	726	726	726	726	726
Carcass ID Number	104	145	142	120	137	109	119	121	143	148	106	136	125	144	127	141	112	111	139	101	102	105	107	108	110
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatoblastoma	X	X		X	X			X	X		X					X	X	X	X	X		X			
Hepatoblastoma, multiple			X							X					X										
Hepatocellular carcinoma					X	X		X		X				X					X						X
Hepatocellular carcinoma, multiple			X								X		X		X		X	X		X	X	X	X	X	
Hepatocellular adenoma		X	X			X													X						
Hepatocellular adenoma, multiple				X	X		X		X	X			X	X						X	X	X		X	X
Mast cell tumor malignant		X																							
Mesentery																							+		
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatoblastoma, metastatic, liver																						X			
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, adenoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	+	+	+	M	+	+	+	+	+	M	+	+	M	+	+	+	M	M	+	+	+	+	M	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																						X			
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatoblastoma, metastatic, liver																						X			
Preputial gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Primidone: 600 ppm

Number of Days on Study	726	726	726	726	726	726	726	726	726	726	726	726	726	726	727	727	727	727	727	727	727	727	727	727	727	
Carcass ID Number	113	115	116	117	122	129	130	131	132	134	138	140	149	150	103	114	118	123	124	126	128	133	135	146	147	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	46
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatoblastoma	X								X	X			X	X	X			X							X	21
Hepatoblastoma, multiple																						X	X			5
Hepatocellular carcinoma								X					X		X			X	X					X		13
Hepatocellular carcinoma, multiple	X			X	X	X	X		X	X				X								X	X		X	22
Hepatocellular adenoma			X																							5
Hepatocellular adenoma, multiple		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	34
Mast cell tumor malignant																										1
Mesentery																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatoblastoma, metastatic, liver																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Capsule, adenoma																				X						1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																									X	1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	40
Pituitary gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	48
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma																				X				X		3
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatoblastoma, metastatic, liver																										1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Primidone: 600 ppm

Number of Days on Study	422	566	575	578	602	614	619	621	625	643	645	646	652	658	667	681	687	692	701	726	726	726	726	726	726
Carcass ID Number	104	145	142	120	137	109	119	121	143	148	106	136	125	144	127	141	112	111	139	101	102	105	107	108	110
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node																									
Lymph node, mandibular	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	M	+	+	M	+
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	+	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle											+														
Hepatoblastoma, metastatic, liver											X														
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																				X				X	
Alveolar/bronchiolar carcinoma														X											
Hepatoblastoma, metastatic, liver					X						X				X	X		X		X		X			
Hepatocellular carcinoma, metastatic, liver											X						X								
Mediastinum, hepatoblastoma, metastatic, liver																						X			
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland																					+				
Adenoma																					X				
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatoblastoma, metastatic, liver																						X			
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant												X													

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Primidone: 600 ppm

Number of Days on Study	726	726	726	726	726	726	726	726	726	726	726	726	726	726	727	727	727	727	727	727	727	727	727	727	727	
Carcass ID Number	113	115	116	117	122	129	130	131	132	134	138	140	149	150	103	114	118	123	124	126	128	133	135	146	147	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																								+		1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	46
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	M	+	+	+	+	M	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	42
Integumentary System																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Hepatoblastoma, metastatic, liver																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma											X				X		X									5
Alveolar/bronchiolar carcinoma																										1
Hepatoblastoma, metastatic, liver													X	X	X										X	11
Hepatocellular carcinoma, metastatic, liver																		X						X		4
Mediastinum, hepatoblastoma, metastatic, liver																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Harderian gland																										1
Adenoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatoblastoma, metastatic, liver																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant											X															2

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Primidone: 1,300 ppm

Number of Days on Study	022	368	470	492	516	551	559	562	565	606	617	625	625	625	632	637	638	646	656	658	674	674	674	697	698
Carcass ID Number	191	185	172	174	195	182	163	173	154	192	198	159	161	176	175	157	152	184	181	153	180	186	194	197	164
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Intestine large, rectum	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	M	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+
Intestine small, jejunum	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Histiocytic sarcoma						X																			
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Histiocytic sarcoma						X																			
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatoblastoma						X								X				X						X	
Hepatoblastoma, multiple																									
Hepatocellular carcinoma						X			X	X		X		X				X		X		X			
Hepatocellular carcinoma, multiple			X								X								X		X		X	X	X
Hepatocellular adenoma								X	X					X						X	X				
Hepatocellular adenoma, multiple		X	X				X					X	X		X	X	X	X							X
Histiocytic sarcoma						X		X																	
Mesentery						+																			
Fat, histiocytic sarcoma						X																			
Pancreas	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																									
Squamous cell papilloma																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma								X																	
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	+	+	+	M	+	M	+	+	+	+	+	+	M	M	+	+	M	+	+	M	M	M	M	M
Pituitary gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																					X	X			
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Primidone: 1,300 ppm

Number of Days on Study	699	702	706	712	716	720	726	726	726	726	726	726	726	726	726	726	726	727	727	727	727	727	727	727	727	
Carcass ID Number	188	196	197	169	156	199	151	158	162	165	166	167	170	178	179	183	187	190	155	160	168	171	189	193	200	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	45
Intestine large, colon	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, rectum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, cecum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, jejunum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Histiocytic sarcoma																										1
Intestine small, ileum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Histiocytic sarcoma																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatoblastoma			X			X																				6
Hepatoblastoma, multiple														X												1
Hepatocellular carcinoma	X	X	X	X			X			X			X	X			X		X						X	19
Hepatocellular carcinoma, multiple								X	X		X	X			X	X		X		X	X	X	X	X		19
Hepatocellular adenoma								X				X		X	X						X					10
Hepatocellular adenoma, multiple	X					X	X		X	X	X		X			X		X	X					X	X	22
Histiocytic sarcoma					X	X																				4
Mesentery																										1
Fat, histiocytic sarcoma																										1
Pancreas	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell carcinoma											X															1
Squamous cell papilloma																									X	1
Stomach, glandular	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Parathyroid gland	M	+	+	M	+	+	+	+	+	+	+	M	+	M	+	+	M	+	+	+	+	+	+	+	+	34
Pituitary gland	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma						X						X		X						X						6
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Primidone: 1,300 ppm

Number of Days on Study	022	368	470	492	516	551	559	562	565	606	617	625	625	625	632	637	638	646	656	658	674	674	674	697	698
Carcass ID Number	191	185	172	174	195	182	163	173	154	192	198	159	161	176	175	157	152	184	181	153	180	186	194	197	164
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node					+														+			+			
Lymph node, mandibular	M	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Histiocytic sarcoma																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma						X																			
Thymus	+	+	M	M	+	+	M	+	M	M	M	+	+	+	M	+	+	M	+	+	M	M	+	M	+
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, histiocytic sarcoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma		X								X										X					
Alveolar/bronchiolar adenoma, multiple																									
Alveolar/bronchiolar carcinoma														X	X										
Hepatoblastoma, metastatic, liver																						X	X	X	
Hepatocellular carcinoma, metastatic, liver																		X							X
Histiocytic sarcoma						X																			
Sarcoma, metastatic, uncertain primary site												X													
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland																									+
Adenoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma								X																	
Renal tubule, carcinoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma						X		X																	

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Primidone: 1,300 ppm

Number of Days on Study	699	702	706	712	716	720	726	726	726	726	726	726	726	726	726	726	726	726	727	727	727	727	727	727	727	
Carcass ID Number	188	196	197	169	156	199	151	158	162	165	166	167	170	178	179	183	187	190	155	160	168	171	189	193	200	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																										3
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Lymph node, mesenteric	A	+	M	+	+	+	+	+	+	+	+	M	+	+	+	M	M	+	+	+	+	+	+	+	+	42
Histiocytic sarcoma					X																					1
Spleen	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma						X																				2
Thymus	+	+	+	M	M	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	34
Integumentary System																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, histiocytic sarcoma																X										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma					X								X													5
Alveolar/bronchiolar adenoma, multiple						X																				1
Alveolar/bronchiolar carcinoma																						X				3
Hepatoblastoma, metastatic, liver						X								X												5
Hepatocellular carcinoma, metastatic, liver		X							X													X				5
Histiocytic sarcoma																										1
Sarcoma, metastatic, uncertain primary site																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Harderian gland									+																	2
Adenoma									X																	1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Renal tubule, carcinoma		X																								1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma					X	X										X										5

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

	0 ppm	300 ppm	600 ppm	1,300 ppm
Harderian Gland: Adenoma or Carcinoma				
Overall rate[a]	2/50 (4%)	3/50 (6%)	1/50 (2%)	1/50 (2%)
Adjusted rate[b]	5.7%	7.6%	3.2%	5.3%
Terminal rate[c]	2/35 (6%)	1/34 (3%)	1/31 (3%)	1/19 (5%)
First incidence (days)	726 (T)	639	726 (T)	726 (T)
Life table test[d]	P=0.456N	P=0.501	P=0.543N	P=0.708N
Logistic regression test[d]	P=0.332N	P=0.499	P=0.543N	P=0.708N
Cochran-Armitage test[d]	P=0.288N			
Fisher exact test[d]		P=0.500	P=0.500N	P=0.500N
Liver: Hemangiosarcoma				
Overall rate	2/50 (4%)	3/50 (6%)	0/50 (0%)	0/50 (0%)
Adjusted rate	4.4%	8.8%	0.0%	0.0%
Terminal rate	0/35 (0%)	3/34 (9%)	0/31 (0%)	0/19 (0%)
First incidence (days)	552	726 (T)	—[e]	—
Life table test	P=0.121N	P=0.511	P=0.226N	P=0.252N
Logistic regression test	P=0.062N	P=0.417	P=0.266N	P=0.152N
Cochran-Armitage test	P=0.079N			
Fisher exact test		P=0.500	P=0.247N	P=0.247N
Liver: Hepatocellular Adenoma				
Overall rate	22/50 (44%)	41/50 (82%)	39/50 (78%)	32/50 (64%)
Adjusted rate	59.2%	93.1%	92.6%	87.3%
Terminal rate	20/35 (57%)	31/34 (91%)	28/31 (90%)	15/19 (79%)
First incidence (days)	551	603	566	368
Life table test	P<0.001	P<0.001	P<0.001	P<0.001
Logistic regression test	P=0.040	P<0.001	P<0.001	P=0.013
Cochran-Armitage test	P=0.155			
Fisher exact test		P<0.001	P<0.001	P=0.035
Liver: Hepatocellular Carcinoma				
Overall rate	12/50 (24%)	31/50 (62%)	35/50 (70%)	38/50 (76%)
Adjusted rate	29.1%	71.6%	81.1%	100.0%
Terminal rate	7/35 (20%)	22/34 (65%)	23/31 (74%)	19/19 (100%)
First incidence (days)	526	614	575	470
Life table test	P<0.001	P<0.001	P<0.001	P<0.001
Logistic regression test	P<0.001	P<0.001	P<0.001	P<0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		P<0.001	P<0.001	P<0.001
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	31/50 (62%)	48/50 (96%)	47/50 (94%)	46/50 (92%)
Adjusted rate	73.5%	100.0%	100.0%	100.0%
Terminal rate	24/35 (69%)	34/34 (100%)	31/31 (100%)	19/19 (100%)
First incidence (days)	526	603	566	368
Life table test	P<0.001	P=0.002	P<0.001	P<0.001
Logistic regression test	P<0.001	P<0.001	P<0.001	P<0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		P<0.001	P<0.001	P<0.001

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

	0 ppm	300 ppm	600 ppm	1,300 ppm
Liver: Hepatoblastoma				
Overall rate	0/50 (0%)	17/50 (34%)	26/50 (52%)	7/50 (14%)
Adjusted rate	0.0%	39.9%	56.9%	23.4%
Terminal rate	0/35 (0%)	9/34 (26%)	12/31 (39%)	1/19 (5%)
First incidence (days)	—	617	422	551
Life table test	P=0.043	P<0.001	P<0.001	P=0.003
Logistic regression test	P=0.271	P<0.001	P<0.001	P=0.009
Cochran-Armitage test	P=0.254			
Fisher exact test		P<0.001	P<0.001	P=0.006
Liver: Hepatocellular Carcinoma or Hepatoblastoma				
Overall rate	12/50 (24%)	39/50 (78%)	40/50 (80%)	39/50 (78%)
Adjusted rate	29.1%	81.3%	83.2%	100.0%
Terminal rate	7/35 (20%)	25/34 (74%)	23/31 (74%)	19/19 (100%)
First incidence (days)	526	614	422	470
Life table test	P<0.001	P<0.001	P<0.001	P<0.001
Logistic regression test	P<0.001	P<0.001	P<0.001	P<0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		P<0.001	P<0.001	P<0.001
Liver: Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma				
Overall rate	31/50 (62%)	49/50 (98%)	49/50 (98%)	46/50 (92%)
Adjusted rate	73.5%	100.0%	100.0%	100.0%
Terminal rate	24/35 (69%)	34/34 (100%)	31/31 (100%)	19/19 (100%)
First incidence (days)	526	603	422	368
Life table test	P<0.001	P=0.001	P<0.001	P<0.001
Logistic regression test	P<0.001	P<0.001	P<0.001	P<0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		P<0.001	P<0.001	P<0.001
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	7/50 (14%)	7/50 (14%)	5/50 (10%)	6/50 (12%)
Adjusted rate	18.6%	19.4%	16.1%	20.7%
Terminal rate	5/35 (14%)	6/34 (18%)	5/31 (16%)	1/19 (5%)
First incidence (days)	583	617	726 (T)	368
Life table test	P=0.345	P=0.610	P=0.455N	P=0.426
Logistic regression test	P=0.467N	P=0.585N	P=0.394N	P=0.504N
Cochran-Armitage test	P=0.412N			
Fisher exact test		P=0.613N	P=0.380N	P=0.500N
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	4/50 (8%)	2/50 (4%)	1/50 (2%)	3/50 (6%)
Adjusted rate	10.7%	5.9%	2.7%	10.3%
Terminal rate	3/35 (9%)	2/34 (6%)	0/31 (0%)	1/19 (5%)
First incidence (days)	578	726 (T)	658	625
Life table test	P=0.515	P=0.337N	P=0.202N	P=0.609
Logistic regression test	P=0.497N	P=0.324N	P=0.180N	P=0.517N
Cochran-Armitage test	P=0.487N			
Fisher exact test		P=0.339N	P=0.181N	P=0.500N

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

	0 ppm	300 ppm	600 ppm	1,300 ppm
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	11/50 (22%)	9/50 (18%)	6/50 (12%)	9/50 (18%)
Adjusted rate	28.4%	25.2%	18.4%	29.1%
Terminal rate	8/35 (23%)	8/34 (24%)	5/31 (16%)	2/19 (11%)
First incidence (days)	578	617	658	368
Life table test	P=0.322	P=0.404N	P=0.200N	P=0.411
Logistic regression test	P=0.415N	P=0.367N	P=0.144N	P=0.413N
Cochran-Armitage test	P=0.364N			
Fisher exact test		P=0.402N	P=0.143N	P=0.402N
Thyroid Gland (Follicular Cell): Adenoma				
Overall rate	0/49 (0%)	3/48 (6%)	3/50 (6%)	6/50 (12%)
Adjusted rate	0.0%	9.1%	9.7%	25.3%
Terminal rate	0/35 (0%)	3/33 (9%)	3/31 (10%)	3/19 (16%)
First incidence (days)	—	726 (T)	726 (T)	674
Life table test	P<0.001	P=0.110	P=0.100	P=0.003
Logistic regression test	P=0.003	P=0.110	P=0.100	P=0.008
Cochran-Armitage test	P=0.016			
Fisher exact test		P=0.117	P=0.125	P=0.014
All Organs: Hemangiosarcoma				
Overall rate	3/50 (6%)	3/50 (6%)	0/50 (0%)	0/50 (0%)
Adjusted rate	7.1%	8.8%	0.0%	0.0%
Terminal rate	1/35 (3%)	3/34 (9%)	0/31 (0%)	0/19 (0%)
First incidence (days)	552	726 (T)	—	—
Life table test	P=0.067N	P=0.654N	P=0.123N	P=0.167N
Logistic regression test	P=0.033N	P=0.616	P=0.131N	P=0.085N
Cochran-Armitage test	P=0.039N			
Fisher exact test		P=0.661N	P=0.121N	P=0.121N
All Organs: Hemangioma or Hemangiosarcoma				
Overall rate	4/50 (8%)	3/50 (6%)	0/50 (0%)	0/50 (0%)
Adjusted rate	9.9%	8.8%	0.0%	0.0%
Terminal rate	2/35 (6%)	3/34 (9%)	0/31 (0%)	0/19 (0%)
First incidence (days)	552	726 (T)	—	—
Life table test	P=0.037N	P=0.495N	P=0.070N	P=0.114N
Logistic regression test	P=0.017N	P=0.536N	P=0.067N	P=0.049N
Cochran-Armitage test	P=0.019N			
Fisher exact test		P=0.500N	P=0.059N	P=0.059N
All Organs: Histiocytic Sarcoma				
Overall rate	1/50 (2%)	0/50 (0%)	0/50 (0%)	5/50 (10%)
Adjusted rate	2.9%	0.0%	0.0%	18.1%
Terminal rate	1/35 (3%)	0/34 (0%)	0/31 (0%)	1/19 (5%)
First incidence (days)	726 (T)	—	—	551
Life table test	P=0.001	P=0.506N	P=0.524N	P=0.040
Logistic regression test	P=0.008	P=0.506N	P=0.524N	P=0.101
Cochran-Armitage test	P=0.007			
Fisher exact test		P=0.500N	P=0.500N	P=0.102

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

	0 ppm	300 ppm	600 ppm	1,300 ppm
All Organs: Malignant Lymphoma				
Overall rate	7/50 (14%)	4/50 (8%)	2/50 (4%)	0/50 (0%)
Adjusted rate	18.3%	10.6%	5.7%	0.0%
Terminal rate	5/35 (14%)	3/34 (9%)	1/31 (3%)	0/19 (0%)
First incidence (days)	432	603	646	—
Life table test	P=0.015N	P=0.268N	P=0.112N	P=0.042N
Logistic regression test	P=0.004N	P=0.278N	P=0.082N	P=0.010N
Cochran-Armitage test	P=0.004N			
Fisher exact test		P=0.262N	P=0.080N	P=0.006N
All Organs: Benign Neoplasms				
Overall rate	26/50 (52%)	42/50 (84%)	39/50 (78%)	36/50 (72%)
Adjusted rate	68.1%	93.2%	92.6%	91.5%
Terminal rate	23/35 (66%)	31/34 (91%)	28/31 (90%)	16/19 (84%)
First incidence (days)	551	603	566	368
Life table test	P<0.001	P=0.001	P=0.002	P<0.001
Logistic regression test	P=0.023	P=0.001	P=0.005	P=0.010
Cochran-Armitage test	P=0.109			
Fisher exact test		P<0.001	P=0.006	P=0.032
All Organs: Malignant Neoplasms				
Overall rate	22/50 (44%)	42/50 (84%)	42/50 (84%)	42/50 (84%)
Adjusted rate	49.3%	85.7%	85.7%	100.0%
Terminal rate	13/35 (37%)	27/34 (79%)	24/31 (77%)	19/19 (100%)
First incidence (days)	432	603	422	470
Life table test	P<0.001	P=0.002	P<0.001	P<0.001
Logistic regression test	P<0.001	P<0.001	P<0.001	P<0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		P<0.001	P<0.001	P<0.001
All Organs: Benign or Malignant Neoplasms				
Overall rate	40/50 (80%)	50/50 (100%)	50/50 (100%)	47/50 (94%)
Adjusted rate	86.8%	100.0%	100.0%	100.0%
Terminal rate	29/35 (83%)	34/34 (100%)	31/31 (100%)	19/19 (100%)
First incidence (days)	432	603	422	368
Life table test	P<0.001	P=0.058	P=0.017	P<0.001
Logistic regression test	P=0.007	P=0.002	P=0.001	P=0.010
Cochran-Armitage test	P=0.042			
Fisher exact test		P<0.001	P<0.001	P=0.036

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for liver, lung, and thyroid gland; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence are the P values 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 life table test regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in an exposure group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group

TABLE C4a
Historical Incidence of Liver Neoplasms in Untreated Male B6C3F$_1$ Mice[a]

Study	Incidence in Controls			
	Hepatocellular Adenoma	Hepatocellular Carcinoma	Hepatoblastoma	Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma
Historical Incidence at Battelle Columbus Laboratories				
4,4′-Thiobis(6-*t*-butyl-*m*-cresol)	17/50	11/50	0/50	25/50
5,5-Diphenylhydantoin	19/50	13/50	0/50	29/50
Pentachlorophenol (Dowicide EC-7)	5/35	1/35	0/35	6/35
Ethylene Thiourea	11/49	13/49	0/49	20/49
Polybrominated Biphenyls (Firemaster FF-1®)	9/50	8/50	0/50	16/50
Manganese (II) Sulfate Monohydrate	30/50	9/50	0/50	34/50
Oxazepam	17/49	9/49	0/49	23/49
Pentachlorophenol (Technical Grade)	5/32	2/32	0/32	7/32
Triamterene	17/50	5/50	0/50	20/50
Triamterene	21/50	9/50	0/50	25/50
Tricresyl Phosphate	18/52	15/52	0/52	28/52
Overall Historical Incidence				
Total	413/1,465 (28.2%)	252/1,465 (17.2%)	0/1,465 (0%)	596/1,465 (40.7%)
Standard deviation	14.2%	7.1%		14.5%
Range	4%-60%	3%-29%		10%-68%

[a] Data as of 12 May 1995

TABLE C4b
Historical Incidence of Thyroid Gland Follicular Cell Adenoma in Untreated Male B6C3F$_1$ Mice[a]

Study	Incidence in Controls
Historical Incidence at Battelle Columbus Laboratories	
4,4′-Thiobis(6-*t*-butyl-*m*-cresol)	0/50
5,5-Diphenylhydantoin	0/49
Pentachlorophenol (Dowicide EC-7)	0/35
Ethylene Thiourea	0/50
Polybrominated Biphenyls (Firemaster FF-1®)	1/50
Manganese (II) Sulfate Monohydrate	0/50
Oxazepam	0/49
Pentachlorophenol (Technical Grade)	1/31
Triamterene	0/50
Triamterene	1/50
Tricresyl Phosphate	0/52
Overall Historical Incidence	
Total	22/1,455 (1.5%)
Standard deviation	1.5%
Range	0%-4%

[a] Data as of 12 May 1995

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of Primidone[a]

	0 ppm	300 ppm	600 ppm	1,300 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	6	7	6	17
Natural deaths	9	9	13	14
Survivors				
Died last week of study		1		
Terminal sacrifice	35	33	31	19
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine small, duodenum	(44)	(48)	(48)	(45)
Necrosis, focal				1 (2%)
Ulcer			1 (2%)	1 (2%)
Intestine small, jejunum	(46)	(49)	(50)	(47)
Peyer's patch, hyperplasia, lymphoid	1 (2%)			
Intestine small, ileum	(42)	(47)	(49)	(48)
Congestion				1 (2%)
Liver	(50)	(50)	(50)	(50)
Angiectasis	2 (4%)	1 (2%)		
Basophilic focus	2 (4%)	1 (2%)		
Clear cell focus	11 (22%)	7 (14%)	8 (16%)	1 (2%)
Clear cell focus, multiple	6 (12%)	4 (8%)	2 (4%)	
Eosinophilic focus	7 (14%)	4 (8%)	8 (16%)	5 (10%)
Hematopoietic cell proliferation	1 (2%)	1 (2%)	2 (4%)	
Inflammation, chronic		2 (4%)		1 (2%)
Mixed cell focus	1 (2%)	1 (2%)		1 (2%)
Necrosis	6 (12%)	7 (14%)	6 (12%)	6 (12%)
Thrombosis, acute			1 (2%)	
Centrilobular, hypertrophy	3 (6%)	30 (60%)	21 (42%)	18 (36%)
Hepatocyte, vacuolization cytoplasmic	1 (2%)	8 (16%)	3 (6%)	2 (4%)
Mesentery	(1)	(2)	(1)	(1)
Fat, inflammation, chronic	1 (100%)	1 (50%)	1 (100%)	1 (100%)
Pancreas	(46)	(48)	(50)	(47)
Duct, cyst	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Stomach, forestomach	(50)	(49)	(50)	(49)
Hyperplasia, diffuse, squamous	2 (4%)			
Hyperplasia, focal, squamous	6 (12%)	9 (18%)	9 (18%)	3 (6%)
Stomach, glandular	(50)	(49)	(50)	(49)
Epithelium, hyperplasia, focal	1 (2%)			
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Infiltration cellular, focal, lymphocyte				1 (2%)
Inflammation, chronic active	1 (2%)			
Mineralization, diffuse				1 (2%)

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

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of Primidone

	0 ppm	300 ppm	600 ppm	1,300 ppm
Endocrine System				
Adrenal cortex	(50)	(49)	(50)	(50)
Hyperplasia, focal				2 (4%)
Hypertrophy, focal	2 (4%)	2 (4%)	2 (4%)	1 (2%)
Necrosis				1 (2%)
Capsule, accessory adrenal cortical nodule			1 (2%)	
Capsule, hyperplasia	3 (6%)	4 (8%)	2 (4%)	
Islets, pancreatic	(45)	(48)	(49)	(47)
Hyperplasia	32 (71%)	34 (71%)	18 (37%)	4 (9%)
Pituitary gland	(45)	(46)	(48)	(47)
Pars distalis, cyst		2 (4%)	1 (2%)	
Thyroid gland	(49)	(48)	(50)	(50)
Follicle, cyst		1 (2%)	1 (2%)	
Follicular cell, hyperplasia	8 (16%)	20 (42%)	31 (62%)	42 (84%)
General Body System				
None				
Genital System				
Epididymis	(50)	(50)	(50)	(50)
Granuloma sperm, focal	1 (2%)			
Spermatocele, focal			1 (2%)	
Preputial gland	(50)	(50)	(48)	(50)
Inflammation, chronic active	1 (2%)			
Duct, cyst	23 (46%)	32 (64%)	26 (54%)	30 (60%)
Prostate	(49)	(50)	(50)	(50)
Inflammation, chronic active				1 (2%)
Testes	(50)	(50)	(50)	(50)
Germinal epithelium, atrophy	1 (2%)	1 (2%)		
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Myeloid cell, hyperplasia	2 (4%)	1 (2%)		1 (2%)
Lymph node	(1)	(4)	(1)	(3)
Hyperplasia, lymphoid				1 (33%)
Inflammation, chronic				1 (33%)
Mediastinal, hyperplasia, lymphoid		1 (25%)		
Renal, hematopoietic cell proliferation				1 (33%)
Renal, hyperplasia, lymphoid			1 (100%)	
Lymph node, mandibular	(39)	(43)	(46)	(46)
Hyperplasia, lymphoid		1 (2%)		
Infiltration cellular, plasma cell		1 (2%)		
Lymph node, mesenteric	(48)	(48)	(49)	(42)
Angiectasis				1 (2%)
Congestion	1 (2%)			
Hematopoietic cell proliferation		1 (2%)	1 (2%)	2 (5%)
Hyperplasia, lymphoid		1 (2%)		
Spleen	(48)	(49)	(50)	(49)
Atrophy	2 (4%)	3 (6%)		4 (8%)
Hematopoietic cell proliferation	14 (29%)	15 (31%)	26 (52%)	37 (76%)
Infiltration cellular, plasma cell			1 (2%)	
Capsule, fibrosis				1 (2%)

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of Primidone

	0 ppm	300 ppm	600 ppm	1,300 ppm
Hematopoietic System (continued)				
Thymus	(42)	(40)	(42)	(34)
Atrophy	39 (93%)	36 (90%)	35 (83%)	29 (85%)
Hyperplasia, lymphoid		1 (3%)	1 (2%)	
Integumentary System				
Skin	(50)	(50)	(50)	(50)
Hyperplasia, squamous				1 (2%)
Inflammation, chronic active			1 (2%)	2 (4%)
Ulcer		1 (2%)	1 (2%)	2 (4%)
Subcutaneous tissue, edema				1 (2%)
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Hyperostosis		1 (2%)		
Nervous System				
None				
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Infiltration cellular, focal, mast cell	1 (2%)			
Alveolar epithelium, hyperplasia, focal	4 (8%)	6 (12%)	3 (6%)	3 (6%)
Perivascular, inflammation, chronic				1 (2%)
Special Senses System				
None				
Urinary System				
Kidney	(50)	(49)	(50)	(50)
Hydronephrosis	1 (2%)		1 (2%)	
Infiltration cellular, focal, mast cell	1 (2%)			
Inflammation, acute				1 (2%)
Nephropathy	34 (68%)	30 (61%)	25 (50%)	20 (40%)
Cortex, cyst	1 (2%)		1 (2%)	
Cortex, infarct, focal	1 (2%)			
Renal tubule, pigmentation, hemosiderin		7 (14%)	8 (16%)	2 (4%)

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

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

	0 ppm	300 ppm	600 ppm	1,300 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	7	1	3	8
Natural deaths	2	7	2	3
Survivors				
Terminal sacrifice	41	42	44	39
Missing			1	
Animals examined microscopically	50	50	49	50
Alimentary System				
Esophagus	(50)	(50)	(49)	(50)
Squamous cell carcinoma			1 (2%)	
Intestine small, jejunum	(50)	(49)	(49)	(50)
Intestine small, ileum	(45)	(49)	(49)	(49)
Liver	(50)	(50)	(49)	(50)
Fibrosarcoma, metastatic, skin			1 (2%)	
Hemangiosarcoma			1 (2%)	
Hepatoblastoma	1 (2%)	3 (6%)	3 (6%)	4 (8%)
Hepatoblastoma, multiple		1 (2%)	1 (2%)	
Hepatocellular carcinoma	3 (6%)	7 (14%)	14 (29%)	13 (26%)
Hepatocellular carcinoma, multiple		4 (8%)	5 (10%)	25 (50%)
Hepatocellular adenoma	8 (16%)	5 (10%)	6 (12%)	5 (10%)
Hepatocellular adenoma, multiple	7 (14%)	37 (74%)	39 (80%)	42 (84%)
Histiocytic sarcoma		2 (4%)	1 (2%)	
Mesentery	(5)	(5)	(6)	(2)
Histiocytic sarcoma			1 (17%)	
Pancreas	(50)	(48)	(49)	(50)
Salivary glands	(50)	(48)	(49)	(50)
Cardiovascular System				
None				
Endocrine System				
Adrenal cortex	(50)	(49)	(49)	(50)
Capsule, adenoma		1 (2%)		
Islets, pancreatic	(50)	(47)	(49)	(50)
Adenoma	1 (2%)		1 (2%)	
Pituitary gland	(49)	(48)	(49)	(48)
Histiocytic sarcoma		1 (2%)		
Pars distalis, adenoma	3 (6%)	5 (10%)	6 (12%)	6 (13%)
Pars intermedia, adenoma				1 (2%)
Thyroid gland	(50)	(48)	(48)	(50)
Follicular cell, adenoma	1 (2%)	1 (2%)		2 (4%)
General Body System				
None				

