NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS

STUDIES OF OXAZEPAM

(CAS NO. 604-75-1)

IN F344/N RATS

(FEED STUDIES)

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

October 1998

NTP TR 468

NIH Publication No. 99-3958

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. 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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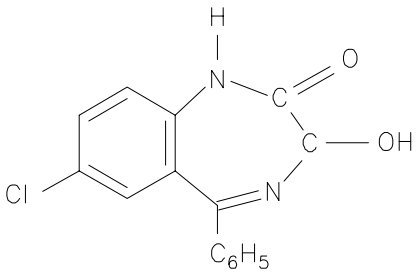
ABSTRACT



OXAZEPAM

CAS No. 604-75-1

Chemical Formula: $C_{15}H_{11}ClN_2O_2$ Molecular Weight: 286.74

Synonym: 7-Chloro-1,3-dihydro-3-hydroxy-5-phenyl-2*H*-1,4-benzodiazepin-2-one
Trade Names: Serax, Tazepam, Wy-3498

Oxazepam and related benzodiazepine drugs are used in the treatment of anxiety. All benzodiazepines currently in use share a number of effects, including sedation, hypnosis, decreased anxiety, muscle relaxation, amnesia, and anticonvulsant activity. Oxazepam and four other benzodiazepines (chlordiazepoxide, chlorazepate, diazepam, and flurazepam) were nominated for study by the Food and Drug Administration (FDA) and by the NIEHS based on their widespread use, use by pregnant women, and the lack of adequate rodent carcinogenicity studies. Oxazepam was evaluated in 14-week and 2-year studies by the NTP, and Technical Report No. 443 contains the results of the studies performed with the Swiss-Webster and B6C3F$_1$ strains of mice. Studies with rats were not initiated at the same time as the mouse studies because adequate carcinogenicity studies of oxazepam with the Sprague-Dawley rat strain had been submitted to the FDA. Subsequently, because of the marked neoplastic responses found in the two mouse strains, the NTP initiated 2-year studies of oxazepam with the F344/N rat. Groups of male and female F344/N rats were exposed to oxazepam (greater than 99% pure) in feed for 2 years. Genetic toxicology studies were conducted in *Salmonella typhimurium* and cultured Chinese hamster ovary cells, and mouse peripheral blood samples were analyzed for the frequency of micronucleated normochromatic erythrocytes.

2-YEAR STUDY

Groups of 50 male and 50 female F344/N rats were fed diets containing 0, 625, 2,500, or 5,000 ppm oxazepam for up to 105 weeks. A stop-exposure group of 50 males and 50 females received 10,000 ppm oxazepam in feed for 26 weeks, after which animals received undosed feed for the remainder of the 2-year study. The continuous-exposure concentrations resulted in average daily doses of 25, 100, or 250 mg oxazepam/kg body weight to males and 25, 110, or 220 mg/kg to females. Stop- exposure males and females received an average daily dose of 630 mg/kg during the exposure period.

Survival, Body Weights, and Clinical Findings

All 5,000 ppm continuous-exposure and 10,000 ppm stop-exposure males died before the end of the study. Survival of 2,500 ppm continuous-exposure males and females was significantly less than that of the controls. The mean body weight gains of 2,500 and 5,000 ppm males and females were less than those of the controls throughout the study. The mean body weights of 10,000 ppm stop-exposure males were generally less than those of the controls throughout the study; those of 10,000 ppm stop-exposure females were less than those of the controls during the exposure portion of the study but increased steadily after the cessation of dosing at week 27. Feed consumption by exposed groups was similar to that by the controls after week 1 of the study. Treatment-related eye/nasal discharge, hyperactivity when handled, and/or ataxia were observed in exposed male and female rats on or about day 2 of exposure but were no longer apparent after day 7.

Plasma Oxazepam Determinations

Plasma oxazepam concentrations were measured at the end of the study. The concentrations ranged from approximately 0.5 (625 ppm males) to 2.8 μg/mL (5,000 ppm females).

Pathology Findings

In the standard histopathologic evaluation, the incidence of renal tubule adenoma was slightly increased in male rats exposed to 2,500 ppm and was at the upper limit of the historical control range for this neoplasm in 2-year NTP feed studies. In an extended evaluation (step section) of the kidneys of male rats, the incidences of renal tubule adenoma occurred with a positive trend in exposed groups. In standard and step sections (combined), male rats exposed to 2,500 or 5,000 ppm showed a significant increase in the incidences of renal tubule adenoma and hyperplasia. In addition, the incidences of renal tubule adenoma and hyperplasia were significantly increased in the 10,000 ppm stop-exposure group. The incidences of nephropathy in continuously exposed female rats were significantly greater than in the controls, and the severity of nephropathy increased with increasing exposure concentration in males.

The incidences of epithelial hyperplasia and chronic inflammation of the forestomach in males exposed to 2,500 and 5,000 ppm and of ulcers in 2,500 ppm males were significantly greater than in the controls. Incidences of mineralization of the glandular stomach in 5,000 ppm and 10,000 ppm (stop-exposure) males and of erosion of the duodenum in 5,000 ppm males were significantly greater than in the controls. Female rats exposed to 2,500 ppm had greater incidences of epithelial hyperplasia, chronic inflammation, and ulcers of the forestomach and of erosion in the glandular stomach.

Centrilobular hepatocyte hypertrophy occurred more frequently in 2,500 and 5,000 ppm males and females than in the controls.

GENETIC TOXICOLOGY

Oxazepam was not mutagenic in any of several strains of *S. typhimurium*, nor did it induce sister chromatid exchanges or chromosomal aberrations in cultured Chinese hamster ovary cells. These *in vitro* tests were performed with and without S9 metabolic activation. Results from an *in vivo* mouse peripheral blood micronucleus test performed on B6C3F_1 mice used in a 14-week study were also negative.

CONCLUSIONS

In summary, under the conditions of these 2-year dosed-feed studies, there was *equivocal evidence of carcinogenic activity** in male F344/N rats, based on small increases in the incidences of renal tubule adenomas in exposed groups also exhibiting significantly enhanced nephropathy. There was *no evidence of carcinogenic activity* of oxazepam in female F344/N rats exposed to feed containing 625, 2,500, or 5,000 ppm for 2 years or 10,000 ppm for 6 months.

Administration of oxazepam to rats resulted in nonneoplastic lesions in the forestomach, glandular stomach, and small intestine as well as centrilobular hypertrophy of hepatocytes in the liver. In addition, nephropathy was increased in incidence in female rats and was markedly increased in severity in male rats, resulting in early mortality at the higher exposure concentrations.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 9. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 11.

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

	Male F344/N Rats		Female F344/N Rats	
	(2-Year Study)	**(Stop-Exposure Study)**	**(2-Year Study)**	**(Stop-Exposure Study)**
Concentrations	0, 625, 2,500, or 5,000 ppm	10,000 ppm for 26 weeks	0, 625, 2,500, or 5,000 ppm	10,000 ppm for 26 weeks
Body weights	2,500 ppm and 5,000 ppm groups less than control group	10,000 ppm group generally less than control group	2,500 and 5,000 ppm groups less than control group	10,000 ppm group similar to control group
2-Year survival rates	17/50, 11/50, 6/50, 0/50	0/50	32/50, 26/50, 20/50, 31/50	25/50
Nonneoplastic effects	Kidney: severity of nephropathy (1.9, 2.3, 2.7, 3.2) Forestomach: chronic inflammation (6/50, 8/48, 23/50, 15/50); ulcer (9/50, 12/48, 20/50, 10/50); epithelial hyperplasia (5/50, 8/48, 25/50, 16/50) Glandular stomach: mineralization (0/50, 3/48, 1/50, 4/50) Small intestine: duodenum, erosion (4/50, 3/48, 9/49, 16/50) Liver: hepatocyte centrilobular hypertrophy (0/50, 1/50, 8/49, 14/50)	Kidney: severity of nephropathy (3.3) Forestomach: chronic inflammation (10/49); ulcer (7/49); epithelial hyperplasia (15/49) Glandular stomach: mineralization (16/47)	Kidney: nephropathy (32/50, 43/50, 41/50, 48/50) Forestomach: chronic inflammation (1/50, 5/50, 16/50, 3/50); ulcer (1/50, 2/50, 9/50, 6/50); epithelial hyperplasia (2/50, 6/50, 16/50, 5/50) Glandular stomach: erosion (0/50, 4/50, 7/50, 2/50) Liver: hepatocyte centrilobular hypertrophy (0/50, 0/50, 10/50, 31/50)	Forestomach: chronic inflammation (5/50); ulcer (4/50); epithelial hyperplasia (5/50)
Neoplastic effects	None	None	None	None
Uncertain findings	Kidney: renal tubule adenoma (extended evaluation - 1/50, 1/50, 4/50, 5/50; standard and extended evaluations combined - 2/50, 1/50, 7/50, 6/50)	Kidney: renal tubule adenoma (extended evaluation - 6/45; standard and extended evaluations combined - 6/45)	None	None
Level of evidence of carcinogenic activity	Equivocal evidence		No evidence	
Genetic toxicology				
Salmonella typhimurium gene mutations:	Negative with and without S9 in strains TA97, TA98, TA100, TA102, and TA1535			
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 normochromatic erythrocytes in $B6C3F_1$ mice:	Negative at 14 weeks			

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 oxazepam on 11 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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SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

On 11 December 1996, the draft Technical Report on the toxicology and carcinogenesis studies of oxazepam received public review by the National Toxicology Program's Board of Scientific Counselors' Technical Reports Review Subcommittee. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Dr. J.R. Bucher, NIEHS, introduced the toxicology and carcinogenesis studies of oxazepam 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 and nonneoplastic lesions in rats. Dr. Bucher noted that the Subcommittee had reviewed a bioassay of oxazepam in Swiss-Webster and $B6C3F_1$ mice in 1993. The proposed conclusions for the present study were *some evidence of carcinogenic activity* in male F344/N rats and *no evidence of carcinogenic activity* in female F344/N rats.

Dr. Taylor, a principal reviewer, agreed in principle with the proposed conclusions. He stated that because there was substantial reduction in body weight gain and survival in 2,500 and 5,000 ppm male rats along with a dose response that was not very dramatic, he would argue for changing the proposed conclusion in male rats to *equivocal evidence of carcinogenic activity*. Noting the figure illustrating the metabolism of oxazepam in F344 rats, Dr. Taylor stated that some discussion of metabolism in rats and mice would be useful as an aid in trying to explain the difference between the mouse and rat in sites of toxicity and neoplasia.

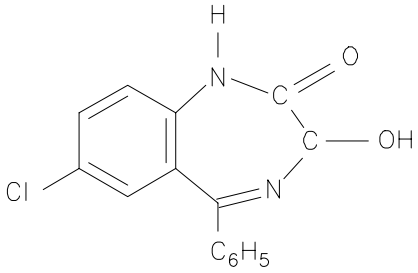
Dr. Brown, the second principal reviewer, agreed with the proposed conclusions. He said that it would be helpful if additional information could be provided in the Abstract regarding the background against which this bioassay was conducted, i.e., the unpublished study by industry in Sprague-Dawley rats. Dr. Bucher observed that the 1996 edition of the *Physicians' Desk Reference* provides a description of the rat study performed by Wyeth Laboratories, although no doses are listed. The citation indicates that there were increased incidences of prostate adenoma, interstitial cell adenoma of the testes, and thyroid gland follicular cell adenoma, none of which were replicated in the current study in F344/N rats. Dr. W.R. Allaben, NCTR/FDA, pointed out that the data are considered proprietary information and by law cannot be released publicly. Dr. Bucher mentioned that this was one of four benzodiazepines nominated and selected for study. Three were products of Hoffmann-LaRoche, which agreed to carry out the studies with the NTP's assistance in the study design. The studies were completed, and data were submitted to the FDA.

There was a discussion about the appropriateness of step sectioning kidneys in male rats and about the exposure concentrations used in the study. Dr. Bucher said that in retrospect, the 1,250 ppm group, which was terminated after 26 weeks with the thought that it would be uninformative, would have been the best high exposure group. Dr. LeBoeuf argued that if the 5,000 ppm group were excluded from analysis because of very poor survival, and if the results for renal tubule adenomas in the 625 and 2,500 ppm groups were compared with those in the controls, then he would conclude that there was *equivocal evidence of carcinogenic activity*. Dr. J.K. Haseman, NIEHS, noted that the increased incidence of renal tubule adenoma in the 2,500 ppm group was significant at $P = 0.018$. Dr. Goldsworthy asked under what circumstances the NTP would consider a study to be inadequate for evaluation. Dr. Bucher said that, generally, the NTP might consider a study to be inadequate if there is poor survival and if there is no neoplasm response, such that the ability of the study to detect a response may be compromised. Dr. Goldsworthy asked whether excluding a 13-week study would occur more often in future bioassays. Dr. G.A. Boorman, NIEHS, pointed out that in the case of oxazepam, a 26-week study did not predict very well; however, the decision of whether to employ a 13-week study would have to be determined on a case-by-case basis by drawing on other available toxicity information.

Dr. Taylor moved that the Technical Report on oxazepam be accepted with the revisions discussed and the conclusion as written for female rats, *no evidence of carcinogenic activity*, but changed for male rats, from *some evidence of carcinogenic activity* to *equivocal evidence of carcinogenic activity*.

Dr. Brown seconded the motion. In discussion, Dr. Ward stated that having toxicity in an organ such as the kidney, where there were also neoplasms, strengthened the evidence for the neoplasms being chemically induced because the organ is a target site for the chemical. Dr. Taylor's motion was accepted with five yes votes to three no votes (Goldsworthy, Reddy, and Ward).

INTRODUCTION



OXAZEPAM

CAS No. 604-75-1

Chemical Formula: $C_{15}H_{11}ClN_2O_2$ Molecular Weight: 286.74

Synonym: 7-Chloro-1,3-dihydro-3-hydroxy-5-phenyl-2*H*-1,4-benzodiazepin-2-one
Trade Names: Serax, Tazepam, Wy-3498

CHEMICAL AND PHYSICAL PROPERTIES

Oxazepam is a bitter-tasting, white, crystalline powder that is insoluble in water but soluble in alcohol, chloroform, and ether (*Remington's Pharmaceutical Sciences*, 1980). The material is nonhygroscopic and stable in light. It has a melting-point range of 205° to 206° C (*Merck Index*, 1983).

PRODUCTION, USE, AND HUMAN EXPOSURE

Oxazepam and related benzodiazepine drugs are used in the treatment of anxiety. Most clinically useful drugs for this purpose are variants of the 1,4-benzodiazepine structure (Figure 1) consisting of two aromatic rings and a 7-membered heterocycle. One of the aromatic rings is fused to the 7-membered ring and contains a chlorine or other electronegative group as a substituent. All clinically important derivatives contain a 5-aryl or 5-cyclohexenyl group. Most of the drugs vary in substituent groups at the 1 and 3 positions (*Goodman and Gilman's*, 1996). Oxazepam, known under the trade name Serax®, is produced and sold by Wyeth Laboratories and has been on the market since 1965. Generic forms produced by other manufacturers are also now available (*PDR*, 1996).

No definite production data are available for oxazepam or for the benzodiazepine drugs; however, the use of benzodiazepines by the general population has been reported as 8% in the United Kingdom, 7% in the United States, and 8% to 10% in Norway (Pedersen and Lavik, 1991). In 1983, 2.6 million prescriptions for oxazepam were written in the United States, and oxazepam ranked 132nd and 125th in overall frequency of prescriptions written for all drugs in 1984 and 1985, respectively (Anonymous, 1986; C. Baum correspondence, 1986). Oxazepam is also a common metabolite of several other benzodiazepines, some of which are more widely prescribed, including diazepam (Valium®). In 1983, 25.5 million prescriptions for diazepam were written in the United States, making it the fourth most prescribed drug, and although newer benzodiazepines are replacing some of the older drugs, over 2.3 million prescriptions for diazepam were still written in 1995 (Anonymous, 1996).

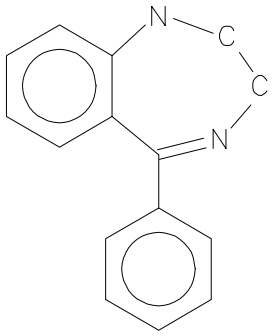


FIGURE 1
1,4-Benzodiazepine Structure

REGULATORY STATUS

Benzodiazepines are prescription drugs regulated under the Food, Drug, and Cosmetic Act of 1938 and are on Schedule IV of the Drug Enforcement Administration Controlled Substances Code (Tocus *et al.*, 1983). Although production workers and dispensers are exposed to benzodiazepines, no workplace exposure limits have been recommended for these types of chemicals (ACGIH, 1996). Environmental contamination has not been shown.

PHARMACOLOGY

All benzodiazepines currently in use share a number of effects, including sedation, hypnosis, decreased anxiety, muscle relaxation, amnesia, and anti-convulsant activity. Benzodiazepines are considered central nervous system (CNS) depressants but are not general depressants and, within therapeutic dose ranges, all effects are related to specific CNS events (*Goodman and Gilman's*, 1996). Each drug differs slightly within this spectrum of actions (e.g., flurazepam has a strong hypnotic effect in humans) (Randall *et al.*, 1969). Other drugs are marketed specifically for use in obstetrics, for epilepsy, or for insomnia (CRM, 1980). These differences may reflect the different intrinsic affinities of the drugs for benzodiazepine receptors. In addition, the various drugs have different pharmacokinetics (Greenblatt and Shader, 1978; Eadie, 1984), and differences in disposition and rates of biotransformation may affect the spectrum of effects. Oxazepam is a relatively short-acting agent typically prescribed for relief of anxiety and given orally at dose levels of 10, 15, or 30 mg, three or four times per day (*PDR*, 1996).

The therapeutic effects of the benzodiazepines are thought to be due to a receptor-mediated response that increases the efficiency of submaximal GABAergic transmission mediated by a variety of long-fiber neurons and interneurons in the CNS (Richards *et al.*, 1986). A GABAergic receptor protein complex has been isolated and cloned from brain tissue, and some information is known on subunit structure in relation to benzodiazepine binding (*Goodman and Gilman's*, 1996). This complex is associated with a chloride ion channel and has associated proteins that are separate binding sites for barbiturates and the benzodiazepines (Barnard *et al.*, 1984). The benzodiazepine binding site is on the alpha subunit (Levitan *et al.*, 1988). The clinically useful benzodiazepines likely all act to increase the binding of GABA to the GABA receptor complex rather than changing the kinetics of chloride conductance in relation to the amount of GABA bound (Rogers *et al.*, 1994). GABAergic neurons are most concentrated in the substantia nigra, globus pallidus, and hypothalamus in the human brain (Cooper *et al.*, 1978). However, the density of CNS-type benzodiazepine receptors is highest in the cortical regions of the cerebrum and cerebellum, suggesting other functions for the CNS-type receptors (Saano, 1988). The anxiety-reducing effect of benzodiazepines in the rat brain has been associated with GABAergic circuits in the mammillary body (Kataoka *et al.*, 1982). At least one other benzodiazepine receptor type has been identified in the brain, specifically in glial tissues in

the pineal gland and olfactory bulb, and is also found in heart, liver, lung, testis, and other tissues. The role of this receptor is not clear, but it appears to be a mitochondrial protein that may use porphyrins as endogenous ligands (Snyder *et al.*, 1987; Verma and Snyder, 1989; Calvo *et al.*, 1991) and may be involved in the regulation of steroid biosynthesis (Krueger and Papadopoulos, 1992), specifically in the transport of cholesterol to the inner mitochondrial membrane (Papadopoulos and Brown, 1995). Some structural requirements for binding to these receptors have been described (Campiani *et al.*, 1996).

ABSORPTION, DISPOSITION, METABOLISM, AND EXCRETION

Experimental Animals

The toxicokinetics and metabolism of oxazepam in F344 rats and $B6C3F_1$ and Swiss-Webster mice have been described in detail by Yuan *et al.* (1994) and Griffin and Burka (1993, 1995). Oxazepam was well absorbed after oral administration, with peak blood concentrations achieved within 2 to 3.5 hours, and with female rats and mice having higher blood concentrations than males. Elimination of oxazepam from plasma was first order and best described by a two-compartment model with terminal elimination half-lives of 4 to 5 hours for rats and 5 to 7 hours for mice. The bioavailability of oxazepam from the diet was about 40% of that achieved following a gavage dose of oxazepam (50 mg/kg) in methyl cellulose vehicle, and apparently decreased with increasing oxazepam concentrations. Thus, steady-state blood concentrations, reached after about 4 days on dosed feed, were not proportional to dose (Yuan *et al.*, 1994).

The metabolism of oxazepam in the F344 rat is demonstrated in Figure 2. The metabolism of oxazepam is complex, with major pathways including ring oxidation through the dihydrodiol and conjugation with glucuronic acid or sulfate. A nonenzymatic condensation of the benzodiazepine ring also occurs. Not all metabolites have been identified. The metabolites are excreted primarily in feces and urine and appear in differing amounts depending on the size of the dose and the time of collection. In contrast to the mouse, pretreatment of rats with oxazepam did not significantly alter the metabolism or elimination profiles (Griffin and Burka, 1995). Pretreatment of mice tended to shift metabolites from feces to urine and increased excretion of glucuronide and unchanged drug. There was evidence of extensive enterohepatic circulation in the mouse (Griffin and Burka, 1993; Griffin *et al.*, 1995a), and this may influence the ultimate metabolic profile in the mouse to a greater extent than in rats or humans.

Humans

Oxazepam is readily absorbed following oral administration, and peak blood levels in humans are achieved in 0.75 to 8 hours when oxazepam is given in tablet form, with an average of 2.7 hours (Shader and Greenblatt, 1981). The half-life of oxazepam in the blood of humans is 6.8 ± 1.3 hours. It has a volume of distribution of 0.6 ± 0.2 L/kg and a clearance of 1.05 ± 0.36 mL/min per kilogram. Approximately 98% of the drug is bound to plasma proteins (*Goodman and Gilman's*, 1996). About 95% is converted to the C3 glucuronide conjugate by UDP glucuronyl transferase 2 (Rajaonarison *et al.*, 1991) and excreted in the urine; minor amounts of six other metabolites have been identified (Sisenwine *et al.*, 1972). Only the parent compound is thought to have antianxiety activity.

TOXICITY

Experimental Animals

Oral LD_{50} values for oxazepam have been reported to range from about 1,500 mg/kg to greater than 5,000 mg/kg in various strains of mice (Marcucci *et al.*, 1968; Randall *et al.*, 1970; Scrollini *et al.*, 1975; Petrescu *et al.*, 1981) and were greater than 5,000 mg/kg in Wistar and Charles River CD rats (Owen *et al.*, 1970; Scrollini *et al.*, 1975). Owen *et al.* (1970) administered oxazepam in feed to Charles River CD rats at concentrations of 0.06%, 0.125%, 0.25%, and 0.5%. After 6 weeks, 2 of 20 rats in the 0.5% group died, and body weight gain was decreased in the 0.25% males. Liver, adrenal gland, and kidney weights were greater in exposed rats than in controls. The only histopathologic finding was an increase in liver parenchymal fat in exposed rats.

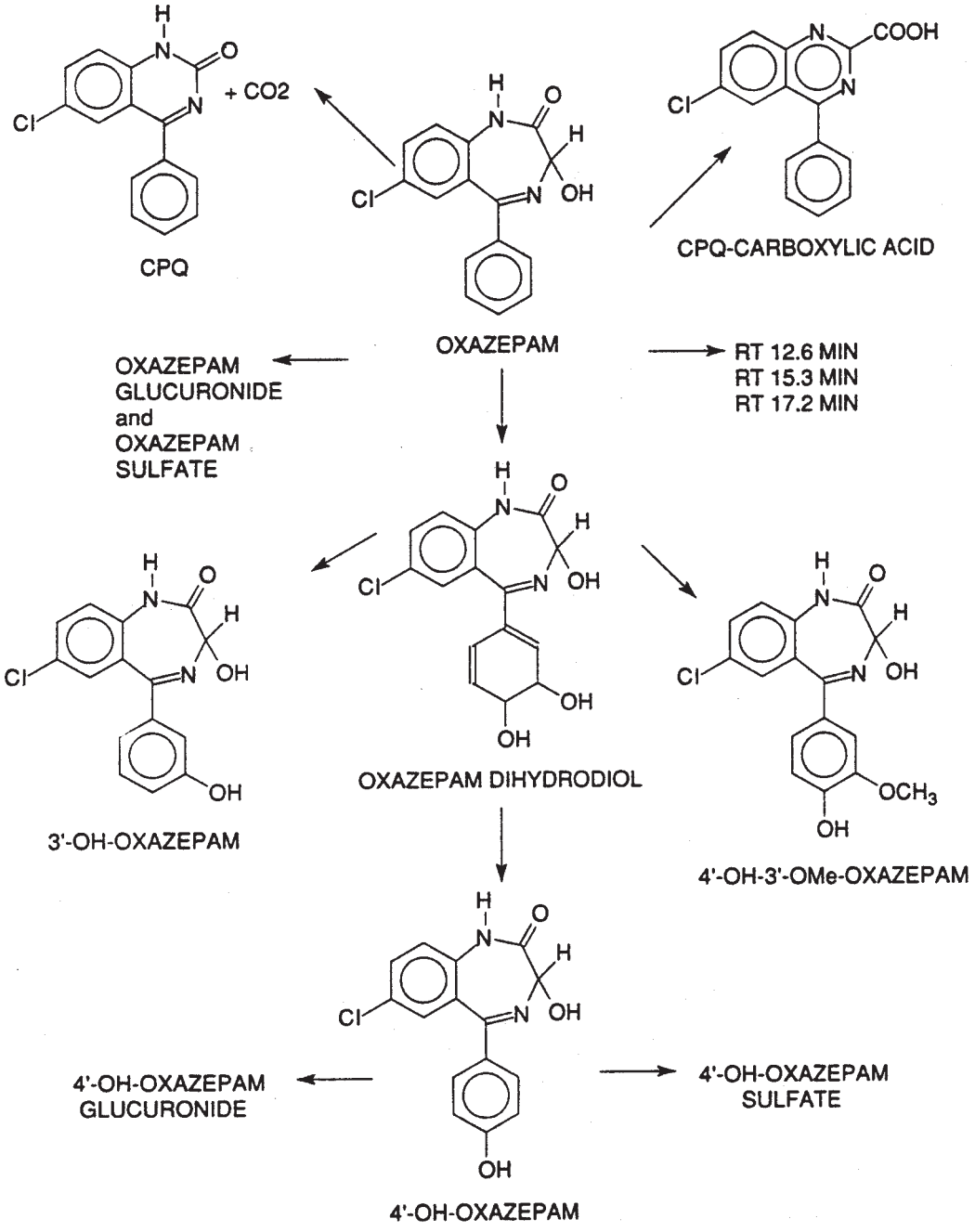


FIGURE 2
Metabolism of Oxazepam in F344 Rats (Griffin and Burka, 1995)

Groups of 30 male and 30 female rats were fed diets containing 0, 0.015%, 0.03%, 0.06%, or 0.12% oxazepam for 55 weeks. Deaths were not clearly chemical related, and other than increased liver weights, no effects on body weight gain, hematology parameters, or significant chemical-related gross or histopathologic lesions were observed (Owen *et al.*, 1970).

The principal effects seen in Swiss-Webster and $B6C3F_1$ mice in 13- or 14-week studies using dosed feed at concentrations as high as 10,000 ppm were marked liver weight increases and increased incidences of centrilobular hypertrophy. These changes occurred at all doses including the lowest dose, 625 ppm (NTP, 1993).

The increased liver weights observed in these and other studies with benzodiazepines suggest stimulation of proliferation of smooth endoplasmic reticulum (Orlandi *et al.*, 1975). However, the benzodiazepines do not appear to stimulate their own metabolism and have been found to inhibit metabolism of other drugs such as morphine or aminopyrine in Wistar rats (Vega *et al.*, 1984) and to stimulate metabolism of certain chemicals (i.e., benzene and aniline) (Jabłońska *et al.*, 1975). This coincides with the benzodiazepines' reputation of not producing significant tolerance during long-term therapy (*Goodman and Gilman's*, 1996). Physical dependence has been demonstrated in rats with several of the drugs, including diazepam (Martin *et al.*, 1982).

Humans

The benzodiazepines are a poor choice for suicide purposes and, despite many attempts, deaths by overdose are rare (Finkle *et al.*, 1979; Buckley *et al.*, 1995). Overdoses of oxazepam commonly result in drowsiness, blurred vision, and ataxia. As in rats, stimulation of proliferation of smooth endoplasmic reticulum has been shown in liver biopsies from humans taking diazepam (Orlandi *et al.*, 1975). Physical dependence is produced in humans given benzodiazepines.

CARCINOGENICITY

Experimental Animals

Several long-term rodent studies have been performed with the benzodiazepines. Fox and Lahcen (1974) observed liver neoplasms in oxazepam-treated Swiss-Webster mice during the course of reproductive toxicity studies. Mice were housed as breeding pairs from 3 to 12 months of age and were fed an oxazepam-supplemented diet at doses of 0.05% and 0.15%. They were killed at 14 months of age. The incidences of liver neoplasms increased in males (0/13, 3/12, 8/13) and females (0/10, 0/10, 5/8) with dose. The neoplasms were generally multiple and gave the livers a massively nodular appearance. Histopathologically, the neoplasms were diagnosed as hepatocellular adenomas, which showed peliosis and extramedullary hematopoiesis.

De la Iglesia *et al*. (1981) administered diazepam or prazepam in feed at concentrations sufficient to result in doses of up to 75 mg/kg body weight per day to male and female CF_1 mice and Wistar rats for 80 and 104 weeks, respectively. The incidences of malignant liver neoplasms were increased in male mice receiving diazepam. Temazepam, which is metabolized to oxazepam in the mouse, was administered in feed to Charles River CD rats for 2 years and to Charles River CD-1 mice for 18 months at doses of 10 to 160 mg/kg per day. Exposed female mice had slightly increased incidences of liver adenoma (Robinson *et al.*, 1984).

As a follow-up to the Fox and Lachen (1974) observation, groups of 60 male and 60 female Swiss-Webster mice were exposed to feed containing 0, 2,500, or 5,000 ppm oxazepam for 57 weeks. The study was then terminated because of poor survival in the exposed groups. Mice receiving oxazepam were found to have very high rates of hepatocellular neoplasms (males, combined hepatocellular adenomas and carcinomas: control, 1/60; 2,500 ppm, 35/60; 5,000 ppm, 52/60; females: 1/60, 23/59, 47/59), as well as an exacerbated amyloidosis. Amyloidosis is commonly seen in this strain of mice, but the condition was severe, particularly in the heart, and likely contributed to the low survival. A similar study was carried out with the $B6C3F_1$ mouse, with an additional dose group receiving oxazepam at 125 ppm. This lower exposure concentration was projected to give blood concentrations in the therapeutic range for humans. Again, mice receiving 2,500 or 5,000 ppm oxazepam suffered from reduced survival and high rates of hepatocellular neoplasms (males, combined hepatocellular adenomas, carcinomas, and hepatoblastomas: control, 23/49; 125 ppm, 19/50; 2,500 ppm, 50/50; 5,000 ppm, 50/50; females: 28/50, 36/50, 50/50, 47/50). The incidences of thyroid gland

follicular cell adenoma were also increased in exposed females (0/50, 4/50, 5/50, 6/50) (NTP, 1993; Bucher *et al.*, 1994).

Humans

No studies on the carcinogenicity of oxazepam in humans were found in the literature.

PROMOTION STUDIES

The benzodiazepines have been tested in various promotion assays because of reports, primarily from one laboratory, that diazepam treatment accelerated the growth of intrarenally implanted neoplasm cells (Walker 256) (Horrobin *et al.*, 1979) and that it was positive in an *in vitro* metabolic cooperation assay for neoplasm promoters (Trosko and Horrobin, 1980). These reports appeared following publication of an epidemiological study that suggested an association between increased incidences of breast cancer and benzodiazepine use in women (Stoll, 1976). This association was later discounted (Kleinerman *et al.*, 1984), but further animal experimentation has provided mixed results.

Remandet *et al.* (1984) fed F344/N rats 2-acetylaminofluorene for 8 weeks and followed this for 12 weeks with diets containing one of six benzodiazepines. They reported no increased incidences of liver neoplasms or enzyme-altered foci. Préat *et al.* (1987) reported positive promotional activity with oxazepam in Wistar rats in two different assays for hepatocarcinogenesis. In one, animals were initiated with diethylnitrosamine (DEN) and were treated with 2-acetylaminofluorene and carbon tetrachloride during the next 2 weeks; they then received oxazepam in feed for 30 weeks. In the other protocol, initiation with DEN was preceded by partial hepatectomy, and promotion was effected by dietary administration for 1 year. Diwan *et al.* (1986) found diazepam and oxazepam to be promoters of DEN-initiated liver neoplasms in mice. In this study, groups of $B6C3F_1$ mice received injections of DEN at 5 weeks of age; at 7 weeks, they were fed diets containing diazepam or oxazepam at 0.05% or 0.15%, or were given phenobarbital in water at 500 ppm. Mice were killed periodically through 60 weeks of age. The incidences of neoplasms were increased in mice receiving diazepam and in those receiving 0.15% oxazepam. A few adenomas were also observed in uninitiated mice receiving 0.15% diazepam (3/15) or 0.05% oxazepam (2/16), and none were observed in mice receiving only phenobarbital. Diazepam and oxazepam were also found to induce hepatic P_{450} content and to increase aminopyrine *N*-demethylase activity. Diwan *et al.* (1986) have proposed that promotion of hepatocellular carcinogenesis is associated with induction of *N*-demethylase activity and appears to be quite species and strain specific. Diazepam did not induce cytochrome P_{450} in the liver of Sprague-Dawley rats (Vorne and Idänpään-Heikkilä, 1975), and this was considered consistent with the negative promotional findings of Remandet *et al.* (1984) in their study with F344/N rats.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Experimental Animals

Although the benzodiazepines have been used in treating toxemia and preeclampsia as well as the psychiatric complications of pregnancy (Shannon *et al.*, 1972; Kanto, 1982), there are many reports of fetotoxic and teratogenic effects of these and other minor tranquilizers when given to pregnant animals. Tucker (1985) provided a critical review of studies of developmental toxicity of benzodiazepines in the rat. Saito *et al.* (1984) found increases in fetal toxicity (resorptions, dead fetuses, and malformations) in pregnant rats given doses of diazepam or chlordiazepoxide of 100 mg/kg *per os* during gestational days 7 to 14. Miller and Becker (1975) first found diazepam produced cleft palate following oral administration of 87.5 or 125 mg/kg to Swiss-Webster mice on days 11 to 13. This has since received considerable study and is now attributed to potentiation of the GABAergic inhibition of the palate shelf reorientation (Wee and Zimmerman, 1983). In general, exposures to high doses *in utero* produce decreased litter sizes, decreased pup weights, and increased numbers of malformations. Exposures to lower doses (5 to 20 mg/kg per day) during critical periods (after gestational day 14 in rats) produce no immediately obvious effects at birth but result in various behavioral deficits during later life and a variety of poorly understood changes in the concentration of neurotransmitters in various brain areas (Livezey *et al.*, 1986a; Ryan and Pappas, 1986; Shibuya *et al.*, 1986). Central to these studies have been attempts to correlate changes in benzodiazepine receptor concentration with altered behavior. Livezey *et al.* (1986b) have argued that *in utero* exposure to benzodiazepines during the

period of receptor development (after gestational day 14 in rats) results in a decreased benzodiazepine receptor concentration and results in rats that suffer chronic anxiety demonstrated by hyperarousal, inability of the animals to habituate to a novel environment, and a large reduction in the amount of deep slow-wave sleep. Changes in passive avoidance have also been reported in mice following *in utero* exposure to oxazepam (Ricceri *et al.*, 1994).

Humans

Exposure of the human fetus to diazepam results in a set of symptoms collectively known as the "floppy infant syndrome," which includes hypothermia, hyperbilirubinemia, hypotonia, asphyxia, respiratory complications, and poor sucking response. This is likely due to the ready transfer of the drugs across the placenta. Pharmacologic effects are exaggerated in the unborn because higher levels accumulate due to the slower elimination from the fetus. There have been reports of increases in severe congenital anomalies in infants whose mothers took chlordiazepoxide and other benzodiazepines (including oxazepam) during pregnancy (Milkovich and van den Berg, 1974); there have also been reports claiming no link between benzodiazepine use and fetal abnormalities (Hartz *et al.*, 1975).

GENETIC TOXICITY

Oxazepam has not been tested extensively for mutagenicity, but the data reported for oxazepam and its structural analogues indicate that this class of chemicals is probably not genotoxic. There is one report of a positive response in a *Salmonella* gene mutation assay (Batzinger *et al.*, 1978). The authors described an increase in revertants for strains TA98 and TA100 when exposure was carried out in the presence of rat liver S9 activation enzymes. The data reported were insufficient for a critical evaluation of the results. Other laboratories that have tested oxazepam for mutagenicity in *Salmonella* have reported negative results. Matula and Downie (1983), in a brief abstract which presented little experimental detail, reported negative results, with and without S9, in strains TA98 and TA100. Balbi *et al*. (1980) detected no mutagenic activity with oxazepam in four strains of *Salmonella*, with or without S9, but their report did not include complete data tables for those tests that gave negative results. NTP mutagenicity tests with five strains of *Salmonella* yielded negative results, with and without S9 (Appendix C).

No evidence of chromosome nondisjunction was observed in *Aspergillus nidulans* treated with an unspecified concentration of oxazepam in the absence of S9 (Bignami *et al.*, 1974). Unscheduled DNA synthesis was not detected in rat liver cells *in vitro* (Swierenga *et al.*, 1983), and no induction of chromosomal aberrations was observed in bone marrow cells of mice administered 0.85 mg/kg oxazepam by intraperitoneal injection five times weekly for 8 weeks (Degraeve *et al.*, 1985). In addition, results from NTP (1993) studies (Appendix C) showed no induction of sister chromatid exchanges or chromosomal aberrations in cultured Chinese hamster ovary cells treated with oxazepam, with or without rat liver S9, and no increase in micronucleus frequency was noted in peripheral blood erythrocytes of male and female mice treated with oxazepam for 90 days.

A variety of genotoxicity tests has been performed with two of the widely used structural analogues of oxazepam, diazepam, and chlordiazepoxide. Diazepam was nonmutagenic in *Salmonella* (Batzinger *et al.*, 1978; Waskell, 1978; Preiss *et al.*, 1982; Zeiger *et al.*, 1992). There was no evidence of diazepam-induced chromosome loss or nondisjunction in yeast (Bignami *et al.*, 1974; Matula and Downie, 1983; Crebelli *et al.*, 1989, 1991; Parry *et al.*, 1989; Whittaker *et al.*, 1989). The effects reported for diazepam in cultured mammalian cells varied. No induction of chromosomal aberrations was noted in cultured Chinese hamster ovary cells treated with diazepam with or without S9 in two laboratories (Ishidate *et al.*, 1978; Matsuoka *et al.*, 1979), but positive results were reported in one study using cultured Chinese hamster ovary cells treated in the absence of S9 (Lafi and Parry, 1988). Disruption of mitosis with concomitant chromosome loss was observed in cultured Chinese hamster ovary cells after treatment with diazepam in the absence of S9 (Hsu *et al.*, 1983; Parry *et al.*, 1986; Lafi *et al.*, 1987). Results of tests for induction of chromosomal aberrations and sister chromatid exchanges in human lymphocytes (Staiger, 1970; Zhurkov, 1975) or fibroblasts (Staiger, 1969; Kawachi *et al.*, 1980; Sasaki *et al.*, 1980) treated *in vitro* with diazepam were uniformly negative. Unscheduled DNA synthesis was not detected in rat liver cells treated *in vitro*

with diazepam (Swierenga *et al.*, 1983; Williams *et al.*, 1989).

In vivo tests with diazepam showed little indication of genotoxic activity. No evidence of mitotic disruption or induction of chromosomal aberrations was observed in mouse bone marrow cells following administration of up to 100 or 150 mg/kg diazepam, respectively (Miller and Adler, 1989; Xu and Adler, 1990). Negative results were reported for diazepam in bone marrow chromosomal aberration assays in hamsters (Schmid and Staiger, 1969) and rats (Ishimura *et al.*, 1975; Kawachi *et al.*, 1980). In addition, no increases in chromosomal aberrations (Stenchever *et al.*, 1970a; White *et al.*, 1974) or sister chromatid exchanges (Torigoe, 1979; Husum *et al.*, 1985) were observed in peripheral lymphocytes obtained from patients treated with diazepam either chronically, as a management for anxiety or muscle spasm, or acutely, as part of a surgical routine.

Fewer genotoxicity test results are available for chlordiazepoxide, but indications are that it, too, is not genetically active. Chlordiazepoxide did not induce nondisjunction in *A. nidulans* (Bignami *et al.*, 1974) or chromosomal aberrations in cultured Chinese hamster cells (Sasaki *et al.*, 1980), human fibroblasts (Staiger, 1969), or leucocytes (Bregman, 1970; Stenchever *et al.*, 1970b). *In vitro* micronucleus tests with hamster and human cells were negative (Sasaki *et al.*, 1980). Results of *in vivo* investigations indicate that chlordiazepoxide does not induce chromosomal aberrations in mouse (Petersen *et al.*, 1978; Degraeve *et al.*, 1985) or hamster (Schmid and Staiger, 1969) bone marrow cells. Finally, no induction of chromosomal aberrations was observed in lymphocytes obtained from patients administered chlordiazepoxide (up to 200 mg/day) (Stenchever *et al.*, 1970b).

STUDY RATIONALE

Oxazepam and four other benzodiazepines (chlordiazepoxide, chlorazepate, diazepam, and flurazepam) were nominated for study by the Food and Drug Administration (FDA) and by the NIEHS based on their widespread use, use by pregnant women, and the lack of adequate rodent carcinogenicity studies. An agreement was reached with Hoffmann-LaRoche, Inc., the manufacturer of chlordiazepoxide, diazepam, and flurazepam, for studies to be carried out on these drugs under its auspices in cooperation with the NTP. These studies are completed and results have been submitted to the FDA. No studies were performed on chlorazepate because of the very similar metabolite profile between this drug and diazepam. Oxazepam was evaluated in 14-week and 2-year studies by the NTP, and Technical Report No. 443 contains the results of studies performed with the Swiss-Webster and $B6C3F_1$ strains of mice (NTP, 1993). Studies with rats were not initiated at the same time as the mouse studies because adequate carcinogenicity studies of oxazepam with the Sprague-Dawley rat strain had been submitted to the FDA by the manufacturer, Wyeth Laboratories. Subsequently, because of the marked neoplastic responses found in the two mouse strains, the NTP initiated further 2-year studies of oxazepam with the F344/N rat.

