NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 455

TOXICOLOGY AND CARCINOGENESIS STUDIES OF CODEINE (CAS NO. 76-57-3) IN F344/N RATS AND B6C3F$_1$ MICE

(FEED STUDIES)

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.

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NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS STUDIES OF CODEINE

(CAS NO. 76-57-3)

IN F344/N RATS AND B6C3F$_1$ MICE

(FEED STUDIES)

NATIONAL TOXICOLOGY PROGRAM
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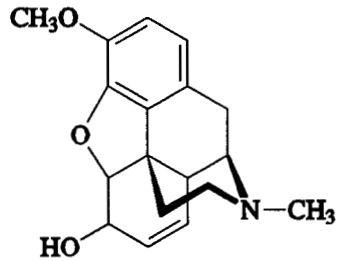
ABSTRACT



CODEINE
CAS No. 76-57-3
Chemical Formula: $C_{18}H_{21}NO_3$ Molecular Weight: 299.36

Synonyms: 7,8-didehydro-4,5-epoxy-3-methoxy-17-methylmorphinan-6-ol; methylmorphine; 3-*O*-methylmorphine monohydrate; *N*-methylnorcodeine; morphine-3-methyl ether; morphine monomethyl ether
Trade names: Codeinum, Codicept, Coducept, Metilmorfina

Codeine is used in a variety of pharmaceuticals including analgesics, sedatives, hypnotics, antiperistaltics, and antitussive agents. The National Cancer Institute and the Food and Drug Administration nominated codeine for study because it is a widely used drug and it is representative of the morphine class of compounds, for which chronic carcinogenicity studies had not been conducted. The oral route of administration was selected because it is the primary route of human exposure. Male and female F344/N rats and B6C3F$_1$ mice were given codeine (99% pure) in feed for 14 days, 13 weeks, or 2 years. Genetic toxicology studies were conducted in *Salmonella typhimurium* and cultured Chinese hamster ovary cells.

14-Day Study in Rats

Groups of five male and five female F344/N rats were given 0, 1,562, 3,125, 6,250, 12,500, or 25,000 ppm codeine in feed for 14 days, which resulted in daily doses of approximately 125, 250, 450, 650, or 750 mg codeine/kg body weight to males and 125, 250, 500, 700, or 300 mg/kg to females. One female exposed to 6,250 ppm, one male and three females exposed to 12,500 ppm, and all males and females exposed to 25,000 ppm died during the study. Final mean body weights and mean body weight gains of all exposed groups except 1,562 ppm females were significantly lower than those of the controls.

No chemical-related gross lesions were observed in rats at necropsy. Thickening of the forestomach mucosa (hyperplasia and hyperkeratosis) and lymphoid depletion of the thymus in exposed males and females and testicular degeneration in exposed males, observed primarily in the 12,500 and 25,000 ppm groups, were associated with decreased survival and increased morbidity in these groups.

14-Day Study in Mice

Groups of five male and five female B6C3F$_1$ mice were given 0, 781, 1,562, 3,125, 6,250, or 12,500 ppm codeine in feed for 14 days, which resulted in daily doses of approximately 150, 300, 600, 1,300, or 3,000 mg codeine/kg body weight to males and 200, 400, 750, 1,500, or 3,000 mg/kg to females. All mice survived to the end of the study. The final mean body weight of 3,125 ppm females was significantly greater than that of the controls; the final mean body weight of 12,500 ppm females and the mean body weight gains of 12,500 ppm males and females were significantly lower than those of the controls.

Absolute and relative liver weights of 3,125, 6,250, and 12,500 ppm males and of 12,500 ppm females and the absolute and relative right kidney weights of 12,500 ppm males were significantly lower than those of the controls. No gross or histopathologic lesions were attributed to codeine exposure.

13-Week Study in Rats

Groups of 10 male and 10 female F344/N rats were given 0, 390, 781, 1,562, 3,125, or 6,250 ppm codeine in feed for 13 weeks, which resulted in daily doses of approximately 25, 50, 100, 200, or 450 mg codeine/kg body weight to males and 25, 50, 100, 250, or 500 mg/kg to females. There were no chemical-related deaths during the study. Final mean body weights and mean body weight gains of all groups of exposed males and of females exposed to 1,562, 3,125, or 6,250 ppm were significantly lower than those of the controls. Feed consumption decreased with increasing exposure concentration during the first week of the study; however, by the end of the study, feed consumption by most exposed groups was similar to that by the controls. There were alterations of various hematology and clinical chemistry parameters at the end of the study. There was a mild dose-dependent lymphopenia in females receiving 1,562 ppm and above and in 6,250 ppm males. There also was a minimal to mild macrocytosis that occurred in all exposed groups of males and in females exposed to 781, 3,125, or 6,250 ppm. No significant differences between control and exposed rats were observed in sperm morphology or vaginal cytology parameters.

Absolute and relative adrenal gland weights of exposed males and of 3,125 and 6,250 ppm females were significantly greater than those of the controls. Absolute and relative liver weights of exposed males were significantly lower than those of the controls. Relative thymus weights of 3,125 and 6,250 ppm males were significantly lower than that of the controls. No chemical-related gross or histopathologic lesions were observed in male or female rats.

13-Week Study in Mice

Groups of 10 male and 10 female B6C3F$_1$ mice were given 0, 390, 781, 1,562, 3,125, or 6,250 ppm codeine in feed for 13 weeks, which resulted in daily doses of approximately 60, 120, 260, 460, or 1,000 mg codeine/kg body weight to males and 60, 130, 280, 530, or 1,200 mg/kg to females. Two male mice in the 3,125 ppm group died during week 7. All other mice survived to the end of the study. Final mean body weights of exposed males and females were similar to those of the controls. Feed consumption by exposed males and females was similar to that by the controls. Abnormal posture was observed in all exposed groups of males. There were no significant differences in hematology or urinalysis parameters in male or female mice. Minor, sporadic changes occurred in a few of the clinical chemistry parameters; they were not considered biologically significant. No significant differences in sperm morphology or vaginal cytology parameters were attributed to codeine exposure.

Absolute and relative kidney weights of 3,125 and 6,250 ppm males were lower than those of the controls. No chemical-related differences in organ weights were observed in females. No chemical-related gross or histopathologic lesions were observed in male or female mice.

2-Year Study in Rats

Groups of 60 male and 60 female F344/N rats were fed diets containing 0, 400, 800, or 1,600 ppm codeine for up to 106 weeks, with 9 or 10 rats per group evaluated at 15 months. These exposure concentrations resulted in average daily doses of approximately 15, 30, and 70 mg codeine/kg body weight to males and 15, 40, and 80 mg/kg to females.

Survival, Body Weights, Feed Consumption, and Clinical Findings

Survival of 400 ppm females was significantly greater than that of the controls; survival of all groups of exposed males and of 800 and 1,600 ppm females was similar to that of the controls. There was an exposure-related decrease in mean body weights of males and females. The final mean body weight of 1,600 ppm males was 88% that of the controls, and the final mean body weight of 1,600 ppm females was 89% that of the controls. Feed consumption by exposed groups was similar to that by the controls. Chemical-related clinical findings were limited to ocular discharge in exposed males and females.

Pathology Findings

Absolute and relative adrenal gland weights of 800 and 1,600 ppm males were significantly greater than those of the controls at 15 months. There were no

increased incidences of neoplasms attributable to codeine exposure at any site. At 2 years, there were exposure-related decreases in the incidences of adrenal medulla hyperplasia in males and females. There was an exposure-related decrease in the incidence of benign pheochromocytomas in males, and the incidences in exposed males were significantly lower than that in the controls. In 1,600 ppm females the incidences of mammary gland fibroadenomas and of fibroadenomas or adenocarcinomas (combined) were significantly lower than those in the controls. The decreased incidences of benign pheochromocytomas in males and mammary gland neoplasms in females were considered to be related to codeine exposure.

2-Year Study in Mice

Groups of 60 male and 60 female $B6C3F_1$ mice were fed diets containing 0, 750, 1,500, or 3,000 ppm codeine for up to 106 weeks, with 9 or 10 mice per group evaluated at 15 months. These exposure concentrations resulted in average daily doses of approximately 100, 200, or 400 mg codeine/kg body weight to males and females.

Survival, Body Weights, Feed Consumption, and Clinical Findings

Survival of exposed males and females was similar to that of the controls. Mean body weights of 750 and 1,500 ppm males and females were similar to those of the controls throughout most of the study. Mean body weights of 3,000 ppm males and females were less than those of the controls from about week 13, and the final mean body weights of these groups were 86% and 82% those of the respective controls. Feed consumption by exposed groups was similar to that by the controls.

Pathology Findings

There were no increased incidences of neoplasms attributable to codeine exposure at any site. At 15 months, the incidence of thyroid gland follicular cell hyperplasia in 3,000 ppm males was significantly greater than that of the controls, and this lesion was observed in 1,500 and 3,000 ppm females. At 2 years, the incidences of follicular cell hyperplasia in all exposed groups of mice were significantly greater than those in the controls, but there were no increases in thyroid gland follicular cell neoplasms. The incidence of centrilobular fatty change in the liver of 3,000 ppm males was significantly lower than that in the controls at 15 months, and the decreased incidence appeared to be related to exposure level. At 2 years, the incidences of eosinophilic foci, foci of fatty change, centrilobular cytomegaly, and centrilobular fatty change in 3,000 ppm males were lower than those in the controls. The incidence of hepatocellular adenomas and the incidence of hepatocellular adenomas or carcinomas (combined) in 3,000 ppm males and females were significantly lower than those in the controls; this was considered to be related to lower body weights in these groups.

Genetic Toxicology

Codeine phosphate was not mutagenic in any of four strains of *Salmonella typhimurium*, with or without S9 metabolic activation enzymes. In cytogenetic tests with cultured Chinese hamster ovary cells, codeine phosphate induced dose-related increases in sister chromatid exchanges, with and without S9, only at concentration levels that caused cell cycle delay. No induction of chromosomal aberrations was noted in cultured Chinese hamster ovary cells treated with codeine phosphate, with or without S9.

Conclusions

Under the conditions of these 2-year feed studies, there was *no evidence of carcinogenic activity** of codeine in male or female F344/N rats exposed to 400, 800, or 1,600 ppm. There was *no evidence of carcinogenic activity* of codeine in male or female $B6C3F_1$ mice exposed to 750, 1,500, or 3,000 ppm.

Thyroid gland follicular cell hyperplasia was increased in exposed male and female mice.

Decreased incidences of benign pheochromocytomas of the adrenal medulla in male rats and mammary gland fibroadenomas and fibroadenomas or adenocarcinomas (combined) in female rats were related to codeine exposure.

* 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 Codeine

	Male F344/N Rats	Female F344/N Rats	Male B6C3F$_1$ Mice	Female B6C3F$_1$ Mice
Doses	0, 400, 800, or 1,600 ppm (approximately 15, 30, or 70 mg/kg in feed)	0, 400, 800, or 1,600 ppm (approximately 15, 40, or 80 mg/kg in feed)	0, 750, 1,500, or 3,000 ppm (approximately 100, 200, or 400 mg/kg in feed)	0, 750, 1,500, or 3,000 ppm (approximately 100, 200, or 400 mg/kg in feed)
Body weights	1,600 ppm group lower than controls	1,600 ppm group lower than controls	3,000 ppm group lower than controls	3,000 ppm group lower than controls
2-Year survival rates	29/50, 20/50, 21/50, 20/50	28/50, 38/50, 29/51, 32/51	41/50, 38/50, 45/50, 43/50	36/50, 36/51, 43/51, 35/50
Nonneoplastic effects	None	None	Thyroid gland: follicular cell hyperplasia (7/49, 25/50, 29/50, 34/50)	Thyroid gland: follicular cell hyperplasia (14/48, 29/51, 42/51, 44/50)
Neoplastic effects	None	None	None	None
Decreased neoplasm incidences	Adrenal medulla: benign pheochromocytoma (16/49, 6/50, 6/50, 3/50)	Mammary gland: fibroadenoma (27/50, 21/50, 27/51, 8/51); fibroadenoma or adenocarcinoma (30/50, 23/50, 29/51, 8/51)	None	None
Level of evidence of carcinogenic activity	No evidence	No evidence	No evidence	No evidence

Genetic toxicology

Salmonella typhimurium gene mutations:	Negative in strains TA97, TA98, TA100, and TA1535 with and without S9
Sister chromatid exchanges	
Cultured Chinese hamster ovary cells *in vitro*:	Positive with and without S9
Chromosomal aberrations	
Cultured Chinese hamster ovary cells *in vitro*:	Negative with and without S9

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 codeine on June 20, 1995, 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 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 June 20, 1995 the Technical Report on the toxicology and carcinogenesis studies of codeine received public review by the National Toxicology Program's Board of Scientific Counselors' Technical Reports Review Subcommittee. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Dr. J.K. Dunnick, NIEHS, introduced the toxicology and carcinogenesis studies of codeine by discussing the chemical's uses and the rationale for study, describing the experimental design, reporting on survival and body weight effects, and commenting on compound-related nonneoplastic lesions in mice. Dr. Dunnick also reported on toxicokinetic studies in rats and mice performed in collaboration with investigators at Burroughs Wellcome. The proposed conclusions for the 2-year studies were *no evidence of carcinogenic activity* in male or female F344/N rats or in male or female $B6C3F_1$ mice.

Dr. Taylor, a principal reviewer, agreed with the proposed conclusions. He observed that as noted in the Technical Report, the analgesic action of codeine depends on *O*-demethylation to morphine, a reaction that is mediated in humans by cytochrome P_{450} IID6. He provided additional references and said the discussion on human metabolism of codeine should be expanded. Dr. Dunnick said the additional references would be included.

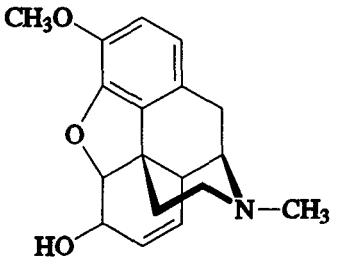
Dr. Miller, the second principal reviewer, agreed with the proposed conclusions. She asked for clarification regarding the significance of dose-related increases in sister chromatid exchanges occurring at concentrations that caused cell cycle delay in cultured Chinese hamster ovary cells. Dr. Dunnick said she would clarify these findings (page 56).

Dr. Vodicnik, the third principal reviewer, agreed with the proposed conclusions. She was pleased that toxicokinetic data were included (Appendix M).

Dr. A. Turturro, National Center for Toxicological Research, asked if some quantification could be added relating lower body weights with decreased incidences of mammary gland and adrenal gland neoplasms in rats. Dr. J. Haseman, NIEHS, responded that incidences of adrenal gland neoplasms were decreased at all three concentrations, including two that had no body weight differences. However, he said that decreased incidences of mammary gland neoplasms could in part be explained by lower body weight, and perhaps some quantification of the extent of this association could be added (page 59).

Dr. Vodicnik moved that the Technical Report on codeine be accepted with the revisions discussed and with the proposed conclusions as written for male and female rats and mice, *no evidence of carcinogenic activity*. Dr. Miller seconded the motion, which was accepted unanimously with nine votes.

INTRODUCTION



CODEINE
CAS No. 76-57-3
Chemical Formula: $C_{18}H_{21}NO_3$ Molecular Weight: 299.36

Synonyms: 7,8-didehydro-4,5-epoxy-3-methoxy-17-methylmorphinan-6-ol; methylmorphine; 3-*O*-methylmorphine monohydrate; *N*-methylnorcodeine; morphine-3-methyl ether; morphine monomethyl ether
Trade names: Codeinum, Codicept, Coducept, Metilmorfina

CHEMICAL AND PHYSICAL PROPERTIES

Codeine is a bitter tasting, odorless, colorless to white material that occurs as a powder or crystallizes as monohydrate into orthorhombic, sphenoidal rods or octahedral tablets. It has a specific gravity of 1.32 (20/4° C), a boiling point of 250° C, and a melting point of 154° to 156° C; it sublimes at 140° to 145° C at a pressure of 1.5 mm Hg. Codeine is slightly soluble in water (1:120), sparingly soluble in ether (1:18), very soluble in chloroform (1:5), and freely soluble in alcohol (1:2), and has a pK of 6.05 at 15° C (Haley, 1983; *Merck Index*, 1989; RTECS, 1991; Willette, 1991).

PRODUCTION, USE, AND HUMAN EXPOSURE

Codeine is the most widely used of the many alkaloids that occur naturally in opium, the air-dried milky exudate of the poppy plant (*Papaver somniferum*). It belongs to the group of phenanthrene derivatives, which also includes morphine and thebaine. As a constituent of opium, codeine has been used for centuries; it has been available as a pure alkaloid since the middle of the 19th century. Codeine is extracted from opium in amounts usually too small to be of commercial importance; yields vary from 0.8% to 3.5%, depending on the country of origin (Swinyard, 1980). Commercial codeine is prepared from morphine by methylating the phenolic hydroxyl group or from thebaine by appropriate reduction and demethylation (Tyler *et al.*, 1981; Willette, 1991).

Codeine and its phosphate and sulfate salts are used in a variety of pharmaceuticals as analgesics, sedatives, hypnotics, antiperistaltics, and antitussive agents. In 1981, approximately 58 million prescriptions for codeine-containing analgesics were written in the United States, making codeine analgesics the most prescribed class of therapeutic drugs (DHHS, 1982). In 1993, combinations of codeine and codeine phosphate with acetaminophen were among the top 100 prescription drugs dispensed in the United States (American Druggist, 1994). The *American Hospital Formulary Service Drug Information* (AHFS, 1995) lists two products containing codeine, three containing codeine sulfate, and 88 containing codeine phosphate. Codeine phosphate is the most widely used form of codeine because of its greater water solubility (Shanahan *et al.*, 1983; Hunskaar and Dragsund, 1985).

For adults, the usual prescribed analgesic dosage is 15 to 60 mg taken orally every 4 hours, and the usual prescribed antitussive dosage is 10 to 20 mg every 4 to 6 hours; the peak antitussive effect usually occurs within 1 to 2 hours (AHFS, 1995). The typical daily adult therapeutic dose is 1 to 4 mg/kg body weight per day or 40 to 160 mg/m^2 body surface area; the daily pediatric dose is generally 3 mg/kg or 100 mg/m^2 in six equally divided oral, subcutaneous, or intramuscular doses (Jaffe and Martin, 1990; AHFS, 1995). Although the potential for abuse of cough preparations and analgesics containing codeine led to their regulation under Schedule II of the Comprehensive Drug Abuse Prevention and Control Act of 1970 (Swinyard, 1980; 21 CFR Parts 1300-1316), in some states codeine is available without prescription as a component of over-the-counter cough medicines containing up to 10 mg of codeine in an average 5 mL dose. In other states however, these cough medicines are available only by prescription (Willette, 1991).

According to the International Narcotics Control Board, 54,000 kg of codeine was manufactured at three United States facilities in 1986; no specific federal standards for workplace exposure to narcotic dusts such as codeine exist, and exposure control defaults to the nuisance dust standard of 10 mg/m^3 as an 8-hour, time-weighted average (Biagini *et al.*, 1990). The National Occupational Exposure Survey estimated that the potential workplace exposure to codeine, codeine phosphate, and codeine sulfate combined during 1981 through 1983 was 36,000 workers, 33,000 of whom were women in the health care services. The majority of the workers, 31,000, were potentially exposed to codeine phosphate, 1,000 to codeine, and less than 6,000 to codeine sulfate (NIOSH, 1990). The Drug Abuse Warning Network reported 2,482 emergency room mentions of codeine abuse from January 1985 to September 1988 (Cone *et al.*, 1991).

PHARMACOKINETICS, ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION

Experimental Animals

Codeine is metabolized by conjugation with glucuronic acid, *O*-demethylation to morphine, *N*-demethylation to norcodeine, and conjugation of morphine and norcodeine with glucuronic acid (Adler and Latham, 1950; Phillipson *et al.*, 1978) (Figure 1). Studies with rats, mice, dogs, hamsters, guinea pigs, rabbits, cats, and monkeys have shown that, while qualitatively the metabolic pathways are similar among the species, there are quantitative differences in the amount of each metabolite formed (Adler and Latham, 1950; Woods *et al.*, 1956; Yeh and Woods, 1970, 1971; Bechtal and Sinterhauf, 1978; Phillipson *et al.*, 1978; Cone *et al.*, 1979; Suzuki *et al.*, 1988; Oguri *et al.*, 1990; Yuan *et al.*, 1994; Appendix M). However, published studies quantifying codeine metabolism in various species are difficult to compare because the routes of administration, the species, and the routes of recovery vary, and the codeine conjugates are not always identified.

Biological disposition studies by Yeh and Woods (1969) demonstrated that 74% of a 2 mg/kg subcutaneous dose of N-[^{14}C]-methyl-codeine (base) was excreted by male Sprague-Dawley rats within 24 hours as free codeine, free morphine, and conjugated morphine via pulmonary, biliary, intestinal, and urinary routes. In female rats, 86% was excreted via the same routes. Hepatic clearance of codeine accounted for about half of the systemic clearance, indicating significant extrahepatic elimination. Only 2% of the administered radioactivity was retained in the body 24 hours after injection.

Morphine formed by metabolic conversion of codeine has been found in plasma, urine, bile, and feces (Jóhannesson and Woods, 1964; Yeh and Woods, 1969; Yoshimura *et al.*, 1970) and in the brain of rats (Jóhannesson and Schou, 1963; Dahlström and Paalzow, 1976; Chen *et al.*, 1990). Morphine in the brain originates primarily by *O*-demethylation of codeine in the liver. However, codeine crosses the blood-brain barrier faster than morphine due to its greater lipid solubility (Jaffe and Martin, 1990) and is also *O*-demethylated to morphine within the brain (Chen *et al.*, 1990).

Interspecies differences in conjugation of codeine with glucuronic acid, *O*-demethylation to morphine, and *N*-demethylation to norcodeine *in vivo* appear to originate from different activities of the microsomal enzyme, uridine diphosphate-glucuronyltransferase (UDPGT) and cytochrome P_{450}. Phillipson *et al.*

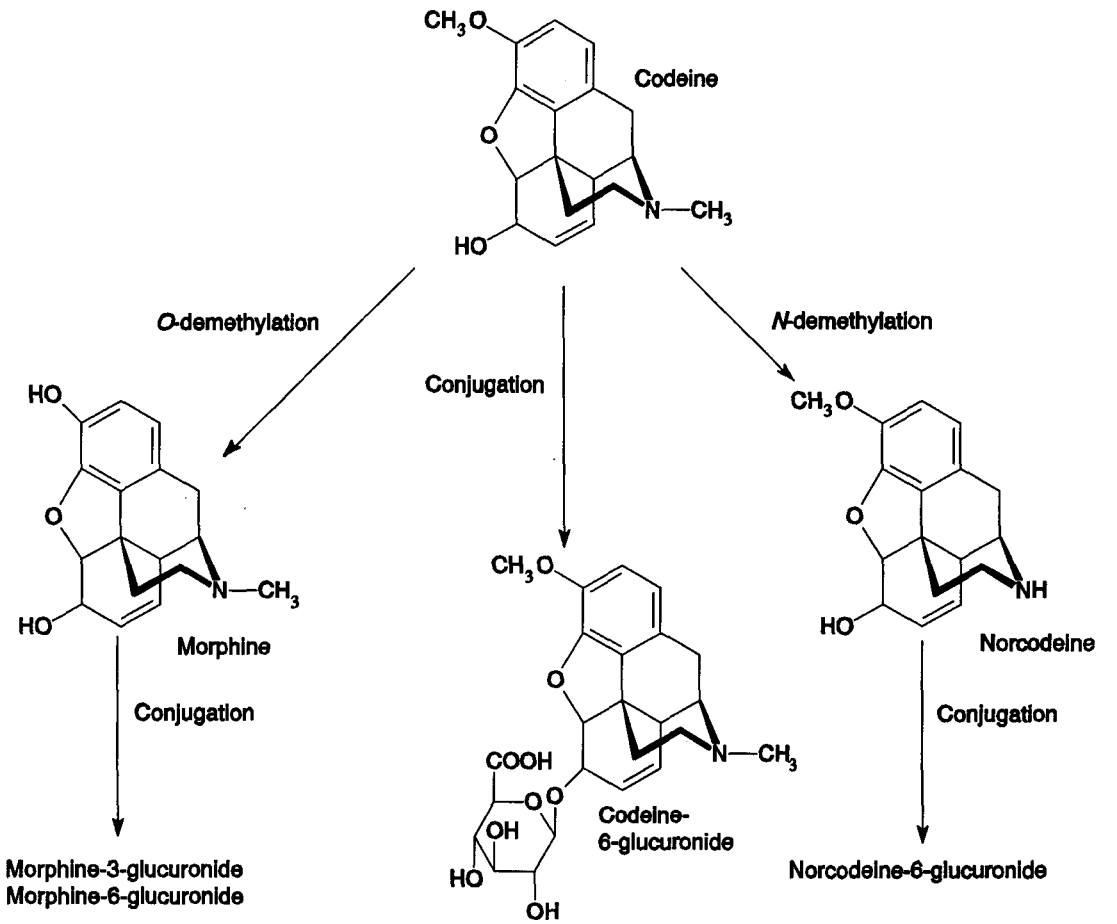


FIGURE 1
Metabolic Pathways of Codeine in Rats (Findlay *et al.*, 1977)

(1978) demonstrated conversion of codeine into norcodeine (10%), morphine (8%), normorphine (2%), and codeine-*N*-oxide (20%) by liver microsomal preparations from guinea pigs; 60% of the dose was recovered as unchanged codeine. Hanioka *et al.* (1990) reported that UDPGT activity (as measured by conjugation of codeine/metabolite) was higher in the liver microsomal preparations from guinea pigs (2.87 nmol/min per mg protein) and rabbits (2.34 nmol/min per mg) than that from rats (0.32 nmol/min per mg) or mice (0.30 nmol/min per mg). Although the UDPGT activity in mice was similar to that of rats, urinary excretion of codeine glucuronide by mice was nine-fold higher.

The *O*-demethylation of codeine to morphine is a function of a polymorphic cytochrome P_{450} enzyme ($CYPP_{450}$IID6 in man and $CYPP_{450}$IID1 in rat) (Mikus *et al.*, 1991, 1994). The female Dark-Agouti rat is an animal model for the human poor metabolizer phenotype (individuals who are poor hydroxylators of debrisoquine), while the Sprague-Dawley rat is a model for the human extensive metabolizer phenotype (individuals who readily metabolize both debrisoquine and codeine). In an *in vitro* study of codeine *O*-demethylation by liver microsomes, the intrinsic clearance of codeine to morphine was tenfold lower in female Dark-Agouti rats than in female Sprague-Dawley rats (Mikus *et al.*, 1991).

The pharmacokinetics of codeine have been shown to be linear in a dose-ranging study in male Sprague-Dawley rats administered single intravenous bolus doses of 1, 1.5, 3, or 4 mg codeine phosphate/kg (Shah and Mason, 1991). A 3 mg/kg bolus dose of codeine phosphate delivered intravenously to male Sprague-Dawley rats was rapidly metabolized and excreted (Shah and Mason, 1990a). In addition, the mean volume of systemic distribution was greater than the total blood volume, suggesting that codeine sequesters out of the blood into various organs and tissues like most other organic bases. Following oral administration of codeine phosphate, the half life of codeine or morphine in rat plasma is estimated at one hour (Shah and Mason, 1990a). Enterohepatic recirculation may cause secondary morphine peaks 60 minutes or more after administration of codeine phosphate in the rat (Shah and Mason, 1991). Up to 30% of intravenously administered morphine undergoes enterohepatic recirculation in the rat (Walsh and Levine, 1975). The mean residence time of morphine in the body is more than two times that of codeine (Jóhannesson and Woods, 1964; Spector, 1971).

In F344/N rats, the bioavailability of codeine was approximately 25% when administered in feed at a concentration of 1,600 ppm (Yuan *et al.*, 1994; Appendix M), and the bioavailability of codeine phosphate was approximately 8% when administered by gavage at 5 mg/kg to Sprague-Dawley rats (Shah and Mason, 1990a). Bioavailability of codeine increased with increasing concentration in feed. As the F344/N rats aged, exposure resulted in decreased plasma concentrations of codeine and increased total morphine concentrations (Yuan *et al.*, 1994; Appendix M).

Humans

The metabolic pathways of codeine in humans are similar to those in the rat – i.e., partial conjugation with glucuronic acid, *O*-demethylation to morphine, and *N*-demethylation to norcodeine; the methyl moiety is then converted to CO_2 via formaldehyde and exhaled (Adler *et al.*, 1955). However, after oral administration, *O*-demethylation to morphine is a minor pathway in humans, as evidenced by an $AUC_{morphine}$:$AUC_{codeine}$ ratio of approximately 0.03 in humans (Shah and Mason 1990b) compared to a ratio of 0.9 in rats (Shah and Mason, 1991). The mean codeine C_{max} achieved in healthy humans following a 60 mg oral dose of codeine phosphate (88 ng/mL) (Shah and Mason, 1990b) or codeine sulfate (173 ng/mL) (Guay *et al.*, 1988) were comparable to the C_{max} in F344/N rats exposed to 800 ppm codeine (estimated to deliver 30 to 50 mg/kg per day) in feed (128 ng/mL) (Yuan *et al.*, 1994; Appendix M). Peak plasma concentrations for morphine in humans given an oral dose of 60 mg codeine phosphate were lower than that of rats exposed to 800 ppm of codeine in feed (Yuan *et al.*, 1994; Appendix M).

The major metabolic pathway of codeine in humans is conjugation with glucuronic acid to codeine-6-glucuronide. In a study with healthy male and female volunteers given a single oral dose of 30 mg codeine phosphate (22 mg codeine base), the half-life of codeine was 1.8 hours and it was detected in plasma for 5 hours; the half-life of codeine-6-glucuronide was 3 hours and it was detected in the plasma for at least 15 hours. Following an oral dose of codeine phosphate (using AUC analysis), it is estimated that in plasma 90% of the dose is codeine-6-glucuronide, 4% is codeine, and 6% is morphine or other metabolites (Vree and Verwey-van Wissen, 1992). Other researchers have also shown that the main metabolite of codeine in humans is codeine-6-glucuronide (Chen *et al.*, 1991; Yue *et al.*, 1991a).

In humans, codeine is readily absorbed after oral ingestion, injection, or rectal administration, and the half-life in plasma is 2 to 4 hours (Jaffe and Martin, 1990). Following oral or subcutaneous administration, peak concentrations in plasma and the brain are attained within 15 to 30 minutes, which correlates with the onset of action (AHFS, 1995). Since codeine is a lipophilic opioid, it is absorbed transdermally and from the nasal and buccal mucosa. It is distributed in the lung, liver, kidney, and spleen (Jaffe and Martin, 1990).

In a study of the biological disposition of codeine phosphate in humans, 10% of the dose was excreted unchanged, 40% as conjugated codeine, 10% as norcodeine, and 10% as morphine (Parke, 1968). Urinary excretion profiles of four healthy male volunteers with a history of heroin abuse showed free codeine (7%), conjugated codeine (38%), free morphine (<1%), and conjugated morphine (4%) (Cone *et al.*, 1991). Most of the free and bound

codeine (95%), free morphine (88%), and bound morphine (70%) was excreted within 24 hours. In another study, both unchanged codeine and norcodeine were found in the urine of healthy male volunteers given single 30 mg oral doses of codeine. As in the guinea pig, hydrocodone and its metabolites, 6α-hydrocodol, 6β-hydrocodol, and norhydrocodone, were also detected in the urine (Cone *et al.*, 1979). The main urinary metabolite identified in the Vree and Verwey-van Wissen (1992) study of eight volunteers was codeine-6-glucuronide, accounting for 81.8% of the dose; 4.4% of the dose was excreted as free codeine, 0.6% as morphine, 2.1% as morphine-3-glucuronide, and 0.8% as morphine-6-glucuronide.

Interindividual variations in the ability to glucuronidate codeine, related to UDPGT activities, have been demonstrated both *in vivo* and *in vitro* in human liver and kidney microsomes (Yue *et al.*, 1989a,b, 1990). Furthermore, interethnic differences in both the glucuronidation and demethylation of codeine have been noted in a number of studies, in particular those of Yue *et al.* (1989a, 1991b) comparing Swedish Caucasians with Han Chinese. Caucasians excreted significantly less codeine and morphine and significantly more codeine-6-glucuronide and morphine-6-glucuronide; the glucuronidation efficiency of Chinese subjects was consistently lower.

Studies have shown that the analgesic activity of codeine depends to a large extent on *o*-demethylation to morphine, a reaction that is mediated by cytochrome P_{450} IID6. The analgesic effect may be diminished in segments of the population that are poor metabolizers of codeine or are exposed to other environmental factors that affect codeine metabolism (Mortimer *et al.*, 1990; Desmeules *et al.*, 1991; Sindrup *et al.*, 1991).

Codeine has been identified in human breast milk. Codeine concentrations in the milk of two lactating women given single oral doses of a compound analgesic containing 60 mg of codeine phosphate were 1.5 to 2.4 times as high as codeine concentrations in maternal plasma at the same time intervals after administration (Findlay *et al.*, 1981). Metabolically produced morphine levels in breast milk were low but exceeded those in maternal plasma after 1 hour. Codeine and morphine were also detected in the plasma of newborns 1 to 4 hours after nursing when their mothers received a single oral dose of 60 mg codeine sulfate 1 hour before nursing (Meny *et al.*, 1993). Codeine plasma levels ranged from less than 0.8 to 4.5 ng/mL, and morphine plasma levels ranged from less than 0.5 to 2.2 ng/mL. Free codeine levels in breast milk 20 to 240 minutes after administration ranged from 33.8 to 314 ng/mL and free morphine levels ranged from 1.9 to 20.5 ng/mL.

PHARMACOLOGY

Codeine has pharmacologic effects on the central nervous system (e.g., analgesia, drowsiness, mood changes, respiratory depression, nausea, and dysfunction of the endocrine and autonomic nervous systems) and the gastrointestinal tract (e.g., decreased gastrointestinal motility). Alkaloids of this type tend to cause physical dependence, tolerance, and addiction (Jaffe and Martin, 1990). These pharmacologic effects (and recent research to understand the mechanisms involved) have been summarized (Almeida and Shippenberg, 1991; Herz, 1993a,b).

Opioid receptors belong to a larger family of receptors that share the ability to modify the function of membrane enzymes or ion channels by interacting with one or more guanine nucleotide regulatory proteins in the cell membrane (Costa *et al.*, 1991), and the amino acid sequences of rat opioid receptors have been deduced by cloning and sequencing cDNAs (Evans *et al.*, 1992; Kieffer *et al.*, 1992; Chen *et al.*, 1993; Fukuda *et al.*, 1993).

The general pharmacologic action of codeine is similar to that of morphine; however, its analgesic potency, degree of respiratory depression, toxicity, and potential for addiction are less than those of morphine. In rats, subcutaneous doses of 60 mg codeine phosphate/kg and intraperitoneal doses of 30 mg/kg were equianalgesic with 5 and 10 mg morphine sulfate/kg, respectively; depending on the route of administration, the relative analgesic potencies of codeine and morphine varied as much as fourfold (Jóhannesson and Woods, 1964). However, the bioavailability of orally administered codeine in man is about 60% whereas that of morphine is about 25% (Jaffe and Martin, 1990). Codeine undergoes less first-pass metabolism in the liver than does morphine, resulting in an oral-parenteral potency ratio of 1:1.5 (Wallenstein *et al.*, 1967).

Codeine has been used in the treatment of pain for more than a century; about 60% of the clinical use of codeine is for pain relief (Shah and Mason, 1990a). The binding affinity of codeine to opioid receptors is relatively weak, approximately 1/3,000 that of morphine (Chen *et al.*, 1990), and it is thought the analgesic effect of codeine is due to its biotransformation to morphine. Codeine exerts a drying effect on respiratory tract mucosa and increases viscosity of bronchial secretions (AHFS, 1995). Along with other opiates, codeine causes the release of histamine through degranulation of mast cells, which may cause peripheral vasodilatation with related hypotension (Casale *et al.*, 1984).

TOXICITY

Experimental Animals

For rats, the oral LD_{50} is 427 mg codeine/kg body weight, the intraperitoneal LD_{50} is 130 mg/kg, the subcutaneous LD_{50} is 229 mg/kg, and the intravenous LD_{50} is 75 mg/kg; for mice, the respective LD_{50} values are 250, 60, 84, and 54 mg/kg. The intramuscular LD_{50} in mice is 290 mg/kg. The intravenous LD_{50} in dogs is 69 mg/kg, and in rabbits it is 34 mg/kg (RTECS, 1991).

Induction of physical dependence on codeine has been demonstrated in male Sprague-Dawley rats given 0.5 mg codeine/g food. Abrupt codeine withdrawal in rats treated for more than 2 days was associated with body weight loss, diarrhea, ptosis, and vocalization, which increased in intensity as the duration of codeine treatment increased (Suzuki *et al.*, 1984). In a study of three inbred strains of mice, the severity of withdrawal signs precipitated by the opioid antagonist naloxone indicated that C57BL/6 mice developed greater physical dependence on codeine in feed than did C3H/He and DBA/2 mice (Suzuki *et al.*, 1991). In addition, the role of genotype in determining the degree of preference for morphine and codeine was demonstrated in a study in which Lewis rats (a strain derived from Sprague-Dawley rats) displayed a significantly greater preference for both codeine and morphine in feed than did F344 rats (Suzuki *et al.*, 1988).

Codeine causes cytotoxicity in isolated rat hepatocytes as measured by a time- and dose-dependent leakage of lactate dehydrogenase (Ellington and Rosen, 1987). At concentrations of 0.5 or 1.25 mM, cell death began after 60 minutes and viability decreased to less than 10% after 120 to 150 minutes. Hepatotoxicity was inhibited by the addition of metyrapone, an inhibitor of cytochrome P_{450} metabolism, indicating that the cytotoxicity was caused by a P_{450}-generated metabolite of codeine.

Humans

In sporadic cases, therapeutic doses of opioids may be associated with side effects, including respiratory depression, nausea, vomiting, dizziness, mental clouding, dysphoria, constipation, increased pressure in the biliary tract, urinary retention, and hypotension. Acute opioid toxicity, circulatory collapse, respiratory paralysis, coma, and death have been reported from overdosage. The exact amount of any opioid that is toxic or lethal in humans has not been determined, although older literature suggests that a normal, pain-free adult is not likely to die after oral morphine doses of less than 120 mg, or to have serious toxic effects with less than 30 mg parenterally (Jaffe and Martin, 1990).

Opioids have been implicated in allergic phenomena and hypersensitivity reactions related to histamine release and manifested as itching, swelling, urticaria and other types of skin rashes such as fixed eruptions, exfoliative dermatitis with eosinophilia, pruritus, and scarlatiniform rashes (Feldberg and Paton, 1951; Jaffe and Martin, 1990). Wheals at the site of codeine or morphine injection are also probably related to release of histamine (Shanahan *et al.*, 1983; Hunskaar and Dragsund, 1985).