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

	0 ppm	300 ppm	600 ppm	1,300 ppm
Genital System				
Ovary	(49)	(49)	(48)	(50)
Cystadenoma	3 (6%)		2 (4%)	1 (2%)
Hemangiosarcoma		1 (2%)		
Histiocytic sarcoma		1 (2%)	1 (2%)	
Uterus	(50)	(49)	(49)	(50)
Histiocytic sarcoma		1 (2%)	1 (2%)	
Polyp stromal	1 (2%)	3 (6%)	1 (2%)	1 (2%)
Sarcoma stromal	1 (2%)			
Cervix, histiocytic sarcoma			1 (2%)	
Hematopoietic System				
Bone marrow	(50)	(49)	(49)	(50)
Hemangioma	1 (2%)			
Histiocytic sarcoma		1 (2%)		
Lymph node	(6)	(8)	(7)	(4)
Deep cervical, alveolar/bronchiolar carcinoma, metastatic, lung		1 (13%)		
Lumbar, histiocytic sarcoma		1 (13%)		
Renal, histiocytic sarcoma		1 (13%)		
Lymph node, mandibular	(48)	(44)	(45)	(46)
Histiocytic sarcoma		1 (2%)	1 (2%)	
Lymph node, mesenteric	(48)	(48)	(47)	(47)
Histiocytic sarcoma		1 (2%)	1 (2%)	
Spleen	(50)	(48)	(49)	(50)
Hemangiosarcoma	1 (2%)			
Histiocytic sarcoma		1 (2%)	1 (2%)	
Thymus	(45)	(47)	(44)	(44)
Fibrosarcoma, metastatic, skin			1 (2%)	
Histiocytic sarcoma		1 (2%)		
Integumentary System				
Mammary gland	(50)	(50)	(49)	(47)
Carcinoma	1 (2%)			
Skin	(50)	(50)	(49)	(50)
Subcutaneous tissue, fibrosarcoma	3 (6%)	2 (4%)	1 (2%)	2 (4%)
Subcutaneous tissue, hemangiosarcoma	1 (2%)	1 (2%)		
Musculoskeletal System				
Bone	(50)	(50)	(49)	(50)
Maxilla, carcinoma, metastatic, harderian gland	1 (2%)			
Nervous System				
None				

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

	0 ppm	300 ppm	600 ppm	1,300 ppm
Respiratory System				
Lung	(50)	(50)	(49)	(50)
Alveolar/bronchiolar adenoma	4 (8%)	2 (4%)	3 (6%)	2 (4%)
Alveolar/bronchiolar adenoma, multiple			1 (2%)	
Alveolar/bronchiolar carcinoma	4 (8%)	3 (6%)		1 (2%)
Fibrosarcoma, metastatic, skin	1 (2%)		1 (2%)	1 (2%)
Hepatoblastoma, metastatic, liver		1 (2%)		1 (2%)
Hepatocellular carcinoma, metastatic, liver	1 (2%)			
Histiocytic sarcoma		1 (2%)		
Special Senses System				
Harderian gland	(5)	(5)	(3)	(1)
Adenoma	3 (60%)	5 (100%)	3 (100%)	1 (100%)
Carcinoma	2 (40%)			
Urinary System				
Kidney	(50)	(49)	(49)	(50)
Urinary bladder	(50)	(49)	(48)	(49)
Histiocytic sarcoma			1 (2%)	
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(49)	(50)
Histiocytic sarcoma		2 (4%)	1 (2%)	
Lymphoma malignant	8 (16%)	6 (12%)	8 (16%)	5 (10%)
Neoplasm Summary				
Total animals with primary neoplasms[c]	34	47	47	50
Total primary neoplasms	57	89	97	111
Total animals with benign neoplasms	26	45	46	47
Total benign neoplasms	32	59	62	61
Total animals with malignant neoplasms	20	23	26	40
Total malignant neoplasms	25	30	35	50
Total animals with metastatic neoplasms	3	2	1	2
Total metastatic neoplasms	3	2	3	2

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

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

Number of Days on Study	420	519	595	596	621	621	645	673	694	727	727	727	727	728	728	728	728	728	728	728	728	728	728	728	728
Carcass ID Number	201	223	241	220	205	212	118	207	216	208	222	227	230	202	206	209	211	215	217	219	221	228	232	234	236
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatoblastoma																									
Hepatocellular carcinoma									X															X	
Hepatocellular adenoma																						X		X	
Hepatocellular adenoma, multiple								X	X									X							X
Mesentery						+		+	+										+						+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma															X										
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									
General Body System																									
None																									
Genital System																									
Clitoral gland	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma											X														
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal																									
Sarcoma stromal																	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 Primidone: 0 ppm

Number of Days on Study	728	728	728	728	728	728	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	237	240	243	244	245	246	003	004	010	013	014	024	025	026	029	031	033	035	038	039	042	047	048	049	050	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	M	M	+	+	+	45
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatoblastoma																			X							1
Hepatocellular carcinoma										X																3
Hepatocellular adenoma									X			X	X		X	X								X		8
Hepatocellular adenoma, multiple	X																X		X							7
Mesentery																										5
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma						X																				1
Parathyroid gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	45
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma		X																					X			3
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma																	X									1
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	47
Ovary	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cystadenoma								X													X					3
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal																							X			1
Sarcoma stromal																										1

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

Number of Days on Study	420	519	595	596	621	621	645	673	694	727	722	727	727	728	728	728	728	728	728	728	728	728	728	728	728
Carcass ID Number	201	223	241	220	205	212	218	207	216	208	222	227	230	202	206	209	211	215	217	219	221	228	232	234	236
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Lymph node							+																		
Lymph node, mandibular	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma			X	X																					
Subcutaneous tissue, hemangiosarcoma								X																	
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Maxilla, carcinoma, metastatic, harderian gland						X																			
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve							+																		
Spinal cord							+																		
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																			X		X				
Alveolar/bronchiolar carcinoma						X		X																	
Fibrosarcoma, metastatic, skin			X																						
Hepatocellular carcinoma, metastatic, liver																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye		+																							
Harderian gland		+				+											+			+					
Adenoma																	X			X					
Carcinoma		X				X																			
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant						X		X															X		

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

Number of Days on Study	728	728	728	728	728	728	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	237	240	243	244	245	246	003	004	010	013	014	024	025	026	029	031	033	035	038	039	042	047	048	049	050	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma								X																		1
Lymph node				+					+			+	+			+										6
Lymph node, mandibular	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma														X												1
Thymus	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	45
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma	X																									1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibrosarcoma																					X					3
Subcutaneous tissue, hemangiosarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Maxilla, carcinoma, metastatic, harderian gland																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve																										1
Spinal cord																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma										X														X		4
Alveolar/bronchiolar carcinoma										X	X															4
Fibrosarcoma, metastatic, skin																										1
Hepatocellular carcinoma, metastatic, liver										X																1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																										1
Harderian gland								+																		5
Adenoma								X																		3
Carcinoma																										2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant				X					X			X	X			X										8

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Primidone: 300 ppm

Number of Days on Study	613	673	690	701	718	720	724	726	727	727	727	727	727	727	727	727	727	727	727	727	727	727	727	728	728
Carcass ID Number	271	284	264	257	267	293	287	268	252	253	259	260	263	274	275	277	282	286	290	292	295	297	298	251	255
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatoblastoma					X																				
Hepatoblastoma, multiple																							X		
Hepatocellular carcinoma				X				X			X												X		
Hepatocellular carcinoma, multiple														X											
Hepatocellular adenoma					X																X	X			
Hepatocellular adenoma, multiple				X			X	X	X	X	X	X	X	X	X	X		X	X	X			X	X	X
Histiocytic sarcoma		X				X																			
Mesentery	+					+																		+	
Pancreas	+	+	+	+	A	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	M	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, adenoma																									
Adrenal medulla	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	A	+	+	A	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	M	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Pituitary gland	+	+	+	+	A	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma		X																							
Pars distalis, adenoma																	X				X				X
Thyroid gland	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									
General Body System																									
None																									
Genital System																									
Clitoral gland	M	+	M	M	A	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Histiocytic sarcoma		X																							
Uterus	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma		X																							
Polyp stromal									X	X															

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Primidone: 300 ppm

Number of Days on Study	728	728	728	728	728	728	728	728	728	728	728	728	728	728	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	256	262	265	266	269	270	279	280	281	283	285	288	291	299	254	258	261	272	273	276	278	289	294	296	300	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatoblastoma			X									X														3
Hepatoblastoma, multiple																										1
Hepatocellular carcinoma												X			X					X						7
Hepatocellular carcinoma, multiple			X	X							X															4
Hepatocellular adenoma																			X			X				5
Hepatocellular adenoma, multiple	X	X	X	X		X			X	X	X	X	X	X	X	X	X	X		X	X		X	X	X	37
Histiocytic sarcoma																										2
Mesentery						+							+													5
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Capsule, adenoma								X																		1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Parathyroid gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	44
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Histiocytic sarcoma																										1
Pars distalis, adenoma	X																						X			5
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Follicular cell, adenoma										X																1
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma						X																				1
Histiocytic sarcoma																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Polyp stromal					X																					3

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Primidone: 300 ppm

Number of Days on Study	613	673	690	701	718	720	724	726	727	727	727	727	727	727	727	727	727	727	727	727	727	727	727	728	728
Carcass ID Number	271	284	264	257	267	293	287	268	252	253	259	260	263	274	275	277	282	286	290	292	295	297	298	251	255
Hematopoietic System																									
Bone marrow	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma		X																							
Lymph node						+	+	+			+							+							
Deep cervical, alveolar/bronchiolar carcinoma, metastatic, lung											X														
Lumbar, histiocytic sarcoma						X																			
Renal, histiocytic sarcoma						X																			
Lymph node, mandibular	+	M	+	+	A	+	+	+	M	M	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+
Histiocytic sarcoma						X																			
Lymph node, mesenteric	+	M	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma						X																			
Spleen	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma						X																			
Thymus	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Histiocytic sarcoma						X																			
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma																									
Subcutaneous tissue, hemangiosarcoma								X																	
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma														X											
Alveolar/bronchiolar carcinoma											X		X												
Hepatoblastoma, metastatic, liver					X																				
Histiocytic sarcoma						X																			
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland								+	+																
Adenoma								X	X																
Urinary System																									
Kidney	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma		X				X																			
Lymphoma malignant							X	X										X							

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Primidone: 300 ppm

Number of Days on Study	728	728	728	728	728	728	728	728	728	728	728	728	728	728	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	256	262	265	266	269	270	279	280	281	283	285	288	291	299	254	258	261	272	273	276	278	289	294	296	300	Total Tissues/ Tumors
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Lymph node													+			+							+			8
Deep cervical, alveolar/bronchiolar carcinoma, metastatic, lung																										1
Lumbar, histiocytic sarcoma																										1
Renal, histiocytic sarcoma																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Histiocytic sarcoma																										1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Histiocytic sarcoma																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Histiocytic sarcoma																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Histiocytic sarcoma																										1
Integumentary System																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibrosarcoma				X					X																	2
Subcutaneous tissue, hemangiosarcoma																										1
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma													X													2
Alveolar/bronchiolar carcinoma								X																		3
Hepatoblastoma, metastatic, liver																										1
Histiocytic sarcoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																											
Harderian gland		+									+										+					5
Adenoma		X									X										X					5
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										2
Lymphoma malignant													X			X							X			6

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Primidone: 600 ppm

Number of Days on Study	498	677	680	694	699	727	727	727	727	727	727	727	727	727	727	727	727	727	727	727	727	727	727	727	727
Carcass ID Number	346	329	303	316	317	302	305	306	309	313	314	315	323	324	325	332	334	338	339	343	344	345	347	350
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																						X			
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin				X																					
Hemangiosarcoma															X										
Hepatoblastoma		X													X										
Hepatoblastoma, multiple																									
Hepatocellular carcinoma					X	X							X	X	X	X			X						X
Hepatocellular carcinoma, multiple																							X		
Hepatocellular adenoma					X		X			X															
Hepatocellular adenoma, multiple			X			X		X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Histiocytic sarcoma																		X							
Mesentery	+											+				+		+							
Histiocytic sarcoma																		X							
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	+	M	M	M	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma				X			X																	X	
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																									
None																									
Genital System																									
Clitoral gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma															X										
Histiocytic sarcoma																		X							
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																		X							
Polyp stromal																									
Cervix, histiocytic sarcoma																		X							

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Primidone: 600 ppm

Number of Days on Study	728	728	728	728	728	728	728	728	728	728	728	728	729	729	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	311	312	318	320	321	326	327	328	330	335	342	348	301	304	307	308	310	319	322	331	333	336	340	341	349		Total Tissues/ Tumors
Alimentary System																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Squamous cell carcinoma																											1
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+		47
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Fibrosarcoma, metastatic, skin																											1
Hemangiosarcoma																											1
Hepatoblastoma												X															3
Hepatoblastoma, multiple													X														1
Hepatocellular carcinoma				X	X					X	X	X								X							14
Hepatocellular carcinoma, multiple	X						X						X												X		5
Hepatocellular adenoma				X													X					X					6
Hepatocellular adenoma, multiple	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X		X	X	X		39
Histiocytic sarcoma																											1
Mesentery										+		+															6
Histiocytic sarcoma																											1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Cardiovascular System																											
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Endocrine System																											
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Adenoma	X																										1
Parathyroid gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+		42
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Pars distalis, adenoma							X					X								X							6
Thyroid gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
General Body System																											
None																											
Genital System																											
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Cystadenoma			X																								2
Histiocytic sarcoma																											1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Histiocytic sarcoma																											1
Polyp stromal																				X							1
Cervix, histiocytic sarcoma																											1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Primidone: 600 ppm

Number of Days on Study	498	677	680	694	699	727	727	727	727	727	727	727	727	727	727	727	727	727	727	727	727	727	727	727	727
Carcass ID Number	346	329	303	316	317	302	305	306	309	313	314	315	323	324	325	332	334	338	339	343	344	345	347	350
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node			+		+							+													
Lymph node, mandibular	M	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+
Histiocytic sarcoma																		X							
Lymph node, mesenteric	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Histiocytic sarcoma																		X							
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																		X							
Thymus	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin				X																					
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma				X																					
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma						X																			X
Alveolar/bronchiolar adenoma, multiple					X																				
Fibrosarcoma, metastatic, skin				X																					
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pleura																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland																									
Adenoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																		X							
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																		X							
Lymphoma malignant			X		X																				

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Primidone: 600 ppm

Number of Days on Study	728	728	728	728	728	728	728	728	728	728	728	728	729	729	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	311	312	318	320	321	326	327	328	330	335	342	348	301	304	307	308	310	319	322	331	333	336	340	341	349		Total Tissues/ Tumors
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Lymph node				+	+				+													+					7
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		45
Histiocytic sarcoma																											1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		47
Histiocytic sarcoma																											1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Histiocytic sarcoma																											1
Thymus	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+		44
Fibrosarcoma, metastatic, skin																											1
Integumentary System																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Subcutaneous tissue, fibrosarcoma																											1
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Alveolar/bronchiolar adenoma			X																								3
Alveolar/bronchiolar adenoma, multiple																											1
Fibrosarcoma, metastatic, skin																											1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Pleura										+																	1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Special Senses System																											
Harderian gland					+									+			+										3
Adenoma					X									X			X										3
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Histiocytic sarcoma																											1
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Histiocytic sarcoma																											1
Lymphoma malignant				X	X				X				X		X										X		8

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Primidone: 1,300 ppm

Number of Days on Study	583	597	631	638	673	673	673	673	677	693	721	727	727	727	727	727	727	727	727	727	727	727	727	727	727
Carcass ID Number	372	386	382	387	381	387	388	396	366	393	365	351	352	355	356	358	362	363	364	368	369	374	378	384	391
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatoblastoma								X																	
Hepatocellular carcinoma				X		X	X			X		X										X	X		X
Hepatocellular carcinoma, multiple					X				X				X	X	X			X	X	X	X				
Hepatocellular adenoma			X	X							X										X				
Hepatocellular adenoma, multiple	X	X				X	X	X		X		X	X	X	X	X	X	X	X	X		X	X	X	X
Mesentery			+					+																	
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	M	+	+	+	+	+	+	+	M
Pituitary gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+
Pars distalis, adenoma													X						X						
Pars intermedia, adenoma																									X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma							X																		
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma																						X			
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal																									

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Primidone: 1,300 ppm

Number of Days on Study	727	727	727	728	728	728	728	728	728	728	728	728	728	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	392	395	399	359	360	367	371	375	376	383	385	394	400	353	354	357	361	370	373	379	380	389	390	397	398	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatoblastoma							X							X			X									4
Hepatocellular carcinoma			X			X				X					X		X									13
Hepatocellular carcinoma, multiple	X	X			X		X	X			X	X	X	X				X		X	X	X	X	X	X	25
Hepatocellular adenoma															X											5
Hepatocellular adenoma, multiple	X	X	X	X	X	X		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	42
Mesentery																										2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	43
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pars distalis, adenoma		X			X										X									X		6
Pars intermedia, adenoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma															X											2
General Body System																										
None																										
Genital System																										
Clitoral gland	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cystadenoma																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal																X										1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Primidone: 1,300 ppm

Number of Days on Study	583	597	631	638	673	673	673	673	677	693	721	727	727	727	727	727	727	727	727	727	727	727	727	727	727
Carcass ID Number	372	386	382	377	381	387	388	396	366	393	365	351	352	355	356	358	362	363	364	368	369	374	378	384	391
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node																						+			
Lymph node, mandibular	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Integumentary System																									
Mammary gland	M	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma	X			X																					
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																									
Fibrosarcoma, metastatic, skin	X																								
Hepatoblastoma, metastatic, liver																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland																									
Adenoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant										X												X	X		

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Primidone: 1,300 ppm

Number of Days on Study	727	727	727	728	728	728	728	728	728	728	728	728	728	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	392	395	399	359	360	367	371	375	376	383	385	394	400	353	354	357	361	370	373	379	380	389	390	397	398	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node		+												+			+									4
Lymph node, mandibular	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	46
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	47
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	M	+	+	+	M	M	+	M	+	+	+	+	+	+	+	+	+	+	+	44
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibrosarcoma																										2
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma				X														X								2
Alveolar/bronchiolar carcinoma										X																1
Fibrosarcoma, metastatic, skin																										1
Hepatoblastoma, metastatic, liver							X																			1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Harderian gland																						+				1
Adenoma																						X				1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant			X																		X					5

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

	0 ppm	300 ppm	600 ppm	1,300 ppm
Harderian Gland: Adenoma				
Overall rate[a]	3/50 (6%)	5/50 (10%)	3/49 (6%)	1/50 (2%)
Adjusted rate[b]	7.3%	11.6%	6.8%	2.6%
Terminal rate[c]	3/41 (7%)	4/42 (10%)	3/44 (7%)	1/39 (3%)
First incidence (days)	727 (T)	726	727 (T)	727 (T)
Life table test[d]	P=0.168N	P=0.372	P=0.630N	P=0.323N
Logistic regression test[d]	P=0.167N	P=0.399	P=0.630N	P=0.323N
Cochran-Armitage test[d]	P=0.155N			
Fisher exact test[d]		P=0.357	P=0.651	P=0.309N
Harderian Gland: Adenoma or Carcinoma				
Overall rate	5/50 (10%)	5/50 (10%)	3/49 (6%)	1/50 (2%)
Adjusted rate	11.2%	11.6%	6.8%	2.6%
Terminal rate	3/41 (7%)	4/42 (10%)	3/44 (7%)	1/39 (3%)
First incidence (days)	519	726	727 (T)	727 (T)
Life table test	P=0.064N	P=0.609N	P=0.329N	P=0.113N
Logistic regression test	P=0.064N	P=0.534	P=0.444N	P=0.134N
Cochran-Armitage test	P=0.058N			
Fisher exact test		P=0.630N	P=0.369N	P=0.102N
Liver: Hepatocellular Adenoma				
Overall rate	15/50 (30%)	42/50 (84%)	45/49 (92%)	47/50 (94%)
Adjusted rate	34.9%	91.3%	97.8%	97.9%
Terminal rate	13/41 (32%)	38/42 (90%)	43/44 (98%)	38/39 (97%)
First incidence (days)	673	701	680	583
Life table test	P<0.001	P<0.001	P<0.001	P<0.001
Logistic regression test	P<0.001	P<0.001	P<0.001	P<0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		P<0.001	P<0.001	P<0.001
Liver: Hepatocellular Carcinoma				
Overall rate	3/50 (6%)	11/50 (22%)	19/49 (39%)	38/50 (76%)
Adjusted rate	7.1%	24.9%	42.2%	84.4%
Terminal rate	2/41 (5%)	9/42 (21%)	18/44 (41%)	32/39 (82%)
First incidence (days)	694	701	699	638
Life table test	P<0.001	P=0.029	P<0.001	P<0.001
Logistic regression test	P<0.001	P=0.032	P<0.001	P<0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		P=0.020	P<0.001	P<0.001
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	16/50 (32%)	42/50 (84%)	45/49 (92%)	50/50 (100%)
Adjusted rate	37.2%	91.3%	97.8%	100.0%
Terminal rate	14/41 (34%)	38/42 (90%)	43/44 (98%)	39/39 (100%)
First incidence (days)	673	701	680	583
Life table test	P<0.001	P<0.001	P<0.001	P<0.001
Logistic regression test	P<0.001	P<0.001	P<0.001	P<0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		P<0.001	P<0.001	P<0.001

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

	0 ppm	300 ppm	600 ppm	1,300 ppm
Liver: Hepatoblastoma				
Overall rate	1/50 (2%)	4/50 (8%)	4/49 (8%)	4/50 (8%)
Adjusted rate	2.4%	9.2%	8.8%	9.7%
Terminal rate	1/41 (2%)	3/42 (7%)	3/44 (7%)	3/39 (8%)
First incidence (days)	727 (T)	718	677	673
Life table test	P=0.199	P=0.195	P=0.208	P=0.174
Logistic regression test	P=0.220	P=0.212	P=0.182	P=0.185
Cochran-Armitage test	P=0.220			
Fisher exact test		P=0.181	P=0.175	P=0.181
Liver: Hepatocellular Carcinoma or Hepatoblastoma				
Overall rate	4/50 (8%)	12/50 (24%)	20/49 (41%)	39/50 (78%)
Adjusted rate	9.5%	26.5%	43.4%	84.7%
Terminal rate	3/41 (7%)	9/42 (21%)	18/44 (41%)	32/39 (82%)
First incidence (days)	694	701	677	638
Life table test	P<0.001	P=0.040	P<0.001	P<0.001
Logistic regression test	P<0.001	P=0.042	P<0.001	P<0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		P=0.027	P<0.001	P<0.001
Liver: Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma				
Overall rate	16/50 (32%)	42/50 (84%)	46/49 (94%)	50/50 (100%)
Adjusted rate	37.2%	91.3%	97.9%	100.0%
Terminal rate	14/41 (34%)	38/42 (90%)	43/44 (98%)	39/39 (100%)
First incidence (days)	673	701	677	583
Life table test	P<0.001	P<0.001	P<0.001	P<0.001
Logistic regression test	P<0.001	P<0.001	P<0.001	P<0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		P<0.001	P<0.001	P<0.001
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	4/50 (8%)	2/50 (4%)	4/49 (8%)	2/50 (4%)
Adjusted rate	9.8%	4.8%	8.9%	5.1%
Terminal rate	4/41 (10%)	2/42 (5%)	3/44 (7%)	2/39 (5%)
First incidence (days)	727 (T)	727 (T)	699	727 (T)
Life table test	P=0.369N	P=0.326N	P=0.602N	P=0.360N
Logistic regression test	P=0.355N	P=0.326N	P=0.608N	P=0.360N
Cochran-Armitage test	P=0.345N			
Fisher exact test		P=0.339N	P=0.631	P=0.339N
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	4/50 (8%)	3/50 (6%)	0/49 (0%)	1/50 (2%)
Adjusted rate	9.1%	7.1%	0.0%	2.6%
Terminal rate	2/41 (5%)	3/42 (7%)	0/44 (0%)	1/39 (3%)
First incidence (days)	621	727 (T)	—[e]	727 (T)
Life table test	P=0.087N	P=0.476N	P=0.057N	P=0.186N
Logistic regression test	P=0.088N	P=0.543N	P=0.079N	P=0.192N
Cochran-Armitage test	P=0.084N			
Fisher exact test		P=0.500N	P=0.061N	P=0.181N

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

	0 ppm	300 ppm	600 ppm	1,300 ppm
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	7/50 (14%)	5/50 (10%)	4/49 (8%)	3/50 (6%)
Adjusted rate	16.1%	11.9%	8.9%	7.7%
Terminal rate	5/41 (12%)	5/42 (12%)	3/44 (7%)	3/39 (8%)
First incidence (days)	621	727 (T)	699	727 (T)
Life table test	P=0.140N	P=0.356N	P=0.227N	P=0.174N
Logistic regression test	P=0.124N	P=0.372N	P=0.276N	P=0.154N
Cochran-Armitage test	P=0.126N			
Fisher exact test		P=0.380N	P=0.274N	P=0.159N
Ovary: Cystadenoma				
Overall rate	3/49 (6%)	0/49 (0%)	2/48 (4%)	1/50 (2%)
Adjusted rate	7.5%	0.0%	4.5%	2.6%
Terminal rate	3/40 (8%)	0/42 (0%)	2/44 (5%)	1/39 (3%)
First incidence (days)	727 (T)	—	727 (T)	727 (T)
Life table test	P=0.359N	P=0.113N	P=0.456N	P=0.314N
Logistic regression test	P=0.359N	P=0.113N	P=0.456N	P=0.314N
Cochran-Armitage test	P=0.343N			
Fisher exact test		P=0.121N	P=0.510N	P=0.301N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	3/49 (6%)	5/48 (10%)	6/49 (12%)	6/48 (13%)
Adjusted rate	7.5%	12.2%	13.3%	15.8%
Terminal rate	3/40 (8%)	5/41 (12%)	5/44 (11%)	6/38 (16%)
First incidence (days)	727 (T)	727 (T)	694	727 (T)
Life table test	P=0.190	P=0.369	P=0.293	P=0.216
Logistic regression test	P=0.199	P=0.369	P=0.286	P=0.216
Cochran-Armitage test	P=0.216			
Fisher exact test		P=0.346	P=0.243	P=0.233
Skin (Subcutaneous Tissue): Fibrosarcoma				
Overall rate	3/50 (6%)	2/50 (4%)	1/49 (2%)	2/50 (4%)
Adjusted rate	6.5%	4.8%	2.2%	4.1%
Terminal rate	1/41 (2%)	2/42 (5%)	0/44 (0%)	0/39 (0%)
First incidence (days)	595	727 (T)	694	583
Life table test	P=0.434N	P=0.484N	P=0.293N	P=0.489N
Logistic regression test	P=0.358N	P=0.660N	P=0.428N	P=0.683
Cochran-Armitage test	P=0.427N			
Fisher exact test		P=0.500N	P=0.316N	P=0.500N
Uterus: Stromal Polyp				
Overall rate	1/50 (2%)	3/50 (6%)	1/49 (2%)	1/50 (2%)
Adjusted rate	2.4%	7.1%	2.3%	2.6%
Terminal rate	1/41 (2%)	3/42 (7%)	1/44 (2%)	1/39 (3%)
First incidence (days)	727 (T)	727 (T)	727 (T)	727 (T)
Life table test	P=0.468N	P=0.314	P=0.746N	P=0.751
Logistic regression test	P=0.468N	P=0.314	P=0.746N	P=0.751
Cochran-Armitage test	P=0.449N			
Fisher exact test		P=0.309	P=0.747	P=0.753N

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

	0 ppm	300 ppm	600 ppm	1,300 ppm
Uterus: Stromal Polyp or Stromal Sarcoma				
Overall rate	2/50 (4%)	3/50 (6%)	1/49 (2%)	1/50 (2%)
Adjusted rate	4.9%	7.1%	2.3%	2.6%
Terminal rate	2/41 (5%)	3/42 (7%)	1/44 (2%)	1/39 (3%)
First incidence (days)	727 (T)	727 (T)	727 (T)	727 (T)
Life table test	P=0.303N	P=0.511	P=0.475N	P=0.518N
Logistic regression test	P=0.303N	P=0.511	P=0.475N	P=0.517N
Cochran-Armitage test	P=0.289N			
Fisher exact test		P=0.500	P=0.508N	P=0.500N
All Organs: Hemangioma or Hemangiosarcoma				
Overall rate	3/50 (6%)	2/50 (4%)	1/49 (2%)	0/50 (0%)
Adjusted rate	7.1%	4.7%	2.3%	0.0%
Terminal rate	2/41 (5%)	1/42 (2%)	1/44 (2%)	0/39 (0%)
First incidence (days)	673	726	727 (T)	—
Life table test	P=0.069N	P=0.478N	P=0.279N	P=0.125N
Logistic regression test	P=0.065N	P=0.487N	P=0.305N	P=0.119N
Cochran-Armitage test	P=0.067N			
Fisher exact test		P=0.500N	P=0.316N	P=0.121N
All Organs: Malignant Lymphoma				
Overall rate	8/50 (16%)	6/50 (12%)	8/49 (16%)	5/50 (10%)
Adjusted rate	18.4%	13.6%	17.4%	12.4%
Terminal rate	6/41 (15%)	4/42 (10%)	6/44 (14%)	4/39 (10%)
First incidence (days)	621	724	680	693
Life table test	P=0.311N	P=0.361N	P=0.542N	P=0.301N
Logistic regression test	P=0.272N	P=0.368N	P=0.597	P=0.268N
Cochran-Armitage test	P=0.275N			
Fisher exact test		P=0.387N	P=0.590	P=0.277N
All Organs: Benign Neoplasms				
Overall rate	26/50 (52%)	45/50 (90%)	46/49 (94%)	47/50 (94%)
Adjusted rate	60.5%	97.8%	97.9%	97.9%
Terminal rate	24/41 (59%)	41/42 (98%)	43/44 (98%)	38/39 (97%)
First incidence (days)	673	701	680	583
Life table test	P<0.001	P<0.001	P<0.001	P<0.001
Logistic regression test	P<0.001	P<0.001	P<0.001	P<0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		P<0.001	P<0.001	P<0.001
All Organs: Malignant Neoplasms				
Overall rate	20/50 (40%)	23/50 (46%)	26/49 (53%)	40/50 (80%)
Adjusted rate	42.3%	47.9%	54.2%	85.0%
Terminal rate	14/41 (34%)	17/42 (40%)	22/44 (50%)	32/39 (82%)
First incidence (days)	519	673	677	583
Life table test	P<0.001	P=0.421	P=0.271	P<0.001
Logistic regression test	P<0.001	P=0.288	P=0.080	P<0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		P=0.343	P=0.135	P<0.001

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

	0 ppm	300 ppm	600 ppm	1,300 ppm
All Organs: Benign or Malignant Neoplasms				
Overall rate	34/50 (68%)	47/50 (94%)	47/49 (96%)	50/50 (100%)
Adjusted rate	72.2%	97.9%	97.9%	100.0%
Terminal rate	28/41 (68%)	41/42 (98%)	43/44 (98%)	39/39 (100%)
First incidence (days)	519	673	677	583
Life table test	P<0.001	P=0.014	P=0.025	P<0.001
Logistic regression test	P<0.001	P=0.003	P<0.001	P<0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		P<0.001	P<0.001	P<0.001

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for liver, lung, ovary, and pituitary gland; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence are the P values 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 life table test regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in an exposure group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group

TABLE D4
Historical Incidence of Liver Neoplasms in Untreated Female B6C3F$_1$ Mice[a]

Study	Incidence in Controls			
	Hepatocellular Adenoma	Hepatocellular Carcinoma	Hepatoblastoma	Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma
Historical Incidence at Battelle Columbus Laboratories				
4,4′-Thiobis(6-*t*-butyl-*m*-cresol)	17/51	4/51	0/51	20/51
5,5-Diphenylhydantoin	5/48	0/48	0/48	5/48
Pentachlorophenol (Dowicide EC-7)	1/34	0/34	0/34	1/34
Ethylene Thiourea	2/50	2/50	0/50	4/50
Polybrominated Biphenyls (Firemaster FF-1®)	4/50	1/50	0/50	5/50
Manganese (II) Sulfate Monohydrate	12/51	3/51	0/51	13/51
Oxazepam	25/50	9/50	0/50	28/50
Pentachlorophenol (Technical Grade)	3/33	0/33	0/33	3/33
Triamterene	10/50	4/50	0/50	13/50
Triamterene	7/50	5/50	0/50	10/50
Tricresyl Phosphate	12/50	10/50	0/50	21/50
Overall Historical Incidence				
Total	213/1,464 (15.8%)	108/1,464 (7.4%)	1/1,464 (0.1%)	313/1,464 (21.4%)
Standard deviation	10.6%	6.1%	0.4%	13.0%
Range	2%-50%	0%-20%	0%-2%	3%-56%