The current studies include measures of serum oxazepam concentrations and histopathologic evaluation of tissues from the 2-year animals. No 13-week studies were performed with oxazepam in rats because it was determined that the prior 13-week studies with mice gave very little information on which to base dose selection for the 2-year studies. For this reason, five exposure concentrations were chosen for the 2-year evaluation. After 26 weeks, one exposure group considered uninformative was terminated, and the highest exposure group was removed from dosed feed for the duration of the study. A separate set of studies evaluating a number of biochemical changes in the F344/N rat following short-term exposure to oxazepam is summarized in Appendix H.

MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF OXAZEPAM

Oxazepam was obtained from Roussel Corporation (Englewood Cliffs, NJ) in one lot (86017.01). Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO) (Appendix D). Reports on analyses performed in support of the oxazepam studies are on file at the NIEHS.

The chemical, a white, powdered solid, was identified as oxazepam by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. Purity of oxazepam was determined by elemental analyses, Karl Fischer water analysis, functional group titration, thin-layer chromatography (two systems), and high-performance liquid chromatography. Elemental analyses for carbon, hydrogen, nitrogen, and chlorine were in agreement with the theoretical values for oxazepam. Karl Fischer water analysis indicated 0.026% ± 0.001% water. Functional group titration indicated a purity of 101.4% ± 0.5%. Thin-layer chromatography indicated a major spot and one trace impurity in one system, and only a major spot in a second system. High-performance liquid chromatography revealed a major peak with no impurity peaks with areas greater than 0.1% of the major peak area. The overall purity was determined to be greater than 99%.

Stability studies of the bulk chemical were performed by the analytical chemistry laboratory using high-performance liquid chromatography. These studies indicated that oxazepam was stable as a bulk chemical for 2 weeks when stored protected from light at temperatures up to 60° C. To ensure stability, the bulk chemical was stored at room temperature, protected from light, in metal cans or amber glass bottles.

Stability was monitored during the 2-year study using high-performance liquid chromatography. No degradation of the bulk chemical was detected.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

The dose formulations were prepared every 2 weeks by mixing oxazepam with feed (Table D1). Homogeneity and stability studies of a 500 ppm dose formulation were performed by the analytical chemistry laboratory using high-performance liquid chromatography. Homogeneity was confirmed and the stability of the dose formulation was confirmed for at least 3 weeks at 5° C when stored protected from light.

Periodic analyses of the dose formulations of oxazepam were conducted at the study laboratory and analytical chemistry laboratory using high-performance liquid chromatography. During the 2-year study, dose formulations were analyzed every 8 weeks (Table D2). All 50 of the dose formulations analyzed were within 10% of the target concentrations; 89% (17/19) of the animal room samples analyzed were within 10% of the target concentrations with no value differing more than 12% from the target concentration.

2-YEAR STUDY

Study Design

Groups of 50 male and 50 female F344/N rats were fed diets containing 0, 625, 1,250, 2,500, 5,000, or 10,000 ppm oxazepam for up to 105 weeks. The exposure concentrations were selected to provide a wide exposure range. No 13-week rat studies were performed because the data from the 13-week mouse study did not provide useful information for the selection of exposure concentrations for the prior 2-year mouse studies (NTP, 1993), and it was not anticipated that useful information would be gained from a 13-week rat study. The 5,000 ppm exposure concentration was determined during the course of the study to be the maximum tolerated dose. Concentrations of 0, 625, 2,500, and 5,000 ppm were selected for the continuous-exposure study. After

26 weeks of exposure, rats in the 1,250 ppm group were eliminated from the study because it was anticipated that this group would provide no useful information. Rats in the 625, 2,500, and 5,000 ppm groups received dosed feed throughout the 2-year study. Rats in the 10,000 ppm group stopped receiving oxazepam in feed at 26 weeks and remained on control feed until study termination.

Source and Specification of Animals

Male and female F344/N rats were obtained from Taconic Farms (Germantown, NY) for use in the 2-year study. Rats were quarantined for 13 days (males) or 14 days (females) before the beginning of the studies and were approximately 6 weeks old at the beginning of the study. Five male and five female rats were randomly selected for parasite evaluation and gross observation of disease at the end of the quarantine period. The health of the animals was monitored during the study according to the protocols of the NTP Sentinel Animal Program (Appendix G).

Animal Maintenance

Rats were housed five per cage. Feed and water were available *ad libitum*. Feed consumption was measured for a 7-day interval during weeks 1 and 4 and every 4 weeks thereafter by cage. Cages were changed twice per week, and racks were rotated every 2 weeks. Further details of animal maintenance are given in Table 1. Information on feed composition and contaminants is provided in Appendix F.

Clinical Examinations and Pathology

All animals were observed twice daily. Clinical findings were recorded every 4 weeks and at study termination. Individual body weights were recorded weekly for 13 weeks, monthly thereafter, and at the end of the study.

During study weeks 105 (males) and 104 (females) (1 to 3 days prior to necropsy), blood samples were collected from the retroorbital sinus of up to six males and six females in the 625, 2,500, and 5,000 ppm groups either at 6:00 a.m. or 6:00 p.m. On the days of necropsy, blood samples were similarly collected from up to 17 randomly selected female rats that had not been bled earlier. Plasma oxazepam concentrations were measured in all samples by Midwest Research Institute.

A complete necropsy and microscopic examination were performed on all rats in the 0, 625, 2,500, and 5,000 ppm groups. Rats in the 1,250 ppm group were discarded without tissue collection at 26 weeks. Histopathologic evaluation of rats in the 10,000 ppm group was limited to gross lesions, stomach (forestomach and glandular), small intestine, kidney, thyroid gland, and the liver. 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 (i.e., adrenal gland, kidney, and ovary), samples from each organ were examined. Tissues examined microscopically are listed in Table 1.

Microscopic evaluations were completed by the study laboratory pathologist, and the pathology data were entered into the Toxicology Data Management System. The slides, paraffin blocks, and residual wet tissues were sent to the NTP Archives for inventory, slide/block match, and wet tissue audit. The slides, individual animal data records, and pathology tables were 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 study, a quality assessment pathologist evaluated slides from all tumors and all potential target organs, which included the adrenal cortex, forestomach, glandular stomach, and liver of males and females; the adrenal medulla, duodenum, eye, kidney, pancreas, preputial gland, rectum, and skin of males; and the spleen and thyroid gland of females.

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 diagnoses made by the laboratory and quality assessment

pathologists. Representative histopathology slides containing examples of lesions related to chemical administration, examples of disagreements in diagnoses between the laboratory and quality assessment pathologist, 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).

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 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 as presented in Tables A1, A5, B1, and B5 are given as the number of animals bearing such lesions at a specific anatomic site and the number of animals with that site examined microscopically. For calculation of statistical significance, the incidences of most neoplasms (Tables A3a, A3b, B3a, and B3b) 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 A3a, A3b, B3a, and B3b 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 nonneoplastic lesion prevalence was modeled as a logistic function of chemical exposure and time.

Analysis of Continuous Variables

Prior to 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 using the Mann-Whitney U test (Hollander and Wolfe, 1973).

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 2-year study was conducted in compliance with Food and Drug Administration Good Laboratory Practice Regulations (21 CFR, Part 58). In addition, as records from the 2-year study were submitted to the NTP Archives, this study was 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 oxazepam 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 erythrocytes in peripheral blood of mice. The protocols for these studies and the results are given in Appendix C.

The genetic toxicity studies of oxazepam 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 effects of the chemical in short-term *in vitro* and *in vivo* genetic toxicity tests. These genetic toxicity tests were originally developed to study mechanisms of chemical-induced DNA damage and to predict carcinogenicity in animals, based on the electrophilicity theory of chemical mutagenesis and the somatic mutation theory of cancer (Miller and Miller, 1977; Straus, 1981; Crawford, 1985).

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.

TABLE 1
Experimental Design and Materials and Methods in the 2-Year Feed Study of Oxazepam

Study Laboratory
Battelle Columbus Laboratories (Columbus, OH)

Strain and Species
F344/N rats

Animal Source
Taconic Farms (Germantown, NY)

Time Held Before Studies
13 days (males) or 14 days (females)

Average Age When Studies Began
6 weeks

Date of First Dose
23 September (males) or 24 September (females) 1991

Duration of Dosing
1,250 and 10,000 ppm groups: 26 weeks
0, 625, 2,500, and 5,000 ppm groups: 105 weeks

Date of Last Dose
1,250 and 10,000 ppm groups: 23 - 24 March 1992
625, 2,500, and 5,000 ppm groups: 21 - 23 September 1993

Necropsy Dates
21 - 23 September 1993

Average Age at Necropsy
111 weeks

Size of Study Groups
50 males and 50 females

Method of Animal Distribution
Animals were distributed randomly into groups of approximately equal initial mean body weights.

Animals per Cage
5

Method of Animal Identification
Tail tattoo

Diet
NIH-07 Open Formula meal diet (Zeigler Brothers Inc., Gardners, PA), available *ad libitum*, changed weekly or as necessary

Water Distribution
Tap water (Columbus, OH, municipal supply) distributed via automatic watering system (Edstrom Industries Inc., Waterford, WI), available *ad libitum*

Cages
Polycarbonate (Lab Products Inc., Maywood, NJ), changed twice weekly

Bedding
Sani-Chips® heat-treated hardwood chips (P.J. Murphy Forest Products Corp., Montville, NJ), changed twice weekly

TABLE 1
Experimental Design and Materials and Methods in the 2-Year Feed Study of Oxazepam (continued)

Cage Filters
DuPont 2024 spun-bonded polyester filters (Snow Filtration Co., Cincinnati, OH), changed once every 2 weeks

Racks
Stainless steel (Lab Products Inc., Maywood, NJ), rotated every 2 weeks

Animal Room Environment
Temperature: 19.4° to 25.6° C
Relative humidity: 36% to 66%
Fluorescent light: 12 hours/day
Room air: minimum of 10 changes/hour

Doses
0, 625, 1,250, 2,500, 5,000, or 10,000 ppm in feed

Type and Frequency of Observation
Rats were observed twice daily; clinical findings were recorded every 4 weeks and at study termination; individual body weights were recorded weekly for 13 weeks, monthly thereafter, and at study termination. Feed consumption was recorded for a 7-day interval during study weeks 1 and 4, and every 4 weeks thereafter by cage.

Method of Sacrifice
CO_2 asphyxiation

Necropsy
Necropsy performed on all rats except the 1,250 ppm group

Histopathology
Complete histopathology was performed on all 0, 625, 2,500, and 5,000 ppm rats. In addition to gross lesions, tissue masses, and associated lymph nodes, the tissues examined included: adrenal gland, brain, clitoral gland, esophagus, eyes, heart, large intestine (cecum, colon, and rectum), small intestine (duodenum, jejunum, and ileum), kidney, liver, lung, lymph nodes (mandibular and mesenteric), mammary gland, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, skin, spleen, stomach (forestomach and glandular stomach), testis, thymus, thyroid gland, trachea, urinary bladder, and uterus. Histopathologic evaluation was limited to gross lesions, stomach (forestomach and glandular), small intestine, kidney, thyroid gland, and liver for the 10,000 ppm group.

Plasma Oxazepam Determinations
At weeks 27 (1,250 ppm group) and 105 (males) and 104 (females) (625, 2,500, and 5,000 ppm groups), blood was collected from the vena cava or retroorbital sinus for plasma oxazepam assays.

RESULTS

2-YEAR STUDY

Survival

Estimates of 2-year survival probabilities for male and female rats are shown in Table 2 and in the Kaplan-Meier survival curves (Figures 3 and 4). All 5,000 ppm continuous-exposure and 10,000 ppm stop-exposure males died before the end of the study. Survival of 2,500 ppm continuous-exposure males and females was significantly less than that of the controls. However, survival of 5,000 ppm females did not differ from that of the controls.

TABLE 2
Survival of Rats in the 2-Year Feed Study of Oxazepam

	0 ppm	625 ppm	2,500 ppm	5,000 ppm	10,000 ppm (Stop-Exposure)
Male					
Animals initially in study	50	50	50	50	50
Moribund	25	27	33	43	39
Natural deaths	8	12	11	7	11
Animals surviving to study termination	17	11	6	0	0
Percent probability of survival at end of study[a]	34	22	12	0	0
Mean survival (days)[b]	662	616	621	531	617
Survival analysis[c]	P < 0.001	P = 0.070	P = 0.002	P < 0.001	P < 0.001
Female					
Animals initially in study	50	50	50	50	50
Accidental death[d]	1	0	0	0	0
Moribund	11	18	18	16	19
Natural deaths	6	6	12	3	6
Animals surviving to study termination	32	26	20	31	25
Percent probability of survival at end of study	66	52	40	62	50
Mean survival (days)	676	679	655	686	685
Survival analysis	P = 1.000	P = 0.339	P = 0.019	P = 0.967	P = 0.257

[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 (the 10,000 ppm stop-exposure group was excluded from the trend test), and the results of the life table pairwise comparisons (Cox, 1972) with the controls are in the exposed group columns.
[d] Censored from survival analyses

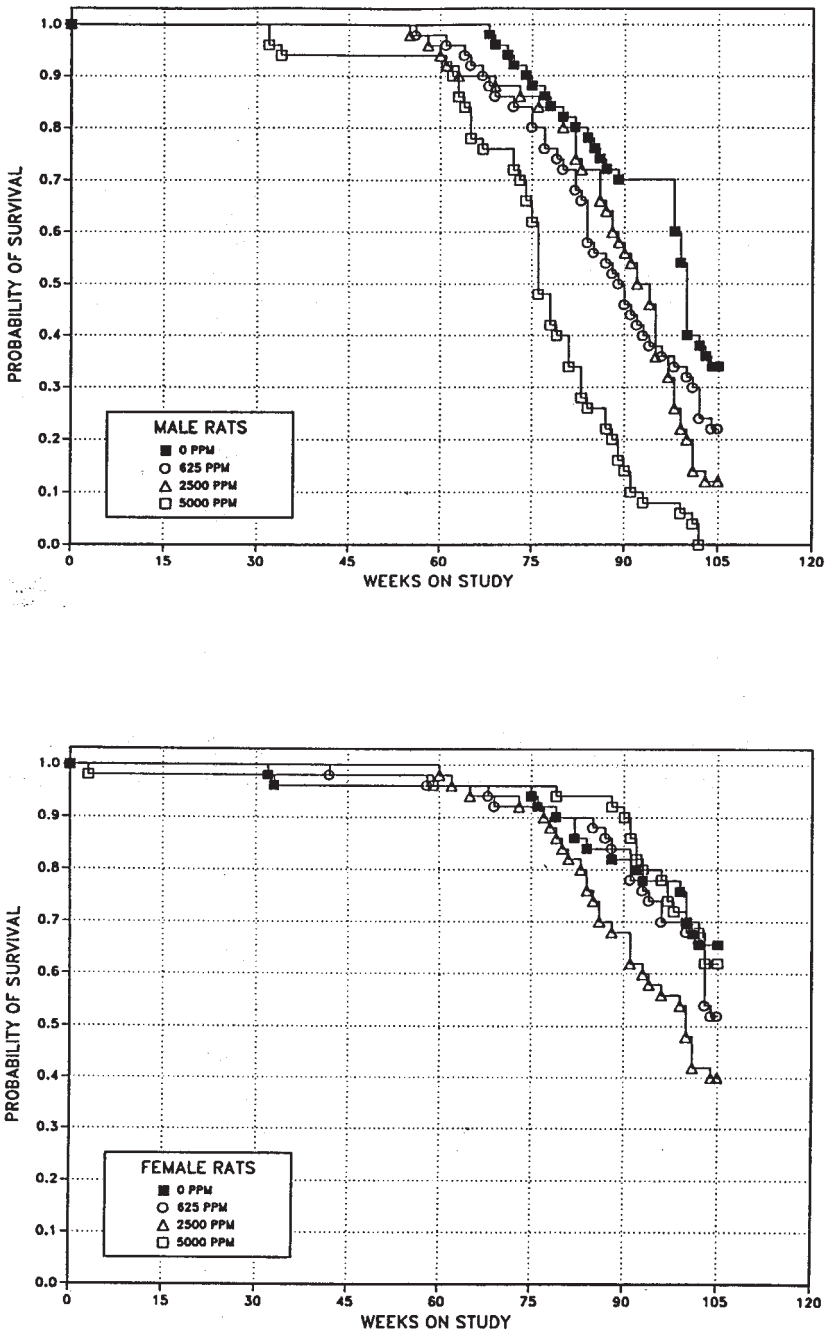


FIGURE 3
Kaplan-Meier Survival Curves for Male and Female Rats Administered Oxazepam in Feed for 2 Years

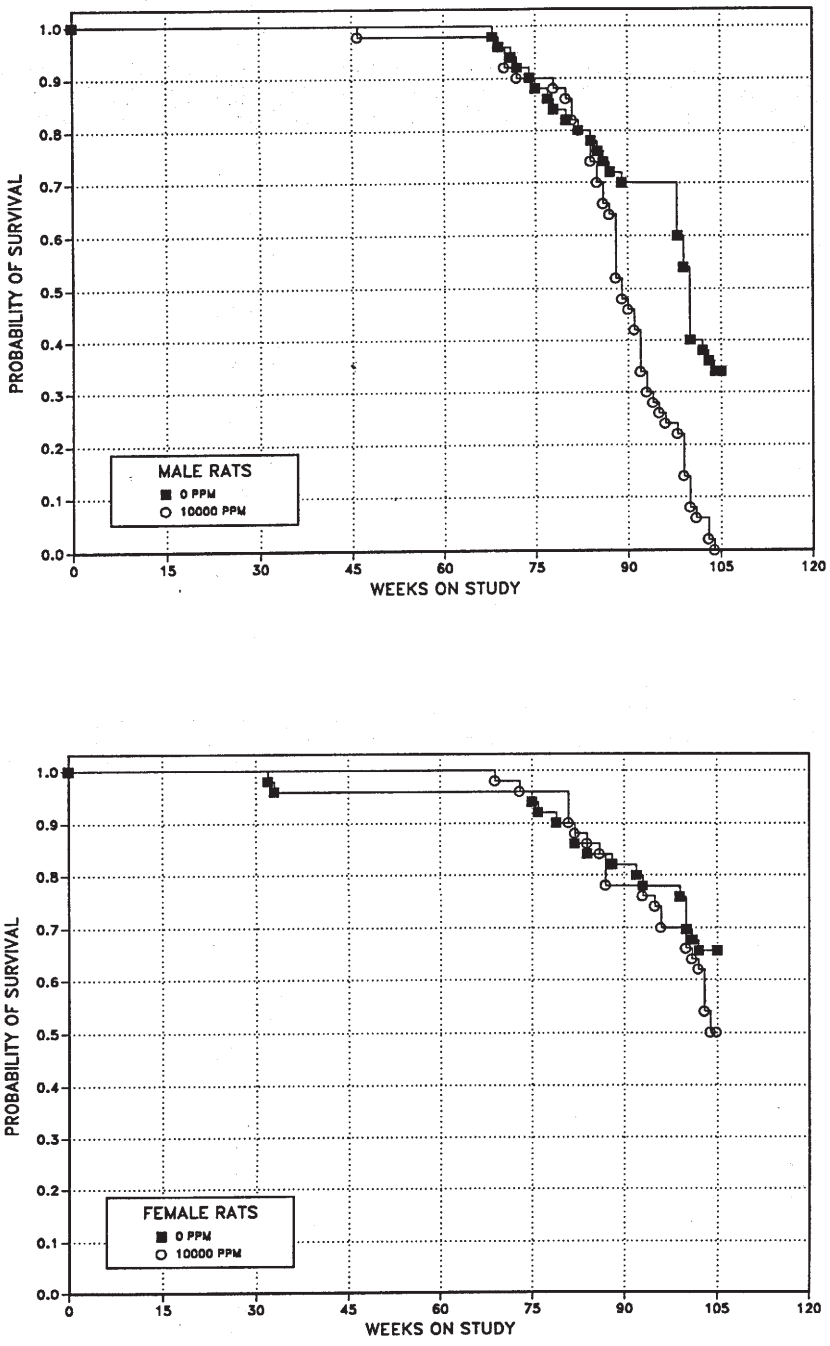


FIGURE 4
Kaplan-Meier Survival Curves for Male and Female Rats in the 2 Year Stop-Exposure Feed Study of Oxazepam

Body Weights, Feed and Compound Consumption, and Clinical Findings

The mean body weight gains of 2,500 and 5,000 ppm males and females were less than those of the controls throughout the study (Figure 5, Tables 3 and 4). The final mean body weights were 74% (2,500 ppm males), 62% (5,000 ppm males), 85% (2,500 ppm females), and 82% (5,000 ppm females) that of the respective controls. The mean body weights of 10,000 ppm stop-exposure males were generally less than those of the controls throughout the study (Figure 6). The mean body weight of 10,000 ppm stop-exposure females was approximately 18% less than that of the controls at week 29, but increased steadily after the cessation of dosing at week 27, and was similar to that of the controls at the end of the study.

During the first week of the study, there was a slight exposure concentration-related decrease in the amount of feed consumed by exposed rats compared to that by the controls (Tables E1 and E2). The reduction in feed consumption was not apparent after the first week of the study, and the reduced consumption was attributed to the initial ataxia experienced during the first week of the study rather than to poor palatability of the dosed feed. At the end of the study, the average daily feed consumption by exposed male and female rats was similar to that by the controls. In 10,000 ppm stop-exposure males and females, the feed consumption was also similar to that by the controls. Dietary levels of 625, 2,500, 5,000, and 10,000 ppm delivered average daily doses of 25, 100, 250, and 630 mg oxazepam/kg body weight to males and 25, 110, 220, and 630 mg/kg to females. Treatment-related eye/nasal discharge, hyperactivity when handled, and/or ataxia were observed in exposed males and females on or about day 2 of exposure but were no longer apparent after day 7. The duration and severity of ataxia were exposure-concentration dependent. On day 2, ataxia was slight in male and female rats exposed to 625 or 1,250 ppm, moderate in male and female rats exposed to 2,500 ppm and female rats exposed to 5,000 ppm, and severe in male rats exposed to 5,000 ppm and male and female rats exposed to 10,000 ppm.

The severity of ataxia diminished daily and was not apparent after day 2 in rats exposed to 625 ppm or 2,500 ppm or after days 3 (males) or 6 (females) in rats exposed to 5,000 ppm. Hyperactivity and eye/nasal discharge were observed in male and female rats exposed to 5,000 ppm but were not apparent after days 3 (males) or 6 (females) of exposure. Male and female stop-exposure rats were hyperactive on day 197 after being switched to undosed feed.

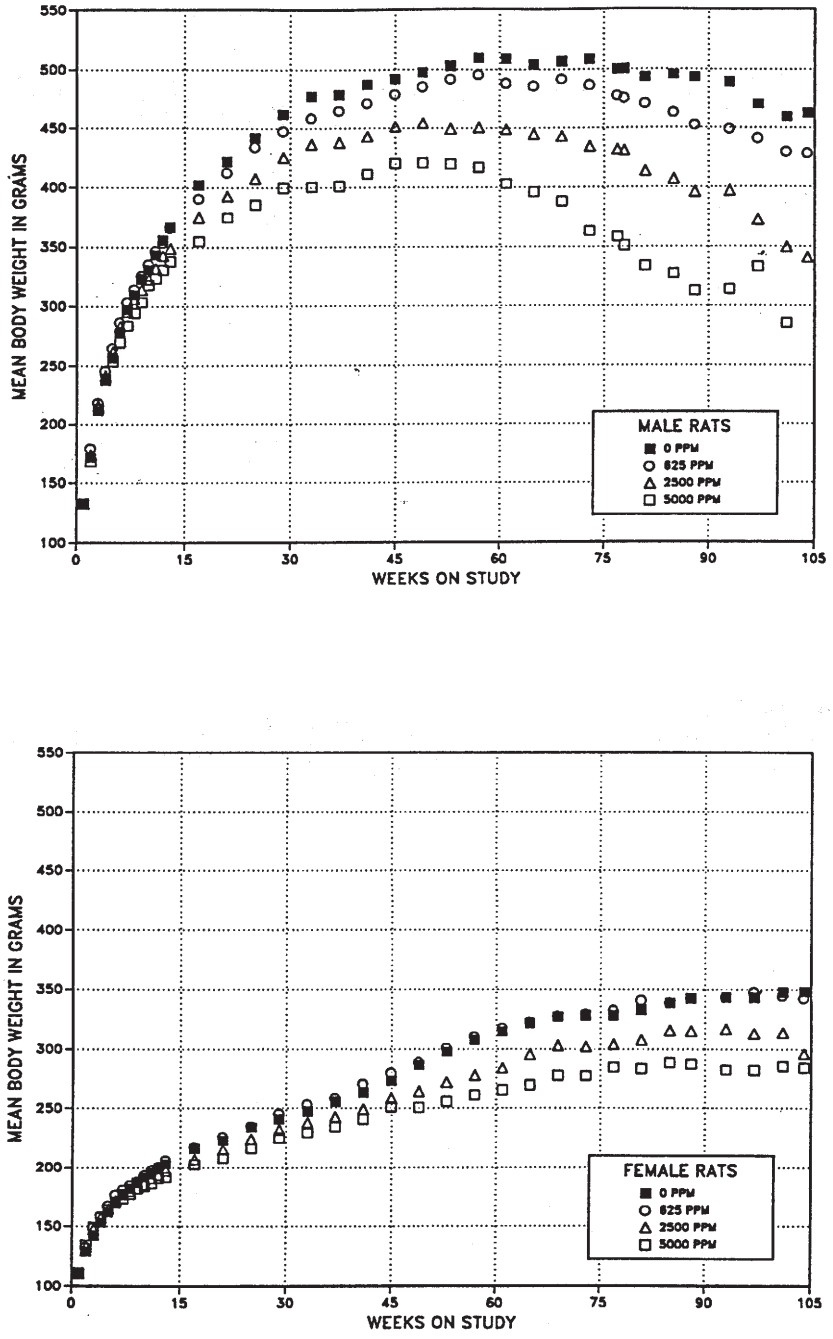


FIGURE 5
Growth Curves for Male and Female Rats Administered Oxazepam in Feed for 2 Years

TABLE 3
Mean Body Weights and Survival of Male Rats in the 2-Year Feed Study of Oxazepam

Weeks on Study	0 ppm		625 ppm			2,500 ppm		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	132	50	132	100	50	132	100	50
2	172	50	179	104	50	174	101	50
3	211	50	218	103	50	216	102	50
4	240	50	246	103	50	242	101	50
5	257	50	265	103	50	262	102	50
6	278	50	286	103	50	283	102	50
7	297	50	304	102	50	296	99	50
8	310	50	315	102	50	306	99	50
9	323	50	326	101	50	314	97	50
10	331	50	336	102	50	323	98	50
11	344	50	347	101	50	332	97	50
12	356	50	354	99	50	343	96	50
13	367	50	366	100	50	349	95	50
17	402	50	391	97	50	375	93	50
21	422	50	413	98	50	393	93	50
25	442	50	434	98	50	408	92	50
29	462	50	448	97	50	426	92	50
33	477	50	459	96	50	437	92	50
37	479	50	465	97	50	438	92	50
41	487	50	471	97	50	443	91	50
45	492	50	479	97	50	451	92	50
49	497	50	485	98	50	454	91	50
53	503	50	492	98	50	449	89	50
57	509	50	496	97	49	451	89	49
61	509	50	488	96	49	449	88	47
65	504	50	486	96	47	445	88	45
69	506	49	492	97	44	443	88	45
73	508	46	487	96	42	434	86	44
77	500	44	478	96	40	432	86	42
78	500	43	476	95	38	431	86	42
81	493	41	471	96	36	414	84	40
85	495	39	463	94	28	407	82	36
88	493	36	452	92	27	396	80	32
93	489	35	449	92	21	397	81	25
97	470	35	441	94	18	372	79	17
101	459	20	429	94	16	349	76	9
104	463	17	428	93	11	341	74	6
Mean for weeks								
1-13	278		283	102		275	99	
14-52	462		449	97		425	92	
53-104	493		469	95		414	84	

TABLE 3
Mean Body Weights and Survival of Male Rats in the 2-Year Feed Study of Oxazepam (continued)

Weeks on Study	5,000 ppm			10,000 ppm[a]		
	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	132	100	50	132	99	50
2	168	98	50	164	96	50
3	213	101	50	208	99	50
4	238	100	50	232	97	50
5	254	99	50	247	96	50
6	270	97	50	263	95	50
7	284	95	50	275	93	50
8	294	95	50	284	92	50
9	304	94	50	290	90	50
10	318	96	50	303	92	50
11	324	94	50	309	90	50
12	331	93	50	322	91	50
13	338	92	50	323	88	50
17	355	88	50	344	86	50
21	375	89	50	358	85	50
25	386	87	50	366	83	50
29	400	87	50	361	78	50
33	401	84	48	404	85	50
37	401	84	47	424	89	50
41	411	84	47	437	90	50
45	420	85	47	449	91	50
49	421	85	47	462	93	49
53	420	84	47	467	93	49
57	417	82	47	472	93	49
61	403	79	47	473	93	49
65	396	79	42	469	93	49
69	388	77	38	469	93	49
73	363	72	36	474	93	45
77	358	72	24	469	94	45
78	351	70	24	469	94	45
81	334	68	20	458	93	43
85	328	66	13	445	90	37
88	313	63	10	425	86	31
93	314	64	5	427	87	17
97	333	71	4	403	86	12
101	285	62	3			
Mean for weeks						
1-13	267	96		258	94	
14-52	397	86		401	87	
53-101	357	72		455	91	

[a] Stop-exposure group

TABLE 4
Mean Body Weights and Survival of Female Rats in the 2-Year Feed Study of Oxazepam

Weeks on Study	0 ppm		625 ppm			2,500 ppm		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	111	50	111	100	50	111	100	50
2	129	50	132	103	50	133	103	50
3	142	50	149	105	50	148	104	50
4	153	50	159	104	50	157	103	50
5	162	50	167	103	50	165	102	50
6	171	50	177	103	50	172	100	50
7	178	50	181	102	50	177	100	50
8	182	50	185	102	50	180	99	50
9	187	50	188	101	50	182	98	50
10	191	50	193	101	50	186	97	50
11	195	50	198	101	50	190	97	50
12	200	50	200	101	50	194	97	50
13	203	50	206	101	50	197	97	50
17	216	50	218	101	50	207	96	50
21	223	50	226	101	50	216	97	50
25	234	50	235	100	50	224	96	50
29	241	50	245	102	50	232	96	50
33	247	49	253	102	50	238	96	50
37	255	48	258	101	50	243	95	50
41	263	48	270	103	50	249	95	50
45	273	48	280	103	49	259	95	50
49	286	48	289	101	49	264	92	50
53	298	48	301	101	49	272	91	50
57	308	48	311	101	49	277	90	50
61	315	48	318	101	48	284	90	49
65	322	48	323	100	48	296	92	48
69	328	48	328	100	47	303	93	47
73	328	48	330	101	46	302	92	47
77	328	46	333	101	46	304	93	46
81	333	45	341	102	45	308	92	42
85	339	42	339	100	45	316	93	37
88	343	40	343	100	42	316	92	34
93	343	39	344	100	39	317	92	31
97	343	38	348	101	35	314	91	28
101	348	34	345	99	34	314	90	23
104	348	32	343	98	27	296	85	21
Mean for weeks								
1-13	170		173	102		169	100	
14-52	249		253	102		237	95	
53-104	330		332	100		301	91	

TABLE 4
Mean Body Weights and Survival of Female Rats in the 2-Year Feed Study of Oxazepam (continued)

Weeks on Study	5,000 ppm			10,000 ppm[a]		
	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	111	100	50	111	99	50
2	134	104	50	133	103	50
3	150	105	50	147	104	50
4	158	103	49	156	102	50
5	164	101	49	162	100	50
6	170	99	49	168	98	50
7	174	98	49	173	97	50
8	177	97	49	175	96	50
9	182	97	49	177	95	50
10	184	96	49	183	96	50
11	187	96	49	185	95	50
12	191	96	49	187	94	50
13	192	94	49	188	93	50
17	203	94	49	197	91	50
21	208	93	49	202	91	50
25	216	92	49	208	89	50
29	225	94	49	198	82	50
33	229	93	49	224	90	50
37	235	92	49	235	92	50
41	241	92	49	245	93	50
45	251	92	49	255	94	50
49	251	88	49	266	93	50
53	256	86	49	277	93	50
57	261	85	49	290	94	50
61	265	84	48	304	96	50
65	270	84	48	316	98	50
69	278	85	48	323	99	50
73	277	84	48	324	99	49
77	285	87	48	330	101	48
81	283	85	47	331	100	48
85	288	85	47	336	99	43
88	287	84	47	346	101	39
93	282	82	41	352	102	39
97	282	82	39	357	104	35
101	285	82	35	356	103	33
104	284	82	31	346	100	27
Mean for weeks						
1-13	167	99		165	98	
14-52	229	92		226	91	
53-104	277	84		328	99	

[a] Stop-exposure group

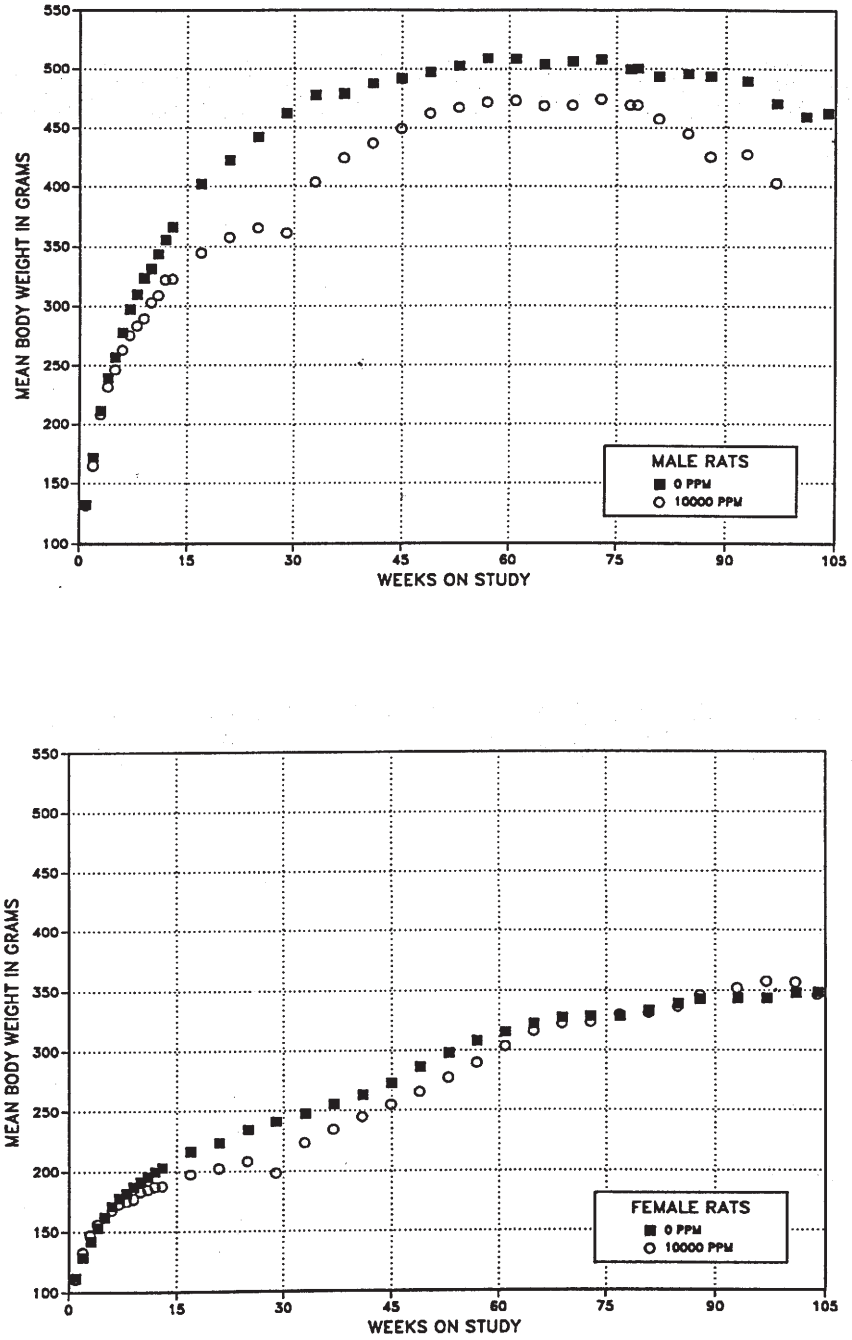


FIGURE 6
Growth Curves for Male and Female Rats in the 2 Year Stop-Exposure Feed Study of Oxazepam

Plasma Oxazepam Determinations

Plasma oxazepam concentrations were measured at the end of the study. Due to mortality, no blood samples from males exposed to 5,000 ppm were available at the end of the study. Plasma oxazepam concentrations were similar between males and females at each exposure concentration (Table 5). The concentrations were somewhat higher than reported serum concentrations in humans (0.3 to 1 µg/mL) receiving a therapeutic dose of oxazepam (Greenblatt *et al.*, 1980; Salzman *et al.*, 1983).

TABLE 5
Plasma Concentrations of Oxazepam in Rats in the 2-Year Feed Study of Oxazepam[a]

	625 ppm	2,500 ppm	5,000 ppm
Male			
n	10	6	—[b]
Week 105	0.50 ± 0.04	1.94 ± 0.34	—
Female			
n	25	19	28
Weeks 104-105	0.60 ± 0.05	1.61 ± 0.16	2.79 ± 0.24

[a] Mean ± standard error; values given as μg/mL
[b] No samples collected due to 100% mortality

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 kidney (with parathyroid gland and bone), gastrointestinal tract (forestomach, glandular stomach, and small intestine), liver, mammary gland, adrenal medulla, pituitary gland, and pancreas. 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.

Kidney (with parathyroid gland and bone): At histopathologic examination of the standard kidney sections, three renal tubule adenomas were seen in male rats exposed to 2,500 ppm, which was at the upper limit of the historical range for this neoplasm in 2-year NTP feed studies (Tables 6, A3a, and A4a).

This increased incidence of renal tubule adenoma in male rats exposed to 2,500 ppm suggested a compound-related effect; therefore, an extended step-section evaluation of the kidneys was performed (male rats only, exposed and control groups) using the remaining residual formalin-fixed kidney wet tissue. Additional rats with renal tubule adenoma and numerous additional incidences of renal epithelial hyperplasia were identified. The incidences of these proliferative lesions observed in the extended step-section evaluation and the combined incidences of standard and step sections in male rats are presented in Tables 6, A3a, and A3b. The incidences of renal tubule adenomas in the extended evaluation and the

TABLE 6
Incidences of Neoplasms and Nonneoplastic Lesions of the Kidney of Rats in the 2-Year Feed Study of Oxazepam

	0 ppm	625 ppm	2,500 ppm	5,000 ppm	10,000 ppm (Stop-Exposure)
Male					
Single Sections (Standard Evaluation)					
Number Examined Microscopically	50	50	50	50	42
Nephropathy[a]	49 (1.9)[b]	44 (2.3)	49 (2.7)**	50 (3.2)**	42 (3.3)**
Renal Tubule Hyperplasia	0	1 (1.0)	3 (2.3)	1 (2.0)	0
Renal Tubule Adenoma[c]					
Overall rate[d]	1/50 (2%)	0/50 (0%)	3/50 (6%)	1/50 (2%)	0/50 (0%)
Adjusted rate[e]	5.6%	0.0%	23.8%	16.7%	0.0%
Terminal rate[f]	0/17 (0%)	0/11 (0%)	1/6 (17%)	0/0	0/0
First incidence (days)	723	—[h]	641	634	—
Logistic regression test[g]	P = 0.103	P = 0.588N	P = 0.188	P = 0.503	P = 0.588N
Step Sections (Extended Evaluation)					
Number Examined Microscopically	50	50	50	50	50
Renal Tubule Hyperplasia	5	6	9	8	21**
Renal Tubule Hyperplasia, Oncocytic	0	1	2	2	3
Renal Tubule Adenoma, Multiple	0	1	1	1	1
Renal Tubule Adenoma (includes multiple)					
Overall rate	1/50 (2%)	1/50 (2%)	4/50 (8%)	5/50 (10%)	6/45 (13%)
Adjusted rate	5.9%	9.1%	31.3%	19.5%	31.9%
Terminal rate	1/17 (6%)	1/11 (9%)	1/6 (17%)	0/0	0/0
First incidence (days)	730 (T)	730 (T)	653	467	613
Logistic regression test	P = 0.006	P = 0.663	P = 0.071	P = 0.151	P = 0.024
Renal Tubule, Oncocytoma	0	0	0	1	0
Single Sections and Step Sections (Combined)					
Number Examined Microscopically	50	50	50	50	45
Renal Tubule Hyperplasia	5	6	12*	9*	21**
Renal Tubule Hyperplasia, Oncocytic	0	1	2	2	3[i]
Renal Tubule Adenoma, Multiple	0	1	2	1	1
Renal Tubule Adenoma (includes multiple)					
Overall rate	2/50 (4%)	1/50 (2%)	7/50 (14%)	6/50 (12%)	6/45 (13%)
Adjusted rate	11.1%	9.1%	49.7%	32.9%	39.1%
Terminal rate	1/17 (6%)	1/11 (9%)	2/6 (33%)	0/0	0/0
First Incidence (days)	723	730 (T)	641	467	613
Logistic regression test	P = 0.018	P = 0.647	P = 0.018	P = 0.109	P = 0.046
Renal Tubule, Oncocytoma	0	0	0	1	0

TABLE 6
Incidences of Neoplasms and Nonneoplastic Lesions of the Kidney of Rats in the 2-Year Feed Study of Oxazepam (continued)

	0 ppm	625 ppm	2,500 ppm	5,000 ppm	10,000 ppm (Stop-Exposure)
Female					
Number Examined Microscopically	50	50	50	50	1[j]
Nephropathy	32 (1.1)	43** (1.3)	41** (1.3)	48** (1.7)**	1 (2.0)

* Significantly different ($P \leq 0.05$) from the control group by the logistic regression test (incidence) or by the Mann-Whitney U test (severity)
** $P \leq 0.01$
[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 for 2-year NTP feed studies with untreated control groups (mean ± standard deviation): 9/1,301 (0.7% ± 1.5%); range, 0%-6%
[d] Number of animals with neoplasms per number of animals with kidney 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 are the P values associated with the trend test (the 10,000 ppm stop-exposure group was excluded from the trend test). In the exposure group columns are the P values corresponding to pairwise comparisons between the controls and that exposure group. The logistic regression test regards lesions in animals dying prior to terminal kill as nonfatal. A lower incidence in an exposed group is indicated by **N**.
[h] Not applicable; no neoplasms in animal group
[i] Number examined microscopically equals 42.
[j] Tissue was examined microscopically only when it was observed to be abnormal at necropsy; thus, statistical comparisons with the controls are not appropriate.

combined incidences in standard and step sections were increased in 2,500, 5,000, and 10,000 ppm (stop-exposure) groups and were significantly greater in male rats in the 10,000 ppm (stop-exposure) group than in the controls. The incidences of renal tubule adenomas in the extended evaluation and the combined incidences in standard and step sections in these groups increased with a positive trend (Tables 6, A3a, A3b, and A4b). The incidences of renal tubule hyperplasia in standard and step sections (combined) in the male rats exposed to 2,500, 5,000, or 10,000 ppm (stop-exposure) were significantly greater than that in the controls.