Rare anaphylactoid reactions have been reported after intravenous administration of codeine and morphine, and three cases of severe adverse reactions to intravenous codeine phosphate reported in children were attributed to histamine release and thought to be dose related (Shanahan *et al.*, 1983). These three children had no adverse reaction to codeine administered intramuscularly. In three adults undergoing surgical anesthesia, life-threatening hypotension followed intravenous bolus injections of 10 to 60 mg codeine phosphate (Parke *et al.*, 1992). Because the amount of histamine released from mast cells depends on the speed as well as the dose, the reactions were attributed to the fact that the dose was administered as a bolus injection. Hypotension, which is increased

under general anesthesia, results from vasodilation and peripheral pooling of blood, and appears after a latency of 15 to 20 seconds, a typical finding with histamine releasers (Feldberg and Paton, 1951). Codeine is a more potent histamine releaser in equianalgesic doses than morphine, and the American Medical Association's Drug Evaluations state that codeine should not be administered intravenously (AMA, 1986).

Opioids should be used with caution in patients with hepatic disease, since increased bioavailability after oral administration or cumulative effects may occur. Renal disease greatly alters the pharmacokinetics of opioids (Barnes *et al.*, 1985; Matzke *et al.*, 1986); cases have been reported of renal failure and severe narcosis associated with codeine administration or abuse (Murray, 1973; Park *et al.*, 1989; Hill *et al.*, 1991). The active metabolite, morphine-6-glucuronide, may accumulate during repeated administration of codeine to patients with impaired renal function, resulting in symptoms of opioid overdose including profound narcosis (Matzke *et al.*, 1986, Barnes *et al.*, 1985; Hill *et al.*, 1991).

Reproductive and Developmental Toxicity

Experimental Animals

Oral administration of codeine twice a day to hamsters and mice during major organogenesis has been shown to result in developmental toxicity in the presence and absence of maternal toxicity. The doses at which these effects are seen are usually several times higher than estimated human exposures when codeine is prescribed (Williams *et al.*, 1991).

Administration of codeine in water to LVG Syrian hamsters (0, 10, 50, or 150 mg/kg) twice a day on gestation days 5 through 13 and Swiss CD-1 mice (0, 37.5, 75, 150, or 300 mg/kg) on gestation days 6 through 15 increased the percentage of resorptions per dam, and the number of dams with 100% resorptions was increased in 150 mg/kg hamsters and 300 mg/kg mice; however, the numbers of live fetuses per litter were unaffected (Williams *et al.*, 1991). Mean fetal body weights were significantly decreased in 50 and 150 mg/kg hamsters and 150 and 300 mg/kg mice. Although not statistically significant, meningoencephalocele was observed in 3% of the fetuses and 19% of the litters in the 150 mg/kg hamster group. The oral no-observable-adverse-effect-level (NOAEL) for developmental toxicity was 10 mg codeine/kg in hamsters and 75 mg/kg in mice; the NOAEL for maternal toxicity was 50 mg/kg in hamsters and 150 mg/kg in mice.

Rats given 10, 35, or 120 mg codeine base/kg body weight orally on gestation days 6 to 15 and rabbits given 5, 12.5, or 30 mg/kg on gestation days 6 to 18 showed no teratogenic effects, but 120 mg/kg was embryotoxic to rats when given at the time of implantation (Lehman, 1976).

A 50% reduction in serum testosterone level was observed in male Sprague-Dawley rats 4 hours after a single subcutaneous injection of 8.6 mg codeine/kg (Cicero, 1977). Male rats administered subcutaneous injections of morphine sulfate at 50 mg/kg per day for up to 9 weeks showed decreased serum luteinizing hormone and testosterone levels and reduced seminal vesicle and prostate gland weights; these effects were reversed within the 13-week withdrawal period (James *et al.*, 1980).

Codeine was not teratogenic in the chicken embryo but was shown to be a teratogen in rodents after subcutaneous injection (Ancel and Scheiner, 1951). In Lakeview outbred golden hamsters, a single subcutaneous injection of codeine phosphate (73 mg codeine base/kg) on day 8 of gestation caused cranioschisis in 6% of 12-day-old fetuses (Geber and Schramm, 1975). Administration of 110 mg codeine phosphate/kg body weight to JBT/Jd mice on day 9 of gestation caused hydrocephalic dilation of the fourth brain ventricle in 15% of 13-day-old fetuses and was much less teratogenic than heroin (Jurand, 1980). In CF-1 albino mice, subcutaneous injection of 100 mg/kg codeine sulfate on gestation days 8 and 9 produced delayed ossification of the supraoccipital bone, paws, xiphoid and sternebrae along with checkerboard sternebrae and polysternebrae in 18-day-old fetuses (Zellers and Gautieri, 1977).

Humans

There have been several studies on the reproductive and developmental toxicity of codeine in humans, but the interpretation of these studies is complicated by many factors, including multiple drug intake and the clinical condition requiring codeine treatment. For

example, the collaborative perinatal project of Heinonen *et al.* (1977) did not show any increased risk of malformation from analgesic or antipyretic use of codeine, while others have reported an association between maternal intake of opiates, primarily codeine, and cleft lip and palate in children (Saxén, 1975; Lourwood and Riedlinger, 1989).

Opiates cross the placental barrier (Villee, 1965) and are present in the neonatal body fluids (Waddell, 1972) and are found in maternal milk (Welch and Findlay, 1981). Some studies suggest that codeine exposure can produce long-lasting effects on postnatal development (Mellin, 1964; Johnston, 1972; Rothman *et al.*, 1979; Sonderegger and Zimmerman, 1979; Lourwood and Riedlinger, 1989). It is difficult to establish the role of codeine in producing congenital anomalies versus a variety of other drugs taken in addition to codeine during pregnancy and often without medical supervision.

CARCINOGENICITY

No information on the carcinogenic potential of codeine in experimental animals or in humans was found in the literature.

GENETIC TOXICITY

Codeine has shown little evidence of mutagenic potential in any of the standard *in vitro* or *in vivo* genotoxicity assays. It was not mutagenic in *Salmonella typhimurium* (Bruce and Heddle, 1979; King *et al.*, 1979; Zeiger *et al.*, 1992), *Escherichia coli* (King *et al.*, 1979), or in germ cells of *Drosophila melanogaster* (Nasrat *et al.*, 1977; King *et al.*, 1979). It did not induce chromosomal aberrations in cultured Chinese hamster ovary cells, but it did induce a significant increase in sister chromatid exchanges in cultured Chinese hamster ovary cells in both the presence and absence of S9 metabolic activation enzymes (NTP, unpublished; Appendix E). There is one report of increased frequencies of micronuclei in cultured rat kidney fibroblasts exposed to a combination of codeine phosphate and paracetamol (Dunn *et al.*, 1987); however, a similar increase in micronucleated cells was observed after treatment with paracetamol alone, suggesting that paracetamol was solely responsible for the increased frequency of micronucleated cells.

In vivo, no increase in the frequency of micronucleated polychromatic erythrocytes was observed in the bone marrow of female mice administered 100 to 500 mg/kg (252 to 1258 μmol/kg) codeine phosphate by intraperitoneal injection once a day for 5 days and sacrificed 4 hours after the final injection (Bruce and Heddle, 1979). However, because only 1,000 polychromatic erythrocytes were scored per dose group (333 cells in each of three mice compared to the usual 2,000 polychromatic erythrocytes in each of three to five mice per dose group), the validity of these data is questionable. A second bone marrow micronucleus study with male and female NMRI mice, at a lower total dose than that used by Bruce and Heddle (1979), also gave negative results (King *et al.*, 1979). In this investigation, mice were administered codeine phosphate in doses up to 0.25 mmol/kg by intraperitoneal injection or up to 0.5 mmol/kg by gavage, once a day for 2 days, and sacrificed 6 hours after the final dose. Although 1,000 polychromatic erythrocytes were scored in each of four mice per group, no data were presented. Because the optimum time interval between final dosing and harvest is usually 24 hours, the short interval between the times of final dosing and the sacrifice times in these two studies effectively eliminated the potential effects of the final doses from the analyses.

In conclusion, the only indications of codeine-induced mutagenicity are the results of an *in vitro* sister chromatid exchange test in cultured Chinese hamster ovary cells that showed increases in sister chromatid exchanges both with and without S9.

Morphine, a major metabolite of codeine, has been tested in a variety of mutagenicity assays. Morphine induced significant, dose-dependent increases in DNA damage (single-strand breaks, detected by single-cell microgel electrophoresis) in cultured human T-cells treated with 0.001 to 0.03 μg/mL for 1, 3, 4, or 7 days (Shafer *et al.*, 1994). In addition, a highly significant increase in the frequency of mutations at the HPRT locus of these human T-cells was observed after treatment with 0.01 μg/mL morphine for 4 days. Knapp and Kramers (1976) tested morphine in the *Drosophila melanogaster* sex-linked recessive lethal assay and found no increase in germ cell mutations in males. No increase in the frequency of chromosomal aberrations was observed in human

cord blood lymphocytes treated with 0.2 to 6.0 μg/mL morphine for 24, 48, or 68 hours (Falek *et al.*, 1972); however, this report, which presented data from several studies, did not present data from this particular experiment. Badr and Rabouh (1983) reported the results of dominant lethal and spermatocyte cytogenetic tests in male mice administered 10 to 60 mg/kg morphine. Total embryonic losses appeared markedly increased weeks 1 to 3 post-treatment for all dose groups, indicating generalized toxicity to spermatids and mature sperm. It appears from their data that morphine may induce dominant lethality in late sperm cell stages. However, these data are difficult to interpret because control data from individual mating periods (weeks) were not presented and it appears that most of the observed effects resulted from preimplantation losses (an endpoint not scored in the analysis of dominant lethality). The cytogenetic data from diakinesis-metaphase I spermatocytes scored 45 to 50 days after treatment showed extraordinary levels of translocation multivalents, e.g., approximately 25% of cells scored in the 40 and 60 mg/kg groups were aberrant. Such an observation implies morphine-induced chromosomal damage in spermatogonial stem cells of treated mice. Even the most potent alkylating germ cell mutagens are not capable of inducing such damage. Additional experiments are needed to confirm these results and, if confirmed, to further assess the germ cell mutagenicity of morphine.

Study Rationale

The National Cancer Institute and the Food and Drug Administration nominated codeine for study because it is a widely used drug and because it is a representative of the morphine class of compounds, for which chronic carcinogenicity studies had not been conducted. The feed rather than gavage exposure route was selected to more closely approximate oral exposure in humans when codeine is taken 3 to 4 times per day. It was expected that animals would be able to tolerate higher exposure levels in feed than in oral bolus dosing, and 25,000 ppm was selected as the high dose for rats in the 14-day study (estimated delivery of 2,000 mg codeine/kg body weight per day), and 12,500 ppm was selected as the high dose for mice (3,000 mg/kg per day).

MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF CODEINE

Codeine was obtained from Penick Corporation (Newark, NJ) in two lots (471NFN003 and 471NIN001/A). Lot 471NFN003 was used during the 14-day and 13-week studies, lot 471NIN001/A was used during the 2-year studies. Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO) (Appendix I). Reports on analyses performed in support of the codeine studies are on file at the National Institute of Environmental Health Sciences (NIEHS).

The chemical, a white powder, was identified as codeine by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. Purity of each lot was determined by elemental analyses, Karl Fischer water analysis, functional group titration, thin-layer chromatography, and gas chromatography. Elemental analyses for carbon, hydrogen and nitrogen were in agreement with the theoretical values for codeine when corrected for water content. Karl Fischer water analysis indicated 1.98% ± 0.07% water in lot 471NFN003 and 4.66% ± 0.05% water in lot 471NIN001/A. Functional group titration indicated a purity (anhydrous basis) of 100.0% ± 0.5% for lot 471NFN003 and 99.8% ± 0.8% for lot 471NIN001/A. Thin-layer chromatography for both lots indicated a major spot and no impurities (system 1) or a major spot and one trace impurity (system 2). Gas chromatography using system A indicated one major peak and one impurity with areas greater than 0.1% relative to the major peak for both lots. The overall purity of each lot was determined to be at least 99% on an anhydrous basis. Each lot of the chemical also met the United States Pharmacopeia XX standards for identity and purity.

Stability studies of the bulk chemical were performed by the analytical chemistry laboratory using gas chromatography. These studies indicated that codeine was stable as a bulk chemical for 2 weeks when stored protected from light at temperatures up to 25° C. To ensure stability, the bulk chemical was stored at approximately 20° C, in the dark, in sealed amber glass bottles in a secure cabinet.

Stability was monitored by the study laboratory during the 14-day, 13-week, and 2-year studies using functional group titration and/or gas chromatography. No degradation of the bulk chemical was detected.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

The dose formulations were prepared weekly by mixing codeine with feed (Table I1). Homogeneity and stability studies of a 160 ppm and a 30,000 ppm (homogeneity only) formulation were performed by the analytical chemistry laboratory using high-performance liquid chromatography. Homogeneity was confirmed, and the stability of the formulations was confirmed for up to 3 weeks when stored in the dark at room temperature.

Periodic analyses of the dose formulations of codeine were conducted at the study laboratory and analytical chemistry laboratory using high-performance liquid chromatography. During the 14-day studies, formulations were analyzed at the beginning of the study (Table I2). For the 13-week studies, formulations were analyzed at the beginning, midpoint, and end of the study (Table I3). During the 2-year studies, formulations were analyzed every 6 to 10 weeks (Table I4). Of the dose formulations analyzed for the rat study, 97% (86/89) were within 10% of the target concentration. For the mouse study, 100% (40/40) were within 10% of the target concentration. Results of periodic referee analyses performed by the analytical chemistry laboratory agreed with the results obtained by the study laboratory (Table I5).

14-DAY STUDIES

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Frederick Cancer Research Facility

(Frederick, MD). On receipt, the rats and mice were 4 weeks old. Rats were quarantined for 12 days (males) or 14 days (females) and mice were quarantined for 12 days; rats and mice were 6 weeks old on the first day of the studies. Before initiation of the studies, two male and two female rats and mice were randomly selected for parasite evaluation and gross observation for evidence of disease. Groups of five male and five female rats were fed diets containing 0, 1,562, 3,125, 6,250, 12,500, or 25,000 ppm codeine. Groups of five male and five female mice were fed diets containing 0, 781, 1,562, 3,125, 6,250, or 12,500 ppm codeine. Feed and water were available *ad libitum*. Rats and mice were housed five per cage. Clinical findings were recorded daily for rats and mice. Feed consumption was recorded daily by cage. The animals were weighed initially, after the first week, and at the end of the studies. Details of the study design and animal maintenance are summarized in Table 1.

A necropsy was performed on all rats and mice. The brain, heart, right kidney, liver, lung, right testis, and thymus were weighed. Complete histopathologic examinations were performed on 0, 6,250 (female only), 12,500, and 25,000 ppm (male and female) rats and 0 and 12,500 ppm mice. Additionally, the stomach, testis, and thymus were examined in 1,562 and 3,125 ppm male and female rats and in 6,250 ppm male rats. Table 1 lists the tissues and organs examined.

13-Week Studies

The 13-week studies were conducted to evaluate the cumulative toxic effects of repeated exposure to codeine and to determine the appropriate doses to be used in the 2-year studies.

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Simonsen Laboratories (Gilroy, CA). On receipt, the rats and mice were 4 weeks old. Animals were quarantined for 8 days (females) or 12 days (males) and were 6 weeks old on the first day of the studies. Before initiation of the studies, five male and five female rats and mice were randomly selected for parasite evaluation and gross observation for evidence of disease. At the end of the studies, serologic analyses were performed on five male and five female control rats and mice using the protocols of the NTP Sentinel Animal Program (Appendix L).

Groups of 10 male and 10 female rats and mice were fed diets containing 0, 390, 781, 1,562, 3,125, or 6,250 ppm codeine. Feed and water were available *ad libitum*. Rats and mice were housed five per cage. Clinical findings were recorded weekly for rats and mice. Feed consumption was recorded weekly by cage. The animals were weighed initially, weekly, and at the end of the studies. Details of the study design and animal maintenance are summarized in Table 1.

At the end of the 13-week studies, samples were collected for sperm morphology and vaginal cytology evaluations from male and female rats and mice in the 0, 1,562, 3,125, and 6,250 ppm groups. The parameters evaluated are listed in Table 1. Methods used were those described in the NTP's sperm morphology and vaginal cytology evaluations protocol (NTP, 1983). For 7 consecutive days before the scheduled terminal sacrifice, the vaginal vaults of the females were moistened with saline, if necessary, and samples of vaginal fluid and cells were stained. Relative numbers of leukocytes, nucleated epithelial cells, and large squamous epithelial cells were determined and used to ascertain estrous cycle stage (i.e., diestrus, proestrus, estrus, and metestrus). Male animals were evaluated for sperm morphology, count, and motility. The right epididymis and right testis were isolated and weighed. The tail of the epididymis (cauda epididymis) was then removed from the epididymal body (corpus epididymis) and weighed. Test yolk (rats) or modified Tyrode's buffer (mice) was applied to slides, and a small incision was made at the distal border of the cauda epididymis. The sperm effluxing from the incision were dispersed in the buffer on the slides, and the motile and nonmotile spermatozoa were counted for five fields per slide by two observers. Following completion of sperm motility estimates, each right cauda epididymis was placed in buffered saline solution. Caudae were finely minced, and the tissue was incubated in the saline solution and then heat fixed at 65° C. Sperm density was then determined microscopically with the aid of a hemacytometer. To quantify spermatogenesis, the testicular spermatid head count was determined by removing the tunica albuginea and homogenizing the right testis in

phosphate-buffered saline containing 10% dimethyl sulfoxide. Homogenization-resistant spermatid nuclei were counted with a hemacytometer. Four sperm morphology slides were prepared for each animal evaluated. An aliquot of killed sperm suspension was stained in a test tube, spread on a microscope slide, and examined.

At the end of the 13-week studies, rats and mice were anesthetized with a short-acting barbiturate and blood was collected from the tails of all rats and mice for hematology analyses and from the external jugular vein for clinical chemistry analyses. Blood for hematology determinations was placed in tubes containing potassium EDTA as the anticoagulant. Blood for serum analyses was collected in containers without anticoagulant, allowed to clot at room temperature, and centrifuged, and serum was separated. Hematology parameters were measured on a Baker Series 7000 Cell Counter (Baker Instrument Corp., Allentown, PA). Platelet counts were determined on a Baker Series 810 Platelet Analyzer (Baker Instruments Corp., Allentown, PA). Clinical chemistry parameters were measured on a Gemini centrifugal analyzer (Electro Nucleonics Inc., Fairfield, NJ). The hematology and clinical chemistry parameters measured are listed in Table 1.

Urinalysis studies were performed after week 12 of the studies; rats and mice were housed individually in metabolism cages for a 16-hour collection period. Urine collection containers were immersed in an ice-water bath during the sampling period to minimize evaporation and to suppress bacterial growth. Feed was withheld, but water was available *ad libitum* during the collection period. Urine volume was measured and specific gravity was determined with a refractometer (Table 1).

A necropsy was performed on all animals. The adrenal glands, brain, heart, right kidney, liver, lung, right testis, thymus, and spleen were weighed. Tissues for microscopic examination were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned to a thickness of 5 to 6 μm, and stained with hematoxylin and eosin. A complete histopathologic examination was performed on 0 and 6,250 ppm rats and mice and all mice that died before the end of the study. Additionally, the liver was examined in 3,125 ppm female rats. Table 1 lists the tissues and organs routinely examined.

2-Year Studies

Study Design

Groups of 60 male and 60 female rats were fed diets containing 0, 400, 800, or 1,600 ppm codeine. Groups of 60 male and 60 female mice were fed diets containing 0, 750, 1,500, or 3,000 ppm codeine. Ten male and 9 or 10 female rats and mice from each group were evaluated at 15 months for histopathology and organ weights.

Source and Specification of Animals

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Taconic Farms (Germantown, NY) for use in the 2-year studies. Rats were quarantined for 15 days and mice were quarantined for 13 days before the beginning of the studies. Five male and five female rats and mice were selected for parasite evaluation and gross observation of disease. Serology samples were collected for viral screening. Rats and mice were approximately 6 weeks old at the beginning of the studies. The health of the animals was monitored during the studies according to the protocols of the NTP Sentinel Animal Program (Appendix L).

Animal Maintenance

Rats were housed five per cage and mice were housed individually. Feed and water were available *ad libitum*. Feed consumption was measured monthly by cage. Cages 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 K.

Clinical Examinations and Pathology

All animals were observed twice daily. Clinical findings were recorded every 4 weeks. Body weights were recorded initially, weekly for 13 weeks, monthly thereafter, and at the end of the studies.

A complete necropsy and microscopic examination were performed on all rats and mice. At the 15-month interim evaluation necropsy, the adrenal gland, kidney, and liver of rats and mice were weighed. 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 all paired organs (i.e., adrenal gland, kidney, ovary), samples from each organ are 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 microscopic slides, paraffin blocks, and residual wet tissues were sent to the NTP Archives for inventory, slide/block match, and wet tissue audit. The slides, individual animal data records, and pathology tables were evaluated by an independent quality assessment laboratory. The individual animal records and tables were compared for accuracy, the slide and tissue counts were verified, and the histotechnique was evaluated. For the 2-year studies, a quality assessment pathologist reviewed the adrenal gland (cortex and medulla), lymph nodes (mandibular), forestomach, nose, and other tissues of interest for rats and thyroid gland, kidney, liver, and other tissues of interest for mice.

The quality assessment report and slides were submitted to the NTP Pathology Working Group (PWG) chair, who reviewed the selected tissues and any other tissues for which a disagreement in diagnosis between the laboratory and quality assessment pathologists existed. 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 chair 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. Thus, the final diagnoses represent a consensus of contractor pathologists 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 diagnosed lesions for each tissue type were evaluated separately or combined according to 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 or missing were censored from the survival analyses; animals dying from natural causes were not censored. Statistical analyses for possible dose-related effects on survival used Cox's (1972) method for testing two groups for equality and Tarone's (1975) life table test to identify dose-related trends. All reported P values for the survival analyses are two sided.

Calculation of Incidence

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

Analysis of Neoplasm Incidences

The majority of neoplasms in these studies were considered to be incidental to the cause of death or not rapidly lethal. Thus, the primary statistical method used was logistic regression analysis, which

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

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

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

Analysis of Nonneoplastic Lesion Incidences

Because all nonneoplastic lesions in this study were considered to be incidental to the cause of death or not rapidly lethal, the primary statistical analysis used was a logistic regression analysis in which nonneoplastic lesion prevalence was modeled as a logistic function of chemical exposure and time. For lesions detected at the interim evaluation, the Fisher exact test was used, a procedure based on the overall proportion of affected animals.

Analysis of Continuous Variables

Two approaches were employed to assess the significance of pairwise comparisons between exposed and control groups in the analysis of continuous variables. Organ and body weight data, which have approximately normal distributions, were analyzed using the parametric multiple comparison procedures of Dunnett (1955) and Williams (1971, 1972). Clinical chemistry, hematology, spermatid, and epididymal spermatozoal data, which have typically skewed distributions, were analyzed using the nonparametric multiple comparison methods of Shirley (1977) and Dunn (1964). Jonckheere's test (Jonckheere, 1954) was used to assess the significance of the dose-related trends and to determine whether a trend-sensitive test (Williams' or Shirley's test) was more appropriate for pairwise comparisons than a test that does not assume a monotonic dose-related trend (Dunnett's or Dunn's test). Prior to 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). Because the vaginal cytology data are proportions (the proportion of the observation period that an animal was in a given estrous stage), an arcsine transformation was used to bring the data into closer conformance with normality assumptions. Treatment effects were investigated by applying a multivariate analysis of variance (Morrison, 1976) to the transformed data to test for simultaneous equality of measurements across exposure levels.

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 (Haseman *et al.*, 1984, 1985) are included in the NTP reports for neoplasms appearing to show compound-related effects.

Quality Assurance Methods

The 13-week and 2-year studies were conducted in compliance with Food and Drug Administration Good Laboratory Practice Regulations (21 CFR, Part 58). In addition, as records from the 2-year studies were submitted to the NTP Archives, these studies were audited retrospectively by an independent quality assurance contractor. Separate audits covering completeness and accuracy of the pathology data, pathology specimens, final pathology tables, and a draft of this NTP Technical Report were conducted. Audit procedures and findings are presented in the reports and are on file at NIEHS. The audit findings were reviewed and assessed by NTP staff, so all comments had been resolved or were otherwise addressed during the preparation of this Technical Report.

Genetic Toxicology

The genetic toxicity of codeine was assessed by testing the ability of the chemical to induce mutations in various strains of *Salmonella typhimurium* and sister chromatid exchanges and chromosomal aberrations in cultured Chinese hamster ovary cells. The protocols for these studies and the results are given in Appendix E.

The genetic toxicity studies of codeine 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 structure and responses 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 chemically induced DNA damage and to predict carcinogenicity in animals, based on the electrophilic theory of chemical carcinogenesis and the somatic mutation theory (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 do not correlate 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 currently the most predictive *in vitro* test for rodent carcinogenicity (89% of the *Salmonella* mutagens were 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 is not yet defined.

TABLE 1
Experimental Design and Materials and Methods in the Feed Studies of Codeine

14-Day Studies	13-Week Studies	2-Year Studies
Study Laboratory		
EG&G Mason Research Institute (Worcester, MA)	EG&G Mason Research Institute (Worcester, MA)	Microbiological Associates, Inc. (Bethesda, MD)
Strain and Species		
Rats: F344/N Mice: $B6C3F_1$	Rats: F344/N Mice: $B6C3F_1$	Rats: F344/N Mice: $B6C3F_1$
Animal Source		
Frederick Cancer Research Facility (Frederick, MD)	Simonsen Laboratories (Gilroy, CA)	Taconic Farms (Germantown, NY)
Time Held Before Studies		
Rats: 12 days (males) or 14 days (females) Mice: 12 days	Rats: 12 days (males) or 8 days (females) Mice: 12 days (males) or 8 days (females)	Rats: 15 days Mice: 13 days
Average Age When Studies Began		
6 weeks	6 weeks	7 weeks
Date of First Dose		
Rats: 2 April (males) or 4 April (females) 1984 Mice: 9 April (males) or 16 April (females) 1984	Rats: 23 October (males) or 19 October (females) 1984 Mice: 13 November (males) 9 November (females) 1984	Rats: 14 April 1989 Mice: 29 March 1989
Duration of Dosing		
14 days	13 weeks	Rats: 105-106 weeks Mice: 105-106 weeks
Date of Last Dose		
Rats: 16 April (males) or 18 April (females) 1984 Mice: 23 April (males) or 30 April (females) 1984	Rats: 23 or 25 January (males) 16 or 18 January (females) 1985 Mice: 13 or 15 February (males) 6 or 8 February (females) 1985	Rats: 19 April 1991 Mice: 3 April 1991
Necropsy Dates		
Rats: 16 April (males) or 18 April (females) 1984 Mice: 23 April (males) or 30 April (females) 1984	Rats: 23 or 25 January (males) or 16 or 18 January (females) 1985 Mice: 13 or 15 February (males) or 6 or 8 February (females) 1985	Rats: 15-Month interim evaluation — 12-13 July 1990 Terminal — 15-19 April 1991 Mice: 15-Month interim evaluation — 27-28 June 1990 Terminal — 27 March-3 April 1991
Average Age at Necropsy		
8 weeks	19 weeks	15-Month interim evaluation — 72 weeks Terminal — 111-112 weeks

TABLE 1
Experimental Design and Materials and Methods in the Feed Studies of Codeine (continued)

14-Day Studies	13-Week Studies	2-Year Studies
Size of Study Groups		
5 males and 5 females	10 males and 10 females	15-Month interim evaluation — 10 males and 10 females Terminal — 50 males and 50 females
Method of Distribution		
Animals of similar weight classes were assigned to cages using a computer-generated list of random numbers; cages were assigned to test groups using an additional computer-generated list of random numbers	Same as 14-day studies	Same as 14-day studies
Animals per Cage		
5	5	Rats: 5 Mice: 1
Method of Animal Identification		
Toe clip	Toe clip	Tail tattoo
Diet		
NIH-07 open formula meal diet (Zeigler Brothers, Inc., Gardners, PA), available *ad libitum*, changed weekly.	Same as 14-day studies	NIH-07 open formula powdered diet (Zeigler Brothers, Inc., Gardners, PA), available *ad libitum*, changed weekly.
Water Distribution		
Tap water (Worcester municipal supply) via automatic watering system (Edstrom Industries, Waterford, WI), available *ad libitum*	Same as 14-day studies	Tap water (Washington Suburban Sanitary Commission, Potomac plant) via automatic watering system (Edstrom Industries, Waterford, WI), available *ad libitum*
Cages		
See-Through II System (Lab Products, Rochelle Park, NJ), changed twice per week.	Same as 14-day studies	Same as 14-day studies, except mice cages changed weekly.
Bedding		
Beta-Chip (Northeastern Products Corp., Warrensburg, NY), changed twice per week	Same as 14-day studies	Sani-Chips (P.J. Murphy Forest Products, Montville, NJ), changed twice per week (rats) or once per week (mice)
Cage Filters		
Non-woven fiber (Snow Filtration, Cincinnati, OH), changed once every two weeks	Same as 14-day studies	Spun-Bonded Polyester (Snow Filtration, Cincinnati, OH), changed once every two weeks
Racks		
See-Through II System (Lab Products, Rochelle Park, NJ), changed once every two weeks	Same as 14-day studies	Same as 14-day studies

TABLE 1
Experimental Design and Materials and Methods in the Feed Studies of Codeine (continued)

14-Day Studies	13-Week Studies	2-Year Studies
Animal Room Environment		
Temperature: 21.1° to 23.9° C Relative humidity: 28% to 60% Fluorescent light: 12 hours/day Room air: at least 10 changes per hour	Temperature: 20.5° to 25.0° C Relative humidity: 34% to 55% Fluorescent light: 12 hours/day Room air: at least 10 changes per hour	Temperature: 19.4° to 26.7° C (rats), 20° to 25° C (mice) Relative humidity: 25% to 95% (rats), 23% to 94% (mice) Fluorescent light: 12 hours/day Room air: at least 10 changes per hour
Doses		
Rats: 0, 1,562, 3,125, 6,250, 12,500, or 25,000 ppm in feed, available *ad libitum* Mice: 0, 781, 1,562, 3,125, 6,250, or 12,500 ppm in feed, available *ad libitum*	0, 390, 781, 1,562, 3,125, or 6,250 ppm in feed, available *ad libitum*	Rats: 0, 400, 800, or 1,600 ppm in feed, available *ad libitum* Mice: 0, 750, 1,500, or 3,000 ppm in feed, available *ad libitum*
Type and Frequency of Observation		
Observed twice daily; animals were weighed initially, after the first week, and at the end of the studies; clinical observations were recorded daily. Feed consumption was recorded daily by cage.	Observed twice daily; animals were weighed initially, weekly, and at the end of the studies; clinical observations were recorded weekly. Feed consumption was recorded weekly by cage.	Observed twice daily and clinical observations were recorded every 4 weeks; animals were weighed initially, weekly for 13 weeks, monthly thereafter, and at the end of the studies. Feed consumption was recorded monthly by cage.
Method of Sacrifice		
Sodium thiamylal asphyxiation	Carbon dioxide asphyxiation	Carbon dioxide asphyxiation
Necropsy		
Necropsy performed on all animals. Organs weighed were brain, heart, right kidney, liver, lung, right testis, and thymus.	Necropsy performed on all animals. Organs weighed were adrenal gland, brain, heart, right kidney, liver, lung, spleen, right testis, and thymus.	Necropsy performed on all animals. Organs weighed at the 15-month interim evaluation were adrenal gland, right kidney, and liver.
Clinical Pathology		
None	Blood was collected from the tail of all animals for hematology and from the external jugular vein for clinical chemistry. Urine was collected from animals housed individually in metabolism cages for 16 hours. ***Hematology:*** Hematocrit, hemoglobin, erythrocytes, reticulocytes, nucleated erythrocytes, mean cell volume, mean cell hemoglobin, mean cell hemoglobin concentration, platelets, and leukocytes and differentials ***Clinical Chemistry:*** urea nitrogen, creatinine, glucose, total protein, albumin, alkaline aminotransferase, alkaline phosphatase, and aspartate aminotransferase ***Urinalysis:*** specific gravity and volume	None

TABLE 1
Experimental Design and Materials and Methods in the Feed Studies of Codeine (continued)

14-Day Studies	13-Week Studies	2-Year Studies
Histopathology		
Complete histopathology was performed on all animals in the 0, 6,250 (females only), 12,500, and 25,000 ppm (rats) and 0 and 12,500 ppm (mice). In addition to gross lesions and tissue masses, the tissues examined included: adrenal gland, brain, clitoral gland (rats only), esophagus, femur with marrow and epiphysis, heart, large intestine (cecum, colon and rectum), small intestine (duodenum, jejunum, and ileum), kidney, liver, lungs and mainstem bronchi, lymph nodes (mandibular and mesenteric), mammary gland, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland (rats only), prostate gland, salivary gland, skin, spleen, stomach (forestomach and glandular), testis, thymus, thyroid gland, trachea, urinary bladder, and uterus. In addition, the stomach, testis, and thymus were examined in 1,562 and 3,125 ppm male and female rats and 6,250 ppm male rats.	Complete histopathology was performed on all 0 and 6,250 ppm rats and mice and all mice that died before the end of the study. In addition to gross lesions and tissue masses, the tissues examined included: adrenal gland, brain, clitoral gland (rats only), esophagus, heart, large intestine (cecum, colon and rectum), small intestine (duodenum, jejunum, and ileum), kidney, liver, lungs and mainstem bronchi, lymph nodes (mandibular and mesenteric), mammary gland, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, skin, sternebrae with marrow, spleen, stomach (forestomach and glandular), testis, thymus, thyroid gland, trachea, urinary bladder, uterus, and vagina. Additionally, the liver was examined in 3,125 ppm female rats.	Complete histopathology was performed on all rats and mice. In addition to gross lesions and tissue masses, the tissues examined included: adrenal gland, brain, clitoral gland, esophagus, femur with marrow and epiphysis, heart, large intestine (cecum, colon and rectum), small intestine (duodenum, jejunum, and ileum), kidney, liver, lungs and mainstem bronchi, 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), testis, thymus, thyroid gland, trachea, urinary bladder, and uterus.
Sperm Morphology and Vaginal Cytology Evaluations		
None	Rats and mice in the 0, 1,562, 3,125, and 6,250 ppm groups were evaluated. Sperm samples were collected at the end of the studies and evaluated for sperm morphology, count, and motility. The right cauda, epididymis, and testis were weighed. Vaginal samples were collected for 7 consecutive days before the end of the studies and evaluated for the relative frequency of estrous stages and for estrous cycle length.	None

RESULTS

RATS

14-DAY STUDY

One female exposed to 6,250 ppm, one male and three females exposed to 12,500 ppm, and all males and females exposed to 25,000 ppm died during the study (Table 2). Final mean body weights and mean body weight gains of all exposed groups except 1,562 ppm females were significantly lower than those of the controls. Initial feed consumption by exposed groups was lower than that by the controls.

Although feed consumption by exposed groups had improved by day 14, feed consumption by all groups of exposed males and by 12,500 ppm females remained lower than that by the controls. Dietary levels of 1,562, 3,125, 6,250, 12,500, or 25,000 ppm codeine resulted in daily doses of approximately 125, 250, 450, 650, or 750 mg codeine/kg body weight to males and 125, 250, 500, 700, or 300 mg/kg to females.

The absolute and relative thymus weights of 12,500 ppm males and females and the absolute and relative testis weights of 12,500 ppm males were significantly lower than those of the controls (Table F1); reduced organ weights were considered secondary to reduced body weights.

No chemical-related gross lesions were observed in rats at necropsy. Nonneoplastic lesions were observed primarily in the 12,500 and 25,000 ppm groups and were associated with decreased survival and increased morbidity in these groups. These lesions included thickening of the forestomach mucosa consisting of hyperplasia (males: 0 ppm, 0/5; 1,562 ppm, 0/5; 3,125 ppm, 2/5; 6,250 ppm, 1/5; 12,500 ppm, 2/5; 25,000 ppm, 1/5; females: 0/5, 0/5, 0/5, 0/5, 1/4, 2/4) and hyperkeratosis (males: 0/5, 0/5, 1/5, 0/5, 2/5, 1/5; females: 0/5, 0/5, 0/5, 1/5, 1/4, 2/4), lymphoid depletion of the thymus (males: 0/5, 0/5, 0/5, 0/5, 1/5, 5/5; females: 0/5, 0/5, 0/5, 1/5, 3/3, 4/4), and testicular degeneration (0/5, 0/5, 0/5, 0/5, 3/5, 2/5).

Because of the lower body weights in the 12,500 ppm groups, the high dose selected for the 13-week study was 6,250 ppm.

TABLE 2
Survival, Mean Body Weights, and Feed Consumption of Rats in the 14-Day Feed Study of Codeine

Dose (ppm)	Survival[a]	Mean Body Weight[b] (g) Initial	Final	Change	Final Weight Relative to Controls (%)	Feed Consumption[c] Day 1	Day 14
Male							
0	5/5	123 ± 2	193 ± 5	70 ± 3		13.6	15.9
1,562	5/5	125 ± 2	172 ± 3**	46 ± 2**	89	0.4	13.5
3,125	5/5	123 ± 3	165 ± 4**	42 ± 1**	85	0.3	13.3
6,250	5/5	126 ± 3	151 ± 2**	25 ± 1**	78	0.4	12.8
12,500	4/5[d]	125 ± 3	119 ± 5**	−4 ± 3**	62	0.3	11.2
25,000	0/5[e]	128 ± 2	—	—	—	—	—
Female							
0	5/5	113 ± 2	141 ± 3	28 ± 1		10.6	11.3
1,562	5/5	115 ± 3	140 ± 4	25 ± 2	99	5.1	12.8
3,125	5/5	113 ± 2	126 ± 5**	13 ± 3**	89	7.3	11.5
6,250	4/5[f]	114 ± 3	128 ± 3*	13 ± 0**	90	3.4	13.3
12,500	2/5[g]	115 ± 2	112 ± 7**	−6 ± 3**	80	7.8	10.0
25,000	0/5[h]	113 ± 2	—	—	—	—	—

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Number of animals surviving/number initially in group
[b] Weights and weight changes are given as mean ± standard error. Subsequent calculations are based on animals surviving to the end of the study. No final mean body weights were calculated for groups with 100% mortality.
[c] Feed consumption data are based on 10 animals per group and expressed as grams of feed consumed per animal per day. No feed consumption data available for 25,000 ppm rats.
[d] Day of death: 12
[e] Day of death: 10, 12, 12, 12, 13
[f] Day of death: 4
[g] Day of death: 7, 9, 9
[h] Day of death: 7, 7, 8, 9, 9

13-Week Study

One male rat in the 390 ppm group died during week 2; all other rats survived until the end of the study (Table 3). Final mean body weights and mean body weight gains of all groups of males exposed to codeine and of females exposed to 1,562, 3,125, and 6,250 ppm were significantly lower than those of the controls. Feed consumption decreased with increasing exposure level during the first week of the study; however, by the end of the study, feed consumption by most exposed groups was similar to that by the controls. Dietary levels of 390, 781, 1,562, 3,125, or 6,250 ppm codeine resulted in daily doses of approximately 25, 50, 100, 200, or 450 mg codeine/kg body weight to males and 25, 50, 100, 250, or 500 mg/kg to females. Altered clinical observations included ruffled fur, alopecia, and abnormal posture in 3,125 and 6,250 ppm females.