[a] Data as of 12 May 1995

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of Primidone[a]

	0 ppm	300 ppm	600 ppm	1,300 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	7	1	3	8
Natural deaths	2	7	2	3
Survivors				
Terminal sacrifice	41	42	44	39
Missing			1	
Animals examined microscopically	50	50	49	50
Alimentary System				
Intestine small, duodenum	(50)	(49)	(49)	(50)
Ulcer, chronic, focal				1 (2%)
Intestine small, jejunum	(50)	(49)	(49)	(50)
Peyer's patch, hyperplasia, lymphoid	1 (2%)			
Serosa, inflammation, chronic, granulomatous	1 (2%)			
Liver	(50)	(50)	(49)	(50)
Angiectasis	1 (2%)			
Basophilic focus	1 (2%)	1 (2%)		1 (2%)
Clear cell focus	1 (2%)	4 (8%)	1 (2%)	4 (8%)
Congestion			1 (2%)	
Eosinophilic focus	8 (16%)	23 (46%)	24 (49%)	17 (34%)
Hematopoietic cell proliferation	3 (6%)	2 (4%)	2 (4%)	
Inflammation, chronic			1 (2%)	
Mixed cell focus	1 (2%)	1 (2%)		
Necrosis	4 (8%)		2 (4%)	3 (6%)
Thrombosis, diffuse	1 (2%)			
Centrilobular, hypertrophy	1 (2%)	11 (22%)	11 (22%)	21 (42%)
Centrilobular, necrosis	1 (2%)			
Hepatocyte, vacuolization cytoplasmic	3 (6%)	35 (70%)	39 (80%)	28 (56%)
Mesentery	(5)	(5)	(6)	(2)
Fat, inflammation, chronic	4 (80%)	5 (100%)	5 (83%)	2 (100%)
Pancreas	(50)	(48)	(49)	(50)
Inflammation, chronic	1 (2%)			
Acinus, atrophy	2 (4%)	2 (4%)	1 (2%)	1 (2%)
Duct, cyst				1 (2%)
Salivary glands	(50)	(48)	(49)	(50)
Duct, cyst				1 (2%)
Stomach, forestomach	(50)	(49)	(49)	(50)
Hyperplasia, focal, squamous	4 (8%)	11 (22%)	3 (6%)	7 (14%)
Stomach, glandular	(50)	(49)	(49)	(50)
Necrosis, focal				1 (2%)
Polyp, inflammatory		1 (2%)		
Cardiovascular System				
Blood vessel	(50)	(49)	(49)	(50)
Inflammation, chronic	1 (2%)			

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

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of Primidone

	0 ppm	300 ppm	600 ppm	1,300 ppm
Endocrine System				
Adrenal cortex	(50)	(49)	(49)	(50)
Hematopoietic cell proliferation		1 (2%)		
Hyperplasia, focal	1 (2%)			
Hypertrophy, focal		2 (4%)	2 (4%)	1 (2%)
Capsule, hyperplasia	2 (4%)		1 (2%)	
Zona reticularis, angiectasis, focal	1 (2%)			
Zona reticularis, vacuolization cytoplasmic				1 (2%)
Adrenal medulla	(50)	(49)	(49)	(50)
Hyperplasia			1 (2%)	
Islets, pancreatic	(50)	(47)	(49)	(50)
Hyperplasia	15 (30%)	17 (36%)	6 (12%)	5 (10%)
Pituitary gland	(49)	(48)	(49)	(48)
Pars distalis, angiectasis	1 (2%)		1 (2%)	
Pars distalis, hemorrhage	1 (2%)			
Pars distalis, hyperplasia	13 (27%)	12 (25%)	19 (39%)	10 (21%)
Pars intermedia, hyperplasia			1 (2%)	1 (2%)
Rathke's cleft, cyst			1 (2%)	
Thyroid gland	(50)	(48)	(48)	(50)
Inflammation, chronic				1 (2%)
Follicle, cyst		1 (2%)		
Follicular cell, hyperplasia	13 (26%)	12 (25%)	28 (58%)	49 (98%)
General Body System				
None				
Genital System				
Clitoral gland	(47)	(45)	(48)	(48)
Inflammation, chronic				1 (2%)
Ovary	(49)	(49)	(48)	(50)
Angiectasis	1 (2%)			
Atrophy	37 (76%)	47 (96%)	39 (81%)	42 (84%)
Hematocyst	5 (10%)		1 (2%)	1 (2%)
Hemorrhage		1 (2%)		
Hyperplasia, cystic			1 (2%)	
Inflammation, chronic, granulomatous	1 (2%)			
Follicle, cyst	12 (24%)	7 (14%)	9 (19%)	9 (18%)
Periovarian tissue, cyst		2 (4%)		
Uterus	(50)	(49)	(49)	(50)
Angiectasis	1 (2%)			
Hydrometra	28 (56%)	23 (47%)	17 (35%)	20 (40%)
Inflammation, suppurative		2 (4%)	2 (4%)	
Endometrium, hyperplasia, cystic	36 (72%)	39 (80%)	42 (86%)	42 (84%)
Endometrium, inflammation, chronic active		1 (2%)		
Hematopoietic System				
Bone marrow	(50)	(49)	(49)	(50)
Depletion cellular	1 (2%)			
Myelofibrosis, focal			1 (2%)	
Myeloid cell, hyperplasia	1 (2%)	1 (2%)	3 (6%)	2 (4%)

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of Primidone

	0 ppm	300 ppm	600 ppm	1,300 ppm
Hematopoietic System (continued)				
Lymph node	(6)	(8)	(7)	(4)
Lumbar, infiltration cellular, histiocyte	1 (17%)		1 (14%)	
Lumbar, pigmentation	1 (17%)			
Mediastinal, hyperplasia, lymphoid			1 (14%)	3 (75%)
Renal, infiltration cellular, histiocyte			1 (14%)	
Lymph node, mandibular	(48)	(44)	(45)	(46)
Cyst		1 (2%)		
Hyperplasia, lymphoid	1 (2%)	1 (2%)		2 (4%)
Infiltration cellular, plasma cell	1 (2%)			
Infiltration cellular, histiocyte			1 (2%)	
Lymph node, mesenteric	(48)	(48)	(47)	(47)
Hematopoietic cell proliferation		1 (2%)		
Hyperplasia, lymphoid	5 (10%)	2 (4%)		4 (9%)
Spleen	(50)	(48)	(49)	(50)
Atrophy				1 (2%)
Hematopoietic cell proliferation	14 (28%)	13 (27%)	13 (27%)	23 (46%)
Hyperplasia, lymphoid	5 (10%)	5 (10%)	7 (14%)	4 (8%)
Thrombosis		1 (2%)		
Thymus	(45)	(47)	(44)	(44)
Angiectasis			1 (2%)	
Atrophy	30 (67%)	35 (74%)	37 (84%)	35 (80%)
Hyperplasia, lymphoid	6 (13%)	5 (11%)	3 (7%)	2 (5%)
Integumentary System				
Skin	(50)	(50)	(49)	(50)
Inflammation, chronic active	1 (2%)			
Ulcer, chronic active			1 (2%)	
Subcutaneous tissue, cyst, chronic active				1 (2%)
Subcutaneous tissue, edema		1 (2%)		
Musculoskeletal System				
None				
Nervous System				
None				
Respiratory System				
Lung	(50)	(50)	(49)	(50)
Alveolar epithelium, hyperplasia, focal	2 (4%)	3 (6%)		1 (2%)
Special Senses System				
Eye	(1)			
Retina, atrophy	1 (100%)			

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of Primidone

	0 ppm	300 ppm	600 ppm	1,300 ppm
Urinary System				
Kidney	(50)	(49)	(49)	(50)
Cyst			1 (2%)	
Hydronephrosis			1 (2%)	
Infiltration cellular, lymphocyte	1 (2%)			2 (4%)
Nephropathy	7 (14%)	3 (6%)	6 (12%)	3 (6%)
Renal tubule, pigmentation, hemosiderin	1 (2%)		1 (2%)	1 (2%)

APPENDIX E
GENETIC TOXICOLOGY

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GENETIC TOXICOLOGY

SALMONELLA TYPHIMURIUM MUTAGENICITY TEST PROTOCOL

Testing was performed as reported by Mortelmans *et al.* (1986). Primidone was sent to the laboratory as a coded aliquot from Radian Corporation (Austin, TX). It was incubated with the *Salmonella typhimurium* tester strains (TA98, TA100, TA1535, and TA1537) either in buffer or S9 mix (metabolic activation enzymes and cofactors from Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver) for 20 minutes at 37° C. Top agar supplemented with *l*-histidine and *d*-biotin was added, and the contents of the tubes were mixed and poured onto the surfaces of minimal glucose agar plates. Histidine-independent mutant colonies arising on these plates were counted following incubation for 2 days at 37° C.

Each trial consisted of triplicate plates of concurrent positive and negative controls and of at least three doses of primidone. The high dose was limited by experimental design to 10,000 μg/plate. All trials were repeated.

In this assay, a positive response is defined as a reproducible, dose-related increase in histidine-independent (revertant) colonies in any one strain/activation combination. An equivocal response is defined as an increase in revertants that is not dose related, not reproducible, or is not of sufficient magnitude to support a determination of mutagenicity. A negative response is obtained when no increase in revertant colonies is observed following chemical treatment. There was no minimum percentage or fold increase required for a chemical to be judged positive or weakly positive.

CHINESE HAMSTER OVARY CELL CYTOGENETICS PROTOCOLS

Testing was performed as reported by Galloway *et al.* (1987). Primidone was sent to the laboratory as a coded aliquot by Radian Corporation. It was tested in cultured Chinese hamster ovary (CHO) cells for induction of sister chromatid exchanges (SCEs) and chromosomal aberrations (Abs) both in the presence and absence of Aroclor 1254-induced male Sprague-Dawley rat liver S9 and cofactor mix. Cultures were handled under gold lights to prevent photolysis of bromodeoxyuridine-substituted DNA. Each test consisted of concurrent solvent and positive controls and three doses of primidone; the high dose was limited by toxicity. A single flask per dose was used.

Sister Chromatid Exchange Test: In the SCE test without S9, CHO cells were incubated for 26 hours with primidone in McCoy's 5A medium. Bromodeoxyuridine (BrdU) was added 2 hours after culture initiation. After 26 hours, the medium containing primidone was removed and replaced with fresh medium plus BrdU and Colcemid, and incubation was continued for 2 hours. Cells were then harvested by mitotic shake-off, fixed, and stained with Hoechst 33258 and Giemsa. In the SCE test with S9, cells were incubated with primidone, serum-free medium, and S9 for 2 hours. The medium was then removed and replaced with medium containing serum and BrdU and no primidone and incubation proceeded for an additional 26 hours, with Colcemid present for the final 2 hours. Harvesting and staining were the same as for cells treated without S9. All slides were scored blind and those from a single test were read by the same person. Fifty second-division metaphase cells were scored for frequency of SCE/cell from each dose level. Because significant chemical-induced cell cycle delay was seen, incubation time was lengthened to ensure a sufficient number of scorable (second-division metaphase) cells.

Statistical analyses were conducted on the slopes of the dose-response curves and the individual dose points (Galloway *et al.*, 1987). An SCE frequency 20% above the concurrent solvent control value was chosen as a statistically conservative positive response. The probability of this level of difference occurring by chance at one dose point is less than 0.01; the probability for such a chance occurrence at two dose points is less

than 0.001. An increase of 20% or greater at any single dose was considered weak evidence of activity; increases at two or more doses resulted in a determination that the trial was positive. A statistically significant trend ($P < 0.005$) in the absence of any responses reaching 20% above background led to a call of equivocal.

Chromosomal Aberrations Test: In the test without S9, cells were incubated in McCoy's 5A medium with primidone for 12 hours; Colcemid was added and incubation continued for 2 hours. The cells were then harvested by mitotic shake-off, fixed, and stained with Giemsa. For the Abs test with S9, cells were treated with primidone and S9 for 2 hours, after which the treatment medium was removed and the cells were incubated for 10.3 hours in fresh medium, with Colcemid present for the final 2 hours. Cells were harvested in the same manner as for the treatment without S9. The harvest time for the Abs test was based on the cell cycle information obtained in the SCE test: if cell cycle delay was anticipated, the incubation period was extended.

Cells were selected for scoring on the basis of good morphology and completeness of karyotype (21 ± 2 chromosomes). All slides were scored blind and those from a single test were read by the same person. Two hundred first-division metaphase cells were scored at each dose level. Classes of aberrations included simple (breaks and terminal deletions), complex (rearrangements and translocations), and other (pulverized cells, despiralized chromosomes, and cells containing 10 or more aberrations).

Chromosomal aberration data are presented as percentage of cells with aberrations. To arrive at a statistical call for a trial, analyses were conducted on both the dose response curve and individual dose points. For a single trial, a statistically significant ($P \leq 0.05$) difference for one dose point and a significant trend ($P \leq 0.015$) was considered weak evidence for a positive response; significant differences for two or more doses indicated the trial was positive. A positive trend in the absence of a statistically significant increase at any one dose resulted in an equivocal call (Galloway *et al.*, 1987). Ultimately, the trial calls were based on a consideration of the statistical analyses as well as the biological information available to the reviewers.

MOUSE BONE MARROW MICRONUCLEUS TEST PROTOCOL

Preliminary range-finding studies were performed. Factors affecting dose selection included chemical solubility and toxicity and the extent of cell cycle delay induced by primidone exposure. The standard three-exposure protocol is described in detail by Shelby *et al.* (1993). Male $B6C3F_1$ mice were injected intraperitoneally three times at 24-hour intervals with primidone dissolved in corn oil. The total dosing volume was 0.4 mL. Solvent control animals were injected with 0.4 mL of corn oil only. The positive control mice received injections of dimethybenzanthracene (12.5 mg/kg body weight). The mice were killed 24 hours after the final injection, and blood smears were prepared from bone marrow cells obtained from the femurs. Air-dried smears were fixed and stained; 2,000 polychromatic erythrocytes (PCEs) were scored for the frequency of micronucleated cells in each of up to five animals per dose group.

The results were tabulated as the mean of the pooled results from all animals within a treatment group plus or minus the standard error of the mean. The frequency of micronucleated cells among PCEs was analyzed by a statistical software package that tested for increasing trend over dose groups using a one-tailed Cochran-Armitage trend test, followed by pairwise comparisons between each dose group and the control group (Margolin and Risko, 1988). In the presence of excess binomial variation, as detected by a binomial dispersion test, the binomial variance of the Cochran-Armitage test was adjusted upward in proportion to the excess variation. In the micronucleus test, an individual trial was considered positive if the trend test P value was less than or equal to 0.025 or the P value for any single dose group was less than or equal to 0.025 divided by the number of dose groups. A final call of positive for micronucleus induction was preferably based on reproducibly positive trials (as noted above). Ultimately, the final call was determined

by the scientific staff after considering the results of statistical analyses, the reproducibility of any effects observed, and the magnitudes of those effects.

RESULTS

Primidone (33 to 10,000 μg/plate) induced mutations in *Salmonella typhimurium* strain TA1535 in trials conducted in the absence of exogenous metabolic activation (S9); no mutagenic response was detected in TA1535 with S9 (Mortelmans *et al.,* 1986; Table E1). Negative results were obtained in the *S. typhimurium* assay with strains TA98, TA100, and TA1537, with and without S9. No induction of SCEs (Table E2) or Abs (Table E3) was noted in cultured CHO cells treated with concentrations of primidone ranging from 125 to 1,250 μg/mL, with or without S9. *In vivo*, no significant increase was observed in the frequency of micronucleated PCEs in bone marrow of male mice treated with 87.5 to 350 mg primidone/kg body weight three times at 24-hour intervals in either of two trials (Table E4).

In summary, primidone induced gene mutations in *S. typhimurium* in the absence of S9 activation but did not induce chromosomal damage in mammalian cells, *in vitro* or *in vivo*, even at doses associated with marked toxicity.

TABLE E1
Mutagenicity of Primidone in *Salmonella typhimurium*[a]

Strain	Dose (μg/plate)	Revertants/plate[b] -S9 Trial 1	-S9 Trial 2	+10% hamster S9 Trial 1	+10% hamster S9 Trial 2	+10% rat S9 Trial 1	+10% rat S9 Trial 2
TA100	0	131 ± 2.1	123 ± 3.8	137 ± 14.4	121 ± 11.3	156 ± 9.0	127 ± 7.2
	33		136 ± 1.7		132 ± 6.1		128 ± 2.1
	100	153 ± 14.7		160 ± 12.7		157 ± 7.4	
	333	140 ± 2.4		120 ± 8.5		148 ± 0.7	
	1,000	148 ± 3.3	131 ± 1.5	153 ± 6.4	124 ± 4.4	155 ± 9.8	143 ± 2.6
	3,333	152 ± 3.7	143 ± 3.7	134 ± 8.2	117 ± 2.3	158 ± 2.0	136 ± 0.9
	6,666		135 ± 14.6		131 ± 3.4		131 ± 10.1
	10,000	177 ± 9.6	151 ± 6.9	164 ± 7.5	121 ± 11.2	147 ± 8.5	134 ± 13.4
Trial summary		Equivocal	Negative	Negative	Negative	Negative	Negative
Positive control[c]		325 ± 12.3	327 ± 2.2	2,147 ± 92.9	1,639 ± 24.4	839 ± 41.0	591 ± 30.6

Strain	Dose (μg/plate)	– S9 Trial 1	– S9 Trial 2	– S9 Trial 3	+10% hamster S9 Trial 1	+10% hamster S9 Trial 2
TA1535	0	23 ± 4.0	18 ± 4.4	19 ± 2.8	7 ± 1.2	10 ± 3.1
	33		28 ± 4.9		12 ± 2.4	
	100	28 ± 1.9			12 ± 0.0	
	333	22 ± 4.2		17 ± 2.0	5 ± 1.0	
	1,000	31 ± 3.0	30 ± 3.0	17 ± 2.2	9 ± 2.7	7 ± 0.7
	3,333	43 ± 0.7	39 ± 1.0	34 ± 4.2	8 ± 2.7	5 ± 1.5
	6,666		53 ± 5.3	44 ± 4.1	9 ± 1.8	
	10,000	47 ± 4.0	56 ± 5.2	54 ± 2.2	6 ± 1.2	10 ± 1.7
Trial summary		Weakly Positive	Positive	Positive	Negative	Negative
Positive control		288 ± 13.0	305 ± 14.2	385 ± 7.1	530 ± 28.3	342 ± 28.3

Strain	Dose (μg/plate)	+10% rat S9 Trial 1	+10% rat S9 Trial 2
TA1535 (continued)	0	6 ± 0.7	6 ± 0.9
	33		8 ± 0.9
	100	9 ± 2.0	
	333	9 ± 2.6	
	1,000	9 ± 3.5	10 ± 1.7
	3,333	8 ± 1.8	15 ± 1.8
	6,666		10 ± 3.2
	10,000	7 ± 0.6	10 ± 2.0
Trial summary		Negative	Negative
Positive control		183 ± 6.4	146 ± 7.5

TABLE E1
Mutagenicity of Primidone in *Salmonella typhimurium*

Strain	Dose (μg/plate)	Revertants/plate					
		-S9		+10% hamster S9		+10% rat S9	
		Trial 1	Trial 2	Trial 1	Trial 2	Trial 1	Trial 2
TA1537	0	4 ± 0.3	9 ± 1.8	6 ± 1.5	8 ± 0.9	8 ± 1.7	9 ± 0.9
	33		6 ± 0.9		14 ± 0.6		7 ± 1.2
	100	7 ± 3.2		8 ± 1.9		7 ± 0.0	
	333	6 ± 0.6		7 ± 2.2		8 ± 2.3	
	1,000	6 ± 3.2	9 ± 2.7	8 ± 3.2	13 ± 0.3	7 ± 0.7	11 ± 2.5
	3,333	4 ± 1.2	9 ± 2.0	9 ± 1.8	13 ± 2.6	6 ± 1.8	10 ± 1.5
	6,666		6 ± 1.8		9 ± 1.7		13 ± 0.0
	10,000	10 ± 2.3	5 ± 1.0	8 ± 3.2	11 ± 2.7	7 ± 1.3	12 ± 2.0
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		114 ± 13.6	150 ± 10.6	316 ± 36.2	546 ± 26.3	158 ± 27.3	133 ± 3.6
TA98	0	22 ± 2.5	23 ± 1.3	31 ± 3.5	30 ± 2.0	30 ± 5.5	26 ± 5.2
	33		15 ± 1.8		32 ± 5.7		31 ± 6.8
	100	18 ± 1.2		30 ± 4.5		31 ± 2.9	
	333	19 ± 0.7		34 ± 3.2		30 ± 3.0	
	1,000	13 ± 2.6	17 ± 2.0	31 ± 2.6	30 ± 1.2	26 ± 2.7	35 ± 2.2
	3,333	20 ± 3.3	20 ± 2.0	30 ± 1.8	37 ± 2.3	27 ± 3.1	37 ± 5.9
	6,666		19 ± 4.0		36 ± 2.9		26 ± 3.2
	10,000	18 ± 1.2	16 ± 4.4	36 ± 2.1	31 ± 6.4	29 ± 3.8	26 ± 1.2
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		809 ± 12.7	989 ± 15.5	1,919 ± 26.9	1,466 ± 63.4	585 ± 43.1	437 ± 19.6

[a] Study was performed at SRI International. The detailed protocol and these data are presented by Mortelmans *et al*. (1986).
[b] Revertants are presented as mean ± standard error from three plates.
[c] The positive controls in the absence of metabolic activation were sodium azide (TA100 and TA1535), 9-aminoacridine (TA1537), and 4-nitro-*o*-phenylenediamine (TA98). The positive control for metabolic activation with all strains was 2-aminoanthracene.

TABLE E2
Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by Primidone[a]

Compound	Dose (μg/mL)	Total Cells Scored	No. of Chromosomes	No. of SCEs	SCEs/ Chromosome	SCEs/ Cell	Hrs in BrdU	Relative Change of SCEs/ Chromosome[b] (%)
–S9								
Summary: Negative								
Dimethylsulfoxide		50	1,048	365	0.34	7.3	26.0	
		50	1,048	417	0.39	8.3	31.0[c]	
Mitomycin-C	0.001	50	1,052	672	0.63	13.4	26.0	60.54
	0.005	10	210	269	1.28	26.9	26.0	221.93
Primidone	125	50	1,048	411	0.39	8.2	26.0	–1.44
	417	50	1,048	416	0.39	8.3	31.0[c]	–0.24
	1,250	50	1,037	454	0.43	9.1	31.0[c]	10.03
					P=0.082[d]			
+S9								
Summary: Negative								
Dimethylsulfoxide		50	1,048	427	0.40	8.5	26.0	
Cyclophosphamide	0.125	50	1,053	567	0.53	11.3	26.0	32.16
	0.500	10	210	184	0.87	18.4	26.0	115.05
Primidone	125	50	1,046	457	0.43	9.1	26.0	7.23
	417	50	1,045	418	0.40	8.4	26.0	–1.83
	1,250	50	1,045	368	0.35	7.4	26.0	–13.57
					P=0.989			

[a] Study was performed at SITEK Research Laboratories. A detailed description of the protocol is presented by Galloway *et al.* (1987). SCE=sister chromatid exchange; BrdU=bromodeoxyuridine
[b] SCEs/chromosome in treated cells versus SCEs/chromosome in solvent control cells
[c] Because a delay in the cell division cycle was induced, harvest time was extended to maximize the proportion of second-division metaphase cells available for analysis.
[d] Significance of relative SCEs/chromosome tested by the linear regression trend versus log of the dose

TABLE E3
Induction of Chromosomal Aberrations in Chinese Hamster Ovary Cells by Primidone[a]

–S9					+S9				
Dose (μg/mL)	Total Cells Scored	No. of Abs	Abs/ Cell	Cells with Abs (%)	Dose (μg/mL)	Total Cells	No. of Abs	Abs/ Cell	Cells with Abs (%)
Harvest time: 14.0 hours					Harvest time: 12.3 hours				
Summary: Negative					Summary: Negative				
Dimethylsulfoxide					Dimethylsulfoxide				
	200	0	0.00	0.0		200	2	0.01	1.0
Mitomycin-C					Cyclophosphamide				
0.4	50	28	0.56	46.0	15	50	61	1.22	46.0
Primidone					Primidone				
270	200	0	0.00	0.0	270	200	2	0.01	1.0
581	200	3	0.02	1.5	581	200	7	0.04	2.0
1,250	200	0	0.00	0.0	1,250	200	3	0.02	1.5
				P=0.219[b]					P=0.249

[a] Study was performed at SITEK Research Laboratories. The detailed protocol is presented by Galloway *et al.* 1987. Abs=aberrations.
[b] Significance of percent cells with aberrations tested by the linear regression trend test versus log of the dose

TABLE E4
Frequency of Micronuclei in Bone Marrow Polychromatic Erythrocytes of Mice Treated with Primidone by Intraperitoneal Injection[a]

Dose	Number of Mice	Micronucleated PCEs/1,000 Cells[b]
Trial 1		
Corn oil		
0.4 mL	5	0.6 ± 0.2
Dimethylbenzanthracene[c]		
12.5 mg/kg	5	2.4 ± 0.3
Primidone		
87.5 mg/kg	5	0.4 ± 0.2
175 mg/kg	5	0.9 ± 0.2
300 mg/kg	2[d]	1.2 ± 0.2
		P=0.200[e]
Trial 2		
Corn oil		
0.4 mL	5	0.6 ± 0.2
Dimethylbenzanthracene		
12.5 mg/kg	4	4.2 ± 1.5
Primidone		
87.5 mg/kg	5	1.1 ± 0.3
175 mg/kg	5	1.1 ± 0.4
300 mg/kg	3	1.3 ± 0.3
350 mg/kg	3	1.5 ± 0.6
		P=0.041

[a] Study was performed at Environmental Health Research and Testing, Inc. The detailed protocol is presented by Shelby *et al*. (1993).
[b] Mean ± standard error
[c] Positive control
[d] The 300 mg/kg dose group was omitted from the trend analysis because fewer than three animals survived in this group.
[e] Significance of micronucleated cells/1,000 cells tested by the one-tailed trend test; significant at P≤0.025 (Margolin *et al.*, 1986)

APPENDIX F
ORGAN WEIGHTS AND ORGAN-WEIGHT-TO-BODY-WEIGHT RATIOS

TABLE F1 Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 14-Week Feed Study of Primidone 220
TABLE F2 Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 14-Week Feed Study of Primidone 221

TABLE F1
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 14-Week Feed Study of Primidone[a]

	0 ppm	300 ppm	600 ppm	1,300 ppm	2,500 ppm	5,000 ppm
Male						
n	10	10	10	10	5[b]	5[b]
Necropsy body wt	363 ± 6	376 ± 8	373 ± 3	359 ± 6	334 ± 8**	332 ± 3**
Heart						
Absolute	1.090 ± 0.029	1.101 ± 0.023	1.095 ± 0.008	1.096 ± 0.037	1.058 ± 0.042	1.023 ± 0.021
Relative	3.00 ± 0.06	2.94 ± 0.06	2.94 ± 0.02	3.06 ± 0.10	3.17 ± 0.09	3.09 ± 0.05
R. Kidney						
Absolute	1.259 ± 0.029	1.326 ± 0.026	1.367 ± 0.021*	1.337 ± 0.037	1.314 ± 0.024	1.336 ± 0.034
Relative	3.46 ± 0.05	3.53 ± 0.06	3.67 ± 0.06*	3.72 ± 0.05**	3.94 ± 0.05**	4.03 ± 0.10**
Liver						
Absolute	15.069 ± 0.416	16.742 ± 0.685	18.184 ± 0.580**	18.729 ± 1.146**	22.977 ± 0.419**	25.264 ± 0.399**
Relative	41.45 ± 0.77	44.48 ± 1.29	48.79 ± 1.44**	51.92 ± 2.58**	68.85 ± 1.30**	76.26 ± 1.54**
Lung						
Absolute	1.739 ± 0.033	1.768 ± 0.043	1.818 ± 0.061	1.760 ± 0.063	1.516 ± 0.091	1.542 ± 0.052
Relative	4.79 ± 0.09	4.74 ± 0.19	4.88 ± 0.16	4.91 ± 0.19	4.54 ± 0.26	4.66 ± 0.19
R. Testis						
Absolute	1.417 ± 0.051	1.477 ± 0.027	1.467 ± 0.021	1.463 ± 0.022	1.440 ± 0.027	1.357 ± 0.118
Relative	3.90 ± 0.13	3.94 ± 0.06	3.94 ± 0.07	4.08 ± 0.06	4.32 ± 0.11	4.09 ± 0.34
Thymus						
Absolute	0.410 ± 0.010	0.416 ± 0.016	0.448 ± 0.016	0.413 ± 0.020	0.395 ± 0.021	0.423 ± 0.019
Relative	1.13 ± 0.03	1.11 ± 0.04	1.21 ± 0.05	1.15 ± 0.05	1.18 ± 0.06	1.28 ± 0.06
Thyroid Gland						
Absolute	0.028 ± 0.001	0.028 ± 0.001	0.029 ± 0.002	0.028 ± 0.002	0.030 ± 0.002	0.028 ± 0.003
Relative	0.08 ± 0.00	0.08 ± 0.00	0.08 ± 0.01	0.08 ± 0.01	0.09 ± 0.01	0.09 ± 0.01
Female						
n	10	10	10	10	10	10
Necropsy body wt	201 ± 3	201 ± 3	199 ± 3	195 ± 3	190 ± 3**	187 ± 2**
Heart						
Absolute	0.720 ± 0.022	0.683 ± 0.012	0.695 ± 0.017	0.684 ± 0.010	0.699 ± 0.018	0.704 ± 0.016
Relative	3.58 ± 0.10	3.40 ± 0.07	3.50 ± 0.06	3.51 ± 0.04	3.69 ± 0.09	3.76 ± 0.10
R. Kidney						
Absolute	0.725 ± 0.016	0.739 ± 0.012	0.744 ± 0.015	0.752 ± 0.014	0.755 ± 0.015	0.739 ± 0.013
Relative	3.61 ± 0.06	3.68 ± 0.05	3.75 ± 0.04	3.86 ± 0.04**	3.98 ± 0.06**	3.95 ± 0.06**
Liver						
Absolute	6.628 ± 0.146	7.280 ± 0.138*	7.219 ± 0.229*	8.173 ± 0.161**	9.578 ± 0.225**	10.913 ± 0.306**
Relative	32.94 ± 0.54	36.24 ± 0.46*	36.33 ± 0.85*	41.99 ± 0.58**	50.54 ± 1.13**	58.22 ± 1.45**
Lung						
Absolute	1.256 ± 0.050	1.137 ± 0.032	1.119 ± 0.030	1.194 ± 0.023	1.168 ± 0.059	1.174 ± 0.036
Relative	6.23 ± 0.20	5.66 ± 0.12	5.63 ± 0.12	6.14 ± 0.10	6.15 ± 0.28	6.26 ± 0.18
Thymus						
Absolute	0.305 ± 0.011	0.292 ± 0.012	0.307 ± 0.014	0.313 ± 0.008	0.312 ± 0.014	0.333 ± 0.009
Relative	1.52 ± 0.05	1.46 ± 0.06	1.54 ± 0.06	1.61 ± 0.05	1.64 ± 0.06	1.78 ± 0.05**
Thyroid Gland						
Absolute	0.027 ± 0.002	0.020 ± 0.002	0.023 ± 0.002	0.028 ± 0.003	0.025 ± 0.002	0.027 ± 0.002
Relative	0.13 ± 0.01	0.10 ± 0.01	0.12 ± 0.01	0.14 ± 0.02	0.13 ± 0.01	0.15 ± 0.01

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error).
[b] Five animals omitted from analysis due to dehydration

TABLE F2
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 14-Week Feed Study of Primidone[a]