One adenoma in each of the control and 2,500 and 5,000 ppm groups was a grossly visible lesion at necropsy. Microscopically, approximately 50% of the adenomas in exposed groups in standard and step sections were approximately 1 mm in diameter. All were discrete, well-circumscribed lesions, five or more tubule diameters in size, and were distinguished from hyperplasia by having a more complex structure (Plates 1 and 2).

Most hyperplasias were generally minimal to mild focal lesions consisting of tubules that were enlarged up to two to three times that of a normal tubule and were lined by increased numbers of epithelial cells which partially or totally filled the tubule lumen (Plates 3 and 4). Hyperplasia was considered a preneoplastic lesion and was distinguished from regenerative epithelial changes commonly seen as a component of chronic nephropathy.

The incidences of nephropathy in the continuously exposed and stop-exposure male rats were similar to that in the controls (Tables 6 and A5). However, there was an exposure concentration-related increase in the severity (exacerbation) of nephropathy; the severities of nephropathy in male rats exposed to 2,500, 5,000, or 10,000 ppm (stop-exposure) were significantly greater than that in the controls. The incidences of nephropathy in continuously exposed

female rats were significantly greater than that in the controls; however, the severity was significantly increased only in the 5,000 ppm group (Tables 6 and B5). Nephropathy in male rats was generally mild in the control and 625 ppm groups and moderate to marked in the 2,500, 5,000, and 10,000 ppm (stop-exposure) groups. Mild nephropathy involved less than 50% of the kidney and was composed of multifocal renal tubule regeneration, minimal to mild tubule dilatation, and interstitial fibrosis with mononuclear infiltrates (Plate 5). Moderate nephropathy involved a greater proportion of the kidney and consisted of a spectrum of changes that included dilatation of renal tubules with hyaline or cellular casts, increased interstitial fibrosis with mononuclear inflammatory cell infiltrates, and multifocal tubule regeneration. Severe nephropathy involved most of the kidney and consisted of a similar spectrum of lesions of greater severity (Plate 6). In addition, there was marked thickening and mineralization of the basement membrane of tubules, blood vessels, and glomeruli; atrophy of the glomerular tuft; dilatation of the glomerular urinary space; and transitional epithelial hyperplasia of the renal papilla.

Parathyroid gland hyperplasia and fibrous osteodystrophy of the bone were considered secondary to the exacerbated nephropathy that occurred in exposed male rats. In male rats, the incidences of parathyroid gland hyperplasia (0 ppm, 3/39; 625 ppm, 6/41; 2,500 ppm, 9/46; 5,000 ppm, 16/40) and fibrous osteodystrophy of the bone (0/50, 1/50, 6/50, 8/50) occurred with positive trends (Table A5). The incidences of parathyroid gland hyperplasia in male rats exposed to 5,000 ppm and fibrous osteodystrophy of the bone in male rats exposed to 2,500 or 5,000 ppm were greater than those in the controls.

Gastrointestinal Tract (forestomach, glandular stomach, and small intestine): In male rats, there were positive trends in the incidences of epithelial hyperplasia and chronic inflammation of the forestomach. The incidences of epithelial hyperplasia and chronic inflammation of the forestomach of males exposed to 2,500 or 5,000 ppm and of ulcers in 2,500 ppm males were significantly greater than those in the controls (Tables 7 and A5). In male rats exposed to 5,000 ppm, the incidences of mineralization of the glandular stomach and erosion of the duodenum were significantly greater than those in the controls. In the 10,000 ppm stop-exposure males, the incidence of mineralization of the glandular stomach was significantly greater than that in the controls. In female rats exposed to 2,500 ppm, the incidences of epithelial hyperplasia, chronic inflammation, and ulcers in the forestomach and of erosion of the glandular stomach were significantly greater than those in the controls (Tables 7 and B5).

Epithelial hyperplasia of the forestomach occurred as focal or multifocal lesions of varying severity. Most lesions occurred as slightly to moderately raised thickenings of the mucosa, due to an increase in the number of epithelial cells at all levels of the epithelium (Plates 7 and 8). Others were focal broad-based lesions in which the epithelium was markedly thickened and thrown into papillary folds (Plates 9 and 10). In some cases, focal nests or finger-like projections of proliferative basal epithelium extended into the submucosa. Forestomach ulcers were also focal or multifocal lesions characterized by loss of the mucosal squamous epithelium with necrosis and inflammation of the adjacent muscularis mucosa and superficial submucosa, with or without accompanying fibrosis (Plates 11 and 12). Variable thickening (hyperplasia) of the epithelium and keratin layer (hyperkeratosis) at the edges of ulcers were consistent and frequently striking components of ulcerative lesions. Ulcers were sometimes accompanied by focal erosion of the mucosal epithelium. Chronic active inflammation of varying severity almost invariably occurred in the submucosa beneath hyperplastic and ulcerative lesions and consisted of a combination of edema and infiltrates of neutrophils, macrophages, and lymphocytes with occasional focal hemorrhage (Plates 8, 10, and 12). In male rats, the incidence of mucosal erosions in the duodenum in the 5,000 ppm group was significantly greater than in the controls. Erosions of the duodenum were characterized by focal loss and necrosis of the superficial mucosal epithelium.

TABLE 7
Incidences of Selected Nonneoplastic Lesions of the Gastrointestinal Tract of Rats in the 2-Year Feed Study of Oxazepam

	0 ppm		625 ppm		2,500 ppm		5,000 ppm		10,000 ppm (Stop-Exposure)	
Male										
Forestomach[a]	50		48		50		50		49	
Chronic Inflammation[b]	6	(1.5)[c]	8	(1.5)	23**	(2.0)	15*	(1.9)	10	(2.2)
Ulcer	9	(2.7)	12	(2.9)	20*	(2.8)	10	(3.0)	7	(3.1)
Epithelium, Hyperplasia	5	(2.2)	8	(2.0)	25**	(2.3)	16**	(2.4)	15*	(2.5)
Glandular Stomach	50		48		50		50		47	
Erosion	5	(2.2)	5	(1.4)	9	(2.3)	4	(2.5)	5	(1.4)
Mineralization	0		3	(2.3)	1	(1.0)	4*	(2.0)	16**	(2.8)
Ulcer	2	(2.5)	7	(2.0)	7	(1.6)	4	(1.8)	4	(2.8)
Small Intestine, Duodenum	50		48		49		50		44	
Erosion	4	(2.0)	3	(2.3)	9	(1.8)	16*	(2.4)	1	(1.0)
Female										
Forestomach	50		50		50		50		50	
Chronic Inflammation	1	(2.0)	5	(1.8)	16**	(2.0)	3	(1.7)	5	(1.4)
Ulcer	1	(3.0)	2	(2.5)	9*	(2.1)	6	(2.2)	4	(3.3)
Epithelium, Hyperplasia	2	(3.0)	6	(2.2)	16**	(2.3)	5	(2.2)	5	(1.8)
Glandular stomach	50		50		50		50		49	
Erosion	0		4	(2.0)	7**	(2.3)	2	(2.0)	0	
Ulcer	2	(2.0)	3	(1.7)	5	(2.0)	0		4	(2.0)
Mineralization	1	(1.0)	0		1	(2.0)	2	(1.5)	0	

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

Liver: The incidences of minimal to mild centrilobular hepatocyte hypertrophy in 2,500 and 5,000 ppm males and females were significantly greater than those in the controls (Tables 8, A5, and B5). In continuous-exposure females, the incidences of clear cell foci in the 2,500 and 5,000 ppm groups were significantly greater than in the controls but not in the 10,000 ppm stop-exposure group. The incidences of basophilic foci in 2,500 ppm continuous-exposure males and females, 5,000 ppm continuous-exposure females, and 10,000 ppm stop-exposure females were significantly less than in the controls. Centrilobular hypertrophy was characterized by enlargement of hepatocytes around central veins; affected hepatocytes had more abundant and more eosinophilic cytoplasm and slightly larger nuclei than the surrounding unaffected hepatocytes.

TABLE 8
Incidences of Nonneoplastic Lesions of the Liver of Rats in the 2-Year Feed Study of Oxazepam

	0 ppm	625 ppm	2,500 ppm	5,000 ppm	10,000 ppm (Stop-Exposure)
Male					
Number Examined Microscopically	50	50	49	50	50
Basophilic Focus[a]	21	11	4** (2.0)[b]	2	13
Clear Cell Focus	2	4	0	0	0
Eosinophilic Focus	8	5	5	6	2
Mixed Cell Focus	2	4	2	1	1
Hepatocyte, Centrilobular, Hypertrophy	0	1 (1.0)	8** (1.0)	14** (1.3)	0
Female					
Number Examined Microscopically	50	50	50	50	49
Basophilic Focus	44	41	28**	26**	16**
Clear Cell Focus	6	3	11*	22**	0
Eosinophilic Focus	17	18	4**	11	11
Mixed Cell Focus	5	15*	7	3	2
Hepatocyte, Centrilobular, Hypertrophy	0	0	10** (1.2)	31** (1.5)	0

* 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

Mammary Gland: In females exposed to 2,500 and 5,000 ppm, the incidences of fibroadenoma were significantly less than that in the controls (Tables 9 and B3). The incidences of fibroadenoma; carcinoma; and fibroadenoma, adenoma, or carcinoma (combined) occurred with negative trends. All neoplasm incidences were within the historical control ranges from NTP 2-year feed studies (Table B4). The decreased incidences in 2,500 and 5,000 ppm females were most likely due to the significant reductions in mean body weights observed at these exposure concentrations. The incidences of mammary gland neoplasms in stop-exposure females were similar to those in the controls.

Adrenal Medulla: In continuous-exposure males, there was a negative trend in the incidences of benign pheochromocytoma of the adrenal medulla (0 ppm, 14/50; 625 ppm, 9/50; 2,500 ppm, 6/50; 5,000 ppm, 3/50; Table A1), and the incidences in the 2,500 and 5,000 ppm males were significantly less than that in the controls. The incidence of benign pheochromocytoma in 5,000 ppm male rats was less than the historical control range from 2-year NTP feed studies (Table A4b). Adrenal glands were not routinely examined in the 10,000 ppm stop-exposure group. The incidence of adrenal medulla hyperplasia in males exposed to 5,000 ppm was significantly ($P \leq 0.05$) greater than that in the controls (9/50, 9/50, 15/50, 16/50; Table A5); the severities of this lesion in exposed rats were similar to that in the controls. This shift in the pattern of proliferative lesions of the adrenal medulla may be a consequence of the earlier mortality in the 2,500 and 5,000 ppm and 10,000 ppm stop-exposure groups.

TABLE 9
Incidences of Mammary Gland Neoplasms in Female Rats in the 2-Year Study of Oxazepam

	0 ppm	625 ppm	2,500 ppm	5,000 ppm (Stop-Exposure)	10,000 ppm
Fibroadenoma[a]					
Overall rate[b]	25/50 (50%)	19/50 (38%)	9/50 (18%)	13/50 (26%)	23/50 (46%)
Adjusted rate[c]	67.0%	52.8%	33.2%	35.1%	66.7%
Terminal rate[d]	20/32 (63%)	10/26 (38%)	4/20 (20%)	8/31 (26%)	14/25 (56%)
First incidence (days)	529	612	589	550	562
Logistic regression test[e]	P = 0.003N	P = 0.152N	P = 0.003N	P = 0.007N	P = 0.428N
Adenoma					
Overall rate	1/50 (2%)	2/50 (4%)	0/50 (0%)	0/50 (0%)	0/50 (0%)
Fibroadenoma or Adenoma[f]					
Overall rate	26/50 (52%)	20/50 (40%)	9/50 (18%)	13/50 (26%)	23/50 (46%)
Adjusted rate	67.8%	55.7%	33.2%	35.1%	66.7%
Terminal rate	20/32 (63%)	11/26 (42%)	4/20 (20%)	8/31 (26%)	14/25 (56%)
First incidence (days)	529	612	589	550	562
Logistic regression test	P = 0.002N	P = 0.153N	P = 0.001N	P = 0.004N	P = 0.340N
Carcinoma[g]					
Overall rate	2/50 (4%)	3/50 (6%)	0/50 (0%)	0/50 (0%)	1/50 (2%)
Adjusted rate	5.1%	10.3%	0.0%	0.0%	2.1%
Terminal rate	1/32 (3%)	2/26 (8%)	0/20 (0%)	0/31 (0%)	0/25 (0%)
First incidence (days)	228	697	—[h]	—	562
Logistic regression test	P = 0.048N	P = 0.483	P = 0.288N	P = 0.213N	P = 0.713N
Adenoma or Carcinoma[i]					
Overall rate	3/50 (6%)	5/50 (10%)	0/50 (0%)	0/50 (0%)	1/50 (2%)
Adjusted rate	7.4%	16.8%	0.0%	0.0%	2.1%
Terminal rate	1/32 (3%)	3/26 (12%)	0/20 (0%)	0/31 (0%)	0/25 (0%)
First incidence (days)	228	697	—	—	562
Logistic regression test	P = 0.013N	P = 0.347	P = 0.130N	P = 0.109N	P = 0.466N
Fibroadenoma, Adenoma, or Carcinoma[j]					
Overall rate	27/50 (54%)	23/50 (46%)	9/50 (18%)	13/50 (26%)	23/50 (46%)
Adjusted rate	68.4%	62.7%	33.2%	35.1%	66.7%
Terminal rate	20/32 (63%)	13/26 (50%)	4/20 (20%)	8/31 (26%)	14/25 (56%)
First incidence (days)	228	612	589	550	562
Logistic regression test	P < 0.001N	P = 0.268N	P < 0.001N	P = 0.003N	P = 0.346N

[a] Historical incidence for 2-year NTP feed studies with untreated control groups (mean ± standard deviation): 524/1,301 (40.3% ± 13.1%); range, 8%-58%
[b] Number of animals with neoplasms per number of animals with mammary gland necropsied
[c] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[d] Observed incidence in animals surviving until the end of the study
[e] In the control column are the P values associated with the trend test (the 10,000 ppm stop-exposure group was excluded from the trend test). In the exposure group columns are the P values corresponding to pairwise comparisons between the controls and that exposure group. The logistic regression test regards lesions in animals dying prior to terminal kill as nonfatal. A negative trend or lower incidence in an exposure group is indicated by **N**.
[f] Historical incidence: 540/1,301 (41.5% ± 13.2%); range, 8%-62%
[g] Historical incidence: 36/1,301 (2.8% ± 2.7%); range, 0%-8%
[h] Not applicable; no neoplasms in animal group.
[i] Historical incidence: 60/1,301 (4.6% ± 3.2%); range, 0%-10%
[j] Historical incidence: 568/1,301 (43.7% ± 13.9%); range, 8%-64%

Pituitary Gland: There were negative trends in the incidences of pituitary gland (pars distalis) adenoma in males (17/49, 12/50, 10/50, 2/48) and females (31/50, 28/50, 21/50, 12/50) (Tables A3a and B3a). In males and females exposed to 5,000 ppm, incidences of adenoma were significantly less than those in the controls, and the incidences were below the historical ranges from 2-year NTP feed studies (Tables A4c and B4b). In females exposed to 5,000 ppm, the incidence of adenoma or carcinoma (combined) was also significantly less than that in the controls and was below the historical control range. There was a negative trend in the incidence of hyperplasia in male rats (9/49, 5/50, 3/50, 1/48; Table A5). In males exposed to 5,000 ppm, the incidence of hyperplasia was significantly less than that in the controls. The decreasing trends were most likely due at least in part to a combination of decreased body weights and survival in males and to decreased body weights in females, although it is unlikely that these reasons could fully account for the effects observed.

Pancreas: The incidence of atrophy of the pancreatic acinus in males in the 5,000 ppm group was significantly less than that in the controls (17/50, 10/48, 14/49, 1/50; Table A5), and the incidences of this lesion occurred with a negative trend. The lower incidences of this lesion may have been related to reduced survival of exposed males.

GENETIC TOXICOLOGY

Oxazepam (3 to 3,333 μg/plate) did not induce mutations in *Salmonella typhimurium* strains TA97, TA98, TA100, TA102, or TA1535 when tested in a preincubation protocol with or without Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver S9 (Table C1). In cytogenetic tests with cultured Chinese hamster ovary cells, oxazepam did not induce sister chromatid exchanges (Table C2) or chromosomal aberrations (Table C3), with or without S9. Cell cycle delay was noted at the 50 μg/mL dose in the sister chromatid exchange test without S9; harvest time was extended to allow accumulation of sufficient second-division metaphase cells for analysis. Peripheral blood samples obtained from $B6C3F_1$ mice in a 14-week toxicity study were analyzed for frequency of micronucleated normochromatic erythrocytes; no increase in the frequency of micronucleated normochromatic erythrocytes was observed in any of the exposed groups (Table C4).

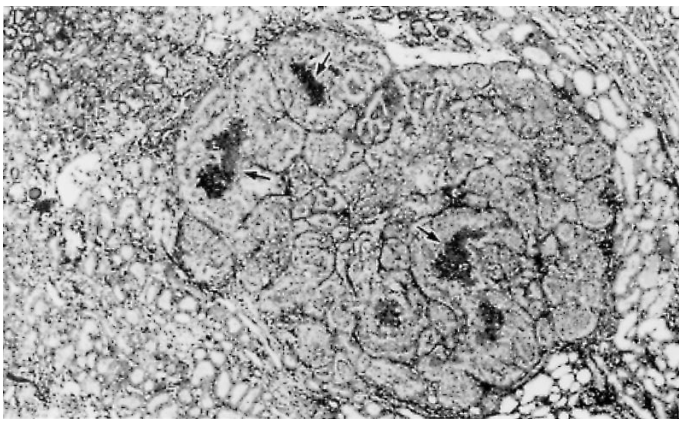


PLATE 1
Renal tubule adenoma in the kidney of a male F344/N rat administered 2,500 ppm oxazepam for 2 years. Mass is well circumscribed with cells arranged in variably sized packets, some of which have central areas of cellular degeneration and hemorrhage (arrows). H&E; 35 ×

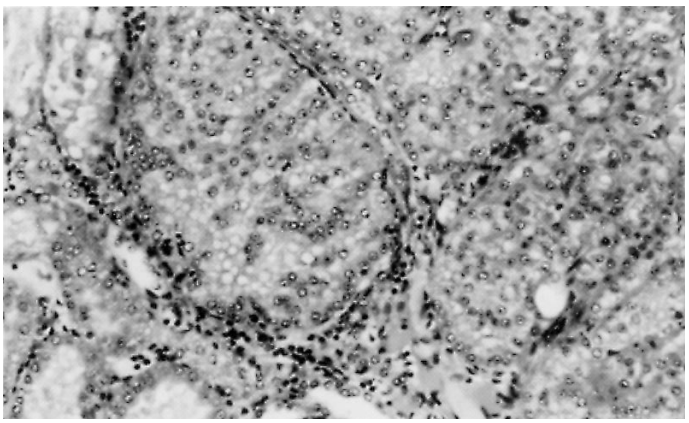


PLATE 2
Higher magnification of Plate 1. Neoplastic cells resemble epithelial cells of normal adjacent tubules and form small packets separated by delicate fibrovascular septae. H&E; 175 ×

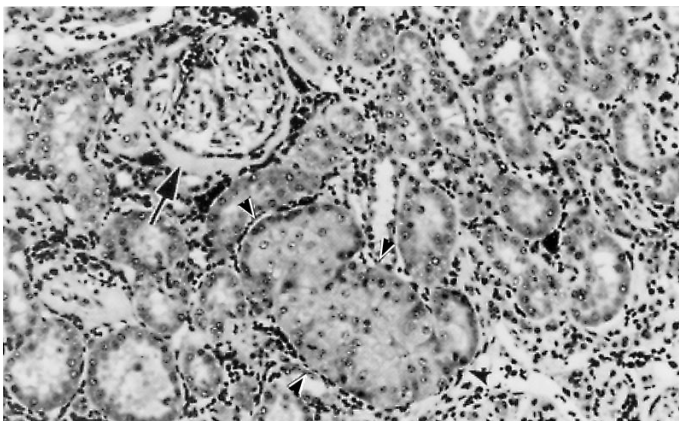


PLATE 3
Mild renal tubule hyperplasia (arrowheads) in the kidney of a male F344/N rat administered 2,500 ppm oxazepam for 2 years. Group of hyperplastic tubules are surrounded by relatively normal renal tubules. Glomerulus (arrow). H&E; 140 ×

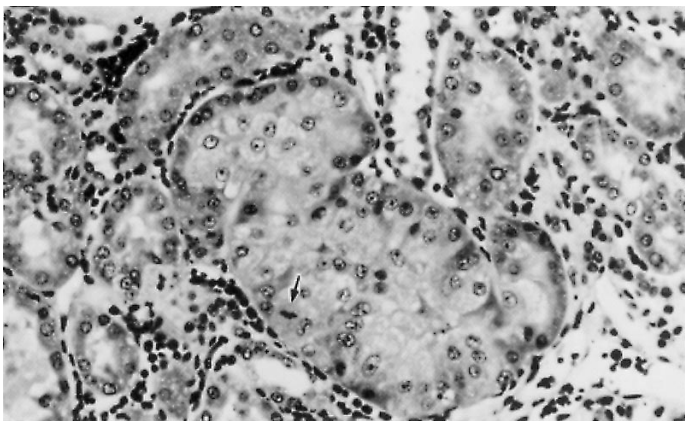


PLATE 4
Higher magnification of Plate 3. Hyperplastic tubules are filled with cuboidal to polygonal tubular epithelial cells. Note mitotic figure (arrow). H&E; 230 ×

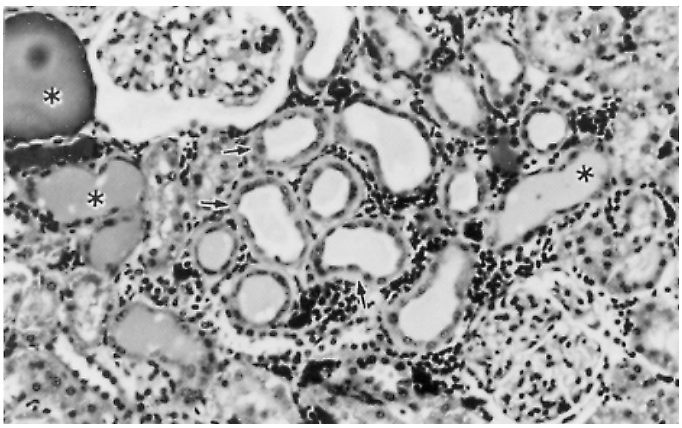


PLATE 5
Mild nephropathy in a male F344/N rat administered 625 ppm oxazepam for 2 years. Note group of regenerative tubules with slight thickening of the tubular basement membrane (arrows) and slightly dilated tubules containing protein casts(*). H&E; 175×

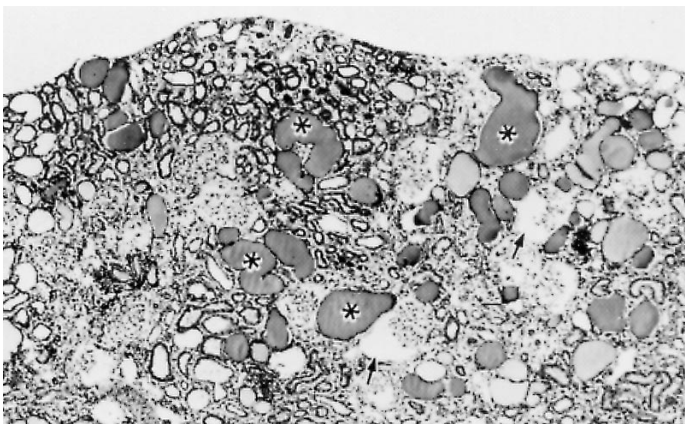


PLATE 6
Marked nephropathy in a male F344/N rat administered 2,500 ppm oxazepam for 2 years. Note focal renal tubule regeneration, interstitial fibrosis, dilated glomeruli (arrows), and variably dilated renal tubules, many of which contain protein casts(*). H&E;45.5×

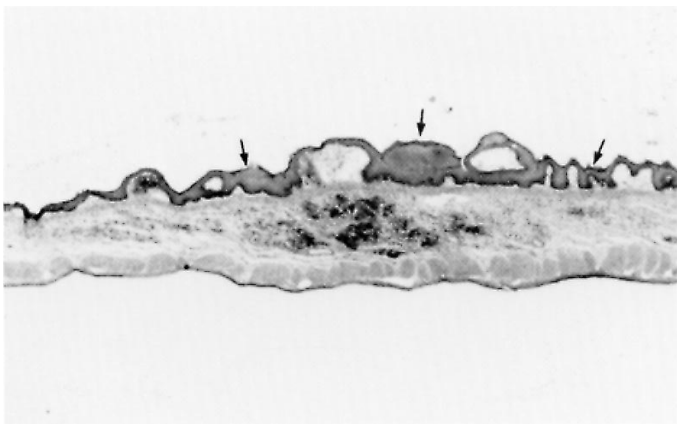


PLATE 7
Focal epithelial hyperplasia in the forestomach of a male F344/N rat administered 2,500 ppm oxazepam for 2 years. Note focal thickening of the mucosal epithelium (arrows). Normal mucosal epithelium is shown at left. H&E; 16.5×

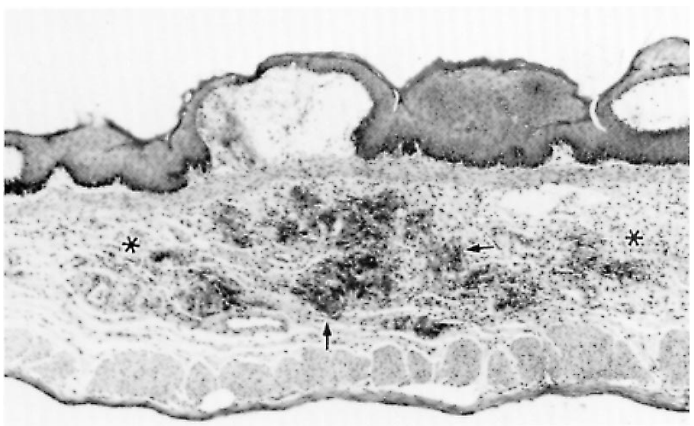


PLATE 8
Higher magnification of Plate 7. Note hyperplastic mucosal epithelium. The adjacent submucosal is expanded by chronic active inflammation and edema (*).Focal areas of submucosal hemorrhage are also evident (arrows). H&E; 40×

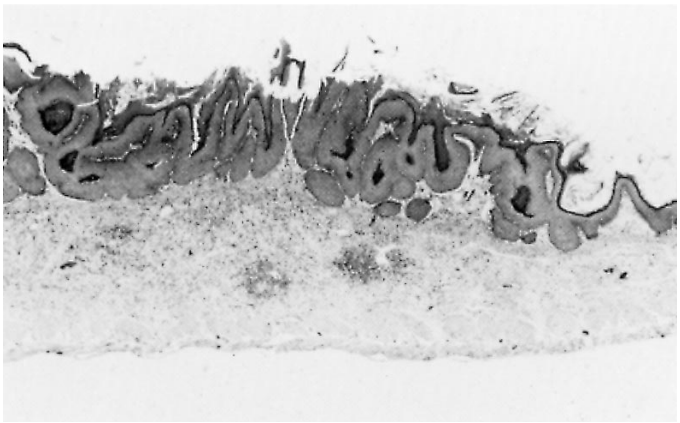


PLATE 9
Marked focal epithelial hyperplasia in the forestomach of a male F344/N rat administered 2,500 ppm oxazepam for 2 years. The hyperplastic mucosal epithelium forms multiple thick papillary folds that project into the lumen. There is also thickening of the keratin layer (hyperkeratosis) covering the epithelial surface. H&E; 20 ×

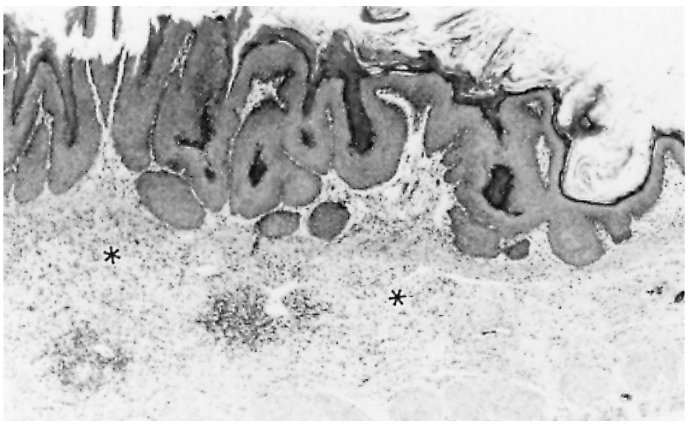


PLATE 10
Higher magnification of Plate 9. Chronic active inflammation and edema are within the adjacent submucosal and extend into the muscle (tunica muscularis) layers (*). H&E; 33 ×

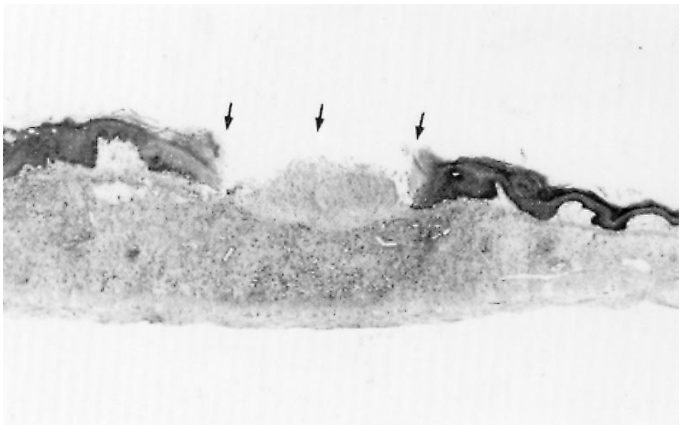


PLATE 11
Focal mucosal ulcer in the forestomach of a male F344/N rat administered 5,000 ppm oxazepam for 2 years. The cavity (ulcer) formed by the loss of the mucosal epithelium is partially filled with a coagulum of necrotic cellular debris and degenerate inflammatory cells (arrows). H&E; 16.5 ×

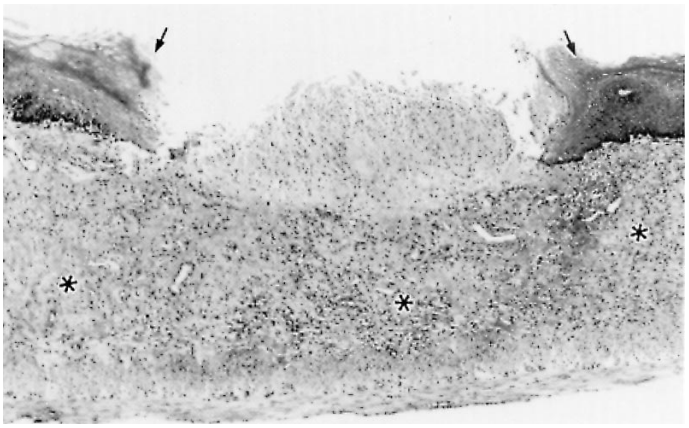


PLATE 12
Higher magnification of Plate 11. Marked chronic active inflammation and fibrosis within the submucosa and extending into the muscle (tunica muscularis) layers (*). Note mucosal epithelial hyperplasia with hyperkeratosis at the margins of the ulcer (arrows). H&E; 33 ×

DISCUSSION AND CONCLUSIONS

Evaluation of the toxicity and carcinogenicity of oxazepam in F344/N rats was prompted by the finding of a marked hepatocellular neoplasm response in similar studies with Swiss-Webster and B6C3F$_1$ mice (NTP, 1993; Bucher *et al.*, 1994). Studies of the carcinogenicity of oxazepam in Sprague-Dawley rats were performed previously and reported to the FDA. However, given the widespread use of benzodiazepines and the fact that oxazepam is a common metabolite of several of the more widely used variants of this drug class, cancer studies in a second strain of rat were deemed necessary to examine possible differences in response.

No 13-week rat studies were performed prior to the 2-year studies summarized in this report because there was some sense of urgency to begin the rat studies and because relatively little useful information was obtained from the 13-week studies conducted in preparation for the 2-year mouse studies. Instead, based on information from the literature, a five-dose 2-year study was begun in anticipation that sufficient information would be gained during the first 6 months of the 2-year study to determine which exposure groups would be allowed to proceed to study termination. Based on low body weight gains, groups of male and female rats exposed to 10,000 ppm were removed from dosed feed and allowed to consume control diet until the end of the study. Groups consuming feed containing 1,250 ppm were terminated because it was predicted that little additional information would be gained from these animals.

In retrospect, the decision to forego performance of 13-week studies was incorrect. The 2,500 and 5,000 ppm exposure concentrations selected for the continuous administration portion of the study were sufficiently high to result in substantial reductions in both body weight gains and in survival of male rats. Survival was somewhat reduced in the 625 ppm male group, and mean body weights were also slightly lower in this group during most of the study. From the standpoint of body weight and survival, 625 ppm was sufficient for an adequate chronic toxicity and carcinogenicity study in male rats.

In female rats, adverse effects on body weights and survival were not nearly as severe as in males, although both body weights and survival were reduced in an exposure-related fashion. The incidences of nephropathy were increased in females, but the severities were mild. The difference between the responses of males and females to oxazepam appeared to be in the unexpected and marked enhancement of the nephropathy commonly seen in control male F344/N rats. Varying degrees of nephropathy normally develop in the aging rat, and this condition is worsened when the animals are maintained on a relatively high protein diet, such as the NIH-07 diet used in these studies (Rao *et al.*, 1993). Nephropathy is considered to be a major contributor to early mortality in rats and likely accounts for the pattern of deaths observed in this study. It is possible that this kidney lesion would have been seen in certain exposure groups in 13-week studies because nephropathy was more severe in the 10,000 ppm stop-exposure group of males, 18 months after exposure ceased. However, enhanced nephropathy was not seen in mice receiving oxazepam, nor was it reported in rats or mice in chronic studies with prazepam (de la Iglesia *et al.*, 1981), temazepam (Robinson *et al.*, 1984), or ripazepam (Fitzgerald *et al.*, 1984), although some renal tubule dilatation in rats was reported with the last compound.

In the current study, the parathyroid gland hyperplasia and fibrous osteodystrophy of bone that occurred in the male rats are consistent sequelae to severe nephropathy and secondary hyperparathyroidism of chronic renal failure (Leininger and Riley, 1990; Seely and Hildebrandt, 1990; Capen, 1994). Mineralization of the glandular stomach is also a common manifestation of severe nephropathy and is due to hypercalcemia induced by secondary renal hyperparathyroidism. It has been shown experimentally that stress-related ulceration of the glandular stomach can be enhanced by either acidotic or non-acidotic renal insufficiency (Fischer *et al.*, 1974), and mineralization of the glandular stomach and the forestomach can be sequelae to uremia (Brown and Hardisty, 1990).

Male rats exposed to 2,500 or 5,000 ppm and female rats exposed to 2,500 ppm had increased incidences of epithelial hyperplasia, ulceration, and inflammation of the forestomach. Degenerative and proliferative forestomach lesions are relatively common in studies in which chemicals are administered orally (Gonipath *et al.*, 1987). The spectrum of degenerative lesions includes erosions, ulceration, and necrosis with associated inflammation of the submucosa, which may extend to the serosal surface. Proliferative lesions range from mild hyperplasia to marked papillomatous hyperplasia of the squamous epithelium of the forestomach, with or without the development of papillomas. Papillomas were not noted in this study; however, severe papillary hyperplasia was observed in some animals. The increased incidences of these lesions in the forestomach of continuously exposed animals suggest that the development of these lesions was probably a direct effect of chemical administration. In the stop-exposure study, the significantly increased incidences of nonneoplastic lesions in the forestomach indicate a failure of these lesions to resolve during the prolonged recovery period. This is rather unexpected. It suggests that these lesions may have been due in part to the abrupt removal of the drug from the diet, eliciting stress related to dependence, coupled with compromised renal function later in the study.

A few renal tubule adenomas were seen, principally in the 2,500 ppm group in the initial evaluation of kidneys of exposed male rats, although a dose response was not evident. Additional sections of the remaining embedded kidneys were taken and additional microscopic adenomas were observed. The NTP experience with multiple-step sectioning of kidneys has been reported by Eustis *et al.* (1994). In 13 prior studies, additional renal tubule neoplasms and oncocytomas were observed with step sectioning in both control and exposed groups. Although no additional neoplasms were found in the control rat kidneys for many of the studies, as many as six were found in one study. Even greater numbers of additional neoplasms were found in some exposure groups. Eustis *et al.* (1994) noted that the studies in which additional renal neoplasms were found were also those in which nephropathy was more severe than usual, or those in which the chemical enhanced the nephropathy. This was the case in the present study with oxazepam.

Although the renal tubule neoplasms occurred with a positive trend, this was considered an uncertain finding. The incidence of 14% in the 2,500 ppm group is similar to the upper range of neoplasms found in historical controls after step sectioning (Eustis *et al.*, 1994). While it is unlikely that the 2,500, 5,000, and 10,000 ppm stop-exposure groups incidences would all fall close to the upper range of historical control incidences by chance alone, the severe nephropathy complicated interpretation of these findings. There was no increase in renal tubule neoplasms in the 625 ppm group. Whether these renal neoplasms represent an intrinsic carcinogenic effect of oxazepam or are secondary to the oxazepam-enhanced nephropathy cannot be determined from these studies. There is no convincing evidence to suggest that oxazepam is mutagenic or has the ability to induce chromosomal aberrations or other adverse genetic effects.

The effects of oxazepam on the liver of male and female rats were limited to centrilobular hepatocyte hypertrophy commonly seen with a wide variety of agents, including other benzodiazepines and barbiturates, and changes in the incidences of basophilic and clear cell foci. There was no evidence of an increase in hepatocellular neoplasms in male or female rats exposed to oxazepam. This is in sharp contrast to the increases in liver neoplasms reported with the two mouse strains studied earlier (NTP, 1993; Bucher *et al.*, 1994).

The reasons for the species differences in liver neoplasm response are not known. The response of the mouse liver to oxazepam includes a transient induction of hepatocyte replication, which, coupled with hepatocyte hypertrophy, accounts for the increase in liver weight. Increases in cytochrome P_{450} and b5 content and glucuronyl transferase activity are seen; however, there is little evidence to suggest that oxidative stress or cytotoxicity is induced (Bucher *et al.*, 1994; Cunningham *et al.*, 1994; Griffin *et al.*, 1996). In similar studies reported in Appendix H, hepatocyte proliferation in rats was also transient and hypertrophy was a persistent change. Again, oxazepam did not induce significant cytotoxicity. In *in vitro* incubations of oxazepam with microsomes from human, rat, and mouse liver, evidence of covalent protein binding was found in all three cases, but the magnitude was greatest in rats,

followed by mice, and then humans (Griffin *et al.*, 1995a,b), suggesting that this activity is unrelated to the carcinogenic response.

One area in which there are clear differences between rats and mice is in comparative metabolism. The metabolism of oxazepam is complex and has been extensively documented in the F344/N rat and the $B6C3F_1$ and Swiss-Webster mouse (Griffin and Burka, 1993, 1995). Oxidative metabolism (of the phenyl ring) occurs in both rats and mice (Griffin *et al.*, 1995c) but is more pronounced in rats. There are also differences in the major conjugation reactions with glucuronic acid and sulfate, as well as differences in fecal and urinary excretion patterns. On repeated dosing, there is a shift in the metabolite pattern in mice, but not rats, suggesting an induction of enzymes which are involved in oxazepam metabolism. Serum concentrations of oxazepam were higher at comparable dosed feed concentrations in mice (NTP, 1993) than in rats in the current study, but the differences appeared due at least in part to the relatively greater consumption of dosed feed by mice than rats on a body weight basis. Mice also eliminated less oxazepam in the feces than did rats and had a slightly longer terminal elimination half-life from plasma, suggesting that enterohepatic circulation may be greater in mice (Yuan *et al.*, 1994; Griffin and Burka, 1993, 1995). This may indicate a greater degree of exposure of the liver of mice to oxazepam and its metabolites when compared to rats. Nonetheless, as indicated earlier, despite considerable effort devoted to examining the basis for the differential carcinogenic response in rats and mice, no clear biochemical basis for this effect has been identified.

Two recent epidemiology studies have evaluated the association between human cancers and benzodiazepine use. Neither examined oxazepam specifically. Rosenberg *et al.* (1995) did not find an association between sustained benzodiazepine use (at least 4 days per week for at least 1 month, initiated at least 2 years prior to hospital admission) and any one of 11 cancers (breast, large bowel, malignant melanoma, lung, uterine endometrium, ovary, non-Hodgkin's lymphoma, testis, Hodgkin's disease, thyroid gland, and liver) in a large United States hospital-based surveillance study. Harlow and Cramer (1995) reported an association between prior use of benzodiazepines exceeding 1 to 6 months with subsequent development of ovarian cancer (adjusted odds ratio 1.8, 95% CI 1.0 -3.1). These authors proposed that the induction of hepatic microsomal enzymes by benzodiazepines might enhance the metabolism of estrogen, thus stimulating higher gonadotropin levels. Ovarian neoplasms were not increased in female rats in the present studies or in studies with mice reported earlier (NTP, 1993).

CONCLUSIONS

In summary, under the conditions of these 2-year dosed-feed studies, there was *equivocal evidence of carcinogenic activity** in male F344/N rats based on small increases in the incidences of renal tubule adenomas in exposed groups also exhibiting significantly enhanced nephropathy. There was *no evidence of carcinogenic activity* of oxazepam in female F344/N rats exposed to feed containing 625, 2,500, or 5,000 ppm for 2 years or 10,000 ppm for 6 months.

Administration of oxazepam to rats resulted in nonneoplastic lesions in the forestomach, glandular stomach, and small intestine as well as centrilobular hypertrophy of hepatocytes in the liver. In addition, nephropathy was increased in incidence in female rats and was markedly increased in severity in male rats, resulting in early mortality at the higher exposure concentrations.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 9. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 11.