As shown in Table G1, there were alterations of various hematology, clinical chemistry, and urinalysis parameters at the end of the 13-week rat study. There was mild dose-dependent leukopenia and lymphopenia, evidenced by decreased leukocyte and lymphocyte counts in females receiving 1,562 ppm and above and in 6,250 ppm males. The decreased leukocyte counts were attributed to decreased lymphocyte numbers. A decrease in lymphopoiesis is often associated with lymphopenia and has been associated with such conditions as lower body weight gain or malnutrition. In this study, the exposed animals gained much less weight than controls,

Table 3
Survival, Mean Body Weights, and Feed Consumption of Rats in the 13-Week Feed Study of Codeine

Dose (ppm)	Survival[a]	Mean Body Weight[b] (g) Initial	Final	Change	Final Weight Relative to Controls (%)	Feed Consumption[c] Week 1	Week 13[d]
Male							
0	10/10	130 ± 3	379 ± 7	249 ± 6		11.8	19.2
390	9/10[e]	130 ± 3	352 ± 6**	223 ± 6**	93	11.3	19.3
781	10/10	128 ± 3	348 ± 6**	220 ± 5**	92	11.2	18.6
1,562	10/10	132 ± 3	330 ± 7**	198 ± 6**	87	10.7	17.0
3,125	10/10	129 ± 3	311 ± 5**	182 ± 5**	82	9.8	17.5
6,250	10/10	131 ± 3	309 ± 7**	178 ± 6**	82	8.3	19.2
Female							
0	10/10	92 ± 2	195 ± 4	103 ± 4		8.9	10.2
390	10/10	92 ± 2	193 ± 3	101 ± 3	99	8.4	10.4
781	10/10	92 ± 2	190 ± 4	99 ± 4	97	8.4	10.0
1,562	10/10	91 ± 2	180 ± 6*	88 ± 6*	92	7.7	10.7
3,125	10/10	89 ± 2	173 ± 5**	84 ± 5**	89	7.8	11.9
6,250	10/10	91 ± 2	170 ± 3**	79 ± 3**	87	6.0	12.1

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Number of animals surviving/number initially in group
[b] Weights and weight changes are given as mean ± standard error. Subsequent calculations are based on animals surviving to the end of the study.
[c] Feed consumption is expressed as grams of feed consumed per animal per day.
[d] Feed consumption data for females from week 12
[e] Week of death: 2

indicating a decreased nutritional status, and there was a dose-related decrease in thymus weight. Therefore, the lymphopenia would be consistent with decreased lymphopoiesis related to decreased nutrition and possibly compounded by a stress-related increase in endogenous steroid production. There also was a minimal to mild macrocytosis, evidenced by increased mean cell volumes, that occurred in all exposed groups of males and in females exposed to 781, 3,125, or 6,250 ppm. The presence of larger red cells in the absence of an erythropoietic response would be consistent with altered iron metabolism or hemoglobin production and could also be related to the decreased body weights and altered nutritional status. Most other changes were minimal and only occurred in male rats exposed to 1,562 ppm and above. For example, there were minimal decreases in red cell counts, reticulocyte counts, serum glucose concentrations, and alkaline phosphatase activities; each of these parameters can be affected by a decreased nutritional status or feed intake.

No significant differences in sperm morphology or vaginal cytology parameters between control and exposed rats were observed (Table H1).

Absolute and relative adrenal gland weights of all groups of exposed males and of 3,125 and 6,250 ppm females were significantly greater than those of the controls (Table F2). Absolute and relative liver weights of exposed males were significantly lower than those of the controls. Relative thymus weights of 3,125 and 6,250 ppm males were significantly lower than those of the controls. No chemical-related gross or histopathologic lesions were observed in male or female rats.

Dose Selection Rationale: Based on markedly lower final mean body weights in groups exposed to 3,125 and 6,250 ppm, codeine exposure levels selected for the 2-year feed study in male and female rats were 400, 800, and 1,600 ppm.

2-Year Study

Survival

Estimates of 2-year survival probabilities for male and female rats are shown in Table 4 and in the Kaplan-Meier survival curves (Figure 2). Survival of 400 ppm females was significantly greater than that of the controls; survival of all groups of exposed males and of 800 and 1,600 ppm females was similar to that of the controls.

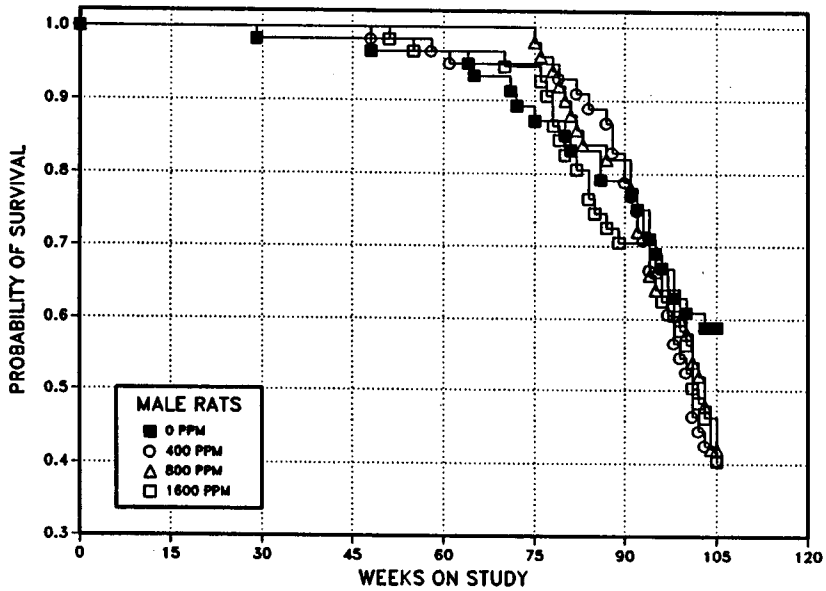
Body Weights, Feed and Compound Consumption, and Clinical Findings

There was an exposure-related decrease in mean body weights of males and females (Figure 3 and Tables 5 and 6). Mean body weights of 1,600 ppm males and females were lower than those of the controls from week 2, and the final mean body weights were 88% (males) and 89% (females) those of the controls. Feed consumption by exposed groups was similar to that by the controls (Tables J1 and J2). Dietary levels of 400, 800, and 1,600 ppm codeine resulted in daily doses of approximately 15, 30, and 70 mg codeine/kg body weight to males and 15, 40, and 80 mg/kg to females. Chemical-related clinical findings were limited to ocular discharge in exposed males and females.

Table 4
Survival of Rats in the 2-Year Feed Study of Codeine

	0 ppm	400 ppm	800 ppm	1,600 ppm
Male				
Animals initially in study	60	60	60	60
15-Month interim evaluation[a]	10	10	10	10
Moribund	14	23	24	23
Natural deaths	7	7	5	7
Animals surviving to study termination	29	20	21	20
Percent probability of survival at end of study[b]	59	40	42	40
Mean survival (days)[c]	629	635	643	628
Survival analysis[d]	P=0.244	P=0.216	P=0.319	P=0.193
Female				
Animals initially in study	60	60	60	60
15-Month interim evaluation[a]	10	10	9	9
Moribund	15	9	17	14
Natural deaths	7	3	5	5
Animals surviving to study termination	28	38[e]	29[e]	32
Percent probability of survival at end of study	56	76	57	63
Mean survival (days)	628	665	659	663
Survival analysis	P=0.782N	P=0.035N	P=0.718N	P=0.369N

[a] Censored from survival analyses
[b] Kaplan-Meier determinations based on the number of animals alive on the first day of terminal sacrifice
[c] Mean of all deaths (uncensored, censored, and terminal sacrifice)
[d] The result of the life table trend test (Tarone, 1975) is in the control column, and the results of the life table pairwise comparisons (Cox, 1972) with the controls are in the exposure columns. A negative trend or a lower mortality in an exposure group is indicated by N.
[e] Includes one animal that died during the last week of the study.



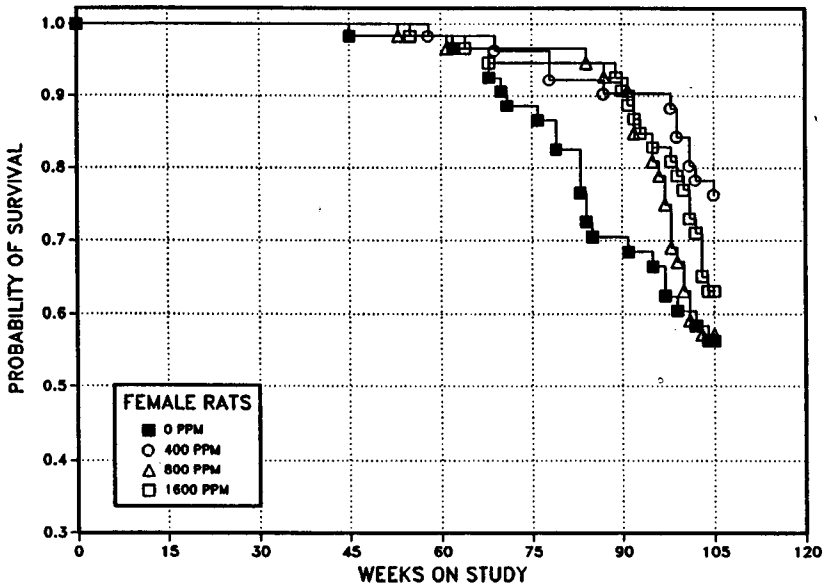
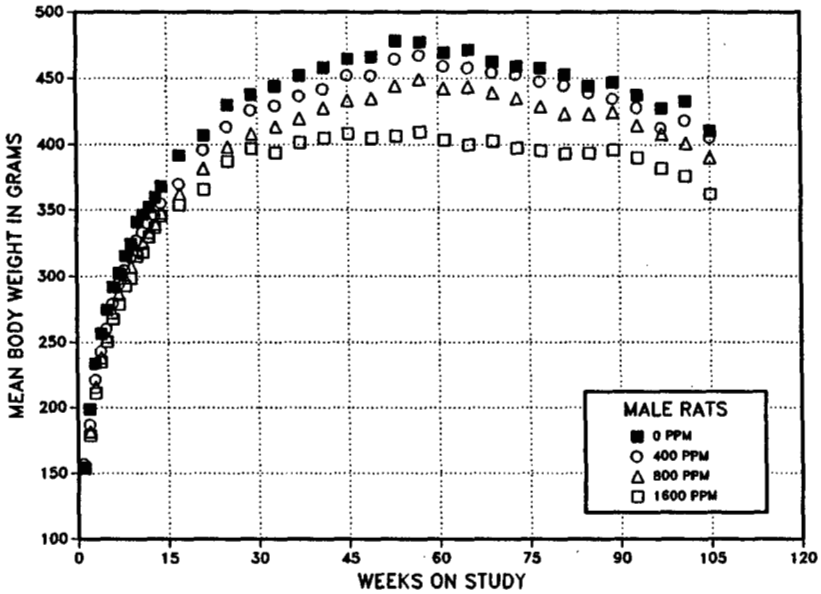


FIGURE 2
Kaplan-Meier Survival Curves for Rats Administered Codeine in Feed for 2 Years



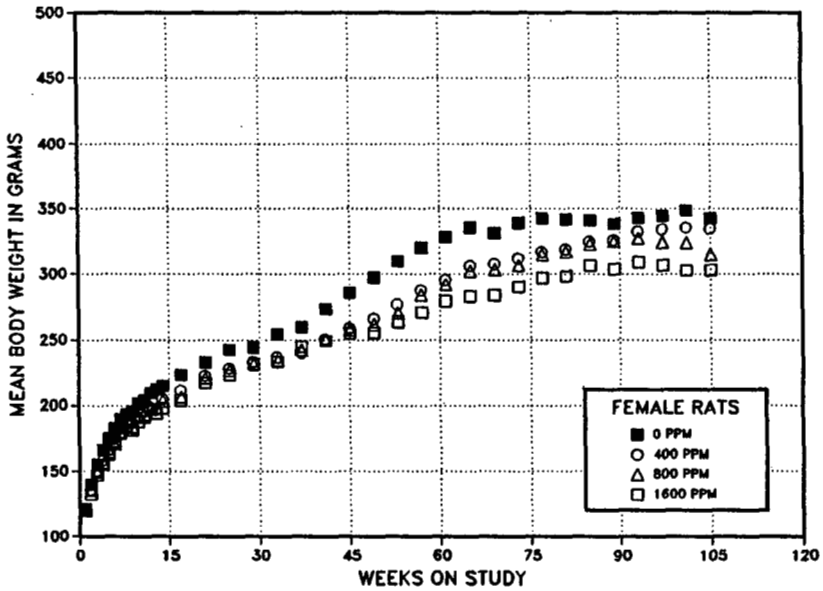


FIGURE 3
Growth Curves for Rats Administered Codeine in Feed for 2 Years

TABLE 5
Mean Body Weights and Survival of Male Rats in the 2-Year Feed Study of Codeine

Weeks on Study	0 ppm Av. Wt. (g)	0 ppm No. of Survivors	400 ppm Av. Wt. (g)	400 ppm Wt. (% of controls)	400 ppm No. of Survivors	800 ppm Av. Wt. (g)	800 ppm Wt. (% of controls)	800 ppm No. of Survivors	1,600 ppm Av. Wt. (g)	1,600 ppm Wt. (% of controls)	1,600 ppm No. of Survivors
1	154	60	157	102	60	154	100	60	155	100	60
2	199	60	187	94	60	182	92	60	179	90	60
3	234	60	221	95	60	216	92	60	211	90	60
4	257	60	243	95	60	238	93	60	235	92	60
5	274	60	260	95	60	254	93	60	250	91	60
6	292	60	279	96	60	272	93	60	268	92	60
7	302	60	294	97	60	286	95	60	279	92	60
8	316	60	305	97	60	299	95	60	293	93	60
9	325	60	314	97	60	307	95	60	298	92	60
10	341	60	327	96	60	320	94	60	315	92	60
11	347	60	333	96	60	325	94	60	318	92	60
12	352	60	340	96	60	333	95	60	330	94	60
13	360	60	346	96	60	339	94	60	337	94	60
14	368	60	355	96	60	348	94	60	346	94	60
17	392	60	370	95	60	363	93	60	354	90	60
21	407	60	396	97	60	382	94	60	366	90	60
25	430	60	414	96	60	398	93	60	387	90	60
29	438	60	426	97	60	408	93	60	397	91	60
33	444	59	429	97	60	414	93	60	394	89	60
37	452	59	437	97	60	420	93	60	402	89	60
41	458	59	442	96	60	428	93	60	405	88	60
45	465	59	452	97	60	434	93	60	408	88	60
49	466	58	452	97	59	435	93	60	405	87	60
53	478	58	465	97	59	444	93	60	407	85	59
57	477	58	468	98	59	450	94	60	409	86	58
61	470	58	459	98	58	443	94	60	404	86	58
65	471	56	458	97	57	444	94	60	400	85	58
69[a]	463	46	454	98	47	439	95	50	403	87	48
73	459	44	453	99	47	435	95	50	397	87	47
77	458	43	448	98	47	429	94	48	395	86	46
81	453	42	444	98	46	423	94	45	393	87	41
85	444	41	439	99	44	423	95	42	393	89	38
89	447	39	434	97	41	424	95	41	396	89	36
93	437	37	428	98	37	415	95	36	390	89	35
97	427	33	412	97	33	408	96	32	382	89	31
101	433	30	418	97	26	401	93	29	376	87	28
105	411	29	405	99	20	390	95	21	362	88	22
Mean for weeks											
1-13	289		277	96		271	94		267	93	
14-52	432		417	97		403	93		386	90	
53-105	452		442	98		426	94		393	87	

[a] Interim evaluation occurred during week 65.

TABLE 6
Mean Body Weights and Survival of Female Rats in the 2-Year Feed Study of Codeine

Weeks on Study	0 ppm Av. Wt. (g)	0 ppm No. of Survivors	400 ppm Av. Wt. (g)	400 ppm Wt. (% of controls)	400 ppm No. of Survivors	800 ppm Av. Wt. (g)	800 ppm Wt. (% of controls)	800 ppm No. of Survivors	1,600 ppm Av. Wt. (g)	1,600 ppm Wt. (% of controls)	1,600 ppm No. of Survivors
1	121	60	121	100	60	121	100	60	120	99	60
2	140	60	136	97	60	136	97	60	133	95	60
3	155	60	150	97	60	149	96	60	147	95	60
4	167	60	158	95	60	156	94	60	155	93	60
5	175	60	166	95	60	165	94	60	163	93	60
6	182	60	175	96	60	171	94	60	173	95	60
7	190	60	183	96	60	179	95	60	180	95	60
8	193	60	187	97	60	184	95	60	184	95	60
9	195	60	187	96	60	184	94	60	182	93	60
10	201	60	192	95	60	191	95	60	188	93	60
11	204	60	196	96	60	193	95	60	191	94	60
12	209	60	199	95	60	197	94	60	197	94	60
13	212	60	196	93	60	198	93	60	194	91	60
14	215	60	205	95	60	203	95	60	198	92	60
17	224	60	211	95	60	206	92	60	204	91	60
21	233	60	223	96	60	221	95	60	217	93	60
25	242	60	228	94	60	227	94	60	223	92	60
29	244	60	233	96	60	232	95	60	232	95	60
33	255	60	237	93	60	235	92	60	234	92	60
37	260	60	240	93	60	243	93	60	245	94	60
41	273	60	251	92	60	251	92	60	249	91	60
45	286	60	259	91	60	258	90	60	255	89	60
49	297	59	266	89	60	262	88	60	256	86	60
53	310	59	277	89	60	270	87	60	264	85	60
57	320	59	288	90	60	284	89	59	271	85	59
61	328	59	295	90	59	292	89	59	279	85	59
65	336	58	306	91	59	302	90	58	283	84	58
69[a]	331	46	308	93	49	304	92	49	284	86	48
73	339	44	312	92	48	307	91	49	290	86	48
77	342	43	317	93	48	315	92	49	297	87	48
81	342	41	319	93	46	317	93	49	298	87	48
85	341	36	325	95	46	323	95	48	307	90	48
89	338	35	326	96	45	325	96	47	304	90	48
93	343	34	333	97	45	327	95	43	309	90	43
97	345	33	334	97	45	324	94	40	307	89	42
101	349	30	336	96	42	324	93	32	303	87	39
105	342	28	335	98	39	315	92	29	303	89	32
Mean for weeks											
1-13	180		173	96		171	95		170	94	
14-52	253		235	93		234	93		231	92	
53-105	336		315	94		309	92		293	87	

[a] Interim evaluation occurred during week 66.

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 adrenal gland, clitoral/preputial gland, mammary gland, pituitary gland, respiratory system, and liver. 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.

Adrenal Gland: Absolute and relative adrenal gland weights of 800 and 1,600 ppm males were significantly greater than those of the controls at 15 months (Table F3). In histological sections, the overall cross-sectional area of the adrenal gland was similar between controls and exposure groups. However, when compared to that of the controls, there was generally a smaller amount of adrenal medulla relative to the amount of adrenal cortex in 800 and 1,600 ppm males. In these exposure groups, the zona reticularis appeared to be slightly thickened and the cells of the inner portion of the zona fasicularis were slightly smaller than those of the controls. Vascular dilatation in the medulla and inner cortex was also slightly more prominent in 800 and 1,600 ppm males. These effects were not present in 400 ppm males or in any group of exposed females. At 2 years, there were exposure-related decreased incidences of adrenal medulla hyperplasia in males and females (Tables 7, A5, and B5). There was an exposure-related decrease in the incidence of benign pheochromocytoma in males, and the incidences in exposed males were significantly lower than that in the controls. The incidence of benign pheochromocytoma in 1,600 ppm males was lower than had been seen in any historical control group (Tables 7 and A4b). These decreases were considered to be related to codeine exposure.

TABLE 7
Incidences of Neoplasms and Nonneoplastic Lesions of the Adrenal Medulla in Rats in the 2-Year Feed Study of Codeine

	0 ppm	400 ppm	800 ppm	1,600 ppm
Male				
Number Examined Microscopically	49	50	50	50
Hyperplasia[a]	25 (1.8)[b]	12**(1.8)	10**(1.5)	9**(1.9)
Benign Pheochromocytoma[c]				
Overall rate[d]	16/49 (33%)	6/50 (12%)	6/50 (12%)	3/50 (6%)
Adjusted rate[e]	49.1%	24.9%	21.7%	13.6%
Terminal rate[f]	12/28 (43%)	3/20 (15%)	3/21 (14%)	2/20 (10%)
First incidence (days)	599	678	608	708
Logistic regression test[g]	P=0.001N	P=0.013N	P=0.010N	P=0.001N
Female				
Number Examined Microscopically	50	50	50	51
Hyperplasia	8 (1.4)	5 (1.4)	2* (1.5)	2* (1.5)
Benign Pheochromocytoma[h]				
Overall rate	2/50 (4%)	5/50 (10%)	1/50 (2%)	1/51 (2%)
Adjusted rate	6.6%	12.2%	2.7%	3.1%
Terminal rate	1/28 (4%)	3/38 (8%)	0/28 (0%)	1/32 (3%)
First incidence (days)	677	689	686	733 (T)
Logistic regression test	P=0.158N	P=0.296	P=0.472N	P=0.437N

* Significantly different ($P \leq 0.05$) from the control group by the logistic regression test
** $P \leq 0.01$
[a] Number of animals with lesion
[b] Average severity of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked
[c] Historical incidence for 2-year NTP feed studies with untreated control groups (mean ± standard deviation): 379/1,182 (32.1% ± 11.7%); range 10%-63%
[d] Number of animals with neoplasm per number of animals with adrenal medulla 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. In the exposure group columns are the P values corresponding to the pairwise comparison 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 a lower incidence in an exposure group is indicated by N.
[h] Historical incidence: 49/1175 (4.17% ± 2.50%); range 0%-8%

Clitoral/Preputial Gland: In 1,600 ppm females, the incidence of clitoral gland ectasia was significantly greater than that in the controls (Tables 8 and B5). The incidence of clitoral gland adenoma or carcinoma (combined) in 1,600 ppm females was significantly lower than that in the controls (Tables 8 and B1), and it was at the low end of the historical control range (2%-21%, Tables 8 and B4a). The incidence of preputial gland hyperplasia in 1,600 ppm males (0 ppm, 3/50; 400 ppm, 1/50; 800 ppm, 4/48; 1,600 ppm, 11/50) and the incidence of preputial gland ectasia in 400 ppm males (1/50, 9/50, 6/48, 4/50) were significantly greater than those in the controls at 2 years (Table A5).

Mammary Gland: The incidences of mammary gland fibroadenoma and fibroadenoma or adenocarcinoma (combined) in 1,600 ppm females were significantly lower than those in the controls (Table 9).

TABLE 8
Incidences of Neoplasms and Nonneoplastic Lesions of the Clitoral Gland in Female Rats in the 2-Year Feed Study of Codeine

	0 ppm	400 ppm	800 ppm	1,600 ppm
Number Examined Microscopically	47	47	50	51
Ectasia[a]	5 (2.2)[b]	9 (2.7)	7 (2.4)	20**(2.3)
Inflammation	0	0	1 (3.0)	3 (3.0)
Adenoma				
Overall rate[c]	5/47 (11%)	6/47 (13%)	12/50 (24%)	1/51 (2%)
Adenoma or Carcinoma[d]				
Overall rate	6/47 (13%)	6/47 (13%)	12/50 (24%)	1/51 (2%)
Adjusted rate[e]	19.0%	15.7%	37.8%	3.1%
Terminal rate[f]	3/27 (11%)	5/36 (14%)	10/29 (34%)	1/32 (3%)
First incidence (days)	587	546	662	733 (T)
Logistic regression test[g]	P=0.052N	P=0.568N	P=0.189	P=0.033N

(T) Terminal sacrifice
** Significantly different ($P \leq 0.01$) from the control group by the logistic regression test
[a] Number of animals with lesion
[b] Average severity of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked
[c] Number of animals with neoplasm per number of animals with clitoral gland examined microscopically
[d] Historical incidence for 2-year NTP feed studies with untreated control groups (mean ± standard deviation): 119/1,117 (10.7% ± 5.6%); range 2%-21%
[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. In the exposure group columns are the P values corresponding to the pairwise comparison 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 a lower incidence in an exposure group is indicated by N.

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

	0 ppm	400 ppm	800 ppm	1,600 ppm
Fibroadenoma[a]				
Overall rate[b]	27/50 (54%)	21/50 (42%)	27/51 (53%)	8/51 (16%)
Adjusted rate[c]	70.3%	47.4%	68.2%	23.0%
Terminal rate[d]	17/28 (61%)	15/38 (39%)	17/29 (59%)	6/32 (19%)
First incidence (days)	475	400	641	645
Logistic regression test[e]	P<0.001N	P=0.087N	P=0.359N	P<0.001N
Adenocarcinoma[f]				
Overall rate	3/50 (6%)	2/50 (4%)	3/51 (6%)	0/51 (0%)
Adjusted rate	8.5%	5.3%	10.3%	0.0%
Terminal rate	1/28 (4%)	2/38 (5%)	3/29 (10%)	0/32 (0%)
First incidence (days)	495	733 (T)	733 (T)	—[g]
Logistic regression test	P=0.102N	P=0.533N	P=0.650N	P=0.147N
Fibroadenoma or Adenocarcinoma[h]				
Overall rate	30/50 (60%)	23/50 (46%)	29/51 (57%)	8/51 (16%)
Adjusted rate	74.4%	52.0%	73.5%	23.0%
Terminal rate	18/28 (64%)	17/38 (45%)	19/29 (66%)	6/32 (19%)
First incidence (days)	475	400	641	645
Logistic regression test	P<0.001N	P=0.063N	P=0.284N	P<0.001N

[a] Historical incidence for 2-year NTP feed studies with untreated control groups (mean ± standard deviation): 465/1,202 (38.7% ± 12.7%); range 8%-58%
[b] Number of animals with neoplasm per number of animals with mammary gland examined microscopically
[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. In the exposure group columns are the P values corresponding to the pairwise comparison 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 a lower incidence in an exposure group is indicated by N.
[f] Historical incidence (carcinoma): 32/1,202 (2.7% ± 2.9%); range 0%-10%
[g] Not applicable; no neoplasms in animal group
[h] Historical incidence (includes data for adenoma): 507/1,202 (42.2% ± 13.5%); range 8%-64%

Pituitary Gland: The incidence of pituitary gland (pars distalis) focal hyperplasia in 400 ppm males was greater than that in the controls at 2 years (5/50, 14/50, 5/48, 3/47; Table A5). The incidences of pituitary gland (pars distalis) angiectasis in 400 and 1,600 ppm females were lower than that in the controls (13/46, 7/50, 10/50, 7/51; Table B5). The incidence of pituitary gland adenoma or carcinoma (combined) in 1,600 ppm females was significantly lower than that in the controls (17/46, 18/50, 19/50, 12/51; Tables B1 and B3), and the incidence was lower than the historical control range (30%-80%; Table B4c).

Respiratory System: The incidences of cytoplasmic alteration of the olfactory epithelium in 800 ppm males and 1,600 ppm males and females were greater than those in the controls at 2 years (males: 12/50, 16/50, 28/50, 47/50; females: 38/50, 45/50, 42/51, 49/51; Tables A5 and B5).

Liver: Absolute and relative liver weights of exposed males were significantly lower than those of the controls at 15 months (Table F3). At 2 years, there was an exposure-related decrease in the incidence of cystic degeneration of the liver (14/50, 5/50, 1/50, 0/50; Table A5).

MICE

14-DAY STUDY

All mice survived to the end of the study (Table 10). The final mean body weight of 3,125 ppm females was significantly greater than that of the controls; the final mean body weight of 12,500 ppm females and the mean body weight gains of 12,500 ppm males and females were significantly lower than those of the controls. Initially, feed consumption by 6,250 and 12,500 ppm males and females was lower than that by the controls. At day 14, feed consumption by exposed males and females, except 12,500 ppm females, was similar to that by the controls. Dietary levels of 781, 1,562, 3,125, 6,250, or 12,500 ppm codeine resulted in daily doses of approximately 150, 300, 600, 1,300, or 3,000 mg/kg body weight to males and 200, 400, 750, 1,500, or 3,000 mg/kg to females.

Absolute and relative liver weights of 3,125, 6,250, and 12,500 ppm males and of 12,500 ppm females and the absolute and relative right kidney weights of 12,500 ppm males were significantly lower than those of the controls (Table F4). No gross or histopathologic lesions were attributed to codeine exposure.

Because of the lower mean body weight gains of 12,500 ppm males and females, the high dose selected for the 13-week study was 6,250 ppm.

TABLE 10
Survival, Mean Body Weights, and Feed Consumption of Mice in the 14-Day Feed Study of Codeine

Dose (ppm)	Survival[a]	Mean Body Weight[b] (g) Initial	Final	Change	Final Weight Relative to Controls (%)	Feed Consumption[c] Day 1	Day 14
Male							
0	5/5	21.1 ± 0.6	25.2 ± 0.9	4.1 ± 0.4		4.0	4.1
781	5/5	21.2 ± 0.6	25.7 ± 1.0	4.5 ± 0.4	102	4.2	4.6
1,562	5/5	21.5 ± 1.0	25.9 ± 1.2	4.4 ± 0.3	103	4.1	5.0
3,125	5/5	20.9 ± 0.6	24.4 ± 1.0	3.4 ± 0.5	97	3.6	4.9
6,250	5/5	21.8 ± 0.5	24.7 ± 0.8	2.9 ± 0.3	98	2.4	3.8
12,500	5/5	20.9 ± 0.5	22.8 ± 0.7	1.9 ± 1.1*	90	2.2	3.5
Female							
0	5/5	16.7 ± 0.4	18.7 ± 0.3	2.0 ± 0.3		4.5	3.9
781	5/5	16.8 ± 0.4	18.8 ± 0.2	2.0 ± 0.2	101	4.3	4.1
1,562	5/5	14.8 ± 0.9	18.2 ± 0.4	3.4 ± 0.7*	97	4.4	4.7
3,125	5/5	17.0 ± 0.4	20.1 ± 0.5*	3.1 ± 0.2	108	4.2	4.2
6,250	5/5	17.0 ± 0.3	19.0 ± 0.2	2.0 ± 0.2	102	2.8	3.1
12,500	5/5	16.4 ± 0.4	16.8 ± 0.3**	0.4 ± 0.3*	90	2.3	2.9

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Number of animals surviving/number initially in group
[b] Weights and weight changes are given as mean ± standard error.
[c] Feed consumption data are based on 25 animals per group and expressed as grams of feed consumed per animal per day.

13-Week Study

Two male mice in the 3,125 ppm group died during week 7 (Table 11), and these deaths were not related to codeine administration. All other mice survived to the end of the study. Final mean body weights of exposed males and females were similar to those of the controls, although the final mean body weight of 6,250 ppm males was 9% lower and that of 6,250 ppm females was 6% lower than that of the respective controls. Feed consumption by exposed males and females was similar to that by the controls. Dietary levels of 390, 781, 1,562, 3,125, or 6,250 ppm codeine resulted in daily doses of approximately 60, 120, 260, 460, or 1,000 mg codeine/kg body weight to males and 60, 130, 280, 530, or 1,200 mg/kg to females. Abnormal posture was observed in all exposed groups of males.

There were no chemical-related differences in hematology or urinalysis parameters in male or female mice (Table G2). Minor, sporadic changes occurred in a few of the clinical chemistry parameters; they were not considered biologically significant.

Sperm motility in 1,562 ppm males was significantly less than that of the controls (Table H2); however, this finding was not observed at 3,125 or 6,250 ppm. No significant differences in sperm morphology or vaginal cytology were attributed to codeine exposure.

Absolute and relative kidney weights of 3,125 and 6,250 ppm males were significantly lower than those of the controls (Table F5). No chemical-related differences in organ weights were observed in females. No chemical-related gross or histopathologic lesions were observed in male or female mice.

Dose Selection Rationale: Because of the lower body weights at 6,250 ppm and above, the exposure levels selected for the 2-year feed study in mice were 750, 1,500, and 3,000 ppm.

Table 11
Survival, Mean Body Weights, and Feed Consumption of Mice in the 13-Week Feed Study of Codeine

Dose (ppm)	Survival[a]	Mean Body Weight[b] (g) Initial	Final	Change	Final Weight Relative to Controls (%)	Feed Consumption[c] Week 1	Week 13[d]
Male							
0	10/10	22.5 ± 0.3	30.7 ± 0.7	8.2 ± 0.6		2.8	4.6
390	10/10	22.0 ± 0.3	30.3 ± 0.3	8.3 ± 0.4	99	2.9	4.4
781	10/10	22.7 ± 0.2	27.8 ± 1.3	5.1 ± 1.3	91	3.1	5.3
1,562	10/10	21.5 ± 0.2	29.7 ± 0.8	8.2 ± 0.7	97	3.1	5.2
3,125	8/10[e]	22.2 ± 0.3	28.8 ± 0.9	6.7 ± 0.9	94	2.9	4.4
6,250	10/10	22.8 ± 0.2	27.9 ± 0.6	5.2 ± 0.4	91	2.8	5.0
Female							
0	10/10	16.9 ± 0.3	22.5 ± 0.7	5.6 ± 0.7		2.6	6.6
390	10/10	17.2 ± 0.4	24.6 ± 0.4	7.3 ± 0.2	109	2.5	4.4
781	10/10	16.6 ± 0.5	24.5 ± 0.5	7.9 ± 0.5	109	2.4	4.7
1,562	10/10	17.1 ± 0.2	23.5 ± 0.8	6.3 ± 0.8	104	2.6	4.3
3,125	10/10	17.1 ± 0.3	23.0 ± 0.7	5.9 ± 0.7	102	2.5	4.3
6,250	10/10	17.5 ± 0.3	21.2 ± 0.8	3.7 ± 0.8	94	2.4	5.4

[a] Number of animals surviving/number initially in group
[b] Weights and weight changes are given as mean ± standard error. Subsequent calculations are based on animals surviving to the end of the study. Differences from the control group were not significant by Williams' or Dunnett's test.
[c] Feed consumption is expressed as grams of feed consumed per animal per day.
[d] Feed consumption data for females from week 12
[e] Week of death: 7, 7

2-Year Study

Survival

Estimates of 2-year survival probabilities for male and female mice are shown in Table 12 and in the Kaplan-Meier survival curves (Figure 4). Survival of exposed males and females was similar to that of the controls.

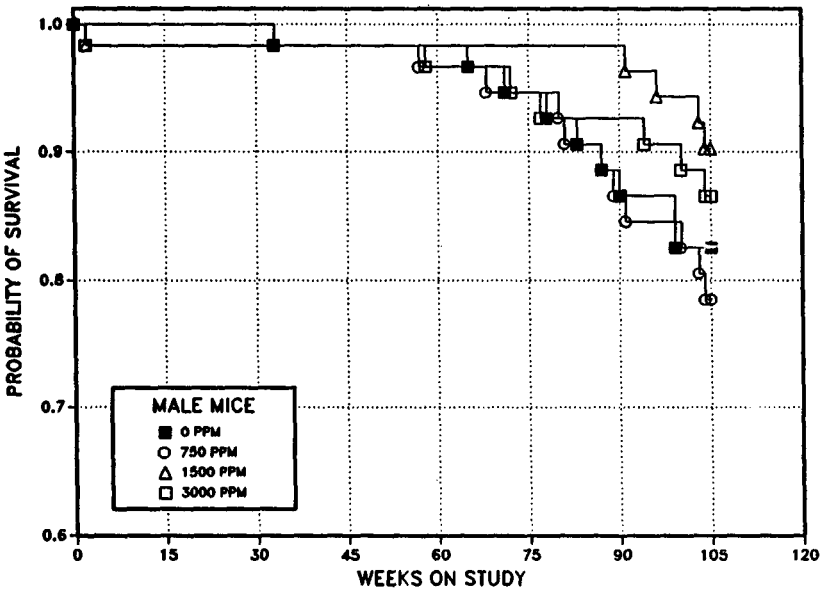
Body Weights, Feed and Compound Consumption, and Clinical Findings

Mean body weights of 750 and 1,500 ppm males and females were similar to those of the controls throughout most of the study (Tables 13 and 14, Figure 5). Mean body weights of 3,000 ppm males and females were lower than those of the controls from about week 13, and the final mean body weights of these groups were 86% and 82% those of the respective controls. Feed consumption by exposed groups was similar to that by the controls (Tables J3 and J4). Dietary levels of 750, 1,500, and 3,000 ppm codeine resulted in daily doses of approximately 100, 200, and 400 mg codeine/kg body weight. Clinical findings included alopecia on the ventral body surface in 1,500 ppm males and 3,000 ppm males and females beginning on day 57 and ruffled fur in 1,500 ppm males and 3,000 ppm males and females from day 85.

Table 12
Survival of Mice in the 2-Year Feed Study of Codeine

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
Male				
Animals initially in study	60	60	60	60
15-Month interim evaluation[a]	10	10	10	10
Accidental death[a]	0	1	0	0
Moribund	4	4	2	1
Natural deaths	5	7	3	6
Animals surviving to study termination	41	38	45	43
Percent probability of survival at end of study[b]	83	79	90	87
Mean survival (days)[c]	656	650	669	657
Survival analysis[d]	P=0.417N	P=0.810	P=0.350N	P=0.766N
Female				
Animals initially in study	60	60	60	60
15-Month interim evaluation[a]	10	9	9	9
Missing[a]	0	0	0	1
Moribund	7	9	6	4
Natural deaths	7	6	2	11
Animals surviving to study termination	36[e]	36	43	35[e]
Percent probability of survival at end of study	73	72	85	71
Mean survival (days)	641	627	662	641
Survival analysis	P=0.979N	P=0.945	P=0.185N	P=1.000

[a] Censored from survival analyses
[b] Kaplan-Meier determinations based on the number of animals alive on the first day of terminal sacrifice
[c] Mean of all deaths (uncensored, censored, and terminal sacrifice)
[d] The result of the life table trend test (Tarone, 1975) is in the control column, and the results of the life table pairwise comparisons (Cox, 1972) with the controls are in the exposed columns. A negative trend or a lower mortality in an exposure group is indicated by N.
[e] Includes one animal that died during the last week of the study.