	0 ppm	300 ppm	600 ppm	1,300 ppm	2,500 ppm	5,000 ppm
Male						
n	10	10	10	10	10	7
Necropsy body wt	32.5 ± 0.7	32.5 ± 0.8	33.2 ± 1.1	32.1 ± 0.7	32.6 ± 0.8	29.9 ± 0.6
Heart						
Absolute	0.167 ± 0.005	0.156 ± 0.005	0.178 ± 0.010	0.175 ± 0.009	0.166 ± 0.007	0.188 ± 0.009
Relative	5.16 ± 0.18	4.79 ± 0.09	5.39 ± 0.31	5.45 ± 0.26	5.11 ± 0.18	6.32 ± 0.38**
R. Kidney						
Absolute	0.294 ± 0.006	0.281 ± 0.005	0.295 ± 0.009	0.292 ± 0.006	0.302 ± 0.010	0.280 ± 0.008
Relative	9.08 ± 0.22	8.69 ± 0.18	8.93 ± 0.16	9.11 ± 0.15	9.29 ± 0.20	9.36 ± 0.17
Liver						
Absolute	1.587 ± 0.036	1.714 ± 0.053	1.989 ± 0.087**	2.225 ± 0.076**	2.709 ± 0.117**	2.956 ± 0.111**
Relative	48.97 ± 1.12	52.74 ± 1.06	59.91 ± 1.11**	69.26 ± 1.64**	82.97 ± 1.97**	98.60 ± 2.11**
Lung						
Absolute	0.243 ± 0.011	0.230 ± 0.007	0.243 ± 0.011	0.236 ± 0.007	0.236 ± 0.016	0.239 ± 0.017
Relative	7.53 ± 0.45	7.09 ± 0.21	7.34 ± 0.23	7.36 ± 0.22	7.22 ± 0.39	8.01 ± 0.61
R. Testis						
Absolute	0.123 ± 0.004	0.122 ± 0.002	0.124 ± 0.003	0.120 ± 0.003	0.126 ± 0.003	0.123 ± 0.003
Relative	3.80 ± 0.13	3.76 ± 0.08	3.75 ± 0.10	3.75 ± 0.05	3.86 ± 0.06	4.11 ± 0.11
Thymus						
Absolute	0.046 ± 0.003	0.050 ± 0.002	0.047 ± 0.003	0.044 ± 0.002	0.040 ± 0.004	0.042 ± 0.003
Relative	1.43 ± 0.07	1.53 ± 0.07	1.42 ± 0.07	1.37 ± 0.07	1.22 ± 0.10	1.40 ± 0.11
Thyroid Gland						
Absolute	0.011 ± 0.001	0.013 ± 0.001	0.011 ± 0.001	0.013 ± 0.001	0.013 ± 0.001	0.010 ± 0.001
Relative	0.32 ± 0.04	0.41 ± 0.04	0.34 ± 0.04	0.42 ± 0.04	0.41 ± 0.03	0.33 ± 0.05
Female						
n	10	10	10	10	10	8
Necropsy body wt	28.4 ± 0.6	29.9 ± 0.6	31.0 ± 0.8	29.9 ± 1.0	29.3 ± 0.6	27.6 ± 0.6
Heart						
Absolute	0.142 ± 0.006	0.141 ± 0.004	0.149 ± 0.006	0.143 ± 0.006	0.145 ± 0.006	0.143 ± 0.006
Relative	5.05 ± 0.24	4.72 ± 0.10	4.84 ± 0.17	4.80 ± 0.16	4.95 ± 0.14	5.17 ± 0.21
R. Kidney						
Absolute	0.202 ± 0.007	0.216 ± 0.009	0.223 ± 0.005	0.223 ± 0.005	0.217 ± 0.005	0.215 ± 0.007
Relative	7.14 ± 0.31	7.23 ± 0.31	7.22 ± 0.19	7.48 ± 0.19	7.39 ± 0.08	7.79 ± 0.17
Liver						
Absolute	1.382 ± 0.027	1.519 ± 0.032	1.739 ± 0.032**	1.981 ± 0.073**	2.299 ± 0.053**	2.746 ± 0.112**
Relative	48.82 ± 1.03	50.95 ± 0.94	56.31 ± 0.87**	66.17 ± 1.26**	78.42 ± 1.04**	99.20 ± 2.23**
Lung						
Absolute	0.226 ± 0.008	0.234 ± 0.010	0.230 ± 0.011	0.233 ± 0.014	0.226 ± 0.009	0.251 ± 0.016
Relative	8.02 ± 0.38	7.85 ± 0.26	7.44 ± 0.34	7.77 ± 0.29	7.72 ± 0.28	9.17 ± 0.79
Thymus						
Absolute	0.061 ± 0.005	0.066 ± 0.003	0.064 ± 0.004	0.063 ± 0.003	0.059 ± 0.003	0.058 ± 0.004
Relative	2.16 ± 0.14	2.21 ± 0.12	2.06 ± 0.10	2.12 ± 0.08	2.03 ± 0.11	2.09 ± 0.13
Thyroid Gland						
Absolute	0.006 ± 0.001	0.007 ± 0.001	0.007 ± 0.002	0.007 ± 0.001	0.006 ± 0.001	0.009 ± 0.002
Relative	0.22 ± 0.04	0.25 ± 0.05	0.22 ± 0.05	0.23 ± 0.04	0.22 ± 0.04	0.31 ± 0.08

** Significantly different ($P \leq 0.01$) from the control group by Williams' or Dunnett's test
[a] Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error).

APPENDIX G
HEMATOLOGY
AND CLINICAL CHEMISTRY RESULTS

TABLE G1 Hematology and Clinical Chemistry Data for Rats in the 14-Week Feed Study of Primidone 224

TABLE G1
Hematology and Clinical Chemistry Data for Rats in the 14-Week Feed Study of Primidone[a]

	0 ppm	300 ppm	600 ppm	1,300 ppm	2,500 ppm	5,000 ppm
Male						
n	10	10	10	10	10	10
Hematology						
Hematocrit (%)						
Day 4	40.0 ± 0.4	38.7 ± 0.2	39.0 ± 0.4[b]	39.0 ± 0.3	39.0 ± 0.4	40.2 ± 0.5
Day 22	44.6 ± 0.5	46.0 ± 0.4	45.4 ± 0.5	44.8 ± 0.3	45.0 ± 0.5	44.4 ± 0.5
Week 14	45.6 ± 0.4	44.9 ± 0.4[b]	46.3 ± 0.5	47.6 ± 0.7	44.6 ± 0.3	44.6 ± 0.3
Hemoglobin (g/dL)						
Day 4	13.3 ± 0.1	13.0 ± 0.1	13.2 ± 0.1	13.1 ± 0.1	13.1 ± 0.1	13.4 ± 0.2
Day 22	14.7 ± 0.2	15.0 ± 0.1	14.9 ± 0.1	14.6 ± 0.1	14.4 ± 0.1	14.3 ± 0.2
Week 14	15.0 ± 0.1	14.9 ± 0.1	15.1 ± 0.2	15.3 ± 0.1	14.5 ± 0.1**	14.4 ± 0.1**
Erythrocytes ($10^6/\mu L$)						
Day 4	6.28 ± 0.07	6.05 ± 0.04	6.14 ± 0.07	6.12 ± 0.07	6.15 ± 0.07	6.41 ± 0.09
Day 22	7.29 ± 0.10	7.39 ± 0.11	7.26 ± 0.08	7.13 ± 0.05	7.10 ± 0.09	7.01 ± 0.11
Week 14	8.23 ± 0.06	8.12 ± 0.07	8.24 ± 0.09	8.43 ± 0.11	8.09 ± 0.06	8.13 ± 0.07
Reticulocytes ($10^6/\mu L$)						
Day 4	0.42 ± 0.03	0.40 ± 0.02	0.38 ± 0.02	0.38 ± 0.02	0.40 ± 0.02	0.35 ± 0.02
Day 22	0.22 ± 0.02	0.21 ± 0.01	0.22 ± 0.02	0.23 ± 0.01	0.22 ± 0.01	0.22 ± 0.01
Week 14	0.12 ± 0.01	0.13 ± 0.01	0.13 ± 0.01	0.14 ± 0.01	0.14 ± 0.01	0.14 ± 0.01
Nucleated erythrocytes ($10^3/\mu L$)						
Day 4	0.12 ± 0.03	0.04 ± 0.02	0.14 ± 0.03	0.08 ± 0.02	0.12 ± 0.03	0.07 ± 0.03
Day 22	0.02 ± 0.01	0.00 ± 0.00	0.05 ± 0.02	0.03 ± 0.01	0.04 ± 0.03	0.04 ± 0.02
Week 14	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Mean cell volume (fL)						
Day 4	63.7 ± 0.4	63.9 ± 0.3	63.6 ± 0.2	63.7 ± 0.2	63.3 ± 0.3	62.7 ± 0.3*
Day 22	61.2 ± 0.3	62.2 ± 0.4	62.6 ± 0.4*	62.8 ± 0.3**	63.4 ± 0.4**	63.3 ± 0.4**
Week 14	55.5 ± 0.3	55.3 ± 0.3	56.3 ± 0.3	56.5 ± 0.3	55.2 ± 0.1	54.8 ± 0.2
Mean cell hemoglobin (pg)						
Day 4	21.2 ± 0.2	21.5 ± 0.2	21.4 ± 0.1	21.4 ± 0.1	21.3 ± 0.1	21.0 ± 0.2
Day 22	20.2 ± 0.1	20.3 ± 0.1	20.5 ± 0.1	20.4 ± 0.1	20.3 ± 0.2	20.4 ± 0.1
Week 14	18.2 ± 0.1	18.4 ± 0.1	18.3 ± 0.1	18.1 ± 0.1	17.9 ± 0.1*	17.8 ± 0.1**
Mean cell hemoglobin concentration (g/dL)						
Day 4	33.4 ± 0.2	33.6 ± 0.1	33.7 ± 0.1	33.6 ± 0.2	33.6 ± 0.1	33.5 ± 0.2
Day 22	32.9 ± 0.1	32.7 ± 0.1	32.7 ± 0.2	32.5 ± 0.1*	32.1 ± 0.3*	32.3 ± 0.1**
Week 14	32.9 ± 0.3	33.2 ± 0.2	32.6 ± 0.2	32.1 ± 0.3*	32.4 ± 0.1	32.4 ± 0.1
Platelets ($10^3/\mu L$)						
Day 4	910.5 ± 23.3	956.1 ± 9.6	968.4 ± 15.7	922.8 ± 10.4	911.3 ± 13.1	936.9 ± 10.0
Day 22	822.7 ± 13.1	885.5 ± 15.1**	874.9 ± 13.1*	915.6 ± 10.8**	926.1 ± 10.3**	900.1 ± 8.1**
Week 14	684.3 ± 13.4	697.4 ± 8.3	755.2 ± 9.3**	785.1 ± 15.0**	804.2 ± 9.7**	818.5 ± 12.9**
Leukocytes ($10^3/\mu L$)						
Day 4	7.59 ± 0.48	7.38 ± 0.28	7.79 ± 0.37	7.48 ± 0.49	7.54 ± 0.51	7.22 ± 0.37
Day 22	7.13 ± 0.31	7.10 ± 0.35	8.77 ± 0.46*	8.60 ± 0.62*	9.16 ± 0.33**	9.50 ± 0.46**
Week 14	10.75 ± 0.32	8.88 ± 0.72	10.16 ± 0.50	9.80 ± 0.65	8.19 ± 0.32**	8.83 ± 0.28
Segmented neutrophils ($10^3/\mu L$)						
Day 4	0.92 ± 0.09	0.76 ± 0.09	1.03 ± 0.09	1.00 ± 0.11	0.91 ± 0.11	0.97 ± 0.06
Day 22	0.80 ± 0.06	1.00 ± 0.14	0.81 ± 0.06	0.81 ± 0.07	0.95 ± 0.07	0.91 ± 0.11
Week 14	1.70 ± 0.18	1.08 ± 0.12*	1.25 ± 0.13	1.28 ± 0.09	1.23 ± 0.12	1.38 ± 0.07
Lymphocytes ($10^3/\mu L$)						
Day 4	6.51 ± 0.42	6.46 ± 0.26	6.57 ± 0.36	6.35 ± 0.46	6.50 ± 0.41	6.13 ± 0.36
Day 22	6.14 ± 0.30	6.00 ± 0.31	7.74 ± 0.47*	7.61 ± 0.62*	8.11 ± 0.34**	8.36 ± 0.43**
Week 14	8.79 ± 0.18	7.51 ± 0.61	8.63 ± 0.50	8.24 ± 0.58	6.75 ± 0.27**	7.17 ± 0.27

TABLE G1
Hematology and Clinical Chemistry Data for Rats in the 14-Week Feed Study of Primidone

	0 ppm	300 ppm	600 ppm	1,300 ppm	2,500 ppm	5,000 ppm
Male (continued)						
n	10	10	10	10	10	10
Hematology (continued)						
Monocytes ($10^3/\mu L$)						
Day 4	0.05 ± 0.02	0.10 ± 0.02	0.13 ± 0.02	0.07 ± 0.02	0.10 ± 0.03	0.09 ± 0.02
Day 22	0.15 ± 0.03	0.07 ± 0.02	0.13 ± 0.03	0.16 ± 0.03	0.07 ± 0.02	0.16 ± 0.04
Week 14	0.19 ± 0.04	0.18 ± 0.05	0.14 ± 0.02	0.17 ± 0.05	0.11 ± 0.03	0.17 ± 0.04
Eosinophils ($10^3/\mu L$)						
Day 4	0.06 ± 0.02	0.06 ± 0.02	0.05 ± 0.01	0.07 ± 0.03	0.03 ± 0.01	0.03 ± 0.01
Day 22	0.04 ± 0.02	0.04 ± 0.02	0.09 ± 0.03	0.02 ± 0.01	0.03 ± 0.01	0.07 ± 0.03
Week 14	0.08 ± 0.03	0.11 ± 0.03	0.10 ± 0.03	0.12 ± 0.03	0.10 ± 0.03	0.11 ± 0.04
Clinical Chemistry						
Urea nitrogen (mg/dL)						
Day 4	22.4 ± 0.8	21.3 ± 0.7	21.5 ± 0.3	21.1 ± 0.4	20.9 ± 0.3	22.8 ± 0.4
Day 22	23.6 ± 0.7	20.9 ± 0.9	23.9 ± 0.7	23.3 ± 0.4	22.9 ± 0.6	23.3 ± 0.6
Week 14	22.2 ± 0.6	22.4 ± 0.4	21.5 ± 0.3	22.5 ± 0.5	23.1 ± 0.8	23.2 ± 0.6
Creatinine (mg/dL)						
Day 4	0.63 ± 0.03	0.61 ± 0.01	0.63 ± 0.02	0.61 ± 0.01	0.62 ± 0.01	0.61 ± 0.02
Day 22	0.65 ± 0.02	0.61 ± 0.01	0.66 ± 0.02	0.67 ± 0.02	0.60 ± 0.00	0.63 ± 0.02
Week 14	0.72 ± 0.02	0.78 ± 0.07	0.74 ± 0.02	0.71 ± 0.02	0.68 ± 0.01	0.71 ± 0.01
Total protein (g/dL)						
Day 4	5.8 ± 0.1	5.8 ± 0.0	5.8 ± 0.1	5.7 ± 0.0	5.5 ± 0.1*	5.7 ± 0.1
Day 22	6.6 ± 0.0	6.9 ± 0.1**	7.0 ± 0.1**	7.1 ± 0.1**	7.1 ± 0.1**	7.1 ± 0.1**
Week 14	7.2 ± 0.1	7.1 ± 0.1	7.5 ± 0.1*	7.8 ± 0.1**	8.0 ± 0.1**	8.1 ± 0.1**
Albumin (g/dL)						
Day 4	4.3 ± 0.1	4.2 ± 0.0	4.2 ± 0.1	4.1 ± 0.0*	4.0 ± 0.0**	4.1 ± 0.1**
Day 22	4.7 ± 0.0	4.8 ± 0.1	4.9 ± 0.1	4.9 ± 0.1	4.9 ± 0.1	4.9 ± 0.1
Week 14	5.0 ± 0.0	5.0 ± 0.0	5.2 ± 0.1*	5.4 ± 0.0**	5.5 ± 0.0**	5.4 ± 0.1**
Alanine aminotransferase (IU/L)						
Day 4	44 ± 2	41 ± 1	42 ± 2	46 ± 1	47 ± 1	50 ± 1**
Day 22	45 ± 1	40 ± 2*	42 ± 2	35 ± 1**	32 ± 1**	33 ± 1**
Week 14	45 ± 1	47 ± 2	41 ± 2	43 ± 1	49 ± 3	50 ± 5
Alkaline phosphatase (IU/L)						
Day 4	1,645 ± 40	1,684 ± 30	1,652 ± 30	1,732 ± 48	1,682 ± 26	1,698 ± 52
Day 22	1,225 ± 27	1,131 ± 26*	1,232 ± 28	1,141 ± 26	1,054 ± 15**	981 ± 19**
Week 14	553 ± 13	527 ± 12	552 ± 13	423 ± 30**	476 ± 16**	427 ± 10**
Creatine kinase (IU/L)						
Day 4	273 ± 30	250 ± 14	245 ± 21	314 ± 42	245 ± 12	273 ± 23
Day 22	404 ± 85	358 ± 65	410 ± 57	401 ± 61	366 ± 56	419 ± 90
Week 14	252 ± 32	322 ± 28	296 ± 33	361 ± 36*	500 ± 42**	507 ± 30**
Sorbitol dehydrogenase (IU/L)						
Day 4	18 ± 1	17 ± 1	18 ± 1	19 ± 1	20 ± 1	23 ± 1**
Day 22	21 ± 1	18 ± 1	21 ± 1	22 ± 2	23 ± 3	23 ± 1
Week 14	22 ± 1	25 ± 1	24 ± 3	21 ± 2	18 ± 1	20 ± 1
Bile salts (μmol/L)						
Day 4	25.1 ± 3.6	22.8 ± 1.8	26.3 ± 3.1	37.0 ± 2.8*	38.8 ± 7.2	45.3 ± 6.2*
Day 22	22.1 ± 3.2	17.2 ± 1.8	17.7 ± 1.3	27.8 ± 4.7	21.0 ± 2.3	21.9 ± 1.4
Week 14	11.0 ± 2.1	12.2 ± 1.2	10.9 ± 1.9	8.4 ± 0.8	11.0 ± 1.4	9.4 ± 1.0

TABLE G1
Hematology and Clinical Chemistry Data for Rats in the 14-Week Feed Study of Primidone

	0 ppm	300 ppm	600 ppm	1,300 ppm	2,500 ppm	5,000 ppm
Female						
n	10	10	10	10	10	10
Hematology						
Hematocrit (%)						
Day 4	40.5 ± 0.3	40.4 ± 0.4	41.2 ± 0.4	40.9 ± 0.4	40.6 ± 0.5	42.8 ± 0.7
Day 22	47.8 ± 0.4	47.7 ± 0.5	48.6 ± 0.3	47.7 ± 0.4	47.2 ± 0.3	46.5 ± 0.4
Week 14	45.6 ± 0.5	45.7 ± 0.3	45.5 ± 0.3	45.8 ± 0.3	45.3 ± 0.3	44.5 ± 0.4
Hemoglobin (g/dL)						
Day 4	13.6 ± 0.1	13.5 ± 0.1	13.6 ± 0.1	13.7 ± 0.1	13.6 ± 0.2	14.1 ± 0.3
Day 22	15.7 ± 0.1	15.5 ± 0.1	15.6 ± 0.1	15.5 ± 0.1	15.2 ± 0.1*	15.1 ± 0.1**
Week 14	15.0 ± 0.1	15.2 ± 0.1	15.0 ± 0.1	15.0 ± 0.1	14.8 ± 0.1	14.5 ± 0.1**
Erythrocytes ($10^6/\mu L$)						
Day 4	6.35 ± 0.08	6.34 ± 0.07	6.49 ± 0.08	6.50 ± 0.09	6.41 ± 0.09	6.90 ± 0.10**
Day 22	7.62 ± 0.09	7.51 ± 0.09	7.66 ± 0.06	7.55 ± 0.08	7.40 ± 0.07	7.45 ± 0.07
Week 14	7.66 ± 0.07	7.71 ± 0.06	7.65 ± 0.06	7.76 ± 0.04	7.75 ± 0.05	7.66 ± 0.08
Reticulocytes ($10^6/\mu L$)						
Day 4	0.29 ± 0.02	0.31 ± 0.02	0.30 ± 0.02	0.30 ± 0.02	0.31 ± 0.02	0.28 ± 0.02
Day 22	0.12 ± 0.01	0.11 ± 0.01	0.12 ± 0.01	0.11 ± 0.01	0.13 ± 0.01	0.14 ± 0.01
Week 14	0.10 ± 0.01	0.12 ± 0.01	0.10 ± 0.01	0.09 ± 0.01	0.11 ± 0.01	0.12 ± 0.01
Nucleated erythrocytes ($10^3/\mu L$)						
Day 4	0.07 ± 0.02	0.09 ± 0.02	0.08 ± 0.03	0.04 ± 0.02	0.07 ± 0.02	0.03 ± 0.02
Day 22	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Week 14	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Mean cell volume (fL)						
Day 4	63.7 ± 0.5	63.8 ± 0.3	63.5 ± 0.3	63.0 ± 0.4	63.3 ± 0.5	62.0 ± 0.2**
Day 22	62.8 ± 0.3	63.6 ± 0.3	63.4 ± 0.3	63.2 ± 0.3	63.7 ± 0.3	62.5 ± 0.3
Week 14	59.5 ± 0.2	59.3 ± 0.3	59.5 ± 0.1	59.0 ± 0.2	58.4 ± 0.2**	58.1 ± 0.1**
Mean cell hemoglobin (pg)						
Day 4	21.4 ± 0.2	21.3 ± 0.1	21.0 ± 0.2	21.1 ± 0.2	21.3 ± 0.1	20.5 ± 0.1**
Day 22	20.6 ± 0.1	20.6 ± 0.2	20.4 ± 0.1	20.5 ± 0.1	20.6 ± 0.1	20.3 ± 0.1
Week 14	19.6 ± 0.1	19.7 ± 0.1	19.6 ± 0.1	19.3 ± 0.1**	19.1 ± 0.1**	18.9 ± 0.1**
Mean cell hemoglobin concentration (g/dL)						
Day 4	33.5 ± 0.1	33.4 ± 0.1	33.2 ± 0.2	33.4 ± 0.2	33.6 ± 0.1	33.0 ± 0.2
Day 22	32.8 ± 0.1	32.5 ± 0.2	32.2 ± 0.2**	32.5 ± 0.1	32.3 ± 0.1**	32.5 ± 0.1
Week 14	33.0 ± 0.3	33.1 ± 0.3	32.9 ± 0.1	32.8 ± 0.2	32.7 ± 0.1	32.6 ± 0.2
Platelets ($10^3/\mu L$)						
Day 4	938.9 ± 15.2	967.1 ± 17.9	961.9 ± 14.1	960.6 ± 20.8	920.3 ± 17.9	959.9 ± 19.5
Day 22	697.9 ± 28.0	721.7 ± 14.6	754.7 ± 14.9	804.6 ± 18.4**	813.3 ± 13.5**	840.3 ± 17.8**
Week 14	698.0 ± 8.4	684.8 ± 9.0	710.7 ± 14.0	754.9 ± 6.6**	752.2 ± 15.2**	768.3 ± 17.4**
Leukocytes ($10^3/\mu L$)						
Day 4	7.39 ± 0.41	8.11 ± 0.21	8.10 ± 0.35	8.49 ± 0.40	7.68 ± 0.26	9.31 ± 0.42*
Day 22	6.28 ± 0.38	7.19 ± 0.31*	7.36 ± 0.37*	7.09 ± 0.22	6.88 ± 0.24	8.13 ± 0.23**
Week 14	5.89 ± 0.47	6.42 ± 0.31	6.63 ± 0.46	6.51 ± 0.31	6.02 ± 0.30	6.76 ± 0.27
Segmented neutrophils ($10^3/\mu L$)						
Day 4	0.84 ± 0.12	0.78 ± 0.08	0.94 ± 0.09	0.77 ± 0.09	0.80 ± 0.07	1.10 ± 0.09
Day 22	0.69 ± 0.11	0.83 ± 0.06	0.86 ± 0.10	0.70 ± 0.07	0.70 ± 0.06	1.04 ± 0.12
Week 14	1.02 ± 0.13	1.07 ± 0.12	1.06 ± 0.12	0.99 ± 0.10	0.88 ± 0.09	0.76 ± 0.10
Lymphocytes ($10^3/\mu L$)						
Day 4	6.42 ± 0.33	7.19 ± 0.24	7.03 ± 0.35	7.55 ± 0.39	6.77 ± 0.29	7.96 ± 0.35*
Day 22	5.45 ± 0.29	6.22 ± 0.34	6.35 ± 0.28	6.20 ± 0.22	6.08 ± 0.25	6.95 ± 0.23**
Week 14	4.68 ± 0.35	5.23 ± 0.31	5.32 ± 0.34	5.35 ± 0.29	5.04 ± 0.30	5.84 ± 0.22*

TABLE G1
Hematology and Clinical Chemistry Data for Rats in the 14-Week Feed Study of Primidone

	0 ppm	300 ppm	600 ppm	1,300 ppm	2,500 ppm	5,000 ppm
Female (continued)						
n	10	10	10	10	10	10
Hematology (continued)						
Monocytes ($10^3/\mu L$)						
Day 4	0.08 ± 0.01	0.10 ± 0.02	0.11 ± 0.03	0.12 ± 0.03	0.08 ± 0.02	0.19 ± 0.04
Day 22	0.09 ± 0.02	0.11 ± 0.03	0.05 ± 0.02	0.15 ± 0.04	0.07 ± 0.02	0.10 ± 0.03
Week 14	0.11 ± 0.03	0.07 ± 0.03	0.18 ± 0.03	0.06 ± 0.02	0.06 ± 0.02	0.09 ± 0.03
Eosinophils ($10^3/\mu L$)						
Day 4	0.06 ± 0.02	0.04 ± 0.02	0.02 ± 0.01	0.05 ± 0.02	0.03 ± 0.02	0.06 ± 0.03
Day 22	0.04 ± 0.02	0.03 ± 0.02	0.09 ± 0.03	0.04 ± 0.02	0.03 ± 0.01	0.05 ± 0.02
Week 14	0.09 ± 0.02	0.05 ± 0.02	0.07 ± 0.03	0.11 ± 0.02	0.04 ± 0.02	0.07 ± 0.02
Clinical Chemistry						
Urea nitrogen (mg/dL)						
Day 4	22.2 ± 0.6	22.7 ± 0.7	24.4 ± 1.0	23.6 ± 0.6	23.4 ± 0.9	23.4 ± 0.9
Day 22	23.9 ± 0.7	23.7 ± 0.5	23.6 ± 0.8	23.1 ± 0.7	23.1 ± 0.7	23.4 ± 0.6
Week 14	20.4 ± 0.6	20.2 ± 0.7	18.7 ± 0.5	17.8 ± 0.2*	17.5 ± 0.6**	19.5 ± 0.7
Creatinine (mg/dL)						
Day 4	0.56 ± 0.02	0.58 ± 0.01	0.55 ± 0.02	0.56 ± 0.02	0.58 ± 0.01	0.57 ± 0.02
Day 22	0.66 ± 0.02	0.62 ± 0.01	0.63 ± 0.02	0.64 ± 0.02	0.63 ± 0.02	0.64 ± 0.02
Week 14	0.64 ± 0.02	0.66 ± 0.02	0.66 ± 0.02	0.66 ± 0.02	0.68 ± 0.01	0.68 ± 0.01
Total protein (g/dL)						
Day 4	5.7 ± 0.0	5.6 ± 0.1	5.7 ± 0.0	5.7 ± 0.1	5.6 ± 0.1	5.8 ± 0.1
Day 22	6.5 ± 0.1	6.6 ± 0.1	6.6 ± 0.1	6.8 ± 0.1	6.7 ± 0.0	6.8 ± 0.1**
Week 14	7.1 ± 0.1	7.2 ± 0.1	7.2 ± 0.1	7.3 ± 0.1	7.5 ± 0.1**	7.6 ± 0.1**
Albumin (g/dL)						
Day 4	4.2 ± 0.0	4.2 ± 0.0	4.3 ± 0.0	4.2 ± 0.1	4.2 ± 0.1	4.2 ± 0.1
Day 22	4.8 ± 0.1	4.8 ± 0.1	4.7 ± 0.1	4.8 ± 0.1	4.7 ± 0.0	4.7 ± 0.0
Week 14	5.2 ± 0.1	5.2 ± 0.1	5.2 ± 0.1	5.2 ± 0.0	5.2 ± 0.1	5.4 ± 0.0
Alanine aminotransferase (IU/L)						
Day 4	33 ± 1	36 ± 1**	38 ± 1**	39 ± 1**	39 ± 1**	39 ± 1**
Day 22	34 ± 1	32 ± 1	32 ± 2	30 ± 2	30 ± 1	32 ± 1
Week 14	32 ± 2	32 ± 1	32 ± 1	29 ± 1	27 ± 1**	30 ± 1
Alkaline phosphatase (IU/L)						
Day 4	1,316 ± 22	1,354 ± 31	1,385 ± 34	1,345 ± 31	1,369 ± 27	1,220 ± 32
Day 22	869 ± 16	853 ± 29	831 ± 15	738 ± 14**	719 ± 18**	714 ± 15**
Week 14	434 ± 13	379 ± 7**	373 ± 10**	308 ± 9**	303 ± 8**	282 ± 7**
Creatine kinase (IU/L)						
Day 4	216 ± 20	186 ± 18	231 ± 32	267 ± 25	237 ± 34	214 ± 13
Day 22	342 ± 37	434 ± 56	374 ± 51	306 ± 30	338 ± 46	368 ± 57
Week 14	201 ± 23[b]	290 ± 35	280 ± 68	224 ± 34	216 ± 17	312 ± 40
Sorbitol dehydrogenase (IU/L)						
Day 4	15 ± 1	15 ± 1	17 ± 1	20 ± 1**	20 ± 1**	24 ± 1**
Day 22	22 ± 1	21 ± 1	20 ± 1	27 ± 3	24 ± 1	26 ± 1
Week 14	19 ± 2	19 ± 1	21 ± 1	22 ± 1**	20 ± 1	22 ± 1*
Bile salts (μmol/L)						
Day 4	21.9 ± 3.0	23.9 ± 1.0	17.9 ± 2.6	18.1 ± 2.7	30.7 ± 3.1	22.1 ± 3.3
Day 22	25.2 ± 4.7	20.6 ± 2.3	11.8 ± 1.5*	14.3 ± 1.8	16.5 ± 1.6	15.5 ± 1.3
Week 14	21.5 ± 4.4	20.5 ± 2.6	21.2 ± 2.5	13.8 ± 2.0	17.9 ± 1.8	21.5 ± 4.9

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error. Statistical tests were performed on unrounded data.
[b] n=9 for the male 300 ppm group at week 14 and for the 600 ppm group on day 4 for hematology data.

APPENDIX H
DETERMINATIONS
OF PRIMIDONE AND PHENOBARBITAL
IN PLASMA

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FIGURE H4 Plasma Concentrations of Phenobarbital in Female Mice after Exposure to 300, 600, or 1,300 ppm Primidone in Feed for 2 Years 233

TABLE H1
Plasma Concentrations of Primidone in Female Rats in the 2-Year Feed Study of Primidone[a]

Time of Day[b]	600 ppm	1,300 ppm	2,500 ppm
n	3	3	3
Day 721			
8:30 a.m.	0.73 ± 0.52	1.46 ± 0.95	2.55 ± 1.10
2:30 p.m.	0.95 ± 0.39	1.52 ± 1.64	1.98 ± 1.28
8:00 p.m.	1.37 ± 0.71	2.54 ± 0.45	8.27 ± 5.56
10:00 p.m.	1.62 ± 0.56	3.28 ± 0.93	6.32 ± 2.24
Day 722			
8:30 a.m.	1.22 ± 0.34	2.16 ± 0.63	2.95 ± 1.74

[a] Data are given in μg/mL as mean ± standard deviation.
[b] Samples were collected on the last 2 days of the study.