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

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

	0 ppm	625 ppm	2,500 ppm	5,000 ppm	10,000 ppm (Stop-Exposure)
Disposition Summary					
Animals initially in study	50	50	50	50	50
Early deaths					
Moribund	25	27	33	43	39
Natural deaths	8	12	11	7	11
Survivors					
Terminal sacrifice	17	11	6		
Animals examined microscopically	50	50	50	50	50
Alimentary System					
Intestine large, colon	(50)	(47)	(50)	(50)	(1)
Polyp adenomatous		1 (2%)			
Intestine large, rectum	(50)	(48)	(49)	(50)	(1)
Polyp adenomatous		1 (2%)			
Intestine small, jejunum	(49)	(48)	(46)	(49)	
Carcinoma	2 (4%)				
Leiomyosarcoma	1 (2%)				
Liver	(50)	(50)	(49)	(50)	(50)
Fibrous histiocytoma, metastatic, lung		1 (2%)			
Hepatocellular carcinoma	1 (2%)				
Hepatocellular adenoma	1 (2%)			3 (6%)	1 (2%)
Mesentery	(7)	(6)	(4)	(4)	(5)
Leiomyosarcoma, metastatic, intestine small, jejunum	1 (14%)				
Leiomyosarcoma, metastatic, stomach, glandular		1 (17%)			
Oral mucosa			(1)		
Gingival, squamous cell carcinoma			1 (100%)		
Pancreas	(50)	(48)	(49)	(50)	
Adenoma		1 (2%)			
Fibrous histiocytoma, metastatic, lung		1 (2%)			
Acinus, adenoma	1 (2%)		1 (2%)		
Acinus, adenoma, mixed cell	1 (2%)				
Stomach, forestomach	(50)	(48)	(50)	(50)	(49)
Leiomyosarcoma			1 (2%)		
Stomach, glandular	(50)	(48)	(50)	(50)	(47)
Leiomyosarcoma		1 (2%)			
Tongue		(1)		(1)	
Squamous cell carcinoma				1 (100%)	
Squamous cell papilloma		1 (100%)			
Tooth	(1)				
Odontoma	1 (100%)				
Cardiovascular System					
Heart	(50)	(50)	(50)	(50)	(7)
Schwannoma malignant		1 (2%)			

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of Oxazepam (continued)

	0 ppm	625 ppm	2,500 ppm	5,000 ppm	10,000 ppm (Stop-Exposure)
Endocrine System					
Adrenal cortex	(50)	(50)	(50)	(50)	
Adenoma		1 (2%)			
Fibrous histiocytoma, metastatic, lung		1 (2%)			
Adrenal medulla	(50)	(50)	(50)	(50)	(1)
Pheochromocytoma malignant					1 (100%)
Pheochromocytoma benign	9 (18%)	8 (16%)	5 (10%)	1 (2%)	
Bilateral, pheochromocytoma benign	5 (10%)	1 (2%)	1 (2%)	2 (4%)	
Islets, pancreatic	(50)	(48)	(49)	(50)	
Adenoma	1 (2%)				
Carcinoma	2 (4%)				
Pituitary gland	(49)	(50)	(50)	(48)	(5)
Pars distalis, adenoma	17 (35%)	12 (24%)	9 (18%)	2 (4%)	5 (100%)
Pars distalis, adenoma, multiple			1 (2%)		
Thyroid gland	(50)	(49)	(50)	(50)	(50)
Bilateral, C-cell, adenoma	1 (2%)		2 (4%)		
C-cell, adenoma	9 (18%)	5 (10%)	4 (8%)	2 (4%)	1 (2%)
C-cell, carcinoma					1 (2%)
Follicular cell, adenoma	1 (2%)		1 (2%)	2 (4%)	2 (4%)
Follicular cell, carcinoma	3 (6%)	3 (6%)	3 (6%)	4 (8%)	1 (2%)
General Body System					
Peritoneum	(2)	(1)	(1)	(2)	(1)
Genital System					
Epididymis	(50)	(49)	(50)	(50)	(1)
Preputial gland	(48)	(50)	(50)	(49)	(14)
Adenoma	6 (13%)	9 (18%)	5 (10%)	3 (6%)	7 (50%)
Carcinoma	1 (2%)				
Fibrous histiocytoma, metastatic, lung		1 (2%)			
Bilateral, adenoma	1 (2%)			1 (2%)	3 (21%)
Seminal vesicle	(50)	(50)	(50)	(50)	(1)
Testes	(50)	(50)	(50)	(50)	(48)
Bilateral, interstitial cell, adenoma	35 (70%)	42 (84%)	47 (94%)	46 (92%)	44 (92%)
Interstitial cell, adenoma	10 (20%)	6 (12%)	2 (4%)	1 (2%)	4 (8%)
Hematopoietic System					
Bone marrow	(50)	(50)	(50)	(50)	
Fibrous histiocytoma, metastatic, lung		1 (2%)			
Lymph node	(5)	(8)	(8)	(1)	(9)
Deep cervical, carcinoma, metastatic, thyroid gland					1 (11%)
Lymph node, mandibular	(50)	(49)	(49)	(50)	(4)
Lymph node, mesenteric	(49)	(49)	(50)	(47)	(4)
Spleen	(50)	(50)	(50)	(50)	(33)
Fibroma	1 (2%)				
Hemangiosarcoma		1 (2%)	1 (2%)		
Histiocytic sarcoma		1 (2%)	1 (2%)		
Thymus	(49)	(47)	(49)	(47)	
Thymoma malignant		1 (2%)			

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of Oxazepam (continued)

	0 ppm	625 ppm	2,500 ppm	5,000 ppm	10,000 ppm (Stop-Exposure)
Integumentary System					
Mammary gland	(50)	(44)	(48)	(48)	(2)
Adenoma					1 (50%)
Carcinoma				1 (2%)	1 (50%)
Fibroadenoma	4 (8%)	5 (11%)	4 (8%)	2 (4%)	
Skin	(50)	(49)	(49)	(50)	(8)
Fibroma	3 (6%)	1 (2%)	1 (2%)	2 (4%)	2 (25%)
Fibrosarcoma	2 (4%)	3 (6%)			1 (13%)
Keratoacanthoma	3 (6%)	5 (10%)	1 (2%)	2 (4%)	2 (25%)
Keratoacanthoma, multiple				1 (2%)	
Liposarcoma				1 (2%)	
Osteosarcoma			1 (2%)		
Sarcoma	1 (2%)				
Schwannoma malignant	3 (6%)				
Squamous cell papilloma	2 (4%)		1 (2%)		
Sebaceous gland, adenoma	1 (2%)				2 (25%)
Musculoskeletal System					
Bone	(50)	(50)	(50)	(50)	(4)
Chordoma			1 (2%)		
Nervous System					
Brain	(50)	(50)	(50)	(50)	(2)
Astrocytoma malignant			1 (2%)		
Fibrous histiocytoma, metastatic, lung		1 (2%)			
Oligodendroglioma malignant			1 (2%)		
Respiratory System					
Lung	(50)	(50)	(50)	(50)	(3)
Alveolar/bronchiolar adenoma	1 (2%)		1 (2%)		
Alveolar/bronchiolar carcinoma		1 (2%)	1 (2%)		
Chordoma, metastatic, bone			1 (2%)		
Fibrosarcoma, metastatic, skin	1 (2%)				
Fibrous histiocytoma		1 (2%)			
Schwannoma malignant, metastatic, skin	1 (2%)				
Special Senses System					
Zymbal's gland		(1)		(1)	(1)
Carcinoma		1 (100%)		1 (100%)	1 (100%)
Urinary System					
Kidney	(50)	(50)	(50)	(50)	(42)
Fibrous histiocytoma, metastatic, lung		1 (2%)			
Renal tubule, adenoma	1 (2%)		3 (6%)	1 (2%)	
Urinary bladder	(50)	(50)	(50)	(50)	(1)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of Oxazepam (continued)

	0 ppm	625 ppm	2,500 ppm	5,000 ppm	10,000 ppm (Stop-Exposure)
Systemic Lesions					
Multiple organs[b]	(50)	(50)	(50)	(50)	(50)
Histiocytic sarcoma		1 (2%)	1 (2%)		
Leukemia mononuclear	27 (54%)	36 (72%)	33 (66%)	19 (38%)	34 (68%)
Lymphoma malignant					1 (2%)
Mesothelioma malignant	2 (4%)	2 (4%)	1 (2%)	1 (2%)	1 (2%)
Neoplasm Summary					
Total animals with primary neoplasms[c]	50	50	50	48	48
Total primary neoplasms	160	151	135	99	116
Total animals with benign neoplasms	47	50	50	47	48
Total benign neoplasms	115	99	89	71	74
Total animals with malignant neoplasms	38	43	40	25	35
Total malignant neoplasms	45	52	46	28	42
Total animals with metastatic neoplasms	3	2	1		1
Total metastatic neoplasms	3	8	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 A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Oxazepam: 0 ppm

Number of Days on Study	4 7 1	4 8 0	4 9 1	4 9 8	5 1 7	5 1 9	5 3 7	5 4 1	5 5 4	5 7 1	5 8 5	5 9 2	6 0 1	6 0 8	6 2 1	6 8 1	6 8 2	6 8 2	6 8 2	6 8 4	6 8 8	6 9 0	6 9 0	6 9 4	6 9 5
Carcass ID Number	0 3 0	0 3 2	0 1 9	0 2 5	0 2 9	0 2 7	0 0 6	0 4 3	0 3 5	0 0 7	0 4 4	0 4 8	0 4 1	0 3 1	0 2 2	0 1 7	0 1 2	0 2 8	0 3 7	0 5 0	0 3 9	0 0 4	0 0 9	0 1 8	0 2 1
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																						X			
Leiomyosarcoma																									
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma														X											
Hepatocellular adenoma																									
Mesentery				+		+																			
Leiomyosarcoma, metastatic, intestine small, jejunum																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinus, adenoma																									
Acinus, adenoma, mixed cell																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																									
Odontoma																									
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign												X					X	X		X					
Bilateral, pheochromocytoma benign										X						X							X		X
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																							X		
Carcinoma																	X								X
Parathyroid gland	M	M	+	+	+	M	+	+	M	+	M	+	+	+	+	+	+	M	+	+	M	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma	X					X														X			X		X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, C-cell, adenoma																									
C-cell, adenoma										X								X	X		X			X	
Follicular cell, adenoma									X																
Follicular cell, carcinoma																					X				X
General Body System																									
Peritoneum												+					+								

+: 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 Oxazepam: 0 ppm (continued)

Number of Days on Study	6 9 5	6 9 6	6 9 8	6 9 8	6 9 8	7 1 1	7 1 6	7 2 3	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	0 4 0	0 2 3	0 0 1	0 1 6	0 3 6	0 4 9	0 0 8	0 1 0	0 0 2	0 0 3	0 0 5	0 1 1	0 1 3	0 1 4	0 1 5	0 2 0	0 2 4	0 2 6	0 3 3	0 3 4	0 3 8	0 4 2	0 4 5	0 4 6	0 4 7	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	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma															X											2
Leiomyosarcoma							X																			1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma																										1
Hepatocellular adenoma															X											1
Mesentery							+	+							+								+	+		7
Leiomyosarcoma, metastatic, intestine small, jejunum							X																			1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Acinus, adenoma									X																	1
Acinus, adenoma, mixed cell																									X	1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth							+																			1
Odontoma							X																			1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	49
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign	X						X									X				X		X				9
Bilateral, pheochromocytoma benign			X																							5
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Carcinoma																										2
Parathyroid gland	+	+	+	+	+	+	+	+	M	+	+	+	+	M	M	+	+	M	+	+	+	+	+	+	+	39
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma	X	X		X	X				X	X				X	X	X				X				X	X	17
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, C-cell, adenoma																		X								1
C-cell, adenoma		X	X										X									X				9
Follicular cell, adenoma																										1
Follicular cell, carcinoma									X																	3
General Body System																										
Peritoneum																										2

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Oxazepam: 0 ppm (continued)

Number of Days on Study	4 7 1	4 8 0	4 9 1	4 9 8	5 1 7	5 1 9	5 3 7	5 4 1	5 5 4	5 7 1	5 8 5	5 9 2	6 0 1	6 0 8	6 2 1	6 8 1	6 8 2	6 8 2	6 8 2	6 8 4	6 8 8	6 9 0	6 9 0	6 9 4	6 9 5
Carcass ID Number	0 3 0	0 3 2	0 1 9	0 2 5	0 2 9	0 2 7	0 0 6	0 4 3	0 3 5	0 0 7	0 4 4	0 4 8	0 4 1	0 3 1	0 2 2	0 1 7	0 1 2	0 2 8	0 3 7	0 5 0	0 3 9	0 0 4	0 0 9	0 1 8	0 2 1
Genital System																									
Coagulating gland								+											+						
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Adenoma													X												
Carcinoma								X																	
Bilateral, adenoma																							X		
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma							X					X	X		X	X	X	X	X	X	X	X			X
Interstitial cell, adenoma					X			X	X	X	X			X									X	X	
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node										+						+					+				
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																									
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																									
Fibrosarcoma			X																						
Keratoacanthoma											X						X								
Sarcoma																									
Schwannoma malignant		X																							
Squamous cell papilloma					X											X									
Sebaceous gland, adenoma																	X								
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma					X																				
Fibrosarcoma, metastatic, skin			X																						
Schwannoma malignant, metastatic, skin																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																									
Eye																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Oxazepam: 0 ppm (continued)

Number of Days on Study	6 9 5	6 9 6	6 9 8	6 9 8	6 9 8	7 1 1	7 1 6	7 2 3	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	0 4 0	0 2 3	0 0 1	0 1 6	0 3 6	0 4 9	0 0 8	0 1 0	0 0 2	0 0 3	0 0 5	0 1 1	0 1 3	0 1 4	0 1 5	0 2 0	0 2 4	0 2 6	0 3 3	0 3 4	0 3 8	0 4 2	0 4 5	0 4 6	0 4 7	Total Tissues/ Tumors
Genital System																										
Coagulating gland																										2
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma					X		X		X							X	X									6
Carcinoma																										1
Bilateral, adenoma																										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	X	35
Interstitial cell, adenoma															X						X					10
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node							+	+																		5
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroma		X																								1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	49
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroadenoma			X	X	X					X																4
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroma						X							X											X		3
Fibrosarcoma			X																							2
Keratoacanthoma						X																				3
Sarcoma						X																				1
Schwannoma malignant		X									X															3
Squamous cell papilloma																										2
Sebaceous gland, adenoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										1
Fibrosarcoma, metastatic, skin																										1
Schwannoma malignant, metastatic, skin		X																								1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear																			+							1
Eye																+							+			2

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Oxazepam: 0 ppm (continued)

Number of Days on Study	471	480	491	498	517	519	537	541	554	571	585	592	600	601	608	621	641	642	642	642	642	644	648	690	690	694	695
Carcass ID Number	00330	00332	00119	00225	00229	00227	00206	00243	00335	00307	00444	00448	00441	00431	00322	00217	00117	00212	00228	00337	00550	00339	00004	00049	00118	00221
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																											
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				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 Oxazepam: 0 ppm (continued)

Number of Days on Study	6 9 5	6 9 6	6 9 8	6 9 8	6 9 8	7 1 1	7 1 6	7 2 3	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	0 4 0	0 2 3	0 0 1	0 1 6	0 3 6	0 4 9	0 0 8	0 1 0	0 0 2	0 0 3	0 0 5	0 1 1	0 1 3	0 1 4	0 1 5	0 2 0	0 2 4	0 2 6	0 3 3	0 3 4	0 3 8	0 4 2	0 4 5	0 4 6	0 4 7	Total Tissues/ Tumors
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Renal tubule, adenoma								X																		1	
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Leukemia mononuclear	X	X		X			X	X				X		X			X	X		X		X	X	X		27	
Mesothelioma malignant																										2	

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Oxazepam: 625 ppm

Number of Days on Study	3 8 6	4 2 6	4 4 8	4 5 2	4 6 6	4 7 3	4 8 1	5 0 1	5 2 3	5 2 4	5 3 6	5 3 6	5 5 0	5 5 7	5 7 1	5 7 2	5 7 8	5 8 5	5 8 5	5 8 6	5 8 6	5 8 9	6 0 4	6 1 4	6 2 0
Carcass ID Number	0 5 2	0 5 7	0 6 7	0 9 3	0 6 3	0 6 0	0 5 3	0 9 8	0 6 2	0 8 3	0 5 4	0 7 8	0 7 2	0 5 5	0 8 4	0 8 7	0 7 4	0 7 1	0 8 6	0 9 2	0 9 5	0 6 4	0 7 5	0 5 9	0 5 8
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Polyp adenomatous															X										
Intestine large, rectum	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp adenomatous																									
Intestine large, cecum	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	A	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, lung								X																	
Mesentery		+	+																+						
Leiomyosarcoma, metastatic, stomach, glandular																									
Pancreas	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Fibrous histiocytoma, metastatic, lung								X																	
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Stomach, forestomach	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma																									
Tongue																		+							
Squamous cell papilloma																		X							
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant																									
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Fibrous histiocytoma, metastatic, lung								X																	
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign														X									X	X	
Bilateral, pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	M	+	+	+	+	M	+	M	+	+	M	+	M	+	+	+	+	+	+	+	M	+	M	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma							X				X				X	X	X				X				
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
C-cell, adenoma																								X	
Follicular cell, carcinoma																								X	
General Body System																									
Peritoneum																					+				
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma									X		X	X		X				X							X
Fibrous histiocytoma, metastatic, lung								X																	
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Oxazepam: 625 ppm (continued)

Number of Days on Study	6 2 5	6 2 8	6 3 4	6 4 2	6 5 1	6 5 2	6 6 7	6 8 2	6 9 8	7 0 2	7 0 9	7 1 2	7 1 4	7 2 2	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	0 8 8 9	0 8 8 0	0 7 7 3	0 8 8 2	0 5 1	0 9 1 7	1 0 0	0 6 6	0 6 5	0 6 8	0 9 1	0 6 9	0 5 6	0 8 5	0 6 1	0 7 0	0 7 6	0 7 7	0 7 9	0 8 1	0 8 8	0 9 0	0 9 4	0 9 6	0 9 9	Total Tissues/ Tumors
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Polyp adenomatous																									1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Polyp adenomatous																	X								1
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma, metastatic, lung																									1
Mesentery											+						+					+			6
Leiomyosarcoma, metastatic, stomach, glandular											X														1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma				X																					1
Fibrous histiocytoma, metastatic, lung																									1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leiomyosarcoma											X														1
Tongue																									1
Squamous cell papilloma																									1
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma malignant					X																				1
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																					X				1
Fibrous histiocytoma, metastatic, lung																									1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign					X						X			X	X						X				8
Bilateral, pheochromocytoma benign			X																						1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	41
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X		X		X	X								X			X								12
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell, adenoma											X						X				X		X		5
Follicular cell, carcinoma			X																X						3
General Body System																									
Peritoneum																									1
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																X					X			X	9
Fibrous histiocytoma, metastatic, lung																									1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Oxazepam: 625 ppm (continued)

Number of Days on Study	3 8 6	4 2 6	4 4 8	4 5 2	4 6 6	4 7 3	4 8 1	5 0 1	5 2 3	5 2 4	5 3 6	5 3 6	5 5 0	5 5 7	5 7 1	5 7 2	5 7 8	5 8 5	5 8 5	5 8 6	5 8 6	5 8 9	6 0 4	6 1 4	6 2 0
Carcass ID Number	0 5 2	0 5 7	0 6 7	0 9 3	0 6 3	0 6 0	0 5 3	0 9 8	0 6 2	0 8 3	0 5 4	0 7 8	0 7 2	0 5 5	0 8 4	0 8 7	0 7 4	0 7 1	0 8 6	0 9 2	0 9 5	0 6 4	0 7 5	0 5 9	0 5 8
Genital System (continued)																									
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma		X	X	X		X	X	X	X	X	X	X		X	X		X	X		X	X	X	X	X	X
Interstitial cell, adenoma	X				X								X			X			X						
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, lung								X																	
Lymph node		+															+	+	+	+					
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Lymph node, mesenteric	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Histiocytic sarcoma																									
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Thymoma malignant			X																						
Integumentary System																									
Mammary gland	+	+	M	+	+	M	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Fibroadenoma							X																		
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Fibroma																X									
Fibrosarcoma												X											X		
Keratoacanthoma										X						X								X	
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, lung								X																	
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma																									
Fibrous histiocytoma								X																	
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																	+								
Zymbal's gland														+											
Carcinoma														X											
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, lung								X																	
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Oxazepam: 625 ppm (continued)

Number of Days on Study	625	628	634	642	651	652	667	682	698	702	709	712	714	722	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	08809	08800	07733	08822	05511	09197	10100	06666	06525	06688	09911	06919	05616	08525	06161	07070	07676	07737	07979	08181	08808	09000	09404	09706	09909	Total Tissues/ Tumors
Genital System (continued)																										
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	42
Interstitial cell, adenoma						X																				6
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma, metastatic, lung																										1
Lymph node	+											+	+													8
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma											X															1
Histiocytic sarcoma																X										1
Thymus	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	47
Thymoma malignant																										1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	44
Fibroadenoma								X							X					X			X			5
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibroma																										1
Fibrosarcoma				X																						3
Keratoacanthoma													X										X			5
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma, metastatic, lung																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma																X										1
Fibrous histiocytoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye			+																		+					3
Zymbal's gland																										1
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma, metastatic, lung																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Oxazepam: 625 ppm (continued)

Number of Days on Study	3 8 6	4 2 6	4 4 8	4 5 2	4 6 6	4 7 3	4 8 1	5 0 1	5 2 3	5 2 4	5 3 6	5 3 6	5 5 0	5 5 7	5 7 1	5 7 2	5 7 8	5 8 5	5 8 5	5 8 6	5 8 6	5 8 9	6 0 4	6 1 4	6 2 0
Carcass ID Number	0 5 2	0 5 7	0 6 7	0 9 3	0 6 3	0 6 0	0 5 3	0 9 8	0 6 2	0 8 3	0 5 4	0 7 8	0 7 2	0 5 5	0 8 4	0 8 7	0 7 4	0 7 1	0 8 6	0 9 2	0 9 5	0 6 4	0 7 5	0 5 9	0 5 8
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Leukemia mononuclear		X			X				X	X	X	X	X		X	X	X	X	X	X	X	X	X		X
Mesothelioma malignant																					X				

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Oxazepam: 625 ppm (continued)

Number of Days on Study	6 2 5	6 2 8	6 3 4	6 4 2	6 5 1	6 5 2	6 6 7	6 8 2	6 9 8	7 0 2	7 0 9	7 1 2	7 1 4	7 2 2	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	0 8 9	0 8 0	0 7 3	0 8 2	0 5 1	0 9 7	1 0 0	0 6 6	0 6 5	0 6 8	0 9 1	0 6 9	0 5 6	0 8 5	0 6 1	0 7 0	0 7 6	0 7 7	0 7 9	0 8 1	0 8 8	0 9 0	0 9 4	0 9 6	0 9 9	Total Tissues/ Tumors
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																X										1
Leukemia mononuclear	X	X		X		X	X	X	X	X		X	X	X		X	X		X	X	X	X	X		X	36
Mesothelioma malignant								X																		2

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

Number of Days on Study	3 8 1	4 0 0	4 1 5	4 2 4	4 4 0	4 7 9	5 0 7	5 2 6	5 5 4	5 5 8	5 6 8	5 7 0	5 7 1	5 7 6	5 9 6	5 9 9	6 0 0	6 0 5	6 1 3	6 1 3	6 2 0	6 2 6	6 3 3	6 4 1	6 4 1
Carcass ID Number	1 9 3	1 8 6	1 5 5	1 6 1	1 9 1	1 6 7	1 9 8	1 6 2	1 9 4	1 9 7	1 5 4	1 9 9	1 5 7	1 7 3	1 6 5	1 7 1	1 7 8	1 6 4	1 6 3	1 8 0	1 6 9	1 8 5	1 9 5	1 7 5	1 9 2
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	A	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	A	A	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery						+										+							+		
Oral mucosa																									
Gingival, squamous cell carcinoma																									
Pancreas	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinus, adenoma																							X		
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma									X																
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Bilateral, pheochromocytoma benign																									
Islets, pancreatic	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	M	+	M	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma																	X								
Pars distalis, adenoma, multiple																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, C-cell, adenoma																									
C-cell, adenoma										X															X
Follicular cell, adenoma																				X					
Follicular cell, carcinoma				X																					
General Body System																									
Peritoneum																									+
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																			X						X
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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
Interstitial cell, adenoma		X						X																	

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

Number of Days on Study	6 5 3	6 5 5	6 5 9	6 5 9	6 6 2	6 6 3	6 6 3	6 7 3	6 7 6	6 8 0	6 8 1	6 8 4	6 8 7	6 8 9	6 9 5	7 0 1	7 0 2	7 0 5	7 1 6	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	1 5 3	1 5 2	1 8 1	1 8 8	1 6 8	1 7 2	1 9 0	1 5 1	1 6 6	1 8 2	1 8 9	1 7 0	1 8 7	1 7 6	1 8 3	1 7 7	1 5 6	1 7 9	1 5 9	1 5 8	1 6 0	1 7 4	1 8 4	1 9 6	2 0 0	Total Tissues/ Tumors
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Mesentery					+																					4
Oral mucosa																									+	1
Gingival, squamous cell carcinoma																									X	1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Acinus, adenoma																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign		X					X		X			X								X						5
Bilateral, pheochromocytoma benign													X													1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X		X					X	X	X	X							X	X							9
Pars distalis, adenoma, multiple																									X	1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, C-cell, adenoma						X												X								2
C-cell, adenoma									X			X														4
Follicular cell, adenoma																										1
Follicular cell, carcinoma			X								X															3
General Body System																										
Peritoneum																										1
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma		X								X											X					5
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	X	X	X	47
Interstitial cell, adenoma																										2

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

Number of Days on Study	3 8 1	4 0 0	4 1 5	4 2 4	4 4 0	4 7 9	5 0 7	5 2 6	5 5 4	5 5 8	5 6 8	5 7 0	5 7 1	5 7 6	5 9 6	5 9 9	6 0 0	6 0 5	6 1 3	6 1 3	6 2 0	6 2 6	6 3 3	6 4 1	6 4 1
Carcass ID Number	1 9 3	1 8 6	1 5 5	1 6 1	1 9 1	1 6 7	1 9 8	1 6 2	1 9 4	1 9 7	1 5 4	1 9 9	1 5 7	1 7 3	1 6 5	1 7 1	1 7 8	1 6 4	1 6 3	1 8 0	1 6 9	1 8 5	1 9 5	1 7 5	1 9 2
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node			+			+	+					+				+			+		+		+		
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Histiocytic sarcoma																									
Thymus	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Fibroadenoma																									
Skin	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																			X						
Keratoacanthoma																									
Osteosarcoma				X																					
Squamous cell papilloma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Chordoma																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant																									
Oligodendroglioma malignant																									
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																									
Chordoma, metastatic, bone																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																									X
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Leukemia mononuclear	X	X	X		X	X	X		X	X	X		X	X		X	X	X	X	X		X	X	X	
Mesothelioma malignant																									X

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

Number of Days on Study	6 5 3	6 5 5	6 5 9	6 5 9	6 6 2	6 6 3	6 6 3	6 7 3	6 7 6	6 8 0	6 8 1	6 8 4	6 8 7	6 8 9	6 9 5	7 0 1	7 0 2	7 0 5	7 1 6	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0		
Carcass ID Number	1 5 3	1 5 2	1 8 1	1 8 8	1 6 8	1 7 2	1 9 0	1 5 1	1 6 6	1 8 2	1 8 9	1 7 0	1 8 7	1 7 6	1 8 3	1 7 7	1 5 6	1 7 9	1 5 9	1 5 8	1 6 0	1 7 4	1 8 4	1 9 6	2 0 0	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																										8
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma													X													1
Histiocytic sarcoma																							X			1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Fibroadenoma		X	X																	X					X	4
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibroma																										1
Keratoacanthoma							X																			1
Osteosarcoma																										1
Squamous cell papilloma														X												1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Chordoma													X													1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma malignant																	X									1
Oligodendroglioma malignant					X																					1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																						X				1
Alveolar/bronchiolar carcinoma														X												1
Chordoma, metastatic, bone													X													1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye					+																				+	2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma						X																		X		3
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																							X			1
Leukemia mononuclear	X	X		X	X	X	X	X			X	X					X		X		X	X		X		33
Mesothelioma malignant																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Oxazepam: 5,000 ppm

Number of Days on Study	2 2 3	2 2 4	2 3 7	4 2 2	4 3 2	4 3 9	4 3 9	4 4 2	4 5 1	4 5 1	4 5 2	4 6 7	4 9 8	4 9 8	5 0 7	5 1 2	5 1 6	5 1 9	5 2 1	5 2 6	5 2 8	5 2 9	5 2 9	5 2 9	5 3 0
Carcass ID Number	2 0 9	2 3 5	2 1 0	2 0 8	2 3 7	2 0 1	2 0 7	2 4 0	2 2 3	2 2 6	2 1 3	2 4 5	2 1 2	2 1 4	2 1 6	2 0 6	2 4 9	2 4 8	2 3 1	2 4 4	2 4 3	2 2 4	2 3 4	2 5 0	2 4 6
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma										X											X	X			
Mesentery																							+		
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue										+															
Squamous cell carcinoma										X															
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																			X						
Bilateral, pheochromocytoma benign											X												X		
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	M	M	+	M	+	+	M	+	M	+	+	+	M	+	+	M	+	+	+	M	M	+	+	+
Pituitary gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma																						X			
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma											X														
Follicular cell, adenoma																									
Follicular cell, carcinoma								X								X									
General Body System																									
Peritoneum			+																						
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									X
Bilateral, 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	X	X	X	X		X	X
Interstitial cell, adenoma																							X		

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Oxazepam: 5,000 ppm (continued)

Number of Days on Study	5 3 0	5 4 1	5 4 1	5 4 3	5 5 0	5 6 2	5 6 2	5 6 2	5 7 5	5 7 6	5 7 7	5 8 5	6 0 5	6 0 5	6 1 0	6 1 8	6 2 0	6 2 8	6 3 1	6 3 4	6 4 7	6 8 8	7 0 5	7 1 0	7 1 2	
Carcass ID Number	2 4 7	2 2 0	2 3 6	2 2 7	2 3 0	2 1 5	2 1 7	2 1 9	2 0 2	2 2 5	2 4 2	2 3 2	2 2 8	2 4 1	2 3 3	2 2 2	2 3 9	2 0 3	2 0 5	2 3 8	2 2 9	2 1 1	2 2 1	2 0 4	2 1 8	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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma																										3
Mesentery									+			+													+	4
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue																										1
Squamous cell carcinoma																										1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																										1
Bilateral, pheochromocytoma benign																										2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	40
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	48
Pars distalis, adenoma													X													2
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma										X																2
Follicular cell, adenoma									X															X		2
Follicular cell, carcinoma			X		X																					4
General Body System																										
Peritoneum															+											2
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	49
Adenoma								X			X															3
Bilateral, adenoma																										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	X	X	X	46
Interstitial cell, adenoma																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Oxazepam: 5,000 ppm (continued)

Number of Days on Study	2 2 3	2 2 4	2 3 7	4 2 2	4 3 2	4 3 9	4 3 9	4 4 2	4 5 1	4 5 1	4 5 2	4 6 7	4 9 8	4 9 8	5 0 7	5 1 2	5 1 6	5 1 9	5 2 1	5 2 6	5 2 8	5 2 9	5 2 9	5 3 0
Carcass ID Number	2 0 9	2 3 5	2 1 0	2 0 8	2 3 7	2 0 1	2 0 7	2 4 0	2 2 3	2 2 6	2 1 3	2 4 5	2 1 2	2 1 4	2 1 6	2 0 6	2 4 9	2 4 8	2 3 1	2 4 4	2 4 3	2 2 4	2 3 4	2 5 0	2 4 6
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node																									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Carcinoma											X														
Fibroadenoma											X														
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																									
Keratoacanthoma															X										
Keratoacanthoma, multiple																									
Liposarcoma					X																				
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye													+												
Zymbal's gland																									
Carcinoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X	X		X	X			X		X				X		X		X
Mesothelioma malignant			X																						

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Oxazepam: 5,000 ppm (continued)

Number of Days on Study	5 3 0	5 4 1	5 4 1	5 4 3	5 5 0	5 6 2	5 6 2	5 6 2	5 7 5	5 7 6	5 7 7	5 8 5	6 0 5	6 0 5	6 1 0	6 1 8	6 2 0	6 2 8	6 3 1	6 3 4	6 4 7	6 8 8	7 0 5	7 1 0	7 1 2	
Carcass ID Number	2 4 7	2 2 0	2 3 6	2 2 7	2 3 0	2 1 5	2 1 7	2 1 9	2 0 2	2 2 5	2 4 2	2 3 2	2 2 8	2 4 1	2 3 3	2 2 2	2 3 9	2 0 3	2 0 5	2 3 8	2 2 9	2 1 1	2 2 1	2 0 4	2 1 8	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node				+																						1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	M	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Integumentary System																										
Mammary gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma																										1
Fibroadenoma								X																		2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroma												X													X	2
Keratoacanthoma															X											2
Keratoacanthoma, multiple											X															1
Liposarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																										1
Zymbal's gland							+																			1
Carcinoma							X																			1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma																				X						1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear				X		X	X	X				X		X			X			X				X	X	19
Mesothelioma malignant																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Oxazepam: 10,000 ppm (Stop-Exposure)

Number of Days on Study	3 1 7	4 8 0	4 8 4	4 9 0	4 9 8	5 4 2	5 5 8	5 6 4	5 6 7	5 7 2	5 8 4	5 8 5	5 8 7	5 9 0	5 9 0	5 9 6	5 9 6	6 0 5	6 1 3	6 1 3	6 1 3	6 1 4	6 1 4	6 1 6	6 1 8
Carcass ID Number	2 5 1	2 7 8	2 5 9	2 6 8	2 7 9	2 8 5	2 5 2	2 5 3	2 9 9	2 8 1	2 8 9	2 9 0	2 6 2	2 6 9	2 6 8	2 8 7	2 5 5	2 7 5	2 9 3	2 6 3	2 7 2	2 7 4	2 5 8	2 9 6	2 7 6	2 5 6
Alimentary System																									
Intestine large, colon	+																								
Intestine large, rectum	+																								
Intestine large, cecum	+																								
Intestine small, duodenum	A	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	A	+	+	+	+	A	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma												X													
Mesentery				+	+			+										+							
Stomach, forestomach	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	A	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart																		+							
Endocrine System																									
Adrenal medulla																									
Pheochromocytoma malignant																									
Parathyroid gland												+			+	+		+					+		
Pituitary gland																									
Pars distalis, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																									
C-cell, carcinoma																									
Follicular cell, adenoma																									
Follicular cell, carcinoma																									
General Body System																									
Peritoneum																			+						
Genital System																									
Epididymis																			+						
Preputial gland	+							+			+							+				+	+	
Adenoma											X											X	X		
Bilateral, adenoma																		X							
Seminal vesicle																									
Testes		+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma		X	X	X	X		X	X					X	X	X	X	X	X	X	X	X	X	X	X	X
Interstitial cell, adenoma						X				X	X	X													
Hematopoietic System																									
Lymph node			+		+	+				+				+	+										
Deep cervical, carcinoma, metastatic, thyroid gland																									
Lymph node, mandibular					+	+																	+		
Lymph node, mesenteric					+	+																			
Spleen		+	+	+	+	+		+		+	+		+	+	+	+	+			+	+	+			+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Oxazepam: 10,000 ppm (Stop-Exposure) (continued)

Number of Days on Study	6 2 0	6 2 7	6 3 1	6 3 4	6 3 8	6 4 1	6 4 1	6 4 1	6 4 5	6 4 7	6 5 3	6 5 9	6 7 0	6 8 1	6 8 7	6 9 0	6 9 1	6 9 2	6 9 4	6 9 6	6 9 7	7 0 2	7 1 9	7 1 9	7 2 2	
Carcass ID Number	2 9 4	2 9 5	2 9 7	2 9 8	2 6 5	2 6 0	2 6 1	2 8 3	2 6 4	2 9 2	2 8 0	3 0 0	2 8 4	2 6 7	2 8 2	2 8 8	2 7 7	2 7 0	2 5 7	2 7 3	2 6 6	2 9 1	2 5 4	2 7 1	2 8 6	Total Tissues/ Tumors
Alimentary System																										
Intestine large, colon																										1
Intestine large, rectum																										1
Intestine large, cecum																										1
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	44
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma																										1
Mesentery																					+					5
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Cardiovascular System																										
Heart						+	+								+	+	+					+				7
Endocrine System																										
Adrenal medulla																+										1
Pheochromocytoma malignant																X										1
Parathyroid gland				+		+	+		+							+			+		+	+				13
Pituitary gland		+									+					+				+		+				5
Pars distalis, adenoma		X									X					X				X		X				5
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma															X											1
C-cell, carcinoma				X																						1
Follicular cell, adenoma					X	X																				2
Follicular cell, carcinoma					X																					1
General Body System																										
Peritoneum																										1
Genital System																										
Epididymis																										1
Preputial gland					+				+							+	+	+	+	+			+			14
Adenoma					X											X	X			X						7
Bilateral, adenoma									X														X			3
Seminal vesicle																						+				1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Bilateral, interstitial cell, adenoma	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	44
Interstitial cell, adenoma																										4
Hematopoietic System																										
Lymph node				+											+							+				9
Deep cervical, carcinoma, metastatic, thyroid gland				X																						1
Lymph node, mandibular					+																					4
Lymph node, mesenteric			+																			+				4
Spleen	+		+	+	+			+	+	+	+	+	+	+	+						+	+	+		+	33

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Oxazepam: 10,000 ppm (Stop-Exposure) (continued)

Number of Days on Study	3 1 7	4 8 0	4 8 4	4 9 0	4 9 8	5 4 2	5 5 8	5 6 4	5 6 7	5 7 2	5 8 4	5 8 5	5 8 7	5 9 0	5 9 0	5 9 6	5 9 6	6 0 5	6 1 3	6 1 3	6 1 3	6 1 4	6 1 4	6 1 6	6 1 8
Carcass ID Number	2 5 1	2 7 8	2 5 9	2 6 8	2 7 9	2 8 5	2 5 2	2 5 3	2 9 9	2 8 1	2 8 9	2 9 0	2 6 2	2 6 9	2 8 7	2 5 5	2 7 5	2 9 3	2 6 3	2 7 2	2 7 4	2 5 8	2 9 6	2 7 6	2 5 6
Integumentary System																									
Mammary gland																						+			
Adenoma																									
Carcinoma																						X			
Skin						+	+						+									+			
Fibroma							X																		
Fibrosarcoma																									
Keratoacanthoma						X							X												
Sebaceous gland, adenoma																						X			
Musculoskeletal System																									
Bone																									
Nervous System																									
Brain						+																			
Peripheral nerve						+																			
Spinal cord						+																			
Respiratory System																									
Lung										+															
Special Senses System																									
Eye																									
Zymbal's gland																									
Carcinoma																									
Urinary System																									
Kidney		+	+			+	+		+	+	+	+			+	+	+	+	+	+	+	+	+	+	+
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
Lymphoma malignant																									
Mesothelioma malignant																			X						

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Oxazepam: 10,000 ppm (Stop-Exposure) (continued)

Number of Days on Study	620	627	631	634	638	641	644	651	654	657	653	659	700	801	817	900	901	912	944	966	967	702	719	719	722	
Carcass ID Number	29 4	29 5	29 7	29 8	26 5	26 0	26 1	26 3	26 4	29 2	28 0	30 0	28 4	26 7	28 2	28 8	27 7	27 0	25 7	27 3	26 6	29 1	25 4	27 1	28 6	Total Tissues/ Tumors
Integumentary System																										
Mammary gland																+										2
Adenoma																X										1
Carcinoma																										1
Skin																			+	+	+		+			8
Fibroma																							X			2
Fibrosarcoma																					X					1
Keratoacanthoma																										2
Sebaceous gland, adenoma																				X						2
Musculoskeletal System																										
Bone		+		+							+									+						4
Nervous System																										
Brain					+																					2
Peripheral nerve																				+						2
Spinal cord																				+						2
Respiratory System																										
Lung															+						+					3
Special Senses System																										
Eye													+											+		2
Zymbal's gland													+													1
Carcinoma													X													1
Urinary System																										
Kidney	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	42
Urinary bladder																										1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X		X	X	X			X		X	X	X	X	X	X	X				X	X	X	X		X	34
Lymphoma malignant			X																							1
Mesothelioma malignant																										1

TABLE A3a
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of Oxazepam

	0 ppm	625 ppm	2,500 ppm	5,000 ppm
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate[a]	14/50 (28%)	9/50 (18%)	6/50 (12%)	3/50 (6%)
Adjusted rate[b]	44.1%	42.4%	38.8%	8.8%
Terminal rate[c]	3/17 (18%)	2/11 (18%)	1/6 (17%)	0/0
First incidence (days)	571	557	655	452
Life table test[d]	P = 0.481	P = 0.562N	P = 0.529N	P = 0.543
Logistic regression test[d]	P = 0.043N	P = 0.259N	P = 0.022N	P = 0.049N
Cochran-Armitage test[d]	P = 0.003N			
Fisher exact test[d]		P = 0.171N	P = 0.039N	P = 0.003N
Kidney (Renal Tubule): Adenoma (Single Sections)				
Overall rate	1/50 (2%)	0/50 (0%)	3/50 (6%)	1/50 (2%)
Adjusted rate	5.6%	0.0%	23.8%	16.7%
Terminal rate	0/17 (0%)	0/11 (0%)	1/6 (17%)	0/0
First incidence (days)	723	—[e]	641	634
Life table test	P = 0.009	P = 0.598N	P = 0.099	P = 0.159
Logistic regression test	P = 0.103	P = 0.588N	P = 0.188	P = 0.503
Cochran-Armitage test	P = 0.399			
Fisher exact test		P = 0.500N	P = 0.309	P = 0.753N
Kidney (Renal Tubule): Adenoma (Step Sections)				
Overall rate	1/50 (2%)	1/50 (2%)	4/50 (8%)	5/50 (10%)
Adjusted rate	5.9%	9.1%	31.3%	19.5%
Terminal rate	1/17 (6%)	1/11 (9%)	1/6 (17%)	0/0
First incidence (days)	730 (T)	730 (T)	653	467
Life table test	P < 0.001	P = 0.663	P = 0.027	P = 0.008
Logistic regression test	P = 0.009	P = 0.663	P = 0.071	P = 0.151
Cochran-Armitage test	P = 0.028			
Fisher exact test		P = 0.753N	P = 0.181	P = 0.102
Kidney (Renal Tubule): Adenoma (Single and Step Sections)				
Overall rate	2/50 (4%)	1/50 (2%)	7/50 (14%)	6/50 (12%)
Adjusted rate	11.1%	9.1%	49.7%	32.9%
Terminal rate	1/17 (6%)	1/11 (9%)	2/6 (33%)	0/0
First incidence (days)	723	730 (T)	641	467
Life table test	P < 0.001	P = 0.656N	P = 0.004	P = 0.001
Logistic regression test	P = 0.002	P = 0.647N	P = 0.018	P = 0.109
Cochran-Armitage test	P = 0.027			
Fisher exact test		P = 0.500N	P = 0.080	P = 0.134
Liver: Hepatocellular Adenoma				
Overall rate	1/50 (2%)	0/50 (0%)	0/49 (0%)	3/50 (6%)
Adjusted rate	5.9%	0.0%	0.0%	8.9%
Terminal rate	1/17 (6%)	0/11 (0%)	0/6 (0%)	0/0
First incidence (days)	730 (T)	—	—	451
Life table test	P = 0.011	P = 0.587N	P = 0.707N	P = 0.073
Logistic regression test	P = 0.125	P = 0.587N	P = 0.707N	P = 0.419
Cochran-Armitage test	P = 0.072			
Fisher exact test		P = 0.500N	P = 0.505N	P = 0.309