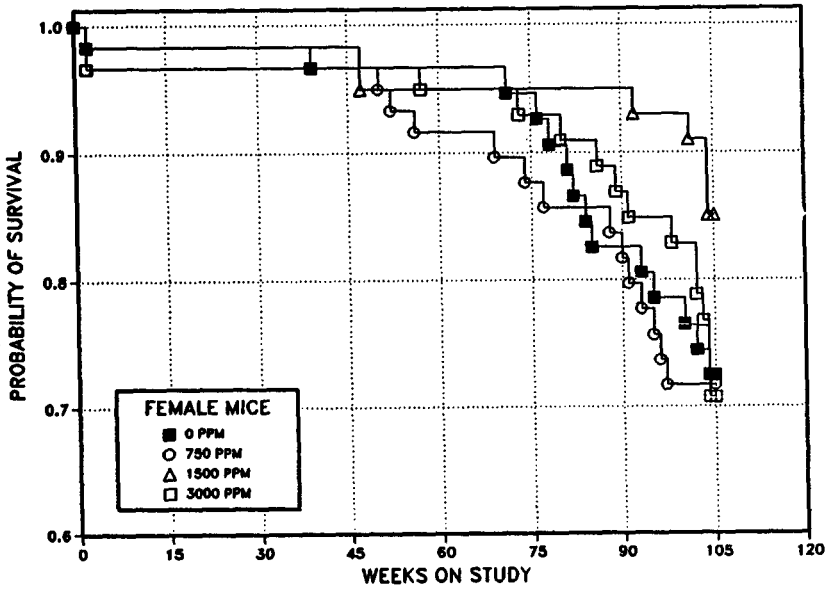


FIGURE 4
Kaplan-Meier Survival Curves for Mice Administered Codeine in Feed for 2 Years

TABLE 13
Mean Body Weights and Survival of Male Mice in the 2-Year Feed Study of Codeine

Weeks on Study	0 ppm Av. Wt. (g)	0 ppm No. of Survivors	750 ppm Av. Wt. (g)	750 ppm Wt. (% of controls)	750 ppm No. of Survivors	1,500 ppm Av. Wt. (g)	1,500 ppm Wt. (% of controls)	1,500 ppm No. of Survivors	3,000 ppm Av. Wt. (g)	3,000 ppm Wt. (% of controls)	3,000 ppm No. of Survivors
1	23.2	60	23.1	100	60	22.6	97	60	23.3	100	60
2	23.8	60	23.6	99	60	23.4	98	60	22.8	96	60
3	25.6	60	24.9	97	59	25.2	98	59	24.7	97	59
4	26.7	60	25.9	97	59	25.8	97	59	24.8	93	59
5	27.7	60	27.3	99	59	26.6	96	59	26.5	96	59
6	28.1	60	27.7	99	59	27.2	97	59	26.9	96	59
7	29.7	60	29.1	98	59	28.6	96	59	27.9	94	59
8	30.6	60	30.0	98	59	29.3	96	59	28.4	93	59
9	31.6	60	30.2	96	59	29.9	95	59	29.2	92	59
10	32.4	60	31.1	96	59	30.5	94	59	29.8	92	59
11	33.4	60	32.2	96	59	31.6	95	59	30.6	92	59
12	34.1	60	33.0	97	59	32.2	94	59	31.5	92	59
13	34.6	60	33.3	96	59	32.5	94	59	31.2	90	59
14	35.2	60	34.0	97	59	32.8	93	59	31.7	90	59
17	38.1	60	36.9	97	59	35.0	92	59	33.3	87	59
21	41.6	60	40.0	96	59	37.2	89	59	34.9	84	59
25	42.3	60	41.1	97	59	39.3	93	59	36.6	87	59
29	44.9	60	44.8	100	59	42.3	94	59	38.9	87	59
33	46.1	60	45.1	98	59	42.5	92	59	38.5	84	59
37	48.3	59	46.8	97	59	44.2	92	59	40.4	84	59
41	48.9	59	48.9	100	59	45.7	94	59	41.7	85	59
45	49.5	59	49.9	101	59	47.0	95	59	43.3	88	59
49	49.4	59	50.0	101	59	47.4	96	59	43.8	89	59
53	50.0	59	51.3	103	59	48.7	97	59	44.6	89	59
57	50.4	59	51.6	102	59	49.2	98	59	45.2	90	59
61	50.7	59	51.7	102	58	49.4	97	59	45.4	90	58
65	50.3	59	51.5	102	58	49.0	97	59	45.0	90	58
69[a]	50.6	48	51.3	101	47	49.5	98	49	44.7	88	48
73	49.4	47	50.5	102	47	48.6	98	49	43.4	88	47
77	49.2	47	50.4	102	47	48.5	99	49	43.4	88	47
81	49.9	46	50.6	101	46	47.5	95	49	43.7	88	46
85	49.5	45	50.3	102	45	47.5	96	49	43.8	89	46
89	50.2	44	51.4	102	44	48.1	96	49	44.2	88	46
93	48.5	43	50.3	104	42	45.9	95	48	41.8	86	46
97	49.0	43	51.0	104	42	46.0	94	47	42.2	86	45
101	49.0	41	50.3	103	41	45.1	92	47	41.7	85	44
104	48.2	41	50.4	105	39	44.3	92	45	41.4	86	43
Mean for weeks											
1-13	29.3		28.6	98		28.1	96		27.5	94	
14-52	44.4		43.8	98		41.3	93		38.3	87	
53-104	49.6		50.9	103		47.7	96		43.6	88	

[a] Interim evaluation occurred during week 66.

TABLE 14
Mean Body Weights and Survival of Female Mice in the 2-Year Feed Study of Codeine

Weeks on Study	0 ppm Av. Wt. (g)	0 ppm No. of Survivors	750 ppm Av. Wt. (g)	750 ppm Wt. (% of controls)	750 ppm No. of Survivors	1,500 ppm Av. Wt. (g)	1,500 ppm Wt. (% of controls)	1,500 ppm No. of Survivors	3,000 ppm Av. Wt. (g)	3,000 ppm Wt. (% of controls)	3,000 ppm No. of Survivors
1	18.3	60	18.5	101	60	18.4	101	60	18.3	100	60
2	19.5	60	19.6	101	59	19.2	99	59	18.9	97	58
3	21.2	59	21.2	100	58	21.4	101	59	21.0	99	58
4	22.1	59	22.3	101	58	22.3	101	59	21.7	98	58
5	23.5	59	23.6	100	58	23.4	100	59	23.1	98	58
6	24.5	59	24.5	100	58	24.1	98	59	23.6	96	58
7	25.9	59	25.9	100	58	25.5	99	59	25.3	98	58
8	26.7	59	26.7	100	58	26.3	99	59	26.0	97	58
9	27.6	59	26.9	98	58	26.6	96	59	25.8	94	58
10	28.3	59	27.7	98	58	27.3	97	59	26.6	94	58
11	29.3	59	28.4	97	58	27.7	95	59	26.8	92	58
12	30.4	59	29.0	95	58	28.0	92	59	27.5	91	58
13	29.8	59	28.6	96	58	27.7	93	59	26.9	90	58
14	31.1	59	30.0	97	58	29.0	93	59	28.1	90	58
17	34.5	59	33.3	97	58	31.2	90	59	29.5	86	58
21	39.1	59	36.9	94	58	34.0	87	59	31.7	81	58
25	40.7	59	38.8	95	58	36.6	90	59	33.6	83	58
29	42.5	59	41.7	98	58	38.9	92	59	35.1	83	58
33	44.6	59	42.4	95	58	39.8	89	59	35.5	80	58
37	46.2	59	44.6	97	58	41.4	90	59	36.5	79	58
41	47.5	58	47.2	99	58	43.8	92	59	38.5	81	58
45	48.9	58	49.0	100	58	45.3	93	59	39.9	82	58
49	48.7	58	49.5	102	58	46.5	96	57	40.4	83	58
53	50.2	58	51.0	102	56	48.3	96	57	42.2	84	58
57	51.2	58	52.7	103	55	50.4	98	57	43.6	85	58
61	52.5	58	54.3	103	55	51.7	99	57	44.4	85	57
65	52.4	58	54.0	103	55	51.3	98	57	44.2	84	56
69[a]	52.6	48	53.5	102	46	52.5	100	48	44.2	84	47
73	50.9	47	53.2	105	45	52.4	103	48	44.3	87	47
77	49.8	46	53.2	107	44	52.3	105	48	43.7	88	46
81	51.4	45	53.9	105	43	53.2	104	48	44.3	86	45
85	53.0	42	54.2	102	43	54.1	102	48	44.1	83	45
89	53.2	41	53.5	101	42	53.7	101	48	43.6	82	44
93	51.3	41	52.1	102	40	52.4	102	47	41.7	81	42
97	52.5	39	53.2	101	37	52.5	100	47	42.4	81	42
101	51.6	38	53.5	104	36	51.3	99	47	41.4	80	41
104	49.6	36	51.3	103	36	49.1	99	44	40.6	82	37
Mean for weeks											
1-13	25.2		24.8	99		24.5	98		24.0	96	
14-52	42.4		41.3	97		38.7	91		34.9	83	
53-104	51.6		53.1	103		51.8	100		43.2	84	

[a] Interim evaluation occurred during week 66.

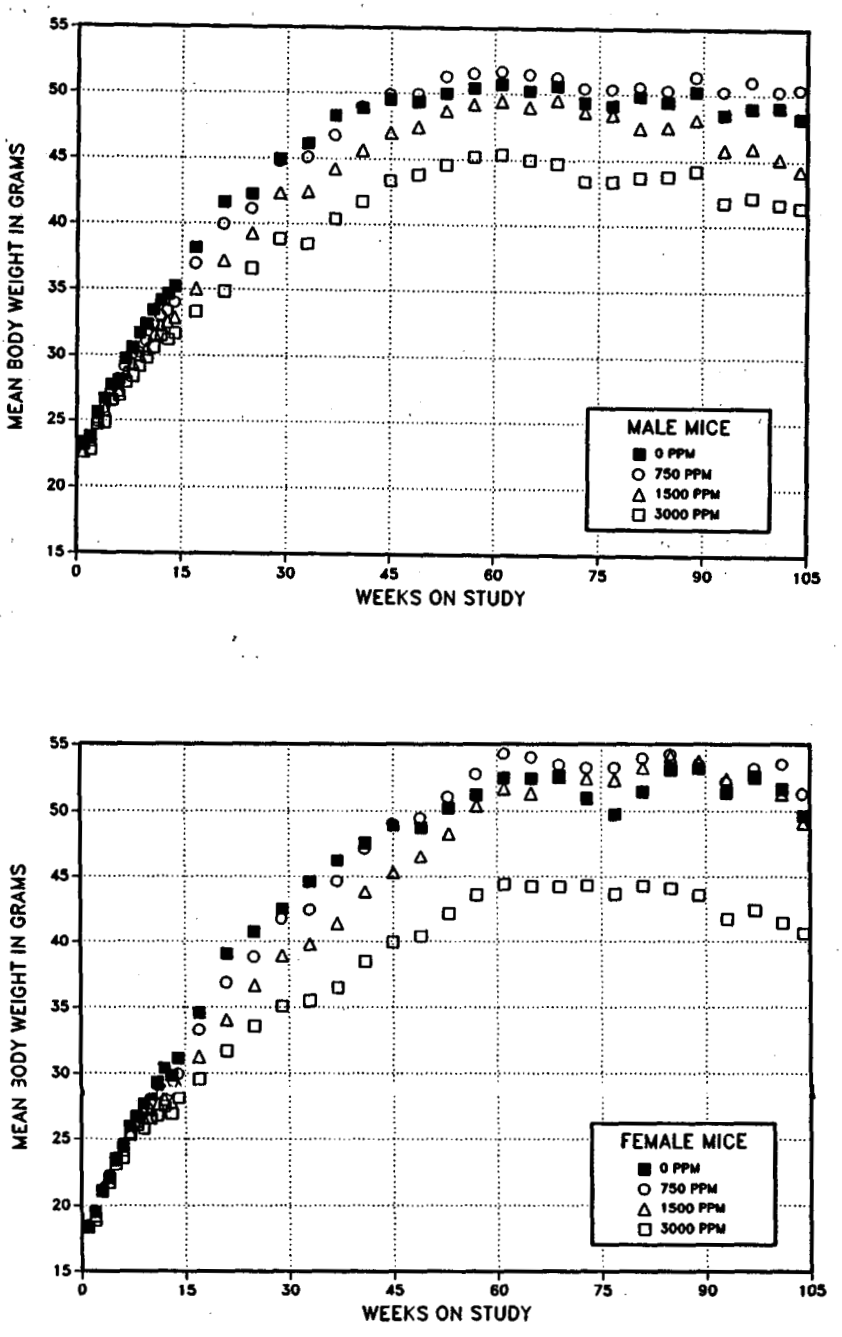


FIGURE 5
Growth Curves for Mice Administered Codeine in Feed for 2 Years

Pathology and Statistical Analyses

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

Thyroid Gland: At 15 months, the incidence of thyroid gland follicular cell hyperplasia in 3,000 ppm males was significantly greater than that in the controls, and follicular cell hyperplasia was observed in 1,500 and 3,000 ppm females but not in controls (Tables 15, C5, and D5). At 2 years, the incidences of follicular cell hyperplasia in all exposed groups of males and females were significantly greater than those in the controls. Hyperplasia was characterized by an increase in the number of follicular epithelial cells lining the thyroid follicles. This change was minimal to mild in severity, generally focal in distribution, and involved one to three adjacent follicles. The severity was similar among exposed and control groups. Mild papillary infolding of the epithelium was sometimes present within the follicle. Cellular atypia and evidence of local invasion were not present. No effect on thyroid gland neoplasia was observed in mice.

TABLE 15
Incidences of Nonneoplastic Lesions of the Thyroid Gland in Mice in the 2-Year Feed Study of Codeine

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
Male				
15-Month Interim Evaluation				
Number Examined Microscopically	10	10	10	10
Follicular Cell Hyperplasia[a]	0	0	0	6**(1.2)[b]
2-Year Study				
Number Examined Microscopically	49	50	50	50
Follicular Cell Hyperplasia	7 (1.1)	25**(1.2)	29**(1.3)	34**(1.5)
Female				
15-Month Interim Evaluation				
Number Examined Microscopically	10	9	9	9
Follicular Cell Hyperplasia	0	0	1 (1.0)	1 (1.0)
2-Year Study				
Number Examined Microscopically	48	51	51	50
Follicular Cell Hyperplasia	14 (1.4)	29**(1.6)	42**(1.7)	44**(1.9)

** Significantly different ($P \leq 0.01$) from the control group by the Fisher exact test (interim evaluation) or the logistic regression test (2-year study)

[a] Number of animals with lesion

[b] Average severity grade of lesion in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

Liver: The incidence of centrilobular fatty change, which normally occurs in the liver of *ad libitum*-fed mice, was significantly lower in 3,000 ppm males than in the controls at 15 months, and the decreased incidence appeared to be related to exposure level (Tables 16 and C5). At 2 years, the incidences of eosinophilic focus, foci of fatty change, centrilobular cytomegaly, and centrilobular fatty change in 3,000 ppm males were lower than those in the controls, and the incidence of clear cell focus in 3,000 ppm males was significantly lower than that in the controls. Similar effects in the incidences of nonneoplastic liver lesions were not observed in female mice. There were exposure-related decreases in the incidences of hepatocellular adenomas and the incidences of hepatocellular adenomas or carcinomas (combined) in males and females, and the incidences in the 3,000 ppm groups were lower than those in the controls (Tables 16, C3, and D3). However, the incidence of hepatocellular adenomas or carcinomas (combined) in all groups of males and females were in the mid-range of the historical controls (males, 10%-68%; females, 3%-56%; Tables 16, C4, and D4). Decreased incidences of hepatocellular neoplasms have been associated with low body weights in previous studies. Because the low neoplasm incidences in 3,000 ppm males and females are associated with reduced body weight effects in this study, there is no clear anticarcinogenic effect.

TABLE 16
Incidences of Neoplasms and Nonneoplastic Lesions of the Liver in Mice in the 2-Year Feed Study of Codeine

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
Male				
15-Month Interim Evaluation				
Number Examined Microscopically	10	10	10	10
Eosinophilic Focus[a]	1	0	0	0
Foci of Fatty Change	0	0	0	0
Centrilobular Cytomegaly	0	0	1 (1.0)[b]	0
Centrilobular Fatty Change	10 (1.4)	10 (1.5)	6 (1.0)	1**(1.0)
2-Year Study				
Number Examined Microscopically	50	50	50	50
Clear Cell Focus	7	4	2	0**
Eosinophilic Focus	8	12	5	4
Foci of Fatty Change	4	4	0	0
Centrilobular Cytomegaly	3 (1.0)	0	0	0
Centrilobular Fatty Change	3 (2.0)	8 (1.1)	0	0
Hepatocellular Adenoma				
Overall rate[c]	23/50 (46%)	25/50 (50%)	16/50 (32%)	10/50** (20%)
Hepatocellular Carcinoma				
Overall rate	13/50 (26%)	8/50 (16%)	13/50 (26%)	7/50 (14%)
Hepatocellular Adenoma or Carcinoma[d]				
Overall rate	29/50 (58%)	29/50 (58%)	23/50 (46%)	16/50 (32%)
Adjusted rate[e]	63.0%	62.8%	47.9%	34.0%
Terminal rate[f]	24/41 (59%)	21/38 (55%)	20/45 (44%)	12/43 (28%)
First incidence (days)	497	396	635	500
Logistic regression test[g]	P=0.002N	P=0.567	P=0.118N	P=0.007N

(continued)

TABLE 16
Incidences of Neoplasms and Nonneoplastic Lesions of the Liver in Mice in the 2-Year Feed Study of Codeine (continued)

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
Female				
2-Year Study				
Number Examined Microscopically	50	51	51	50
Clear Cell Focus	0	0	1	0
Eosinophilic Focus	6	7	9	2
Foci of Fatty Change	0	0	1	0
Hepatocellular Adenoma				
Overall rate	12/50 (24%)	10/51 (20%)	13/51 (25%)	5/50* (10%)
Hepatocellular Carcinoma				
Overall rate	5/50 (10%)	6/51 (12%)	6/51 (12%)	4/50 (8%)
Hepatocellular Adenoma or Carcinoma[h]				
Overall rate	16/50 (32%)	15/51 (29%)	15/51 (29%)	8/50 (16%)
Adjusted rate	40.3%	37.3%	34.9%	21.4%
Terminal rate	13/36 (36%)	11/36 (31%)	15/43 (35%)	6/35 (17%)
First incidence (days)	497	616	731	720
Logistic regression test	P=0.028N	P=0.520N	P=0.413N	P=0.047N

* Significantly different ($P \leq 0.05$) from the control group by the Fisher exact test (interim evaluation) or the logistic regression test (2-year study)
** $P \leq 0.01$
[a] Number of animals with lesion
[b] Average severity grade of lesion in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked
[c] Number of animals with neoplasm per number of animals with liver examined microscopically
[d] Historical incidence for 2-year NTP feed studies with untreated control groups (mean ± standard deviation): 509/1,316 (38.7% ± 13.9%); range 10%-68%
[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. In the exposure group columns are the P values corresponding to the pairwise comparison 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 a lower incidence in an exposure group is indicated by N.
[h] Historical incidence: 260/1,312 (19.8% ± 12.8%); range 3%-56%

Other Organs: The incidences of malignant lymphoma were lower in exposed males than in controls (0 ppm, 7/50; 750 ppm, 1/50; 1,500 ppm, 1/50; 3,000 ppm, 0/50; Table C3) but not in exposed females (7/50, 5/51, 6/51, 8/50; Table D3). Except in 3,000 ppm males, the incidences of malignant lymphomas in the control and exposed groups of males were within the historical control range from NTP feed studies (2% to 24%; Table C4b); therefore, the decreased incidences could not be clearly attributed to codeine exposure.

By statistical analysis, the incidences of nonneoplastic lesions at several sites in 3,000 ppm males and females were significantly less than those of the controls. These included mineralization of the brain (males: 33/50, 21/50, 14/50, 18/50; females: 23/50, 18/51, 21/51, 10/50; Tables C5 and D5), chronic inflammation of the preputial gland (25/50, 22/50, 23/50, 15/50), chronic inflammation of the salivary glands in males (22/50, 21/50, 15/50, 13/50), chronic inflammation of the clitoral gland (3/41, 4/43, 5/45, 10/44), and hyaline degeneration

(cytoplasmic alteration) of the olfactory epithelium in females (27/50, 32/51, 27/50, 41/50).

GENETIC TOXICOLOGY

Codeine phosphate (100 to 10,000 μg/plate) was not mutagenic in *Salmonella typhimurium* strains TA97, TA98, TA100, or TA1535, with or without induced liver S9 enzymes (Table E1; Zeiger *et al.*, 1992). Dose-related increases in the frequency of sister chromatid exchanges were induced by codeine phosphate in cultured Chinese hamster ovary cells, with and without S9 (Table E2), but these significantly increased frequencies were noted only at doses that caused marked cell cycle delay, indicative of a high level of cytotoxicity. The role of confounding factors, such as toxicity-related changes in DNA metabolism, needs to be considered in the evaluation of cytogenetic data. Slowly cycling cells undergo prolonged exposure to 5-bromodeoxyuridine, which can also result in an increased level of sister chromatid exchanges. A clear association between cytotoxicity and sister chromatid exchange frequencies has not been shown. There are numerous examples of chemicals that induce cell cycle delay without inducing sister chromatid exchanges (Galloway *et al.*, 1987). Acidic pH shifts were noted in cultures exposed to higher concentrations of codeine phosphate; in some trials, addition of buffer *N*-(2-hydroxyethyl)piperazine-*N'*-(2-ethanesulfonic acid) stabilized the pH. Sister chromatid exchange frequencies did not appear to be affected by the pH shifts; increases were noted both in acidic and neutral cultures. No increases in the frequency of chromosomal aberrations were noted in cultured Chinese hamster ovary cells treated with codeine phosphate at doses similar to those used in the sister chromatid exchange test (Table E3); codeine phosphate-induced cell cycle delay was also observed in these cultures.

DISCUSSION AND CONCLUSIONS

Codeine (methylmorphine) is used orally and parenterally as an analgesic and as a respiratory depressant. Two-year studies were conducted because no previous carcinogenesis bioassays of codeine or other opioid compounds had been reported in the literature. Codeine, codeine phosphate, and codeine sulfate are available in tablets of 15 to 60 mg, and are usually taken four times a day (60 to 240 mg/day or 1 to 4 mg/kg per day for a 60 kg person).

In the 14-day study, all rats receiving 25,000 ppm died and final mean body weights of 12,500 ppm males and females were 62% and 80% those of the controls, respectively. There were no chemical-related deaths or histopathologic lesions in mice in the 14-day study; however, final mean body weights of 12,500 ppm males and females were 90% those of the controls.

Although the cause of death in the 25,000 ppm rats could not be determined, the central and peripheral neuroendocrine effects of the chemical are believed to be important factors in the events leading to the animals' death. Endogenous codeine and its metabolite, morphine, are found in various tissues of the rat, including the brain, spinal cord, heart, adrenal glands, and liver (Donnerer *et al.*, 1986). *O*-Demethylation of codeine to morphine has been demonstrated in rat brain homogenates and it has been suggested that morphine formation in the brain (or transfer of morphine across the blood-brain barrier) may be an important mechanism for codeine pharmacologic effects (Chen *et al.*, 1990). This hypothesis is further supported by the low affinity of codeine for the μ-opiate receptor when compared with that of morphine (Pert and Snyder, 1973; Shah and Mason, 1991).

In the 13-week studies, there were no chemical-related deaths, histopathologic lesions, or reproductive effects (as measured by the sperm morphology and vaginal cytology protocol) in either rats or mice. Absolute and relative adrenal gland weights of all groups of exposed male rats and of 3,125 and 6,250 ppm female rats were significantly greater than those of the controls. Body weights in rats exposed to 3,125 or 6,250 ppm and in mice exposed to 6,250 ppm were lower than those of the controls, and reduced body weights have been reported previously as a codeine-related effect (Thornhill *et al.*, 1978). Based on the body weight effects, the high doses selected for the 2-year studies were 1,600 ppm for rats and 3,000 ppm for mice.

One of the characteristics of the physiological and behavioral effects of repeated exposure to codeine or morphine drugs is tolerance, which is measured as an increase over time in the amount of drug needed to produce an analgesic effect (Dambisya *et al.*, 1991). Tolerance to the body weight effects of codeine have not been reported previously (Koga, 1976; Thornhill *et al.*, 1978; Suzuki *et al.*, 1984) and were not seen in the current 2-year studies.

In the 2-year feed studies of codeine in rats and mice, there were no chemical-related effects on survival. Mean body weights of 800 and 1,600 ppm male and female rats ranged from 4% to 16% lower than those of the controls throughout most of the study. Mean body weights of 1,500 and 3,000 ppm mice ranged from 1% to 16% lower than those of the controls in males and from 5% higher to 21% lower than controls in females. Feed consumption by exposed groups was similar to that by the controls (Table 17).

Codeine metabolism in humans and rodents follows the same metabolic pathways, including conjugation with glucuronic acid, *O*-demethylation to morphine (Mikus *et al.*, 1991, 1994), *N*-demethylation to norcodeine, and conjugation of morphine and norcodeine with glucuronic acid (Cone *et al.*, 1979; Chen *et al.*, 1991). The amount of each metabolite varies across and within species (Hanioka *et al.*, 1990; Mortimer *et al.*, 1990; Yue *et al.*, 1990). The exposure levels used in the rat studies gave plasma codeine levels that overlapped plasma levels for codeine reported in humans (Yuan *et al.*, 1994; Appendix M). *O*-Demethylation to morphine is a minor pathway and conjugation of codeine is a major pathway in humans.

TABLE 17
Comparison of Doses in Codeine 2-Year Feed Studies[a]

	Males				Females			
Rats								
Dose in ppm	0	400	800	1,600	0	400	800	1,600
Grams feed/day	16.5	16.4	16.8	18.5	12.1	12.2	13.1	11.5
mg codeine/kg body weight	0	14	30	73	0	18	39	70
mg/m^2	0	73	156	380	0	91	203	364
Mice								
Dose in ppm	0	750	1,500	3,000	0	750	1,500	3,000
Grams feed/day	4.7	4.9	5.1	5.0	5.2	5.5	5.6	5.5
mg codeine/kg body weight	0	72	156	337	0	81	174	389
mg/m^2	0	216	468	1,011	0	243	522	1,167
Humans (Male or Female)								
1–4 mg/kg								
37–148 mg/m^2								

[a] The dose is calculated as an average at 1 year. Calculation for body surface area dose based on Freireich *et al.*, 1966; $mg/m^2 = K_m x$ (dose in mg/kg) where K_m is 37 for humans, 5.2 for rats, and 3.0 for mice. (K_m is a conversion based on average height-to-body-weight ratios.)

Morphine plasma levels in mice were also greater than those found in humans, and codeine and morphine plasma levels generally overlapped in rats and mice at the doses used in the NTP studies (NTP, unpublished data).

Exposure to codeine increased the adrenal gland weights in male rats at 15 months; however, the mechanism for this effect is not clear. Dose-related increases in adrenal gland weight were also present at 13 weeks in male and female rats, but males were more strongly affected. There was no morphologic alteration (hyperplasia, hypertrophy) to explain the increased adrenal gland weight in exposed males. It is possible that the increase in adrenal gland weight may have been related to vascular dilatation and/or hypertrophy of cells of the inner cortex, which is not evident following tissue processing. There did appear to be a decrease in the amount of medullary tissue relative to cortex tissue in adrenal gland sections. This finding was consistent with the findings at 2 years; the incidences of proliferative lesions of the adrenal medulla in exposed male rats were significantly lower than those in the controls. Historically, enhanced cell proliferation in the adrenal medulla has been associated with increased incidences of adrenal gland neoplasms (Tischler *et al.*, 1991). The adrenal gland normally contains the highest endogenous tissue concentration of codeine in the rat (Donnerer *et al.*, 1987). Opioid peptide immunostaining is seen in some cells of the adrenal medulla but this expression is enhanced in human pheochromocytomas (Bostwick *et al.*, 1987). The high exogenous codeine levels in rats in this study may have resulted in a decreased requirement or expression of endogenous opioid peptides and possibly was associated with the decrease in spontaneous proliferative lesions at this site.

The incidences of thyroid gland follicular cell hyperplasia were significantly greater than those in the controls in 3,000 ppm male mice at 15 months and in all exposed groups of males and females at 2 years; however, there were no chemical-related thyroid

gland neoplasms in mice. Other studies have indicated that morphine can suppress the release of thyrotrophic hormone-releasing hormone (which induces release of thyroid stimulating hormone) and reduce serum thyroid stimulating hormone levels under resting conditions at 15 and 50 mg/kg in the rat (Rúzsás and Mess, 1983), but a similar effect was not reported in mice given daily 500 μg injections for 5 days (approximately 20 mg codeine or morphine/kg) (Redding *et al.*, 1966). Differences in plasma levels of codeine or its metabolites between rats and mice do not appear to completely explain this thyroid effect, and differences in brain levels might provide one basis for the difference in species response in the thyroid. There was no treatment-related increase for proliferative lesions of the pituitary gland in male or female mice.

The incidence of cytoplasmic alteration of the olfactory epithelium was increased in exposed rats and 3,000 ppm females mice after 2 years. This lesion may be considered an adaptive response to chemical exposure (Monticello *et al.*, 1990). The cause of this effect in the current study was not clear; however, it was probably not related to the local irritation/inhalation effect. While codeine is used as a depressant for the respiratory system in man and to inhibit cough and reflex bronchoconstriction, there have been no reports in the literature to suggest codeine-related lesions of the respiratory system after codeine administration to humans (Karlsson *et al.*, 1990; Shook *et al.*, 1990; Biagini *et al.*, 1992). In the guinea pig model, interaction of codeine (rather than its metabolites) with receptors in the tracheobronchial tree may be responsible for inhibition of the cough reflex (Karlsson *et al.*, 1990).

In the current 2 year studies, the incidences of several spontaneously occurring neoplasms decreased, including mammary gland fibroadenoma in female rats, adrenal gland pheochromocytoma in male rats and hepatocellular neoplasms in male and female mice.

It has been reported that reduced body weight gain is closely associated with reduced neoplasm incidence at certain sites in rodents (Schneider and Reed, 1985; Rao *et al.*, 1987; NTP, 1996); reduced body weight and feed restriction are also associated with reducing the incidence of chemically induced cancer. However, the reduced body weights do not completely explain the decreased incidences of mammary gland and adrenal gland neoplasms in rats in this study. For example, the maximum mean body weight achieved by female rats in the 1,600 ppm group in this study averaged 309 g (Table 6). There are four untreated control groups in the current NTP historical control database with similar maximum mean body weights (averaging 307 g). The mammary gland tumor incidence in these historical control groups is 35% (71/201), compared with the rate of 16% (8/51) observed in the 1,600 ppm codeine group. Similarly, the Seilkop (1995) logistic model predicts a mammary gland tumor incidence of 37% for controls with 52-week body weight and survival rates equivalent to those observed in the female rat group receiving 1,600 ppm codeine.

The adrenal gland neoplasms were reduced in all exposed groups of male rats, even at exposure concentrations where there were no significant decreases in body weight. These decreased neoplasm incidences may have been due in part to the pharmacologic effects of codeine, and have been seen previously with other chemicals having neuroendocrine effects (such as *dl*-amphetamine sulfate and methylphenidate hydrochloride) (NTP, 1991; NTP, 1995).

The decreased incidences of hepatic neoplasms in 3,000 ppm mice may have been related to the decreased body weights (10% to 15% lower than those of the controls) that were seen during the last year of the study. Rous (1914) first observed that tumor growth is retarded in animals consuming less feed, with concomitant reduced body weight gain. The relationship between feed restriction and tumor growth has been investigated using transplanted or induced tumors (Sylvester *et al.*, 1981; Gross and Dreyfuss, 1984; Ershler *et al.*, 1986) or by studying the effects of feed restriction on the development of naturally occurring tumors. A lifespan study in SPF Fischer 344 rats, in which the feed restricted group received 60% of the feed received by the controls, resulted in decreased incidences of testicular interstitial cell tumors, bile duct hyperplasia, myocardial fibrosis, and myocardial degeneration (Yu *et al.*, 1982). It is estimated that the final body weight of the feed-restricted group was approximately 70% that of the controls.

In a study using Charles River rats, dietary restriction over the lifespan of the animals resulted in reduced incidences of benign mesenchymal neoplasms and neoplasms of epithelial tissue (lung, pancreas, pituitary gland, and thyroid gland) (Ross and Bras, 1971). A 20% restriction of feed in Wistar rats or Swiss mice for 24 months caused decreases in the incidences of neoplasms of the mammary gland, pituitary gland, and skin in rats and pituitary gland in mice (Tucker, 1979). Spontaneous lymphomas were inhibited by feed restriction in mice (Weindruch and Walford, 1982).

Codeine is nongenotoxic in the *Salmonella* assay and in other genotoxicity tests, and in these carcinogenesis bioassays there was no evidence that codeine had carcinogenic activity in either rats or mice.

CONCLUSIONS

Under the conditions of these 2-year feed studies, there was *no evidence of carcinogenic activity** of codeine in male or female F344/N rats exposed to 400, 800, or 1,600 ppm. There was *no evidence of carcinogenic activity* of codeine in male or female $B6C3F_1$ mice exposed to 750, 1,500, or 3,000 ppm.

Thyroid gland follicular cell hyperplasia was increased in exposed male and female mice.

Decreased incidences of benign pheochromocytomas of the adrenal medulla in male rats and mammary gland fibroadenomas and fibroadenomas or adenocarcinomas (combined) in female rats were related to codeine exposure.

* 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 CODEINE

TABLE A1 Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of Codeine 73
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TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of Codeine[a]

	0 ppm	400 ppm	800 ppm	1,600 ppm
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	10	10	10	10
Early deaths				
Moribund	14	23	24	23
Natural deaths	7	7	5	7
Survivors				
Terminal sacrifice	29	20	21	20
Animals examined microscopically	60	60	60	60
15-Month Interim Evaluation				
Alimentary System				
Intestine large, colon	(10)	(10)	(10)	(10)
Polyp adenomatous				1 (10%)
Liver	(10)	(10)	(10)	(10)
Mesentery	(3)	(3)	(7)	(4)
Endocrine System				
Adrenal cortex	(10)	(10)	(10)	(10)
Adenoma			1 (10%)	
Adrenal medulla	(10)	(10)	(9)	(10)
Pheochromocytoma benign		1 (10%)		
Pituitary gland	(10)	(10)	(10)	(10)
Pars distalis, adenoma	1 (10%)	1 (10%)		
Genital System				
Epididymis	(10)	(10)	(10)	(10)
Testes	(10)	(10)	(10)	(10)
Bilateral, interstitial cell, adenoma	2 (20%)	6 (60%)	3 (30%)	8 (80%)
Interstitial cell, adenoma	4 (40%)	4 (40%)	4 (40%)	1 (10%)
Respiratory System				
Lung	(10)	(9)	(10)	(10)
Alveolar/bronchiolar adenoma	1 (10%)			
Systemic Lesions				
Multiple organs[b]	(10)	(10)	(10)	(10)
Leukemia mononuclear	1 (10%)		1 (10%)	
Mesothelioma malignant			1 (10%)	

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

	0 ppm	400 ppm	800 ppm	1,600 ppm
15-Month Interim Evaluation (continued)				
Systems Examined With No Neoplasms Observed				
Cardiovascular System				
General Body System				
Hematopoietic System				
Integumentary System				
Musculoskeletal System				
Nervous System				
Special Senses System				
Urinary System				
2-Year Study				
Alimentary System				
Esophagus	(50)	(50)	(50)	(50)
Intestine large, colon	(50)	(50)	(50)	(50)
Polyp adenomatous, multiple	1 (2%)			
Intestine large, rectum	(49)	(48)	(50)	(50)
Intestine large, cecum	(47)	(48)	(49)	(50)
Adenoma		1 (2%)	1 (2%)	
Intestine small, duodenum	(48)	(49)	(50)	(48)
Sarcoma, metastatic, mesentery				1 (2%)
Intestine small, jejunum	(46)	(48)	(47)	(46)
Adenocarcinoma			1 (2%)	
Intestine small, ileum	(46)	(46)	(47)	(47)
Liver	(50)	(50)	(50)	(50)
Hepatocellular carcinoma	1 (2%)			
Hepatocellular adenoma	1 (2%)			1 (2%)
Hepatocellular adenoma, multiple	1 (2%)			
Pheochromocytoma malignant, metastatic, adrenal medulla			1 (2%)	
Sarcoma, metastatic, mesentery				1 (2%)
Mesentery	(10)	(21)	(17)	(17)
Sarcoma				1 (6%)
Pancreas	(50)	(50)	(50)	(50)
Sarcoma, metastatic, mesentery				1 (2%)
Salivary glands	(50)	(50)	(50)	(50)
Stomach, forestomach	(50)	(50)	(50)	(50)
Sarcoma, metastatic, mesentery				1 (2%)
Stomach, glandular	(49)	(50)	(50)	(50)
Tongue	(1)			
Squamous cell papilloma	1 (100%)			
Cardiovascular System				
Blood vessel	(49)	(50)	(50)	(50)
Heart	(50)	(50)	(50)	(50)
Alveolar/bronchiolar carcinoma, metastatic, lung		1 (2%)		

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

	0 ppm	400 ppm	800 ppm	1,600 ppm
2-Year Study (continued)				
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Adrenal medulla	(49)	(50)	(50)	(50)
Pheochromocytoma malignant	1 (2%)			
Pheochromocytoma complex	1 (2%)			
Pheochromocytoma benign	13 (27%)	6 (12%)	5 (10%)	3 (6%)
Bilateral, pheochromocytoma malignant			1 (2%)	
Bilateral, pheochromocytoma benign	3 (6%)		1 (2%)	
Islets, pancreatic	(50)	(50)	(50)	(50)
Adenoma		3 (6%)		
Parathyroid gland	(38)	(45)	(42)	(46)
Carcinoma, metastatic, thyroid gland				1 (2%)
Pituitary gland	(50)	(50)	(48)	(47)
Pars distalis, adenoma	9 (18%)	4 (8%)	6 (13%)	4 (9%)
Pars intermedia, adenoma		1 (2%)		
Thyroid gland	(50)	(50)	(50)	(50)
Bilateral, C-cell, adenoma				1 (2%)
C-cell, adenoma	3 (6%)	3 (6%)	2 (4%)	1 (2%)
C-cell, carcinoma	2 (4%)	2 (4%)	4 (8%)	3 (6%)
Follicular cell, adenoma		1 (2%)		
Follicular cell, carcinoma	1 (2%)			
General Body System				
None				
Genital System				
Epididymis	(50)	(50)	(49)	(49)
Penis			(1)	
Preputial gland	(50)	(50)	(48)	(50)
Adenoma	3 (6%)	6 (12%)	5 (10%)	2 (4%)
Carcinoma			1 (2%)	
Bilateral, adenoma			2 (4%)	
Prostate	(49)	(49)	(50)	(50)
Seminal vesicle	(50)	(50)	(50)	(50)
Sarcoma, metastatic, mesentery				1 (2%)
Testes	(50)	(50)	(50)	(50)
Bilateral, interstitial cell, adenoma	38 (76%)	39 (78%)	46 (92%)	47 (94%)
Interstitial cell, adenoma	9 (18%)	8 (16%)	3 (6%)	1 (2%)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Pheochromocytoma malignant, metastatic, adrenal medulla			1 (2%)	
Lymph node	(20)	(17)	(14)	(22)
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung		1 (6%)		
Mediastinal, sarcoma, metastatic, mesentery				1 (5%)
Lymph node, mandibular	(50)	(49)	(49)	(49)
Lymph node, mesenteric	(50)	(50)	(50)	(50)