TABLE H2
Plasma Concentrations of Phenobarbital in Female Rats in the 2-Year Feed Study of Primidone[a]

Time of Day[b]	600 ppm	1,300 ppm	2,500 ppm
n	3	3	3
Day 721			
8:30 a.m.	5.84 ± 0.88	10.3 ± 1.7	17.9 ± 0.1
2:30 p.m.	4.52 ± 0.47	9.1 ± 1.4	18.0 ± 1.3
8:00 p.m.	4.47 ± 1.33	12.6 ± 3.5	19.7 ± 2.5
10:00 p.m.	5.84 ± 0.30	12.2 ± 0.7	19.2 ± 2.1
Day 722			
8:30 a.m.	4.68 ± 2.13	10.5 ± 0.6	16.6 ± 1.4

[a] Data are given in μg/mL as mean ± standard deviation.
[b] Samples were collected on the last 2 days of the study.

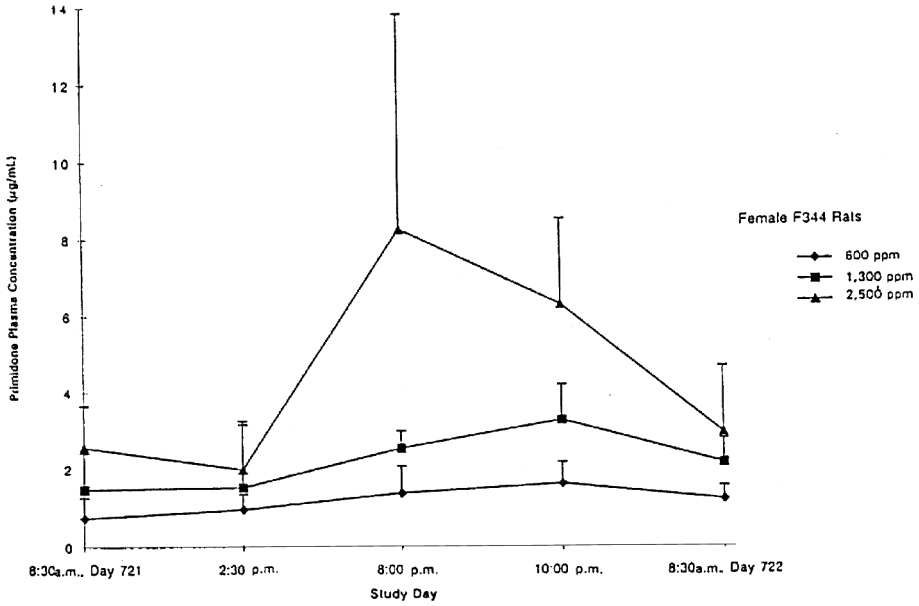

Figure H1
Plasma Concentrations of Primidone in Female Rats after Exposure to 600, 1,300, or 2,500 ppm Primidone in feed for 2 Years

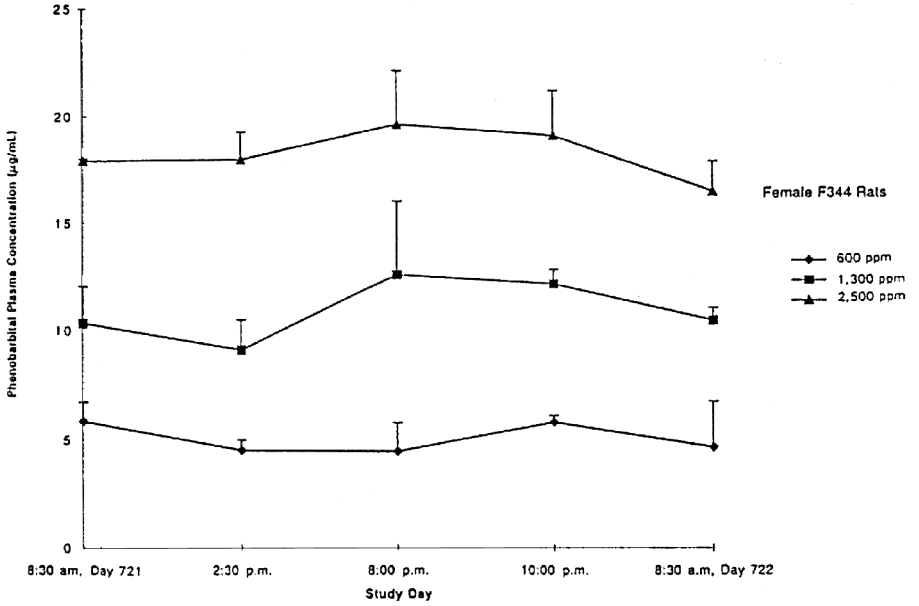

Figure H2
Plasma Concentrations of Phenobarbital in Female Rats after Exposure to 600, 1,300, or 2,500 ppm Primidone in feed for 2 Years

TABLE H3
Plasma Concentrations of Phenobarbital in Male Mice in the 2-Year Feed Study of Primidone[a]

Time of Day[b]	300 ppm	600 ppm	1,300 ppm
n	3	3	3
Day 726			
8:30 a.m.	2.73 ± 1.80	5.50 ± 1.89	7.88 ± 4.27
2:30 p.m.	1.83 ± 1.23	1.61 ± 0.51	1.86 ± 1.50
8:00 p.m.	3.31 ± 1.31	3.33 ± 1.47	5.88 ± 1.63
10:00 p.m.	3.82 ± 0.23	6.07 ± 1.07	11.8 ± 2.5
Day 727			
8:30 a.m.	3.43 ± 0.25	6.17 ± 2.69	12.0 ± 3.2

[a] Data are given in μg/mL as mean ± standard deviation.
[b] Samples were collected on the last 2 days of the study.

TABLE H4
Plasma Concentrations of Phenobarbital in Female Mice in the 2-Year Feed Study of Primidone[a]

Time of Day[b]	300 ppm	600 ppm	1,300 ppm
n	3	3	3
Day 727			
8:30 a.m.	3.41 ± 1.07	5.68 ± 1.99	13.0 ± 3.5
2:30 p.m.	2.16 ± 0.62	4.14 ± 1.07	3.05 ± 2.35
8:00 p.m.	0.95 ± 0.61[c]	2.28 ± 0.85	1.12 ± 0.76
10:00 p.m.	1.03 ± 0.26	2.13 ± 0.79	3.36 ± 2.12
Day 728			
8:30 a.m.	2.17 ± 0.72	7.57 ± 1.86	16.6 ± 11.6

[a] Data are given in μg/mL as mean ± standard deviation.
[b] Samples were collected on the last 2 days of the study.
[c] n=2

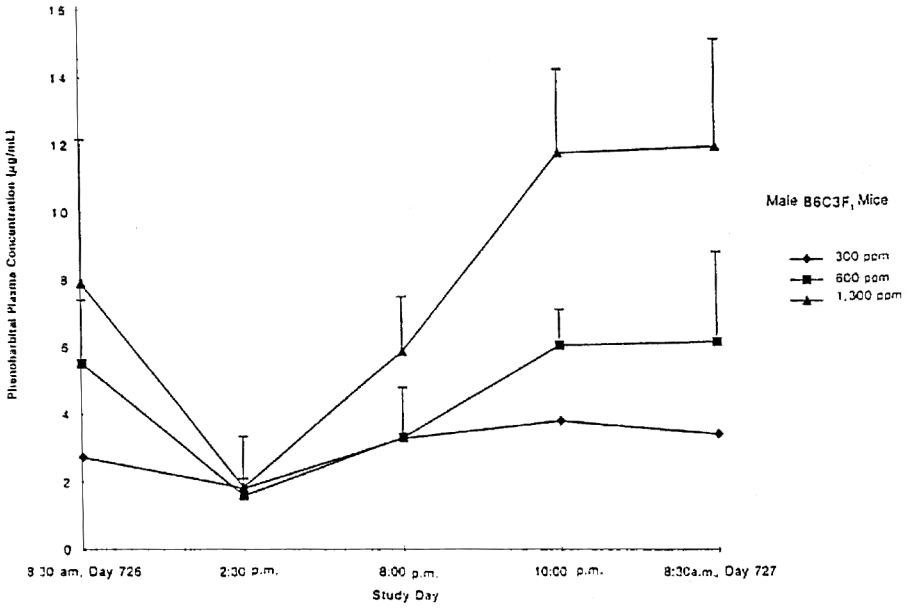

Figure H3
Plasma Concentrations of Phenobarbital in Male Mice after Exposure to 300, 600, or 1,300 ppm Primidone in Feed for 2 Years

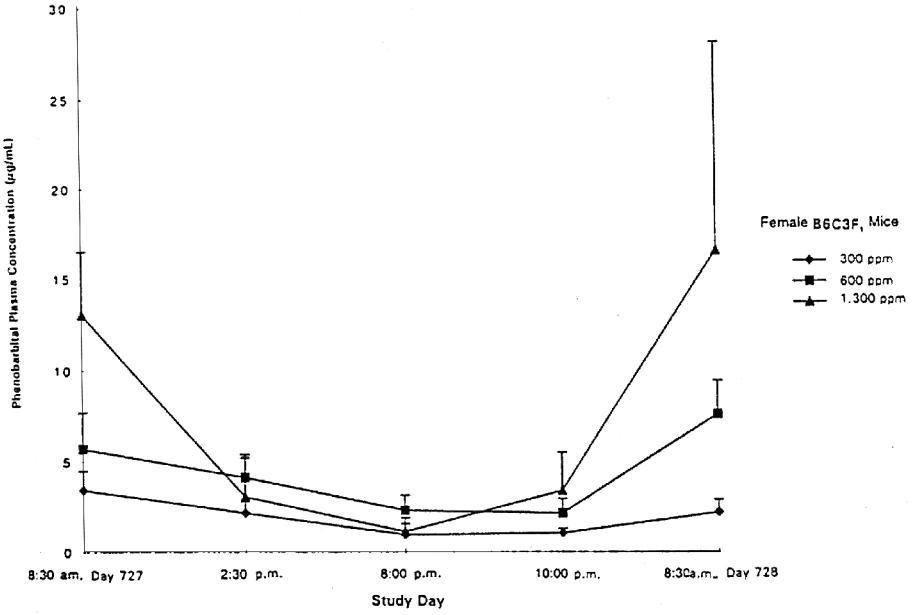

Figure H4
Plasma Concentrations of Phenobarbital in Female Mice after Exposure to 300, 600, or 1,300 ppm Primidone in Feed for 2 Years

APPENDIX I
REPRODUCTIVE TISSUE EVALUATIONS AND ESTROUS CYCLE CHARACTERIZATION

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TABLE I1
Summary of Reproductive Tissue Evaluations and Estrous Cycle Characterization for Rats in the 14-Week Feed Study of Primidone[a]

	0 ppm	1,300 ppm	2,500 ppm	5,000 ppm
Male				
n	10	10	10	10
Weights (g)				
Necropsy body wt	363 ± 6	359 ± 6	334 ± 8**	332 ± 3**
L. cauda	0.1532 ± 0.0044	0.1529 ± 0.0043	0.1536 ± 0.0039	0.1414 ± 0.0061
L. epididymis	0.4272 ± 0.0068	0.4355 ± 0.0077	0.4265 ± 0.0069	0.4146 ± 0.0143
L. testis	1.4584 ± 0.0307	1.5167 ± 0.0274	1.5011 ± 0.0168	1.4495 ± 0.0530
Spermatid measurements				
Spermatid heads (10^7/g testis)	9.36 ± 0.40	8.62 ± 0.24	8.20 ± 0.31	9.37 ± 0.30
Spermatid heads (10^7/testis)	13.64 ± 0.61	13.06 ± 0.34	12.30 ± 0.45	13.61 ± 0.72
Spermatid count (mean/10^{-4} mL suspension)	68.20 ± 3.03	65.28 ± 1.71	61.48 ± 2.25	68.03 ± 3.59
Epididymal spermatozoal measurements				
Motility (%)	70.69 ± 2.55	73.18 ± 1.68	73.38 ± 1.57	70.34 ± 2.17
Concentration (10^6/g cauda epididymal tissue)	719 ± 64	611 ± 60	824 ± 71	699 ± 63
Female				
n	10	10	10	10
Necropsy body wt (g)	201 ± 3	195 ± 3	190 ± 3**	187 ± 2**
Estrous cycle length (days)	4.95 ± 0.16	5.00 ± 0.00	5.10 ± 0.10	5.17 ± 0.22[b]
Estrous stages (% of cycle)				
Diestrus	41.7	38.3	38.3	40.8
Proestrus	15.0	16.7	17.5	15.8
Estrus	24.2	23.3	25.8	23.3
Metestrus	19.2	21.7	18.3	20.0

** Significantly different ($P \leq 0.01$) from the control group by Williams' or Dunnett's test

[a] Weights, spermatid and epididymal spermatozoal parameters, and estrous cycle lengths are presented as mean ± standard error. Differences from the control group for organ weights are not significant by Dunnett's test; differences from the control group for spermatid and epididymal spermatozoal parameters and estrous cycle length are not significant by Dunn's test. By multivariate analysis of variance, exposed females do not differ significantly from the control females in relative length of time spent in the estrous stages.

[b] Estrous cycle was longer than 12 days or unclear in 1 of 10 animals.

TABLE I2
Summary of Reproductive Tissue Evaluations and Estrous Cycle Characterization for Mice in the 14-Week Feed Study of Primidone[a]

	0 ppm	1,300 ppm	2,500 ppm	5,000 ppm
Male				
n	10	10	10	7
Weights (g)				
Necropsy body wt	32.5 ± 0.7	32.1 ± 0.7	32.6 ± 0.8	29.9 ± 0.6
L. cauda	0.0133 ± 0.0006	0.0135 ± 0.0004	0.0132 ± 0.0004	0.0131 ± 0.0006
L. epididymis	0.0387 ± 0.0009	0.0388 ± 0.0007	0.0389 ± 0.0006	0.0379 ± 0.0008
L. testis	0.1125 ± 0.0022	0.1121 ± 0.0028	0.1151 ± 0.0022	0.1116 ± 0.0037
Spermatid measurements				
Spermatid heads (10^7/g testis)	18.55 ± 0.50	19.84 ± 0.73	18.73 ± 0.73	19.00 ± 0.99
Spermatid heads (10^7/testis)	2.08 ± 0.04	2.22 ± 0.08	2.15 ± 0.08	2.10 ± 0.07
Spermatid count (mean/10^{-4} mL suspension)	65.00 ± 1.31	69.25 ± 2.43	67.20 ± 2.50	65.71 ± 2.21
Epididymal spermatozoal measurements				
Motility (%)	72.92 ± 2.35	72.58 ± 2.51	69.58 ± 3.50	69.63 ± 2.62
Concentration (10^6/g cauda epididymal tissue)	1,248 ± 161	1,261 ± 212	1,647 ± 170	1,385 ± 225
Female				
n	10	10	10	8
Necropsy body wt (g)	28.4 ± 0.6	29.9 ± 1.0	29.3 ± 0.6	27.6 ± 0.6
Estrous cycle length (days)	4.2 ± 0.1	4.9 ± 0.1**	4.9 ± 0.1**	5.1 ± 1.1**[c]
Estrous stages[b] (% of cycle)				
Diestrus	28.3	21.7	24.2	28.1
Proestrus	24.2	16.7	20.0	16.7
Estrus	26.7	42.5	37.5	38.5
Metestrus	20.8	19.2	18.3	16.7

** Significantly different from the control group (P≤0.01) by Shirley's test

[a] Weights, spermatid and epididymal spermatozoal parameters, and estrous cycle length are presented as mean ± standard error. Differences from the control group for weights were not significant by Dunnett's test; differences from the control group for spermatid and epididymal spermatozoal parameters were not significant by Dunn's test.

[b] Evidence shows that females exposed to 1,300, 2,500, or 5,000 ppm differ significantly (Wilk's Criterion, P≤0.01) from the control females in the relative length of time spent in the estrous stages. Exposed females spent more time in estrus and less time in proestrus and metestrus than control females.

[c] Estrous cycle was longer than 12 days or unclear in one of eight animals.

APPENDIX J
CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

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CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

PROCUREMENT AND CHARACTERIZATION OF PRIMIDONE

Primidone was obtained from Siegfried, LTD (Zofingen, Switzerland) in one lot (G041889), which was used during the 14-day, 14-week, and 2-year studies. Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory, Research Triangle Institute (Research Triangle Park, NC). Reports on analyses performed in support of the primidone studies are on file at the National Institute of Environmental Health Sciences.

The chemical, a white crystalline powder, was identified as primidone by infrared, ultraviolet/visible, nuclear magnetic resonance spectroscopy, and low- and high-resolution mass spectroscopy. All spectra were consistent with those expected for the structure of primidone; the low-resolution mass spectrum was also consistent with a literature reference (NIST Database). The infrared and nuclear magnetic spectra are presented in Figures J1 and J2. The melting point range of 282° to 283° C was consistent with a literature reference range of 281° to 282° C (*Merck Index*, 1983).

The purity of lot G041889 was determined by Karl Fischer water analysis, thin-layer chromatography (TLC), and high-performance liquid chromatography (HPLC). TLC was performed on silica gel 60 F-254 plates with two solvent systems: A) acetone:chloroform:*t*-butanol (30:68:2) and B) hexane:ethyl acetate:ethanol (50:40:10). Visualization was accomplished with I_2 vapors, ultraviolet light, and a PMA/ceric sulfate spray. HPLC analyses were performed with two column systems: 1) a DuPont Zorbax® C8 column using ultraviolet detection (210 nm) and a gradient solvent system of 0.01M aqueous ammonium acetate:methanol (90:10 to 10:90) and 2) a DuPont Zorbax CN column using ultraviolet detection (210 nm) and a gradient solvent system of hexane:ethanol (90:10 to 10:90). The flow rate was 1.0 mL/minute for each system.

Karl Fischer water analysis indicated 0.27% ± 0.01% water. TLC by each system indicated a major product spot and no impurities. HPLC indicated one major peak and one impurity with an area of 0.06% (first HPLC system) or 0.32% (second HPLC system) relative to the major peak area. The overall purity was determined to be greater than 99%.

Accelerated stability studies of the bulk chemical were performed by the analytical chemistry laboratory. HPLC was performed with system 1 but with ultraviolet detection at 215 nm and a solvent ratio of 70:30. These studies indicated that primidone was stable as a bulk chemical for 2 weeks when stored protected from light at room temperature (22° to 27° C). To ensure stability, the bulk chemical was stored at room temperature protected from light in plastic bags in metal containers. Stability was monitored during the 14-day, 14-week, and 2-year studies with HPLC, using the same system as the bulk chemical stability studies. No degradation of the bulk chemical was detected.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

The dose formulations were prepared once during the 14-day studies, five times during the 14-week studies, and approximately every 6 weeks during the 2-year studies by mixing primidone with feed (Table J1). Mixtures were made by preparing by hand a primidone/feed premix, which was then blended with additional feed in a Patterson-Kelly twin-shell blender (East Stroudsberg, PA) for 15 minutes, using an

intensifier bar for the initial 5 minutes. The dose formulations were stored in plastic containers in the dark at 5° C for up to 4 weeks (14-week studies) or up to 35 days (2-year studies).

Homogeneity studies of the 300 and 5,000 ppm dose formulations for the 14-week studies and of 300 and 2,500 ppm dose formulations for the 2-year studies were performed by the study laboratory. Primidone was extracted from the dose formulations with methanol with phthalamide added as an internal standard. Extracted feed samples were analyzed by HPLC with the system described for the bulk purity analyses. The analytical chemistry laboratory tested the homogeneity and stability of a 0.2 mg/g formulation with HPLC by the methods described for the bulk stability analyses. Homogeneity was confirmed, and stability was confirmed for at least 28 days for dose formulations stored frozen (-14° to -19° C) or refrigerated (3° to 7° C) in sealed glass bottles. The study laboratory confirmed stability for dose formulations stored in plastic containers at 5° C for at least 35 days.

Periodic analyses of the dose formulations of primidone were conducted at the study laboratory with the HPLC system used for the homogeneity studies. Dose formulations were analyzed once during the 14-day studies, three times during the 14-week studies (Table J2), and approximately every 8 weeks during the 2-year studies (Table J3). All dose formulations for rats and mice were within 10% of the target concentration during the 14-day studies. All dose formulations for rats and mice were within 10% of the target concentration during the 14-week studies with no concentration less than 92% or greater than 107% of the target concentration; all animal room samples for rats and 14 of 15 animal room samples for mice were also within 10% of the target concentration (Table J2). During the 2-year studies, 56 of 57 dose formulations for rats and 36 of 38 dose formulations for mice were within 10% of the target concentration; all animal room samples for rats and 9 of 12 animal room samples for mice were also within 10% of the target concentration. One dose formulation that was 111% of the target concentration was fed to mice; no dose formulation given to rats was greater than 110% of the target concentration.

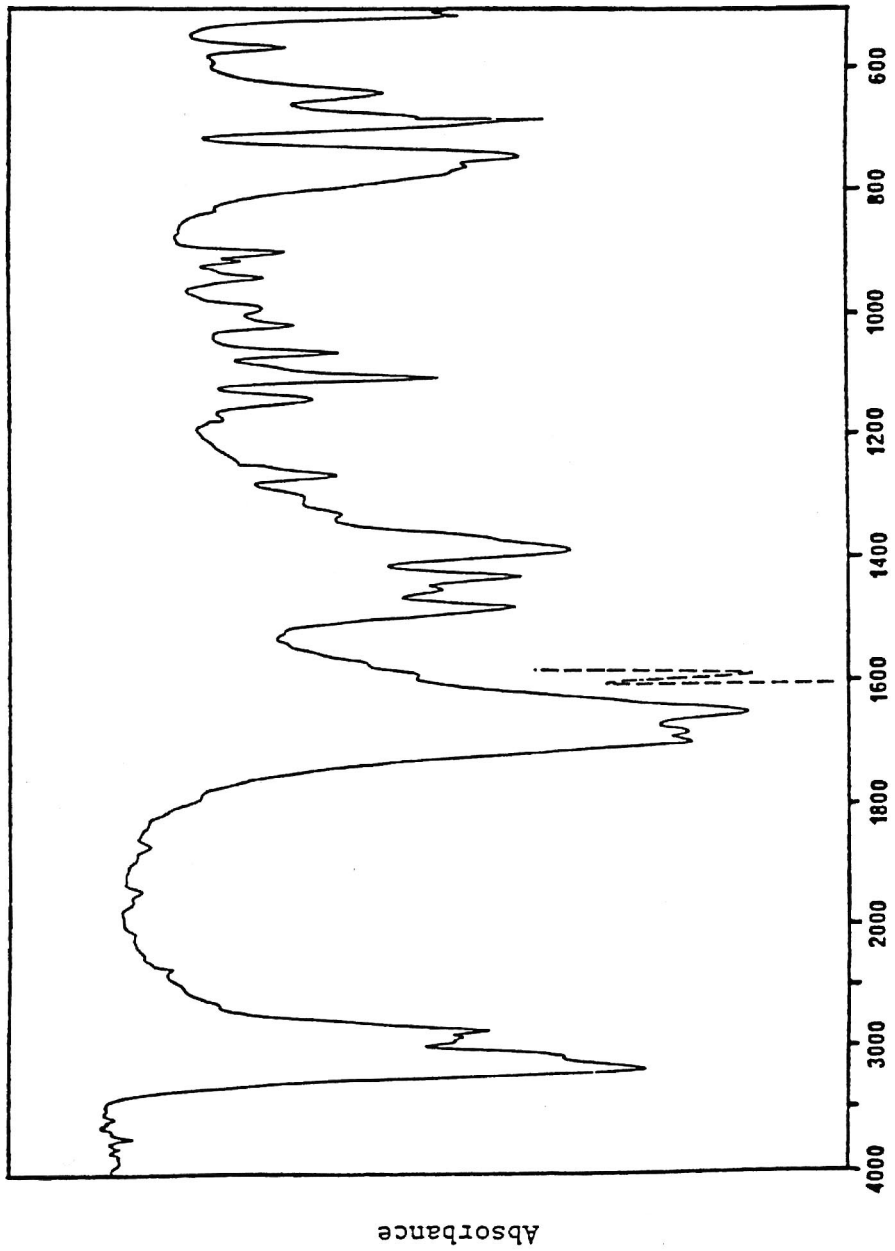

Figure J1
Infrared Absorption Spectrum of Primidone

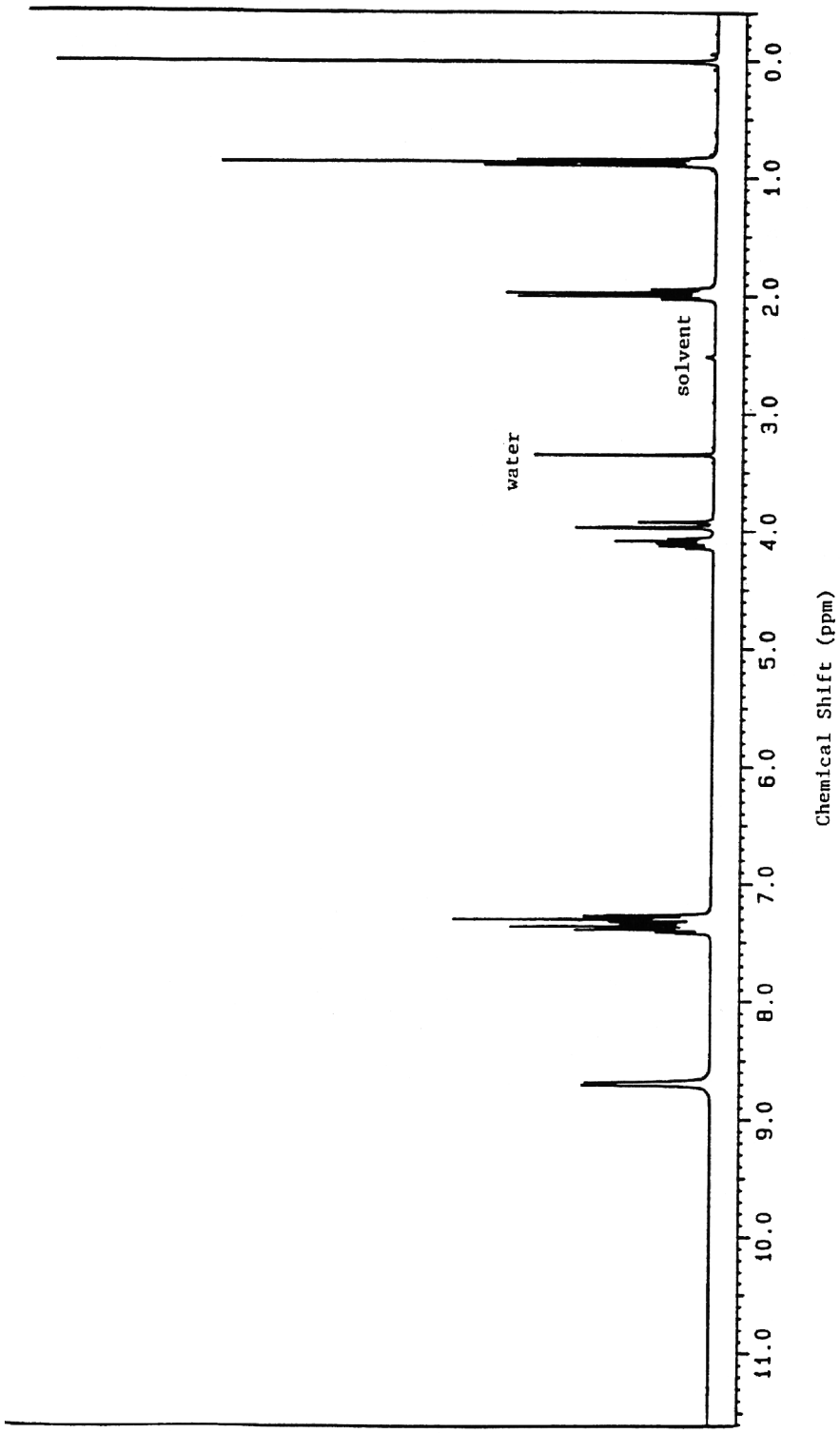

Figure J2
Nuclear Magnetic Resonance Spectrum of Primidone

TABLE J1
Preparation and Storage of Dose Formulations in the Feed Studies of Primidone

14-Day Studies	14-Week Studies	2-Year Studies
Preparation		
A premix of feed and primidone was prepared by hand, then layered into the remaining feed and blended in a Patterson-Kelly twin-shell blender with the intensifier bar on for 5 minutes and off for 10 minutes. Dose formulations were prepared once.	Same as the 14-day studies except dose formulations were prepared monthly.	Same as the 14-day studies except dose formulations were blended for 15 minutes, with the intensifier bar on for the first 5 minutes for formulations blended prior to 18 March 1993. Dose formulations were prepared every 2 months.
Chemical Lot Number		
G041889	G041889	G041889
Maximum Storage Time		
4 weeks	4 weeks	35 days
Storage Conditions		
Stored at 5° C (container not specified)	Stored in plastic bags inside buckets at 5° C	Stored in plastic containers protected from light at 5° C
Study Laboratory		
Battelle Columbus Laboratories (Columbus, OH)	Battelle Columbus Laboratories (Columbus, OH)	Battelle Columbus Laboratories (Columbus, OH)

TABLE J2
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 14-Week Feed Studies of Primidone

Date Prepared	Date Analyzed	Target Concentration (mg/g)	Determined Concentration[a] (mg/g)	Difference from Target (%)
Rats				
3 December 1990	6 December 1990	0.3[b]	0.308	+3
		0.3[c]	0.303	+1
		0.3[d]	0.314	+5
		0.6	0.64	+7
		1.3	1.36	+5
		2.5	2.46	−2
		5.0[b]	5.04	+1
		5.0[c]	5.14	+3
		5.0[d]	5.06	+1
	10 January 1991[e]	0.3	0.283	−6
		0.6	0.588	−2
		1.3	1.28	−2
		2.5	2.43	−3
		5.0	5.09	+2
9 January 1991	10 January 1991	0.3	0.296	−1
		0.6	0.609	+2
		1.3	1.34	+3
		2.5	2.38	−5
		5.0	5.12	+2
	7 February 1991[e]	0.3	0.289	−4
		0.6	0.625	+4
		1.3	1.31	+1
		2.5	2.55	+2
		5.0	5.17	+3
19 February 1991	21 February 1991	0.3	0.293	−2
		0.6	0.600	0
		1.3	1.35	+4
		2.5	2.42	−3
		5.0	5.00	0
	22 March 1991[e]	0.3	0.311	+4
		0.6	0.627	+5
		1.3	1.35	+4
		2.5	2.50	0
		5.0	4.99	0

TABLE J2
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 14-Week Feed Studies of Primidone

Date Prepared	Date Analyzed	Target Concentration (mg/g)	Determined Concentration (mg/g)	Difference from Target (%)
Mice				
3 December 1990	6 December 1990	0.3[b]	0.296	−1
		0.3[c]	0.295	−2
		0.3[d]	0.294	−2
		0.6	0.64	+7
		1.3	1.36	+5
		2.5	2.29	−8
		5.0[b]	4.99	0
		5.0[c]	5.03	+1
		5.0[d]	4.97	−1
	10 January 1991[e]	0.3	0.300	0
		0.6	0.595	−1
		1.3	1.29	−1
		2.5	2.27	−9
		5.0	5.14	+3
9 January 1991	10 January 1991	0.3	0.302	+1
		0.6	0.599	0
		1.3	1.32	+2
		2.5	2.40	−4
		5.0	5.21	+4
	7 February 1991[e]	0.3	0.297	−1
		0.6	0.629	+5
		1.3	1.33	+2
		2.5	2.56	+2
		5.0	4.94	−1
19 February 1991	21 February 1991	0.3	0.295	−2
		0.6	0.612	+2
		1.3	1.31	+1
		2.5	2.50	0
		5.0	4.99	0
	5 April 1991[e]	0.3	0.268	−11
		0.6	0.563	−6
		1.3	1.31	+1
		2.5	2.70	+8
		5.0	5.10	+2