TABLE A3a
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of Oxazepam (continued)

	0 ppm	625 ppm	2,500 ppm	5,000 ppm
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	2/50 (4%)	0/50 (0%)	0/49 (0%)	3/50 (6%)
Adjusted rate	8.4%	0.0%	0.0%	8.9%
Terminal rate	1/17 (6%)	0/11 (0%)	0/6 (0%)	0/0
First incidence (days)	608	—	—	451
Life table test	P = 0.047	P = 0.325N	P = 0.368N	P = 0.144
Logistic regression test	P = 0.299	P = 0.269N	P = 0.268N	P = 0.637
Cochran-Armitage test	P = 0.201			
Fisher exact test		P = 0.247N	P = 0.253N	P = 0.500
Mammary Gland: Fibroadenoma				
Overall rate	4/50 (8%)	5/50 (10%)	4/50 (8%)	2/50 (4%)
Adjusted rate	18.2%	32.9%	38.9%	7.4%
Terminal rate	1/17 (6%)	3/11 (27%)	2/6 (33%)	0/0
First incidence (days)	698	481	655	452
Life table test	P = 0.094	P = 0.280	P = 0.213	P = 0.330
Logistic regression test	P = 0.575N	P = 0.336	P = 0.384	P = 0.592N
Cochran-Armitage test	P = 0.200N			
Fisher exact test		P = 0.500	P = 0.643N	P = 0.339N
Mammary Gland: Fibroadenoma or Carcinoma				
Overall rate	4/50 (8%)	5/50 (10%)	4/50 (8%)	2/50 (4%)
Adjusted rate	18.2%	32.9%	38.9%	7.4%
Terminal rate	1/17 (6%)	3/11 (27%)	2/6 (33%)	0/0
First incidence (days)	698	481	655	452
Life table test	P = 0.094	P = 0.280	P = 0.213	P = 0.330
Logistic regression test	P = 0.575N	P = 0.336	P = 0.384	P = 0.592N
Cochran-Armitage test	P = 0.200N			
Fisher exact test		P = 0.500	P = 0.643N	P = 0.339N
Pancreatic Islets: Adenoma or Carcinoma				
Overall rate	3/50 (6%)	0/48 (0%)	0/49 (0%)	0/50 (0%)
Adjusted rate	9.9%	0.0%	0.0%	0.0%
Terminal rate	0/17 (0%)	0/11 (0%)	0/6 (0%)	0/0
First incidence (days)	682	—	—	—
Life table test	P = 0.257N	P = 0.232N	P = 0.321N	P = 0.648N
Logistic regression test	P = 0.142N	P = 0.170N	P = 0.173N	P = 0.404N
Cochran-Armitage test	P = 0.073N			
Fisher exact test		P = 0.129N	P = 0.125N	P = 0.121N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	17/49 (35%)	12/50 (24%)	10/50 (20%)	2/48 (4%)
Adjusted rate	61.7%	41.5%	56.7%	10.9%
Terminal rate	8/17 (47%)	1/11 (9%)	1/6 (17%)	0/0
First incidence (days)	471	481	600	529
Life table test	P = 0.478N	P = 0.577N	P = 0.330	P = 0.573N
Logistic regression test	P = 0.007N	P = 0.246N	P = 0.246N	P = 0.030N
Cochran-Armitage test	P < 0.001N			
Fisher exact test		P = 0.172N	P = 0.078N	P < 0.001N

TABLE A3a
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of Oxazepam (continued)

	0 ppm	625 ppm	2,500 ppm	5,000 ppm
Preputial Gland: Adenoma				
Overall rate	7/48 (15%)	9/50 (18%)	5/50 (10%)	4/49 (8%)
Adjusted rate	29.8%	38.8%	30.2%	17.7%
Terminal rate	3/17 (18%)	3/11 (27%)	1/6 (17%)	0/0
First incidence (days)	601	523	613	529
Life table test	P = 0.142	P = 0.178	P = 0.371	P = 0.069
Logistic regression test	P = 0.251N	P = 0.362	P = 0.558N	P = 0.656N
Cochran-Armitage test	P = 0.101N			
Fisher exact test		P = 0.428	P = 0.351N	P = 0.250N
Preputial Gland: Adenoma or Carcinoma				
Overall rate	8/48 (17%)	9/50 (18%)	5/50 (10%)	4/49 (8%)
Adjusted rate	31.5%	38.8%	30.2%	17.7%
Terminal rate	3/17 (18%)	3/11 (27%)	1/6 (17%)	0/0
First incidence (days)	541	523	613	529
Life table test	P = 0.210	P = 0.257	P = 0.494	P = 0.143
Logistic regression test	P = 0.163N	P = 0.507	P = 0.377N	P = 0.432N
Cochran-Armitage test	P = 0.070N			
Fisher exact test		P = 0.537	P = 0.250N	P = 0.168N
Skin: Keratoacanthoma				
Overall rate	3/50 (6%)	5/50 (10%)	1/50 (2%)	3/50 (6%)
Adjusted rate	10.1%	23.5%	5.0%	17.5%
Terminal rate	0/17 (0%)	1/11 (9%)	0/6 (0%)	0/0
First incidence (days)	585	524	663	507
Life table test	P = 0.199	P = 0.210	P = 0.547N	P = 0.121
Logistic regression test	P = 0.439N	P = 0.343	P = 0.338N	P = 0.606
Cochran-Armitage test	P = 0.351N			
Fisher exact test		P = 0.357	P = 0.309N	P = 0.661N
Skin: Squamous Cell Papilloma or Keratoacanthoma				
Overall rate	5/50 (10%)	5/50 (10%)	2/50 (4%)	3/50 (6%)
Adjusted rate	14.6%	23.5%	12.9%	17.5%
Terminal rate	0/17 (0%)	1/11 (9%)	0/6 (0%)	0/0
First incidence (days)	517	524	663	507
Life table test	P = 0.293	P = 0.422	P = 0.512N	P = 0.292
Logistic regression test	P = 0.268N	P = 0.616N	P = 0.222N	P = 0.411N
Cochran-Armitage test	P = 0.200N			
Fisher exact test		P = 0.630N	P = 0.218N	P = 0.357N
Skin: Malignant Schwannoma				
Overall rate	3/50 (6%)	0/50 (0%)	0/50 (0%)	0/50 (0%)
Adjusted rate	11.6%	0.0%	0.0%	0.0%
Terminal rate	1/17 (6%)	0/11 (0%)	0/6 (0%)	0/0
First incidence (days)	480	—	—	—
Life table test	P = 0.188N	P = 0.181N	P = 0.256N	P = 0.467N
Logistic regression test	P = 0.076N	P = 0.110N	P = 0.109N	P = 0.155N
Cochran-Armitage test	P = 0.074N			
Fisher exact test		P = 0.121N	P = 0.121N	P = 0.121N

TABLE A3a
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of Oxazepam (continued)

	0 ppm	625 ppm	2,500 ppm	5,000 ppm
Skin (Subcutaneous Tissue): Fibroma				
Overall rate	3/50 (6%)	1/50 (2%)	1/50 (2%)	2/50 (4%)
Adjusted rate	16.2%	2.9%	3.1%	100.0%
Terminal rate	2/17 (12%)	0/11 (0%)	0/6 (0%)	0/0
First incidence (days)	711	572	613	585
Life table test	P = 0.088	P = 0.433N	P = 0.609N	P = 0.016
Logistic regression test	P = 0.398	P = 0.398N	P = 0.452N	P = 0.230
Cochran-Armitage test	P = 0.512N			
Fisher exact test		P = 0.309N	P = 0.309N	P = 0.500N
Skin (Subcutaneous Tissue): Fibrosarcoma				
Overall rate	2/50 (4%)	3/50 (6%)	0/50 (0%)	0/50 (0%)
Adjusted rate	6.3%	10.4%	0.0%	0.0%
Terminal rate	0/17 (0%)	0/11 (0%)	0/6 (0%)	0/0
First incidence (days)	491	536	—	—
Life table test	P = 0.137N	P = 0.389	P = 0.339N	P = 0.461N
Logistic regression test	P = 0.030N	P = 0.607	P = 0.182N	P = 0.188N
Cochran-Armitage test	P = 0.051N			
Fisher exact test		P = 0.500	P = 0.247N	P = 0.247N
Skin (Subcutaneous Tissue): Fibrosarcoma or Sarcoma				
Overall rate	3/50 (6%)	3/50 (6%)	0/50 (0%)	0/50 (0%)
Adjusted rate	11.0%	10.4%	0.0%	0.0%
Terminal rate	0/17 (0%)	0/11 (0%)	0/6 (0%)	0/0
First incidence (days)	491	536	—	—
Life table test	P = 0.107N	P = 0.533	P = 0.252N	P = 0.434N
Logistic regression test	P = 0.020N	P = 0.608N	P = 0.107N	P = 0.149N
Cochran-Armitage test	P = 0.027N			
Fisher exact test		P = 0.661N	P = 0.121N	P = 0.121N
Skin (Subcutaneous Tissue): Fibroma, Fibrosarcoma, or Sarcoma				
Overall rate	5/50 (10%)	4/50 (8%)	1/50 (2%)	2/50 (4%)
Adjusted rate	21.5%	12.9%	3.1%	100.0%
Terminal rate	2/17 (12%)	0/11 (0%)	0/6 (0%)	0/0
First incidence (days)	491	536	613	585
Life table test	P = 0.541	P = 0.594	P = 0.318N	P = 0.231
Logistic regression test	P = 0.172N	P = 0.489N	P = 0.124N	P = 0.670N
Cochran-Armitage test	P = 0.107N			
Fisher exact test		P = 0.500N	P = 0.102N	P = 0.218N
Testes: Adenoma				
Overall rate	45/50 (90%)	48/50 (96%)	49/50 (98%)	47/50 (94%)
Adjusted rate	100.0%	100.0%	100.0%	100.0%
Terminal rate	17/17 (100%)	11/11 (100%)	6/6 (100%)	0/0
First incidence (days)	517	386	381	422
Life table test	P < 0.001	P = 0.014	P < 0.001	P < 0.001
Logistic regression test	P = 0.011	P = 0.054	P = 0.012	P < 0.001
Cochran-Armitage test	P = 0.354			
Fisher exact test		P = 0.218	P = 0.102	P = 0.357

TABLE A3a
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of Oxazepam (continued)

	0 ppm	625 ppm	2,500 ppm	5,000 ppm
Thyroid Gland (C-cell): Adenoma				
Overall rate	10/50 (20%)	5/49 (10%)	6/50 (12%)	2/50 (4%)
Adjusted rate	35.5%	34.6%	31.7%	8.6%
Terminal rate	3/17 (18%)	3/11 (27%)	0/6 (0%)	0/0
First incidence (days)	571	614	558	452
Life table test	P = 0.299	P = 0.400N	P = 0.444	P = 0.564
Logistic regression test	P = 0.210N	P = 0.312N	P = 0.351N	P = 0.145N
Cochran-Armitage test	P = 0.023N			
Fisher exact test		P = 0.140N	P = 0.207N	P = 0.014N
Thyroid Gland (Follicular Cell): Carcinoma				
Overall rate	3/50 (6%)	3/49 (6%)	3/50 (6%)	4/50 (8%)
Adjusted rate	12.5%	16.3%	12.6%	13.4%
Terminal rate	1/17 (6%)	1/11 (9%)	0/6 (0%)	0/0
First incidence (days)	688	614	424	442
Life table test	P = 0.021	P = 0.456	P = 0.339	P = 0.057
Logistic regression test	P = 0.395	P = 0.546	P = 0.656	P = 0.516
Cochran-Armitage test	P = 0.405			
Fisher exact test		P = 0.651	P = 0.661N	P = 0.500
Thyroid Gland (Follicular Cell): Adenoma or Carcinoma				
Overall rate	4/50 (8%)	3/49 (6%)	4/50 (8%)	6/50 (12%)
Adjusted rate	14.6%	16.3%	15.4%	59.2%
Terminal rate	1/17 (6%)	1/11 (9%)	0/6 (0%)	0/0
First incidence (days)	554	614	424	442
Life table test	P = 0.002	P = 0.603	P = 0.354	P = 0.010
Logistic regression test	P = 0.188	P = 0.582N	P = 0.617N	P = 0.318
Cochran-Armitage test	P = 0.218			
Fisher exact test		P = 0.511N	P = 0.643N	P = 0.370
All Organs: Mononuclear Cell Leukemia				
Overall rate	27/50 (54%)	36/50 (72%)	33/50 (66%)	19/50 (38%)
Adjusted rate	72.4%	91.4%	86.0%	100.0%
Terminal rate	8/17 (47%)	8/11 (73%)	3/6 (50%)	0/0
First incidence (days)	498	426	381	442
Life table test	P < 0.001	P = 0.005	P = 0.002	P < 0.001
Logistic regression test	P = 0.049N	P = 0.020	P = 0.187	P = 0.459N
Cochran-Armitage test	P = 0.009N			
Fisher exact test		P = 0.048	P = 0.154	P = 0.080N
All Organs: Benign Neoplasms				
Overall rate	47/50 (94%)	50/50 (100%)	50/50 (100%)	47/50 (94%)
Adjusted rate	100.0%	100.0%	100.0%	100.0%
Terminal rate	17/17 (100%)	11/11 (100%)	6/6 (100%)	0/0
First incidence (days)	471	386	381	422
Life table test	P < 0.001	P = 0.014	P < 0.001	P < 0.001
Logistic regression test	P = 0.040	P = 0.011	P = 0.014	P = 0.001
Cochran-Armitage test	P = 0.370N			
Fisher exact test		P = 0.121	P = 0.121	P = 0.661N

TABLE A3a
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of Oxazepam (continued)

	0 ppm	625 ppm	2,500 ppm	5,000 ppm
All Organs: Malignant Neoplasms				
Overall rate	38/50 (76%)	43/50 (86%)	40/50 (80%)	25/50 (50%)
Adjusted rate	85.6%	93.5%	96.5%	100.0%
Terminal rate	11/17 (65%)	8/11 (73%)	5/6 (83%)	0/0
First incidence (days)	480	426	381	237
Life table test	P < 0.001	P = 0.016	P = 0.003	P < 0.001
Logistic regression test	P < 0.001N	P = 0.083	P = 0.477	P = 0.025N
Cochran-Armitage test	P < 0.001N			
Fisher exact test		P = 0.154	P = 0.405	P = 0.006N
All Organs: Benign or Malignant Neoplasms				
Overall rate	50/50 (100%)	50/50 (100%)	50/50 (100%)	48/50 (96%)
Adjusted rate	100.0%	100.0%	100.0%	100.0%
Terminal rate	17/17 (100%)	11/11 (100%)	6/6 (100%)	0/0
First incidence (days)	471	386	381	237
Life table test	P < 0.001	P = 0.035	P = 0.001	P < 0.001
Logistic regression test	—[f]	—	—	—
Cochran-Armitage test	P = 0.043N			
Fisher exact test		P = 1.000N	P = 1.000N	P = 0.247N

(T) Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, kidney, liver, pancreatic islets, pituitary gland, preputial gland, testes, and thyroid gland; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated neoplasm incidence at the end of the study 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 exposed group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group
[f] Value of statistic cannot be computed.

TABLE A3b
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Stop-Exposure Feed Study of Oxazepam

	0 ppm	10,000 ppm
Adrenal Medulla: Benign Pheochromocytoma		
Overall rate[a]	14/50 (28%)	0/1 (0%)[d]
Adjusted rate[b]	44.1%	
Terminal rate[c]	3/17 (18%)	
First incidence (days)	571	
Adrenal Medulla: Benign or Malignant Pheochromocytoma		
Overall rate	14/50 (28%)	1/1 (100%)[d]
Adjusted rate	44.1%	
Terminal rate	3/17 (18%)	
First incidence (days)	571	
Kidney (Renal Tubule): Adenoma (Step Sections)		
Overall rate	1/50 (2%)	6/45 (13%)
Adjusted rate	5.9%	39.1%
Terminal rate	1/17 (6%)	0/0
First incidence (days)	730 (T)	613
Life table test[e]		P = 0.001
Logistic regression test[e]		P = 0.024
Fisher exact test[e]		P = 0.041
Kidney (Renal Tubule): Adenoma (Single and Step Sections)		
Overall rate	2/50 (4%)	6/45 (13%)
Adjusted rate	11.1%	39.1%
Terminal rate	1/17 (6%)	0/0
First incidence (days)	723	613
Life table test		P = 0.001
Logistic regression test		P = 0.046
Fisher exact test		P = 0.103
Mammary Gland: Fibroadenoma		
Overall rate	4/50 (8%)	0/50 (0%)
Adjusted rate	18.2%	0.0%
Terminal rate	1/17 (6%)	0/0
First incidence (days)	698	—[f]
Life table test		P = 0.537N
Logistic regression test		P = 0.214N
Fisher exact test		P = 0.059N
Mammary Gland: Fibroadenoma or Adenoma		
Overall rate	4/50 (8%)	1/50 (2%)
Adjusted rate	18.2%	10.0%
Terminal rate	1/17 (6%)	0/0
First incidence (days)	698	690
Life table test		P = 0.608
Logistic regression test		P = 0.515N
Fisher exact test		P = 0.181N
Mammary Gland: Fibroadenoma, Adenoma, or Carcinoma		
Overall rate	4/50 (8%)	2/50 (4%)
Adjusted rate	18.2%	13.1%
Terminal rate	1/17 (6%)	0/0
First incidence (days)	698	614
Life table test		P = 0.345
Logistic regression test		P = 0.614N
Fisher exact test		P = 0.339N

TABLE A3b
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Stop-Exposure Feed Study of Oxazepam (continued)

	0 ppm	10,000 ppm
Pancreatic Islets: Adenoma or Carcinoma		
Overall rate	3/50 (6%)	0/0[d]
Adjusted rate	9.9%	
Terminal rate	0/17 (0%)	
First incidence (days)	682	
Pituitary Gland (Pars Distalis): Adenoma		
Overall rate	17/49 (35%)	5/5 (100%)[d]
Adjusted rate	61.7%	
Terminal rate	8/17 (47%)	
First incidence (days)	471	
Preputial Gland: Adenoma		
Overall rate	7/48 (15%)	10/14 (71%)[d]
Adjusted rate	29.8%	
Terminal rate	3/17 (18%)	
First incidence (days)	601	
Preputial Gland: Adenoma or Carcinoma		
Overall rate	8/48 (17%)	10/14 (71%)[d]
Adjusted rate	31.5%	
Terminal rate	3/17 (18%)	
First incidence (days)	541	
Skin: Keratoacanthoma		
Overall rate	3/50 (6%)	2/50 (4%)
Adjusted rate	10.1%	4.8%
Terminal rate	0/17 (0%)	0/0
First incidence (days)	585	542
Life table test		P = 0.645
Logistic regression test		P = 0.449N
Fisher exact test		P = 0.500N
Skin: Squamous Cell Papilloma or Keratoacanthoma		
Overall rate	5/50 (10%)	2/50 (4%)
Adjusted rate	14.6%	4.8%
Terminal rate	0/17 (0%)	0/0
First incidence (days)	517	542
Life table test		P = 0.458N
Logistic regression test		P = 0.157N
Fisher exact test		P = 0.218N
Skin: Malignant Schwannoma		
Overall rate	3/50 (6%)	0/50 (0%)
Adjusted rate	11.6%	0.0%
Terminal rate	1/17 (6%)	0/0
First incidence (days)	480	—
Life table test		P = 0.377N
Logistic regression test		P = 0.107N
Fisher exact test		P = 0.121N

TABLE A3b
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Stop-Exposure Feed Study of Oxazepam (continued)

	0 ppm	10,000 ppm
Skin (Subcutaneous Tissue): Fibroma		
Overall rate	3/50 (6%)	2/50 (4%)
Adjusted rate	16.2%	34.8%
Terminal rate	2/17 (12%)	0/0
First incidence (days)	711	558
Life table test		P = 0.154
Logistic regression test		P = 0.629
Fisher exact test		P = 0.500N
Skin (Subcutaneous Tissue): Fibrosarcoma or Sarcoma		
Overall rate	3/50 (6%)	1/50 (2%)
Adjusted rate	11.0%	20.0%
Terminal rate	0/17 (0%)	0/0
First incidence (days)	491	697
Life table test		P = 0.712
Logistic regression test		P = 0.323N
Fisher exact test		P = 0.309N
Skin (Subcutaneous Tissue): Fibroma, Fibrosarcoma, or Sarcoma		
Overall rate	5/50 (10%)	3/50 (6%)
Adjusted rate	21.5%	47.9%
Terminal rate	2/17 (12%)	0/0
First incidence (days)	491	558
Life table test		P = 0.187
Logistic regression test		P = 0.492N
Fisher exact test		P = 0.357N
Testes: Adenoma		
Overall rate	45/50 (90%)	48/48 (100%)
Adjusted rate	100.0%	100.0%
Terminal rate	17/17 (100%)	0/0
First incidence rate	517	480
Life table test		P < 0.001
Logistic regression test		P = 0.014
Fisher exact test		P = 0.031
Thyroid Gland (C-cell): Adenoma		
Overall rate	10/50 (20%)	1/50 (2%)
Adjusted rate	35.5%	9.1%
Terminal rate	3/17 (18%)	0/0
First incidence (days)	571	687
Life table test		P = 0.320N
Logistic regression test		P = 0.030N
Fisher exact test		P = 0.004N
Thyroid Gland (C-cell): Adenoma or Carcinoma		
Overall rate	10/50 (20%)	2/50 (4%)
Adjusted rate	35.5%	13.2%
Terminal rate	3/17 (18%)	0/0
First incidence (days)	571	634
Life table test		P = 0.516N
Logistic regression test		P = 0.068N
Fisher exact test		P = 0.014N

TABLE A3b
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Stop-Exposure Feed Study of Oxazepam (continued)

	0 ppm	10,000 ppm
Thyroid Gland (Follicular Cell): Carcinoma		
Overall rate	3/50 (6%)	1/50 (2%)
Adjusted rate	12.5%	4.8%
Terminal rate	1/17 (6%)	0/0
First incidence (days)	688	638
Life table test		P = 0.660
Logistic regression test		P = 0.513N
Fisher exact test		P = 0.309N
Thyroid Gland (Follicular Cell): Adenoma or Carcinoma		
Overall rate	4/50 (8%)	2/50 (4%)
Adjusted rate	14.6%	9.5%
Terminal rate	1/17 (6%)	0/0
First incidence (days)	554	638
Life table test		P = 0.573
Logistic regression test		P = 0.400N
Fisher exact test		P = 0.339N
All Organs: Mononuclear Cell Leukemia		
Overall rate	27/50 (54%)	34/50 (68%)
Adjusted rate	72.4%	100.0%
Terminal rate	8/17 (47%)	0/0
First incidence (days)	498	480
Life table test		P < 0.001
Logistic regression test		P = 0.075
Fisher exact test		P = 0.109
All Organs: Benign Neoplasms		
Overall rate	47/50 (94%)	48/50 (96%)
Adjusted rate	100.0%	100.0%
Terminal rate	17/17 (100%)	0/0
First incidence (days)	471	480
Life table test		P < 0.001
Logistic regression test		P = 0.331
Fisher exact test		P = 0.500
All Organs: Malignant Neoplasms		
Overall rate	38/50 (76%)	35/50 (70%)
Adjusted rate	85.6%	100.0%
Terminal rate	11/17 (65%)	0/0
First incidence (days)	480	480
Life table test		P < 0.001
Logistic regression test		P = 0.363N
Fisher exact test		P = 0.326N

TABLE A3b
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Stop-Exposure Feed Study of Oxazepam (continued)

	0 ppm	10,000 ppm
All Organs: Benign or Malignant Neoplasms		
Overall rate	50/50 (100%)	48/50 (96%)
Adjusted rate	100.0%	100.0%
Terminal rate	17/17 (100%)	0/0
First incidence (days)	471	480
Life table test		P < 0.001
Logistic regression test		P = 0.423N
Fisher exact test		P = 0.247N

[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, kidney, pancreatic islets, pituitary gland, preputial gland, testes, and thyroid gland; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Tissue was examined microscopically only when it was observed to be abnormal at necropsy; thus, statistical comparisons with the controls are not appropriate.
[e] Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and the 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 Fisher exact test compares directly the overall incidence rates. For all tests, a lower incidence in the exposed group is indicated by **N**.
[f] Not applicable; no neoplasms in animal group

TABLE A4a
Historical Incidence of Renal Tubule Adenoma in Untreated Male F344/N Rats[a]

Study	Incidence in Controls
Historical Incidence at Battelle Columbus Laboratories	
4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol)	0/50
5,5-Diphenylhydantoin	0/50
Ethylene Thiourea	0/50
Polybrominated Biphenyls (Firemaster FF-1®)	0/50
Manganese (II) Sulfate Monohydrate	1/52
Triamterene	1/50
Tricresyl Phosphate	0/51
Overall Historical Incidence	
Total	9/1,301 (0.7%)
Standard deviation	1.5%
Range	0%-6%

[a] Data as of 12 May 1995

TABLE A4b
Historical Incidence of Benign Adrenal Medulla Pheochromocytoma in Untreated Male F344/N Rats[a]

Study	Incidence in Controls
Historical Incidence at Battelle Columbus Laboratories	
4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol)	14/50
5,5-Diphenylhydantoin	19/50
Ethylene Thiourea	22/50
Polybrominated Biphenyls (Firemaster FF-1®)	12/49
Manganese (II) Sulfate Monohydrate	14/52
Triamterene	9/50
Tricresyl Phosphate	5/50
Overall Historical Incidence	
Total	396/1,283 (30.9%)
Standard deviation	12.1%
Range	10%-63%

[a] Data as of 12 May 1995

TABLE A4c
Historical Incidence of Pituitary Gland (Pars Distalis) Adenoma in Untreated Male F344/N Rats[a]

Study	Incidence in Controls
Historical Incidence at Battelle Columbus Laboratories	
4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol)	14/50
5,5-Diphenylhydantoin	14/50
Ethylene Thiourea	19/50
Polybrominated Biphenyls (Firemaster FF-1®)	13/50
Manganese (II) Sulfate Monohydrate	13/52
Triamterene	8/50
Tricresyl Phosphate	8/51
Overall Historical Incidence	
Total	377/1,284 (29.4%)
Standard deviation	10.6%
Range	14%-60%

[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 Oxazepam[a]

	0 ppm	625 ppm	2,500 ppm	5,000 ppm	10,000 ppm (Stop-Exposure)
Disposition Summary					
Animals initially in study	50	50	50	50	50
Early deaths					
Moribund	25	27	33	43	39
Natural deaths	8	12	11	7	11
Survivors					
Terminal sacrifice	17	11	6		
Animals examined microscopically	50	50	50	50	50
Alimentary System					
Intestine large, colon	(50)	(47)	(50)	(50)	(1)
Parasite metazoan		4 (9%)		2 (4%)	
Serosa, inflammation, chronic					1 (100%)
Intestine large, rectum	(50)	(48)	(49)	(50)	(1)
Congestion			1 (2%)		
Edema			1 (2%)		
Parasite metazoan			1 (2%)	2 (4%)	
Serosa, inflammation, chronic					1 (100%)
Intestine large, cecum	(50)	(48)	(49)	(50)	(1)
Congestion			1 (2%)		
Edema			1 (2%)		
Serosa, inflammation, chronic					1 (100%)
Intestine small, duodenum	(50)	(48)	(49)	(50)	(44)
Erosion	4 (8%)	3 (6%)	9 (18%)	16 (32%)	1 (2%)
Inflammation, chronic active					1 (2%)
Mineralization					6 (14%)
Ulcer	1 (2%)		2 (4%)	2 (4%)	
Intestine small, ileum	(50)	(47)	(46)	(49)	
Ulcer	1 (2%)				
Liver	(50)	(50)	(49)	(50)	(50)
Angiectasis	1 (2%)				1 (2%)
Basophilic focus	21 (42%)	11 (22%)	4 (8%)	2 (4%)	13 (26%)
Clear cell focus	2 (4%)	4 (8%)			
Degeneration, cystic	3 (6%)	1 (2%)	1 (2%)		
Degeneration, fatty	1 (2%)		1 (2%)		
Eosinophilic focus	8 (16%)	5 (10%)	5 (10%)	6 (12%)	2 (4%)
Hepatodiaphragmatic nodule	1 (2%)	3 (6%)	1 (2%)	2 (4%)	3 (6%)
Mixed cell focus	2 (4%)	4 (8%)	2 (4%)	1 (2%)	1 (2%)
Necrosis, focal	1 (2%)		5 (10%)	4 (8%)	
Bile duct, hyperplasia	1 (2%)		1 (2%)		
Centrilobular, congestion		1 (2%)			
Centrilobular, degeneration	1 (2%)			1 (2%)	1 (2%)
Centrilobular, necrosis	3 (6%)	1 (2%)	4 (8%)	3 (6%)	2 (4%)
Hepatocyte, centrilobular, hypertrophy		1 (2%)	8 (16%)	14 (28%)	
Serosa, fibrosis		1 (2%)			
Serosa, inflammation, chronic					1 (2%)
Mesentery	(7)	(6)	(4)	(4)	(5)
Accessory spleen	1 (14%)	1 (17%)			1 (20%)
Necrosis, acute, focal		1 (17%)			
Fat, necrosis	6 (86%)	3 (50%)	3 (75%)	4 (100%)	4 (80%)
Pancreas	(50)	(48)	(49)	(50)	
Acinus, atrophy	17 (34%)	10 (21%)	14 (29%)	1 (2%)	
Acinus, hyperplasia				1 (2%)	
Artery, inflammation, granulomatous	1 (2%)	1 (2%)			

[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 Oxazepam (continued)

	0 ppm	625 ppm	2,500 ppm	5,000 ppm	10,000 ppm (Stop-Exposure)
Alimentary System (continued)					
Salivary glands	(50)	(49)	(50)	(50)	
Parotid gland, degeneration				1 (2%)	
Parotid gland, hyperplasia, focal				1 (2%)	
Stomach, forestomach	(50)	(48)	(50)	(50)	(49)
Erosion		1 (2%)	1 (2%)	2 (4%)	1 (2%)
Hyperplasia	1 (2%)				
Inflammation, chronic			1 (2%)		
Inflammation, chronic active	6 (12%)	8 (17%)	22 (44%)	15 (30%)	10 (20%)
Mineralization			1 (2%)		4 (8%)
Ulcer	9 (18%)	12 (25%)	20 (40%)	10 (20%)	7 (14%)
Epithelium, hyperplasia	5 (10%)	8 (17%)	25 (50%)	16 (32%)	15 (31%)
Serosa, inflammation				3 (6%)	
Stomach, glandular	(50)	(48)	(50)	(50)	(47)
Erosion	5 (10%)	5 (10%)	9 (18%)	4 (8%)	5 (11%)
Inflammation, chronic active					2 (4%)
Mineralization		3 (6%)	1 (2%)	4 (8%)	16 (34%)
Ulcer	2 (4%)	7 (15%)	7 (14%)	4 (8%)	4 (9%)
Serosa, inflammation					2 (4%)
Cardiovascular System					
Blood vessel	(49)	(50)	(50)	(50)	
Aorta, mineralization		1 (2%)		3 (6%)	
Aorta, thrombosis	1 (2%)				
Heart	(50)	(50)	(50)	(50)	(7)
Atrium, thrombosis	7 (14%)		1 (2%)		5 (71%)
Myocardium, degeneration	46 (92%)	40 (80%)	43 (86%)	37 (74%)	1 (14%)
Myocardium, mineralization		1 (2%)	2 (4%)	1 (2%)	4 (57%)
Endocrine System					
Adrenal cortex	(50)	(50)	(50)	(50)	
Degeneration, cystic		1 (2%)			
Hyperplasia, focal	5 (10%)	10 (20%)	8 (16%)	6 (12%)	
Hypertrophy, focal			1 (2%)		
Necrosis, focal	1 (2%)				
Adrenal medulla	(50)	(50)	(50)	(50)	(1)
Hyperplasia	9 (18%)	9 (18%)	15 (30%)	16 (32%)	
Islets, pancreatic	(50)	(48)	(49)	(50)	
Hyperplasia	3 (6%)	2 (4%)		1 (2%)	
Parathyroid gland	(39)	(41)	(46)	(40)	(13)
Hyperplasia	3 (8%)	6 (15%)	9 (20%)	16 (40%)	13 (100%)
Pituitary gland	(49)	(50)	(50)	(48)	(5)
Cyst	1 (2%)				
Degeneration, cystic	1 (2%)				
Pars distalis, cyst		2 (4%)		1 (2%)	
Pars distalis, hyperplasia	9 (18%)	5 (10%)	3 (6%)	1 (2%)	
Pars distalis, thrombosis	1 (2%)				
Pars nervosa, gliosis, focal			1 (2%)		
Thyroid gland	(50)	(49)	(50)	(50)	(50)
Mineralization				1 (2%)	
C-cell, hyperplasia	33 (66%)	36 (73%)	38 (76%)	38 (76%)	41 (82%)
Follicle, cyst	4 (8%)	2 (4%)	4 (8%)	6 (12%)	9 (18%)
Follicle, hyperplasia			1 (2%)		
Follicle, ultimobranchial cyst				1 (2%)	

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of Oxazepam (continued)

	0 ppm	625 ppm	2,500 ppm	5,000 ppm	10,000 ppm (Stop-Exposure)
General Body System					
Peritoneum	(2)	(1)	(1)	(2)	(1)
Inflammation, chronic				1 (50%)	
Genital System					
Epididymis	(50)	(49)	(50)	(50)	(1)
Cyst				1 (2%)	
Inflammation, chronic				1 (2%)	
Preputial gland	(48)	(50)	(50)	(49)	(14)
Cyst	1 (2%)				
Hyperplasia	1 (2%)				
Inflammation, chronic active	2 (4%)			1 (2%)	
Inflammation, suppurative	1 (2%)	1 (2%)		4 (8%)	3 (21%)
Duct, cyst	1 (2%)	4 (8%)	4 (8%)	3 (6%)	1 (7%)
Prostate	(50)	(50)	(50)	(50)	
Inflammation, chronic active	1 (2%)				
Inflammation, suppurative		1 (2%)			
Seminal vesicle	(50)	(50)	(50)	(50)	(1)
Atrophy					1 (100%)
Cyst	1 (2%)			1 (2%)	
Fibrosis		1 (2%)			
Hyperplasia			1 (2%)		
Inflammation, chronic	1 (2%)				
Inflammation, suppurative		1 (2%)			
Testes	(50)	(50)	(50)	(50)	(48)
Germinal epithelium, atrophy	2 (4%)	2 (4%)	1 (2%)	1 (2%)	
Hematopoietic System					
Bone marrow	(50)	(50)	(50)	(50)	
Necrosis	1 (2%)				
Thrombosis				1 (2%)	
Lymph node	(5)	(8)	(8)	(1)	(9)
Renal, ectasia			1 (13%)		
Renal, pigmentation					1 (11%)
Lymph node, mesenteric	(49)	(49)	(50)	(47)	(4)
Congestion			1 (2%)		
Inflammation, chronic active	1 (2%)				
Spleen	(50)	(50)	(50)	(50)	(33)
Fibrosis	7 (14%)	3 (6%)	3 (6%)	4 (8%)	8 (24%)
Hematopoietic cell proliferation	6 (12%)	1 (2%)	3 (6%)	5 (10%)	
Necrosis	1 (2%)	1 (2%)			
Pigmentation, hemosiderin		1 (2%)	3 (6%)	2 (4%)	
Lymphoid follicle, atrophy		1 (2%)		1 (2%)	
Red pulp, congestion		1 (2%)	1 (2%)	2 (4%)	
Thymus	(49)	(47)	(49)	(47)	
Ectopic parathyroid gland				2 (4%)	
Ectopic thyroid				1 (2%)	
Integumentary System					
Mammary gland	(50)	(44)	(48)	(48)	(2)
Hyperplasia, cystic	3 (6%)				
Inflammation, suppurative			1 (2%)		

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of Oxazepam (continued)

	0 ppm	625 ppm	2,500 ppm	5,000 ppm	10,000 ppm (Stop-Exposure)
Integumentary System (continued)					
Skin	(50)	(49)	(49)	(50)	(8)
Ulcer				2 (4%)	
Epidermis, cyst	1 (2%)				
Epidermis, inflammation, suppurative					1 (13%)
Hair follicle, cyst	1 (2%)				
Musculoskeletal System					
Bone	(50)	(50)	(50)	(50)	(4)
Fibrosis					1 (25%)
Fibrous osteodystrophy		1 (2%)	6 (12%)	8 (16%)	3 (75%)
Hyperostosis	3 (6%)		1 (2%)		
Nervous System					
Brain	(50)	(50)	(50)	(50)	(2)
Hydrocephalus	6 (12%)	2 (4%)		1 (2%)	
Necrosis, focal			1 (2%)		
Hypothalamus, degeneration	1 (2%)				
Medulla, gliosis, focal	1 (2%)				
Respiratory System					
Lung	(50)	(50)	(50)	(50)	(3)
Fibrosis			1 (2%)		
Hematopoietic cell proliferation	1 (2%)				
Hemorrhage				1 (2%)	
Inflammation, acute, focal				1 (2%)	
Inflammation, chronic, focal				1 (2%)	
Inflammation, granulomatous	1 (2%)	2 (4%)		3 (6%)	
Metaplasia, squamous			1 (2%)		
Alveolar epithelium, hyperplasia	1 (2%)	1 (2%)		1 (2%)	
Interstitium, inflammation, acute	1 (2%)				
Interstitium, inflammation, chronic	2 (4%)		3 (6%)		
Interstitium, inflammation, chronic, focal	1 (2%)				
Interstitium, mineralization		1 (2%)		1 (2%)	
Mediastinum, inflammation, chronic				1 (2%)	
Vein, thrombosis	1 (2%)				
Nose	(50)	(50)	(50)	(50)	
Inflammation, suppurative	13 (26%)	14 (28%)	9 (18%)	7 (14%)	
Special Senses System					
Eye	(2)	(3)	(2)	(1)	(2)
Cataract		1 (33%)			
Inflammation, suppurative				1 (100%)	
Anterior chamber, inflammation, acute		1 (33%)			1 (50%)
Anterior chamber, inflammation, suppurative			1 (50%)		
Lens, cataract	2 (100%)	1 (33%)	1 (50%)		1 (50%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of Oxazepam (continued)

	0 ppm	625 ppm	2,500 ppm	5,000 ppm	10,000 ppm (Stop-Exposure)
Urinary System					
Kidney	(50)	(50)	(50)	(50)	(42)
Amyloid deposition	1 (2%)				
Fibrosis, focal		1 (2%)			
Infarct	1 (2%)				
Nephropathy	49 (98%)	44 (88%)	49 (98%)	50 (100%)	42 (100%)
Renal tubule, cyst	1 (2%)	1 (2%)	6 (12%)	8 (16%)	3 (7%)
Renal tubule, hyperplasia		1 (2%)	3 (6%)	1 (2%)	
Renal tubule, pigmentation, lipofuscin	1 (2%)				
Urinary bladder	(50)	(50)	(50)	(50)	(1)
Hemorrhage	1 (2%)				
Ulcer					1 (100%)
Transitional epithelium, hyperplasia	1 (2%)				

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

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

	0 ppm	625 ppm	2,500 ppm	5,000 ppm	10,000 ppm (Stop-Exposure)
Disposition Summary					
Animals initially in study	50	50	50	50	50
Early deaths					
Accidental death	1				
Moribund	11	18	18	16	19
Natural deaths	6	6	12	3	6
Survivors					
Terminal sacrifice	32	26	20	31	25
Animals examined microscopically	50	50	50	50	50
Alimentary System					
Intestine large, colon	(50)	(48)	(49)	(50)	
Polyp adenomatous	1 (2%)				
Liver	(50)	(50)	(50)	(50)	(49)
Histiocytic sarcoma, metastatic, skin					1 (2%)
Mesentery	(10)	(9)	(4)	(6)	(13)
Pancreas	(50)	(50)	(49)	(49)	
Acinus, adenoma				1 (2%)	
Salivary glands	(50)	(50)	(48)	(49)	(1)
Myoepithelioma					1 (100%)
Stomach, forestomach	(50)	(50)	(50)	(50)	(50)
Tongue		(1)			
Squamous cell carcinoma		1 (100%)			
Cardiovascular System					
None					
Endocrine System					
Adrenal cortex	(50)	(50)	(50)	(50)	(2)
Adenoma		1 (2%)	1 (2%)		1 (50%)
Adrenal medulla	(50)	(50)	(50)	(50)	
Pheochromocytoma malignant	1 (2%)				
Pheochromocytoma complex	1 (2%)				
Pheochromocytoma benign	1 (2%)	3 (6%)		1 (2%)	
Islets, pancreatic	(50)	(50)	(49)	(49)	
Adenoma	1 (2%)				
Parathyroid gland	(42)	(38)	(38)	(33)	
Adenoma			1 (3%)		
Pituitary gland	(50)	(50)	(50)	(50)	(35)
Pars distalis, adenoma	30 (60%)	28 (56%)	20 (40%)	12 (24%)	23 (66%)
Pars distalis, adenoma, multiple	1 (2%)		1 (2%)		
Pars distalis, carcinoma			1 (2%)		
Thyroid gland	(50)	(50)	(48)	(49)	(50)
Bilateral, C-cell, adenoma					2 (4%)
C-cell, adenoma	6 (12%)	3 (6%)	6 (13%)	2 (4%)	2 (4%)
C-cell, carcinoma	1 (2%)		1 (2%)	1 (2%)	
Follicular cell, adenoma	1 (2%)			2 (4%)	
Follicular cell, carcinoma	1 (2%)		3 (6%)	1 (2%)	

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of Oxazepam (continued)