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

	0 ppm	400 ppm	800 ppm	1,600 ppm
2-Year Study (continued)				
Hematopoietic System (continued)				
Spleen	(50)	(50)	(50)	(50)
Sarcoma, metastatic, mesentery				1 (2%)
Thymus	(46)	(41)	(41)	(41)
Integumentary System				
Mammary gland	(47)	(49)	(50)	(48)
Fibroadenoma	1 (2%)		1 (2%)	1 (2%)
Skin	(50)	(50)	(50)	(50)
Keratoacanthoma	1 (2%)	2 (4%)	2 (4%)	2 (4%)
Lipoma		1 (2%)		
Squamous cell carcinoma			1 (2%)	
Trichoepithelioma			1 (2%)	
Foot, squamous cell papilloma		1 (2%)		
Lip, basosquamous tumor benign	1 (2%)			
Subcutaneous tissue, fibroma	5 (10%)	2 (4%)	3 (6%)	1 (2%)
Subcutaneous tissue, sarcoma		1 (2%)		
Tail, squamous cell papilloma				1 (2%)
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Rib, osteosarcoma				1 (2%)
Skeletal muscle		(1)	(1)	(1)
Abdominal, sarcoma, metastatic, mesentery				1 (100%)
Back, lipoma			1 (100%)	
Thoracic, alveolar/bronchiolar carcinoma, metastatic, lung		1 (100%)		
Nervous System				
Brain	(50)	(50)	(50)	(50)
Astrocytoma malignant		1 (2%)		1 (2%)
Meningioma malignant	1 (2%)			
Spinal cord		(1)		(2)
Hemangioma				1 (50%)
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	1 (2%)			
Alveolar/bronchiolar carcinoma		2 (4%)		
Pheochromocytoma malignant, metastatic, adrenal medulla			1 (2%)	
Sarcoma, metastatic, mesentery				1 (2%)
Schwannoma malignant, metastatic, ear		1 (2%)	1 (2%)	2 (4%)
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung		1 (2%)		
Nose	(50)	(50)	(50)	(50)
Adenoma		2 (4%)		
Chondroma		1 (2%)		
Trachea	(50)	(50)	(50)	(50)

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

	0 ppm	400 ppm	800 ppm	1,600 ppm
2-Year Study (continued)				
Special Senses System				
Ear		(1)	(1)	(2)
Schwannoma malignant				1 (50%)
Pinna, schwannoma malignant		1 (100%)	1 (100%)	1 (50%)
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Sarcoma, metastatic, mesentery				1 (2%)
Renal tubule, adenoma			1 (2%)	
Renal tubule, carcinoma				1 (2%)
Urinary bladder	(50)	(49)	(48)	(49)
Systemic Lesions				
Multiple organs	(50)	(50)	(50)	(50)
Leukemia mononuclear	32 (64%)	27 (54%)	36 (72%)	37 (74%)
Mesothelioma malignant	1 (2%)	2 (4%)	2 (4%)	3 (6%)
Neoplasm Summary				
Total animals with primary neoplasms[c]				
15-Month interim evaluation	7	10	9	9
2-Year Study	50	50	50	50
Total primary neoplasms				
15-Month interim evaluation	9	12	10	10
2-Year study	131	117	127	115
Total animals with benign neoplasms				
15-Month interim evaluation	7	10	7	9
2-Year study	49	47	50	48
Total benign neoplasms				
15-Month interim evaluation	8	12	8	10
2-Year study	91	81	80	66
Total animals with malignant neoplasms				
15-Month interim evaluation	1		2	
2-Year study	36	33	39	41
Total malignant neoplasms				
15-Month interim evaluation	1		2	
2-Year study	40	36	47	49
Total animals with metastatic neoplasms				
2-Year study		2	2	4
Total metastatic neoplasms				
2-Year study		5	4	13

[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 Codeine: 0 ppm

Number of Days on Study	203	334	446	449	495	500	525	554	567	599	601	636	643	652	657	662	670	681	684	700	720	732	732	732	732
Carcass ID Number	0014	0001	0012	0145	0146	0248	0028	0122	0110	0104	0037	0220	0255	0550	0556	0443	0331	0558	0059	0202	0025	0037	0111	0117	0119
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp adenomatous, multiple																									
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Intestine large, cecum	A	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	A	+	+	+	+	+	+	+
Intestine small, duodenum	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	A	+	A	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																									
Hepatocellular adenoma																									
Hepatocellular adenoma, multiple																									
Mesentery							+							+							+			+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue							+																		
Squamous cell papilloma							X																		
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant										X															
Pheochromocytoma complex																									
Pheochromocytoma benign										X						X		X	X			X	X		X
Bilateral, pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	M	+	M	+	+	+	+	+	M	+	+	+	M	M	+	M	+	+	+	+	M	M
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma				X																				X	
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																		X							
C-cell, carcinoma																									
Follicular cell, carcinoma																									
General Body System																									
None																									

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

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

Number of Days on Study	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	733	733	733	733	733	733	733	733	733	
Carcass ID Number	021	023	024	029	030	036	038	040	041	042	045	048	052	053	059	060	066	018	025	026	032	035	039	049	051	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp adenomatous, multiple																							X			1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma																							X			1
Hepatocellular adenoma																								X		1
Hepatocellular adenoma, multiple		X																								1
Mesentery		+	+				+		+								+									10
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tongue																										1
Squamous cell papilloma																										1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma malignant																										1
Pheochromocytoma complex									X																	1
Pheochromocytoma benign						X			X			X		X			X								X	13
Bilateral, pheochromocytoma benign		X					X													X						3
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	M	+	M	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	38
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma		X			X								X		X		X							X	X	9
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma																					X				X	3
C-cell, carcinoma			X				X																			2
Follicular cell, carcinoma										X																1
General Body System																										
None																										

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

Number of Days on Study	203	334	446	449	495	500	525	554	567	599	601	636	643	652	657	662	670	681	684	700	720	732	732	732	732
Carcass ID Number	014	001	002	015	046	028	028	012	010	004	037	020	055	050	056	043	031	058	089	022	025	027	011	017	019
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma									X																
Prostate	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma			X			X		X		X		X	X			X	X	X	X	X	X	X	X	X	
Interstitial cell, adenoma		X			X		X		X		X			X	X										X
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node					+	+				+	+	+	+	+		+	+	+			+			+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	M	+	+	+	+	+	+	M	+	+	+	M	+	+	+	M	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																							X		
Lip, basosquamous tumor benign																									
Subcutaneous tissue, fibroma									X																X
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Meningioma malignant	X																								
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma			X																						
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																						+			
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X	X		X		X	X	X	X	X	X	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 Codeine: 0 ppm (continued)

Number of Days on Study	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	733	733	733	733	733	733	733	733	733	
Carcass ID Number	021	023	024	029	030	036	038	040	041	042	045	048	052	053	059	060	066	018	025	026	032	035	039	049	051	Total Tissues/ Tumors
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma					X		X																			3
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
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	38
Interstitial cell, adenoma	X																									9
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+			+			+		+						+				+		+					20
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Fibroadenoma				X																						1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma																										1
Lip, basosquamous tumor benign						X																				1
Subcutaneous tissue, fibroma			X														X				X					5
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Meningioma malignant																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X		X	X		X	X	X		X					X	X		X	X		X			X	X	32
Mesothelioma malignant																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Codeine: 400 ppm

Number of Days on Study	3	4	4	5	5	5	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	7
	3	0	2	4	7	8	0	1	1	2	2	3	4	5	5	5	5	7	7	7	8	8	9	9	0
	6	4	6	9	4	6	8	5	5	4	7	2	1	1	1	7	8	8	8	9	4	4	3	5	1
Carcass ID Number	1	1	0	1	1	1	0	1	1	0	0	1	0	0	1	1	0	0	1	0	0	0	0	0	0
	0	1	6	0	1	1	8	0	1	9	8	0	7	6	1	1	8	7	1	9	8	9	8	9	9
	1	3	5	9	6	5	1	4	8	7	6	3	2	6	1	9	0	7	0	1	8	3	9	5	4
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Intestine small, duodenum	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+
Intestine small, ileum	+	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	A	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery		+									+			+			+			+					+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung	X																								
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																			X						
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																	X								X
Parathyroid gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma												X									X				
Pars intermedia, adenoma												X													
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																					X				
C-cell, carcinoma																									
Follicular cell, adenoma														X											
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma						X						X											X		
Prostate	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma					X	X	X				X	X		X			X	X	X	X	X	X	X	X	X
Interstitial cell, adenoma			X					X	X	X			X		X	X									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Codeine: 400 ppm (continued)

Number of Days on Study	706	707	711	720	729	732	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	
Carcass ID Number	114	107	102	076	063	061	064	067	068	070	071	073	074	075	078	084	085	087	096	062	082	083	092	099	112	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma		X																								1
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery	+	+	+	+				+	+	+	+		+		+	+		+	+	+				+		21
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign			X		X	X				X	X															6
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																X										3
Parathyroid gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	45
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma				X		X																				4
Pars intermedia, adenoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma		X							X																	3
C-cell, carcinoma															X									X		2
Follicular cell, adenoma																										1
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma	X									X												X				6
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
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	39
Interstitial cell, adenoma										X																8
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Codeine: 400 ppm (continued)

Number of Days on Study	3	4	4	5	5	5	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	7
	3	0	2	4	7	8	0	1	1	2	2	3	4	5	5	5	5	7	7	7	8	8	9	9	0
	6	4	6	9	4	6	8	5	5	4	7	2	1	1	1	7	8	8	8	9	4	4	3	5	1
Carcass ID Number	1	1	0	1	1	1	0	1	1	0	0	1	0	0	1	1	0	0	1	0	0	0	0	0	0
	0	1	6	0	1	1	8	0	1	9	8	0	7	6	1	1	8	7	1	9	8	9	8	9	9
	1	3	5	9	6	5	1	4	8	7	6	3	2	6	1	9	0	7	0	1	8	3	9	5	4
Hematopoietic System (continued)																									
Lymph node	+			+	+				+	+				+	+		+	+	+	+		+		+	
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung	X																								
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	M	+	+	+	+	+	M	M	+	M	+	+	+	+	+	+	M	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																									
Lipoma																									
Foot, squamous cell papilloma																									
Subcutaneous tissue, fibroma																							X		
Subcutaneous tissue, sarcoma			X																						
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle	+																								
Thoracic, alveolar/bronchiolar carcinoma, metastatic, lung	X																								
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant																									
Spinal cord		+																							
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma	X																								
Schwannoma malignant, metastatic, ear																								X	
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung	X																								
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma											X														
Chondroma											X														
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																								+	
Pinna, schwannoma malignant																								X	
Eye																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X		X	X		X	X	X	X			X	X	X	X	X	X	X	X		X		X	
Mesothelioma malignant					X																		X		

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Codeine: 400 ppm (continued)

Number of Days on Study	706	707	711	720	729	732	732	732	732	732	732	732	732	732	732	732	732	732	732	733	733	733	733	733	733	
Carcass ID Number	114	107	102	076	063	061	064	067	068	070	071	073	074	075	078	084	085	087	096	062	082	083	092	099	112	Total Tissues/ Tumors
Hematopoietic System (continued)																										
Lymph node	+		+					+														+				17
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung																										1
Lymph node, mandibular	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	M	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	41
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma					X		X																			2
Lipoma						X																				1
Foot, squamous cell papilloma																X										1
Subcutaneous tissue, fibroma																							X			2
Subcutaneous tissue, sarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Thoracic, alveolar/bronchiolar carcinoma, metastatic, lung																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma malignant											X															1
Spinal cord																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma																					X					2
Schwannoma malignant, metastatic, ear																										1
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma			X																							2
Chondroma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear																										1
Pinna, schwannoma malignant																										1
Eye				+																						1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	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 Codeine: 800 ppm

Number of Days on Study	519	526	546	550	559	567	574	580	608	634	635	638	638	638	655	658	658	665	668	687	695	706	707	712	720
Carcass ID Number	177	154	161	112	141	128	168	137	178	134	159	131	138	148	173	130	180	133	143	146	170	163	160	153	157
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
Adenocarcinoma			X																						
Intestine small, ileum	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	A	M
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant, metastatic, adrenal medulla																							X		
Mesentery	+																			+	+	+	+		
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign									X								X							X	
Bilateral, pheochromocytoma malignant																							X		
Bilateral, pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	M	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma		X																					X		
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																									
C-cell, carcinoma																							X		
General Body System																									
None																									
Genital System																									
Epididymis	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis																							+		
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma															X								X		
Carcinoma																									
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	X
Interstitial cell, adenoma			X			X																			

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Codeine: 800 ppm (continued)

Number of Days on Study	720	722	726	726	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	733	733	733	733	733	733	
Carcass ID Number	174	140	123	167	126	129	132	135	144	147	150	155	165	166	169	171	175	176	179	122	127	139	152	156	172	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma		X																								1
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenocarcinoma																										1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant, metastatic, adrenal medulla																										1
Mesentery			+	+	+	+	+	+	+	+					+	+	+		+							17
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 benign																			X		X					5
Bilateral, pheochromocytoma malignant																										1
Bilateral, pheochromocytoma benign					X																					1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	M	+	+	+	42
Pituitary gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	48
Pars distalis, adenoma							X		X						X				X							6
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma					X																				X	2
C-cell, carcinoma					X						X										X					4
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Penis																										1
Preputial gland	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma																	X			X	X					5
Carcinoma									X																	1
Bilateral, adenoma				X																						2
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	46
Interstitial cell, adenoma		X																								3

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Codeine: 800 ppm (continued)

Number of Days on Study	519	526	546	550	559	567	574	580	608	634	635	638	638	638	655	658	658	665	687	687	695	706	707	712	720
Carcass ID Number	177	154	161	121	141	128	168	137	178	134	159	131	138	148	173	130	180	133	143	146	170	163	160	153	157
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant, metastatic, adrenal medulla																							X		
Lymph node		+			+			+	+				+			+	+	+	+	+			+	
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	M	+	+	+	+	M
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma																							X		
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																									
Squamous cell carcinoma																									
Trichoepithelioma																						X			
Subcutaneous tissue, fibroma											X														
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																									
Back, lipoma																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant, metastatic, adrenal medulla																							X		
Schwannoma malignant, metastatic, ear																									X
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																									+
Pinna, schwannoma malignant																									X
Eye													+												
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																									
Urethra																							+		
Urinary bladder	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	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	X	X	X	X
Mesothelioma malignant																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Codeine: 800 ppm (continued)

Number of Days on Study	720	722	726	726	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	733	733	733	733	733	733	
Carcass ID Number	174	140	123	167	126	129	132	135	144	147	150	155	165	166	169	171	175	176	179	122	127	139	152	156	172	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant, metastatic, adrenal medulla																										1
Lymph node	+			+	+																					14
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	M	M	M	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	41
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroadenoma																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma													X												X	2
Squamous cell carcinoma								X																		1
Trichoepithelioma																										1
Subcutaneous tissue, fibroma										X		X														3
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																					+					1
Back, lipoma																					X					1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant, metastatic, adrenal medulla																										1
Schwannoma malignant, metastatic, ear																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear																										1
Pinna, schwannoma malignant																										1
Eye				+																						2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma																	X									1
Urethra																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X			X		X		X	X	X	X		X				X	X	X		X			X	X	36
Mesothelioma malignant		X		X																						2

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Codeine: 1,600 ppm

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Codeine: 1,600 ppm (continued)

Number of Days on Study	708	715	729	730	731	732	732	732	732	732	732	732	732	732	732	732	733	733	733	733	733	733	733	733	733	
Carcass ID Number	187	226	221	188	200	199	201	204	207	210	212	219	222	237	238	239	182	190	196	197	206	214	232	234	235	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Sarcoma, metastatic, mesentery																										1
Intestine small, jejunum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, ileum	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma									X																	1
Sarcoma, metastatic, mesentery																										1
Mesentery		+						+	+		+	+			+			+		+					+	17
Sarcoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, metastatic, mesentery																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, metastatic, mesentery																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign	X																						X	X		3
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	46
Carcinoma, metastatic, thyroid gland		X																								1
Pituitary gland	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Pars distalis, adenoma	X	X																								4
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, C-cell, adenoma							X																			1
C-cell, adenoma																										1
C-cell, carcinoma		X																								3
General Body System																										
Tissue NOS		+																								1
Genital System																										
Coagulating gland																										1
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma														X												2
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, metastatic, mesentery																										1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	47
Interstitial cell, adenoma																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Codeine: 1,600 ppm (continued)

Number of Days on Study	355	383	484	530	537	543	544	550	559	571	582	585	594	603	621	659	659	670	670	683	687	700	701	705	705
Carcass ID Number	225	217	233	228	198	184	230	223	229	181	191	189	215	240	192	218	227	224	236	231	185	186	216	209	211
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node		+				+				+		+		+	+	+	+	+	+	+				+	+
Mediastinal, sarcoma, metastatic, mesentery		X																							
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, mesentery		X																							
Thymus	+	+	+	+	+	+	+	+	M	M	+	+	+	+	M	M	+	M	+	+	+	+	+	+	M
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma													X												
Subcutaneous tissue, fibroma																			X						
Tail, squamous cell papilloma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Rib, osteosarcoma							X																		
Skeletal muscle		+																							
Abdominal, sarcoma, metastatic, mesentery		X																							
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant																						X			
Spinal cord	+																				+				
Hemangioma																					X				
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, mesentery		X																							
Schwannoma malignant, metastatic, ear																							X		
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																							+		
Schwannoma malignant																							X		
Pinna, schwannoma malignant																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, mesentery		X																							
Renal tubule, carcinoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X			X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X		X	X	X
Mesothelioma malignant			X						X													X			

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Codeine: 1,600 ppm (continued)

Number of Days on Study	708	715	729	730	731	732	732	732	732	732	732	732	732	732	732	732	733	733	733	733	733	733	733	733	733	
Carcass ID Number	187	226	221	188	200	199	201	204	207	210	112	119	122	237	238	239	182	190	196	197	206	214	232	234	235	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node		+		+	+										+	+				+	+	+			+	22
Mediastinal, sarcoma, metastatic, mesentery																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, metastatic, mesentery																										1
Thymus	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	41
Integumentary System																										
Mammary gland	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Fibroadenoma	X																									1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma							X																			2
Subcutaneous tissue, fibroma																										1
Tail, squamous cell papilloma																							X			1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Rib, osteosarcoma																										1
Skeletal muscle																										1
Abdominal, sarcoma, metastatic, mesentery																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma malignant																										1
Spinal cord																										2
Hemangioma																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, metastatic, mesentery																										1
Schwannoma malignant, metastatic, ear										X																2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear										+																2
Schwannoma malignant																										1
Pinna, schwannoma malignant										X																1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, metastatic, mesentery																										1
Renal tubule, carcinoma											X															1
Urinary bladder	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X		X	X	X	X	X	X	X	X	X			X	X	X					X	X			X	37
Mesothelioma malignant																										3

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

	0 ppm	400 ppm	800 ppm	1,600 ppm
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate[a]	16/49 (33%)	6/50 (12%)	6/50 (12%)	3/50 (6%)
Adjusted rate[b]	49.1%	24.9%	21.7%	13.6%
Terminal rate[c]	12/28 (43%)	3/20 (15%)	3/21 (14%)	2/20 (10%)
First incidence (days)	599	678	608	708
Life table test[d]	P=0.005N	P=0.070N	P=0.051N	P=0.007N
Logistic regression test[d]	P=0.001N	P=0.013N	P=0.010N	P=0.001N
Cochran-Armitage test[d]	P<0.001N			
Fisher exact test[d]		P=0.012N	P=0.012N	P<0.001N
Adrenal Medulla: Benign, Complex, or Malignant Pheochromocytoma				
Overall rate	16/49 (33%)	6/50 (12%)	7/50 (14%)	3/50 (6%)
Adjusted rate	49.1%	24.9%	24.5%	13.6%
Terminal rate	12/28 (43%)	3/20 (15%)	3/21 (14%)	2/20 (10%)
First incidence (days)	599	678	608	708
Life table test	P=0.007N	P=0.070N	P=0.089N	P=0.007N
Logistic regression test	P=0.001N	P=0.013N	P=0.020N	P=0.001N
Cochran-Armitage test	P=0.001N			
Fisher exact test		P=0.012N	P=0.024N	P<0.001N
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	3/50 (6%)	0/50 (0%)	0/50 (0%)	1/50 (2%)
Adjusted rate	10.3%	0.0%	0.0%	5.0%
Terminal rate	3/29 (10%)	0/20 (0%)	0/21 (0%)	1/20 (5%)
First incidence (days)	732 (T)	—[e]	—	732 (T)
Life table test	P=0.327N	P=0.192N	P=0.182N	P=0.445N
Logistic regression test	P=0.327N	P=0.192N	P=0.182N	P=0.445N
Cochran-Armitage test	P=0.247N			
Fisher exact test		P=0.121N	P=0.121N	P=0.309N
Pancreatic Islets: Adenoma				
Overall rate	0/50 (0%)	3/50 (6%)	0/50 (0%)	0/50 (0%)
Adjusted rate	0.0%	11.3%	0.0%	0.0%
Terminal rate	0/29 (0%)	1/20 (5%)	0/21 (0%)	0/20 (0%)
First incidence (days)	—	658	—	—
Life table test	P=0.339N	P=0.094	—	—
Logistic regression test	P=0.317N	P=0.119	—	—
Cochran-Armitage test	P=0.311N			
Fisher exact test		P=0.121	—	—
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	9/50 (18%)	4/50 (8%)	6/48 (13%)	4/47 (9%)
Adjusted rate	29.1%	14.6%	24.4%	13.0%
Terminal rate	8/29 (28%)	1/20 (5%)	4/20 (20%)	0/20 (0%)
First incidence (days)	449	632	526	594
Life table test	P=0.253N	P=0.259N	P=0.516N	P=0.249N
Logistic regression test	P=0.177N	P=0.116N	P=0.307N	P=0.151N
Cochran-Armitage test	P=0.167N			
Fisher exact test		P=0.117N	P=0.318N	P=0.142N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of Codeine (continued)

	0 ppm	400 ppm	800 ppm	1,600 ppm
Preputial Gland: Adenoma				
Overall rate	3/50 (6%)	6/50 (12%)	7/48 (15%)	2/50 (4%)
Adjusted rate	9.1%	20.6%	26.8%	7.4%
Terminal rate	2/29 (7%)	2/20 (10%)	3/20 (15%)	1/20 (5%)
First incidence (days)	567	586	655	582
Life table test	P=0.463N	P=0.171	P=0.090	P=0.604N
Logistic regression test	P=0.351N	P=0.245	P=0.142	P=0.501N
Cochran-Armitage test	P=0.342N			
Fisher exact test		P=0.243	P=0.142	P=0.500N
Preputial Gland: Adenoma or Carcinoma				
Overall rate	3/50 (6%)	6/50 (12%)	8/48 (17%)	2/50 (4%)
Adjusted rate	9.1%	20.6%	31.1%	7.4%
Terminal rate	2/29 (7%)	2/20 (10%)	4/20 (20%)	1/20 (5%)
First incidence (days)	567	586	655	582
Life table test	P=0.491N	P=0.171	P=0.049	P=0.604N
Logistic regression test	P=0.373N	P=0.245	P=0.085	P=0.501N
Cochran-Armitage test	P=0.360N			
Fisher exact test		P=0.243	P=0.087	P=0.500N
Skin: Squamous Cell Papilloma, Keratoacanthoma, Trichoepithelioma, or Squamous Cell Carcinoma				
Overall rate	1/50 (2%)	3/50 (6%)	4/50 (8%)	3/50 (6%)
Adjusted rate	3.4%	14.3%	17.2%	12.4%
Terminal rate	1/29 (3%)	2/20 (10%)	3/21 (14%)	2/20 (10%)
First incidence (days)	732 (T)	729	706	594
Life table test	P=0.182	P=0.189	P=0.109	P=0.207
Logistic regression test	P=0.248	P=0.200	P=0.146	P=0.293
Cochran-Armitage test	P=0.282			
Fisher exact test		P=0.309	P=0.181	P=0.309
Skin (Subcutaneous Tissue): Fibroma				
Overall rate	5/50 (10%)	2/50 (4%)	3/50 (6%)	1/50 (2%)
Adjusted rate	15.8%	8.4%	11.8%	3.0%
Terminal rate	4/29 (14%)	1/20 (5%)	2/21 (10%)	0/20 (0%)
First incidence (days)	567	693	635	670
Life table test	P=0.153N	P=0.336N	P=0.487N	P=0.173N
Logistic regression test	P=0.099N	P=0.220N	P=0.346N	P=0.108N
Cochran-Armitage test	P=0.095N			
Fisher exact test		P=0.218N	P=0.357N	P=0.102N
Skin (Subcutaneous Tissue): Fibroma or Sarcoma				
Overall rate	5/50 (10%)	3/50 (6%)	3/50 (6%)	1/50 (2%)
Adjusted rate	15.8%	10.3%	11.8%	3.0%
Terminal rate	4/29 (14%)	1/20 (5%)	2/21 (10%)	0/20 (0%)
First incidence (days)	567	426	635	670
Life table test	P=0.129N	P=0.489N	P=0.487N	P=0.173N
Logistic regression test	P=0.079N	P=0.356N	P=0.346N	P=0.108N
Cochran-Armitage test	P=0.079N			
Fisher exact test		P=0.357N	P=0.357N	P=0.102N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of Codeine (continued)

	0 ppm	400 ppm	800 ppm	1,600 ppm
Testes: Adenoma				
Overall rate	47/50 (94%)	47/50 (94%)	49/50 (98%)	48/50 (96%)
Adjusted rate	97.9%	100.0%	100.0%	100.0%
Terminal rate	28/29 (97%)	20/20 (100%)	21/21 (100%)	20/20 (100%)
First incidence (days)	334	426	519	484
Life table test	P=0.083	P=0.101	P=0.097	P=0.071
Logistic regression test	P=0.495	P=0.500N	P=0.650	P=0.676
Cochran-Armitage test	P=0.343			
Fisher exact test		P=0.661N	P=0.309	P=0.500
Thyroid Gland (C-cell): Adenoma				
Overall rate	3/50 (6%)	3/50 (6%)	2/50 (4%)	2/50 (4%)
Adjusted rate	9.7%	12.0%	9.5%	8.5%
Terminal rate	2/29 (7%)	1/20 (5%)	2/21 (10%)	1/20 (5%)
First incidence (days)	681	684	732 (T)	705
Life table test	P=0.472N	P=0.543	P=0.619N	P=0.614N
Logistic regression test	P=0.404N	P=0.645	P=0.526N	P=0.538N
Cochran-Armitage test	P=0.371N			
Fisher exact test		P=0.661N	P=0.500N	P=0.500N
Thyroid Gland (C-cell): Carcinoma				
Overall rate	2/50 (4%)	2/50 (4%)	4/50 (8%)	3/50 (6%)
Adjusted rate	6.9%	10.0%	17.3%	9.9%
Terminal rate	2/29 (7%)	2/20 (10%)	3/21 (14%)	0/20 (0%)
First incidence (days)	732 (T)	732 (T)	707	659
Life table test	P=0.260	P=0.555	P=0.216	P=0.411
Logistic regression test	P=0.319	P=0.555	P=0.282	P=0.479
Cochran-Armitage test	P=0.357			
Fisher exact test		P=0.691N	P=0.339	P=0.500
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rate	5/50 (10%)	5/50 (10%)	5/50 (10%)	5/50 (10%)
Adjusted rate	16.4%	21.3%	21.9%	17.6%
Terminal rate	4/29 (14%)	3/20 (15%)	4/21 (19%)	1/20 (5%)
First incidence (days)	681	684	707	659
Life table test	P=0.416	P=0.437	P=0.455	P=0.483
Logistic regression test	P=0.513	P=0.572	P=0.585	P=0.593
Cochran-Armitage test	P=0.563			
Fisher exact test		P=0.630N	P=0.630N	P=0.630N
All Organs: Mononuclear Cell Leukemia				
Overall rate	32/50 (64%)	27/50 (54%)	36/50 (72%)	37/50 (74%)
Adjusted rate	72.7%	64.2%	78.8%	81.5%
Terminal rate	17/29 (59%)	7/20 (35%)	12/21 (57%)	12/20 (60%)
First incidence (days)	495	404	519	355
Life table test	P=0.044	P=0.553N	P=0.141	P=0.071
Logistic regression test	P=0.112	P=0.083N	P=0.507N	P=0.299
Cochran-armitage test	P=0.065			
Fisher exact test		P=0.208N	P=0.260	P=0.194

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of Codeine (continued)

	0 ppm	400 ppm	800 ppm	1,600 ppm
All Organs: Malignant Mesothelioma				
Overall rate	1/50 (2%)	2/50 (4%)	2/50 (4%)	3/50 (6%)
Adjusted rate	3.4%	5.7%	8.3%	7.7%
Terminal rate	1/29 (3%)	0/20 (0%)	0/21 (0%)	0/20 (0%)
First incidence (days)	732 (T)	574	722	484
Life table test	P=0.208	P=0.459	P=0.415	P=0.274
Logistic regression test	P=0.232	P=0.500	P=0.465	P=0.296
Cochran-Armitage test	P=0.232			
Fisher exact test		P=0.500	P=0.500	P=0.309
All Organs: Benign Neoplasms				
Overall rate	50/50 (100%)	49/50 (98%)	50/50 (100%)	48/50 (96%)
Adjusted rate	100.0%	100.0%	100.0%	100.0%
Terminal rate	29/29 (100%)	20/20 (100%)	21/21 (100%)	20/20 (100%)
First incidence (days)	203	336	519	484
Life table test	P=0.175	P=0.134	P=0.160	P=0.148
Logistic regression test	P=0.032N	P=0.357N	—[f]	P=0.068N
Cochran-Armitage test	P=0.140N			
Fisher exact test		P=0.500N	P=1.000N	P=0.247N
All Organs: Malignant Neoplasms				
Overall rate	36/50 (72%)	33/50 (66%)	39/50 (78%)	41/50 (82%)
Adjusted rate	79.9%	74.5%	82.3%	83.6%
Terminal rate	20/29 (69%)	10/20 (50%)	13/21 (62%)	12/20 (60%)
First incidence (days)	203	336	519	355
Life table test	P=0.053	P=0.386	P=0.156	P=0.067
Logistic regression test	P=0.077	P=0.337N	P=0.324	P=0.171
Cochran-Armitage test	P=0.073			
Fisher exact test		P=0.333N	P=0.322	P=0.171
All Organs: Benign or Malignant Neoplasms				
Overall rate	50/50 (100%)	50/50 (100%)	50/50 (100%)	50/50 (100%)
Adjusted rate	100.0%	100.0%	100.0%	100.0%
Terminal rate	29/29 (100%)	20/20 (100%)	21/21 (100%)	20/20 (100%)
First incidence (days)	203	336	519	355
Life table test	P=0.122	P=0.108	P=0.160	P=0.097
Logistic regression test	—	—	—	—
Cochran-Armitage test	—			
Fisher exact test		P=1.000N	P=1.000N	P=1.000N

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, 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 A4
Historical Incidence of Benign Pheochromocytomas of the Adrenal Medulla in Untreated Male F344/N Rats[a]

	Incidence in Controls
Historical Incidence at Microbiological Associates, Inc.	
C.I. Direct Blue 218	15/49
dl-Amphetamine Sulfate	23/49
Overall Historical Incidence	
Total	379/1,182 (32.1%)
Standard deviation	11.7%
Range	10%-63%

[a] Data as of 17 June 1994

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

	0 ppm	400 ppm	800 ppm	1,600 ppm
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	10	10	10	10
Early deaths				
Moribund	14	23	24	23
Natural deaths	7	7	5	7
Survivors				
Terminal sacrifice	29	20	21	20
Animals examined microscopically	60	60	60	60
15-Month Interim Evaluation				
Alimentary System				
Intestine small, ileum	(10)	(10)	(10)	(10)
Cyst	1 (10%)			
Liver	(10)	(10)	(10)	(10)
Basophilic focus	5 (50%)	2 (20%)	5 (50%)	5 (50%)
Clear cell focus	3 (30%)	1 (10%)		
Eosinophilic focus			1 (10%)	
Hepatodiaphragmatic nodule	1 (10%)	1 (10%)	1 (10%)	
Inflammation, chronic, focal	1 (10%)			2 (20%)
Mixed cell focus	2 (20%)			
Necrosis	1 (10%)			
Vacuolization cytoplasmic, focal	1 (10%)			
Mesentery	(3)	(3)	(7)	(4)
Fat, necrosis	3 (100%)	3 (100%)	6 (86%)	4 (100%)
Pancreas	(10)	(10)	(10)	(10)
Accessory spleen	1 (10%)		1 (10%)	
Acinar cell, atrophy	5 (50%)	4 (40%)	5 (50%)	5 (50%)
Cardiovascular System				
Heart	(10)	(10)	(10)	(10)
Cardiomyopathy	7 (70%)	7 (70%)	6 (60%)	5 (50%)
Endocrine System				
Adrenal cortex	(10)	(10)	(10)	(10)
Hyperplasia, focal				1 (10%)
Hypertrophy		1 (10%)		
Vacuolization cytoplasmic, focal		3 (30%)	4 (40%)	
Adrenal medulla	(10)	(10)	(9)	(10)
Hyperplasia			1 (11%)	
Pituitary gland	(10)	(10)	(10)	(10)
Pars distalis, hyperplasia, focal	4 (40%)	3 (30%)	6 (60%)	5 (50%)
Thyroid gland	(10)	(10)	(10)	(10)
C-cell, hyperplasia		1 (10%)		1 (10%)
Follicle, cyst				1 (10%)

[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 Codeine (continued)

	0 ppm	400 ppm	800 ppm	1,600 ppm
15-Month Interim Evaluation (continued)				
Genital System				
Epididymis	(10)	(10)	(10)	(10)
Edema, focal		1 (10%)		
Penis				(1)
Hemorrhage				1 (100%)
Preputial gland	(9)	(10)	(10)	(9)
Ectasia		1 (10%)		
Hyperplasia		1 (10%)	1 (10%)	
Inflammation	1 (11%)	1 (10%)		
Prostate	(10)	(10)	(10)	(10)
Atrophy			1 (10%)	
Infiltration cellular, focal, lymphocyte		1 (10%)		
Inflammation	2 (20%)	4 (40%)		1 (10%)
Seminal vesicle	(10)	(10)	(10)	(10)
Depletion cellular		1 (10%)		
Testes	(10)	(10)	(10)	(10)
Congestion, focal			1 (10%)	
Interstitial cell, hyperplasia, focal	3 (30%)	2 (20%)	2 (20%)	1 (10%)
Hematopoietic System				
Bone marrow	(10)	(10)	(10)	(10)
Hyperplasia	1 (10%)			
Lymph node, mandibular	(10)	(10)	(10)	(10)
Hyperplasia, plasma cell				2 (20%)
Thymus	(10)	(10)	(8)	(9)
Atrophy	10 (100%)	8 (80%)	7 (88%)	8 (89%)
Hemorrhage	1 (10%)			
Respiratory System				
Lung	(10)	(9)	(10)	(10)
Hemorrhage	1 (10%)	1 (11%)	2 (20%)	1 (10%)
Infiltration cellular, focal, histiocyte			1 (10%)	3 (30%)
Inflammation			1 (10%)	1 (10%)
Nose	(10)	(10)	(10)	(10)
Edema, focal			1 (10%)	
Foreign body	2 (20%)	1 (10%)		
Fungus	2 (20%)	1 (10%)		
Hemorrhage		1 (10%)	1 (10%)	
Infiltration cellular, focal, lymphocyte		2 (20%)		
Inflammation	4 (40%)	1 (10%)	2 (20%)	
Goblet cell, hyperplasia, focal		1 (10%)	1 (10%)	
Olfactory epithelium, atrophy, focal	2 (20%)	2 (20%)	3 (30%)	2 (20%)
Olfactory epithelium, cytoplasmic alteration	8 (80%)	7 (70%)	8 (80%)	10 (100%)
Olfactory epithelium, hyperplasia, focal				1 (10%)
Olfactory epithelium, vacuolization cytoplasmic, focal		1 (10%)		
Respiratory epithelium, cytoplasmic alteration, focal	1 (10%)			
Special Senses System				
Eye				(1)
Lens, cataract				1 (100%)

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

	0 ppm	400 ppm	800 ppm	1,600 ppm
15-Month Interim Evaluation (continued)				
Urinary System				
Kidney	(10)	(10)	(10)	(10)
Nephropathy, chronic	10 (100%)	9 (90%)	8 (80%)	8 (80%)
Systems Examined With No Lesions Observed				
General Body System				
Integumentary System				
Musculoskeletal System				
Nervous System				
2-Year Study				
Alimentary System				
Intestine large, colon	(50)	(50)	(50)	(50)
Amyloid deposition			1 (2%)	
Inflammation	1 (2%)			
Pigmentation				1 (2%)
Ulcer				1 (2%)
Intestine large, rectum	(49)	(48)	(50)	(50)
Inflammation		1 (2%)		
Pigmentation				1 (2%)
Ulcer			1 (2%)	
Intestine small, jejunum	(46)	(48)	(47)	(46)
Diverticulum	1 (2%)			
Inflammation, chronic	1 (2%)			
Liver	(50)	(50)	(50)	(50)
Abscess				1 (2%)
Angiectasis	3 (6%)			
Atrophy	1 (2%)			
Basophilic focus	17 (34%)	17 (34%)	21 (42%)	16 (32%)
Clear cell focus	2 (4%)		2 (4%)	1 (2%)
Congestion	2 (4%)	1 (2%)		
Degeneration		3 (6%)	1 (2%)	2 (4%)
Degeneration, cystic	14 (28%)	5 (10%)	1 (2%)	
Developmental malformation	2 (4%)		1 (2%)	
Eosinophilic focus	7 (14%)	1 (2%)	5 (10%)	4 (8%)
Fatty change		5 (10%)	1 (2%)	1 (2%)
Fibrosis	3 (6%)	1 (2%)		
Hematopoietic cell proliferation	1 (2%)		1 (2%)	
Hemorrhage	1 (2%)			1 (2%)
Hepatodiaphragmatic nodule	2 (4%)	3 (6%)	2 (4%)	1 (2%)
Hyperplasia, focal				1 (2%)
Infiltration cellular, lymphocyte		1 (2%)	1 (2%)	1 (2%)
Inflammation, chronic, focal		1 (2%)	1 (2%)	
Leukocytosis				1 (2%)
Mixed cell focus	2 (4%)			1 (2%)
Necrosis	1 (2%)	3 (6%)	1 (2%)	1 (2%)
Thrombosis	1 (2%)	1 (2%)	4 (8%)	1 (2%)
Bile duct, cyst		1 (2%)		
Bile duct, fibrosis			1 (2%)	
Bile duct, hyperplasia	1 (2%)	5 (10%)	3 (6%)	1 (2%)