[a] Results of duplicate analyses. 0.3 mg/g = 300 ppm; 0.6 mg/g = 600 ppm; 1.3 mg/g = 1,300 ppm; 2.5 mg/g = 2,500 ppm; and 5.0 mg/g = 5,000 ppm
[b] Sample selection from top left of twin-shell blender
[c] Sample selection from top right of twin-shell blender
[d] Sample selection from bottom of twin-shell blender
[e] Animal room samples

TABLE J3
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 2-Year Feed Studies of Primidone

Date Prepared	Date Analyzed	Target Concentration (mg/g)	Determined Concentration[a] (mg/g)	Difference from Target (%)
Rats				
26 March 1992	26 March 1992	0.6	0.587	−2
		0.6	0.598	0
		1.3	1.33	+2
		1.3	1.29	−1
		2.5	2.52	+1
		2.5	2.46	−2
	27-29 April 1992[b]	0.6	0.605	+1
		0.6	0.610	+2
		1.3	1.35	+4
		1.3	1.32	+2
		2.5	2.47	−1
		2.5	2.51	0
28 May 1992	28-30 May 1992	0.6	0.650	+8
		0.6	0.681	+14
		1.3	1.30	0
		1.3	1.37	+5
		2.5	2.54	+2
		2.5	2.53	+1
2 June 1992[c]	2 June 1992	0.6	0.633	+6
30 July 1992	6-11 August 1992	0.6	0.612	+2
		0.6	0.604	+1
		1.3	1.31	+1
		1.3	1.29	−1
		2.5	2.54	+2
		2.5	2.48	−1
1 October 1992	5-6 October 1992	0.6	0.624	+4
		0.6	0.629	+5
		1.3	1.36	+5
		1.3	1.37	+5
		2.5	2.63	+5
		2.5	2.58	+3
	30 October 1992[b]	0.6	0.583	−3
	3 November 1992	0.6	0.598	0
		1.3	1.26	−3
		1.3	1.34	+3
		2.5	2.49	0
		2.5	2.43	−3

TABLE J3
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 2-Year Feed Studies of Primidone

Date Prepared	Date Analyzed	Target Concentration (mg/g)	Determined Concentration (mg/g)	Difference from Target (%)
Rats (continued)				
3 December 1992	4-7 December 1992	0.6	0.585	−2
		0.6	0.589	−2
		1.3	1.28	−2
		1.3	1.28	−2
		2.5	2.49	0
		2.5	2.46	−2
3 February 1993	4-5 February 1993	0.6	0.599	0
		0.6	0.601	0
		1.3	1.34	+3
		1.3	1.30	0
		2.5	2.54	+2
		2.5	2.51	0
8 April 1993	9-12 April 1993	0.6	0.618	+3
		1.3	1.35	+4
		2.5	2.57	+3
	6-7 May 1993[b]	0.6	0.563	−6
		1.3	1.27	−2
		2.5	2.50	0
10 June 1993	11 and 14 June 1993	0.6	0.563	−6
		1.3	1.33	+2
		2.5	2.53	+1
12 August 1993	13-14 August 1993	0.6	0.604	+1
		1.3	1.29	−1
		2.5	2.43	−3
14 October 1993	18-19 October 1993	0.6	0.610	+2
		1.3	1.31	+1
		2.5	2.54	+2
	18-19 November 1993[b]	0.6	0.586	−2
		1.3	1.28	−2
		2.5	2.50	0
16 December 1993	24 December 1993	0.6	0.593	−1
		0.6	0.584	−3
		1.3	1.26	−3
		1.3	1.28	−2
		2.5	2.44	−2
		2.5	2.51	0
17 February 1994	18-19 February 1994	0.6	0.614	+2
		1.3	1.43	+10
		2.5	2.47	−1

TABLE J3
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 2-Year Feed Studies of Primidone

Date Prepared	Date Analyzed	Target Concentration (mg/g)	Determined Concentration (mg/g)	Difference from Target (%)
Mice				
26 March 1992	26 Mrch 1992	0.3	0.242	−19
		0.6	0.563	−6
		1.3	1.34	+3
	27-29 April 1992[b]	0.6	0.570	−5
		1.3	1.17	−10
31 March 1992[c]	2 April 1992	0.3	0.305	+2
	27-29 April 1992[b]	0.3	0.269	-10
28 May 1992	28-30 May 1992	0.3	0.333	+11
		0.6	0.650	+8
		1.3	1.37	+5
30 July 1992	6-11 August 1992	0.3	0.306	+2
		0.6	0.598	0
		1.3	1.31	+1
1 October 1992	5-6 October 1992	0.3	0.308	+3
		0.6	0.625	+4
		1.3	1.37	+5
	30 October 1992[b]	0.3	0.272	−9
	3 November 1992	0.6	0.503	−16
		1.3	1.28	−2
3 December 1992	4-7 December 1992	0.3	0.314	+5
		0.6	0.597	0
		1.3	1.31	+1
3 February 1993	4-5 February 1993	0.3	0.317	+6
		0.6	0.620	+3
		1.3	1.29	−1
8 April 1993	9-12 April 1993	0.3	0.322	+7
		0.6	0.618	+3
		1.3	1.35	+4
	6-7 May 1993[b]	0.3	0.255	−15
		0.6	0.550	−8
		1.3	1.26	−3
10 June 1993	11 and 14 June 1993	0.3	0.278	−7
		0.6	0.563	−6
		1.3	1.33	+2

TABLE J3
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 2-Year Feed Studies of Primidone

Date Prepared	Date Analyzed	Target Concentration (mg/g)	Determined Concentration (mg/g)	Difference from Target (%)
Mice (continued)				
12 August 1993	13-16 August 1993	0.3	0.307	+2
		0.6	0.604	+1
		1.3	1.29	-1
14 October 1993	18-19 October 1993	0.3	0.294	-2
		0.6	0.610	+2
		1.3	1.31	+1
	18-19 October 1993[b]	0.3	0.263	-12
		0.6	0.544	-9
		1.3	1.30	0
16 December 1993	24 December 1993	0.3	0.282	-6
		0.6	0.593	-1
		0.6	0.584	-3
		1.3	1.26	-3
		1.3	1.28	-2
17 February 1994	18-19 February 1994	0.3	0.288	-4
		0.6	0.614	+2
		1.3	1.43	+10

[a] Results of duplicate analyses. 0.3 mg/g = 300 ppm; 0.6 mg/g = 600 ppm; 1.3 mg/g = 1,300 ppm; and 2.5 mg/g = 2,500 ppm
[b] Animal room samples
[c] Results of remix

APPENDIX K
FEED AND COMPOUND CONSUMPTION IN THE 2-YEAR FEED STUDIES OF PRIMIDONE

TABLE K1 Feed and Compound Consumption by Male Rats in the 2-Year Feed Study of Primidone 252
TABLE K2 Feed and Compound Consumption by Female Rats in the 2-Year Feed Study of Primidone 253
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TABLE K1
Feed and Compound Consumption by Male Rats in the 2-Year Feed Study of Primidone

	0 ppm		600 ppm			1,300 ppm			2,500 ppm		
Week	Feed (g/day)[a]	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose/ Day[b] (mg/kg)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg)
1	16.8	151	17.7	151	70	17.8	150	154	17.4	150	291
2	17.8	191	17.7	192	55	17.7	191	121	18.3	190	241
4	16.7	256	17.8	258	41	17.9	256	91	17.8	258	173
5	17.2	271	18.6	276	41	18.4	276	87	18.8	278	169
8	17.3	327	17.4	330	32	17.7	329	70	18.0	324	139
9	17.5	336	17.1	342	30	17.3	337	67	17.0	329	129
12	18.1	363	17.2	369	28	17.8	364	63	17.4	358	121
13	16.9	372	17.5	378	28	18.0	376	62	17.8	369	121
17	16.4	395	16.9	401	25	17.0	398	55	17.1	386	111
21	17.5	421	17.2	424	24	17.7	423	54	17.5	405	108
25	16.4	440	16.9	442	23	17.6	438	52	17.2	418	103
29	17.0	459	16.6	456	22	16.9	450	49	17.1	432	99
33	16.0	471	16.1	467	21	16.7	458	47	17.1	440	97
37	17.0	480	17.1	474	22	16.6	466	46	18.1	441	103
41	15.9	490	16.3	485	20	17.5	476	48	16.8	454	92
45	17.2	493	17.1	489	21	17.3	479	47	17.1	458	94
49	16.4	506	16.8	498	20	17.5	488	47	15.7	455	86
53	17.4	514	17.0	508	20	15.5	488	41	15.5	464	84
57	16.5	517	16.4	510	19	16.2	496	42	17.1	471	91
60	16.4	518	16.4	509	19	17.3	494	45	16.4	468	88
65	15.6	521	16.6	515	19	16.6	500	43	17.2	468	92
69	16.6	521	15.8	505	19	15.7	493	41	17.4	460	94
73	15.9	522	16.0	510	19	16.9	492	45	17.0	459	92
77	15.1	521	15.3	505	18	15.3	485	41	15.2	444	86
81	16.0	513	16.2	503	19	15.4	481	42	17.0	443	96
85	15.1	510	15.0	500	18	14.7	471	40	11.1	390	71
89	13.6	498	13.4	479	17	14.8	469	41			
93	13.4	485	15.0	477	19	14.0	445	41			
97	15.0	483	14.1	462	18	15.6	432	47			
101	13.8	468	13.8	444	19						
Mean for weeks											
1-13	17.3	283	17.6	287	41	17.8	285	89	17.8	282	173
14-52	16.6	462	16.8	460	22	17.2	453	50	17.1	432	99
53-101	15.4	507	15.5	494	19	15.7	479	43	16.0	452	88

[a] Grams of feed consumed per animal per day
[b] Milligrams of primidone consumed per kilogram body weight per day

TABLE K2
Feed and Compound Consumption by Female Rats in the 2-Year Feed Study of Primidone

	0 ppm		600 ppm			1,300 ppm			2,500 ppm		
Week	Feed (g/day)[a]	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose/ Day[b] (mg/kg)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg)
1	12.4	118	13.9	118	71	13.7	117	152	13.6	118	288
2	11.5	133	11.4	133	51	11.7	135	113	11.8	135	219
4	11.2	160	11.6	158	44	12.0	159	98	11.2	157	178
5	11.9	167	11.5	166	41	11.4	166	90	11.2	165	170
8	10.8	186	11.2	184	37	10.9	182	78	10.6	182	146
9	10.9	190	10.6	186	34	10.7	187	74	10.3	184	140
12	10.9	204	10.2	199	31	10.5	197	70	10.1	195	130
13	10.7	207	10.7	201	32	10.5	199	68	10.5	198	133
17	10.9	219	11.0	212	31	10.9	210	67	10.3	206	125
21	10.7	229	10.4	223	28	10.7	219	64	9.7	212	114
25	10.7	236	10.8	230	28	10.6	225	61	10.0	218	115
29	10.9	247	10.7	242	27	11.0	237	61	10.2	225	113
33	10.4	255	10.6	252	25	10.5	243	56	10.4	233	112
37	11.0	265	10.9	259	25	10.8	252	56	10.5	238	111
41	11.0	273	11.2	268	25	10.6	258	54	10.5	244	108
45	11.3	280	11.2	274	24	10.9	268	53	10.8	251	108
49	10.8	294	10.9	284	23	11.0	278	51	10.9	260	105
53	11.1	301	10.7	288	22	10.8	284	50	10.5	266	98
57	11.6	308	11.3	296	23	11.0	291	49	11.2	276	102
60	11.8	317	11.3	304	22	12.0	300	52	10.7	281	95
65	11.0	322	10.8	309	21	11.1	304.	47	10.8	291	93
69	12.1	328	12.1	317	23	11.7	310	49	11.2	295	95
73	12.4	339	11.9	326	22	11.5	319	47	10.9	302	91
77	11.2	341	10.9	328	20	10.8	322	44	10.6	304	87
81	11.5	342	11.0	328	20	11.8	325	47	11.2	310	91
85	12.0	350	10.9	330	20	10.7	327	43	10.2	308	82
89	11.3	347	11.3	329	21	11.4	330	45	11.4	314	91
93	12.3	358	11.8	340	21	11.8	338	45	11.3	320	88
97	12.5	363	12.1	347	21	12.0	338	46	11.0	315	87
101	11.9	361	11.9	348	21	11.7	337	45	10.9	317	86
Mean for weeks											
1-13	11.3	171	11.4	168	43	11.4	168	93	11.2	167	175
14-52	10.9	255	10.8	249	26	10.8	243	58	10.4	232	112
53-101	11.7	337	11.4	322	21	11.4	317	47	10.9	300	91

[a] Grams of feed consumed per animal per day
[b] Milligrams of primidone consumed per kilogram body weight per day

TABLE K3
Feed and Compound Consumption by Male Mice in the 2-Year Feed Study of Primidone

	0 ppm		300 ppm			600 ppm			1,300 ppm		
Week	Feed (g/day)[a]	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose/ Day[b] (mg/kg)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg)
2	4.6	23.8	4.6	23.8	58	4.3	23.7	108	5.0	23.6	273
5	5.7	28.0	5.8	28.7	61	5.1	28.6	107	5.8	28.6	265
9	5.4	32.6	5.1	33.8	45	4.8	32.9	87	5.1	32.5	203
13	5.4	37.8	5.3	38.0	42	5.0	36.9	82	5.0	36.3	180
17	4.8	42.3	4.7	42.2	34	4.6	41.2	67	4.5	39.1	149
21	4.6	44.5	4.6	45.3	31	4.6	43.7	63	4.6	41.8	142
25	4.7	46.0	4.6	46.6	29	4.4	45.4	58	4.5	43.7	133
29	4.4	47.2	4.4	47.2	28	4.4	46.1	57	4.3	44.3	127
33	4.5	47.5	4.5	48.3	28	4.4	47.3	56	4.4	45.2	126
36	4.8	47.8	4.6	48.4	29	4.7	47.6	59	4.6	45.4	131
41	4.6	49.9	4.4	49.6	27	4.6	48.5	56	4.7	46.8	130
45	4.7	49.2	4.7	49.1	29	4.5	48.2	56	4.7	47.5	127
49	4.3	50.4	4.3	51.3	25	4.2	50.8	49	4.2	49.5	110
53	5.0	50.3	4.8	51.4	28	4.8	51.0	56	4.7	48.8	126
57	4.8	50.5	4.8	52.3	28	4.7	51.8	54	4.6	49.3	121
61	4.7	49.7	4.7	51.3	27	4.5	50.7	53	4.5	48.3	120
65	5.1	50.7	5.0	52.0	29	4.9	52.2	56	4.9	48.4	131
69	5.0	49.9	4.8	51.7	28	4.9	51.5	57	4.8	46.4	135
73	5.1	50.3	4.9	52.1	28	5.1	52.4	59	4.9	45.3	140
77	5.4	49.7	5.1	51.5	30	5.1	50.7	60	5.2	43.4	156
81	5.0	50.2	4.9	51.8	28	5.1	49.5	62	5.0	41.8	157
84	5.0	50.8	5.0	52.2	29	5.1	48.9	62	5.1	41.9	158
88	5.0	51.2	5.0	52.0	29	5.2	46.9	66	5.1	40.7	163
93	4.7	49.6	4.9	50.7	29	5.2	44.1	71	5.1	39.5	169
97	4.5	49.1	5.0	51.1	29	5.3	43.9	72	5.0	38.3	169
101	4.7	48.9	5.0	48.3	31	5.3	43.0	74	5.2	37.9	178
Mean for weeks											
1-13	5.3	30.5	5.2	31.1	51	4.8	30.5	96	5.2	30.3	230
14-52	4.6	47.2	4.5	47.5	29	4.5	46.5	58	4.5	44.8	131
53-101	4.9	50.1	4.9	51.4	29	5.0	49.0	62	4.9	43.8	148

[a] Grams of feed consumed per animal per day
[b] Milligrams of primidone consumed per kilogram body weight per day

TABLE K4
Feed and Compound Consumption by Female Mice in the 2-Year Feed Study of Primidone

	0 ppm		300 ppm			600 ppm			1,300 ppm		
Week	Feed (g/day)[a]	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose/ Day[b] (mg/kg)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg)
1	2.6	18.1	2.4	18.1	39	2.4	18.1	80	2.2	18.0	160
2	3.1	19.0	2.9	19.0	46	3.1	18.8	100	3.5	19.0	236
3	4.5	19.9	4.9	20.5	72	4.8	20.4	140	4.9	20.2	314
4	4.9	21.4	5.0	22.0	68	5.3	21.5	147	5.2	21.6	314
5	5.0	22.8	5.2	23.3	67	5.1	23.0	134	4.7	23.3	262
8	4.9	25.9	4.4	27.8	47	4.2	27.0	93	4.5	26.5	222
9	5.2	27.8	4.7	29.1	48	4.8	28.6	101	4.5	28.2	206
12	4.6	31.5	4.1	33.5	37	4.4	31.8	83	4.3	31.0	180
13	5.0	32.9	4.5	34.3	39	4.9	33.0	89	4.6	32.2	186
17	4.4	37.7	3.8	39.9	29	4.0	37.9	63	3.7	37.1	131
21	4.0	40.7	3.8	42.7	27	4.0	40.2	59	3.5	39.4	117
25	4.0	43.3	3.8	45.5	25	3.8	42.5	54	3.6	41.8	113
29	4.5	43.4	3.6	47.2	23	3.7	43.9	51	3.7	43.0	111
33	3.3	45.2	3.0	48.3	19	2.9	44.8	38	2.9	43.1	87
36	3.8	46.7	3.6	49.6	22	3.7	46.0	48	3.5	44.5	102
41	3.9	49.1	3.8	51.5	22	3.6	48.2	45	3.6	46.3	101
45	3.3	51.1	3.4	53.4	19	3.2	49.8	39	3.4	47.7	93
49	3.8	53.4	3.5	55.3	19	3.7	52.4	42	3.7	49.7	98
53	4.0	54.7	4.0	55.7	21	3.8	53.2	43	3.9	50.4	102
57	4.0	55.6	3.9	57.2	21	3.8	54.5	42	3.8	51.7	95
61	3.7	55.8	3.8	57.1	20	3.9	54.8	42	3.8	52.2	94
65	4.2	56.2	4.2	57.5	22	4.0	54.8	44	4.1	51.8	103
69	3.8	57.4	3.9	58.8	20	3.8	55.8	40	3.8	53.1	94
73	4.2	59.0	4.3	60.0	21	4.2	57.0	44	4.0	54.5	95
77	3.8	58.1	4.0	59.8	20	4.0	56.2	43	4.3	53.5	104
81	4.2	59.3	4.4	61.2	22	4.2	57.8	44	4.6	53.9	111
84	3.9	60.6	4.2	62.7	20	4.0	59.3	40	4.3	54.1	104
88	4.0	60.3	4.2	63.1	20	4.1	59.7	41	4.5	52.2	113
93	4.1	60.7	4.4	63.7	21	4.2	58.7	43	4.2	49.0	112
97	4.0	61.6	4.0	64.7	18	4.0	58.7	41	4.5	47.6	122
101	4.3	61.3	4.1	61.6	20	4.6	57.6	48	4.7	46.0	133
Mean for weeks											
1-13	4.4	24.4	4.2	25.3	52	4.3	24.7	107	4.3	24.4	231
14-52	3.9	45.6	3.6	48.1	23	3.6	45.1	49	3.5	43.6	106
53-101	4.0	58.5	4.1	60.3	20	4.0	56.8	43	4.2	51.5	106

[a] Grams of feed consumed per animal per day
[b] Milligrams of primidone consumed per kilogram body weight per day

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

TABLE L1 Ingredients of NIH-07 Rat and Mouse Ration 258
TABLE L2 Vitamins and Minerals in NIH-07 Rat and Mouse Ration 258
TABLE L3 Nutrient Composition of NIH-07 Rat and Mouse Ration 259
TABLE L4 Contaminant Levels in NIH-07 Rat and Mouse Ration 260

TABLE L1
Ingredients of NIH-07 Rat and Mouse Ration[a]

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

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

TABLE L2
Vitamins and Minerals in NIH-07 Rat and Mouse Ration[a]

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

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

TABLE L3
Nutrient Composition of NIH-07 Rat and Mouse Ration

Nutrient	Mean ± Standard Deviation	Range	Number of Samples
Protein (% by weight)	23.10 ± 0.52	22.2 – 24.0	22
Crude fat (% by weight)	5.34 ± 0.23	4.80 – 5.70	22
Crude fiber (% by weight)	3.17 ± 0.33	2.50 – 3.80	22
Ash (% by weight)	6.46 ± 0.27	6.08 – 7.03	22
Amino Acids (% of total diet)			
Arginine	1.280 ± 0.083	1.110 – 1.390	11
Cystine	0.308 ± 0.071	0.181 – 0.400	11
Glycine	1.158 ± 0.048	1.060 – 1.220	11
Histidine	0.584 ± 0.027	0.531 – 0.630	11
Isoleucine	0.917 ± 0.033	0.867 – 0.965	11
Leucine	1.975 ± 0.051	1.850 – 2.040	11
Lysine	1.274 ± 0.049	1.200 – 1.370	11
Methionine	0.437 ± 0.109	0.306 – 0.699	11
Phenylalanine	0.999 ± 0.120	0.665 – 1.110	11
Threonine	0.904 ± 0.058	0.824 – 0.985	11
Tryptophan	0.218 ± 0.153	0.107 – 0.671	11
Tyrosine	0.685 ± 0.094	0.564 – 0.794	11
Valine	1.086 ± 0.055	0.962 – 1.170	11
Essential Fatty Acids (% of total diet)			
Linoleic	2.407 ± 0.227	1.830 – 2.570	10
Linolenic	0.259 ± 0.065	0.100 – 0.320	10
Vitamins			
Vitamin A (IU/kg)	6,730 ± 529	5,940 – 8,580	22
Vitamin D (IU/kg)	4,450 ± 1,382	3,000 – 6,300	4
α-Tocopherol (ppm)	35.43 ± 8.98	22.5 – 48.9	11
Thiamine (ppm)	16.27 ± 2.29	12.0 – 23.0	22
Riboflavin (ppm)	7.83 ± 0.923	6.10 – 9.00	11
Niacin (ppm)	99.22 ± 24.27	65.00 – 150.00	11
Pantothenic acid (ppm)	30.55 ± 3.52	23.0 – 34.6	11
Pyridoxine (ppm)	9.11 ± 2.53	5.60 – 14.0	11
Folic acid (ppm)	2.46 ± 0.63	1.80 – 3.70	11
Biotin (ppm)	0.268 ± 0.047	0.190 – 0.354	11
Vitamin B_{12} (ppb)	40.5 ± 19.1	10.6 – 65.0	11
Choline (ppm)	2,991 ± 382	2,300 – 3,430	10
Minerals			
Calcium (%)	1.18 ± 0.08	1.04 – 1.32	22
Phosphorus (%)	0.90 ± 0.06	0.770 – 1.00	22
Potassium (%)	0.886 ± 0.063	0.772 – 0.971	9
Chloride (%)	0.529 ± 0.087	0.380 – 0.635	9
Sodium (%)	0.316 ± 0.033	0.258 – 0.371	11
Magnesium (%)	0.166 ± 0.010	0.148 – 0.181	11
Sulfur (%)	0.272 ± 0.059	0.208 – 0.420	10
Iron (ppm)	350.5 ± 87.3	255.0 – 523.0	11
Manganese (ppm)	92.48 ± 5.14	81.7 – 99.4	11
Zinc (ppm)	59.33 ± 10.2	46.1 – 81.6	11
Copper (ppm)	11.81 ± 2.50	8.09 – 15.4	11
Iodine (ppm)	3.54 ± 1.19	1.52 – 5.83	10
Chromium (ppm)	1.66 ± 0.46	0.85 – 2.09	11
Cobalt (ppm)	0.76 ± 0.23	0.49 – 1.15	7

TABLE L4
Contaminant Levels in NIH-07 Rat and Mouse Ration[a]

	Mean ± Standard Deviation[b]	Range	Number of Samples
Contaminants			
Arsenic (ppm)	0.59 ± 0.16	0.10 – 0.80	22
Cadmium (ppm)	0.08 ± 0.07	0.04 – 0.20	22
Lead (ppm)	0.30 ± 0.13	0.18 – 0.70	22
Mercury (ppm)	<0.02		
22			
Selenium (ppm)	0.37 ± 0.08	0.10 – 0.40	22
Aflatoxins (ppb)	<5.0		22
Nitrate nitrogen (ppm)[c]	7.10 ± 2.41	3.0 – 11.0	22
Nitrite nitrogen (ppm)[c]	0.79 ± 0.90	0.02 – 3.10	22
BHA (ppm)[d]	1.50 ± 1.92	1.00 – 10.0	22
BHT (ppm)[d]	1.54 ± 0.96	1.00 – 5.00	22
Aerobic plate count (CFU/g)	172,545 ± 174,369	10,000 – 630,000	22
Coliform (MPN/g)	173 ± 331	3 – 1,100	22
Escherichia coli (MPN/g)	<3		22
Salmonella (MPN/g)	Negative		22
Total nitrosoamines (ppb)[e]	11.56 ± 4.53	4.80 – 19.70	22
N-Nitrosodimethylamine (ppb)[e]	9.21 ± 4.35	3.40 – 18.00	22
N-Nitrosopyrrolidine (ppb)[e]	2.39 ± 1.16	1.00 – 5.80	22
Pesticides (ppm)			
α-BHC	<0.01		22
β-BHC	<0.02		22
γ-BHC	<0.01		22
δ-BHC	<0.01		22
Heptachlor	<0.01		22
Aldrin	<0.01		22
Heptachlor epoxide	<0.01		22
DDE	<0.01		22
DDD	<0.01		22
DDT	<0.01		22
HCB	<0.01		22
Mirex	<0.01		22
Methoxychlor	<0.05		22
Dieldrin	<0.01		22
Endrin	<0.01		22
Telodrin	<0.01		22
Chlordane	<0.05		22
Toxaphene	<0.10		22
Estimated PCBs	<0.20		22
Ronnel	<0.01		22
Ethion	<0.02		22
Trithion	<0.05		22
Diazinon	<0.10		22
Methyl parathion	<0.02		22
Ethyl parathion	<0.02		22
Malathion	0.09 ± 0.10	0.02 – 0.41	22
Endosulfan I	<0.01		22
Endosulfan II	<0.01		22
Endosulfan sulfate	<0.03		22

[a] CFU = colony forming units; MPN = most probable number; BHC = hexachlorocyclohexane or benzene hexachloride
[b] For values less than the limit of detection, the detection limit is given as the mean.
[c] Sources of contamination: alfalfa, grains, and fish meal
[d] Sources of contamination: soy oil and fish meal
[e] All values were corrected for percent recovery.

APPENDIX M
SENTINEL ANIMAL PROGRAM

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SENTINEL ANIMAL PROGRAM

METHODS

Rodents used in the Carcinogenesis Program of the National Toxicology Program are produced in optimally clean facilities to eliminate potential pathogens that may affect study results. The Sentinel Animal Program is part of the periodic monitoring of animal health that occurs during the toxicologic evaluation of chemical compounds. Under this program, the disease state of the rodents is monitored via 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 14-week and 2-year studies of primidone. Blood from each animal was collected and allowed to clot, and the serum was separated. The samples were processed appropriately and sent to Microbiological Associates, Inc. (Bethesda, MD), 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	
14-Week Study	
ELISA	
PVM (pneumonia virus of mice)	Study termination
RCV/SDA (rat coronavirus/ sialodacryoadenitis virus)	Study termination
Sendai	Study termination
Hemagglutination Inhibition	
H-1 (Toolan's H-1 virus)	Study termination
KRV (Kilham rat virus)	Study termination
2-Year Study	
ELISA	
Mycoplasma arthriditis	Study termination
Mycoplasma pulmonis	Study termination
PVM	6, 12, 13 and 18 months, study termination
RCV/SDA	6, 12, 13 and 18 months, study termination
Sendai	6, 12, 13 and 18 months, study termination
Immunoflourescence Assay	
PVM	12 months
RCV/SDA	12 and 13 months
Sendai	12 months
Hemagglutination Inhibition	
H-1	6, 12, 13 and 18 months, study termination
KRV	6, 12, 13 and 18 months, study termination

MICE

14-Week Study

ELISA

Ectromelia virus	Study termination
GDVII (mouse encephalomyelitis virus)	Study termination
LCM (lymphocytic choriomeningitis virus)	Study termination
Mouse adenoma virus-FL	Study termination
MHV (mouse hepatitis virus)	Study termination
PVM	Study termination
Reovirus 3	Study termination
Sendai	Study termination

Immunofluorescence Assay

EDIM (epizootic diarrhea of infant mice)	Study termination
Reovirus 3	Study termination

Hemagglutination Inhibition

MVM (minute virus of mice)	Study termination
K (papovavirus)	Study termination
Polyoma virus	Study termination

2-Year Study

ELISA

Ectromelia virus	6, 12, and 18 months, study termination
EDIM	6, 12, and 18 months, study termination
GDVII	6, 12, and 18 months, study termination
LCM	6, 12, and 18 months, study termination
Mouse adenoma virus-FL	6, 12, and 18 months, study termination
MHV	6, 12, and 18 months, study termination
M. arthritidis	Study termination
M. pulmonis	Study termination
PVM	6, 12, and 18 months, study termination
Reovirus 3	6, 12, and 18 months, study termination
Sendai	6, 12, and 18 months, study termination

Immunofluorescence Assay

MHV	12 months

Hemagglutination Inhibition

K	6, 12, and 18 months, study termination
MVM	6, 12, and 18 months, study termination
Polyoma virus	6, 12, and 18 months, study termination

Results of serology tests are presented in Table M1.

TABLE M1
Murine Virus Antibody Determinations for Rats and Mice in the 14-Week and 2-Year Studies of Primidone

Interval	Incidence of Antibody in Sentinel Animals	Positive Serologic Reaction for
14-Week Studies		
Rats		
Study termination	0/10	None positive
Mice		
Study termination	0/10	None positive
2-Year Studies		
Rats		
6 Months	0/10	None positive
12 Months	1/10	PVM
13 Months	0/9	None positive
18 Months	0/9	None positive
Study termination	3/10[a]	*M. arthriditis*
Mice		
6 Months	0/10	None positive
12 Months	0/10	None positive
18 Months	0/10	None positive
Study termination	0/10	None positive

[a] Further evaluation of samples positive for *M. arthritidis* by immunoblot and Western blot procedures indicated that the positive titers may have been due to a cross reaction with antibodies of nonpathogenic *Mycoplasma* or other agents. Only sporadic samples were positive and there were no clinical findings or histopathologic changes of *M. arthritidis* infection in animals with positive titers. Accordingly, *M. arthritidis*-positive titers were considered false positives.

APPENDIX N
SINGLE-DOSE TOXICOKINETIC STUDIES IN F344/N RATS AND B6C3F$_1$ MICE

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SINGLE-DOSE TOXICOKINETIC STUDIES IN F344/N RATS AND B6C3F$_1$ MICE

INTRODUCTION

Primidone is a congener of the barbiturate phenobarbital, and it is widely used in the management of epileptic seizures. Primidone is converted to two active metabolites, phenobarbital and phenylethylmalonamide. Primidone's anticonvulsant effects are likely due to the combined action of the parent compound and its active metabolites. Primidone was nominated by the National Cancer Institute and the International Agency for Research on Cancer (IARC) for animal testing due to its high production volume and widespread human exposure, its mutagenicity in genotoxicity studies, and the carcinogenicity of the metabolite phenobarbital in rodent studies. The purpose of the present study is to characterize the plasma toxicokinetic profile of primidone and its major metabolite, phenobarbital, following a single oral dose in male and female F344/N rats and B6C3F$_1$ mice. These data will be used to select dosages for the 2-year studies, correlate toxic effects with systemic availability, establish toxicokinetic parameters, improve the usefulness of toxicology study results in risk assessment, and help determine the appropriate bleeding time for the toxicokinetic studies conducted at the end of the 2-year studies.