	0 ppm	625 ppm	2,500 ppm	5,000 ppm	10,000 ppm (Stop-Exposure)
General Body System					
None					
Genital System					
Clitoral gland	(49)	(50)	(50)	(50)	(11)
Adenoma	6 (12%)	3 (6%)	3 (6%)	4 (8%)	7 (64%)
Carcinoma	1 (2%)		1 (2%)		
Bilateral, adenoma	1 (2%)				
Ovary	(50)	(50)	(50)	(50)	(4)
Granulosa cell tumor benign	1 (2%)				
Tubulostromal adenoma				1 (2%)	
Uterus	(50)	(50)	(50)	(50)	(5)
Polyp stromal	2 (4%)	4 (8%)	3 (6%)	4 (8%)	
Sarcoma stromal	1 (2%)			1 (2%)	1 (20%)
Hematopoietic System					
Lymph node	(4)	(2)	(9)	(3)	(4)
Deep cervical, carcinoma, metastatic, thyroid gland	1 (25%)				
Renal, pheochromocytoma malignant, metastatic, adrenal medulla	1 (25%)				
Lymph node, mandibular	(50)	(48)	(48)	(49)	(3)
Squamous cell carcinoma, metastatic, skin					1 (33%)
Lymph node, mesenteric	(50)	(50)	(50)	(49)	(2)
Spleen	(50)	(50)	(50)	(49)	(12)
Thymus	(50)	(48)	(46)	(47)	
Integumentary System					
Mammary gland	(49)	(49)	(49)	(50)	(23)
Adenoma	1 (2%)	2 (4%)			
Carcinoma	2 (4%)	3 (6%)			
Carcinoma, multiple					1 (4%)
Fibroadenoma	11 (22%)	14 (29%)	8 (16%)	12 (24%)	17 (74%)
Fibroadenoma, multiple	14 (29%)	5 (10%)	1 (2%)	1 (2%)	6 (26%)
Skin	(50)	(50)	(50)	(50)	(6)
Basal cell carcinoma		1 (2%)			
Fibroma				1 (2%)	2 (33%)
Fibrosarcoma		2 (4%)			
Keratoacanthoma				1 (2%)	
Squamous cell carcinoma					1 (17%)
Trichoepithelioma			1 (2%)		
Sebaceous gland, adenoma		1 (2%)			
Subcutaneous tissue, histiocytic sarcoma					1 (17%)
Musculoskeletal System					
Bone	(50)	(50)	(50)	(50)	(1)
Osteosarcoma	1 (2%)				

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of Oxazepam (continued)

	0 ppm	625 ppm	2,500 ppm	5,000 ppm	10,000 ppm (Stop-Exposure)
Nervous System					
Brain	(50)	(50)	(50)	(50)	
Astrocytoma benign		1 (2%)			
Carcinoma, metastatic, pituitary gland			1 (2%)		
Oligodendroglioma malignant	1 (2%)				
Respiratory System					
Lung	(50)	(50)	(49)	(49)	
Alveolar/bronchiolar adenoma				2 (4%)	
Alveolar/bronchiolar carcinoma		1 (2%)			
Carcinoma, metastatic, thyroid gland			1 (2%)		
Special Senses System					
Zymbal's gland				(2)	
Carcinoma				2 (100%)	
Urinary System					
Kidney	(50)	(50)	(50)	(50)	(1)
Nephroblastoma		1 (2%)			
Urinary bladder	(48)	(49)	(49)	(50)	
Sarcoma stromal, metastatic, uterus				1 (2%)	
Systemic Lesions					
Multiple organs[b]	(50)	(50)	(50)	(50)	(50)
Histiocytic sarcoma					1 (2%)
Leukemia mononuclear	14 (28%)	19 (38%)	29 (58%)	18 (36%)	15 (30%)
Neoplasm Summary					
Total animals with primary neoplasms[c]	49	49	45	38	43
Total primary neoplasms	101	93	80	67	80
Total animals with benign neoplasms	43	39	30	26	38
Total benign neoplasms	77	65	45	44	61
Total animals with malignant neoplasms	21	26	34	22	17
Total malignant neoplasms	24	28	35	23	19
Total animals with metastatic neoplasms	2		2	1	2
Total metastatic neoplasms	2		2	1	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 B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Oxazepam: 0 ppm

Number of Days on Study	223	228	252	259	550	569	771	783	597	613	641	647	690	696	697	700	701	718	729	730	730	730	730	730
Carcass ID Number	301	302	305	304	401	423	429	450	509	537	608	624	631	715	702	626	628	614	606	603	607	711	712	720
Alimentary System																								
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp adenomatous												X												
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	+	+	+	+	+	+	+	+	+	A	+	A	+	+	A	+	+	+	+	+	+	+	+
Intestine small, ileum	A	+	+	+	+	+	+	+	+	+	M	+	+	+	+	A	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery													+		+					+		+		+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																								
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																								
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																X								
Pheochromocytoma complex																					X			
Pheochromocytoma benign																								
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma				X			X	X		X	X			X	X	X	X	X		X	X	X		X
Pars distalis, adenoma, multiple																								
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma												X	X			X								
C-cell, carcinoma																				X				
Follicular cell, adenoma																								
Follicular cell, carcinoma											X													
General Body System																								
None																								
Genital System																								
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Adenoma												X					X							
Carcinoma																								
Bilateral, adenoma					X																			
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor benign																								
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal																								
Sarcoma stromal																								

+: 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 Oxazepam: 0 ppm (continued)

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	3 2 1	3 3 0	3 3 3	3 3 5	3 3 6	3 3 8	3 3 9	3 4 3	3 4 4	3 4 8	3 1 0	3 1 6	3 1 7	3 1 8	3 1 9	3 2 5	3 2 7	3 3 2	3 3 4	3 4 0	3 4 2	3 4 5	3 4 6	3 4 7	3 4 9	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp adenomatous																										1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
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
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																										1
Pheochromocytoma complex																										1
Pheochromocytoma benign																X										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																						X				1
Parathyroid gland	+	+	M	+	+	M	+	+	+	+	+	M	+	+	+	M	+	+	+	M	+	+	M	M	+	42
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X				X	X		X	X	X	X		X	X	X	X			X		X		X	X	X	30
Pars distalis, adenoma, multiple				X																						1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma					X											X				X						6
C-cell, carcinoma																										1
Follicular cell, adenoma												X														1
Follicular cell, carcinoma																										1
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma				X			X													X		X				6
Carcinoma																	X									1
Bilateral, adenoma																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa cell tumor benign													X													1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal																		X				X				2
Sarcoma stromal															X											1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Oxazepam: 0 ppm (continued)

Number of Days on Study	2 2 3	2 2 8	5 2 2	5 2 9	5 5 0	5 6 9	5 7 1	5 8 3	5 9 7	6 1 3	6 4 1	6 4 7	6 9 0	6 9 6	6 9 7	7 0 0	7 0 1	7 0 8	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0
Carcass ID Number	3 0 1	3 2 2	3 0 5	3 0 4	3 4 1	3 2 3	3 2 9	3 5 0	3 0 9	3 3 7	3 0 8	3 2 4	3 3 1	3 1 5	3 0 2	3 2 6	3 2 8	3 1 4	3 0 6	3 0 3	3 0 7	3 1 1	3 1 2	3 1 3	3 2 0
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node					+								+			+				+					
Deep cervical, carcinoma, metastatic, thyroid gland																				X					
Renal, pheochromocytoma malignant, metastatic, adrenal medulla																X									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma										X															
Carcinoma		X																							
Fibroadenoma								X				X			X						X				
Fibroadenoma, multiple				X										X					X			X			X
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma																X									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Oligodendroglioma malignant	X																								
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																	+								
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X			X							X		X					X	X	X	X		

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Oxazepam: 0 ppm (continued)

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	3 2 1	3 3 0	3 3 3	3 3 5	3 3 6	3 3 8	3 3 9	3 4 3	3 4 4	3 4 8	3 1 0	3 1 6	3 1 7	3 1 8	3 1 9	3 2 5	3 2 7	3 3 2	3 3 4	3 4 0	3 4 2	3 4 5	3 4 6	3 4 7	3 4 9	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																										4
Deep cervical, carcinoma, metastatic, thyroid gland																										1
Renal, pheochromocytoma malignant, metastatic, adrenal medulla																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																										1
Carcinoma														X												2
Fibroadenoma					X		X	X	X		X			X								X				11
Fibroadenoma, multiple		X	X			X				X			X			X	X	X	X							14
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Oligodendroglioma malignant																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye										+																2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	48
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear			X					X						X		X				X		X				14

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Oxazepam: 625 ppm

Number of Days on Study	2 8 8	4 0 0	4 7 5	4 7 8	5 5 0	5 9 0	6 0 6	6 1 2	6 3 1	6 3 3	6 3 4	6 4 7	6 5 4	6 6 6	6 6 9	6 9 7	7 0 8	7 1 5	7 1 7	7 1 8	7 1 8	7 1 8	7 1 8	7 2 8	7 2 9
Carcass ID Number	3 9 0	3 8 0	3 8 4	3 5 8	3 8 1	3 5 7	3 6 6	3 5 6	3 7 5	3 6 4	3 8 3	3 6 7	3 8 2	3 7 4	3 5 2	3 6 3	3 8 7	3 6 9	3 5 5	3 5 4	3 6 5	3 7 0	3 9 3	3 5 1	3 7 3
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery										+								+	+		+		+		
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue															+										
Squamous cell carcinoma															X										
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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		X	X	X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																									X
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma													X												
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal																					X	X			
Vagina										+															
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node						+												+							
Lymph node, mandibular	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Oxazepam: 625 ppm (continued)

Number of Days on Study	729	729	729	729	730	700	700	700	700	700	700	700	700	700	700	701	711	711	711	711	711	711	711	711	
Carcass ID Number	37 6	38 6	39 4	39 7	35 3	55 9	36 1	37 1	37 2	37 7	37 8	37 9	38 5	39 6	40 0	40 0	60	62	68	88	89	91	92	95	98	99	Total Tissues/ Tumors
Alimentary System																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery						+		+		+									+								9
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue																											1
Squamous cell carcinoma																											1
Cardiovascular System																											
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																											
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma			X																								1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																		X									3
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	M	M	+	+	+	+	M	M	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	38
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X		X	X	X			X	X	X		X	X		X	X	X		X	X		X	X	X	X		28
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma							X	X																			3
General Body System																											
None																											
Genital System																											
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma						X													X								3
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal							X												X								4
Vagina																											1
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																											2
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Oxazepam: 625 ppm (continued)

Number of Days on Study	2 8 8	4 0 0	4 7 5	4 7 8	5 5 0	5 9 0	6 0 6	6 1 2	6 3 1	6 3 3	6 3 4	6 4 7	6 5 4	6 6 6	6 6 9	6 9 7	7 0 8	7 1 5	7 1 7	7 1 8	7 1 8	7 1 8	7 1 8	7 2 8	7 2 9
Carcass ID Number	3 9 0	3 8 0	3 8 4	3 5 8	3 8 1	3 5 7	3 6 6	3 5 6	3 7 5	3 6 4	3 8 3	3 6 7	3 8 2	3 7 4	3 5 2	3 6 3	3 8 7	3 6 9	3 5 5	3 5 4	3 6 5	3 7 0	3 9 3	3 5 1	3 7 3
Integumentary System																									
Mammary gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																					X				
Carcinoma																X									
Fibroadenoma								X	X					X			X		X	X		X			X
Fibroadenoma, multiple												X									X				
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma																									
Fibrosarcoma																			X						
Sebaceous gland, adenoma														X											
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma benign																									
Peripheral nerve					+																				
Spinal cord					+																				
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma																						X			
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nephroblastoma	X																								
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 Oxazepam: 625 ppm (continued)

Number of Days on Study	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	37676	38686	39944	39977	35353	35959	36161	37171	37272	37773	37874	37979	38485	39696	40000	36060	36262	36868	38889	38991	39192	39595	39898	39999	Total Tissues/ Tumors	
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Adenoma																						X			2	
Carcinoma										X										X					3	
Fibroadenoma		X	X									X	X	X									X		14	
Fibroadenoma, multiple				X																				X	X	5
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell carcinoma																						X			1	
Fibrosarcoma								X																	2	
Sebaceous gland, adenoma																									1	
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Astrocytoma benign														X											1	
Peripheral nerve																									1	
Spinal cord																									1	
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Alveolar/bronchiolar carcinoma																									1	
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Special Senses System																										
Eye		+																							1	
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Nephroblastoma																									1	
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Leukemia mononuclear	X					X					X	X		X									X		19	

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

Number of Days on Study	4 1 4	4 3 2	4 5 3	5 0 6	5 3 9	5 4 0	5 5 0	5 5 6	5 6 5	5 7 8	5 8 3	5 8 5	5 8 9	5 9 7	5 9 7	6 1 1	6 3 2	6 3 3	6 3 4	6 4 6	6 5 2	6 6 9	6 9 2	6 9 7	7 0 0
Carcass ID Number	4 7 7	4 8 9	4 8 4	4 8 8	4 6 1	4 6 8	4 7 1	4 7 9	4 7 0	4 7 5	4 5 9	4 6 4	4 7 2	4 7 2	4 5 2	4 9 4	4 6 5	4 9 3	4 9 9	4 9 7	4 8 1	4 6 0	4 9 2	4 6 3	4 8 6	4 5 5
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	A	+	+	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
Intestine small, ileum	+	A	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery																									+	+
Pancreas	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																										
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	M	M	+	M	+	+	M	+	+	+	+	+	+	+	M	M	+	+	M	+	+	
Adenoma																										
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Pars distalis, adenoma				X				X		X	X		X	X	X				X		X				
Pars distalis, adenoma, multiple																										
Pars distalis, carcinoma																										
Thyroid gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	
C-cell, adenoma										X												X				
C-cell, carcinoma																										
Follicular cell, carcinoma													X													
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma									X		X															
Carcinoma																				X						
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal																										
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+					+		+							+	+				+						
Lymph node, mandibular	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

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

Number of Days on Study	7 0 0	7 0 1	7 0 3	7 0 3	7 2 8	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	4 8 2	4 7 3	4 7 6	4 9 8	4 8 5	4 5 8	4 6 9	4 8 3	4 9 5	5 0 0	4 5 1	4 5 7	4 6 2	4 6 6	4 6 7	4 7 4	4 7 8	4 8 7	4 9 1	5 1 3	4 5 4	4 5 6	4 8 0	4 9 0	4 9 6	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery							+																+			4
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma	X																									1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	+	+	+	+	+	+	+	M	M	+	+	M	+	+	+	+	+	+	M	+	+	+	+	M	38
Adenoma														X												1
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X	X		X			X		X	X				X	X	X			X				X			20
Pars distalis, adenoma, multiple																									X	1
Pars distalis, carcinoma													X													1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
C-cell, adenoma			X			X								X	X											6
C-cell, carcinoma										X																1
Follicular cell, carcinoma										X									X							3
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma						X																				3
Carcinoma																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal			X												X					X						3
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node			+						+										+							9
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	46

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

Number of Days on Study	4 1 4	4 3 2	4 5 3	5 0 6	5 3 9	5 4 0	5 5 0	5 5 6	5 6 5	5 7 8	5 8 3	5 8 5	5 8 9	5 9 7	5 9 7	6 1 1	6 3 2	6 3 3	6 3 4	6 4 6	6 5 2	6 6 9	6 9 2	6 9 7	7 0 0
Carcass ID Number	4 7 7	4 8 9	4 8 4	4 8 8	4 6 1	4 6 8	4 7 1	4 7 9	4 7 0	4 7 5	4 5 9	4 6 4	4 7 2	4 5 2	4 9 4	4 6 5	4 9 3	4 9 9	4 9 7	4 8 1	4 6 0	4 9 2	4 6 3	4 8 6	4 5 5
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma													X							X	X				
Fibroadenoma, multiple																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trichoepithelioma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pituitary gland																									
Respiratory System																									
Lung	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, thyroid gland																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
None																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X	X	X		X	X	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 Oxazepam: 2,500 ppm (continued)

Number of Days on Study	7 0 0	7 0 1	7 0 3	7 0 3	7 2 8	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	4 8 2	4 7 3	4 7 6	4 9 8	4 8 5	4 5 8	4 6 9	4 8 3	4 9 5	5 0 0	4 5 1	4 5 7	4 6 2	4 6 6	4 6 7	4 7 4	4 7 8	4 8 7	4 9 1	4 5 3	4 5 4	4 5 6	4 8 0	4 9 0	4 9 6	Total Tissues/ Tumors
Integumentary System																										
Mammary gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibroadenoma		X		X																	X			X	X	8
Fibroadenoma, multiple																							X			1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trichoepithelioma													X													1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, pituitary gland													X													1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, metastatic, thyroid gland										X																1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																										
None																										
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X		X	X	X	X	X		X					X			X						X	X		29

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Oxazepam: 5,000 ppm

Number of Days on Study	0 1 7	4 1 3	5 5 0	6 1 0 3	6 2 4	6 3 1	6 3 4	6 3 8	6 4 1	6 4 6	6 6 9	6 7 5	6 7 9	6 8 3	7 0 0	7 1 1	7 1 5	7 1 5	7 2 1	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	5 4 9	5 2 3	5 3 8	5 0 9	5 1 5	5 2 5	5 1 8	5 4 2	5 4 1	5 0 2	5 2 2	5 1 1	5 4 8	5 2 2	5 3 1	5 4 5	5 0 3	5 4 6	5 4 4	5 0 4	5 0 5	5 1 0	5 1 2	5 1 7	5 4 0
Alimentary System																									
Esophagus	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery											+								+				+		
Pancreas	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinus, adenoma																						X			
Salivary glands	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	+	M	M	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												
C-cell, carcinoma																		X							
Follicular cell, adenoma																									
Follicular cell, carcinoma																									
General Body System																									
Peritoneum										+															
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma													X			X							X		
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubulostromal adenoma																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal						X						X													
Sarcoma stromal							X																		
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node				+	+							+													
Lymph node, mandibular	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Oxazepam: 5,000 ppm (continued)

Number of Days on Study	729	730	300	300	300	300	300	300	300	300	300	301	311	311	311	311	311	311	311	311	311	311	311	311	311	
Carcass ID Number	54 7	51 9	52 6	52 7	52 8	53 3	53 4	53 5	53 7	53 9	54 3	50 1	00 6	00 7	00 8	01 3	11 4	11 6	12 0	12 1	12 4	22 9	23 0	33 6	55 0	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery														+								+	+			6
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Acinus, adenoma																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																								X		1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	+	+	+	+	+	M	+	+	+	M	M	+	M	+	M	M	M	+	M	+	+	+	+	+	33
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma			X								X					X									X	12
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell, adenoma											X															2
C-cell, carcinoma																										1
Follicular cell, adenoma							X															X				2
Follicular cell, carcinoma													X													1
General Body System																										
Peritoneum																										1
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma				X																						4
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tubulostromal adenoma																			X							1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal							X						X													4
Sarcoma stromal																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																										3
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Oxazepam: 5,000 ppm (continued)

Number of Days on Study	0 1 7	4 1 3	5 5 0	6 1 3	6 2 4	6 3 1	6 3 4	6 3 8	6 4 1	6 4 6	6 6 9	6 7 5	6 7 9	6 8 3	7 0 0	7 1 1	7 1 5	7 1 5	7 2 1	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	5 4 9	5 2 3	5 3 8	5 0 9	5 1 5	5 2 5	5 1 8	5 4 2	5 4 1	5 0 2	5 2 2	5 1 1	5 4 8	5 3 2	5 3 1	5 4 5	5 0 3	5 4 6	5 4 4	5 0 4	5 0 5	5 1 0	5 1 2	5 1 7	5 4 0
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma			X			X										X	X		X					X	
Fibroadenoma, multiple																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																									
Keratoacanthoma																	X								
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																								X	
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																						+			
Zymbal's gland																		+							
Carcinoma																		X							
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma stromal, metastatic, uterus							X																		
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				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 Oxazepam: 5,000 ppm (continued)

Number of Days on Study	729	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	54 7	51 9	52 6	52 7	52 8	53 3	53 4	53 5	53 7	53 9	54 3	00 1	00 6	00 7	00 8	01 3	11 4	11 6	12 0	12 1	12 4	12 9	13 0	13 6	15 0	Total Tissues/ Tumors
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroadenoma								X			X							X	X	X				X		12
Fibroadenoma, multiple		X																								1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroma						X																				1
Keratoacanthoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma																X										2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																										
Eye																										1
Zymbal's gland							+																			2
Carcinoma							X																			2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma stromal, metastatic, uterus																										1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X		X						X	X						X		X								18

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Oxazepam: 10,000 ppm (Stop-Exposure)

Number of Days on Study	4 7 8	5 0 6	5 6 2	5 6 2	5 6 2	5 7 0	5 8 5	5 9 9	6 0 4	6 0 9	6 0 9	6 4 6	6 6 2	6 6 9	6 6 9	6 9 7	6 9 9	7 0 3	7 1 4	7 1 5	7 1 6	7 1 8	7 1 9	7 2 5	7 2 5
Carcass ID Number	5 6 4	5 9 6	5 6 3	5 7 0	5 9 9	5 8 1	5 7 2	5 6 8	5 7 1	5 6 2	5 6 6	5 9 0	5 6 9	5 5 4	5 8 5	5 8 0	5 7 3	5 7 4	5 7 5	5 9 4	5 8 7	5 9 8	5 7 6	5 5 6	5 5 8
Alimentary System																									
Esophagus																									
Intestine small, duodenum	+	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum																									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+
Histiocytic sarcoma, metastatic, skin																									X
Mesentery			+			+		+										+						+	
Salivary glands																						+			
Myoepithelioma																						X			
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
None																									
Endocrine System																									
Adrenal cortex																+		+							
Adenoma																X									
Pituitary gland			+	+	+			+		+	+	+	+		+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma				X	X			X		X	X	X	X		X	X	X	X		X	X	X		X	
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, C-cell, adenoma			X																						
C-cell, adenoma																									
General Body System																									
None																									
Genital System																									
Clitoral gland															+							+	+		
Adenoma																						X	X		
Ovary						+												+							
Uterus							+										+		+						
Sarcoma stromal																									
Vagina														+											
Hematopoietic System																									
Lymph node							+			+															+
Lymph node, mandibular				+			+																		
Squamous cell carcinoma, metastatic, skin				X																					
Lymph node, mesenteric							+			+															
Spleen		+					+			+			+	+	+				+						+
Integumentary System																									
Mammary gland			+			+										+	+		+	+	+			+	+
Carcinoma, multiple			X																						
Fibroadenoma			X			X										X	X		X		X				X
Fibroadenoma, multiple																				X				X	
Skin				+					+									+	+				+		+
Fibroma																		X	X						
Squamous cell carcinoma				X																					
Subcutaneous tissue, histiocytic sarcoma																									X

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Oxazepam: 10,000 ppm (Stop-Exposure) (continued)

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	5 5 1	5 7 7	5 9 1	5 9 5	5 5 3	5 6 0	5 6 5	5 7 9	5 8 3	5 8 6	5 8 9	5 9 2	6 0 0	5 5 2	5 5 5	5 5 7	5 5 9	5 6 1	5 6 7	5 7 8	5 8 2	5 8 4	5 8 8	5 9 3	5 9 7	Total Tissues/ Tumors
Alimentary System																										
Esophagus																	+									1
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	47
Intestine small, jejunum	+																									1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma, metastatic, skin																										1
Mesentery	+	+					+					+	+	+		+					+					13
Salivary glands																										1
Myoepithelioma																										1
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cardiovascular System																										
None																										
Endocrine System																										
Adrenal cortex																										2
Adenoma																										1
Pituitary gland	+	+		+	+		+	+	+				+	+			+	+	+	+	+	+	+			35
Pars distalis, adenoma	X			X	X		X		X					X				X		X						23
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, C-cell, adenoma																				X						2
C-cell, adenoma			X	X																						2
General Body System																										
None																										
Genital System																										
Clitoral gland						+		+	+	+		+			+					+	+					11
Adenoma						X		X	X						X						X					7
Ovary							+							+												4
Uterus											+													+		5
Sarcoma stromal											X															1
Vagina																										1
Hematopoietic System																										
Lymph node																					+					4
Lymph node, mandibular																					+					3
Squamous cell carcinoma, metastatic, skin																										1
Lymph node, mesenteric																										2
Spleen						+				+											+	+				12
Integumentary System																										
Mammary gland			+	+	+	+		+	+				+	+					+	+	+	+	+		+	23
Carcinoma, multiple																										1
Fibroadenoma			X	X		X		X	X				X						X	X		X			X	17
Fibroadenoma, multiple					X									X							X		X			6
Skin																										6
Fibroma																										2
Squamous cell carcinoma																										1
Subcutaneous tissue, histiocytic sarcoma																										1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Oxazepam: 10,000 ppm (Stop-Exposure) (continued)

Number of Days on Study	4 7 8	5 0 6	5 6 2	5 6 2	5 6 2	5 7 0	5 8 5	5 9 9	6 0 4	6 0 9	6 0 9	6 4 6	6 6 2	6 6 9	6 6 9	6 9 7	6 9 9	7 0 3	7 1 4	7 1 5	7 1 6	7 1 8	7 1 9	7 2 5	7 2 5	
Carcass ID Number	5 6 4	5 9 6	5 6 3	5 7 0	5 9 9	5 8 1	5 7 2	5 6 8	5 7 1	5 6 2	5 6 6	5 9 0	5 6 9	5 5 4	5 8 5	5 8 0	5 7 3	5 7 4	5 7 5	5 9 4	5 8 7	5 9 8	5 7 6	5 5 6	5 5 8	
Musculoskeletal System																										
Bone									+																	
Nervous System																										
None																										
Respiratory System																										
None																										
Special Senses System																										
Eye																	+									
Urinary System																										
Kidney													+													
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Histiocytic sarcoma																									X	
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 Oxazepam: 10,000 ppm (Stop-Exposure) (continued)

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	5 5 1	5 7 7	5 9 1	5 9 5	5 5 3	5 6 0	5 6 5	5 7 9	5 8 3	5 8 6	5 8 9	5 9 2	6 0 0	5 5 2	5 5 5	5 5 7	5 5 9	5 6 1	5 6 7	5 7 8	5 8 2	5 8 4	5 8 8	5 9 3	5 9 7	Total Tissues/ Tumors
Musculoskeletal System																										
Bone																										1
Nervous System																										
None																										
Respiratory System																										
None																										
Special Senses System																										
Eye				+																						2
Urinary System																										
Kidney																										1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Leukemia mononuclear						X				X	X		X								X	X				15

TABLE B3a
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Feed Study of Oxazepam

	0 ppm	625 ppm	2,500 ppm	5,000 ppm
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate[a]	1/50 (2%)	3/50 (6%)	0/50 (0%)	1/50 (2%)
Adjusted rate[b]	3.1%	9.4%	0.0%	3.2%
Terminal rate[c]	1/32 (3%)	1/26 (4%)	0/20 (0%)	1/31 (3%)
First incidence (days)	729 (T)	550	—[e]	729 (T)
Life table test[d]	P = 0.326N	P = 0.258	P = 0.594N	P = 0.755
Logistic regression test[d]	P = 0.316N	P = 0.305	P = 0.594N	P = 0.755
Cochran-Armitage test[d]	P = 0.318N			
Fisher exact test[d]		P = 0.309	P = 0.500N	P = 0.753N
Adrenal Medulla: Benign, Complex, or Malignant Pheochromocytoma				
Overall rate	3/50 (6%)	3/50 (6%)	0/50 (0%)	1/50 (2%)
Adjusted rate	8.9%	9.4%	0.0%	3.2%
Terminal rate	2/32 (6%)	1/26 (4%)	0/20 (0%)	1/31 (3%)
First incidence (days)	700	550	—	729 (T)
Life table test	P = 0.127N	P = 0.596	P = 0.204N	P = 0.312N
Logistic regression test	P = 0.114N	P = 0.663N	P = 0.171N	P = 0.292N
Cochran-Armitage test	P = 0.114N			
Fisher exact test		P = 0.661N	P = 0.121N	P = 0.309N
Clitoral Gland: Adenoma				
Overall rate	7/49 (14%)	3/50 (6%)	3/50 (6%)	4/50 (8%)
Adjusted rate	19.4%	10.1%	9.6%	11.5%
Terminal rate	4/31 (13%)	2/26 (8%)	1/20 (5%)	2/31 (6%)
First incidence (days)	550	654	565	679
Life table test	P = 0.306N	P = 0.210N	P = 0.309N	P = 0.259N
Logistic regression test	P = 0.293N	P = 0.149N	P = 0.153N	P = 0.239N
Cochran-Armitage test	P = 0.297N			
Fisher exact test		P = 0.151N	P = 0.151N	P = 0.251N
Clitoral Gland: Adenoma or Carcinoma				
Overall rate	8/49 (16%)	3/50 (6%)	4/50 (8%)	4/50 (8%)
Adjusted rate	22.4%	10.1%	12.5%	11.5%
Terminal rate	5/31 (16%)	2/26 (8%)	1/20 (5%)	2/31 (6%)
First incidence (days)	550	654	565	679
Life table test	P = 0.253N	P = 0.145N	P = 0.360N	P = 0.179N
Logistic regression test	P = 0.237N	P = 0.093N	P = 0.174N	P = 0.157N
Cochran-Armitage test	P = 0.241N			
Fisher exact test		P = 0.094N	P = 0.168N	P = 0.168N
Mammary Gland: Fibroadenoma				
Overall rate	25/50 (50%)	19/50 (38%)	9/50 (18%)	13/50 (26%)
Adjusted rate	67.0%	52.8%	33.2%	35.1%
Terminal rate	20/32 (63%)	10/26 (38%)	4/20 (20%)	8/31 (26%)
First incidence (days)	529	612	589	550
Life table test	P = 0.010N	P = 0.363N	P = 0.039N	P = 0.017N
Logistic regression test	P = 0.003N	P = 0.152N	P = 0.003N	P = 0.007N
Cochran-Armitage test	P = 0.005N			
Fisher exact test		P = 0.157N	P < 0.001N	P = 0.011N

TABLE B3a
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Feed Study of Oxazepam (continued)

	0 ppm	625 ppm	2,500 ppm	5,000 ppm
Mammary Gland: Fibroadenoma or Adenoma				
Overall rate	26/50 (52%)	20/50 (40%)	9/50 (18%)	13/50 (26%)
Adjusted rate	67.8%	55.7%	33.2%	35.1%
Terminal rate	20/32 (63%)	11/26 (42%)	4/20 (20%)	8/31 (26%)
First incidence (days)	529	612	589	550
Life table test	P = 0.006N	P = 0.372N	P = 0.028N	P = 0.011N
Logistic regression test	P = 0.002N	P = 0.153N	P = 0.001N	P = 0.004N
Cochran-Armitage test	P = 0.002N			
Fisher exact test		P = 0.158N	P < 0.001N	P = 0.007N
Mammary Gland: Carcinoma				
Overall rate	2/50 (4%)	3/50 (6%)	0/50 (0%)	0/50 (0%)
Adjusted rate	5.1%	10.3%	0.0%	0.0%
Terminal rate	1/32 (3%)	2/26 (8%)	0/20 (0%)	0/31 (0%)
First incidence (days)	228	697	—	—
Life table test	P = 0.060N	P = 0.443	P = 0.288N	P = 0.243N
Logistic regression test	P = 0.048N	P = 0.483	P = 0.288N	P = 0.213N
Cochran-Armitage test	P = 0.051N			
Fisher exact test		P = 0.500	P = 0.247N	P = 0.247N
Mammary Gland: Adenoma or Carcinoma				
Overall rate	3/50 (6%)	5/50 (10%)	0/50 (0%)	0/50 (0%)
Adjusted rate	7.4%	16.8%	0.0%	0.0%
Terminal rate	1/32 (3%)	3/26 (12%)	0/20 (0%)	0/31 (0%)
First incidence (days)	228	697	—	—
Life table test	P = 0.018N	P = 0.305	P = 0.163N	P = 0.118N
Logistic regression test	P = 0.013N	P = 0.347	P = 0.130N	P = 0.109N
Cochran-Armitage test	P = 0.014N			
Fisher exact test		P = 0.357	P = 0.121N	P = 0.121N
Mammary Gland: Fibroadenoma, Adenoma, or Carcinoma				
Overall rate	27/50 (54%)	23/50 (46%)	9/50 (18%)	13/50 (26%)
Adjusted rate	68.4%	62.7%	33.2%	35.1%
Terminal rate	20/32 (63%)	13/26 (50%)	4/20 (20%)	8/31 (26%)
First incidence (days)	228	612	589	550
Life table test	P = 0.002N	P = 0.531N	P = 0.019N	P = 0.007N
Logistic regression test	P < 0.001N	P = 0.268N	P < 0.001N	P = 0.003N
Cochran-Armitage test	P < 0.001N			
Fisher exact test		P = 0.274N	P < 0.001N	P = 0.004N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	31/50 (62%)	28/50 (56%)	21/50 (42%)	12/50 (24%)
Adjusted rate	73.6%	79.6%	62.0%	31.8%
Terminal rate	21/32 (66%)	19/26 (73%)	9/20 (45%)	6/31 (19%)
First incidence (days)	529	475	506	646
Life table test	P < 0.001N	P = 0.479	P = 0.504N	P < 0.001N
Logistic regression test	P < 0.001N	P = 0.338N	P = 0.058N	P < 0.001N
Cochran-Armitage test	P < 0.001N			
Fisher exact test		P = 0.342N	P = 0.036N	P < 0.001N

TABLE B3a
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Feed Study of Oxazepam (continued)

	0 ppm	625 ppm	2,500 ppm	5,000 ppm
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma				
Overall rate	31/50 (62%)	28/50 (56%)	22/50 (44%)	12/50 (24%)
Adjusted rate	73.6%	79.6%	65.4%	31.8%
Terminal rate	21/32 (66%)	19/26 (73%)	10/20 (50%)	6/31 (19%)
First incidence (days)	529	475	506	646
Life table test	P < 0.001N	P = 0.479	P = 0.548	P < 0.001N
Logistic regression test	P < 0.001N	P = 0.338N	P = 0.089N	P < 0.001N
Cochran-Armitage test	P < 0.001N			
Fisher exact test		P = 0.342N	P = 0.054N	P < 0.001N
Thyroid Gland (C-cell): Adenoma				
Overall rate	6/50 (12%)	3/50 (6%)	6/48 (13%)	2/49 (4%)
Adjusted rate	16.5%	11.5%	23.4%	5.8%
Terminal rate	3/32 (9%)	3/26 (12%)	3/20 (15%)	1/31 (3%)
First incidence (days)	647	729 (T)	578	679
Life table test	P = 0.217N	P = 0.324N	P = 0.364	P = 0.147N
Logistic regression test	P = 0.199N	P = 0.247N	P = 0.519	P = 0.126N
Cochran-Armitage test	P = 0.215N			
Fisher exact test		P = 0.243N	P = 0.591	P = 0.141N
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rate	7/50 (14%)	3/50 (6%)	7/48 (15%)	3/49 (6%)
Adjusted rate	19.4%	11.5%	27.9%	8.5%
Terminal rate	4/32 (13%)	3/26 (12%)	4/20 (20%)	1/31 (3%)
First incidence (days)	647	729 (T)	578	679
Life table test	P = 0.286N	P = 0.232N	P = 0.324	P = 0.171N
Logistic regression test	P = 0.266N	P = 0.162N	P = 0.480	P = 0.096N
Cochran-Armitage test	P = 0.289N			
Fisher exact test		P = 0.159N	P = 0.581	P = 0.167N
Thyroid Gland (Follicular Cell): Carcinoma				
Overall rate	1/50 (2%)	0/50 (0%)	3/48 (6%)	1/49 (2%)
Adjusted rate	2.5%	0.0%	12.4%	3.2%
Terminal rate	0/32 (0%)	0/26 (0%)	2/20 (10%)	1/31 (3%)
First incidence (days)	641	—	589	729 (T)
Life table test	P = 0.410	P = 0.505N	P = 0.201	P = 0.758N
Logistic regression test	P = 0.395	P = 0.504N	P = 0.285	P = 0.759
Cochran-Armitage test	P = 0.391			
Fisher exact test		P = 0.500N	P = 0.293	P = 0.747
Thyroid Gland (Follicular Cell): Adenoma or Carcinoma				
Overall rate	2/50 (4%)	0/50 (0%)	3/48 (6%)	3/49 (6%)
Adjusted rate	5.5%	0.0%	12.4%	9.7%
Terminal rate	1/32 (3%)	0/26 (0%)	2/20 (10%)	3/31 (10%)
First incidence (days)	641	—	589	729 (T)
Life table test	P = 0.192	P = 0.265N	P = 0.344	P = 0.493
Logistic regression test	P = 0.185	P = 0.237N	P = 0.461	P = 0.517
Cochran-Armitage test	P = 0.170			
Fisher exact test		P = 0.247N	P = 0.480	P = 0.490

TABLE B3a
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Feed Study of Oxazepam (continued)

	0 ppm	625 ppm	2,500 ppm	5,000 ppm
Uterus: Stromal Polyp				
Overall rate	2/50 (4%)	4/50 (8%)	3/50 (6%)	4/50 (8%)
Adjusted rate	6.3%	13.6%	13.9%	10.9%
Terminal rate	2/32 (6%)	2/26 (8%)	2/20 (10%)	2/31 (6%)
First incidence (days)	729 (T)	718	703	631
Life table test	P = 0.373	P = 0.273	P = 0.302	P = 0.340
Logistic regression test	P = 0.378	P = 0.311	P = 0.349	P = 0.349
Cochran-Armitage test	P = 0.365			
Fisher exact test		P = 0.339	P = 0.500	P = 0.339
Uterus: Stromal Polyp or Stromal Sarcoma				
Overall rate	3/50 (6%)	4/50 (8%)	3/50 (6%)	5/50 (10%)
Adjusted rate	9.4%	13.6%	13.9%	12.9%
Terminal rate	3/32 (9%)	2/26 (8%)	2/20 (10%)	2/31 (6%)
First incidence (days)	729 (T)	718	703	631
Life table test	P = 0.338	P = 0.415	P = 0.443	P = 0.364
Logistic regression test	P = 0.340	P = 0.469	P = 0.497	P = 0.366
Cochran-Armitage test	P = 0.325			
Fisher exact test		P = 0.500	P = 0.661N	P = 0.357
All Organs: Mononuclear Cell Leukemia				
Overall rate	14/50 (28%)	19/50 (38%)	29/50 (58%)	18/50 (36%)
Adjusted rate	37.7%	46.9%	67.4%	43.8%
Terminal rate	10/32 (31%)	7/26 (27%)	7/20 (35%)	9/31 (29%)
First incidence (days)	522	400	414	613
Life table test	P = 0.281	P = 0.136	P < 0.001	P = 0.277
Logistic regression test	P = 0.214	P = 0.198	P = 0.003	P = 0.279
Cochran-Armitage test	P = 0.215			
Fisher exact test		P = 0.198	P = 0.002	P = 0.260
All Organs: Benign Neoplasms				
Overall rate	43/50 (86%)	39/50 (78%)	30/50 (60%)	26/50 (52%)
Adjusted rate	95.5%	95.0%	81.9%	66.1%
Terminal rate	30/32 (94%)	24/26 (92%)	14/20 (70%)	18/31 (58%)
First incidence (days)	529	475	506	550
Life table test	P = 0.002N	P = 0.446	P = 0.563	P = 0.003N
Logistic regression test	P < 0.001N	P = 0.174N	P = 0.007N	P < 0.001N
Cochran-Armitage test	P < 0.001N			
Fisher exact test		P = 0.218N	P = 0.003N	P < 0.001N
All Organs: Malignant Neoplasms				
Overall rate	21/50 (42%)	26/50 (52%)	34/50 (68%)	22/50 (44%)
Adjusted rate	51.1%	60.1%	76.4%	51.6%
Terminal rate	13/32 (41%)	10/26 (38%)	10/20 (50%)	11/31 (35%)
First incidence (days)	223	288	414	613
Life table test	P = 0.502	P = 0.146	P = 0.001	P = 0.498
Logistic regression test	P = 0.461	P = 0.205	P = 0.013	P = 0.496
Cochran-Armitage test	P = 0.477			
Fisher exact test		P = 0.212	P = 0.008	P = 0.500

TABLE B3a
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Feed Study of Oxazepam (continued)

	0 ppm	625 ppm	2,500 ppm	5,000 ppm
All Organs: Benign or Malignant Neoplasms				
Overall rate	49/50 (98%)	49/50 (98%)	45/50 (90%)	38/50 (76%)
Adjusted rate	100.0%	98.0%	90.0%	82.5%
Terminal rate	32/32 (100%)	25/26 (96%)	15/20 (75%)	23/31 (74%)
First incidence (days)	223	288	414	550
Life table test	P = 0.041N	P = 0.220	P = 0.085	P = 0.058N
Logistic regression test	P < 0.001N	P = 0.761N	P = 0.063N	P = 0.001N
Cochran-Armitage test	P < 0.001N			
Fisher exact test		P = 0.753N	P = 0.102N	P < 0.001N

(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, thyroid gland, and uterus; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated neoplasm incidence at the end of the study 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 exposed group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group

TABLE B3b
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Stop-Exposure Feed Study of Oxazepam

	0 ppm	10,000 ppm
Adrenal Medulla: Benign, Complex, or Malignant Pheochromocytoma		
Overall rate[a]	3/50 (6%)	0/0[d]
Adjusted rate[b]	8.9%	
Terminal rate[c]	2/32 (6%)	
First incidence (days)	700	
Clitoral Gland: Adenoma		
Overall rate	7/49 (14%)	7/11 (64%)[d]
Adjusted rate	19.4%	
Terminal rate	4/31 (13%)	
First incidence (days)	550	
Clitoral Gland: Adenoma or Carcinoma		
Overall rate	8/49 (16%)	7/11 (64%)[d]
Adjusted rate	22.4%	
Terminal rate	5/31 (16%)	
First incidence (days)	550	
Mammary Gland: Fibroadenoma		
Overall rate	25/50 (50%)	23/50 (46%)
Adjusted rate	67.0%	66.7%
Terminal rate	20/32 (63%)	14/25 (56%)
First incidence (days)	529	562
Life table test[e]		P = 0.394
Logistic regression test[e]		P = 0.428N
Fisher exact test[e]		P = 0.421N
Mammary Gland: Fibroadenoma or Adenoma		
Overall rate	26/50 (52%)	23/50 (46%)
Adjusted rate	67.8%	66.7%
Terminal rate	20/32 (63%)	14/25 (56%)
First incidence (days)	529	562
Life table test		P = 0.468
Logistic regression test		P = 0.340N
Fisher exact test		P = 0.345N
Mammary Gland: Adenoma or Carcinoma		
Overall rate	3/50 (6%)	1/50 (2%)
Adjusted rate	7.4%	2.1%
Terminal rate	1/32 (3%)	0/25 (0%)
First incidence (days)	228	562
Life table test		P = 0.327N
Logistic regression test		P = 0.466N
Fisher exact test		P = 0.309N
Mammary Gland: Fibroadenoma, Adenoma, or Carcinoma		
Overall rate	27/50 (54%)	23/50 (46%)
Adjusted rate	68.4%	66.7%
Terminal rate	20/32 (63%)	14/25 (56%)
First incidence (days)	228	562
Life table test		P = 0.542
Logistic regression test		P = 0.346N
Fisher exact test		P = 0.274N

TABLE B3b
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Stop-Exposure Feed Study of Oxazepam
(continued)

	0 ppm	10,000 ppm
Pituitary Gland (Pars Distalis): Adenoma		
Overall rate	31/50 (62%)	23/35 (66%)
Adjusted rate	73.6%	67.3%
Terminal rate	21/32 (66%)	8/16 (50%)
First incidence (days)	529	562
Life table test		P = 0.438
Logistic regression test		P = 0.507
Fisher exact test		P = 0.453
Thyroid Gland (C-cell): Adenoma		
Overall rate	6/50 (12%)	4/50 (8%)
Adjusted rate	16.5%	13.8%
Terminal rate	3/32 (9%)	3/25 (12%)
First incidence (days)	647	562
Life table test		P = 0.472N
Logistic regression test		P = 0.365N
Fisher exact test		P = 0.370N
Thyroid Gland (C-cell): Adenoma or Carcinoma		
Overall rate	7/50 (14%)	4/50 (8%)
Adjusted rate	19.4%	13.8%
Terminal rate	4/32 (13%)	3/25 (12%)
First incidence (days)	647	562
Life table test		P = 0.366N
Logistic regression test		P = 0.258N
Fisher exact test		P = 0.262N
Uterus: Stromal Polyp or Stromal Sarcoma		
Overall rate	3/50 (6%)	1/50 (2%)
Adjusted rate	9.4%	4.0%
Terminal rate	3/32 (9%)	1/25 (4%)
First incidence (days)	729 (T)	729 (T)
Life table test		P = 0.396N
Logistic regression test		P = 0.396N
Fisher exact test		P = 0.309N
All Organs: Mononuclear Cell Leukemia		
Overall rate	14/50 (28%)	15/50 (30%)
Adjusted rate	37.7%	40.5%
Terminal rate	10/32 (31%)	6/25 (24%)
First incidence (days)	522	506
Life table test		P = 0.336
Logistic regression test		P = 0.507
Fisher exact test		P = 0.500
All Organs: Benign Neoplasms		
Overall rate	43/50 (86%)	38/50 (76%)
Adjusted rate	95.5%	84.3%
Terminal rate	30/32 (94%)	18/25 (72%)
First incidence (days)	529	562
Life table test		P = 0.482
Logistic regression test		P = 0.092N
Fisher exact test		P = 0.154N

TABLE B3b
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Stop-Exposure Feed Study of Oxazepam
(continued)

	0 ppm	10,000 ppm
All Organs: Malignant Neoplasms		
Overall test	21/50 (42%)	17/50 (34%)
Adjusted rate	51.1%	43.0%
Terminal rate	13/32 (41%)	6/25 (24%)
First incidence (days)	223	506
Life table test		P = 0.460N
Logistic regression test		P = 0.293N
Fisher exact test		P = 0.268N
All Organs: Benign or Malignant Neoplasms		
Overall rate	49/50 (98%)	43/50 (86%)
Adjusted rate	100.0%	89.5%
Terminal rate	32/32 (100%)	20/25 (80%)
First incidence (days)	223	506
Life table test		P = 0.515
Logistic regression test		P = 0.030N
Fisher exact test		P = 0.030N

(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 at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Tissue was examined microscopically only when it was observed to be abnormal at necropsy; thus, statistical comparisons with the controls are not appropriate.
[e] Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and the 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 Fisher exact test compares directly the overall incidence rates. For all tests, a lower incidence in the exposed group is indicated by **N**.