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

	0 ppm	400 ppm	800 ppm	1,600 ppm
2-Year Study (continued)				
Alimentary System (continued)				
Mesentery	(10)	(21)	(17)	(17)
Fat, necrosis	9 (90%)	21 (100%)	16 (94%)	15 (88%)
Pancreas	(50)	(50)	(50)	(50)
Accessory spleen			1 (2%)	
Amyloid deposition			1 (2%)	
Ectopic liver		1 (2%)		1 (2%)
Edema			1 (2%)	
Infiltration cellular, lymphocyte			1 (2%)	1 (2%)
Necrosis		1 (2%)		
Acinar cell, atrophy	25 (50%)	29 (58%)	29 (58%)	22 (44%)
Artery, inflammation			1 (2%)	
Salivary glands	(50)	(50)	(50)	(50)
Amyloid deposition			1 (2%)	
Atrophy			1 (2%)	
Infiltration cellular, lymphocyte			1 (2%)	
Inflammation, chronic		1 (2%)		
Stomach, forestomach	(50)	(50)	(50)	(50)
Edema			1 (2%)	
Hyperkeratosis, focal		1 (2%)		
Hyperplasia	3 (6%)	4 (8%)	2 (4%)	4 (8%)
Ulcer	3 (6%)	3 (6%)	2 (4%)	1 (2%)
Stomach, glandular	(49)	(50)	(50)	(50)
Amyloid deposition	1 (2%)			
Hyperkeratosis, focal	1 (2%)			
Necrosis	1 (2%)	3 (6%)	1 (2%)	2 (4%)
Ulcer		4 (8%)	2 (4%)	4 (8%)
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Cardiomyopathy	32 (64%)	24 (48%)	25 (50%)	27 (54%)
Mineralization, focal		1 (2%)		
Atrium, dilatation		1 (2%)	1 (2%)	1 (2%)
Atrium, thrombosis	2 (4%)	2 (4%)	5 (10%)	4 (8%)
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Angiectasis	6 (12%)	7 (14%)	11 (22%)	20 (40%)
Cytologic alterations	1 (2%)			
Hemorrhage		1 (2%)	3 (6%)	2 (4%)
Hyperplasia, focal	3 (6%)	6 (12%)	2 (4%)	5 (10%)
Hypertrophy			1 (2%)	1 (2%)
Necrosis	1 (2%)			1 (2%)
Vacuolization cytoplasmic, focal		1 (2%)	2 (4%)	
Adrenal medulla	(49)	(50)	(50)	(50)
Hyperplasia	25 (51%)	12 (24%)	10 (20%)	9 (18%)
Islets, pancreatic	(50)	(50)	(50)	(50)
Hyperplasia	1 (2%)	1 (2%)	2 (4%)	
Parathyroid gland	(38)	(45)	(42)	(46)
Hyperplasia	1 (3%)	1 (2%)		1 (2%)

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

	0 ppm	400 ppm	800 ppm	1,600 ppm
2-Year Study (continued)				
Endocrine System (continued)				
Pituitary gland	(50)	(50)	(48)	(47)
Congestion	1 (2%)			
Pars distalis, angiectasis	7 (14%)	1 (2%)	3 (6%)	3 (6%)
Pars distalis, cyst	2 (4%)	6 (12%)	3 (6%)	2 (4%)
Pars distalis, degeneration	1 (2%)			
Pars distalis, hyperplasia, focal	5 (10%)	14 (28%)	5 (10%)	3 (6%)
Pars intermedia, angiectasis	2 (4%)			
Pars nervosa, cyst		1 (2%)		
Pars nervosa, developmental malformation				1 (2%)
Thyroid gland	(50)	(50)	(50)	(50)
C-cell, hyperplasia	4 (8%)	3 (6%)	6 (12%)	4 (8%)
Follicle, atrophy		1 (2%)		
Follicle, dilatation	1 (2%)		1 (2%)	
General Body System				
Tissue NOS				(1)
Mediastinum, infiltration cellular, lymphocyte				1 (100%)
Genital System				
Epididymis	(50)	(50)	(49)	(49)
Granuloma sperm		1 (2%)		
Hypoplasia		1 (2%)		
Hypospermia	33 (66%)	35 (70%)	39 (80%)	34 (69%)
Penis			(1)	
Angiectasis			1 (100%)	
Inflammation			1 (100%)	
Preputial gland	(50)	(50)	(48)	(50)
Atrophy	2 (4%)			
Depletion cellular			1 (2%)	
Ectasia	1 (2%)	9 (18%)	6 (13%)	4 (8%)
Hyperplasia	3 (6%)	1 (2%)	4 (8%)	11 (22%)
Inflammation	10 (20%)	3 (6%)	4 (8%)	9 (18%)
Prostate	(49)	(49)	(50)	(50)
Atrophy	3 (6%)	5 (10%)	2 (4%)	
Cytoplasmic alteration				1 (2%)
Dilatation			1 (2%)	
Fibrosis, focal	1 (2%)			
Hemorrhage		1 (2%)		
Hyperplasia, focal	4 (8%)	2 (4%)		2 (4%)
Infiltration cellular, focal, lymphocyte		1 (2%)		
Inflammation	5 (10%)	8 (16%)	9 (18%)	2 (4%)
Seminal vesicle	(50)	(50)	(50)	(50)
Depletion cellular	35 (70%)	41 (82%)	40 (80%)	42 (84%)
Dilatation		1 (2%)		
Ectasia			2 (4%)	
Infiltration cellular, lymphocyte		1 (2%)	1 (2%)	
Testes	(50)	(50)	(50)	(50)
Atrophy	4 (8%)	4 (8%)	1 (2%)	1 (2%)
Bilateral, atrophy	3 (6%)	1 (2%)		
Interstitial cell, hyperplasia, focal	2 (4%)	3 (6%)	3 (6%)	1 (2%)

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

	0 ppm	400 ppm	800 ppm	1,600 ppm
2-Year Study (continued)				
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Atrophy		1 (2%)		
Congestion				1 (2%)
Hemorrhage			1 (2%)	
Hyperplasia	5 (10%)	8 (16%)	5 (10%)	1 (2%)
Myelofibrosis				1 (2%)
Necrosis			1 (2%)	
Erythroid cell, hyperplasia	4 (8%)		2 (4%)	3 (6%)
Myeloid cell, atrophy				1 (2%)
Myeloid cell, hyperplasia		1 (2%)		
Lymph node	(20)	(17)	(14)	(22)
Lumbar, pigmentation				1 (5%)
Mediastinal, hemorrhage	2 (10%)	2 (12%)	2 (14%)	2 (9%)
Mediastinal, pigmentation	1 (5%)		2 (14%)	2 (9%)
Pancreatic, lymphocyte, hyperplasia				1 (5%)
Lymph node, mandibular	(50)	(49)	(49)	(49)
Amyloid deposition			1 (2%)	
Cyst	1 (2%)			
Hemorrhage	3 (6%)	1 (2%)	1 (2%)	
Hyperplasia, lymphoid	1 (2%)	2 (4%)		
Hyperplasia, plasma cell	1 (2%)	1 (2%)	5 (10%)	2 (4%)
Lymphocyte, hyperplasia				1 (2%)
Lymph node, mesenteric	(50)	(50)	(50)	(50)
Amyloid deposition			1 (2%)	
Cyst		2 (4%)		
Cyst, multiple			1 (2%)	
Erythrophagocytosis	1 (2%)	1 (2%)		
Hemorrhage			1 (2%)	1 (2%)
Hyperplasia, plasma cell	1 (2%)			
Infiltration cellular, histiocyte	1 (2%)	1 (2%)		1 (2%)
Pigmentation		1 (2%)		1 (2%)
Lymphocyte, hyperplasia				1 (2%)
Spleen	(50)	(50)	(50)	(50)
Congestion	1 (2%)	2 (4%)		1 (2%)
Developmental malformation	4 (8%)	1 (2%)		
Fibrosis	2 (4%)	3 (6%)	2 (4%)	2 (4%)
Hematopoietic cell proliferation	3 (6%)	4 (8%)	2 (4%)	3 (6%)
Infiltration cellular, histiocyte		1 (2%)		
Necrosis		1 (2%)	2 (4%)	
Pigmentation				1 (2%)
Lymphocyte, hyperplasia				1 (2%)
Thymus	(46)	(41)	(41)	(41)
Atrophy	28 (61%)	26 (63%)	22 (54%)	23 (56%)
Depletion cellular	1 (2%)			
Hemorrhage	2 (4%)	2 (5%)		1 (2%)
Infiltration cellular, lymphocyte				1 (2%)

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

	0 ppm	400 ppm	800 ppm	1,600 ppm
2-Year Study (continued)				
Integumentary System				
Mammary gland	(47)	(49)	(50)	(48)
Fibrosis				1 (2%)
Galactocele			1 (2%)	
Hemorrhage		1 (2%)		
Hyperplasia	3 (6%)	1 (2%)	1 (2%)	1 (2%)
Infiltration cellular, lymphocyte			1 (2%)	
Infiltration cellular, histiocyte			1 (2%)	
Lactation	7 (15%)		4 (8%)	2 (4%)
Pigmentation	2 (4%)	2 (4%)	1 (2%)	6 (13%)
Skin	(50)	(50)	(50)	(50)
Acanthosis	1 (2%)			
Hemorrhage			1 (2%)	
Inflammation			1 (2%)	
Ulcer		1 (2%)		
Hair follicle, atrophy	1 (2%)			
Subcutaneous tissue, inflammation				1 (2%)
Tail, acanthosis, focal	1 (2%)			
Tail, inflammation		1 (2%)		
Tail, necrosis		1 (2%)	1 (2%)	
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Hyperostosis		1 (2%)		
Rib, developmental malformation, focal	1 (2%)			
Nervous System				
Brain	(50)	(50)	(50)	(50)
Compression		1 (2%)		1 (2%)
Hemorrhage		1 (2%)		1 (2%)
Necrosis			1 (2%)	
Cerebellum, necrosis, focal				1 (2%)
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Fibrosis, focal		1 (2%)		
Hemorrhage	1 (2%)	1 (2%)		
Infiltration cellular, focal, histiocyte	6 (12%)	2 (4%)	2 (4%)	3 (6%)
Infiltration cellular, lymphocyte			1 (2%)	
Inflammation	4 (8%)	5 (10%)	6 (12%)	10 (20%)
Leukocytosis		1 (2%)		
Alveolar epithelium, hyperplasia, focal	3 (6%)			

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

	0 ppm	400 ppm	800 ppm	1,600 ppm
2-Year Study (continued)				
Respiratory System (continued)				
Nose	(50)	(50)	(50)	(50)
Angiectasis			2 (4%)	1 (2%)
Edema, focal				1 (2%)
Foreign body	1 (2%)	1 (2%)	2 (4%)	
Fungus	3 (6%)	4 (8%)	2 (4%)	1 (2%)
Inflammation	10 (20%)	11 (22%)	8 (16%)	5 (10%)
Inflammation, acute				1 (2%)
Thrombosis			2 (4%)	1 (2%)
Cartilage, dysplasia	1 (2%)			
Glands, dilatation, focal			1 (2%)	
Goblet cell, hyperplasia, focal	1 (2%)			
Nasolacrimal duct, inflammation	1 (2%)	1 (2%)	1 (2%)	
Nasopharyngeal duct, metaplasia, squamous	1 (2%)			
Olfactory epithelium, atrophy, focal	1 (2%)		1 (2%)	2 (4%)
Olfactory epithelium, cytoplasmic alteration	12 (24%)	16 (32%)	28 (56%)	47 (94%)
Olfactory epithelium, degeneration	1 (2%)			
Olfactory epithelium, necrosis, focal				2 (4%)
Respiratory epithelium, cytoplasmic alteration, focal				1 (2%)
Respiratory epithelium, hyperplasia	1 (2%)		3 (6%)	
Trachea	(50)	(50)	(50)	(50)
Infiltration cellular, focal, lymphocyte	1 (2%)			
Inflammation		1 (2%)		
Special Senses System				
Eye	(1)	(1)	(2)	
Phthisis bulbi			1 (50%)	
Lens, cataract	1 (100%)			
Retina, degeneration	1 (100%)			
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Congestion	1 (2%)			
Infarct			2 (4%)	
Infiltration cellular, lymphocyte			1 (2%)	1 (2%)
Nephropathy, chronic	40 (80%)	37 (74%)	36 (72%)	32 (64%)
Pigmentation	1 (2%)	8 (16%)	4 (8%)	2 (4%)
Bilateral, hydronephrosis		1 (2%)		
Glomerulus, degeneration		1 (2%)		
Transitional epithelium, hyperplasia, focal	1 (2%)			
Urethra			(1)	
Inflammation			1 (100%)	
Transitional epithelium, hyperplasia			1 (100%)	
Urinary bladder	(50)	(49)	(48)	(49)
Amyloid deposition			1 (2%)	
Dilatation		1 (2%)		2 (4%)
Hemorrhage		1 (2%)		
Infiltration cellular, lymphocyte		1 (2%)	1 (2%)	
Inflammation			1 (2%)	
Transitional epithelium, hyperplasia	1 (2%)	1 (2%)	1 (2%)	

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

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

	0 ppm	400 ppm	800 ppm	1,600 ppm
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	10	10	9	9
Early deaths				
Moribund	15	9	17	14
Natural deaths	7	3	5	5
Survivors				
Died last week of study		1	1	
Terminal sacrifice	28	37	28	32
Animals examined microscopically	60	60	60	60
15-Month Interim Evaluation				
Endocrine System				
Pituitary gland	(10)	(10)	(9)	(9)
Pars distalis, adenoma	1 (10%)	1 (10%)	1 (11%)	
Genital System				
Uterus	(10)	(10)	(9)	(9)
Polyp stromal		1 (10%)	1 (11%)	
Integumentary System				
Skin	(10)	(10)	(9)	(9)
Tail, keratoacanthoma			1 (11%)	
Systemic Lesions				
Multiple organs[b]	(10)	(10)	(9)	(9)
Leukemia mononuclear	1 (10%)			
Systems Examined With No Neoplasms Observed				
Alimentary System				
Cardiovascular System				
General Body System				
Hematopoietic System				
Musculoskeletal System				
Nervous System				
Respiratory System				
Special Senses System				
Urinary System				

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

	0 ppm	400 ppm	800 ppm	1,600 ppm
2-Year Study				
Alimentary System				
Esophagus	(50)	(50)	(51)	(51)
Intestine large, colon	(50)	(50)	(51)	(51)
Intestine large, rectum	(50)	(50)	(51)	(51)
Sarcoma, metastatic, uncertain primary site			1 (2%)	
Intestine large, cecum	(50)	(48)	(50)	(50)
Intestine small, duodenum	(50)	(50)	(51)	(50)
Intestine small, jejunum	(49)	(49)	(47)	(50)
Adenocarcinoma	1 (2%)			
Intestine small, ileum	(50)	(48)	(48)	(47)
Liver	(50)	(50)	(51)	(51)
Histiocytic sarcoma			1 (2%)	
Mesentery	(6)	(5)	(6)	(3)
Oral mucosa	(3)			(1)
Buccal, squamous cell carcinoma				1 (100%)
Pancreas	(50)	(50)	(51)	(51)
Salivary glands	(50)	(49)	(51)	(50)
Carcinoma, metastatic, Zymbal's gland		1 (2%)		
Stomach, forestomach	(50)	(50)	(51)	(50)
Stomach, glandular	(50)	(50)	(51)	(51)
Cardiovascular System				
Blood vessel	(50)	(50)	(51)	(51)
Heart	(50)	(50)	(51)	(51)
Endocrine System				
Adrenal cortex	(50)	(50)	(51)	(51)
Adenoma		1 (2%)	1 (2%)	
Adrenal medulla	(50)	(50)	(50)	(51)
Pheochromocytoma malignant	1 (2%)			
Pheochromocytoma benign	2 (4%)	5 (10%)	1 (2%)	1 (2%)
Islets, pancreatic	(50)	(50)	(51)	(51)
Adenoma		1 (2%)	1 (2%)	
Carcinoma	1 (2%)			
Parathyroid gland	(45)	(37)	(41)	(46)
Adenoma	1 (2%)			
Pituitary gland	(46)	(50)	(50)	(51)
Pars distalis, adenoma	16 (35%)	17 (34%)	19 (38%)	12 (24%)
Pars distalis, carcinoma	1 (2%)	1 (2%)		
Thyroid gland	(50)	(50)	(51)	(51)
Bilateral, follicular cell, carcinoma				1 (2%)
C-cell, adenoma	4 (8%)	3 (6%)	5 (10%)	3 (6%)
C-cell, carcinoma	2 (4%)	1 (2%)		
Follicular cell, adenoma	1 (2%)		1 (2%)	1 (2%)
Follicular cell, carcinoma			1 (2%)	

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

	0 ppm	400 ppm	800 ppm	1,600 ppm
2-Year Study (continued)				
General Body System				
None				
Genital System				
Clitoral gland	(47)	(47)	(50)	(51)
Adenoma	5 (11%)	5 (11%)	11 (22%)	1 (2%)
Carcinoma	1 (2%)			
Bilateral, adenoma		1 (2%)	1 (2%)	
Ovary	(50)	(50)	(51)	(51)
Granulosa-theca tumor malignant	1 (2%)			
Luteoma	1 (2%)			
Oviduct			(1)	
Uterus	(50)	(50)	(51)	(51)
Polyp stromal	1 (2%)	6 (12%)	6 (12%)	3 (6%)
Sarcoma			1 (2%)	
Sarcoma stromal			1 (2%)	
Vagina			(2)	(1)
Squamous cell papilloma			1 (50%)	
Hematopoietic System				
Bone marrow	(50)	(50)	(51)	(51)
Histiocytic sarcoma			1 (2%)	
Lymph node	(12)	(10)	(9)	(11)
Mediastinal, histiocytic sarcoma			1 (11%)	
Lymph node, mandibular	(48)	(49)	(49)	(49)
Carcinoma, metastatic, Zymbal's gland		1 (2%)		
Lymph node, mesenteric	(50)	(49)	(49)	(51)
Spleen	(50)	(50)	(51)	(51)
Histiocytic sarcoma			1 (2%)	
Thymus	(44)	(46)	(47)	(46)
Thymoma benign	1 (2%)			1 (2%)
Integumentary System				
Mammary gland	(50)	(50)	(50)	(51)
Adenoacanthoma				1 (2%)
Adenocarcinoma	3 (6%)	2 (4%)	3 (6%)	
Fibroadenoma	22 (44%)	20 (40%)	21 (42%)	6 (12%)
Fibroadenoma, multiple	5 (10%)	1 (2%)	6 (12%)	2 (4%)
Skin	(50)	(50)	(50)	(51)
Keratoacanthoma		1 (2%)		
Squamous cell papilloma	1 (2%)			
Subcutaneous tissue, fibroma	2 (4%)		3 (6%)	1 (2%)
Subcutaneous tissue, fibroma, multiple		1 (2%)		
Subcutaneous tissue, fibrosarcoma	1 (2%)			
Subcutaneous tissue, sarcoma			1 (2%)	
Tail, schwannoma malignant			1 (2%)	

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

	0 ppm	400 ppm	800 ppm	1,600 ppm
2-Year Study (continued)				
Musculoskeletal System				
Skeletal muscle			(1)	
Sarcoma			1 (100%)	
Nervous System				
Brain	(50)	(50)	(51)	(51)
Astrocytoma benign	1 (2%)			
Carcinoma, metastatic, pituitary gland	1 (2%)	1 (2%)		
Spinal cord		(2)		
Respiratory System				
Lung	(50)	(50)	(51)	(51)
Alveolar/bronchiolar adenoma				1 (2%)
Alveolar/bronchiolar carcinoma	1 (2%)			1 (2%)
Chordoma, metastatic, uncertain primary site		1 (2%)		
Sarcoma, metastatic, uncertain primary site			1 (2%)	
Nose	(50)	(50)	(51)	(51)
Carcinoma, metastatic, Zymbal's gland		1 (2%)		
Sarcoma				1 (2%)
Nasolacrimal duct, squamous cell carcinoma			1 (2%)	
Trachea	(50)	(50)	(51)	(51)
Special Senses System				
Ear			(2)	
Pinna, schwannoma malignant			2 (100%)	
Zymbal's gland		(1)	(3)	(1)
Carcinoma		1 (100%)	3 (100%)	1 (100%)
Urinary System				
Kidney	(50)	(50)	(51)	(51)
Lipoma		1 (2%)		
Nephroblastoma			1 (2%)	
Renal tubule, carcinoma				1 (2%)
Urinary bladder	(50)	(49)	(50)	(50)
Systemic Lesions				
Multiple organs	(50)	(50)	(51)	(51)
Histiocytic sarcoma			1 (2%)	
Leukemia mononuclear	14 (28%)	16 (32%)	18 (35%)	12 (24%)
Lymphoma malignant	1 (2%)			

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

	0 ppm	400 ppm	800 ppm	1,600 ppm
Neoplasm Summary				
Total animals with primary neoplasms[c]				
15-Month interim evaluation	2	2	3	
2-Year study	46	44	47	37
Total primary neoplasms				
15-Month interim evaluation	2	2	3	
2-Year study	91	84	112	51
Total animals with benign neoplasms				
15-Month interim evaluation	1	2	3	
2-Year study	38	40	41	27
Total benign neoplasms				
15-Month interim evaluation	1	2	3	
2-Year study	63	63	77	32
Total animals with malignant neoplasms				
15-Month interim evaluation	1			
2-Year study	27	19	28	17
Total malignant neoplasms				
15-Month interim evaluation	1			
2-Year study	28	21	35	19
Total animals with metastatic neoplasms				
2-Year study	1	3	1	
Total metastatic neoplasms				
2-Year study	1	5	2	
Total animals with malignant neoplasms of uncertain primary site				
2-Year study		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 B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Codeine: 0 ppm

Number of Days on Study	3	4	4	4	4	4	5	5	5	5	5	5	5	5	5	6	6	6	6	6	7	7	7	7	7
	1	3	7	7	9	9	3	4	4	7	8	8	8	8	9	3	6	7	7	8	1	2	3	3	3
	3	2	5	5	0	5	2	7	8	5	1	1	6	7	1	1	3	3	7	9	2	5	3	3	3
Carcass ID Number	2	2	2	2	2	3	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
	6	6	4	7	8	0	9	8	9	8	4	5	9	6	7	5	8	6	9	8	5	4	6	7	7
	6	9	1	1	9	0	9	7	8	4	6	5	6	2	3	0	5	1	4	6	2	8	7	4	7
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Adenocarcinoma															X										
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery																							+		
Oral mucosa																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																									
Pheochromocytoma benign																			X						
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Parathyroid gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																							X		
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	M	+	+	+
Pars distalis, adenoma						X											X		X	X					
Pars distalis, carcinoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma			X																				X		
C-cell, carcinoma																					X				
Follicular cell, adenoma			X																						
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Adenoma																	X					X			
Carcinoma														X											

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

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

Number of Days on Study	733	733	734	734	734	734	734	734	734	734	734	734	734	735	735	735	735	735	735	736	736	736	736	736	736	
Carcass ID Number	283	293	257	258	264	272	275	278	281	282	292	295	297	244	247	251	253	288	291	243	249	265	268	279	290	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
Adenocarcinoma																										1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery									+										+			+	+		+	6
Oral mucosa							+				+								+							3
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant				X																						1
Pheochromocytoma benign																			X							2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma													X													1
Parathyroid gland	+	+	+	+	M	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	45
Adenoma																										1
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	46
Pars distalis, adenoma			X			X	X	X				X			X	X	X	X	X	X					X	16
Pars distalis, carcinoma									X																	1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma															X					X						4
C-cell, carcinoma														X												2
Follicular cell, adenoma																										1
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma								X							X								X			5
Carcinoma																										1

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

Number of Days on Study	3	4	4	4	4	4	5	5	5	5	5	5	5	5	5	6	6	6	6	6	7	7	7	7	7
	1	3	7	7	9	9	3	4	4	7	8	8	8	8	9	3	6	7	7	8	1	2	3	3	3
	3	2	5	5	0	5	2	7	8	5	1	1	6	7	1	1	3	3	7	9	2	5	3	3	3
Carcass ID Number	2	2	2	2	2	3	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
	6	6	4	7	8	0	9	8	9	8	4	5	9	6	7	5	8	6	9	8	5	4	6	7	7
	6	9	1	1	9	0	9	7	8	4	6	5	6	2	3	0	5	1	4	6	2	8	7	4	7
Genital System (continued)																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa-theca tumor malignant																									
Luteoma																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+			+														+			+				
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	M
Thymoma benign																						X			
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma						X											X								
Fibroadenoma			X	X	X								X		X	X			X		X	X		X	X
Fibroadenoma, multiple																		X					X		
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Subcutaneous tissue, fibroma								X																	X
Subcutaneous tissue, fibrosarcoma	X																								
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma benign			X																						
Carcinoma, metastatic, pituitary gland																									
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X		X			X			X	X		X					X	X			X	X	X	
Lymphoma malignant																									

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

Number of Days on Study	733	733	734	734	734	734	734	734	734	734	734	734	734	735	735	735	735	735	735	736	736	736	736	736	736	
Carcass ID Number	283	293	257	258	264	272	275	278	281	282	292	295	297	244	247	251	253	288	291	243	249	265	268	279	290	Total Tissues/ Tumors
Genital System (continued)																										
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa-theca tumor malignant																				X						1
Luteoma														X												1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal							X																			1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node		+			+					+				+						+			+	+	+	12
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	48
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	44
Thymoma benign																										1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma																X										3
Fibroadenoma	X		X	X		X	X				X				X		X					X		X	X	22
Fibroadenoma, multiple													X					X			X					5
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																		X								1
Subcutaneous tissue, fibroma																										2
Subcutaneous tissue, fibrosarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma benign																										1
Carcinoma, metastatic, pituitary gland									X																	1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma					X																					1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye						+																				1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear					X	X											X									14
Lymphoma malignant																							X			1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Codeine: 400 ppm

Number of Days on Study	400	479	540	556	606	681	689	689	705	707	712	731	733	733	733	733	733	733	734	734	734	734	734	734	734
Carcass ID Number	314	344	301	320	349	339	310	355	347	308	003	330	302	293	333	352	357	359	304	309	313	317	321	323	326
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery						+	+																+		
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, Zymbal's gland									X																
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign							X				X														
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma		X																							
Parathyroid gland	+	M	+	M	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	M	M	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma				X							X			X	X		X	X		X		X			
Pars distalis, carcinoma										X															
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma					X		X																X		
C-cell, carcinoma														X											
General Body System																									
Tissue NOS																						+			
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+
Adenoma				X														X				X			
Bilateral, adenoma																					X				
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal				X										X	X		X			X					

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Codeine: 400 ppm (continued)

Number of Days on Study	734	734	734	734	734	734	734	734	735	735	735	735	735	735	735	735	735	735	735	736	736	736	736	736	736	
Carcass ID Number	327	336	337	338	441	442	445	446	006	007	015	018	028	035	040	048	050	053	058	012	032	034	043	045	046	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery	+							+																		5
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, metastatic, Zymbal's gland																										1
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																								X		1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign									X				X		X											5
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Parathyroid gland	+	+	M	M	M	+	+	M	+	+	+	M	+	+	+	+	+	M	+	+	+	M	+	+	+	37
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma		X			X					X	X	X						X		X		X		X		17
Pars distalis, carcinoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma																										3
C-cell, carcinoma																										1
General Body System																										
Tissue NOS																										1
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	47
Adenoma																X						X				5
Bilateral, adenoma																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal														X												6

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Codeine: 400 ppm (continued)

Number of Days on Study	400	479	540	546	606	681	689	689	705	707	712	731	733	733	733	733	733	733	734	734	734	734	734	734	734
Carcass ID Number	314	344	301	302	349	339	310	355	347	308	303	330	302	293	333	352	557	559	304	309	313	317	321	323	326
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node		+	+			+	+	+				+		+											+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, Zymbal's gland									X																
Lymph node, mesenteric	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma													X												
Fibroadenoma	X					X		X	X		X	X			X	X		X		X		X	X		X
Fibroadenoma, multiple																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																									
Subcutaneous tissue, fibroma, multiple																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pituitary gland										X															
Spinal cord		+																							
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Chordoma, metastatic, uncertain primary site																X									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, Zymbal's gland									X																
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Zymbal's gland									+																
Carcinoma									X																
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lipoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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 Codeine: 400 ppm (continued)

Number of Days on Study	734	734	734	734	734	734	734	734	735	735	735	735	735	735	735	735	735	735	735	736	736	736	736	736	736	
Carcass ID Number	327	336	337	338	341	342	345	346	306	307	315	318	328	335	340	348	350	353	358	312	332	334	343	344	356	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																				+				+		10
Lymph node, mandibular	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, metastatic, Zymbal's gland																										1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	M	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma																			X							2
Fibroadenoma			X	X						X		X	X											X	X	20
Fibroadenoma, multiple																					X					1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma														X												1
Subcutaneous tissue, fibroma, multiple	X																									1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, pituitary gland																										1
Spinal cord									+																	2
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Chordoma, metastatic, uncertain primary site																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, Zymbal's gland																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Zymbal's gland																										1
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lipoma																							X			1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear									X							X							X			16

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Codeine: 800 ppm

Number of Days on Study	365	427	584	606	635	641	641	643	659	662	670	673	677	684	686	688	687	694	700	707	707	721	733	733	733
Carcass ID Number	372	378	402	363	399	373	376	406	382	413	369	403	411	385	361	420	400	404	408	371	381	419	365	368	380
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, uncertain primary site																					X				
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	A	A	+	+	+
Intestine small, ileum	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																			X						
Mesentery																						+		+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pharynx																									+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma				X																					
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																X									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	M	+	+	M	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	M	+	+	+
Pituitary gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma		X				X			X	X		X			X		X		X					X	X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma															X										
Follicular cell, adenoma								X																	
Follicular cell, carcinoma																									X
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma										X						X									
Bilateral, adenoma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Oviduct																+									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal										X													X		X
Sarcoma																	X								
Sarcoma stromal														X											
Vagina																									+
Squamous cell papilloma																									X

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Codeine: 800 ppm (continued)

Number of Days on Study	733	734	733	734	733	734	733	734	735	735	733	735	735	735	733	735	733	735	735	736	736	736	733	736	733	736	
Carcass ID Number	4164	3644	3704	3774	3383	4412	4417	4418	3377	3779	3386	3390	3991	3992	3994	3996	3997	4401	4409	3375	3388	3389	3393	4405	4410	4414	Total Tissues/ Tumors
Alimentary System																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Sarcoma, metastatic, uncertain primary site																											1
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Histiocytic sarcoma																											1
Mesentery								+				+									+						6
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Pharynx																											1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Cardiovascular System																											
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Endocrine System																											
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adenoma																											1
Adrenal medulla	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																											1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adenoma									X																		1
Parathyroid gland	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	M	+	M	+	+	+	M	+	+	+	+	41
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma			X			X	X	X	X	X		X	X								X						19
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
C-cell, adenoma									X		X			X					X								1
Follicular cell, adenoma																											1
Follicular cell, carcinoma																											
General Body System																											
None																											
Genital System																											
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma	X						X	X	X					X				X		X		X			X		11
Bilateral, adenoma												X															1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Oviduct																											1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Polyp stromal									X		X															X	6
Sarcoma																											1
Sarcoma stromal																											1
Vagina																							+				2
Squamous cell papilloma																											1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Codeine: 800 ppm (continued)

Number of Days on Study	365	427	584	606	635	641	641	643	659	662	670	673	677	684	686	688	687	694	700	707	707	721	733	733	733
Carcass ID Number	372	378	402	363	399	373	376	406	382	413	369	403	411	385	361	420	400	404	408	371	381	419	365	368	380
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																			X						
Lymph node													+			+	+	+	+						
Mediastinal, histiocytic sarcoma																			X						
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																			X						
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Adenocarcinoma																									
Fibroadenoma							X	X	X					X		X	X			X					X
Fibroadenoma, multiple										X	X								X						
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibroma									X	X												X			
Subcutaneous tissue, sarcoma																					X				
Tail, schwannoma malignant											X														
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																					+				
Sarcoma																					X				
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, uncertain primary site																					X				
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nasolacrimal duct, squamous cell carcinoma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																									+
Pinna, schwannoma malignant																									X
Eye																									
Harderian gland																									
Zymbal's gland				+							+				+										
Carcinoma				X							X				X										
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nephroblastoma	X																								
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																			X						
Leukemia mononuclear					X								X			X				X		X	X	X	

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Codeine: 800 ppm (continued)

Number of Days on Study	733	734	734	734	734	734	734	734	735	735	735	735	735	735	735	735	735	735	735	736	736	736	736	736	736	736	
Carcass ID Number	416	364	370	374	383	412	417	418	377	379	386	390	391	392	394	396	397	401	409	375	388	389	393	405	410	414	Total Tissues/ Tumors
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Histiocytic sarcoma																											1
Lymph node											+			+		+				+							9
Mediastinal, histiocytic sarcoma																											1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Histiocytic sarcoma																											1
Thymus	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	47
Integumentary System																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma				X							X			X													3
Fibroadenoma		X			X	X	X	X		X				X		X			X	X	X			X	X		21
Fibroadenoma, multiple	X		X										X														6
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibroma																											3
Subcutaneous tissue, sarcoma																											1
Tail, schwannoma malignant																											1
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Skeletal muscle																											1
Sarcoma																											1
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Sarcoma, metastatic, uncertain primary site																											1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Nasolacrimal duct, squamous cell carcinoma												X															1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Special Senses System																											
Ear																							+				2
Pinna, schwannoma malignant																							X				2
Eye				+																							1
Harderian gland															+												1
Zymbal's gland																											3
Carcinoma																											3
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Nephroblastoma																											1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Histiocytic sarcoma																											1
Leukemia mononuclear				X	X			X			X			X				X	X		X	X	X		X		18

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Codeine: 1,600 ppm

Number of Days on Study	383	444	473	617	624	631	638	645	664	684	691	698	701	702	714	718	719	720	725	733	733	733	733	733	734
Carcass ID Number	429	473	460	478	466	461	440	421	455	449	423	452	422	477	446	432	444	425	462	437	438	442	454	463	428
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	A	+	+	+	+	+	A	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery														+								+			
Oral mucosa												+													
Buccal, squamous cell carcinoma												X													
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue												+													
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma						X				X															
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, follicular cell, carcinoma																									
C-cell, adenoma														X								X			
Follicular cell, adenoma																									
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal			X						X						X										
Vagina																									

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Codeine: 1,600 ppm (continued)

Number of Days on Study	734	734	734	734	734	734	735	735	735	735	735	735	735	735	735	735	735	735	736	736	736	736	736	736	736	736	
Carcass ID Number	4343	4345	4348	4450	4664	4668	4224	4226	4336	4441	4443	4447	4451	4467	4669	4670	4771	4779	4227	4331	4339	4445	4557	4558	4665	4674	Total Tissues/ Tumors
Alimentary System																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Mesentery											+																3
Oral mucosa																											1
Buccal, squamous cell carcinoma																											1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Tongue																											1
Cardiovascular System																											
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Endocrine System																											
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Pheochromocytoma benign							X																				1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	M	+	46
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Pars distalis, adenoma		X						X	X	X		X	X						X					X	X	X	12
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Bilateral, follicular cell, carcinoma																	X										1
C-cell, adenoma									X																		3
Follicular cell, adenoma											X																1
General Body System																											
None																											
Genital System																											
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adenoma							X																				1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Polyp stromal																											3
Vagina													+														1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Codeine: 1,600 ppm (continued)

Number of Days on Study	383	443	473	617	624	631	638	645	664	684	691	698	701	702	714	718	719	720	725	733	733	733	733	733	734
Carcass ID Number	429	473	460	478	466	461	440	421	455	449	423	452	422	427	446	432	444	425	462	437	438	442	454	463	428
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node									+	+	+			+	+		+					+			+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Thymoma benign																									
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoacanthoma																									
Fibroadenoma								X											X					X	
Fibroadenoma, multiple																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibroma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																	X								
Alveolar/bronchiolar carcinoma																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma		X																							
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye							+		+							+									
Harderian gland																+									
Zymbal's gland																+									
Carcinoma																X									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, carcinoma											X														
Urinary bladder	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				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 Codeine: 1,600 ppm (continued)

Number of Days on Study	734	734	734	734	734	734	735	735	735	735	735	735	735	735	735	735	735	736	736	736	736	736	736	736	736		
Carcass ID Number	434	435	448	450	464	468	424	426	436	441	443	447	451	467	469	470	471	479	427	431	439	445	457	458	465	474	Total Tissues/ Tumors
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Lymph node	+																		+		+						11
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Thymus	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	M	+	M	+	+	+	+	+	+	+	+	46
Thymoma benign							X																				1
Integumentary System																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adenoacanthoma					X																						1
Fibroadenoma	X			X																				X			6
Fibroadenoma, multiple		X	X																								2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Subcutaneous tissue, fibroma																		X									1
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Alveolar/bronchiolar adenoma																											1
Alveolar/bronchiolar carcinoma				X																							1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Sarcoma																											1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Special Senses System																											
Eye					+													+									5
Harderian gland																											1
Zymbal's gland																											1
Carcinoma																											1
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Renal tubule, carcinoma																											1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Leukemia mononuclear					X																						12

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

	0 ppm	400 ppm	800 ppm	1,600 ppm
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate[a]	2/50 (4%)	5/50 (10%)	1/50 (2%)	1/51 (2%)
Adjusted rate[b]	6.6%	12.2%	2.7%	3.1%
Terminal rate[c]	1/28 (4%)	3/38 (8%)	0/28 (0%)	1/32 (3%)
First incidence (days)	677	689	686	733 (T)
Life table test[d]	P=0.171N	P=0.362	P=0.457N	P=0.438N
Logistic regression test[d]	P=0.158N	P=0.296	P=0.472N	P=0.437N
Cochran-Armitage test[d]	P=0.188N			
Fisher exact test[d]		P=0.218	P=0.500N	P=0.492N
Adrenal Medulla: Benign or Malignant Pheochromocytoma				
Overall rate	3/50 (6%)	5/50 (10%)	1/50 (2%)	1/51 (2%)
Adjusted rate	10.0%	12.2%	2.7%	3.1%
Terminal rate	2/28 (7%)	3/38 (8%)	0/28 (0%)	1/32 (3%)
First incidence (days)	677	689	686	733 (T)
Life table test	P=0.099N	P=0.535	P=0.275N	P=0.249N
Logistic regression test	P=0.087N	P=0.474	P=0.266N	P=0.235N
Cochran-Armitage test	P=0.110N			
Fisher exact test		P=0.357	P=0.309N	P=0.301N
Clitoral Gland: Adenoma				
Overall rate	5/47 (11%)	6/47 (13%)	12/50 (24%)	1/51 (2%)
Adjusted rate	16.7%	15.7%	37.8%	3.1%
Terminal rate	3/27 (11%)	5/36 (14%)	10/29 (34%)	1/32 (3%)
First incidence (days)	663	546	662	733 (T)
Life table test	P=0.115N	P=0.566N	P=0.081	P=0.071N
Logistic regression test	P=0.078N	P=0.596	P=0.115	P=0.054N
Cochran-Armitage test	P=0.115N			
Fisher exact test		P=0.500	P=0.071	P=0.085N
Clitoral Gland: Adenoma or Carcinoma				
Overall rate	6/47 (13%)	6/47 (13%)	12/50 (24%)	1/51 (2%)
Adjusted rate	19.0%	15.7%	37.8%	3.1%
Terminal rate	3/27 (11%)	5/36 (14%)	10/29 (34%)	1/32 (3%)
First incidence (days)	587	546	662	733 (T)
Life table test	P=0.075N	P=0.430N	P=0.145	P=0.037N
Logistic regression test	P=0.052N	P=0.568N	P=0.189	P=0.033N
Cochran-Armitage test	P=0.075N			
Fisher exact test		P=0.621N	P=0.123	P=0.044N
Mammary Gland: Fibroadenoma				
Overall rate	27/50 (54%)	21/50 (42%)	27/51 (53%)	8/51 (16%)
Adjusted rate	70.3%	47.4%	68.2%	23.0%
Terminal rate	17/28 (61%)	15/38 (39%)	17/29 (59%)	6/32 (19%)
First incidence (days)	475	400	641	645
Life table test	P<0.001N	P=0.019N	P=0.419N	P<0.001N
Logistic regression test	P<0.001N	P=0.087N	P=0.359N	P<0.001N
Cochran-Armitage test	P<0.001N			
Fisher exact test		P=0.158N	P=0.537N	P<0.001N