MATERIALS AND METHODS

Primidone was obtained from Siegfried Limited (Zofingen, Switzerland) in one lot (G041889), which was also used for the 2-year studies conducted at Battelle Columbus Laboratories (Columbus, OH). Methylcellulose was obtained by the National Toxicology Program (Research Triangle Park, NC) in one lot (876672). Results of purity and stability analyses of lot G041889 are presented in Appendix I. Additionally, the identity of the bulk chemical was confirmed by infrared spectroscopy. The relative purity was determined to be 100.4% by comparison to a frozen reference sample. Additional purity reanalyses were performed approximately every 2 to 4 months by comparing test article samples to reference samples; the relative purity ranged from 99% to 102%. Dose formulations administered by gavage were prepared as needed by suspending appropriate amounts of primidone in 0.5% aqueous methylcellulose. Analyses by the study laboratory using high-performance liquid chromatography (HPLC) indicated that all dose formulations administered to the animals were homogeneous and most were within 10% of the target concentrations. Stability studies of the 6, 16, and 26 mg/mL rat dose formulations and the 3, 8, and 20 mg/mL mouse dose formulations conducted by the study laboratory indicated that suspensions were stable for up to 7 days when stored at room temperature and protected from light in sealed containers. The 200 mg/kg dose formulation was also checked to ensure that the doses could be resuspended after storage and successfully administered by gavage. One 20 mg/mL dose formulation in the mouse study was not within 10% of the target concentration.

F344/N rats and the first pool of B6C3F$_1$ mice were obtained from Charles River Laboratories (Kingston, NY) for the rat study and from Charles River Laboratories (Portage, MI) for the mouse study. The second pool of B6C3F$_1$ mice was obtained from Simonsen Laboratories (Gilroy, CA). Upon receipt, the rats and mice were observed for parasites and indications of disease. The rats were quarantined for approximately 14 days and were 13 to 14 weeks old at the start of the studies. The first pool of mice were quarantined for approximately 11 to 14 days and were 12 to 13 weeks old at the start of the studies. The second pool of mice were quarantined for approximately 3 weeks and were 14 to 15 weeks old at the start of the studies. Filtered municipal water and NIH-07 open formula pelleted diet were available *ad libitum*. During the studies, all animals were housed individually.

Doses and sampling time points for the single dose toxicokinetic studies were selected based on analyses of data from preliminary toxicokinetic studies and in preparation for the 2-year toxicokinetic studies.

Groups of 18 male and 18 female rats were administered a single dose of 30, 80, or 130 mg primidone/kg body weight by gavage. Groups of 25 to 28 male and 24 to 28 female mice were administered 30, 80, or 200 mg/kg by gavage. There were no vehicle controls in either study. The dosing volume in the rat study was approximately 5 mL/kg and the dosing volume in the mouse study was approximately 10 mL/kg. The animals were anesthetized with a mixture of carbon dioxide and oxygen, and blood samples were collected from the retroorbital sinus (rats) or by cardiac puncture (mice). In the rat study, blood samples were collected from two male and two female rats in the 30 and 80 mg/kg groups per time point at 0.25, 0.5, 1.5, 3, 6, 9, 12, 18, and 22 hours after the administration of primidone. Two male and two female rats from the 200 mg/kg groups and two to four male and female mice from the 30 or 80 mg/kg groups were sampled at 0.25, 0.5, 1.5, 3, 6, 9, 12, 22, and 30 hours after the administration of primidone. Two to four male and female mice from the 200 mg/kg group were sampled at 0.25, 0.5, 1.5, 3, 6, 9, 12, 22, 30, and 48 hours after the administration of primidone. Blood samples were collected only once from each animal. The samples were collected into heparinized tubes, and the plasma was separated and stored at −20° C or lower until analysis.

All animals were observed twice daily for signs of morbidity and mortality. Individual body weights were recorded at randomization and on study day 1. Body weights from study day 1 were used for the calculation of dosing volumes.

Plasma samples were analyzed using two HPLC systems which used a Supelco Supelcosil LC-18 column, ultraviolet detection (254 nm), and a gradient elution mobile phase of 0.18 M ammonium acetate:acetonitrile (75:25) with a 1.0 mL/minute flow rate.

The average plasma concentrations of primidone and phenobarbital and standard deviations were calculated. The logarithms of these values were plotted as a function of time. The areas under the curve and standard errors for plasma concentration versus time were calculated using the trapezoid rule of the form $AUC_t = \sum\{(C_n+C_{n-1})/2\}\times\{t_n - t_{n-1}\}$, where AUC_t is the cumulative area under the curve to time t and C_{n-1} and C_n are successive concentrations at t_{n-1} and t_n, respectively. The area under the curves to infinity (AUC_0^∞) were calculated from $AUC_0^\infty = AUC_t+C_t/\lambda$, where C_t is the last measured time point and λ is the terminal rate constant determined from the slope of the terminal phase of the log plasma concentration-time profiles. The terminal elimination rate constants (k_e) were determined from the slope of the terminal phases of the log plasma concentration-time profiles. Linear regression of the last two or three data points gave the slope (λ). The half-lives ($t_{½}$) were calculated as $0.693/\lambda$. The total body clearance (Cl_{tot}) was calculated as Dose/AUC_0^∞. The volume of distribution (V_d) was calculated as dose/estimated plasma concentration at t_0. The maximum observed concentration (C_{max}) and corresponding time (T_{max}) were determined from the plasma concentration-time data as the maximum observed plasma concentration and corresponding time, respectively.

RESULTS

The plasma concentrations of primidone in rats are presented in Table N1. The plasma phenobarbital concentrations in rats are presented in Table N2. The semilogarithmic plots of plasma concentration-time data for primidone and phenobarbital for male and female rats administered 30, 80, or 130 mg/kg are shown in Figures N1 to N6. The k_a, k_e, and V_d values were calculated as toxicokinetic parameters for a one compartment model and are presented in Table N3. The parameters were estimated by simultaneously fitting the model to the data from all three dose concentrations (30, 80, 130 mg/kg). The AUC_0^∞, $t_{½}$, Cl_{tot}, C_{max}, and T_{max} values for rats are presented in Table N4.

Plasma concentrations of primidone were dose- and time-dependent for male and female rats. Absorption of primidone administered in 0.5% methyl cellulose by gavage was rapid; for all dosed groups, plasma primidone concentrations were detectable 15 minutes after dosing. Although the time course and dose response profile were similar for male and female rats, primidone plasma concentrations were consistently higher for female rats than for male rats (approximately double at most dose concentrations and time points sampled). Elimination of primidone was rapid and sex-dependent, as plasma half-lives were 2- to 5-fold greater in female rats than in male rats.

Plasma concentrations of phenobarbital were also dose- and time-dependent. However, for a given dose, plasma phenobarbital concentrations were consistently higher for male rats than for female rats. Metabolism of primidone in rats is thus indicated to be sex-dependent, with males metabolizing primidone more rapidly than females. Plasma phenobarbital was detected in male rats within 15 minutes of dosing, but was below the limits of quantitation at 15 and 30 minutes post-dose in female rats. Plasma phenobarbital concentrations had not fallen below the limits of quantitation by the last time points sampled (1,320 or 1,800 minutes) in either male or female rats.

The plasma concentrations of primidone in mice are presented in Table N5. The plasma phenobarbital concentrations in mice are presented in Table N6. The semilogarithmic plots of plasma concentration-time data for primidone and phenobarbital for male and female mice administered 30, 80, or 200 mg/kg are shown in Figures N7 to N12.

Plasma primidone concentrations were dose- and time-dependent for male and female mice. It was determined that the variability of a small sample size and a large number of samples below the limit of quantitation resulted from biological variation. Pharmacokinetics parameters could not be calculated for the mice due to inadequate data. Absorption of primidone administered by gavage was rapid; for all dose groups and males and females, plasma concentrations of primidone were detectable within 15 minutes after dosing. There was a slight trend toward greater plasma primidone concentrations in male mice than in female mice. Plasma primidone concentrations remained above the detection limit for at least 30 hours following a 30 or 80 mg/kg dose and for at least 48 hours after a 200 mg/kg dose.

Plasma phenobarbital concentrations appeared dose- and time-dependent for males and females. Plasma phenobarbital concentrations were detected within 15 minutes after dosing. In agreement with the plasma primidone data, male mice had slightly higher plasma phenobarbital concentrations than the females. Primidone appeared to be more rapidly metabolized to phenobarbital in male mice than in female mice, as peak plasma phenobarbital concentrations were observed at earlier time points in males.

TABLE N1
Plasma Concentrations of Primidone in F344/N Rats after a Single Gavage Dose of Primidone[a]

	30 mg/kg	80 mg/kg	130 mg/kg
n	2	2	2
Male			
Time After Dosing (minutes)			
15	8.1[b]	11.2	—[c]
30	—	25.1	24.4[b]
90	12.0	34.9	51.7
180	7.2	37.2	51.9
360	0.3	13.5	23.7
540	BLQ	3.5	9.7
720	BLQ	1.5	4.3
1,080	BLQ	BLQ	—
1,320	BLQ	BLQ	BLQ
1,800	—	—	BLQ
Female			
Time After Dosing (minutes)			
15	15.8[b]	21.1	—
30	—	40.2	51.5[b]
90	22.3	59.6	73.5
180	22.4	67.6	104
360	12.0	40.2	66.4
540	5.9	22.7	53.2
720	3.9	14.2	20.1
1,080	0.3	2.6	—
1,320	BLQ	0.2	0.9
1,800	—	—	BLQ

[a] Data are given in μg/mL as the mean of two samples. BLQ=Below limit of quantitation
[b] n=4
[c] No samples were analyzed at this time point.

TABLE N2
Plasma Concentrations of Phenobarbital in F344/N Rats after a Single Gavage Dose of Primidone[a]

	30 mg/kg	80 mg/kg	130 mg/kg
n	2	2	2
Male			
Time After Dosing (minutes)			
15	0.33[b]	0.37	—[c]
30	—	1.21	0.53[b]
90	1.99	3.22	4.12
180	2.72	4.43	5.01
360	3.31	5.93	8.69
540	2.83	7.12	9.68
720	2.55	5.75	8.62
1,080	1.60	3.57	—
1,320	1.05	2.87	4.56
1,800	—	—	2.02
Female			
Time After Dosing (minutes)			
15	BLQ[b]	BLQ	—
30	—	BLQ	BLQ[b]
90	0.40	0.72	0.93
180	0.59	1.05	1.03
360	1.03	1.89	2.27
540	0.95	2.28	2.75
720	1.02	2.12	2.49
1,080	0.96	1.93	—
1,320	0.83	1.61	2.27
1,800	—	—	2.02

[a] Data are given in μg/mL as the mean of two samples. BLQ=Below limit of quantitation
[b] n=4
[c] No samples were analyzed at this time point.

TABLE N3
Toxicokinetic Parameters in F344/N Rats after a Single Gavage Dose of Primidone: One-Compartment Model[a]

	k_a[b] (hours^{-1})	k_e[c] (hours^{-1})	V_d[d] (L/kg)
Male	0.433	0.556	0.1934
Female	0.7996	0.1706	0.1425

[a] The parameters were estimated by simultaneously fitting the model to the data from three dose levels (30, 80, and 130 mg/kg).
[b] k_a = Absorption rate constant
[c] k_e = Terminal elimination rate constant
[d] V_d = Volume of distribution

TABLE N4
Toxicokinetic Parameters in F344/N Rats after a Single Gavage Dose of Primidone[a]

Dose (mg/kg)	AUC_0^∞[b] (mg·hour/L)	$t_{½}$[c] (hours)	Cl_{tot}[d] (L/hour·kg)	C_{max}[e] (mg/L)	T_{max}[f] (hours)
Male					
30	39.663	0.70	0.756	12.0	1.50
80	193.06	1.22	0.414	37.2	3.00
130	318.42	1.22	0.408	51.9	3.00
Female					
30	174.8	4.03	0.172	22.4	3.00
80	533	3.72	0.15	67.6	3.00
130	851.5	2.74	0.153	104	3.00

[a] The data were calculated from the plasma concentration-time curves, where each point represents the mean of two male or two female rats.
[b] AUC_0^∞ = Area under the curve to infinity
[c] $t_{½}$ = Elimination half-life
[d] Cl_{tot} = Dose/AUC_0^∞
[e] C_{max} = Maximum mean concentration
[f] T_{max} = Time of maximum mean concentration (estimated from last four time points)

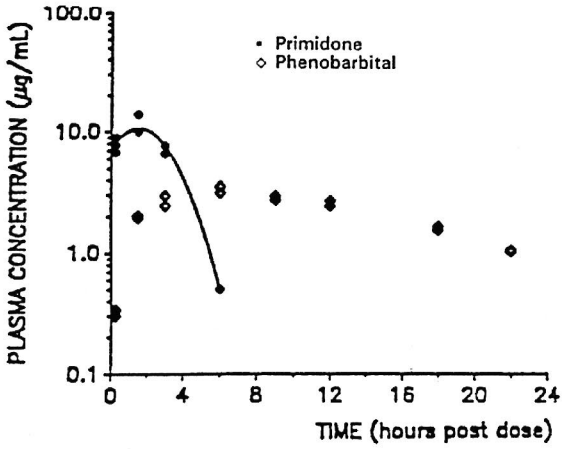

Figure N1
Plasma Concentrations of Primidone and Phenobarbital in Male F344/N Rats after a Single Gavage Dose of 30 mg/kg

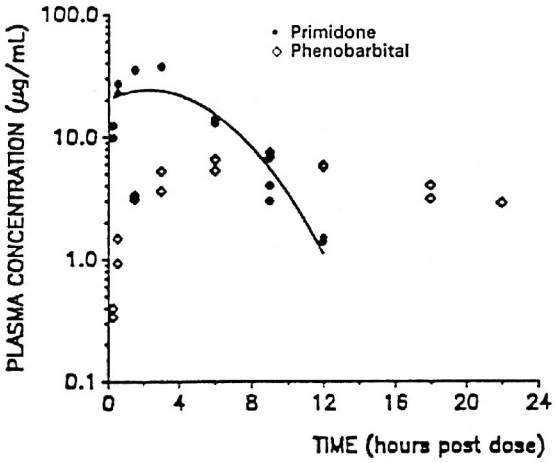

Figure N2
Plasma Concentrations of Primidone and Phenobarbital in Male F344/N Rats after a Single Gavage Dose of 80 mg/kg

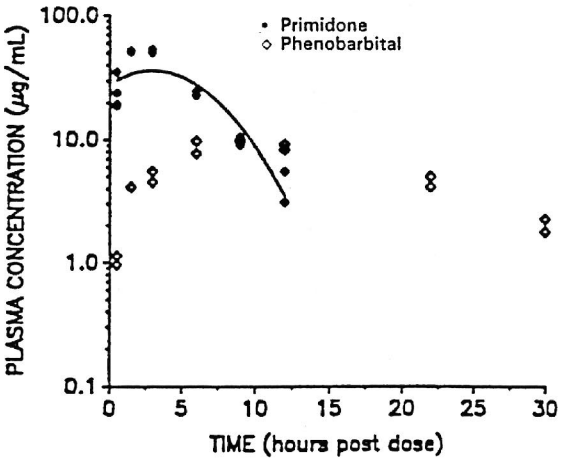

Figure N3
Plasma Concentrations of Primidone and Phenobarbital in Male F344/N Rats after a Single Gavage Dose of 130 mg/kg

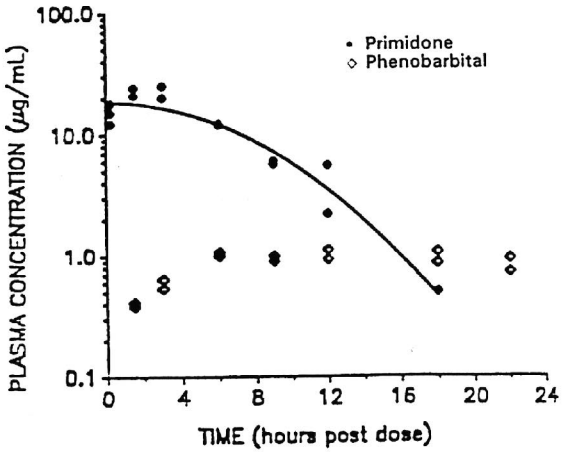

Figure N4
Plasma Concentrations of Primidone and Phenobarbital in Female F344/N Rats after a Single Gavage Dose of 30 mg/kg

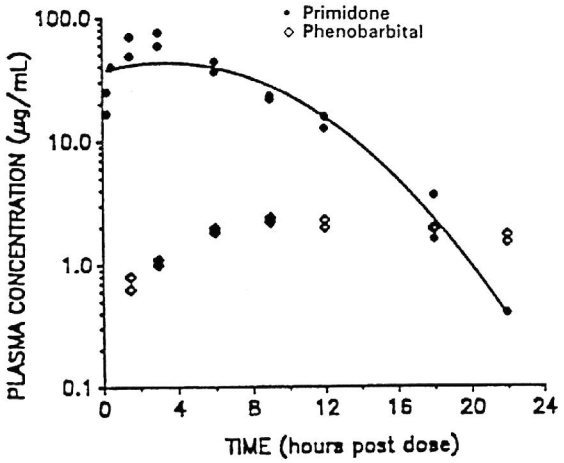

Figure N5
Plasma Concentrations of Primidone and Phenobarbital in Female F344/N Rats after a Single Gavage Dose of 80 mg/kg

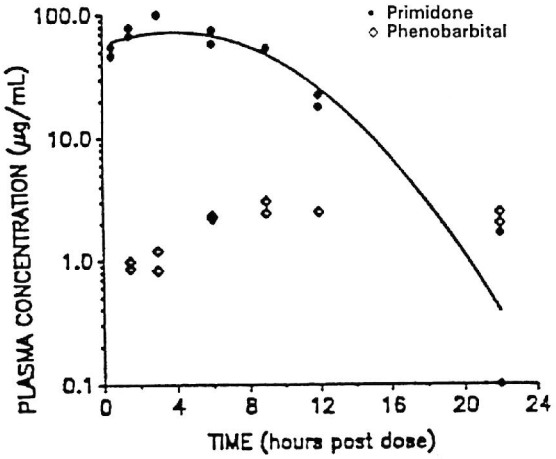

Figure N6
Plasma Concentrations of Primidone and Phenobarbital in Female F344/N Rats after a Single Gavage Dose of 130 mg/kg

TABLE N5
Plasma Concentrations of Primidone in B6C3F$_1$ Mice after a Single Gavage Dose of Primidone[a]

	30 mg/kg	80 mg/kg	200 mg/kg
n	2	2	2
Male			
Time After Dosing (minutes)			
15	65.8[b]	72.2	68.6
30	26.4	120	128[c]
90	58.8	156[b]	157
180	35.8[b]	64.8	123[b]
360	35.9	29.4[b]	125[b]
540	15.1	23.8[b]	30.4[b]
720	21.4[b]	10.2	35.8
1,320	32.0[b]	16.4	41.6
1,800	19.6	16.5	—[d]
2,880	—	—	33.6
Female			
Time After Dosing (minutes)			
15	23.3	32.9	70.2
30	29.0	85.6	133[b]
90	20.8	52.9	122
180	19.2	52.3	130
360	4.0[b]	21.5	75.4[b]
540	10.9	8.8	15.7[b]
720	8.7	2.8[b]	3.0
1,320	18.6[b]	105	5.4
1,800	12.1	9.9[b]	—
2,880	—	—	15.1

[a] Data are given in μg/mL as the mean of two samples.
[b] n=3
[c] n=4
[d] No samples were analyzed at this time point.

TABLE N6
Plasma Concentrations of Phenobarbital in B6C3F$_1$ Mice after a Single Gavage Dose of Primidone[a]

	30 mg/kg	80 mg/kg	200 mg/kg
n	2	2	2
Male			
Time After Dosing (minutes)			
15	0.37	0.46	0.63
30	4.40	1.28	0.92[b]
90	2.62	6.05[c]	2.92
180	2.70[c]	3.34	4.44[c]
360	2.62	4.63[c]	9.85[c]
540	3.66	6.45[c]	11.1[c]
720	1.93[b]	3.83	15.4
1,320	0.87[c]	2.46	4.78
1,800	0.75	BLQ	—[d]
2,880	—	—	BLQ
Female			
Time After Dosing (minutes)			
15	0.40	0.49	0.59
30	0.65	1.13	1.10[c]
90	1.60	1.69	2.75
180	3.09	3.64	4.73
360	3.45[c]	7.59	9.83[c]
540	2.63	4.77	10.3[c]
720	1.35	4.16[b]	5.29
1,320	1.25[e]	0.70[c]	6.59
1,800	BLQ	0.11[e]	—
2,880	—	—	BLQ

[a] Data are given in μg/mL as the mean of two samples. BLQ=Below limit of quantitation
[b] n=4
[c] n=3
[d] No samples were analyzed at this time point.
[e] n=1

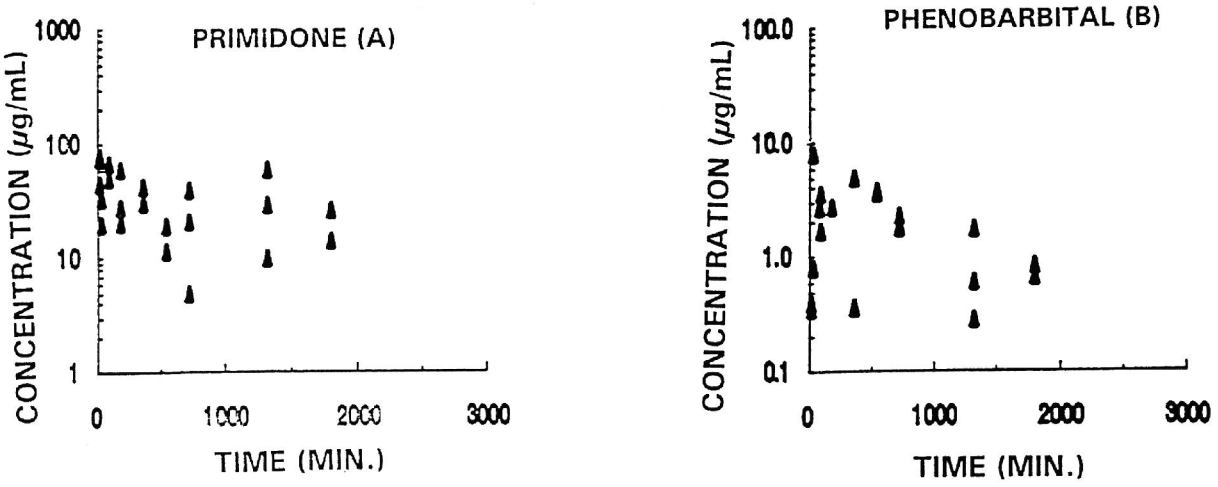

Figure N7
Plasma Concentrations of Primidone (A) and Phenobarbital (B) in Male B6C3F1 Mice after a Single Gavage Dose of 30 mg/kg Primidone

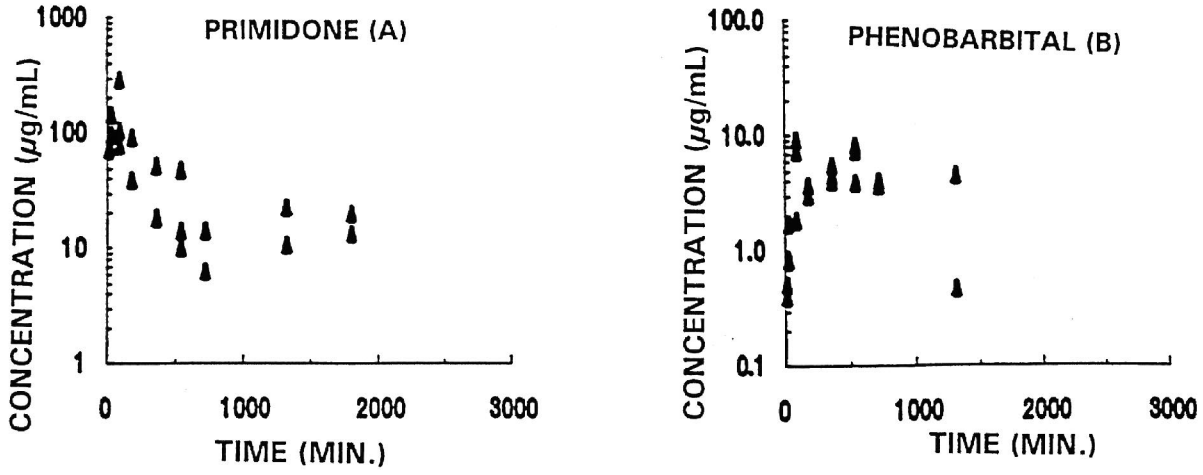

Figure N8
Plasma Concentrations of Primidone (A) and Phenobarbital (B) in Male B6C3F1 Mice after a Single Gavage Dose of 80 mg/kg Primidone

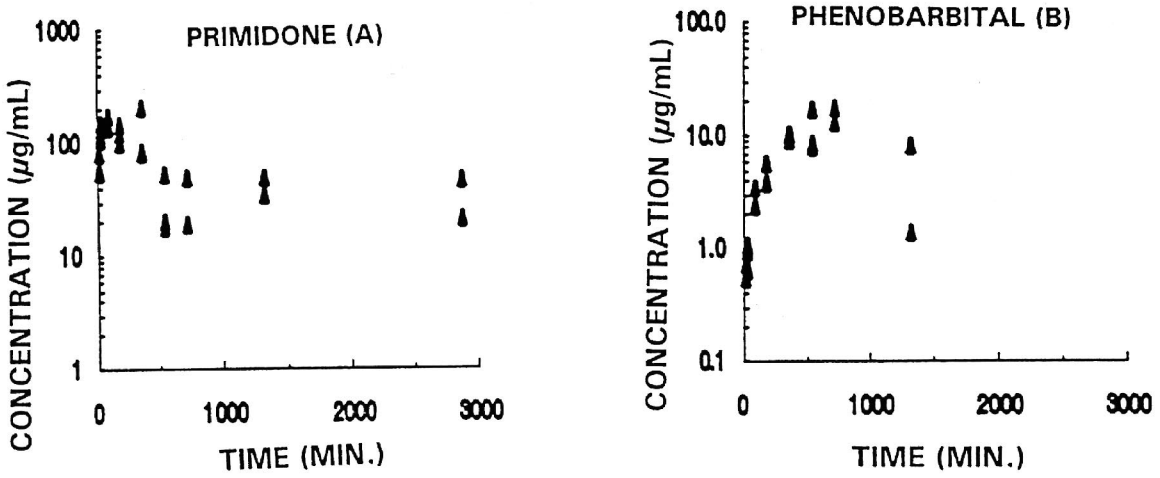

Figure N9
Plasma Concentrations of Primidone (A) and Phenobarbital (B) in Male B6C3F1 Mice after a Single Gavage Dose of 200 mg/kg Primidone

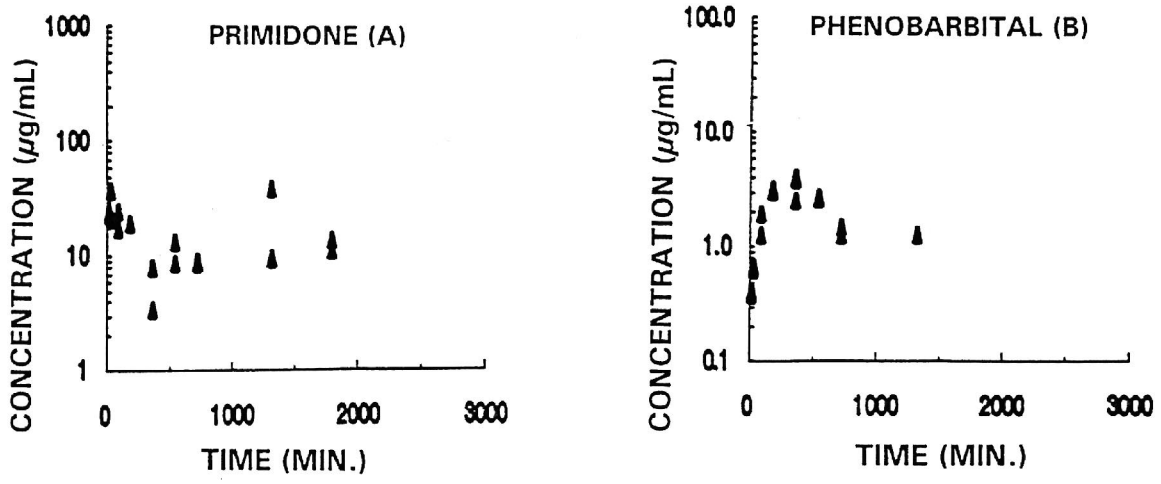

Figure N10
Plasma Concentrations of Primidone (A) and Phenobarbital (B) in Female B6C3F1 Mice after a Single Gavage Dose of 30 mg/kg Primidone

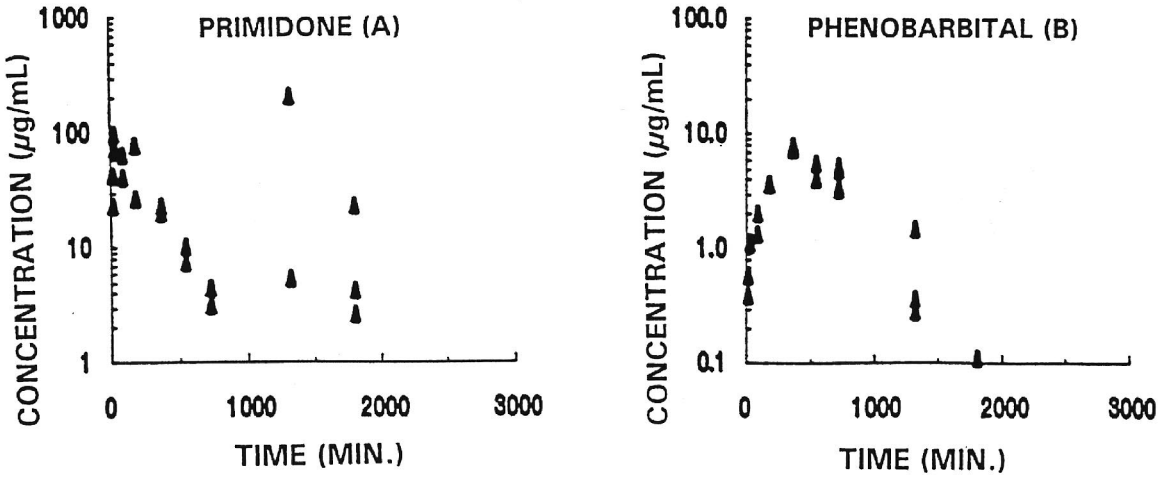

Figure N11
Plasma Concentrations of Primidone (A) and Phenobarbital (B) in Female B6C3F1 Mice after a Single Gavage Dose of 80 mg/kg Primidone

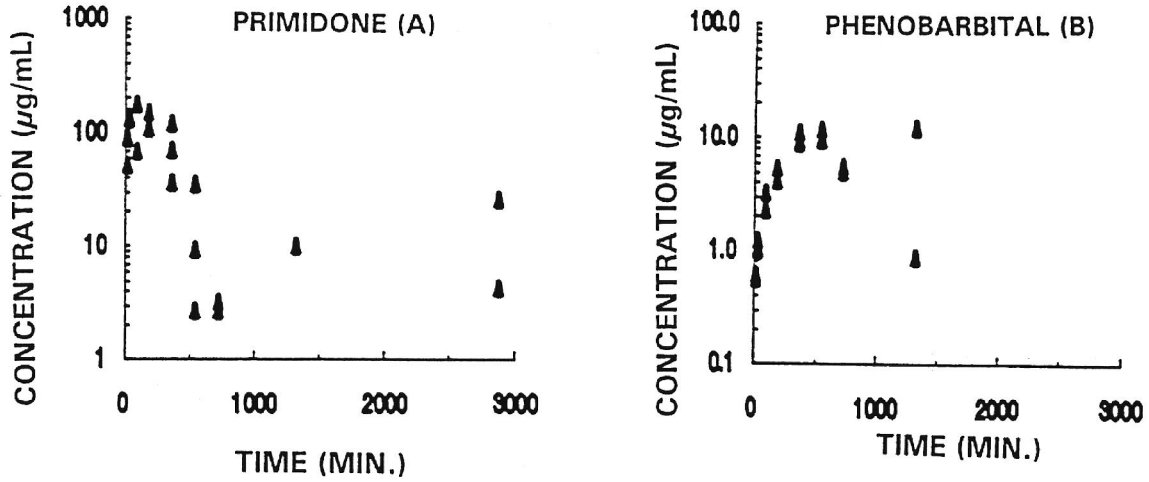

Figure N12
Plasma Concentrations of Primidone (A) and Phenobarbital (B) in Female B6C3F1 Mice after a Single Gavage Dose of 200 mg/kg Primidone

APPENDIX O
CONTINUOUS BREEDING STUDY IN SWISS (CD-1®) MICE

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CONTINUOUS BREEDING STUDY IN SWISS (CD-1®) MICE

INTRODUCTION

The potential reproductive toxicity of primidone was evaluated in Swiss (CD-1®) mice because no information is available in the literature. The effects of exposure to primidone on reproduction were assessed with a continuous breeding study in Swiss (CD-1®) mice administered primidone in feed (NTP, 1991).