TABLE B4a
Historical Incidence of Mammary Gland Neoplasms in Untreated Female F344/N Rats[a]

Study	Incidence in Controls				
	Fibroadenoma	Fibroadenoma or Adenoma	Carcinoma	Adenoma or Carcinoma	Fibroadenoma, Adenoma, or Carcinoma
Historical Incidence at Battelle Columbus Laboratories					
4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol)	29/50	31/50	1/50	3/50	32/50
5,5-Diphenylhydantoin	17/50	18/50	3/50	4/50	21/50
Ethylene Thiourea	13/50	13/50	0/50	0/50	13/50
Polybrominated Biphenyls (Firemaster FF-1®)	4/50	4/50	0/50	0/50	4/50
Manganese (II) Sulfate Monohydrate	19/50	19/50	0/50	0/50	19/50
Triamterene	19/50	22/50	0/50	4/50	22/50
Tricresyl Phosphate	15/51	18/51	0/51	3/51	18/51
Overall Historical Incidence					
Total	524/1,301 (40.3%)	540/1,301 (41.5%)	36/1,301 (2.8%)	60/1,301 (4.6%)	568/1,301 (43.7%)
Standard deviation	13.1%	13.2%	2.7%	3.2%	13.9%
Range	8%-58%	8%-62%	0%-8%	0%-10%	8%-64%

[a] Data as of 12 May 1995

TABLE B4b
Historical Incidence of Pituitary Gland (Pars Distalis) Neoplasms in Untreated Female 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)	27/49	0/49	27/49
5,5-Diphenylhydantoin	25/50	1/50	26/50
Ethylene Thiourea	24/50	0/50	24/50
Polybrominated Biphenyls (Firemaster FF-1®)	21/50	0/50	21/50
Manganese (II) Sulfate Monohydrate	23/50	0/50	23/50
Triamterene	21/50	0/50	21/50
Tricresyl Phosphate	30/51	0/51	30/51
Overall Historical Incidence			
Total	666/1,290 (51.6%)	14/1,290 (1.1%)	680/1,290 (52.7%)
Standard deviation	12.5%	1.4%	12.7%
Range	30%-74%	0%-4%	30%-76%

[a] Data as of 12 May 1995

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

	0 ppm	625 ppm	2,500 ppm	5,000 ppm	10,000 ppm (Stop-Exposure)
Disposition Summary					
Animals initially in study	50	50	50	50	50
Early deaths					
Accidental death	1				
Moribund	11	18	18	16	19
Natural deaths	6	6	12	3	6
Survivors					
Terminal sacrifice	32	26	20	31	25
Animals examined microscopically	50	50	50	50	50
Alimentary System					
Esophagus	(50)	(50)	(50)	(49)	(1)
Periesophageal tissue, necrosis					1 (100%)
Intestine large, colon	(50)	(48)	(49)	(50)	
Parasite metazoan	2 (4%)	2 (4%)	2 (4%)	2 (4%)	
Intestine large, rectum	(50)	(49)	(49)	(50)	
Cyst				1 (2%)	
Parasite metazoan	2 (4%)	2 (4%)	1 (2%)		
Intestine small, duodenum	(50)	(49)	(47)	(49)	(47)
Ulcer			2 (4%)		
Serosa, inflammation					1 (2%)
Intestine small, jejunum	(46)	(48)	(47)	(48)	(1)
Parasite metazoan			1 (2%)		
Ulcer					1 (100%)
Liver	(50)	(50)	(50)	(50)	(49)
Basophilic focus	44 (88%)	41 (82%)	28 (56%)	26 (52%)	16 (33%)
Clear cell focus	6 (12%)	3 (6%)	11 (22%)	22 (44%)	
Degeneration, cystic					2 (4%)
Degeneration, fatty	1 (2%)		2 (4%)		
Eosinophilic focus	17 (34%)	18 (36%)	4 (8%)	11 (22%)	11 (22%)
Hepatodiaphragmatic nodule	12 (24%)	2 (4%)	4 (8%)	5 (10%)	6 (12%)
Inflammation, granulomatous	1 (2%)		2 (4%)	3 (6%)	
Mixed cell focus	5 (10%)	15 (30%)	7 (14%)	3 (6%)	2 (4%)
Necrosis, focal				2 (4%)	1 (2%)
Centrilobular, atrophy	1 (2%)				
Centrilobular, necrosis			1 (2%)	2 (4%)	1 (2%)
Hepatocyte, centrilobular, hypertrophy			10 (20%)	31 (62%)	
Mesentery	(10)	(9)	(4)	(6)	(13)
Accessory spleen	1 (10%)				
Fat, necrosis	8 (80%)	9 (100%)	4 (100%)	6 (100%)	13 (100%)
Pancreas	(50)	(50)	(49)	(49)	
Acinus, atrophy	6 (12%)	6 (12%)	1 (2%)	8 (16%)	
Stomach, forestomach	(50)	(50)	(50)	(50)	(50)
Abscess			1 (2%)		
Erosion			2 (4%)		
Foreign body			2 (4%)		
Inflammation, chronic			3 (6%)		
Inflammation, chronic active	1 (2%)	5 (10%)	13 (26%)	3 (6%)	5 (10%)
Inflammation, granulomatous			1 (2%)	1 (2%)	
Ulcer	1 (2%)	2 (4%)	9 (18%)	6 (12%)	4 (8%)
Epithelium, hyperplasia	2 (4%)	6 (12%)	16 (32%)	5 (10%)	5 (10%)

[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 Oxazepam (continued)

	0 ppm	625 ppm	2,500 ppm	5,000 ppm	10,000 ppm (Stop-Exposure)
Alimentary System (continued)					
Stomach, glandular	(50)	(50)	(50)	(50)	(49)
Erosion		4 (8%)	7 (14%)	2 (4%)	
Inflammation, chronic active			1 (2%)		
Mineralization	1 (2%)		1 (2%)	2 (4%)	
Ulcer	2 (4%)	3 (6%)	5 (10%)		4 (8%)
Serosa, inflammation					1 (2%)
Cardiovascular System					
Blood vessel	(50)	(50)	(50)	(49)	
Aorta, mineralization				1 (2%)	
Heart	(50)	(50)	(49)	(49)	
Atrium, thrombosis		1 (2%)			
Myocardium, degeneration	32 (64%)	34 (68%)	35 (71%)	32 (65%)	
Myocardium, fibrosis, focal				2 (4%)	
Myocardium, mineralization				1 (2%)	
Pericardium, inflammation, chronic	1 (2%)				
Valve, inflammation, chronic			1 (2%)		
Endocrine System					
Adrenal cortex	(50)	(50)	(50)	(50)	(2)
Degeneration			1 (2%)		
Hemorrhage	1 (2%)				
Hyperplasia, diffuse				1 (2%)	
Hyperplasia, focal	9 (18%)	8 (16%)	5 (10%)	4 (8%)	
Hypertrophy, focal		2 (4%)		1 (2%)	
Pigmentation, hemosiderin	1 (2%)		1 (2%)		
Adrenal medulla	(50)	(50)	(50)	(50)	
Degeneration			1 (2%)		
Hyperplasia	8 (16%)	3 (6%)	1 (2%)	4 (8%)	
Islets, pancreatic	(50)	(50)	(49)	(49)	
Hyperplasia	2 (4%)	1 (2%)		1 (2%)	
Pituitary gland	(50)	(50)	(50)	(50)	(35)
Angiectasis				2 (4%)	
Cyst	1 (2%)				2 (6%)
Pars distalis, angiectasis		1 (2%)			
Pars distalis, cyst	5 (10%)	2 (4%)	1 (2%)	3 (6%)	2 (6%)
Pars distalis, degeneration, cystic			1 (2%)	3 (6%)	5 (14%)
Pars distalis, hyperplasia	4 (8%)	5 (10%)	3 (6%)	8 (16%)	1 (3%)
Pars distalis, vacuolization cytoplasmic, focal					1 (3%)
Thyroid gland	(50)	(50)	(48)	(49)	(50)
Ultimobranchial cyst				1 (2%)	
C-cell, hyperplasia	40 (80%)	43 (86%)	35 (73%)	42 (86%)	43 (86%)
Follicle, cyst		1 (2%)	2 (4%)	2 (4%)	1 (2%)
General Body System					
Peritoneum				(1)	
Inflammation, granulomatous				1 (100%)	

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of Oxazepam (continued)

	0 ppm	625 ppm	2,500 ppm	5,000 ppm	10,000 ppm (Stop-Exposure)
Genital System					
Clitoral gland	(49)	(50)	(50)	(50)	(11)
Cyst	1 (2%)				
Hyperplasia			1 (2%)		
Inflammation, chronic				1 (2%)	
Inflammation, chronic active		1 (2%)			
Inflammation, granulomatous			1 (2%)		
Inflammation, suppurative					1 (9%)
Duct, cyst	1 (2%)	4 (8%)	6 (12%)	2 (4%)	3 (27%)
Ovary	(50)	(50)	(50)	(50)	(4)
Cyst	5 (10%)	6 (12%)	5 (10%)	6 (12%)	4 (100%)
Uterus	(50)	(50)	(50)	(50)	(5)
Inflammation, chronic			1 (2%)		
Inflammation, suppurative					1 (20%)
Cervix, cyst	2 (4%)	1 (2%)	1 (2%)		1 (20%)
Cervix, inflammation, suppurative					1 (20%)
Cervix, myometrium, hyperplasia				2 (4%)	1 (20%)
Endometrium, hyperplasia, cystic	1 (2%)	1 (2%)	1 (2%)		
Hematopoietic System					
Bone marrow	(50)	(50)	(50)	(50)	
Necrosis		1 (2%)			
Lymph node	(4)	(2)	(9)	(3)	(4)
Lumbar, ectasia			1 (11%)		
Mediastinal, pigmentation, hemosiderin				1 (33%)	
Pancreatic, inflammation, granulomatous			1 (11%)		
Renal, ectasia	1 (25%)				
Lymph node, mandibular	(50)	(48)	(48)	(49)	(3)
Ectasia		1 (2%)			
Lymph node, mesenteric	(50)	(50)	(50)	(49)	(2)
Ectasia	1 (2%)				
Inflammation, acute	1 (2%)				
Spleen	(50)	(50)	(50)	(49)	(12)
Fibrosis		1 (2%)	2 (4%)	2 (4%)	2 (17%)
Hematopoietic cell proliferation	3 (6%)	2 (4%)	3 (6%)	1 (2%)	
Inflammation, granulomatous			1 (2%)	1 (2%)	1 (8%)
Pigmentation, hemosiderin	25 (50%)	27 (54%)	13 (26%)	22 (45%)	
Lymphoid follicle, atrophy				2 (4%)	
Integumentary System					
Mammary gland	(49)	(49)	(49)	(50)	(23)
Hyperplasia, cystic	2 (4%)	3 (6%)	1 (2%)	1 (2%)	1 (4%)
Metaplasia, squamous			1 (2%)		
Skin	(50)	(50)	(50)	(50)	(6)
Hyperkeratosis					1 (17%)
Ulcer			2 (4%)		
Subcutaneous tissue, edema		1 (2%)			
Subcutaneous tissue, inflammation, chronic	1 (2%)				
Subcutaneous tissue, inflammation, suppurative					1 (17%)

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of Oxazepam (continued)

	0 ppm	625 ppm	2,500 ppm	5,000 ppm	10,000 ppm (Stop-Exposure)
Musculoskeletal System					
Bone	(50)	(50)	(50)	(50)	(1)
Hyperostosis	1 (2%)		2 (4%)		
Inflammation, chronic					1 (100%)
Osteopetrosis			3 (6%)		
Cranium, hyperostosis, focal			1 (2%)		
Nervous System					
Brain	(50)	(50)	(50)	(50)	
Hydrocephalus	7 (14%)	12 (24%)	3 (6%)	3 (6%)	
Cerebellum, mineralization		1 (2%)			
Cerebrum, degeneration, focal			1 (2%)		
Hypothalamus, hemorrhage	2 (4%)	2 (4%)	1 (2%)		
Respiratory System					
Lung	(50)	(50)	(49)	(49)	
Congestion	1 (2%)				
Infiltration cellular, mast cell	1 (2%)				
Infiltration cellular, histiocyte				2 (4%)	
Inflammation, granulomatous	2 (4%)	2 (4%)	5 (10%)	8 (16%)	
Alveolar epithelium, hyperplasia	3 (6%)	4 (8%)	1 (2%)	3 (6%)	
Interstitium, inflammation, chronic	1 (2%)	2 (4%)		2 (4%)	
Serosa, inflammation, chronic	1 (2%)				
Nose	(50)	(50)	(50)	(50)	
Inflammation, suppurative	5 (10%)	2 (4%)	6 (12%)	4 (8%)	
Special Senses System					
Eye	(2)	(1)		(1)	(2)
Choroid, inflammation, chronic				1 (100%)	
Lens, cataract	2 (100%)	1 (100%)			2 (100%)
Urinary System					
Kidney	(50)	(50)	(50)	(50)	(1)
Inflammation, chronic active				1 (2%)	
Nephropathy	32 (64%)	43 (86%)	41 (82%)	48 (96%)	1 (100%)
Pigmentation, lipofuscin			2 (4%)		
Renal tubule, cyst		1 (2%)	1 (2%)	1 (2%)	
Renal tubule, vacuolization cytoplasmic				1 (2%)	
Urinary bladder	(48)	(49)	(49)	(50)	
Inflammation, chronic active				1 (2%)	
Transitional epithelium, hyperplasia	1 (2%)		1 (2%)		

APPENDIX C
GENETIC TOXICOLOGY

GENETIC TOXICOLOGY

SALMONELLA MUTAGENICITY TEST PROTOCOL

Testing was performed as reported by Zeiger *et al*. (1992). Oxazepam was sent to the laboratory as a coded aliquot from Radian Corporation (Austin, TX). Oxazepam was incubated with the *Salmonella typhimurium* tester strains TA97, TA98, TA100, TA102, and TA1535 either in buffer or S9 mix (metabolic activation enzymes and cofactors from Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver) for 20 minutes at 37° C. 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 at least three doses of oxazepam. The high dose was limited by solubility and toxicity.

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 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. No minimum percentage or fold increase is 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). Oxazepam was sent to the laboratory as a coded aliquot by Radian Corporation. Oxazepam 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 of at least three doses of oxazepam. The high dose was limited by toxicity. A single flask per dose was used, and tests yielding positive results were repeated.

Sister Chromatid Exchange Test: In the SCE test without S9, CHO cells were incubated for 26 hours with oxazepam in McCoy's 5A medium. Bromodeoxyuridine (BrdU) was added 2 hours after culture initiation. After 26 hours, the medium containing oxazepam 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 oxazepam, serum-free medium, and S9 for 2 hours. The medium was then removed and replaced with medium containing serum and BrdU and no oxazepam, 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 SCEs/cell from each dose level. Because significant chemical-induced cell cycle delay was seen at the 50 µg/mL dose without S9, 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 ($P \leq 0.05$) in the absence of any responses reaching 20% above background led to a call of equivocal.

Chromosomal Aberrations Test: In the Abs test without S9, cells were incubated in McCoy's 5A medium with oxazepam 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 oxazepam and S9 for 2 hours, after which the treatment medium was removed and the cells were incubated for 10 hours in fresh medium, with Colcemid present for the final 2 hours. Cells were harvested in the same manner as for the treatment without S9.

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 ($P \leq 0.015$) were considered weak evidence for a positive response; significant differences for two or more doses indicated the trial was positive. A positive trend test 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 PERIPHERAL BLOOD MICRONUCLEUS TEST PROTOCOL

A detailed discussion of this assay is presented in MacGregor *et al.* (1990). At the end of a 14-week study (NTP, 1993), peripheral blood samples were obtained from male and female $B6C3F_1$ mice from each dose group and smears were immediately prepared and fixed in absolute methanol. The methanol-fixed slides were stained with a chromatin-specific fluorescent dye mixture of Hoechst 33258/pyronin Y (MacGregor *et al.*, 1983), and coded. Slides were scanned to determine the frequency of micronuclei in 10,000 normochromatic erythrocytes (NCEs) in each of 10 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 NCEs was analyzed by a statistical software package that tested for increasing trend over dose groups with a one-tailed Cochran-Armitage trend test, followed by pairwise comparisions between each dosed group and the control group (Margolin *et al.*, 1990). 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 is considered positive if the trend test P value is less than or equal to 0.025 or if the P value for any single dose group is less than or equal to 0.025 divided by the number of dose groups. A final call of positive for micronucleus induction is preferably based on reproducibly positive trial (as noted above). Results of the 14-week studies were accepted without repeat tests because additional test data could not be obtained. Ultimately, the final call is determined by the scientific staff after considering the results of statistical analyses, the reproducibility of any effects observed, and the magnitude of those effects.

RESULTS

Oxazepam (3 to 3,333 µg/plate) did not induce mutations in *S. typhimurium* strains TA97, TA98, TA100, TA102, or TA1535 when tested in a preincubation protocol with or without Aroclor 1254-induced male

Sprague-Dawley rat or Syrian hamster liver S9 (Table C1). In cytogenetic tests with cultured CHO cells, oxazepam did not induce sister chromatid exchanges (Table C2) or chromosomal Abs (Table C3), with or without S9. Cell cycle delay was noted at the 50 μg/mL dose in the SCE test without S9; harvest time was extended to allow accumulation of sufficient second-division metaphase cells for analysis. Peripheral blood samples obtained from B6C3F_1 mice in a 14-week toxicity study were analyzed for frequency of micronucleated NCEs; no increase in frequencies of micronucleated NCEs was observed in any of the dose groups (Table C4).

TABLE C1
Mutagenicity of Oxazepam in *Salmonella typhimurium*[a]

Strain	Dose (µg/plate)	Revertants/plate[b] -S9	+ hamster S9 10%	+ hamster S9 30%	+ rat S9 10%	+ rat S9 30%
TA102						
	0	131 ± 2.6	213 ± 5.7	341 ± 23.3	197 ± 11.5	443 ± 24.8
	3	136 ± 5.7				
	10	128 ± 10.7				
	33	139 ± 1.8	223 ± 15.0	295 ± 8.1	216 ± 9.5	403 ± 17.1
	100	130 ± 8.3	196 ± 10.0	340 ± 24.6	208 ± 6.4	436 ± 38.4
	333	43 ± 3.9[c]	170 ± 2.7	358 ± 25.0	204 ± 14.3	413 ± 22.0
	1,000	155 ± 12.4	318 ± 1.3	166 ± 28.6	375 ± 19.9	
	1,666		103 ± 21.5[c]		102[c]	
	3,333		172 ± 1.2[c]		133 ± 17.3[c]	
Trial summary		Negative	Negative	Negative	Negative	Negative
Positive control[d]		676 ± 9.5	879 ± 17.9	2,127 ± 104.3	1,291 ± 49.3	1,104 ± 125.0
TA100						
	0	159 ± 8.0	146 ± 1.9	145 ± 8.1	161 ± 10.0	149 ± 2.5
	3	118 ± 4.6				
	10	128 ± 5.5	144 ± 2.3		160 ± 9.0	
	33	137 ± 14.0	159 ± 17.2	145 ± 9.1	157 ± 8.9	137 ± 7.4
	100	139 ± 8.9	137 ± 15.4	146 ± 2.1	156 ± 8.9	127 ± 1.2
	333	115 ± 9.7	141 ± 2.9	113 ± 8.7	133 ± 7.0	134 ± 4.8
	1,000	102 ± 5.8		93 ± 2.8	126 ± 2.5	134 ± 4.1
	1,666			100 ± 14.9	135 ± 13.2	
Trial summary		Negative	Negative	Negative	Negative	Negative
Positive control		316 ± 3.5	445 ± 11.7	462 ± 31.2	599 ± 23.1	244 ± 6.7
TA1535						
	0	20 ± 1.5	8 ± 0.9	12 ± 2.9	12 ± 1.7	14 ± 2.1
	3	20 ± 2.3				
	10	19 ± 1.5				
	33	19 ± 2.9	8 ± 3.0	10 ± 2.0	10 ± 2.0	14 ± 0.3
	100	15 ± 4.2	11 ± 2.0	11 ± 3.4	11 ± 1.5	15 ± 1.5
	333	18 ± 2.0	8 ± 1.0	9 ± 2.5	11 ± 0.6	15 ± 1.9
	1,000		9 ± 1.3	8 ± 0.3	9 ± 0.7	12 ± 2.7
	1,666		8 ± 1.2[e]		7 ± 1.5[e]	
	3,333			5 ± 0.7[e]		9 ± 0.6[e]
Trial summary		Negative	Negative	Negative	Negative	Negative
Positive control		332 ± 10.2	180 ± 18.4	340 ± 22.8	214 ± 27.7	206 ± 4.7

TABLE C1
Mutagenicity of Oxazepam in *Salmonella typhimurium* (continued)

Strain	Dose (µg/plate)	Revertants/plate -S9	+hamster S9 10%	+hamster S9 30%	+rat S9 10%	+rat S9 30%
TA97						
	0	184 ± 6.1	179 ± 3.0	164 ± 8.3	206 ± 1.5	209 ± 6.1
	3	193 ± 7.4				
	10	182 ± 2.6	163 ± 8.2		204 ± 4.2	
	33	180 ± 10.5	163 ± 5.0	183 ± 6.9	203 ± 0.9	191 ± 9.1
	100	160 ± 7.3	167 ± 9.0	187 ± 12.4	200 ± 3.1	150 ± 6.2
	333	148 ± 12.7	175 ± 11.0	174 ± 14.0	198 ± 3.0	162 ± 17.4
	1,000		172 ± 17.3	168 ± 9.1	168 ± 5.8	184 ± 16.8
	3,333			107 ± 5.7[c]		139 ± 11.2[c]
Trial summary		Negative	Negative	Negative	Negative	Negative
Positive control		403 ± 11.1	463 ± 15.8	368 ± 24.9	449 ± 10.1	454 ± 25.6
TA98						
	0	18 ± 2.3	28 ± 2.0	19 ± 0.9	19 ± 1.5	23 ± 1.2
	3	15 ± 2.2				
	10	16 ± 2.0				
	33	19 ± 2.3	18 ± 0.6	27 ± 4.3	24 ± 3.0	28 ± 2.2
	100	20 ± 0.7	21 ± 2.1	27 ± 4.1	22 ± 3.7	33 ± 2.6
	333	17 ± 1.7	20 ± 0.3	23 ± 3.3	23 ± 4.6	31 ± 4.7
	1,000		20 ± 2.3	34 ± 2.3	14 ± 0.7	23 ± 1.7
	1,666		17 ± 0.6[e]	27 ± 1.5	22 ± 3.5[e]	21 ± 2.3
Trial summary		Negative	Negative	Negative	Negative	Negative
Positive control		423 ± 27.7	523 ± 10.6	495 ± 21.7	202 ± 10.9	104 ± 5.9

[a] Study performed at SRI International. A detailed protocol is presented in Zeiger *et al.* (1992).
[b] Revertants are presented as mean ± standard error from three plates.
[c] Slight toxicity
[d] The positive controls in the absence of metabolic activation were sodium azide (TA100 and TA1535), 9-aminoacridine (TA97), 4-nitro-*o*-phenylenediamine (TA98), and mytomycin C (TA102). The positive control for metabolic activation with all strains was 2-aminoanthracene.
[e] Precipitate on plate

TABLE C2
Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by Oxazepam[a]

Compound	Dose (µg/mL)	Total Cells Scored	No. of Chromo-somes	No. of SCEs	SCEs/ Chromo-some	SCEs/ Cell	Hrs in BrdU	Relative Change of SCEs/ Chromosome[b] (%)
-S9								
Summary: Negative								
Dimethylsulfoxide		50	1,049	424	0.40	8.5	26.0	
		50	1,045	393	0.37	7.9	31.0[c]	
Mitomycin-C	0.001	50	1,048	579	0.55	11.6	26.0	46.91
	0.004	10	210	223	1.06	22.3	26.0	182.37
Oxazepam	5	50	1,048	448	0.42	9.0	26.0	13.67
	17	50	1,048	428	0.40	8.6	26.0	8.59
	50	50	1,048	449	0.42	9.0	31.0[c]	13.92
					P = 0.061[d]			
+ S9								
Summary: Negative								
Dimethylsulfoxide		50	1,046	402	0.38	8.0	26.0	
Cyclophosphamide	0.125	50	1,043	579	0.55	11.6	26.0	44.44
	0.500	10	209	205	0.98	20.5	26.0	155.22
Oxazepam	5	50	1,048	452	0.43	9.0	26.0	12.22
	17	50	1,050	460	0.43	9.2	26.0	13.99
	50	50	1,048	445	0.42	8.9	26.0	10.48
					P = 0.075			

[a] Study performed at Sitek Research Laboratories. A detailed description of the protocol is presented in 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 oxazepam induced a delay in the cell division cycle, harvest time was extended to maximize the number of second-division metaphase cells available for analysis.
[d] Significance of SCEs/chromosome tested by the linear regression trend test versus log of the dose

TABLE C3
Induction of Chromosomal Aberrations in Chinese Hamster Ovary Cells by Oxazepam[a]

-S9					+ S9				
Dose (µg/mL)	Total Cells Scored	No. of Abs	Abs/ Cell	Cells with Abs (%)	Dose (µg/mL)	Total Cells Scored	No. of Abs	Abs/ Cell	Cells with Abs (%)
Harvest time: 14.0 hours Summary: Negative					Harvest time: 12.0 hours Summary: Negative				
Dimethylsulfoxide					Dimethylsulfoxide				
	200	5	0.03	1.0		200	1	0.01	0.5
Mitomycin-C					Cyclophosphamide				
0.4	25	9	0.36	36.0	20	25	12	0.48	32.0
Oxazepam					Oxazepam				
25	200	1	0.01	0.5	43	200	0	0.00	0.0
54	200	3	0.02	1.0	93	200	3	0.02	1.5
116	200	0	0.00	0.0	200	200	2	0.01	1.0
				P = 0.842[b]					P = 0.135

[a] Study performed at Sitek Research Laboratories. A detailed description of the protocol is presented in 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 C4
Frequency of Micronuclei in Peripheral Blood Erythrocytes of Mice Following Treatment with Oxazepam by Feed for 14 Weeks[a]

	Dose (ppm)	Number of Mice with Erythrocytes Scored	Micronucleated NCE Cells[b] (%)
Male	0	10	0.082 ± 0.008
	625	10	0.081 ± 0.009
	1,250	10	0.078 ± 0.007
	2,500	10	0.085 ± 0.010
	5,000	10	0.074 ± 0.008
	10,000	10	0.069 ± 0.007
			P = 0.899[c]
Female	0	10	0.042 ± 0.006
	625	10	0.039 ± 0.005
	1,250	10	0.034 ± 0.007
	2,500	10	0.031 ± 0.005
	5,000	10	0.042 ± 0.005
	10,000	10	0.043 ± 0.007
			P = 0.194

[a] Study was performed at SRI International. NCE = normochromatic erythrocyte
[b] Mean ± standard error
[c] Significance of percent micronucleated cells tested by the one-tailed trend test (Margolin *et al*., 1990); significant at $P \leq 0.025$

APPENDIX D
CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

PROCUREMENT AND CHARACTERIZATION OF OXAZEPAM

Oxazepam was obtained from Roussel Corporation (Englewood Cliffs, NJ) in one lot (86017.01), which was used during the 2-year study. Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO). Reports on analyses performed in support of the oxazepam studies are on file at the National Institute of Environmental Health Sciences.

Initially, comparisons were made between samples from the two shipping containers of lot 86017.01. The samples were blended for 15 minutes before being analyzed by high-performance liquid chromatography (HPLC) using the following system: Hewlett-Packard RP-18 column using a solvent system consisting of A) water containing 1% glacial acetic acid and B) methanol containing 1% glacial acetic acid, with a solvent ratio of A:B (50:50), at a flow rate of 1 mL/minute. Detection was with ultraviolet light at 254 nm. Results indicated that the two subbatches were identical within the limits of experimental error.

The chemical, a white, powdered solid, was identified as oxazepam by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. All spectra were consistent with the literature spectra (Florey, 1974) of oxazepam. The infrared and nuclear magnetic resonance spectra are presented in Figures D1 and D2. The observed melting point of 204.5° C was consistent with a literature reference (*Merck Index*, 1989), although the sample decomposed upon heating.

The purity of oxazepam was determined by elemental analyses, Karl Fischer water analysis, functional group titration for phenol, thin-layer chromatography (TLC), and HPLC. Functional group titration was performed by dissolving a sample in dimethylformamide and titrating with 0.1 N tetrabutylammonium hydroxide. The titration was monitored potentiometrically with a glass indicating electrode and a calomel reference electrode containing methanolic 1 M tetrabutylammonium chloride. TLC was performed on Silica Gel 60 F-254 plates with two solvent systems: 1) chloroform:methanol (10:1) and 2) ethyl acetate: methanol:glacial acetic acid (80:20:10). Anthracene in methanol was used as an internal standard. Visualization was accomplished with ultraviolet light (254 and 366 nm) and a spray of 37% formaldehyde solution in concentrated sulfuric acid followed by heating for 5 to 10 minutes at 120° C. HPLC was performed with the system described in the subbatch comparison.

Elemental analyses for carbon, hydrogen, nitrogen, and chlorine were in agreement with the theoretical values for oxazepam. Karl Fischer water analysis indicated 0.026% ± 0.001% water. Functional group titration indicated a purity of 101.4% ± 0.5%. TLC analysis using system 1 indicated a major spot and one trace impurity; using system 2, a major spot was observed. HPLC resolved a major peak with no impurity peaks with areas 0.1% or greater relative to the major peak. Major peak comparison between this lot and a United States Pharmacopeia XXI (USP) oxazepam standard indicated a purity of 103% ± 1% for lot 86017.01 relative to the reference standard. The overall purity of lot 86017.01 was determined to be greater than 99%.

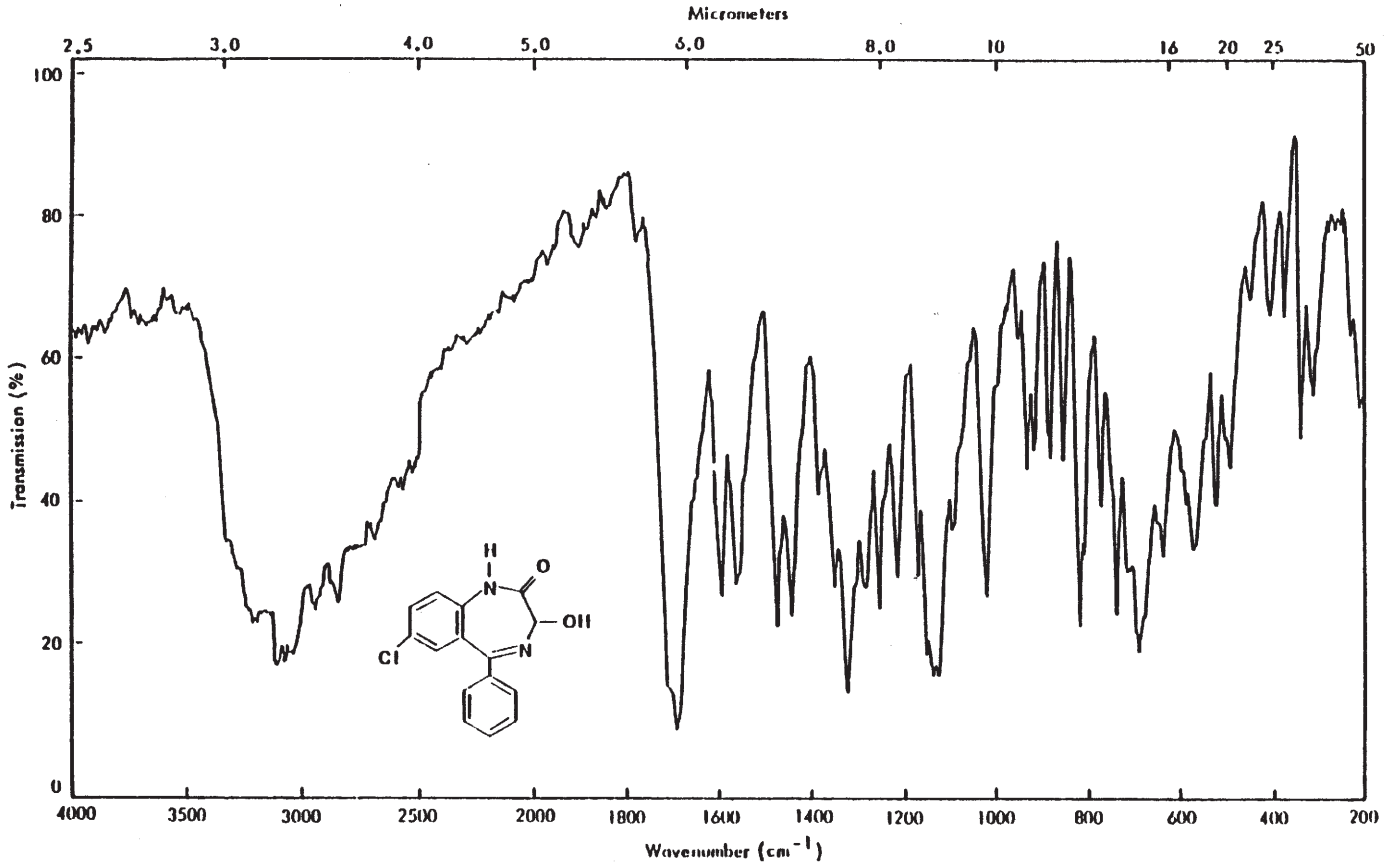
Accelerated stability studies of the bulk chemical were performed by the analytical chemistry laboratory. HPLC was performed using the system described above except with a solvent ratio of 35:65. These studies indicated that oxazepam was stable as a bulk chemical for 2 weeks when stored protected from light at temperatures up to 60° C. To ensure the stability during the 2-year study, the bulk chemical was stored at room temperature, protected from light, in metal cans or amber glass bottles. The stability of the bulk chemical was monitored periodically at the study laboratory with the HPLC system described above. No degradation of the bulk chemical was observed.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

The dose formulations were prepared every 2 weeks by mixing oxazepam with feed (Table D1). Mixtures were made by preparing an oxazepam/feed premix by hand and then blending the premix with feed in a Patterson-Kelly twin-shell blender for 15 minutes, using an intensifier bar for the initial 5 minutes. Formulations were stored in polyethylene bags inside polypropylene buckets at 5° C, protected from light, for up to 21 days.

Homogeneity and stability studies of a 500 ppm dose formulation were performed by the analytical chemistry laboratory. Samples were extracted with methanol, centrifuged, and mixed with internal standard solution (acetophenone in methanol). The samples were then mixed with additional methanol and further diluted with deionized water. HPLC was performed with a Burdick and Jackson C_{18} column with a mobile phase of water:methanol:glacial acetic acid (43:57:1) at a flow rate of 1 mL/minute and ultraviolet detection at 254 nm. Homogeneity was confirmed, and the dose formulation was determined to be stable for at least 3 weeks when stored protected from light at 5° C.

Periodic analyses of the dose formulations of oxazepam were conducted at the study laboratory using HPLC. Dose formulations were analyzed every 8 weeks during the study; animal room samples were analyzed initially and twice a year thereafter (Table D2). All 50 dose formulations were within 10% of the target concentrations; 89% (17/19) of the animal room samples analyzed were within 10% of the target concentrations. One animal room sample was 12% greater than the theoretical value; this was attributed to a difference between the standard curves for the dose formulation and animal room sample analyses.



Abscissa	Ordinate	Scan Time 6 minutes	Rep. Scan - Single Beam -
Expansion 1	Expansion 1	Response 1	Time Drive - Pre Sample Chop -
Suppression -	% T 0-100 ABS -	Slit Program N	Operator N.E. Cameron Date 10 12/87

Sample 8412-01 Oxazepam Lot No.: 86017.01 Batch No.: 01 Sub Batch: A Task: BS/CV-2063	Remarks Trimmer Comb in Reference Beam	Solvent -	Cell Path ~16% (w/w) in a Potassium Bromide disc
		Concentration ~16% (w/w)	Reference 415N

FIGURE D1
Infrared Absorption Spectrum of Oxazepam

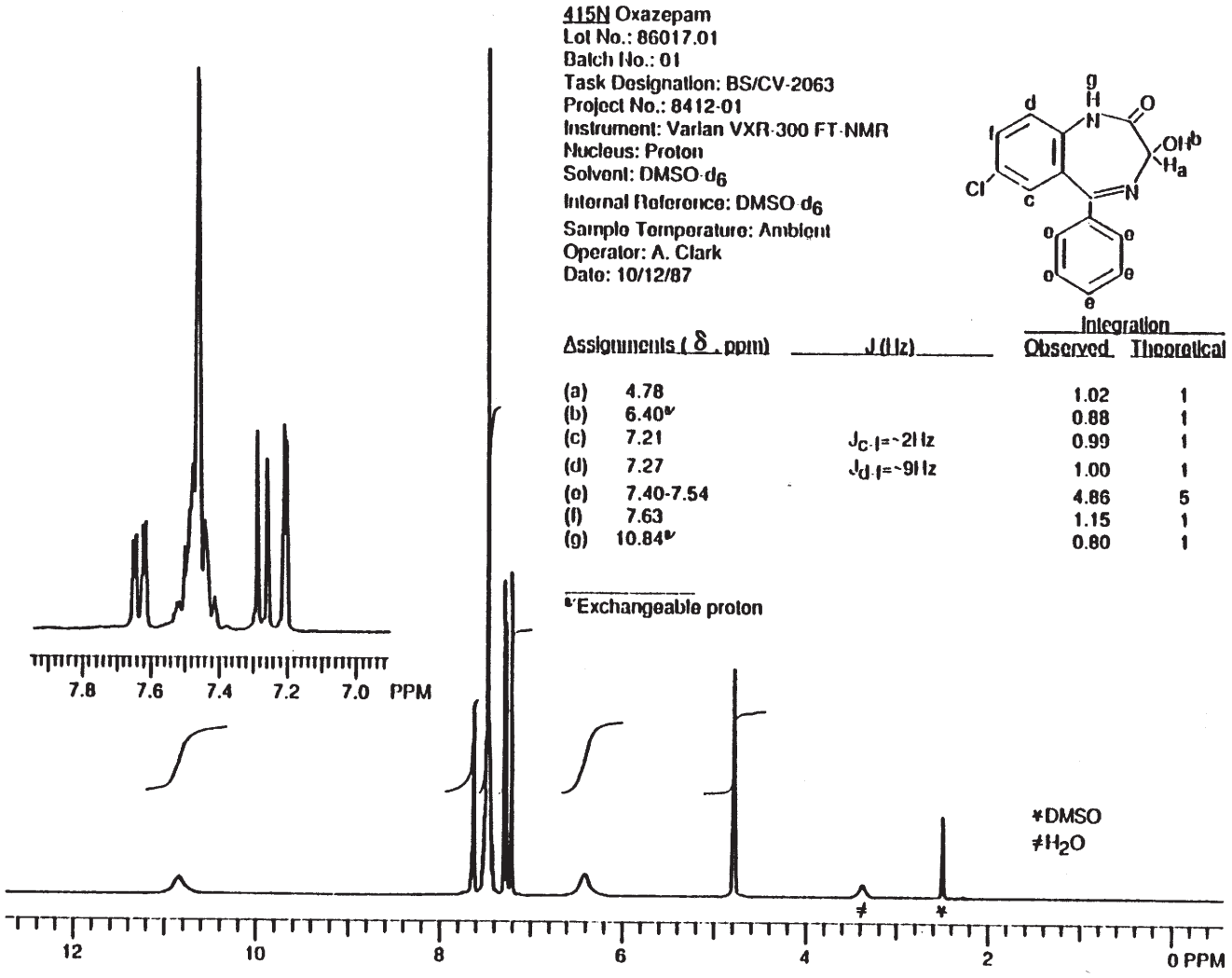


FIGURE D2
Nuclear Magnetic Resonance Spectrum of Oxazepam

TABLE D1
Preparation and Storage of Dose Formulations in the 2-Year Feed Study of Oxazepam

Preparation
A premix of feed and oxazepam was prepared, then layered with 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. Doses were prepared every 2 weeks.