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Feed Study of Codeine (continued)

	0 ppm	400 ppm	800 ppm	1,600 ppm
Mammary Gland: Adenocarcinoma				
Overall rate	3/50 (6%)	2/50 (4%)	3/51 (6%)	0/51 (0%)
Adjusted rate	8.5%	5.3%	10.3%	0.0%
Terminal rate	1/28 (4%)	2/38 (5%)	3/29 (10%)	0/32 (0%)
First incidence (days)	495	733 (T)	733 (T)	—[e]
Life table test	P=0.101N	P=0.388N	P=0.629N	P=0.100N
Logistic regression test	P=0.102N	P=0.533N	P=0.650N	P=0.147N
Cochran-Armitage test	P=0.107N			
Fisher exact test		P=0.500N	P=0.652N	P=0.118N
Mammary Gland: Fibroadenoma, Adenoacanthoma, or Adenocarcinoma				
Overall rate	30/50 (60%)	23/50 (46%)	29/51 (57%)	8/51 (16%)
Adjusted rate	74.4%	52.0%	73.5%	23.0%
Terminal rate	18/28 (64%)	17/38 (45%)	19/29 (66%)	6/32 (19%)
First incidence (days)	475	400	641	645
Life table test	P<0.001N	P=0.011N	P=0.344N	P<0.001N
Logistic regression test	P<0.001N	P=0.063N	P=0.284N	P<0.001N
Cochran-Armitage test	P<0.001N			
Fisher exact test		P=0.115N	P=0.453N	P<0.001N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	16/46 (35%)	17/50 (34%)	19/50 (38%)	12/51 (24%)
Adjusted rate	50.6%	42.2%	49.3%	34.3%
Terminal rate	12/27 (44%)	15/38 (39%)	11/29 (38%)	10/32 (31%)
First incidence (days)	495	546	427	631
Life table test	P=0.142N	P=0.239N	P=0.484	P=0.105N
Logistic regression test	P=0.072N	P=0.279N	P=0.559N	P=0.054N
Cochran-Armitage test	P=0.129N			
Fisher exact test		P=0.553N	P=0.455	P=0.159N
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma				
Overall rate	17/46 (37%)	18/50 (36%)	19/50 (38%)	12/51 (24%)
Adjusted rate	53.9%	43.7%	49.3%	34.3%
Terminal rate	13/27 (48%)	15/38 (39%)	11/29 (38%)	10/32 (31%)
First incidence (days)	495	546	427	631
Life table test	P=0.094N	P=0.224N	P=0.565	P=0.069N
Logistic regression test	P=0.041N	P=0.257N	P=0.456N	P=0.031N
Cochran-Armitage test	P=0.082N			
Fisher exact test		P=0.545N	P=0.542	P=0.111N
Skin (Subcutaneous Tissue): Fibroma				
Overall rate	2/50 (4%)	1/50 (2%)	3/51 (6%)	1/51 (2%)
Adjusted rate	5.8%	2.6%	7.8%	3.1%
Terminal rate	1/28 (4%)	1/38 (3%)	0/29 (0%)	1/32 (3%)
First incidence (days)	547	733 (T)	659	733 (T)
Life table test	P=0.445N	P=0.422N	P=0.557	P=0.456N
Logistic regression test	P=0.475N	P=0.526N	P=0.484	P=0.508N
Cochran-Armitage test	P=0.465N			
Fisher exact test		P=0.500N	P=0.509	P=0.492N

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Feed Study of Codeine (continued)

	0 ppm	400 ppm	800 ppm	1,600 ppm
Skin (Subcutaneous Tissue): Fibroma, Fibrosarcoma, or Sarcoma				
Overall rate	3/50 (6%)	1/50 (2%)	4/51 (8%)	1/51 (2%)
Adjusted rate	7.7%	2.6%	10.7%	3.1%
Terminal rate	1/28 (4%)	1/38 (3%)	0/29 (0%)	1/32 (3%)
First incidence (days)	313	733 (T)	659	733 (T)
Life table test	P=0.316N	P=0.250N	P=0.555	P=0.273N
Logistic regression test	P=0.403N	P=0.488N	P=0.386	P=0.436N
Cochran-Armitage test	P=0.334N			
Fisher exact test		P=0.309N	P=0.511	P=0.301N
Thyroid Gland (C-cell): Adenoma				
Overall rate	4/50 (8%)	3/50 (6%)	5/51 (10%)	3/51 (6%)
Adjusted rate	12.6%	6.9%	16.1%	8.7%
Terminal rate	3/28 (11%)	1/38 (3%)	4/29 (14%)	2/32 (6%)
First incidence (days)	475	606	686	702
Life table test	P=0.444N	P=0.360N	P=0.531	P=0.430N
Logistic regression test	P=0.448N	P=0.538N	P=0.564	P=0.461N
Cochran-Armitage test	P=0.469N			
Fisher exact test		P=0.500N	P=0.513	P=0.489N
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rate	6/50 (12%)	4/50 (8%)	5/51 (10%)	3/51 (6%)
Adjusted rate	18.9%	9.4%	16.1%	8.7%
Terminal rate	4/28 (14%)	2/38 (5%)	4/29 (14%)	2/32 (6%)
First incidence (days)	475	606	686	702
Life table test	P=0.198N	P=0.219N	P=0.470N	P=0.183N
Logistic regression test	P=0.189N	P=0.353N	P=0.417N	P=0.191N
Cochran-Armitage test	P=0.215N			
Fisher exact test		P=0.370N	P=0.486N	P=0.234N
Uterus: Stromal Polyp				
Overall rate	1/50 (2%)	6/50 (12%)	6/51 (12%)	3/51 (6%)
Adjusted rate	3.6%	15.0%	19.2%	6.9%
Terminal rate	1/28 (4%)	5/38 (13%)	5/29 (17%)	0/32 (0%)
First incidence (days)	733 (T)	546	662	473
Life table test	P=0.463	P=0.114	P=0.068	P=0.368
Logistic regression test	P=0.454	P=0.076	P=0.082	P=0.256
Cochran-Armitage test	P=0.444			
Fisher exact test		P=0.056	P=0.059	P=0.316
Uterus: Stromal Polyp or Stromal Sarcoma				
Overall rate	1/50 (2%)	6/50 (12%)	7/51 (14%)	3/51 (6%)
Adjusted rate	3.6%	15.0%	21.3%	6.9%
Terminal rate	1/28 (4%)	5/38 (13%)	5/29 (17%)	0/32 (0%)
First incidence (days)	733 (T)	546	662	473
Life table test	P=0.455	P=0.114	P=0.043	P=0.368
Logistic regression test	P=0.438	P=0.076	P=0.051	P=0.256
Cochran-Armitage test	P=0.429			
Fisher exact test		P=0.056	P=0.032	P=0.316

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Feed Study of Codeine (continued)

	0 ppm	400 ppm	800 ppm	1,600 ppm
Zymbal's Gland: Carcinoma				
Overall rate	0/50 (0%)	1/50 (2%)	3/51 (6%)	1/51 (2%)
Adjusted rate	0.0%	2.4%	7.1%	2.8%
Terminal rate	0/28 (0%)	0/38 (0%)	0/29 (0%)	0/32 (0%)
First incidence (days)	—	705	606	718
Life table test	P=0.401	P=0.567	P=0.169	P=0.543
Logistic regression test	P=0.341	P=0.525	P=0.102	P=0.539
Cochran-Armitage test	P=0.358			
Fisher exact test		P=0.500	P=0.125	P=0.505
All Organs: Mononuclear Cell Leukemia				
Overall rate	14/50 (28%)	16/50 (32%)	18/51 (35%)	12/51 (24%)
Adjusted rate	35.3%	34.3%	52.1%	27.3%
Terminal rate	5/28 (18%)	8/38 (21%)	13/29 (45%)	2/32 (6%)
First incidence (days)	432	479	635	617
Life table test	P=0.267N	P=0.441N	P=0.369	P=0.248N
Logistic regression test	P=0.353N	P=0.272	P=0.305	P=0.587N
Cochran-Armitage test	P=0.311N			
Fisher exact test		P=0.414	P=0.283	P=0.387N
All Organs: Benign Neoplasms				
Overall rate	39/50 (78%)	40/50 (80%)	41/51 (80%)	27/51 (53%)
Adjusted rate	92.7%	83.3%	90.9%	65.1%
Terminal rate	25/28 (89%)	30/38 (79%)	25/29 (86%)	18/32 (56%)
First incidence (days)	475	400	427	473
Life table test	P=0.006N	P=0.059N	P=0.484N	P=0.003N
Logistic regression test	P<0.001N	P=0.460N	P=0.444N	P=0.001N
Cochran-Armitage test	P=0.001N			
Fisher exact test		P=0.500	P=0.480	P=0.007N
All Organs: Malignant Neoplasms				
Overall rate	27/50 (54%)	20/50 (40%)	28/51 (55%)	17/51 (33%)
Adjusted rate	61.7%	41.6%	66.1%	36.9%
Terminal rate	12/28 (43%)	10/38 (26%)	15/29 (52%)	4/32 (13%)
First incidence (days)	313	479	365	444
Life table test	P=0.060N	P=0.027N	P=0.471N	P=0.021N
Logistic regression test	P=0.076N	P=0.228N	P=0.484	P=0.061N
Cochran-Armitage test	P=0.051N			
Fisher exact test		P=0.115N	P=0.543	P=0.029N

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Feed Study of Codeine (continued)

	0 ppm	400 ppm	800 ppm	1,600 ppm
All Organs: Benign or Malignant Neoplasms				
Overall rate	46/50 (92%)	44/50 (88%)	47/51 (92%)	37/51 (73%)
Adjusted rate	95.8%	88.0%	95.9%	75.5%
Terminal rate	26/28 (93%)	32/38 (84%)	27/29 (93%)	20/32 (63%)
First incidence (days)	313	400	365	444
Life table test	P=0.041N	P=0.019N	P=0.382N	P=0.018N
Logistic regression test	P=0.004N	P=0.422N	P=0.633N	P=0.012N
Cochran-Armitage test	P=0.003N			
Fisher exact test		P=0.370N	P=0.631	P=0.010N

(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, mammary 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 exposure group is indicated by N.
[e] Not applicable; no neoplasms in animal group

TABLE B4a
Historical Incidence of Benign Pheochromocytomas of the Adrenal Medulla in Untreated Female F344/N Rats[a]

	Incidence in Controls
Historical Incidence at Microbiological Associates, Inc.	
C.I. Direct Blue 218	1/49
dl-Amphetamine Sulfate	2/49
Overall Historical Incidence	
Total	49/1,175 (4.2%)
Standard deviation	2.5%
Range	0%-8%

[a] Data as of 17 June 1994

TABLE B4b
Historical Incidence of Clitoral Gland Neoplasms in Untreated Female F344/N Rats[a]

	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Microbiological Associates, Inc.			
C.I. Direct Blue 218	2/47	0/47	2/47
dl-Amphetamine Sulfate	2/39	0/39	2/39
Overall Historical Incidence			
Total	92/1,117 (8.2%)	29/1,117 (2.6%)	119/1,117 (10.7%)
Standard deviation	4.3%	3.8%	5.6%
Range	0%-19%	0%-15%	2%-21%

[a] Data as of 17 June 1994

TABLE B4c
Historical Incidence of Mammary Gland Neoplasms in Untreated Female F344/N Rats[a]

	Incidence in Controls		
	Fibroadenoma	Carcinoma	Fibroadenoma, Adenoma, or Carcinoma
Historical Incidence at Microbiological Associates, Inc.			
C.I. Direct Blue 218	19/50	3/50	22/50
dl-Amphetamine Sulfate	21/50	3/50	25/50
Overall Historical Incidence			
Total	465/1,202 (38.7%)	32/1,202 (2.7%)	507/1,202 (42.2%)
Standard deviation	12.7%	2.9%	13.5%
Range	8%-58%	0%-10%	8%-64%

[a] Data as of 17 June 1994

TABLE B4d
Historical Incidence of Pituitary Gland (Pars Distalis) Neoplasms in Untreated Female F344/N Rats[a]

	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Microbiological Associates, Inc.			
C.I. Direct Blue 218	28/50	2/50	30/50
dl-Amphetamine Sulfate	31/50	0/50	31/50
Overall Historical Incidence			
Total	652/1,196 (54.5%)	13/1,196 (1.1%)	665/1,196 (55.6%)
Standard deviation	12.5%	1.4%	13.0%
Range	30%-76%	0%-4%	30%-80%

[a] Data as of 17 June 1994; includes data for unspecified site

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

	0 ppm	400 ppm	800 ppm	1,600 ppm
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	10	10	9	9
Early deaths				
Moribund	15	9	17	14
Natural deaths	7	3	5	5
Survivors				
Died last week of study		1	1	
Terminal sacrifice	28	37	28	32
Animals examined microscopically	60	60	60	60
15-Month Interim Evaluation				
Alimentary System				
Liver	(10)	(10)	(9)	(9)
Basophilic focus	9 (90%)	6 (60%)	2 (22%)	3 (33%)
Developmental malformation	1 (10%)			
Eosinophilic focus		1 (10%)		
Hepatodiaphragmatic nodule	1 (10%)		1 (11%)	
Hyperplasia, focal	1 (10%)			
Inflammation		3 (30%)		
Necrosis			1 (11%)	
Bile duct, hyperplasia, focal	1 (10%)			
Mesentery	(2)			
Fat, necrosis	2 (100%)			
Pancreas	(10)	(10)	(9)	(9)
Infiltration cellular, lymphocyte		1 (10%)	1 (11%)	
Acinar cell, atrophy	3 (30%)	2 (20%)	2 (22%)	3 (33%)
Cardiovascular System				
Heart	(10)	(10)	(9)	(9)
Cardiomyopathy		1 (10%)		
Endocrine System				
Adrenal cortex	(10)	(10)	(9)	(9)
Hemorrhage	1 (10%)			
Hyperplasia, focal	1 (10%)			
Adrenal medulla	(10)	(10)	(9)	(9)
Infiltration cellular, lymphocyte	1 (10%)			
Pituitary gland	(10)	(10)	(9)	(9)
Pars distalis, angiectasis			1 (11%)	
Pars distalis, cyst	3 (30%)	1 (10%)	1 (11%)	1 (11%)
Pars distalis, hyperplasia	3 (30%)	1 (10%)	3 (33%)	1 (11%)
Pars distalis, hyperplasia, focal	2 (20%)	1 (10%)		
Pars distalis, pigmentation				1 (11%)

[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 Codeine (continued)

	0 ppm	400 ppm	800 ppm	1,600 ppm
15-Month Interim Evaluation (continued)				
Genital System				
Clitoral gland	(10)	(10)	(9)	(9)
Ectasia	1 (10%)			1 (11%)
Hyperplasia		1 (10%)	1 (11%)	
Inflammation	1 (10%)			
Ovary	(10)	(10)	(9)	(9)
Cyst	1 (10%)	2 (20%)	1 (11%)	
Uterus	(10)	(10)	(9)	(9)
Dilatation	1 (10%)		1 (11%)	1 (11%)
Hematopoietic System				
Spleen	(10)	(10)	(9)	(9)
Developmental malformation			1 (11%)	
Thymus	(8)	(10)	(9)	(8)
Atrophy	1 (13%)	5 (50%)	3 (33%)	2 (25%)
Hemorrhage				1 (13%)
Integumentary System				
Mammary gland	(10)	(10)	(9)	(9)
Dilatation			1 (11%)	
Respiratory System				
Lung	(10)	(10)	(9)	(9)
Infiltration cellular, histiocyte	1 (10%)	4 (40%)	2 (22%)	2 (22%)
Inflammation		3 (30%)	4 (44%)	2 (22%)
Alveolar epithelium, hyperplasia		1 (10%)	1 (11%)	
Nose	(10)	(10)	(9)	(9)
Edema, focal				1 (11%)
Fungus	1 (10%)			
Hemorrhage		1 (10%)		
Infiltration cellular, focal, lymphocyte				1 (11%)
Inflammation	2 (20%)	2 (20%)	3 (33%)	1 (11%)
Olfactory epithelium, cytoplasmic alteration	8 (80%)	10 (100%)	9 (100%)	8 (89%)
Special Senses System				
Eye		(1)		
Lens, cataract		1 (100%)		
Retina, atrophy		1 (100%)		
Urinary System				
Kidney	(10)	(10)	(9)	(9)
Infarct		1 (10%)		
Mineralization	1 (10%)	1 (10%)		
Nephropathy, chronic	7 (70%)	10 (100%)	9 (100%)	5 (56%)

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

	0 ppm	400 ppm	800 ppm	1,600 ppm
15-Month Interim Evaluation (continued)				
Systems Examined With No Lesions Observed				
General Body System				
Musculoskeletal System				
Nervous System				
2-Year Study				
Alimentary System				
Intestine large, colon	(50)	(50)	(51)	(51)
Inflammation	1 (2%)			
Intussusception		1 (2%)		
Intestine large, cecum	(50)	(48)	(50)	(50)
Inflammation	1 (2%)			
Inflammation, granulomatous				1 (2%)
Liver	(50)	(50)	(51)	(51)
Basophilic focus	38 (76%)	36 (72%)	31 (61%)	29 (57%)
Clear cell focus	5 (10%)	4 (8%)		2 (4%)
Congestion			1 (2%)	3 (6%)
Degeneration	1 (2%)			
Developmental malformation	3 (6%)	2 (4%)		1 (2%)
Eosinophilic focus	5 (10%)	2 (4%)	3 (6%)	1 (2%)
Fatty change	10 (20%)	4 (8%)	4 (8%)	3 (6%)
Hematopoietic cell proliferation	2 (4%)		1 (2%)	
Hepatodiaphragmatic nodule	2 (4%)	5 (10%)	4 (8%)	1 (2%)
Infiltration cellular, lymphocyte	2 (4%)	1 (2%)	2 (4%)	2 (4%)
Inflammation	4 (8%)	1 (2%)	10 (20%)	9 (18%)
Leukocytosis	1 (2%)		1 (2%)	1 (2%)
Mixed cell focus			1 (2%)	
Necrosis	2 (4%)		3 (6%)	
Centrilobular, degeneration			1 (2%)	
Mesentery	(6)	(5)	(6)	(3)
Infiltration cellular, lymphocyte	1 (17%)			
Fat, inflammation		1 (20%)		
Fat, necrosis	5 (83%)	3 (60%)	5 (83%)	3 (100%)
Lymphatic, cyst	1 (17%)			
Oral mucosa	(3)			(1)
Gingival, cyst	1 (33%)			
Pancreas	(50)	(50)	(51)	(51)
Accessory spleen				1 (2%)
Infiltration cellular, lymphocyte	1 (2%)		1 (2%)	
Inflammation	2 (4%)	1 (2%)	1 (2%)	
Acinar cell, atrophy	24 (48%)	12 (24%)	20 (39%)	24 (47%)
Acinar cell, hyperplasia	1 (2%)			
Artery, inflammation		1 (2%)		
Pharynx			(1)	
Palate, hyperplasia			1 (100%)	
Salivary glands	(50)	(49)	(51)	(50)
Atrophy, focal	1 (2%)			

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

	0 ppm	400 ppm	800 ppm	1,600 ppm
2-Year Study (continued)				
Alimentary System (continued)				
Stomach, forestomach	(50)	(50)	(51)	(50)
Hyperplasia	3 (6%)	4 (8%)	3 (6%)	3 (6%)
Inflammation	2 (4%)	1 (2%)	1 (2%)	
Ulcer	2 (4%)		4 (8%)	5 (10%)
Stomach, glandular	(50)	(50)	(51)	(51)
Fibrosis, focal				1 (2%)
Necrosis		3 (6%)		2 (4%)
Ulcer			3 (6%)	1 (2%)
Tongue				(1)
Inflammation				1 (100%)
Cardiovascular System				
Heart	(50)	(50)	(51)	(51)
Cardiomyopathy	12 (24%)	7 (14%)	15 (29%)	9 (18%)
Hypertrophy		1 (2%)		
Infiltration cellular, lymphocyte			1 (2%)	
Atrium, dilatation			1 (2%)	
Atrium, thrombosis			1 (2%)	
Coronary artery, inflammation			1 (2%)	
Valve, inflammation, chronic			1 (2%)	
Valve, pigmentation	1 (2%)			
Endocrine System				
Adrenal cortex	(50)	(50)	(51)	(51)
Accessory adrenal cortical nodule				1 (2%)
Angiectasis	13 (26%)	6 (12%)	6 (12%)	3 (6%)
Congestion			1 (2%)	
Cytologic alterations	1 (2%)		1 (2%)	
Cytoplasmic alteration				2 (4%)
Degeneration				1 (2%)
Fibrosis			1 (2%)	
Hematopoietic cell proliferation			1 (2%)	
Hemorrhage				1 (2%)
Hyperplasia, focal		9 (18%)	8 (16%)	3 (6%)
Hypertrophy	2 (4%)	1 (2%)		1 (2%)
Necrosis			1 (2%)	1 (2%)
Thrombosis			1 (2%)	
Vacuolization cytoplasmic				2 (4%)
Vacuolization cytoplasmic, focal	7 (14%)	6 (12%)	4 (8%)	8 (16%)
Capsule, inflammation				1 (2%)
Adrenal medulla	(50)	(50)	(50)	(51)
Hyperplasia	8 (16%)	5 (10%)	2 (4%)	2 (4%)
Hyperplasia, focal				1 (2%)
Infiltration cellular, lymphocyte	1 (2%)			
Islets, pancreatic	(50)	(50)	(51)	(51)
Hyperplasia				1 (2%)
Parathyroid gland	(45)	(37)	(41)	(46)
Hyperplasia		3 (8%)		

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

	0 ppm	400 ppm	800 ppm	1,600 ppm
2-Year Study (continued)				
Endocrine System (continued)				
Pituitary gland	(46)	(50)	(50)	(51)
Developmental malformation				1 (2%)
Pars distalis, angiectasis	13 (28%)	7 (14%)	10 (20%)	7 (14%)
Pars distalis, cyst	13 (28%)	16 (32%)	16 (32%)	14 (27%)
Pars distalis, hyperplasia	13 (28%)	18 (36%)	13 (26%)	14 (27%)
Pars intermedia, angiectasis			1 (2%)	
Thyroid gland	(50)	(50)	(51)	(51)
C-cell, hyperplasia	4 (8%)	11 (22%)	5 (10%)	5 (10%)
General Body System				
None				
Genital System				
Clitoral gland	(47)	(47)	(50)	(51)
Ectasia	5 (11%)	9 (19%)	7 (14%)	20 (39%)
Hyperplasia	9 (19%)	7 (15%)	8 (16%)	6 (12%)
Inflammation			1 (2%)	3 (6%)
Ovary	(50)	(50)	(51)	(51)
Cyst	7 (14%)	2 (4%)	4 (8%)	4 (8%)
Inflammation, granulomatous				1 (2%)
Corpus luteum, hypertrophy				1 (2%)
Uterus	(50)	(50)	(51)	(51)
Cyst		1 (2%)		
Dilatation	3 (6%)	1 (2%)	6 (12%)	4 (8%)
Fibrosis			1 (2%)	
Hemorrhage	1 (2%)		2 (4%)	1 (2%)
Endometrium, hyperplasia				2 (4%)
Vagina			(2)	(1)
Inflammation			1 (50%)	1 (100%)
Prolapse				1 (100%)
Hematopoietic System				
Bone marrow	(50)	(50)	(51)	(51)
Hemorrhage				1 (2%)
Hyperplasia	2 (4%)	5 (10%)	8 (16%)	7 (14%)
Infiltration cellular, histiocyte		1 (2%)		
Myelofibrosis				1 (2%)
Erythroid cell, atrophy	1 (2%)			
Erythroid cell, hyperplasia	1 (2%)			
Myeloid cell, hyperplasia				1 (2%)
Lymph node	(12)	(10)	(9)	(11)
Iliac, hyperplasia, plasma cell	1 (8%)			
Mediastinal, cyst	1 (8%)			
Mediastinal, hemorrhage	6 (50%)	2 (20%)	2 (22%)	4 (36%)
Mediastinal, pigmentation	3 (25%)	2 (20%)	2 (22%)	2 (18%)
Pancreatic, pigmentation		1 (10%)		
Renal, hemorrhage			2 (22%)	
Renal, pigmentation			1 (11%)	

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

	0 ppm	400 ppm	800 ppm	1,600 ppm
2-Year Study (continued)				
Hematopoietic System (continued)				
Lymph node, mandibular	(48)	(49)	(49)	(49)
Congestion			1 (2%)	
Edema		1 (2%)		
Hemorrhage	2 (4%)	3 (6%)	4 (8%)	3 (6%)
Hyperplasia, lymphoid			1 (2%)	
Hyperplasia, plasma cell	2 (4%)		1 (2%)	3 (6%)
Infiltration cellular, histiocyte	1 (2%)			
Pigmentation	1 (2%)			
Lymph node, mesenteric	(50)	(49)	(49)	(51)
Edema	1 (2%)	2 (4%)		
Hemorrhage	1 (2%)			2 (4%)
Infiltration cellular, histiocyte	1 (2%)		3 (6%)	
Spleen	(50)	(50)	(51)	(51)
Congestion	1 (2%)	1 (2%)		1 (2%)
Depletion lymphoid	1 (2%)			
Hematopoietic cell proliferation	5 (10%)	2 (4%)	5 (10%)	6 (12%)
Hyperplasia, lymphoid		1 (2%)	1 (2%)	1 (2%)
Necrosis		1 (2%)		1 (2%)
Pigmentation			2 (4%)	2 (4%)
Thymus	(44)	(46)	(47)	(46)
Amyloid deposition		1 (2%)		
Atrophy	29 (66%)	29 (63%)	23 (49%)	23 (50%)
Congestion	1 (2%)			
Cyst				1 (2%)
Hemorrhage	2 (5%)	1 (2%)		2 (4%)
Integumentary System				
Mammary gland	(50)	(50)	(50)	(51)
Galactocele	1 (2%)	2 (4%)	3 (6%)	
Hyperplasia	8 (16%)	7 (14%)	7 (14%)	8 (16%)
Infiltration cellular, histiocyte		1 (2%)	3 (6%)	
Inflammation			1 (2%)	
Lactation	14 (28%)	23 (46%)	24 (48%)	16 (31%)
Skin	(50)	(50)	(50)	(51)
Acanthosis		1 (2%)		
Subcutaneous tissue, cyst epithelial inclusion		1 (2%)		
Tail, fibrosis				1 (2%)
Musculoskeletal System				
Bone	(50)	(50)	(51)	(51)
Cranium, hyperostosis	2 (4%)	3 (6%)	3 (6%)	3 (6%)
Femur, hyperostosis	3 (6%)	6 (12%)	3 (6%)	3 (6%)
Maxilla, hyperostosis			1 (2%)	
Turbinate, hyperostosis	2 (4%)	2 (4%)	4 (8%)	1 (2%)

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

	0 ppm	400 ppm	800 ppm	1,600 ppm
2-Year Study (continued)				
Nervous System				
Brain	(50)	(50)	(51)	(51)
Compression	8 (16%)	4 (8%)	10 (20%)	4 (8%)
Degeneration, focal			1 (2%)	
Hemorrhage		2 (4%)	2 (4%)	1 (2%)
Hydrocephalus	2 (4%)	1 (2%)	4 (8%)	1 (2%)
Necrosis		1 (2%)		
Meninges, inflammation, focal			1 (2%)	
Meninges, thrombosis, focal			1 (2%)	
Respiratory System				
Lung	(50)	(50)	(51)	(51)
Congestion			2 (4%)	1 (2%)
Hemorrhage		2 (4%)	3 (6%)	
Infiltration cellular, lymphocyte	3 (6%)		1 (2%)	1 (2%)
Infiltration cellular, histiocyte	6 (12%)	4 (8%)	7 (14%)	15 (29%)
Inflammation	7 (14%)	9 (18%)	4 (8%)	13 (25%)
Leukocytosis	1 (2%)			
Alveolar epithelium, hyperplasia	2 (4%)	1 (2%)	1 (2%)	
Nose	(50)	(50)	(51)	(51)
Cytoplasmic alteration			1 (2%)	
Edema, focal			2 (4%)	
Foreign body			1 (2%)	
Inflammation	2 (4%)	5 (10%)	5 (10%)	4 (8%)
Thrombosis				1 (2%)
Nares, hyperplasia				1 (2%)
Nasolacrimal duct, inflammation		1 (2%)	3 (6%)	3 (6%)
Olfactory epithelium, atrophy, focal			2 (4%)	1 (2%)
Olfactory epithelium, cytoplasmic alteration	38 (76%)	45 (90%)	42 (82%)	49 (96%)
Respiratory epithelium, hyperplasia			2 (4%)	
Trachea	(50)	(50)	(51)	(51)
Infiltration cellular, lymphocyte		1 (2%)		1 (2%)
Special Senses System				
Eye	(1)		(1)	(5)
Hemorrhage			1 (100%)	1 (20%)
Phthisis bulbi				1 (20%)
Cornea, inflammation				1 (20%)
Lens, cataract	1 (100%)			2 (40%)
Lens, hyperplasia	1 (100%)			
Retina, degeneration			1 (100%)	2 (40%)
Harderian gland			(1)	(1)
Infiltration cellular, lymphocyte				1 (100%)
Inflammation			1 (100%)	

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

	0 ppm	400 ppm	800 ppm	1,600 ppm
2-Year Study (continued)				
Urinary System				
Kidney	(50)	(50)	(51)	(51)
Cyst				1 (2%)
Infarct	1 (2%)	3 (6%)	1 (2%)	
Infiltration cellular, lymphocyte		1 (2%)	1 (2%)	
Inflammation				1 (2%)
Mineralization	3 (6%)	1 (2%)		1 (2%)
Necrosis			1 (2%)	2 (4%)
Nephropathy, chronic	39 (78%)	41 (82%)	40 (78%)	40 (78%)
Bilateral, hydronephrosis			1 (2%)	
Transitional epithelium, hyperplasia, focal			1 (2%)	
Urinary bladder	(50)	(49)	(50)	(50)
Infiltration cellular, lymphocyte				1 (2%)

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

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

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	10	10	10	10
Early deaths				
Accidental death		1		
Moribund	4	4	2	1
Natural deaths	5	7	3	6
Survivors				
Terminal sacrifice	41	38	45	43
Animals examined microscopically	60	60	60	60
15-Month Interim Evaluation				
Alimentary System				
Liver	(10)	(10)	(10)	(10)
Hepatocellular carcinoma				1 (10%)
Hepatocellular adenoma	3 (30%)	1 (10%)	2 (20%)	1 (10%)
Hematopoietic System				
Bone marrow	(10)	(10)	(10)	(10)
Fibroma, osseous				1 (10%)
Respiratory System				
Lung	(10)	(10)	(10)	(10)
Alveolar/bronchiolar adenoma	1 (10%)			1 (10%)
Systems Examined With No Neoplasms Observed				
Cardiovascular System				
Endocrine System				
General Body System				
Genital System				
Integumentary System				
Musculoskeletal System				
Nervous System				
Special Senses System				
Urinary System				

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of Codeine (continued)

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
2-Year Study				
Alimentary System				
Gallbladder	(34)	(41)	(42)	(40)
Intestine large, cecum	(50)	(50)	(50)	(48)
Intestine small, duodenum	(49)	(50)	(49)	(48)
Intestine small, jejunum	(50)	(50)	(49)	(48)
Carcinoma			1 (2%)	
Intestine small, ileum	(49)	(50)	(49)	(47)
Liver	(50)	(50)	(50)	(50)
Hemangiosarcoma		1 (2%)		
Hemangiosarcoma, multiple	1 (2%)			
Hepatoblastoma		1 (2%)		
Hepatocellular carcinoma	10 (20%)	8 (16%)	13 (26%)	7 (14%)
Hepatocellular carcinoma, multiple	3 (6%)			
Hepatocellular adenoma	12 (24%)	15 (30%)	11 (22%)	9 (18%)
Hepatocellular adenoma, multiple	11 (22%)	10 (20%)	5 (10%)	1 (2%)
Mesentery	(1)	(3)	(3)	(1)
Histiocytic sarcoma				1 (100%)
Pancreas	(49)	(50)	(50)	(50)
Salivary glands	(50)	(50)	(50)	(50)
Stomach, forestomach	(50)	(50)	(50)	(50)
Stomach, glandular	(49)	(50)	(50)	(49)
Cardiovascular System				
Blood vessel	(50)	(50)	(50)	(50)
Heart	(50)	(50)	(50)	(50)
Endocrine System				
Adrenal cortex	(49)	(48)	(50)	(50)
Adenoma			1 (2%)	1 (2%)
Subcapsular, adenoma		1 (2%)		
Adrenal medulla	(49)	(47)	(48)	(49)
Pheochromocytoma benign		1 (2%)		
Islets, pancreatic	(50)	(50)	(50)	(50)
Adenoma	2 (4%)	1 (2%)		
Pituitary gland	(46)	(49)	(48)	(46)
Pars intermedia, carcinoma	1 (2%)			
Thyroid gland	(49)	(50)	(50)	(50)
Follicular cell, adenoma	1 (2%)	2 (4%)	1 (2%)	2 (4%)
Follicular cell, adenoma, multiple			1 (2%)	
General Body System				
None				
Genital System				
Epididymis	(50)	(50)	(50)	(50)
Prostate	(46)	(49)	(48)	(50)
Seminal vesicle	(50)	(50)	(50)	(49)
Adenoma	1 (2%)			
Testes	(50)	(50)	(50)	(50)
Interstitial cell, adenoma		1 (2%)		

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of Codeine (continued)

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
2-Year Study (continued)				
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Lymph node	(6)	(1)		(2)
Mediastinal, histiocytic sarcoma		1 (100%)		
Lymph node, mandibular	(40)	(44)	(47)	(45)
Lymph node, mesenteric	(49)	(49)	(48)	(48)
Histiocytic sarcoma		1 (2%)		1 (2%)
Spleen	(50)	(50)	(49)	(50)
Hemangiosarcoma	1 (2%)			
Histiocytic sarcoma		1 (2%)		
Thymus	(43)	(34)	(42)	(44)
Histiocytic sarcoma				1 (2%)
Integumentary System				
Skin	(50)	(50)	(50)	(50)
Subcutaneous tissue, histiocytic sarcoma		1 (2%)		1 (2%)
Subcutaneous tissue, sarcoma	2 (4%)	1 (2%)		
Musculoskeletal System				
None				
Nervous System				
Brain	(50)	(50)	(50)	(50)
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	11 (22%)	8 (16%)	13 (26%)	7 (14%)
Alveolar/bronchiolar adenoma, multiple	4 (8%)		1 (2%)	1 (2%)
Alveolar/bronchiolar carcinoma	1 (2%)	2 (4%)	2 (4%)	2 (4%)
Hepatocellular carcinoma, metastatic, liver	4 (8%)	2 (4%)	3 (6%)	2 (4%)
Nose	(50)	(50)	(49)	(50)
Special Senses System				
Harderian gland	(3)	(3)	(5)	(3)
Adenoma	3 (100%)	3 (100%)	5 (100%)	3 (100%)
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Hepatocellular carcinoma, metastatic, liver		1 (2%)		
Urinary bladder	(50)	(50)	(50)	(49)
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Histiocytic sarcoma		2 (4%)		2 (4%)
Lymphoma malignant lymphocytic	3 (6%)			
Lymphoma malignant mixed	4 (8%)	1 (2%)	1 (2%)	

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of Codeine (continued)

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
Neoplasm Summary				
Total animals with primary neoplasms[c]				
15-Month interim evaluation	3	1	2	4
2-Year study	41	39	36	28
Total primary neoplasms				
15-Month interim evaluation	4	1	2	4
2-Year study	71	58	55	35
Total animals with benign neoplasms				
15-Month interim evaluation	3	1	2	3
2-Year study	34	32	30	21
Total benign neoplasms				
15-Month interim evaluation	4	1	2	3
2-Year study	45	42	38	24
Total animals with malignant neoplasms				
15-Month interim evaluation				1
2-Year study	20	15	15	10
Total malignant neoplasms				
15-Month interim evaluation				1
2-Year study	26	16	17	11
Total animals with metastatic neoplasms				
2-Year study	4	2	3	2
Total metastatic neoplasms				
2-Year study	4	3	3	2

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

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

Number of Days on Study	227	450	497	546	579	609	629	689	693	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	730
Carcass ID Number	035	050	015	019	040	028	011	030	039	001	005	010	012	025	029	034	036	042	044	046	047	052	055	056	002
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	A	M	+	+	+	M	M	M	+	+	+	+	+	+	M	+	+	M	M	M	+	+	M
Intestine large, colon	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, multiple																									
Hepatocellular carcinoma						X		X	X				X												X
Hepatocellular carcinoma, multiple			X				X																		
Hepatocellular adenoma			X								X		X			X	X				X				
Hepatocellular adenoma, multiple								X		X		X								X					X
Mesentery		+																							
Pancreas	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth										+		+													
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma				X													X								
Parathyroid gland	M	M	M	+	+	+	+	M	M	+	+	M	+	M	+	+	+	+	+	+	M	+	M	M	+
Pituitary gland	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Pars intermedia, carcinoma				X																					
Thyroid gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									X
General Body System																									
Tissue NOS																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Codeine: 0 ppm (continued)