Reproductive assessment by the methods presented in Lamb (1985), Reel *et al*. (1985), and Heindel *et al*. (1989) consists of four phases: dose range finding, continuous breeding, identification of the affected gender (crossover mating trial), and offspring assessment. A 2-week dose-setting phase is conducted to determine exposure concentrations of the continuous breeding phase. The dose-setting phase of the current study was lengthened by introducing a mating and pup survival trial. During the continuous breeding phase, the effects of the maximum tolerated exposure concentration estimated in the dose-setting phase and two lower exposure concentrations on fertility and reproduction of first-generation (F_0) animals are determined. If fertility is significantly affected during the continuous breeding phase, crossover mating trials are performed to determine if males, females, or both are affected. Offspring assessment includes evaluation of reproductive performance of second-generation (F_1) animals from the final litters of the continuous breeding phase. The F_1 animals are raised to sexual maturity while receiving the same exposure concentrations as their parents, are mated, and are allowed to deliver the third-generation (F_2) offspring.

In the primidone study, the exposure concentrations for the continuous breeding study were based on results of the extended dose-setting study. Because fertility was not significantly affected during the continuous breeding phase, crossover mating trials were not conducted. Pups from all exposure groups were maintained for offspring assessment until weening. Only controls and 1,500 ppm groups were assessed for F_1 fertility measures.

MATERIALS AND METHODS

Primidone was obtained from Siegfried LTD (Zofingen, Switzerland) in one lot (G041889), which was also used for the 14-day, 14-week, and 2-year studies conducted at Battelle Columbus Laboratories (Columbus, OH). Results of purity and stability analyses of lot G041889 are presented in Appendix J. Dose formulations were prepared every 4 weeks, and analyses by Research Triangle Institute (Research Triangle Park, NC) (for the extended dose-setting phase and the continuous breeding phase), Radian Corporation (Austin, TX) (continuous breeding phase), or Midwest Research Institute (Kansas City, MO) (offspring assessment phase) indicated that the dose formulations were homogeneous and within 10% of the target concentration.

Male and female VAF Crl:Swiss CD-1® (ICR)BR outbred albino mice were obtained from Charles River Breeding Laboratories, Inc. (Portage, MI), before the dose-setting phase and again for the continuous breeding phase. Upon receipt, serum samples were collected from sentinel males and females, and the serum samples were analyzed for antibody titers to rodent viruses. All serum samples were negative. Mice were quarantined for 2 weeks and were 11 weeks old at the start of the extended dose-setting phase and the continuous breeding phase. Mice were housed two per cage by gender during quarantine. NIH-07 open formula meal diet containing the appropriate concentrations of primidone was available *ad libitum* and deionized water was available *ad libitum* for all phases of the study. Sentinel animals were monitored for

disease and viral titers throughout the study; sera collected at the end of the study were positive for minute virus of mice.

During the extended dose-setting phase, the mice were housed two per cage by gender for 7 days while being exposed to 0, 125, 250, 500, 1,000, or 2,000 ppm; mice were then housed in breeding pairs for 28 days while exposure continued. Females were allowed to deliver one litter, and pups remained with their dams. During the extended dose-setting phase, clinical findings, feed consumption, dam body weights, pregnancy index, live pups per litter, proportion of pups born alive, gender of live pups, and pup body weights were recorded (Tables O1 and O2).

During the continuous breeding phase, the mice were housed two per cage by gender for 7 days while being exposed to 0, 150, 500, or 1,500 ppm; mice were then housed in breeding pairs for 98 days while exposure continued. After the mating period, mice were housed separately for approximately 21 days while exposure continued to allow delivery of the final litter of pups. During the continuous breeding phase, clinical findings, feed consumption, pregnancy index, litters per pair, length of gestation, dam body weights, live pups per litter, proportion of pups born alive, gender of live pups, and pup body weights were recorded (Tables O3 and O4). For the last litter, pup survival and body weights were recorded on lactation days 0, 4, 7, 14, and 21 (Table O5).

To assess the offspring of exposed mice, the final litter of pups born to each F_0 mouse dam in the 0 and 1,500 ppm groups was raised to sexual maturity. After weaning, siblings were housed two per cage by gender and were administered the same exposure concentrations as their parents. At sexual maturity (74 $\pm$ 10 days of age), nonsibling male and female mice from within the same exposure group (20 pairs per group) were housed as breeding pairs for 7 days. Female mice were examined for a copulatory plug, and mice were then housed separately through the delivery of pups. Clinical findings, feed consumption, mating index, pregnancy index, fertility index, dam body weights, length of gestation, live pups per litter, proportion of pups born alive, gender of live pups, and pup body weights were recorded (Table O6). Before necropsy of the F_1 mice, vaginal cytology data were collected (Table O7). At necropsy, epididymal spermatozoal data were collected (Table O7) and the following organs were weighed: right cauda epididymis, right epididymis, kidneys (with adrenal glands), liver, right ovary, prostate gland, seminal vesicles, and right testis (Table O8). Selected organs were fixed in 10% neutral buffered formalin or Bouin's fixative and imbedded in glycol methacrylate or paraffin. Sections were stained with hematoxylin and eosin or PAS and hematoxylin (testis only).

For data expressed as proportions (fertility, mating, and pregnancy indices), the Cochran-Armitage test (Armitage, 1971) was used to test for dose-related trends, and pairwise comparisons were performed with a chi-square test (Conover, 1971). A chi-square test for homogeneity was used to identify overall differences in fertility across exposure groups.

The number of litters and the number of live pups per litter were determined per fertile pair and then exposure group means were determined. The proportion of live pups was defined as the number of pups born alive divided by the total number of pups produced by each pair. The sex ratio was expressed as the number of male pups born alive divided by the total number of live pups born to each fertile pair.

Exposure group means for data with skewed distributions were analyzed by the nonparametric multiple comparisons methods of Shirley (1977) or Dunn (1964). Jonckheere's test (Jonckheere, 1954) was used to assess the significance of dose-response trends and to determine whether a trend-sensitive test (Shirley's) was more appropriate for pairwise comparisons than a test that does not assume a monotonic dose-related trend (Dunn's). Multiple comparisons were made with Dunn's test or Wilcoxon's test (Conover, 1971).

Analyses of covariance (Neter and Wasserman, 1974) with average litter size as the covariate, were performed to remove the potential effect of number of pups per litter on average pup weight. Least-squares estimates of exposure group means adjusted for litter size were tested for overall equality by an F-test and for pairwise equality by Dunnett's test (Dunnett, 1955) or a *t*-test; these tests were performed on males, females, and males and females (combined) to analyze potential sex differences.

For vaginal cytology data, an arcsine transformation was used to bring the data into closer conformance with normality assumptions. Treatment effects were investigated by applying a multivariate analysis of variance (Morrison, 1976) to the transformed data to test for simultaneous equality of measurements across exposure concentrations (Table O7).

RESULTS

All mice in the extended dose-setting phase survived until the end of the study (Table O1). Final mean body weights of all groups of exposed mice were similar to those of the controls. Feed consumption by the 250 ppm females was significantly greater than that by the controls during week 1. The exposure concentrations of 125, 250, 500, 1,000, or 2,000 ppm primidone administered in feed resulted in average daily doses of 20, 40, 90, 175, or 350 mg primidone/kg body weight for males and 20, 40, 80, 160, or 320 mg/kg for females. Exposure to primidone had no adverse effect on reproductive parameters, live pups per litter, sex ratio, or pup weights (Table O2). Pup survival on day 4 was slightly decreased in the 2,000 ppm groups (Table O2); therefore, the exposure concentrations selected for the continuous breeding phase were 150, 500, and 1,500 ppm.

During the continuous breeding phase, exposure to primidone had no adverse effect on reproductive parameters (Table O3). The numbers of live pups per litter and the total and adjusted total pup weights of exposed groups were similar to those in the controls for individual litters and for the combined litters 1 through 5 (Table O4). For the final litter of pups, the survival rates of male and female pups in exposed groups were similar to the control values at each time point (Table O5). The mean body weight of male pups in the 500 ppm group was significantly greater than that of the controls on lactation day 21; the mean body weights of female pups in all exposed groups were significantly greater than that of the controls on lactation day 21.

During the offspring assessment phase of the continuous breeding study, exposure to 1,500 ppm had no adverse effect on reproductive parameters, live pups per litter, sex ratio, or pup body weights (Table O6).

The estrous cycle length of 1,500 ppm females was significantly longer than that of the controls (Table O7). No significant differences in epididymal spermatozoal motility, percent abnormality, or concentration were observed between 1,500 ppm males and the controls. The absolute and relative liver weights of 1,500 ppm males and females were significantly greater than those of the controls (Table O8); similar effects were observed in the 14-week studies with F344/N rats and $B6C3F_1$ mice. The seminal vesicle weights of 1,500 ppm males were significantly less than those of the controls. These differences may be indicative of altered internal hormone states, perhaps secondary to changes in hepatic hormone clearance induced by the hepatomegalic effects of primidone.

In summary, primidone at concentrations up to 1,500 ppm had only minimal effects on reproductive parameters in the F_0 mice. The only reproductive effects were a significant increase in estrous cycle length and reduced seminal vesicle weight in F_1 mice exposed to 1,500 ppm.

TABLE O1
Survival, Body Weights, and Feed Consumption of F_0 Swiss (CD-1®) Mice in the Extended Dose-Setting Study of Primidone

Dose (ppm)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)	Feed Consumption[c]	
		Initial	Final	Change		Week 1	Week 3
Male							
0	8/8	28.2 ± 0.7	31.1 ± 0.8	2.9		4.9	5.3
125	8/8	28.4 ± 0.6	30.7 ± 0.6	2.3	99	4.8	5.4
250	8/8	28.8 ± 0.6	31.9 ± 0.8	3.1	103	4.7	5.3
500	8/8	27.1 ± 0.4	30.3 ± 0.8	3.2	97	4.8	5.5
1,000	8/8	27.6 ± 0.9	30.6 ± 1.1	3.0	98	5.2	5.1
2,000	8/8	29.1 ± 0.9	31.4 ± 0.9	2.3	101	5.0	5.6
Female							
0	8/8	25.1 ± 0.5	41.0 ± 1.2	15.9		4.8	5.3
125	8/8	25.1 ± 0.4	43.1 ± 2.2	18.0	105	5.2	5.4
250	8/8	25.4 ± 0.4	42.8 ± 0.6	17.4	104	5.8*	5.3
500	8/8	25.0 ± 0.3	41.0 ± 1.5	16.0	100	5.6	5.5
1,000	8/8	25.9 ± 0.5	40.3 ± 0.8	14.4	98	5.3	5.1
2,000	8/8	25.7 ± 0.3	41.8 ± 1.0	16.1	102	5.1	5.6

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
[a] Number of animals surviving at day 28/number initially in group
[b] Weights are given as mean ± standard error; weight changes are given as mean.
[c] Feed consumption is expressed as grams of feed consumed per animal per day.

TABLE O2
Fertility, Reproductive Performance, and Body Weight Data for Swiss (CD-1®) Mice in the Extended Dose-Setting Study of Primidone[a]

	0 ppm	125 ppm	250 ppm	500 ppm	1,000 ppm	2,000 ppm
Adult Data						
Pregnancy index[b]	8/8 (100%)	7/8 (88%)	8/8 (100%)	8/8 (100%)	8/8 (100%)	8/8 (100%)
Dam weight at delivery (g)	34.2 ± 0.96	33.65 ± 0.99	34.3 ± 0.55	34.3 ± 0.62	34.3 ± 0.87[c]	35.9 ± 0.57
Pup Data						
Day 0						
Number of litters	8	7	8	8	7[d]	8
Live male pups/litter	5.3 ± 0.4	5.0 ± 0.4	5.4 ± 0.8	5.4 ± 0.7	4.6 ± 0.5	5.3 ± 0.5
Live female pups/litter	6.8 ± 0.6	6.3 ± 0.7	5.5 ± 0.5	5.5 ± 0.5	5.6 ± 0.7	5.6 ± 0.7
Total live pups/litter	12.0 ± 0.5	11.3 ± 0.8	10.9 ± 0.6	10.9 ± 0.7	10.1 ± 0.7*	10.9 ± 0.4
Live pups/litter (%)	100 ± 0	99 ± 1	100 ± 0	100 ± 0	100 ± 0	98 ± 1
Sex ratio[e] (%)	44 ± 3	45 ± 4	48 ± 5	49 ± 5	45 ± 5	49 ± 5
Male pup weight (g)	1.55 ± 0.03	1.57 ± 0.03	1.61 ± 0.05	1.57 ± 0.03	1.60 ± 0.05	1.53 ± 0.04
Female pup weight (g)	1.49 ± 0.03	1.46 ± 0.03	1.53 ± 0.05	1.47 ± 0.03	1.57 ± 0.02	1.45 ± 0.04
Total live pup weight (g)	1.52 ± 0.03	1.51 ± 0.02	1.57 ± 0.05	1.52 ± 0.03	1.58 ± 0.03	1.49 ± 0.04
Adjusted total pup weight[f] (g)	1.55 ± 0.03	1.52 ± 0.03	1.56 ± 0.03	1.51 ± 0.03	1.55 ± 0.03	1.49 ± 0.03
Day 4						
Male survival (%)	98 ± 4	100 ± 0	100 ± 0	86 ± 12	98 ± 6	85 ± 6[c]
Female survival (%)	96 ± 4	100 ± 0	95 ± 5	88 ± 13	98 ± 2	83 ± 13[c]
Total survival (%)	97 ± 2	100 ± 0	97 ± 3	87 ± 12	98 ± 2	85 ± 8[c]
Male pup weight (g)	3.10 ± 0.13	3.12 ± 0.10	3.04 ± 0.24	3.11 ± 0.15	3.25 ± 0.16	3.02 ± 0.15
Female pup weight (g)	3.03 ± 0.14	2.90 ± 0.11	3.05 ± 0.23	2.93 ± 0.17	3.23 ± 0.16	2.97 ± 0.16[c]

* Significantly different ($P \leq 0.05$) from the control group by Dunn's test
[a] Data for body weights, live pups/litter, and sex ratio are given as mean ± standard error. Differences from the control group were not significant by a chi-square test (pregnancy indices), Dunn's test (sex ratio and body weights), or Dunnett's test (adjusted pup weights).
[b] Fertile pairs/cohabiting pairs
[c] n=7
[d] No data were collected for one of eight litters.
[e] Live male pups/live pups
[f] Least-squares estimate of the mean of the average pup weight adjusted for average litter size

TABLE O3
Fertility, Reproductive Performance, Length of Gestation, and Body Weight Data for F_0 and F_1 Swiss (CD-1®) Mice in the Continuous Breeding Study of Primidone[a]

	0 ppm	150 ppm	500 ppm	1,500 ppm
F_0 Adult Data				
Pregnancy index[b]				
Litter 1	39/39 (100%)	17/17 (100%)	20/20 (100%)	17/17 (100%)
Litter 2	39/39 (100%)	17/17 (100%)	20/20 (100%)	16/17 (94%)
Litter 3	39/39 (100%)	17/17 (100%)	20/20 (100%)	16/17 (94%)
Litter 4	39/39 (100%)	17/17 (100%)	20/20 (100%)	16/17 (94%)
Litter 5	33/39 (85%)	16/17 (94%)	20/20 (100%)	14/17 (82%)
Average litters/pair	4.8 ± 0.1	4.9 ± 0.1	5.0 ± 0.0	4.6 ± 0.2
Cumulative days to litter				
Litter 1	21.5 ± 0.5	22.8 ± 1.0	20.6 ± 0.3	22.1 ± 1.4
Litter 2	42.3 ± 1.0	42.8 ± 1.0	40.6 ± 0.4	43.7 ± 1.7
Litter 3	63.5 ± 1.3	63.1 ± 1.0	61.1 ± 0.6	64.3 ± 1.8
Litter 4	84.0 ± 1.4	84.7 ± 1.1	81.7 ± 0.7	84.9 ± 1.9
Litter 5	101.8 ± 0.6	104.8 ± 1.2*	102.4 ± 0.9	102.9 ± 1.3
Dam weight during lactation of litter 5 (g)				
n	37	16	20	15
Lactation day 0	42.2 ± 0.7	42.5 ± 0.8	43.6 ± 0.9	41.4 ± 1.2
Lactation day 4	44.0 ± 0.7	44.0 ± 0.8	45.9 ± 1.0	44.6 ± 1.2
Lactation day 7	46.2 ± 0.9	46.1 ± 1.1	48.3 ± 1.1	47.5 ± 1.3
Lactation day 14	47.6 ± 1.1	49.3 ± 1.0	50.4 ± 1.1	49.6 ± 1.5
Lactation day 21	40.3 ± 0.7	38.9 ± 2.8	39.6 ± 2.2	40.5 ± 1.4
F_1 Pup Data (Litters 1 Through 5)				
Number of breeding pairs	39	17	20	17
Live male pups/litter	5.7 ± 0.3	5.9 ± 0.2	6.1 ± 0.3	5.8 ± 0.2
Live female pups/litter	5.7 ± 0.3	5.9 ± 0.4	6.2 ± 0.3	6.2 ± 0.2
Total live pups/litter	11.5 ± 0.6	11.6 ± 0.4	12.2 ± 0.5	12.0 ± 0.3
Average live pups/litter (%)	93 ± 3	99 ± 1	98 ± 1	99 ± 0
Sex ratio[c] (%)	51 ± 1	51 ± 2	50 ± 1	48 ± 2
Male pup weight (g)	1.61 ± 0.02	1.60 ± 0.02	1.62 ± 0.02	1.58 ± 0.02
Female pup weight (g)	1.55 ± 0.02	1.53 ± 0.03	1.56 ± 0.02	1.52 ± 0.02
Total live pup weight (g)	1.58 ± 0.02	1.57 ± 0.02	1.59 ± 0.02	1.55 ± 0.02
Adjusted total pup weight[d] (g)	1.58 ± 0.01	1.56 ± 0.02	1.60 ± 0.02	1.54 ± 0.02

* Significantly different ($P \leq 0.05$) from the control group by Dunn's test
[a] Data for average litters/pair, cumulative days to litter, body weights, live pups/litter, and sex ratio are given as mean ± standard error. Differences from the control group were not significant by a chi-square test (pregnancy indices), Dunn's test (average litters per pair, body weights, sex ratio, and live pups/litter), or Dunnett's test (adjusted pup weights).
[b] Females delivering litters/cohabiting pairs
[c] Live male pups/live pups
[d] Least-squares estimate of the mean of the average pup weight adjusted for average litter size

TABLE O4
Litter and Body Weight Data for F_1 Swiss (CD-1®) Mouse Pups in the Continuous Breeding Study of Primidone[a]

	0 ppm	150 ppm	500 ppm	1,500 ppm
Litter 1				
Number of pairs delivering	39[e]	17	20	17
Live pups/litter[b]	11.3 ± 0.5	11.3 ± 0.8	11.1± 0.6	10.5 ± 0.6
Total live pup weight[c] (g)	1.58 ± 0.02	1.60 ± 0.05	1.59 ± 0.02	1.57 ± 0.02
Adjusted total live pup weight[d] (g)	1.59 ± 0.02	1.60 ± 0.02	1.59 ± 0.02	1.54 ± 0.02
Litter 2				
Number of pairs delivering	39[e]	17	20	16
Live pups/litter	11.6 ± 0.6	12.6 ± 0.6	13.1 ± 0.6	12.7± 0.4
Total live pup weight (g)	1.59 ± 0.04	1.58 ± 0.03	1.57 ± 0.02	1.53 ± 0.03
Adjusted total live pup weight (g)	1.58 ± 0.02	1.58 ± 0.03	1.59 ± 0.03	1.53 ± 0.03
Litter 3				
Number of pairs delivering	39[f]	17	20	16
Live pups/litter	11.0 ± 0.8	11.6 ± 1.0	13.0 ± 0.6	13.0 ± 0.9
Total live pup weight (g)	1.62 ± 0.02	1.65 ± 0.05	1.59 ± 0.02	1.56 ± 0.04
Adjusted total live pup weight (g)	1.61 ± 0.02	1.62 ± 0.02	1.61 ± 0.02	1.57 ± 0.02
Litter 4				
Number of pairs delivering	39[f]	17	20	16
Live pups/litter	12.0 ± 0.9	11.8 ± 0.7	12.6 ± 0.7	12.1 ± 0.7
Total live pup weight (g)	1.60 ± 0.03	1.53 ± 0.08	1.63 ± 0.02	1.61 ± 0.04
Adjusted total live pup weight (g)	1.62 ± 0.03	1.51 ± 0.04	1.63 ± 0.04	1.60 ± 0.04
Litter 5				
Number of pairs delivering	33[g]	16[e]	20	14
Live pups/litter	11.8 ± 0.8	11.0 ± 0.9	11.5 ± 0.9	11.3 ± 0.5
Total live pup weight (g)	1.56 ± 0.02	1.57 ± 0.02	1.61 ± 0.03	1.59 ± 0.03
Adjusted total live pup weight (g)	1.58 ± 0.02	1.57 ± 0.03	1.60 ± 0.02	1.56 ± 0.03
Litters 1 Through 5				
Number of pairs delivering	39	17	20	17
Live pups/litter	11.5 ± 0.6	11.6 ± 0.4	12.2 ± 0.5	12.0 ± 0.3
Total live pup weight (g)	1.58 ± 0.02	1.57 ± 0.02	1.59 ± 0.02	1.55 ± 0.02
Adjusted total live pup weight (g)	1.58 ± 0.01	1.56 ± 0.02	1.60 ± 0.02	1.54 ± 0.02

[a] Data are given as mean ± standard error. Differences from the control group were not significant by Dunn's (live pups/litter and total live pup weights) or Dunnett's test (adjusted pup weights).
[b] Mean of average number of live pups per litter for each fertile pair
[c] Mean of average live pup weight for each fertile pair
[d] Least-squares estimate of the mean of the average pup weight adjusted for average litter size for each fertile pair
[e] No live pups were born in one litter.
[f] No live pups were born in four litters.
[g] No live pups were born in two litters.

TABLE O5
Survival and Body Weights of F_1 Swiss (CD-1®) Mouse Pups (Final Litter) in the Continuous Breeding Study of Primidone[a]

	0 ppm	150 ppm	500 ppm	1,500 ppm
Day 0				
Number of litters	33[b]	16[c]	20[d]	14
Male pup weight (g)	1.61 ± 0.02	1.59 ± 0.02	1.65 ± 0.03	1.62 ± 0.04
Female pup weight (g)	1.54 ± 0.02	1.54 ± 0.03	1.57 ± 0.04	1.56 ± 0.03
Day 4				
Male survival (%)	87 ± 6	90 ± 7	89 ± 7	99 ± 1
Female survival (%)	87 ± 6	93 ± 7	92 ± 5	99 ± 1
Total survival (%)	87 ± 6	91 ± 7	88 ± 7	98 ± 1
Male pup weight (g)	3.05 ± 0.06	3.20 ± 0.10	3.21 ± 0.12	2.99 ± 0.14
Female pup weight (g)	2.97 ± 0.07	3.12 ± 0.11	3.05 ± 0.11	2.90 ± 0.12
Day 7				
Male survival (%)	86 ± 6	89 ± 7	89 ± 7	99 ± 1
Female survival (%)	86 ± 6	93 ± 7	92 ± 5	99 ± 1
Total survival (%)	86 ± 6	90 ± 7	88 ± 7	98 ± 1
Male pup weight (g)	4.59 ± 0.11	4.80 ± 0.13	4.76 ± 0.17	4.50 ± 0.20
Female pup weight (g)	4.49 ± 0.11	4.68 ± 0.13	4.58 ± 0.16	4.37 ± 0.17
Day 14				
Male survival (%)	85 ± 6	89 ± 7	89 ± 7	99 ± 1
Female survival (%)	86 ± 6	93 ± 7	92 ± 5	99 ± 1
Total survival (%)	85 ± 6	90 ± 7	88 ± 7	98 ± 1
Male pup weight (g)	7.17 ± 0.18	7.78 ± 0.21	7.73 ± 0.29	7.21 ± 0.31
Female pup weight (g)	6.98 ± 0.18	7.67 ± 0.20*	7.48 ± 0.25	7.13 ± 0.29
Day 21				
Male survival (%)	83 ± 6	87 ± 7	89 ± 7	92 ± 7
Female survival (%)	86 ± 6	91 ± 7	92 ± 5	92 ± 7
Total survival (%)	84 ± 6	89 ± 7	88 ± 7	92 ± 1
Male pup weight (g)	10.82 ± 0.38	11.84 ± 0.55	12.78 ± 0.58*	12.23 ± 0.51
Female pup weight (g)	10.26 ± 0.36	11.62 ± 0.49*	11.85 ± 0.45*	11.68 ± 0.38*

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test.
[a] Data are given as mean ± standard error. Differences from the control group in survival were not significant by Dunn's test.
[b] No live pups were born in two litters. Because only female pups were born in one litter, n=30 for male pup survival and body weights.
[c] No live pups were born in one litter. Because only female pups were born in one litter, n=14 for male pup survival and body weights.
[d] Because only male pups were born in one litter, n=19 for female pup weights at day 0. Thereafter, n=18 for male and female body weights.

TABLE O6
Fertility, Reproductive Performance, Length of Gestation, and Body Weight Data for F_1 and F_2 Swiss (CD-1®) Mice in the Offspring Assessment Phase of the Continuous Breeding Study of Primidone[a]

	0 ppm	1,500 ppm
F_1 Adult Data		
Mating index[b]	20/20 (100%)	20/20 (100%)
Pregnancy index[c]	18/20 (90%)	20/20 (100%)
Fertility index[d]	18/20 (90%)	20/20 (100%)
Dam weight at delivery (g)	36.13 ± 0.86	35.66 ± 0.50
Days to litter	19.1 ± 0.1	19.0 ± 0.1
F_2 Pup Data		
Number of litters	18	20
Live male pups/litter	5.8 ± 0.4	5.0 ± 0.4
Live female pups/litter	5.8 ± 0.4	5.9 ± 0.4
Total live pups/litter	11.6 ± 0.5	10.9 ± 0.3
Total live pups/litter (%)	100 ± 0	99 ± 1
Sex ratio[e] (%)	50 ± 4	45 ± 3
Male pup weight (g)	1.64 ± 0.04	1.61 ± 0.03
Female pup weight (g)	1.57 ± 0.03	1.53 ± 0.03
Total live pup weight (g)	1.60 ± 0.03	1.57 ± 0.03
Adjusted total live pup weight[f] (g)	1.62 ± 0.02	1.55 ± 0.02

[a] Data for body weights, days to litter, live pups/litter, and sex ratio are given as mean ± standard error. Differences from the control group were not significant by a chi-square test (mating indices, pregnancy indices, or fertility indices), Wilcoxon's test (average litters/pair, cumulative days to litter, dam weights, sex ratio, and live pups/litter), Dunn's test (nonadjusted pup weights), or Dunnett's test (adjusted pup weights).
[b] Females with sperm plug/cohabiting pairs
[c] Fertile pairs/cohabiting pairs
[d] Fertile pairs/females with sperm plug
[e] Live male pups/live pups
[f] Least-squares estimate of the mean for all litters of the average (per litter) pup weight adjusted for average litter size

TABLE O7
Sperm Parameters and Estrous Cycle Characterization for F_1 Swiss (CD-1®) Mice in the Offspring Assessment Phase of the Continuous Breeding Study of Primidone[a]

	0 ppm	1,500 ppm
n	20	20
Male		
Epididymal spermatozoal parameters		
Motility (%)	80.2 ± 1.6	76.7 ± 1.4
Abnormal (%)	5.1 ± 0.56[b]	3.7 ± 0.40
Concentration (10^6/g cauda epididymal tissue)	1,019 ± 38	1,011 ± 67
Female		
Estrous cycle length (days)	4.57 ± 0.11	4.92 ± 0.10*
Estrous stages (% of cycle)		
Diestrus	25.8	26.7
Proestrus	22.9	20.0
Estrus	32.1	35.4
Metestrus	19.2	17.9

* Significantly different ($P \leq 0.05$) from the control group by Shirley's test
[a] Epididymal spermatozoal parameters and estrous cycle lengths are given as mean ± standard error. Differences from the control group for epididymal spermatozoal motility, abnormality, and concentration are not significant by Wilcoxon's test. By multivariate analysis of variance, exposed females do not differ significantly from control females in the relative length of time spent in the estrous stages.
[b] n=19

TABLE O8
Organ Weights and Organ-Weight-to-Body-Weight Ratios for F_1 Swiss (CD-1®) Mice Administered Primidone in Feed[a]

	0 ppm	1,500 ppm
n	20	20
Male		
Necropsy body wt	35.8 ± 0.86	35.3 ± 0.60
R. Cauda Epididymis		
Absolute	0.02 ± 0.00	0.02 ± 0.00
Relative	0.51 ± 0.01	0.49 ± 0.03
R. Epididymis		
Absolute	50.2 ± 1.2	49.5 ± 1.1
Relative	1.4 ± 0.03	1.4 ± 0.03
Kidneys and Adrenal Glands		
Absolute	815.7 ± 40.9	699.1 ± 20.2
Relative	22.7 ± 0.96	19.9 ± 0.55*
Liver		
Absolute	1.9 ± 0.06	2.7 ± 0.09*
Relative	53.6 ± 1.3	76.7 ± 1.4*
Prostate Gland		
Absolute	23.4 ± 1.9	21.7 ± 1.3
Relative	0.65 ± 0.05	0.62 ± 0.03
Seminal Vesicles		
Absolute	424.8 ± 19.4	360.2 ± 10.9*
Relative	11.8 ± 0.39	10.2 ± 0.27*
R. Testis		
Absolute	125.1 ± 2.8	125.6 ± 3.1
Relative	3.5 ± 0.09	3.6 ± 0.11
Female		
Necropsy body wt	31.1 ± 0.63	31.1 ± 0.45
Kidneys and Adrenal Glands		
Absolute	516.5 ± 11.6	510.3 ± 8.3
Relative	16.7 ± 0.30	16.4 ± 0.19
Liver		
Absolute	1.8 ± 0.04	2.4 ± 0.07*
Relative	57.0 ± 0.90	75.6 ± 1.5*
R. Ovary		
Absolute	9.7 ± 0.53	9.3± 0.81
Relative	0.31 ± 0.02	0.30 ± 0.03

* Significantly different ($P \leq 0.05$) from the control group by Wilcoxon's test
[a] Liver weights and body weights are given in grams; other organ weights are given in milligrams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error).