Chemical Lot Number
86017.01

Maximum Storage Time
3 weeks

Storage Conditions
Stored in polyethylene bags inside polypropylene buckets, protected from light, at 5° C

Study Laboratory
Battelle Columbus Laboratories
(Columbus, OH)

TABLE D2
Analysis of Dose Formulations Administered to Rats in the 2-Year Feed Study of Oxazepam

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration[a] (ppm)	Difference from Target (%)
13 September 1991	19 September 1991	625	613	−2
		1,250	1,250	0
		2,500	2,550	+2
		5,000	4,980	0
		10,000	9,810	−2
	2 October 1991[b]	625	607	−3
		1,250	1,260	+1
		2,500	2,500	0
		5,000	4,700	−6
		10,000	10,100	+1
8 November 1991	11 November 1991	625	612	−2
		1,250	1,240	−1
		2,500	2,490	0
		5,000	4,940	−1
		10,000	9,900	−1
3 January 1992	7 January 1992	625	658	+5
		1,250	1,280	+2
		2,500	2,590	+4
		5,000	5,000	0
		10,000	10,100	+1
28 February 1992	28 February 1992	625	644	+3
		1,250	1,290	+3
		2,500	2,590	+4
		5,000	5,040	+1
		10,000	9,870	−1
	19 March 1992[b]	625	697	+12
		1,250	1,330	+6
		2,500	2,650	+6
		5,000	5,340	+7
		10,000	10,400	+4
24 April 1992	27 April 1992	625	627	0
		2,500	2,550	+2
		5,000	5,000	0
19 June 1992	23 June 1992	625	599	−4
		2,500	2,530	+1
		5,000	4,700	−6
14 August 1992	14-15 August 1992	625	604	−3
		2,500	2,500	0
		5,000	4,830	−3
	8-9 September 1992[b]	625	581	−7
		2,500	2,220	−11
		5,000	5,040	+1
9 October 1992	9-10 October 1992	625	603	−4
		2,500	2,440	−2
		5,000	4,860	−3

TABLE D2
Analysis of Dose Formulations Administered to Rats in the 2-Year Feed Study of Oxazepam (continued)

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration (ppm)	Difference from Target (%)
4 December 1992	5-8 December 1992	625	625	0
		2,500	2,750	+10
		5,000	4,870	−3
29 January 1993	29-30 January 1993	625	650	+4
		2,500	2,630	+5
		5,000	5,300	+6
	19 February 1993[b]	625	611	−2
		2,500	2,550	+2
		5,000	5,080	+2
26 March 1993	26-27 March 1993	625	617	−1
		2,500	2,490	0
		5,000	5,280	+6
21 May 1993	24-25 May 1993	625	654	+5
		2,500	2,650	+6
		5,000	5,360	+7
16 July 1993	16 July 1993	625	571	−9
		2,500	2,530	+1
		5,000	4,970	−1
	6 August 1993[b]	625	642	+3
		2,500	2,570	+3
		5,000	5,030	+1
13 September 1993	14 September 1993	625	605	−3
		2,500	2,500	0
		5,000	4,810	−4

[a] Results of duplicate analyses
[b] Animal room samples

APPENDIX E
FEED AND COMPOUND CONSUMPTION IN THE 2-YEAR FEED STUDIES OF OXAZEPAM

TABLE E1
Feed and Compound Consumption by Male Rats in the 2-Year Feed Study of Oxazepam

Week	0 ppm		625 ppm			2,500 ppm		
	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)
1	15.1	132	13.7	132	65	11.9	132	226
2	15.6	172	16.5	179	57	16.0	174	230
4	18.3	240	18.7	246	48	19.0	242	196
5	16.8	257	18.0	265	43	17.7	262	169
8	15.7	310	16.5	315	33	16.3	306	133
9	17.4	323	17.9	326	34	17.2	314	137
12	16.6	356	17.8	354	31	17.4	343	127
13	17.8	367	19.2	366	33	18.5	349	132
17	17.0	402	17.3	391	28	17.1	375	114
21	17.0	422	17.4	413	26	16.1	393	102
25	16.8	442	17.3	434	25	17.5	408	107
29	17.3	462	16.5	448	23	15.9	426	93
33	16.3	477	16.1	459	22	16.4	437	94
37	15.9	479	16.4	465	22	15.6	438	89
41	17.0	487	16.2	471	22	16.5	443	93
45	16.7	492	15.9	479	21	16.7	451	92
49	16.4	497	16.4	485	21	15.3	454	84
53	17.0	503	16.3	492	21	16.4	449	91
57	16.0	509	15.9	496	20	15.1	451	84
61	14.8	509	15.0	488	19	14.0	449	78
65	15.9	504	15.2	486	19	14.9	445	84
69	15.9	506	16.1	492	21	15.7	443	88
73	15.2	508	15.0	487	19	14.4	434	83
77	16.4	500	16.3	478	21	15.4	432	89
78	14.9	500	14.2	476	19	14.5	431	84
81	15.4	493	13.7	471	18	13.4	414	81
85	15.2	495	14.9	463	20	14.9	407	92
88	14.6	493	14.5	452	20	13.2	396	83
93	14.7	489	15.0	449	21	14.8	397	93
97	14.0	470	16.0	441	23	15.4	372	104
101	11.7	459	14.5	429	21	15.7	349	112
104	14.8	463	16.7	428	24	15.1	341	111
Mean for weeks								
1-13	16.7	270	17.3	273	43	16.7	265	169
14-52	16.7	462	16.6	449	23	16.3	425	97
53-104	15.1	493	15.3	468	20	14.9	414	90

TABLE E1
Feed and Compound Consumption by Male Rats in the 2-Year Feed Study of Oxazepam (continued)

Week	0 ppm		5,000 ppm			10,000 ppm		
	Feed (g/day)	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg)
1	15.1	132	10.8	132	409	10.4	132	791
2	15.6	172	15.3	168	456	14.8	164	901
4	18.3	240	19.1	238	400	19.3	232	833
5	16.8	257	17.5	254	346	17.5	247	711
8	15.7	310	17.3	294	294	16.1	284	568
9	17.4	323	18.6	304	307	17.1	290	591
12	16.6	356	16.7	331	253	16.9	322	524
13	17.8	367	18.8	338	277	18.1	323	561
17	17.0	402	16.5	355	233	17.4	344	506
21	17.0	422	18.0	375	240	17.3	358	485
25	16.8	442	16.3	386	212	16.7	366	457
29	17.3	462	16.5	400	207	16.0	361	
33	16.3	477	15.5	401	193	17.9	404	
37	15.9	479	15.6	401	194	17.3	424	
41	17.0	487	16.2	411	197	17.4	437	
45	16.7	492	17.7	420	211	16.6	449	
49	16.4	497	16.6	421	197	17.0	462	
53	17.0	503	16.6	420	198	17.3	467	
57	16.0	509	16.0	417	191	16.2	472	
61	14.8	509	15.1	403	187	15.6	473	
65	15.9	504	15.6	396	197	16.0	469	
69	15.9	506	16.2	388	209	15.6	469	
73	15.2	508	16.4	363	226	15.3	474	
77	16.4	500	14.9	358	207	16.2	469	
78	14.9	500	15.2	351	216	15.6	469	
81	15.4	493	14.3	334	214	14.7	458	
85	15.2	495	15.8	328	241	14.7	445	
88	14.6	493	14.3	313	229	12.6	425	
93	14.7	489	14.6	314	233	12.9	427	
97	14.0	470	16.8	333	252	14.5	403	
101	11.7	459	7.6	285	133			
104	14.8	463						
Mean for weeks								
1-13	16.7	270	16.8	258	343	16.3	249	685
14-52	16.7	462	16.5	397	209	17.1	401	482[c]
53-104	15.1	493	15.0	357	210	15.2	455	

[a] Grams of feed consumed per animal per day
[b] Milligrams of oxazepam consumed per kilogram body weight per day
[c] Mean for weeks 14-27

TABLE E2
Feed and Compound Consumption by Female Rats in the 2-Year Feed Study of Oxazepam

Week	0 ppm		625 ppm			2,500 ppm		
	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)
1	11.0	111	10.6	111	59	9.6	111	216
2	11.1	129	11.7	132	55	11.3	133	212
4	12.2	153	12.7	159	50	12.3	157	196
5	11.5	162	11.5	167	43	12.0	165	183
8	11.2	182	10.8	185	37	10.4	180	144
9	10.9	187	11.2	188	37	10.9	182	149
12	11.0	200	11.0	200	34	10.7	194	138
13	10.6	203	11.6	206	35	11.0	197	140
17	11.3	216	11.6	218	33	10.9	207	131
21	10.6	223	10.8	226	30	10.1	216	117
25	10.9	234	10.3	235	27	10.6	224	119
29	10.9	241	11.8	245	30	10.8	232	116
33	10.6	247	10.6	253	26	9.7	238	102
37	10.9	255	10.1	258	25	9.8	243	101
41	11.3	263	11.2	270	26	10.3	249	103
45	12.4	273	10.9	280	24	10.8	259	104
49	12.3	286	11.5	289	25	10.1	264	96
53	11.0	298	11.4	301	24	10.0	272	92
57	11.8	308	11.6	311	23	10.7	277	96
61	11.4	315	11.1	318	22	10.2	284	89
65	11.3	322	11.3	323	22	11.1	296	94
69	12.1	328	11.9	328	23	12.1	303	100
73	11.4	328	11.3	330	21	10.5	302	87
77	11.8	328	11.8	333	22	11.0	304	90
81	11.8	333	12.0	341	22	11.8	308	96
85	12.2	339	11.7	339	21	11.6	316	92
88	12.3	343	11.5	343	21	11.4	316	90
93	11.6	343	11.3	344	20	11.4	317	90
97	11.7	343	11.5	348	21	11.0	314	88
101	12.1	348	11.1	345	20	10.1	314	81
104	11.1	348	11.2	343	20	9.5	296	80
Mean for weeks								
1-13	11.2	166	11.4	169	44	11.0	165	172
14-52	11.2	249	11.0	253	27	10.3	237	110
53-104	11.7	330	11.5	332	22	10.9	301	90

TABLE E2
Feed and Compound Consumption by Female Rats in the 2-Year Feed Study of Oxazepam (continued)

Week	0 ppm		5,000 ppm			10,000 ppm		
	Feed (g/day)	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg)
1	11.0	111	8.9	111	400	8.1	111	730
2	11.1	129	11.9	134	444	11.8	133	886
4	12.2	153	11.9	158	376	12.4	156	793
5	11.5	162	11.0	164	333	11.4	162	707
8	11.2	182	10.6	177	300	11.1	175	636
9	10.9	187	11.1	182	306	10.9	177	612
12	11.0	200	10.7	191	281	10.8	187	578
13	10.6	203	10.7	192	279	10.8	188	576
17	11.3	216	10.6	203	262	10.8	197	548
21	10.6	223	10.1	208	242	10.2	202	504
25	10.9	234	10.0	216	232	9.5	208	459
29	10.9	241	10.3	225	229	10.5	198	
33	10.6	247	9.3	229	203	12.7	224	
37	10.9	255	9.6	235	204	10.8	235	
41	11.3	263	9.7	241	202	11.3	245	
45	12.4	273	11.1	251	221	12.0	255	
49	12.3	286	9.8	251	195	11.4	266	
53	11.0	298	9.4	256	184	11.5	277	
57	11.8	308	10.1	261	193	12.3	290	
61	11.4	315	9.6	265	181	12.0	304	
65	11.3	322	10.1	270	187	12.1	316	
69	12.1	328	11.1	278	199	12.2	323	
73	11.4	328	9.9	277	178	11.4	324	
77	11.8	328	11.8	285	207	11.9	330	
81	11.8	333	10.4	283	184	11.2	331	
85	12.2	339	10.7	288	186	11.7	336	
88	12.3	343	10.5	287	183	12.6	346	
93	11.6	343	10.5	282	186	11.5	352	
97	11.7	343	10.9	282	193	12.0	357	
101	12.1	348	10.5	285	183	10.3	356	
104	11.1	348	11.1	284	196	10.1	346	
Mean for weeks								
1-13	11.2	166	10.9	164	340	10.9	161	690
14-52	11.2	249	10.1	229	221	11.0	225	504[c]
53-104	11.7	330	10.5	277	189	11.6	328	

[a] Grams of feed consumed per animal per day
[b] Milligrams of oxazepam consumed per kilogram body weight per day
[c] Mean for weeks 14-27

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

TABLE F1
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 F2
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
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 F3
Nutrient Composition of NIH-07 Rat and Mouse Ration

Nutrient	Mean ± Standard Deviation	Range	Number of Samples
Protein (% by weight)	23.43 ± 0.51	22.3) 24.2	23
Crude fat (% by weight)	5.38 ± 0.19	5.10) 5.70	23
Crude fiber (% by weight)	3.25 ± 0.22	2.90) 3.80	23
Ash (% by weight)	6.53 ± 0.25	6.08) 7.03	23
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)	6,667 ± 553	5,940) 8,580	23
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)	17.35 ± 3.14	12.0) 25.0	23
Riboflavin (ppm)	7.83 ± 0.923	6.10) 9.00	11
Niacin (ppm)	99.22 ± 24.27	65.0) 150.0	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 (%)	1.17 ± 0.09	1.02) 1.32	23
Phosphorus (%)	0.92 ± 0.06	0.770) 1.00	23
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 F4
Contaminant Levels in NIH-07 Rat and Mouse Ration[a]

	Mean ± Standard Deviation[b]	Range	Number of Samples
Contaminants			
Arsenic (ppm)	0.57 ± 0.13	0.03) 0.80	23
Cadmium (ppm)	0.12 ± 0.08	0.04) 0.20	23
Lead (ppm)	0.30 ± 0.13	0.18) 0.70	23
Mercury (ppm)[c]	0.02	0.02) 0.03	23
Selenium (ppm)	0.36 ± 0.08	0.10) 0.40	23
Aflatoxins (ppm)	< 5.0		23
Nitrate nitrogen (ppm)[d]	6.43 ± 2.62	1.80) 11.0	23
Nitrite nitrogen (ppm)[d]	0.45 ± 0.64	0.02) 2.90	23
BHA (ppm)[e]	1.43 ± 1.88	1.00) 10.0	23
BHT (ppm)[e]	1.30 ± 0.88	1.0) 5.00	23
Aerobic plate count (CFU/g)	135,565 ± 173,947	10,000) 630,000	23
Coliform (MPN/g)	100 ± 244	3) 1,100	23
Escherichia coli (MPN/g)	< 3.0		23
Salmonella (MPN/g)	Negative		23
Total nitrosoamines (ppb)[f]	9.66 ± 4.73	4.80) 19.70	23
N-Nitrosodimethylamine (ppb)[f]	7.48 ± 4.38	3.40) 18.00	23
N-Nitrosopyrrolidine (ppb)[f]	2.21 ± 1.13	1.00) 5.80	23
Pesticides (ppm)			
α-BHC	< 0.01		23
β-BHC	< 0.02		23
γ-BHC	< 0.01		23
δ-BHC	< 0.01		23
Heptachlor	< 0.01		23
Aldrin	< 0.01		23
Heptachlor epoxide	< 0.01		23
DDE	< 0.01		23
DDD	< 0.01		23
DDT	< 0.01		23
HCB	< 0.01		23
Mirex	< 0.01		23
Methoxychlor	< 0.05		23
Dieldrin	< 0.01		23
Endrin	< 0.01		23
Telodrin	< 0.01		23
Chlordane	< 0.05		23
Toxaphene	< 0.10		23
Estimated PCBs	< 0.20		23
Ronnel	< 0.01		23
Ethion	< 0.02		23
Trithion	< 0.05		23
Diazinon	< 0.10		23
Methyl parathion	< 0.02		23
Ethyl parathion	< 0.02		23
Malathion	0.14 ± 0.16	0.05) 0.48	23
Endosulfan I	< 0.01		23
Endosulfan II	< 0.01		23
Endosulfan sulfate	< 0.03		23

[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] All but three values were less than detection limit; detection limit is used for the low end of the range.
[d] Sources of contamination: alfalfa, grains, and fish meal
[e] Sources of contamination: soy oil and fish meal
[f] All values were corrected for percent recovery.

APPENDIX G
SENTINEL ANIMAL PROGRAM

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 rodents is monitored via serology on sera from extra (sentinel) animals in the study rooms. These animals and the study animals are all 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 during the 2-year study. 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 the blood was collected during the studies are also listed.

Method and Test	Time of Analysis
2-Year Study	
ELISA	
Mycoplasma arthritidis	Study termination
Mycoplasma pulmonis	Study termination
PVM (pneumonia virus of mice)	6, 12, and 18 months, study termination
RCV/SDA (rat coronavirus/sialodacryoadenitis virus)	6, 12, and 18 months, study termination
Sendai	6, 12, and 18 months, study termination
Hemagglutination Inhibition	
H-1 (Toolan's H-1 virus)	6, 12, and 18 months, study termination
KRV (Kilham rat virus)	6, 12, and 18 months, study termination

RESULTS

Two rats had positive titers to *M. arthritidis* at study termination. Further evaluations of the serum positive for *M. arthritidis* by immunoblot and Western blot procedures indicated that the positive titers may have been due to 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, the *M. arthritidis*-positive titers were considered false positives.

APPENDIX H
EARLY RESPONSES OF F344/N RATS TO OXAZEPAM

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EARLY RESPONSES OF F344/N RATS TO OXAZEPAM

INTRODUCTION

Oxazepam and related benzodiazepine drugs are used in the treatment of anxiety. Most clinically useful drugs for this purpose are variants of the 1,4-benzodiazepine structure comprising two aromatic rings and a seven-membered heterocycle. One of the aromatic rings is fused to the seven-membered ring and contains a chloro-substituent or some other electronegative group. All clinically important derivatives contain a 5-aryl or 5-cyclohexenyl group. Most of the drugs vary in substituent groups at the 1 and 3 positions (*Goodman and Gilman's*, 1990). Oxazepam, known under the trade name Serax®, is produced and sold by Wyeth Laboratories and has been on the market since 1965.

Two million six hundred thousand prescriptions for oxazepam were written in the United States in 1983, and oxazepam ranked 132nd and 125th in overall frequency of prescriptions written for all drugs in 1984 and 1985, respectively (Anonymous, 1986; C. Baum correspondence, 1986). Oxazepam is also a common metabolite of several other benzodiazepines, some of which are more widely prescribed. These include diazepam (Valium®), for which 25.5 million prescriptions were written in 1983, making it the fourth most prescribed drug. The use of benzodiazepines in the general population in the United States has been reported to be as high as 7% (Pedersen and Lavik, 1991).

In NTP studies, oxazepam was not mutagenic in any of several strains of *Salmonella typhimurium*, nor did it induce sister chromatid exchanges or chromosomal aberrations in cultured Chinese hamster ovary cells with or without metabolic activation. However, Fox and Lahcen (1974) observed liver neoplasms in oxazepam-treated Swiss-Webster mice during the course of reproductive toxicity studies, and oxazepam caused increased incidences of liver neoplasms in male and female Swiss-Webster and $B6C3F_1$ mice in 2-year NTP feed studies (NTP, 1993). A 2-year feed study was subsequently started using F344/N rats. Because of the resemblance of the mouse results to those with other apparently nonnecrogenic and nongenotoxic liver carcinogens and the earlier observation that oxazepam was hepatocarcinogenic in both Swiss-Webster and $B6C3F_1$ mice, oxazepam was concurrently evaluated for clinical pathology and hepatocellular cell replication in a 13-week feed study with male F344/N rats. Exposure concentrations administered via feed were identical to those in the $B6C3F_1$ mouse study (Cunningham *et al.*, 1994a). Serum oxazepam levels were also evaluated for comparison to the previous mouse studies and to therapeutic human levels.

MATERIALS AND METHODS

Animals

Male Fisher 344/N rats (Charles River Breeding Laboratories, Raleigh, NC) weighing 150 g were fed a standard NIH 31 diet *ad libitum* and exposed to a daily cycle of alternating 12-hour periods of light and dark. The rats were acclimated to this environment for 2 weeks prior to the beginning of the study; animal rooms were maintained at 21° to 23° C and 40% to 60% relative humidity throughout the study. Rats were randomly assigned to exposure groups of 10 animals per group and allowed 7 days to adapt to a new cage environment and the powdered chow mixture (without oxazepam) described below. Experiments were performed according to the guidelines established in the NIH Guide for the Care and Use of Laboratory Animals. Animals were killed by CO_2 asphyxiation and exsanguination. Blood samples were allowed to clot for approximately 30 minutes at room temperature, after which they were centrifuged at 5,000 × g for 5 minutes. Serum was collected and immediately analyzed for activities or concentrations of the following: albumin, total protein, alkaline phosphatase, alanine aminotransferase, creatine kinase, sorbitol dehydrogenase, 5′-nucleotidase, total bile acids, creatinine, and total cholesterol. All analyses were performed using a Monarch 2000 chemistry analyzer (Instrumentation Laboratories, Lexington, MA). Except for total bile acids and 5′-nucleotidase, all assays were performed using reagent kits and standard applications developed for the analyzer by the manufacturer. Assays for total bile acids and 5′-nucleotidase

were developed for the analyzer using reagent kits obtained from Sigma Chemical Company (St. Louis, MO). Experimental effects for clinical chemistry measurements were identified by analysis of variance. Significant differences between animals in exposed and control groups were detected using Dunnett's multiple comparison test (Dunnett, 1955).

Chemical Exposure

Oxazepam was acquired from the National Toxicology Program repository from the lots used for the 2-year carcinogenicity studies. Dosed feed was prepared biweekly in 7-kg batches by Radian Corporation (Research Triangle Park, NC) by mixing ground feed and oxazepam in a Patterson-Kelly blender for 15 minutes with the intensifier bar in operation for the first 5 minutes. Aliquots were analyzed by high-performance liquid chromatography (HPLC) using acetophenone as the internal standard (details available upon request). Concentrations of oxazepam in feed were within 10% of target concentrations. Control animals received an identical powdered chow mixture with no oxazepam. Powdered chow was delivered to rats in stainless steel hanging feeders covered with wire mesh to prevent feed scattering. Estimations of feed consumption were performed weekly.

Cell Proliferation Measurements

Seven days before the end of the study, osmotic minipumps (Model 2002, Alza Corporation, Palo Alto, CA) were implanted subcutaneously into the backs of the rats. These minipumps delivered 30 mg bromodeoxyuridine (BrdU) (Sigma Chemical Co.) per hour, which was incorporated into the DNA of newly replicating cells. At the end of the study, animals were killed by CO_2 inhalation, and blood was collected for clinical chemistry measurements and analysis of oxazepam levels. Livers and kidneys were blotted and weighed. A mid-lobe radial section of the right anterior lobe was fixed in neutral buffered formalin for 24 hours. A cross section of small intestine was also fixed as a positive control for the proper operation of the minipump and the staining technique because these cells are constantly in S phase. Tissues were embedded in paraffin, and serial sections were mounted onto slides coated with poly-l-lysine. Following deparaffination and rehydration, one set of slides was stained with hematoxylin and eosin for histological analysis, and another set was stained immunohistochemically for BrdU incorporation as described previously (Cunningham and Matthews, 1991; Cunningham *et al.*, 1991, 1994a, 1994b). Slides were treated with 2 N HCl for 30 minutes at 37 °C to allow the DNA to become single stranded. The acid treatment was quenched with boric acid buffer (pH 7.6) for 1 minute at room temperature, followed by digestion in 0.01% trypsin (Sigma Chemical Co.) and rinsed in PBT [phosphate buffer, pH 7.2, containing 1% bovine serum albumin (Sigma Chemical Co.), 0.05% Tween 20 (Bio-Rad, Richmond, CA) and 7.2% NaCl]. Nonspecific antibody binding was eliminated by blocking (20 minutes) with normal horse serum (1:20) (Vector Laboratories, Inc., Burlington, CA). Following a PBT wash, the slides were incubated with a 1:50 dilution of mouse monoclonal antibody to BrdU (Becton Dickenson, Mountain View, CA) for 20 minutes at room temperature. Following two PBT washes, the slides were incubated with a 1:100 dilution of a biotinylated horse anti-mouse antibody (Vector Laboratories, Inc.; rat absorbed) for 20 minutes at room temperature and visualized with the avidin biotin peroxidase complex (ABC) method using a Vectastain peroxidase standard kit (Vector Laboratories, Inc.). Nuclei binding the ABC reagent (labeled nuclei) were stained for 6 minutes with 3,3′-diaminobenzidine (Sigma Chemical Co.) to give a dark brown color, and nonlabeled nuclei were stained with hematoxylin to yield a blue color. Random areas of the slides were chosen for counting stained and unstained hepatocyte nuclei (> 1,000 hepatocytes/rat). Statistics were performed using Student's *t*-test.

Serum Oxazepam Analysis

Frozen serum was allowed to thaw, and 0.1 mL aliquots were made basic with 10 µL 0.1 M NaOH. Parent oxazepam was extracted from the aqueous layer with 1 mL ethyl acetate followed by centrifugation (1,500 rpm for 5 minutes). The organic layer containing the oxazepam was removed and evaporated to dryness under nitrogen. Samples were reconstituted in 100 µL 0.05 M 60% methanol:40% phosphate buffer; pH 2.8). Samples were analyzed for oxazepam by HPLC (Waters Associates, Milford, MA); the system consisted of two Model 510 HPLC pumps, a 712 WISP multiple sample injector, a

490E multiwavelength detector at 230 nm, and a C_{18} column. Samples were run isocratically at 0.8 mL/minute in a methanol:phosphate buffer (60:40) carrier. Serum oxazepam was quantitated against an oxazepam standard curve created with spiked serum standards.

RESULTS

All rats survived to the end of the study, although oxazepam had a sedative effect on the rats in the 5,000 ppm groups. Rats in the 2,500 and 5,000 ppm groups consumed significantly less feed than did controls at the 15-, 30-, and 45-day intervals (Table H1). Other sporadic differences in feed consumption were also noted. Animals in the 2,500 and 5,000 ppm groups were observed to be sluggish for the first 2 to 4 weeks, but activity levels appeared normal thereafter. On day 15, the final mean body weights and body weight gains of the 2,500 and 5,000 ppm groups were significantly less than those of the control group, but were similar on day 30. The mean body weight gains of the 5,000 ppm group were less than those of the control group on days 45 and 90 as was that of 2,500 ppm rats on day 90 (Table H1).

The amount of hepatocellular proliferation was examined in relation to the amount of oxazepam consumed and the relative increase in liver weight over the course of this study. Male rats exposed to 2,500 or 5,000 ppm oxazepam exhibited a significant increase in the rate of hepatocyte cell proliferation as determined by BrdU incorporation as well as by PCNA staining at the 15-day time point (Table H2). By day 15, BrdU labeling indices in these groups were approximately three- to five-fold the untreated control indices, respectively. Both labeling indices in these groups were also significantly elevated compared to those of the controls on day 30, but this increase more likely reflects the variably lowered control labeling observed for both BrdU labeling and PCNA labeling. Labeling indices of all exposed groups were similar to those of the controls for both BrdU and PCNA at the 45- and 90-day time points.

Liver weight/body weight ratios in the 2,500 and 5,000 ppm groups were significantly greater than the control value at all time points (Table H2). Liver weight/body weight ratios in the 25 and 125 ppm groups were slightly elevated only at the 45-day time point. Rats exposed to 5,000 ppm oxazepam received approximately 19,000 mg oxazepam/kg body weight over 90 days.

Slight variations in serum activities of alanine aminotransferase, alkaline phosphatase, and 5′-nucleotidase were observed in the serum of rats exposed to 2,500 or 5,000 ppm oxazepam at various time points (Table H3). Other mild but statistically significant changes included decreases in cholesterol concentrations in the 2,500 and 5,000 ppm groups on days 30 and 90 and in the 5,000 ppm group on day 45, and an increase in bile acid concentration in the 5,000 ppm group on day 30. Increases in albumin concentrations occurred in 5,000 ppm rats on days 30 and 45 and in 2,500 and 5,000 ppm rats on day 90. Mild, statistically significant decreases in activities of sorbitol dehydrogenase and creatinine occurred in exposed groups. None of these changes was considered to have biological importance.

Histopathologic evaluation of hematoxylin- and eosin-stained slides revealed little histologic evidence of cytotoxicity or hepatocyte degeneration and no generalized or periportal inflammation. The major histological feature of rats exposed to oxazepam was hypertrophy, characterized by enlarged hepatocytes with pale pink, nonvacuolated cytoplasm. In the 25 and 125 ppm groups, hypertrophy was centrilobular, was consistent with proliferation of smooth endoplasmic reticulum, and encompassed hepatocytes two to six cells deep emanating from the central vein. At 2,500 and 5,000 ppm, hypertrophy became more extensive, and the area of enlargement of hepatocytes included the periportal region. Although the largest

hepatocytes were usually found around the central vein, all hepatocytes in rats exposed to 2,500 or 5,000 ppm were markedly enlarged and pale, causing generalized occlusion of sinusoids.

Serum oxazepam concentrations increased as a function of exposure concentration in all groups (Table H4). The highest serum oxazepam concentration, approximately 3.63 µg/mL, occurred in the 5,000 ppm group on day 90. Serum oxazepam concentrations appeared unstable between 15 and 90 days in the 2,500 and 5,000 ppm groups, dropping after 15 days and returning to high concentrations by 90 days. This was apparently due to the induction of drug metabolizing (Phase I) and conjugating enzymes (Phase II), with a concomitant increase in total body clearance of oxazepam (Griffin and Burka, 1995). The serum oxazepam concentrations observed in rats are approximately 10% of those attained in mice exposed for the same amount of time to the same exposure concentrations in earlier studies (Cunningham *et al.*, 1994a).

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TABLE H1
Survival, Body Weights, and Feed Consumption of Male F344/N Rats Administered Oxazepam in Feed for 90 Days

Concentration (ppm)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)	Feed Consumption[c]
		Initial	Final	Change		
15 Days						
0	10/10	201 ± 6	247 ± 10	46 ± 7		14.1
25	10/10	200 ± 5	243 ± 6	43 ± 4	93	12.8*
125	10/10	201 ± 5	246 ± 7	45 ± 4	98	13.2
2,500	10/10	196 ± 6	235 ± 8**	38 ± 10*	83	11.7*
5,000	10/10	203 ± 6	233 ± 12*	32 ± 8**	70	9.8*
30 Days						
0	10/10	198 ± 6	278 ± 9	79 ± 6		15.2
25	10/10	200 ± 5	287 ± 7*	87 ± 5	110	14.3**
125	10/10	200 ± 6	280 ± 7	80 ± 7	101	13.9**
2,500	10/10	197 ± 7	276 ± 11	79 ± 9	100	13.4**
5,000	10/10	192 ± 8	265 ± 17	74 ± 13	94	12.6**
45 Days						
0	10/10	199 ± 7	299 ± 13	100 ± 11		14.4
25	10/10	202 ± 9	310 ± 11	108 ± 5	108	14.6
125	10/10	198 ± 6	307 ± 14	110 ± 12	110	14.2
2,500	10/10	195 ± 7	292 ± 16	98 ± 16	98	13.2*
5,000	10/10	198 ± 6	286 ± 9	87 ± 10**	87	12.9*
90 Days						
0	10/10	197 ± 7	337 ± 20	140 ± 19		13.4
25	10/10	199 ± 6	340 ± 13	142 ± 11	101	13.4
125	10/10	194 ± 6	341 ± 13	146 ± 14	104	14.1*
2,500	10/10	211 ± 8	334 ± 18	123 ± 14*	88	14.1*
5,000	10/10	212 ± 10	317 ± 34	105 ± 28**	75	13.7*

* Significantly different ($P \leq 0.05$) from the control group by Dunnett's test
** $P \leq 0.02$
[a] Number of animals surviving/number initially in group
[b] Weights and weight changes are given as mean ± standard deviation.
[c] Feed consumption is given as grams consumed per animal per day.

TABLE H2
BrdU and Proliferating Cell Nuclear Antigen Labeling Indices, Liver Weight/Body Weight Ratios, and Total Body Burden of Male F344/N Rats Administered Oxazepam in Feed for 90 Days[a]

Concentration (ppm)	Number of Rats	BrdU Labeling Index[b]	Fold Increase Over Control	PCNA Labeling Index	Fold Increase Over Control	Liver Weight/ Body Weight (%)	Total Cumulative Dose[c] (mg/kg)
15 Days							
0	10	3.18 ± 1.3		0.5 ± 0.3		4.0 ± 0.2	
25	10	1.42 ± 0.7	0.45	0.4 ± 0.2	0.8	3.9 ± 0.1	19
125	10	1.94 ± 0.2	0.61	0.2 ± 0.1	0.4	3.9 ± 0.2	101
2,500	10	11.1 ± 7.3*	3.49	1.2 ± 0.7*	2.4	4.9 ± 0.2**	1,868
5,000	10	16.7 ± 7.7**	5.25	1.2 ± 0.5*	2.4	5.6 ± 0.3**	3,155
30 Days							
0	10	0.4 ± 0.2		0.1 ± 0.1		3.7 ± 0.2	
25	10	0.5 ± 0.3	1.25	0.3 ± 0.3	3.0	3.9 ± 0.2	37
125	10	0.5 ± 0.2	1.25	0.3 ± 0.2*	3.0	3.8 ± 0.2	186
2,500	10	1.4 ± 1.4*	3.50	0.6 ± 0.3*	6.0	4.9 ± 0.3**	3,641
5,000	10	3.7 ± 1.8**	9.25	0.6 ± 0.4*	6.0	5.5 ± 0.2**	7,105
45 Days							
0	10	2.6 ± 0.7		0.8 ± 0.4		3.5 ± 0.2	
25	10	1.0 ± 0.7	2.60	0.4 ± 0.3	0.5	3.8 ± 0.1**	53
125	10	1.6 ± 1.7	0.62	0.7 ± 0.4	0.9	3.9 ± 0.2**	260
2,500	10	3.3 ± 1.4	1.27	0.3 ± 0.2	0.4	4.7 ± 0.2**	5,086
5,000	10	3.4 ± 1.2	1.31	0.3 ± 0.2	0.4	5.5 ± 0.2**	10,150
90 Days							
0	10	1.4 ± 0.3		0.2 ± 0.1		3.3 ± 0.1	
25	10	1.4 ± 0.5	1.00	0.1 ± 0.1	0.5	3.3 ± 0.2	89
125	10	1.2 ± 0.4	0.86	0.2 ± 0.1	1.0	3.4 ± 0.1	466
2,500	10	0.6 ± 0.2	0.43	0.2 ± 0.2	1.0	4.5 ± 0.2**	9,501
5,000	10	0.8 ± 0.4	0.57	0.3 ± 0.1	1.5	5.1 ± 0.3**	19,448

* Significantly different ($P \leq 0.05$) from the control group by Dunnett's test
** $P \leq 0.01$
[a] Labeling indices and liver weight data are presented as mean ± standard deviation. BrdU = bromodeoxyuridine; PCNA = proliferating cell nuclear antigen
[b] Number of hepatocytes with labeled nuclei/1,000 hepatocytes scored
[c] Data are calculated as (oxazepam concentration)(feed consumption)(days on study)/final mean body weight.

TABLE H3
Clinical Chemistry Data for Male F344/N Rats Administered Oxazepam in Feed for 90 Days [a]

Concentration (ppm)		AP (IU/L)	ALT (IU/L)	CK (IU/L)	SDH (IU/L)	5'N (IU/L)	Bile Acids (µmol/L)	Albumin (g/dL)	Protein (g/dL)	Creatinine (mg/dL)	Cholesterol (mg/dL)
15 Days											
0	(n=10)	143 ± 8	44 ± 9.4	136 ± 43	21 ± 10	26 ± 1.5	30 ± 6.8	4.5 ± 0.3	7.5 ± 0.4	0.91 ± 0.07	70 ± 6
25	(n=10)	146 ± 13	38 ± 3.0	342 ± 116	14 ± 3.4*	28 ± 1.4	33 ± 8.4	4.7 ± 0.4	7.4 ± 0.3	0.94 ± 0.05	67 ± 5
125	(n=9)	136 ± 12	33 ± 2.8	217 ± 113	12 ± 3.0**	27 ± 2.4	28 ± 4.8	4.6 ± 0.2	7.2 ± 0.6	0.85 ± 0.07	64 ± 4
2,500	(n=10)	145 ± 11	42 ± 5.4	199 ± 48	17 ± 2.1	30 ± 3.0**	32 ± 9.5	4.7 ± 0.2	7.6 ± 0.3	0.79 ± 0.03**	60 ± 6
5,000	(n=10)	176 ± 19**	44 ± 4.4	135 ± 54	19 ± 2.1	35 ± 4.0**	35 ± 14	4.8 ± 0.3	7.7 ± 0.2	0.74 ± 0.05**	71 ± 18
30 Days											
0	(n=10)	130 ± 6	47 ± 6.5	195 ± 66	17 ± 3.4	28.7 ± 4.9	28 ± 6	4.2 ± 0.2	7.2 ± 0.6	0.84 ± 0.1	74 ± 7
25	(n=10)	128 ± 6	41 ± 4.2**	161 ± 81	18 ± 3.1	29.5 ± 2.5	26 ± 6	4.3 ± 0.2	7.5 ± 0.4	0.72 ± 0.08*	68 ± 6
125	(n=9)	115 ± 11	37 ± 2.4**	152 ± 66	15 ± 2.7	26.3 ± 1.7	25 ± 7	4.0 ± 0.2	7.4 ± 0.3	0.72 ± 0.1*	62 ± 5**
2,500	(n=10)	119 ± 9*	32 ± 1.8**	310 ± 99*	14 ± 1.7	23.9 ± 1.0	32 ± 8	4.2 ± 0.2	7.7 ± 0.2*	0.68 ± 0.04**	50 ± 4**
5,000	(n=10)	122 ± 10	28 ± 4.5**	188 ± 88	15 ± 1.7	36.2 ± 24	40 ± 12**	4.5 ± 0.2**	7.8 ± 0.3**	0.62 ± 0.09**	51 ± 11**
45 Days											
0	(n=10)	117 ± 6	54 ± 7.9	150 ± 59	27 ± 7.7	27.0 ± 1.3	26 ± 5	4.1 ± 0.2	7.5 ± 0.3	0.96 ± 0.05	70 ± 3
25	(n=10)	116 ± 7	52 ± 10	235 ± 66**	25 ± 7.3	30.2 ± 2.3**	25 ± 4	4.3 ± 0.2	7.4 ± 0.5	1.05 ± 0.08*	73 ± 6
125	(n=10)	113 ± 5	42 ± 5.0**	148 ± 27	23 ± 5.5	29.8 ± 1.5*	23 ± 8	4.2 ± 0.3	7.5 ± 0.3	0.91 ± 0.06	71 ± 7
2,500	(n=10)	114 ± 11	34 ± 4.8**	105 ± 23	19 ± 3.3**	30 ± 3.2	30 ± 8	4.3 ± 0.4	7.0 ± 0.5*	0.83 ± 0.05**	66 ± 14
5,000	(n=10)	115 ± 11	35 ± 7.1**	194 ± 84	16 ± 2.3**	31 ± 2.2**	27 ± 12	4.6 ± 0.4*	7.0 ± 0.4*	0.88 ± 0.08*	58 ± 6**
90 Days											
0	(n=10)	113 ± 6	62 ± 22	291 ± 71	24 ± 13	29 ± 1.3	28 ± 10	3.7 ± 0.1	7.5 ± 0.2	1.07 ± 0.07	76 ± 6
25	(n=10)	94 ± 8**	47 ± 6*	162 ± 65*	18 ± 3	29 ± 1.2	26 ± 9	3.7 ± 0.2	7.2 ± 0.2	0.91 ± 0.03**	75 ± 5
125	(n=10)	92 ± 6**	46 ± 5*	183 ± 110*	17 ± 3	29 ± 1.9	32 ± 10	3.8 ± 0.4	7.3 ± 0.3	0.89 ± 0.06**	74 ± 7
2,500	(n=10)	107 ± 5	39 ± 6**	317 ± 111	15 ± 4**	26 ± 1.5**	25 ± 6	4.0 ± 0.1**	7.9 ± 0.2**	0.93 ± 0.05**	57 ± 5**
5,000	(n=10)	92 ± 22**	36 ± 8**	281 ± 96	16 ± 3*	28 ± 1.4	28 ± 8	4.2 ± 0.2**	8.1 ± 0.4**	0.87 ± 0.07**	61 ± 8**

* Significantly different ($P \leq 0.05$) from the control group by Dunnett's test
** $P \leq 0.01$
[a] Data are presented as mean ± standard deviation. AP = alkaline phosphatase; ALT = alanine aminotransferase; CK = creatine kinase; SDH = sorbitol dehydrogenase; 5′N = 5′-nucleotidase

TABLE H4
Serum Oxazepam Concentrations in Male F344/N Rats Administered Oxazepam in Feed for 90 Days[a]

Concentration (ppm)	15 Days	30 Days	45 Days	90 Days
25	0.03 ± 0.02	0.04 ± 0.01	0.02 ± 0.01	0.03 ± 0.01
125	0.07 ± 0.02	0.07 ± 0.02	0.12 ± 0.01	0.08 ± 0.03
2,500	0.70 ± 0.13	0.39 ± 0.16	0.52 ± 0.27	3.05 ± 0.16
5,000	2.64 ± 0.90	1.31 ± 0.37	1.37 ± 0.23	3.63 ± 1.38

[a] Values are expressed in μg/mL serum ± standard deviation for groups of 10 animals. Limit of quantification = 0.025 µg/mL