Number of Days on Study	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731	731	731	731	
Carcass ID Number	003	006	008	014	017	021	022	023	027	031	032	037	041	045	051	054	060	009	016	020	033	043	048	053	058	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	47
Gallbladder	+	+	M	+	+	M	+	+	+	+	+	M	+	+	+	M	+	M	+	+	+	+	+	M	+	34
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma, multiple																			X							1
Hepatocellular carcinoma								X				X		X							X			X		10
Hepatocellular carcinoma, multiple																			X							3
Hepatocellular adenoma					X					X			X		X			X							X	12
Hepatocellular adenoma, multiple			X									X				X					X		X	X		11
Mesentery																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tooth			+		+		+	+				+						+				+				9
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										2
Parathyroid gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	M	+	+	36
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	46
Pars intermedia, carcinoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell, adenoma																										1
General Body System																										
Tissue NOS											+															1
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Prostate	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma						X																				1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Codeine: 0 ppm (continued)

Number of Days on Study	227	450	497	546	579	609	629	689	693	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	730
Carcass ID Number	035	050	015	019	040	028	011	030	039	031	045	010	012	025	029	034	036	042	044	046	047	052	055	056	002
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node		+			+	+											+								
Lymph node, mandibular	+	+	+	M	M	+	+	M	+	+	M	M	M	+	+	+	+	+	+	+	M	+	+	+	+
Lymph node, mesenteric	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma													X												
Thymus	+	+	+	M	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, sarcoma	X						X																		
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma												X				X						X			
Alveolar/bronchiolar adenoma, multiple											X		X				X				X				
Alveolar/bronchiolar carcinoma																	X								
Hepatocellular carcinoma, metastatic, liver						X		X																	X
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																			+						
Harderian gland																			+						
Adenoma																			X						
Zymbal's gland																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic		X				X																			
Lymphoma malignant mixed					X												X								

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Codeine: 0 ppm (continued)

Number of Days on Study	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731	731	731	731	
Carcass ID Number	003	006	008	014	017	021	022	023	027	031	032	037	041	045	051	054	060	091	096	120	133	143	148	153	158	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node					+							+														6
Lymph node, mandibular	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	40
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	M	+	43
Integumentary System																										
Mammary gland	M	M	+	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	+	M	2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, sarcoma																										2
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma		X					X		X		X			X					X	X		X				11
Alveolar/bronchiolar adenoma, multiple																										4
Alveolar/bronchiolar carcinoma																										1
Hepatocellular carcinoma, metastatic, liver												X														4
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																										
Eye																										1
Harderian gland													+												+	3
Adenoma													X												X	3
Zymbal's gland																								+		1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																X										3
Lymphoma malignant mixed					X							X														4

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Codeine: 750 ppm

Number of Days on Study	0	3	4	5	5	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	0	9	7	5	6	0	2	3	9	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
	8	6	4	9	6	3	2	3	7	6	4	5	9	9	9	9	9	9	9	9	9	9	9	9	9
Carcass ID Number	1	0	0	0	1	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1
	0	6	8	8	0	7	1	0	6	7	9	7	6	6	7	8	8	8	9	9	9	0	0	1	1
	8	1	4	8	1	0	2	5	6	7	0	9	2	7	6	1	3	6	3	4	7	0	3	7	9
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	M	+	+	+	+	+	+	M	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma				X																					
Hepatoblastoma								X																	
Hepatocellular carcinoma		X				X	X			X		X	X												
Hepatocellular adenoma			X	X			X		X			X					X								X
Hepatocellular adenoma, multiple																X			X		X				
Mesentery																					+				
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth									+						+										+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	I	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Subcapsular, adenoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	I	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign														X											
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									X
Parathyroid gland	+	+	+	+	+	M	M	+	+	M	+	M	M	+	+	+	+	+	M	+	M	+	+	M	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																X									
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma														X											

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Codeine: 750 ppm (continued)

Number of Days on Study	730	730	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	065	074	075	089	095	098	099	101	068	069	071	073	078	080	082	085	091	092	104	106	107	110	111	114	120	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Gallbladder	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	M	+	+	+	M	+	M	+	+	41
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Hepatoblastoma																										1
Hepatocellular carcinoma													X						X							8
Hepatocellular adenoma				X	X					X	X								X			X	X		X	15
Hepatocellular adenoma, multiple	X					X							X	X			X				X			X		10
Mesentery													+	+												3
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth				+									+				+				+		+			8
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Subcapsular, adenoma										X																1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Pheochromocytoma benign																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Parathyroid gland	+	M	+	+	+	M	+	+	+	+	M	+	M	+	M	+	+	+	M	+	+	+	+	+	M	35
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	49
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma																		X								2
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	49
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell, adenoma																										1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Codeine: 750 ppm (continued)

Number of Days on Study	0	3	4	5	5	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	0	9	7	5	6	0	2	3	9	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
	8	6	4	9	6	3	2	3	7	6	4	5	9	9	9	9	9	9	9	9	9	9	9	9	9	9
Carcass ID Number	1	0	0	0	1	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	
	0	6	8	8	0	7	1	0	6	7	9	7	6	6	7	8	8	8	9	9	9	0	0	1	1	
	8	1	4	8	1	0	2	5	6	7	0	9	2	7	6	1	3	6	3	4	7	0	3	7	9	
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Lymph node										+																
Mediastinal, histiocytic sarcoma										X																
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Histiocytic sarcoma										X																
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Histiocytic sarcoma										X																
Thymus	M	+	+	M	+	M	+	M	+	M	M	+	M	+	+	+	+	+	M	+	+	+	+	+	M	
Integumentary System																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	+	M	M	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Subcutaneous tissue, histiocytic sarcoma																		X								
Subcutaneous tissue, sarcoma					X																					
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Skeletal muscle																					+					
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Alveolar/bronchiolar adenoma			X															X		X			X			
Alveolar/bronchiolar carcinoma			X																			X				
Hepatocellular carcinoma, metastatic, liver							X						X													
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Special Senses System																										
Harderian gland																					+		+			
Adenoma																					X		X			
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Hepatocellular carcinoma, metastatic, liver							X																			
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Histiocytic sarcoma										X								X								
Lymphoma malignant mixed																										

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Codeine: 750 ppm (continued)

Number of Days on Study	730	730	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	065	074	075	089	095	098	099	016	068	069	071	073	078	080	082	085	091	092	040	060	070	101	111	114	120	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																										1
Mediastinal, histiocytic sarcoma																										1
Lymph node, mandibular	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	44
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Thymus	+	+	M	+	+	+	M	+	+	+	+	M	M	+	+	+	+	+	+	M	M	+	+	M	+	34
Integumentary System																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, histiocytic sarcoma																										1
Subcutaneous tissue, sarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma							X				X		X		X											8
Alveolar/bronchiolar carcinoma																										2
Hepatocellular carcinoma, metastatic, liver																										2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Harderian gland											+															3
Adenoma											X															3
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic, liver																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										2
Lymphoma malignant mixed															X											1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Codeine: 1,500 ppm

Number of Days on Study	0	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	0	3	6	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	3	3	3	3
	9	5	7	8	7	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	0	0	0	0
Carcass ID Number	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	2	7	6	3	7	2	2	2	3	4	4	4	4	5	5	5	6	6	7	7	7	2	3	3	3
	6	6	4	7	1	2	3	5	2	3	6	7	9	0	2	7	6	8	3	5	7	8	0	5	6
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	M	+	+	+	+	+	M	+	+	+	+	+	M	+	M	+	+	M	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma										X															
Intestine small, ileum	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma		X		X	X	X				X					X	X						X			X
Hepatocellular adenoma						X										X								X	
Hepatocellular adenoma, multiple																			X						X
Mesentery														+											
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth											+	+						+							
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma		X																							
Adrenal medulla	+	+	+	M	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	M	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M
Pituitary gland	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									
Follicular cell, adenoma, multiple																									
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Codeine: 1,500 ppm (continued)

Number of Days on Study	730	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	140	141	142	145	155	156	159	162	163	167	178	121	124	127	131	134	138	144	151	154	161	165	170	172	174	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	M	42
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma																										1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma		X			X																		X	X		13
Hepatocellular adenoma								X		X	X		X	X							X		X	X		11
Hepatocellular adenoma, multiple				X	X												X									5
Mesentery																+			+							3
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth							+									+						+	+			7
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	43
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma																		X								1
Follicular cell, adenoma, multiple								X																		1
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Codeine: 1,500 ppm (continued)

Number of Days on Study	0	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	0	3	6	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	3	3	3	3
	9	5	7	8	7	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	0	0	0	0
Carcass ID Number	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	2	7	6	3	7	2	2	2	3	4	4	4	4	5	5	5	6	6	7	7	7	2	3	3	3
	6	6	4	7	1	2	3	5	2	3	6	7	9	0	2	7	6	8	3	5	7	8	0	5	6
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	+	M	+	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma					X						X	X	X					X			X				
Alveolar/bronchiolar adenoma, multiple								X																	
Alveolar/bronchiolar carcinoma									X																
Hepatocellular carcinoma, metastatic, liver				X		X																			
Nose	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																+									
Harderian gland																+									
Adenoma																X									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																									

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Codeine: 1,500 ppm (continued)

Number of Days on Study	730	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	140	141	142	145	155	156	159	162	163	167	178	121	124	127	131	134	138	144	151	154	161	165	170	172	174	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	47
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	M	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	42
Integumentary System																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	+	M	M	M	M	M	M	M	M	M	M	M	M	M	3
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma		X	X		X		X								X						X			X		13
Alveolar/bronchiolar adenoma, multiple																										1
Alveolar/bronchiolar carcinoma																X										2
Hepatocellular carcinoma, metastatic, liver																								X		3
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																										1
Harderian gland				+							+				+										+	5
Adenoma				X							X				X										X	5
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed					X																					1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Codeine: 3,000 ppm

Number of Days on Study	0	4	5	5	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	0	0	0	3	5	9	2	2	2	2	2	2	2	2	2	2	2	2	3	3	3	3	3	3	3
	9	1	0	7	2	7	6	9	9	9	9	9	9	9	9	9	9	9	0	0	0	0	0	0	0
Carcass ID Number	1	2	1	2	1	2	2	1	1	2	2	2	2	2	2	2	2	2	1	1	1	1	1	2	2
	9	0	9	1	8	2	2	9	9	0	0	0	0	1	2	2	3	3	8	8	8	9	9	0	1
	2	5	3	8	9	2	1	6	9	6	7	8	9	3	3	9	0	7	1	6	8	5	8	4	5
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	A	+	+	A	M	+	+	+	+	M	+	+	+	M	+	+	+	+	+	M	+	+	M	M	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma						X	X		X														X	X	
Hepatocellular adenoma			X		X																X				
Hepatocellular adenoma, multiple															X										
Mesentery																			+						
Histiocytic sarcoma																			X						
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth						+																			
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Adrenal medulla	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	M	+	+	M	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M
Pituitary gland	M	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Codeine: 3,000 ppm (continued)

Number of Days on Study	730	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	220	227	228	232	234	239	240	183	184	190	191	194	197	200	201	210	211	214	216	219	224	226	231	235	238	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma						X									X											7
Hepatocellular adenoma		X				X							X	X								X			X	9
Hepatocellular adenoma, multiple																										1
Mesentery																										1
Histiocytic sarcoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tooth														+												2
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma			X																							1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	M	+	+	M	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	39
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	46
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma		X																						X		2
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Codeine: 3,000 ppm (continued)

Number of Days on Study	0	4	5	5	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	0	0	0	3	5	9	2	2	2	2	2	2	2	2	2	2	2	2	3	3	3	3	3	3	3	3
	9	1	0	7	2	7	6	9	9	9	9	9	9	9	9	9	9	9	0	0	0	0	0	0	0	0
Carcass ID Number	1	2	1	2	1	2	2	1	1	2	2	2	2	2	2	2	2	2	1	1	1	1	1	2	2
	9	0	9	1	8	2	2	9	9	0	0	0	0	1	2	2	3	3	8	8	8	9	9	0	1
	2	5	3	8	9	2	1	6	9	6	7	8	9	3	3	9	0	7	1	6	8	5	8	4	5
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node																					+				
Lymph node, mandibular	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																			X						
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	M	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																			X						
Integumentary System																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	+	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, histiocytic sarcoma																									
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma		X								X														X	
Alveolar/bronchiolar adenoma, multiple																		X							
Alveolar/bronchiolar carcinoma																	X		X						
Hepatocellular carcinoma, metastatic, liver																							X	X	
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																			+						
Harderian gland																			+	+					
Adenoma																			X	X					
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																			X						

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Codeine: 3,000 ppm (continued)

Number of Days on Study	730	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	220	227	228	232	234	239	240	183	184	190	191	194	197	200	201	210	211	214	216	219	224	226	231	235	238	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																					+					2
Lymph node, mandibular	+	M	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Histiocytic sarcoma																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	M	+	+	+	+	+	+	+	+	+	44
Histiocytic sarcoma																										1
Integumentary System																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, histiocytic sarcoma																	X									1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma	X		X									X	X													7
Alveolar/bronchiolar adenoma, multiple																										1
Alveolar/bronchiolar carcinoma																										2
Hepatocellular carcinoma, metastatic, liver																										2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																										1
Harderian gland										+																3
Adenoma										X																3
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																	X									2

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

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
Harderian Gland: Adenoma				
Overall rate[a]	3/50 (6%)	3/50 (6%)	5/50 (10%)	3/50 (6%)
Adjusted rate[b]	7.3%	7.9%	11.1%	7.0%
Terminal rate[c]	3/41 (7%)	3/38 (8%)	5/45 (11%)	3/43 (7%)
First incidence (days)	729	729	729	729
Life table test[d]	P=0.563N	P=0.628	P=0.408	P=0.641N
Logistic regression test[d]	P=0.563N	P=0.628	P=0.408	P=0.641N
Cochran-Armitage test[d]	P=0.537			
Fisher exact test[d]		P=0.661N	P=0.357	P=0.661N
Liver: Hepatocellular Adenoma				
Overall rate	23/50 (46%)	25/50 (50%)	16/50 (32%)	10/50 (20%)
Adjusted rate	53.3%	57.8%	35.6%	22.0%
Terminal rate	21/41 (51%)	20/38 (53%)	16/45 (36%)	8/43 (19%)
First incidence (days)	497	474	729	500
Life table test	P<0.001N	P=0.309	P=0.054N	P=0.004N
Logistic regression test	P<0.001N	P=0.402	P=0.065N	P=0.005N
Cochran-Armitage test	P<0.001N			
Fisher exact test		P=0.421	P=0.109N	P=0.005N
Liver: Hepatocellular Carcinoma				
Overall rate	13/50 (26%)	8/50 (16%)	13/50 (26%)	7/50 (14%)
Adjusted rate	28.2%	18.0%	27.1%	15.6%
Terminal rate	8/41 (20%)	3/38 (8%)	10/45 (22%)	5/43 (12%)
First incidence (days)	497	396	635	697
Life table test	P=0.121N	P=0.214N	P=0.480N	P=0.099N
Logistic regression test	P=0.150N	P=0.154N	P=0.589N	P=0.105N
Cochran-Armitage test	P=0.150N			
Fisher exact test		P=0.163N	P=0.590N	P=0.105N
Liver: Hepatocellular Adenoma or Hepatocellular Carcinoma				
Overall rate	29/50 (58%)	29/50 (58%)	23/50 (46%)	16/50 (32%)
Adjusted rate	63.0%	62.8%	47.9%	34.0%
Terminal rate	24/41 (59%)	21/38 (55%)	20/45 (44%)	12/43 (28%)
First incidence (days)	497	396	635	500
Life table test	P=0.002N	P=0.447	P=0.086N	P=0.008N
Logistic regression test	P=0.002N	P=0.567	P=0.118N	P=0.007N
Cochran-Armitage test	P=0.002N			
Fisher exact test		P=0.580N	P=0.158N	P=0.008N
Liver: Hepatocellular Carcinoma or Hepatoblastoma				
Overall rate	13/50 (26%)	9/50 (18%)	13/50 (26%)	7/50 (14%)
Adjusted rate	28.2%	19.9%	27.1%	15.6%
Terminal rate	8/41 (20%)	3/38 (8%)	10/45 (22%)	5/43 (12%)
First incidence (days)	497	396	635	697
Life table test	P=0.108N	P=0.290N	P=0.480N	P=0.099N
Logistic regression test	P=0.133N	P=0.222N	P=0.589N	P=0.105N
Cochran-Armitage test	P=0.132N			
Fisher exact test		P=0.235N	P=0.590N	P=0.105N

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Feed Study of Codeine (continued)

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
Liver: Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma				
Overall rate	29/50 (58%)	30/50 (60%)	23/50 (46%)	16/50 (32%)
Adjusted rate	63.0%	63.6%	47.9%	34.0%
Terminal rate	24/41 (59%)	21/38 (55%)	20/45 (44%)	12/43 (28%)
First incidence (days)	497	396	635	500
Life table test	P=0.001N	P=0.381	P=0.086N	P=0.008N
Logistic regression test	P=0.002N	P=0.487	P=0.118N	P=0.007N
Cochran-Armitage test	P=0.002N			
Fisher exact test		P=0.500	P=0.158N	P=0.008N
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	15/50 (30%)	8/50 (16%)	14/50 (28%)	8/50 (16%)
Adjusted rate	36.6%	20.1%	30.4%	18.0%
Terminal rate	15/41 (37%)	7/38 (18%)	13/45 (29%)	7/43 (16%)
First incidence (days)	729	474	727	401
Life table test	P=0.089N	P=0.106N	P=0.381N	P=0.059N
Logistic regression test	P=0.119N	P=0.079N	P=0.349N	P=0.071N
Cochran-Armitage test	P=0.132N			
Fisher exact test		P=0.077N	P=0.500N	P=0.077N
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	15/50 (30%)	9/50 (18%)	16/50 (32%)	10/50 (20%)
Adjusted rate	36.6%	22.7%	34.8%	22.5%
Terminal rate	15/41 (37%)	8/38 (21%)	15/45 (33%)	9/43 (21%)
First incidence (days)	729	474	727	401
Life table test	P=0.195N	P=0.162N	P=0.548N	P=0.143N
Logistic regression test	P=0.248N	P=0.124N	P=0.516N	P=0.166N
Cochran-Armitage test	P=0.272N			
Fisher exact test		P=0.121N	P=0.500	P=0.178N
All Organs: Malignant Lymphoma (Lymphocytic or Mixed)				
Overall rate	7/50 (14%)	1/50 (2%)	1/50 (2%)	0/50 (0%)
Adjusted rate	15.4%	2.6%	2.2%	0.0%
Terminal rate	4/41 (10%)	1/38 (3%)	1/45 (2%)	0/43 (0%)
First incidence (days)	450	729	729	—[e]
Life table test	P=0.003N	P=0.043N	P=0.028N	P=0.010N
Logistic regression test	P=0.003N	P=0.029N	P=0.034N	P=0.008N
Cochran-Armitage test	P=0.003N			
Fisher exact test		P=0.030N	P=0.030N	P=0.006N
All Organs: Benign Neoplasms				
Overall rate	34/50 (68%)	32/50 (64%)	30/50 (60%)	21/50 (42%)
Adjusted rate	77.2%	74.2%	63.8%	45.4%
Terminal rate	31/41 (76%)	27/38 (71%)	28/45 (62%)	18/43 (42%)
First incidence (days)	497	474	635	401
Life table test	P=0.001N	P=0.563	P=0.111N	P=0.005N
Logistic regression test	P=0.002N	P=0.438N	P=0.160N	P=0.007N
Cochran-Armitage test	P=0.004N			
Fisher exact test		P=0.417N	P=0.266N	P=0.008N

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Feed Study of Codeine (continued)

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
All Organs: Malignant Neoplasms				
Overall rate	20/50 (40%)	15/50 (30%)	15/50 (30%)	10/50 (20%)
Adjusted rate	40.0%	31.4%	31.2%	22.2%
Terminal rate	11/41 (27%)	6/38 (16%)	12/45 (27%)	8/43 (19%)
First incidence (days)	227	396	635	697
Life table test	P=0.023N	P=0.280N	P=0.153N	P=0.030N
Logistic regression test	P=0.056N	P=0.169N	P=0.255N	P=0.024N
Cochran-Armitage test	P=0.024N			
Fisher exact test		P=0.201N	P=0.201N	P=0.024N
All Organs: Benign or Malignant Neoplasms				
Overall rate	41/50 (82%)	39/50 (78%)	36/50 (72%)	28/50 (56%)
Adjusted rate	82.0%	81.2%	75.0%	58.3%
Terminal rate	32/41 (78%)	29/38 (76%)	33/45 (73%)	23/43 (53%)
First incidence (days)	227	396	635	401
Life table test	P=0.002N	P=0.542	P=0.079N	P=0.010N
Logistic regression test	P=0.003N	P=0.401N	P=0.162N	P=0.005N
Cochran-Armitage test	P=0.001N			
Fisher exact test		P=0.402N	P=0.171N	P=0.004N

[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for liver and lung; 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 exposure group is indicated by N.
[e] Not applicable; no neoplasms in animal group

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

	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Microbiological Associates, Inc.			
C.I. Direct Blue 218	16/50	7/50	21/50
dl-Amphetamine Sulfate	10/50	4/50	14/50
Overall Historical Incidence			
Total	344/1,316 (26.1%)	220/1,316 (16.7%)	509/1,316 (38.7%)
Standard deviation	13.2%	7.2%	13.9%
Range	4%-60%	3%-29%	10%-68%

[a] Data as of 17 June 1994

TABLE C4b
Historical Incidence of Malignant Lymphoma in Untreated Male B6C3F$_1$ Mice[a]

	Incidence in Controls
Historical Incidence at Microbiological Associates, Inc.	
C.I. Direct Blue 218	2/50
dl-Amphetamine Sulfate	4/50
Overall Historical Incidence	
Total	117/1,324 (8.8%)
Standard deviation	6.2%
Range	2%-24%

[a] Data as of 17 June 1994; includes data for histiocytic, lymphocytic, mixed, unspecified, or undifferentiated cell types

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

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	10	10	10	10
Early deaths				
Accidental death		1		
Moribund	4	4	2	1
Natural deaths	5	7	3	6
Survivors				
Terminal sacrifice	41	38	45	43
Animals examined microscopically	60	60	60	60
15-Month Interim Evaluation				
Alimentary System				
Liver	(10)	(10)	(10)	(10)
Basophilic focus	1 (10%)			
Eosinophilic focus	1 (10%)			
Inflammation, chronic active				2 (20%)
Mixed cell focus			2 (20%)	
Centrilobular, cytomegaly			1 (10%)	
Centrilobular, fatty change	10 (100%)	10 (100%)	6 (60%)	1 (10%)
Mesentery				(1)
Fat, necrosis				1 (100%)
Pancreas	(10)	(10)	(10)	(10)
Inflammation, chronic	1 (10%)		1 (10%)	
Acinar cell, vacuolization cytoplasmic			1 (10%)	
Salivary glands	(10)	(10)	(10)	(10)
Inflammation, chronic	5 (50%)	6 (60%)	2 (20%)	1 (10%)
Stomach, glandular	(10)	(10)	(10)	(10)
Developmental malformation			1 (10%)	
Tooth		(1)		
Developmental malformation		1 (100%)		
Endocrine System				
Adrenal cortex	(10)	(10)	(10)	(10)
Subcapsular, hyperplasia	7 (70%)	5 (50%)	4 (40%)	5 (50%)
Islets, pancreatic	(10)	(10)	(10)	(10)
Hyperplasia	3 (30%)	3 (30%)		
Pituitary gland	(10)	(10)	(10)	(9)
Pars distalis, hyperplasia	1 (10%)			
Thyroid gland	(10)	(10)	(10)	(10)
Follicular cell, hyperplasia, focal				6 (60%)

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

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of Codeine (continued)

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
15-Month Interim Evaluation (continued)				
Genital System				
Epididymis	(10)	(10)	(10)	(10)
Inflammation, chronic active			1 (10%)	
Preputial gland	(10)	(10)	(10)	(10)
Dilatation	9 (90%)	9 (90%)	8 (80%)	9 (90%)
Inflammation, chronic	6 (60%)	4 (40%)	4 (40%)	4 (40%)
Prostate	(10)	(10)	(10)	(10)
Inflammation, chronic	1 (10%)	2 (20%)	4 (40%)	
Testes	(10)	(10)	(10)	(10)
Seminiferous tubule, degeneration				1 (10%)
Hematopoietic System				
Lymph node, mandibular	(8)	(9)	(9)	(10)
Hyperplasia, lymphoid			2 (22%)	
Lymph node, mesenteric	(10)	(10)	(10)	(10)
Hyperplasia, lymphoid	1 (10%)			
Spleen	(10)	(10)	(9)	(10)
Hyperplasia, lymphoid			1 (11%)	
Hyperplasia, reticulum cell		1 (10%)		
Thymus	(10)	(10)	(10)	(10)
Hyperplasia, lymphoid	1 (10%)	2 (20%)		
Integumentary System				
Skin	(10)	(10)	(10)	(10)
Inflammation, chronic active		1 (10%)	1 (10%)	1 (10%)
Epidermis, hyperplasia				1 (10%)
Nervous System				
Brain	(10)	(9)	(10)	(10)
Mineralization	7 (70%)	4 (44%)	1 (10%)	1 (10%)
Respiratory System				
Lung	(10)	(10)	(10)	(10)
Congestion				1 (10%)
Infiltration cellular, lymphocyte	5 (50%)	9 (90%)	7 (70%)	3 (30%)
Alveolar epithelium, hyperplasia		1 (10%)		
Nose	(10)	(10)	(10)	(10)
Foreign body				1 (10%)
Olfactory epithelium, degeneration, hyaline	2 (20%)	5 (50%)	6 (60%)	5 (50%)
Respiratory epithelium, degeneration, hyaline	1 (10%)	2 (20%)	4 (40%)	1 (10%)
Respiratory epithelium, hyperplasia, glandular	1 (10%)			
Respiratory epithelium, inflammation, chronic active	2 (20%)			
Respiratory epithelium, metaplasia	1 (10%)			

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of Codeine (continued)

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
15-Month Interim Evaluation (continued)				
Urinary System				
Kidney	(10)	(10)	(10)	(10)
Cyst	2 (20%)			
Inflammation, chronic	3 (30%)	6 (60%)	8 (80%)	7 (70%)
Nephropathy	7 (70%)	4 (40%)	3 (30%)	1 (10%)
Urinary bladder	(10)	(10)	(10)	(10)
Infiltration cellular, lymphocyte	3 (30%)	5 (50%)	3 (30%)	2 (20%)
Systems Examined With No Lesions Observed				
Cardiovascular System				
General Body System				
Musculoskeletal System				
Special Senses System				
2-Year Study				
Alimentary System				
Gallbladder	(34)	(41)	(42)	(40)
Degeneration, hyaline		1 (2%)		
Dilatation		1 (2%)		
Inflammation, chronic		1 (2%)		
Inflammation, chronic active	1 (3%)			
Intestine large, cecum	(50)	(50)	(50)	(48)
Hyperplasia, lymphoid	2 (4%)			
Intestine small, jejunum	(50)	(50)	(49)	(48)
Hyperplasia, lymphoid			1 (2%)	1 (2%)
Intestine small, ileum	(49)	(50)	(49)	(47)
Hyperplasia, lymphoid			1 (2%)	
Hyperplasia, plasma cell		1 (2%)		
Inflammation, chronic active			1 (2%)	
Liver	(50)	(50)	(50)	(50)
Basophilic focus	3 (6%)	4 (8%)	2 (4%)	3 (6%)
Clear cell focus	7 (14%)	4 (8%)	2 (4%)	
Cyst		1 (2%)		1 (2%)
Eosinophilic focus	8 (16%)	12 (24%)	5 (10%)	4 (8%)
Fatty change, focal	4 (8%)	4 (8%)		
Hematopoietic cell proliferation	2 (4%)			
Infarct		3 (6%)	1 (2%)	2 (4%)
Inflammation, chronic active	2 (4%)	4 (8%)	3 (6%)	2 (4%)
Mitotic alteration	1 (2%)	1 (2%)		
Mixed cell focus	1 (2%)	1 (2%)	1 (2%)	
Necrosis	2 (4%)	3 (6%)		
Pigmentation		1 (2%)	1 (2%)	
Centrilobular, cytomegaly	3 (6%)			
Centrilobular, fatty change	3 (6%)	8 (16%)		
Mesentery	(1)	(3)	(3)	(1)
Hemorrhage			1 (33%)	
Artery, inflammation, chronic active			1 (33%)	
Fat, necrosis		3 (100%)	2 (67%)	

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of Codeine (continued)

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
2-Year Study (continued)				
Alimentary System (continued)				
Pancreas	(49)	(50)	(50)	(50)
Inflammation, chronic	1 (2%)			1 (2%)
Acinar cell, atrophy	2 (4%)	2 (4%)	1 (2%)	
Artery, inflammation, chronic active		1 (2%)		
Duct, cyst		1 (2%)		
Salivary glands	(50)	(50)	(50)	(50)
Inflammation, chronic	22 (44%)	21 (42%)	15 (30%)	13 (26%)
Stomach, forestomach	(50)	(50)	(50)	(50)
Hyperplasia		1 (2%)	2 (4%)	
Inflammation, chronic active		1 (2%)		
Necrosis			1 (2%)	
Stomach, glandular	(49)	(50)	(50)	(49)
Dilatation		1 (2%)		
Inflammation, chronic active	2 (4%)	3 (6%)		1 (2%)
Necrosis		1 (2%)	1 (2%)	
Tooth	(9)	(8)	(7)	(2)
Developmental malformation	9 (100%)	8 (100%)	7 (100%)	2 (100%)
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Fibrosis			2 (4%)	1 (2%)
Artery, inflammation, chronic active			1 (2%)	2 (4%)
Atrium, thrombosis			2 (4%)	
Ventricle, thrombosis			1 (2%)	
Endocrine System				
Adrenal cortex	(49)	(48)	(50)	(50)
Hypertrophy, focal	23 (47%)	26 (54%)	22 (44%)	24 (48%)
Extra adrenal tissue, inflammation, chronic active	1 (2%)			
Subcapsular, hyperplasia	31 (63%)	25 (52%)	25 (50%)	26 (52%)
Islets, pancreatic	(50)	(50)	(50)	(50)
Hyperplasia	7 (14%)	10 (20%)	6 (12%)	1 (2%)
Pituitary gland	(46)	(49)	(48)	(46)
Pars distalis, cyst	1 (2%)	2 (4%)	2 (4%)	1 (2%)
Pars distalis, hyperplasia	3 (7%)	2 (4%)		
Thyroid gland	(49)	(50)	(50)	(50)
Inflammation, chronic active		1 (2%)		
C-cell, hyperplasia, focal			1 (2%)	
Follicle, cyst		1 (2%)	1 (2%)	
Follicular cell, hyperplasia, focal	7 (14%)	25 (50%)	29 (58%)	34 (68%)
General Body System				
None				

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of Codeine (continued)

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
2-Year Study (continued)				
Genital System				
Epididymis	(50)	(50)	(50)	(50)
Granuloma sperm	1 (2%)			1 (2%)
Inflammation, chronic active	5 (10%)	4 (8%)	4 (8%)	
Spermatocele			1 (2%)	
Preputial gland	(48)	(50)	(50)	(50)
Abscess	1 (2%)	1 (2%)		1 (2%)
Dilatation	40 (83%)	34 (68%)	37 (74%)	37 (74%)
Hyperplasia				1 (2%)
Inflammation, chronic	2 (4%)	2 (4%)		1 (2%)
Inflammation, chronic active	23 (48%)	20 (40%)	23 (46%)	14 (28%)
Prostate	(46)	(49)	(48)	(50)
Hyperplasia				1 (2%)
Inflammation, acute				1 (2%)
Inflammation, chronic	11 (24%)	12 (24%)	11 (23%)	11 (22%)
Inflammation, chronic active	1 (2%)		2 (4%)	
Seminal vesicle	(50)	(50)	(50)	(49)
Atrophy			1 (2%)	
Dilatation	10 (20%)	7 (14%)	6 (12%)	1 (2%)
Inflammation, chronic active			1 (2%)	
Testes	(50)	(50)	(50)	(50)
Seminiferous tubule, degeneration			3 (6%)	
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Congestion		1 (2%)		1 (2%)
Myeloid cell, hyperplasia	1 (2%)		1 (2%)	
Lymph node	(6)	(1)		(2)
Hemorrhage				1 (50%)
Pancreatic, hyperplasia, lymphoid				1 (50%)
Lymph node, mandibular	(40)	(44)	(47)	(45)
Hyperplasia, lymphoid			1 (2%)	
Pigmentation, hemosiderin			1 (2%)	2 (4%)
Lymph node, mesenteric	(49)	(49)	(48)	(48)
Angiectasis				1 (2%)
Granuloma		1 (2%)		
Hematopoietic cell proliferation	5 (10%)	3 (6%)	1 (2%)	1 (2%)
Hemorrhage	13 (27%)	9 (18%)	9 (19%)	10 (21%)
Hyperplasia, histiocytic		1 (2%)		
Hyperplasia, lymphoid		2 (4%)	2 (4%)	
Spleen	(50)	(50)	(49)	(50)
Hematopoietic cell proliferation	14 (28%)	13 (26%)	15 (31%)	10 (20%)
Hyperplasia, lymphoid			1 (2%)	
Inflammation, chronic active	1 (2%)			
Thymus	(43)	(34)	(42)	(44)
Atrophy	5 (12%)	2 (6%)	7 (17%)	3 (7%)
Cyst		1 (3%)		
Ectopic parathyroid gland			3 (7%)	
Necrosis		1 (3%)		

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of Codeine (continued)

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
2-Year Study (continued)				
Integumentary System				
Skin	(50)	(50)	(50)	(50)
Foreign body	1 (2%)			
Inflammation, chronic active	2 (4%)	2 (4%)	3 (6%)	1 (2%)
Ulcer			1 (2%)	
Epidermis, hyperplasia	1 (2%)	2 (4%)	1 (2%)	4 (8%)
Prepuce, inflammation, chronic active				1 (2%)
Subcutaneous tissue, abscess		1 (2%)		
Subcutaneous tissue, edema		1 (2%)		
Subcutaneous tissue, inflammation, chronic active			1 (2%)	
Musculoskeletal System				
Skeletal muscle		(1)		
Inflammation, chronic		1 (100%)		
Nervous System				
Brain	(50)	(50)	(50)	(50)
Compression	1 (2%)			
Cyst			1 (2%)	
Mineralization	33 (66%)	21 (42%)	14 (28%)	18 (36%)
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Congestion	1 (2%)			
Infiltration cellular, lymphocyte	8 (16%)	10 (20%)	8 (16%)	7 (14%)
Infiltration cellular, histiocyte	2 (4%)		2 (4%)	
Inflammation, chronic active	1 (2%)	2 (4%)	1 (2%)	
Alveolar epithelium, hyperplasia	6 (12%)	4 (8%)	6 (12%)	2 (4%)
Artery, inflammation, chronic active			1 (2%)	
Bronchiole, hyperplasia	1 (2%)			
Interstitium, inflammation, chronic active	2 (4%)	2 (4%)		1 (2%)
Pleura, inflammation, chronic			1 (2%)	
Nose	(50)	(50)	(49)	(50)
Exudate	1 (2%)			1 (2%)
Olfactory epithelium, degeneration, hyaline	23 (46%)	27 (54%)	24 (49%)	24 (48%)
Respiratory epithelium, hyperplasia, glandular	1 (2%)		1 (2%)	1 (2%)
Respiratory epithelium, proliferation connective tissue		1 (2%)		
Special Senses System				
Eye	(1)		(1)	(1)
Cornea, inflammation, chronic active			1 (100%)	
Harderian gland	(3)	(3)	(5)	(3)
Inflammation, chronic active			1 (20%)	
Zymbal's gland	(1)			
Hypertrophy	1 (100%)			

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of Codeine (continued)

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
2-Year Study (continued)				
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Cyst	2 (4%)	2 (4%)		
Hydronephrosis				1 (2%)
Infarct				1 (2%)
Inflammation, chronic	8 (16%)	10 (20%)	3 (6%)	7 (14%)
Inflammation, chronic active	2 (4%)		1 (2%)	
Metaplasia, osseous	2 (4%)	3 (6%)	1 (2%)	
Nephropathy	45 (90%)	43 (86%)	41 (82%)	37 (74%)
Pigmentation		1 (2%)		
Artery, inflammation, chronic active				1 (2%)
Bilateral, hydronephrosis			1 (2%)	
Capsule, fibrosis		1 (2%)		
Renal tubule, degeneration, hyaline	1 (2%)			
Renal tubule, hyperplasia	2 (4%)			
Renal tubule, necrosis		1 (2%)		
Renal tubule, pigmentation		1 (2%)		
Urinary bladder	(50)	(50)	(50)	(49)
Dilatation		2 (4%)	2 (4%)	3 (6%)
Infiltration cellular, lymphocyte	13 (26%)	4 (8%)	6 (12%)	4 (8%)
Inflammation, acute				1 (2%)
Inflammation, chronic active	1 (2%)		1 (2%)	

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

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

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	10	9	9	9
Early deaths				
Moribund	7	9	6	4
Natural deaths	7	6	2	11
Survivors				
Died last week of study	1			1
Terminal sacrifice	35	36	43	34
Missing				1
Animals examined microscopically	60	60	60	59
15-Month Interim Evaluation				
Alimentary System				
Intestine large, cecum	(10)	(9)	(9)	(9)
Intestine small, jejunum	(10)	(9)	(9)	(9)
Liver	(10)	(9)	(9)	(9)
Hepatocellular carcinoma		1 (11%)		
Hepatocellular adenoma	2 (20%)	1 (11%)		
Endocrine System				
Thyroid gland	(10)	(9)	(9)	(9)
Follicular cell, adenoma	1 (10%)			
Respiratory System				
Lung	(10)	(9)	(9)	(9)
Alveolar/bronchiolar adenoma	2 (20%)	1 (11%)		
Systemic Lesions				
Multiple organs[b]	(10)	(9)	(9)	(9)
Lymphoma malignant mixed	1 (10%)			
Systems Examined With No Neoplasms Observed				
Cardiovascular System				
General Body System				
Genital System				
Hematopoietic System				
Integumentary System				
Musculoskeletal System				
Nervous System				
Special Senses System				
Urinary System				

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of Codeine (continued)

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
2-Year Study				
Alimentary System				
Intestine large, rectum	(50)	(51)	(50)	(49)
Adenocarcinoma, metastatic, pancreas				1 (2%)
Intestine large, cecum	(50)	(49)	(51)	(49)
Intestine small, duodenum	(48)	(49)	(48)	(48)
Intestine small, jejunum	(50)	(48)	(50)	(50)
Histiocytic sarcoma				1 (2%)
Intestine small, ileum	(48)	(48)	(48)	(48)
Liver	(50)	(51)	(51)	(50)
Hemangiosarcoma			1 (2%)	
Hepatocellular carcinoma	5 (10%)	6 (12%)	6 (12%)	3 (6%)
Hepatocellular carcinoma, multiple				1 (2%)
Hepatocellular adenoma	7 (14%)	9 (18%)	11 (22%)	4 (8%)
Hepatocellular adenoma, multiple	5 (10%)	1 (2%)	2 (4%)	1 (2%)
Histiocytic sarcoma	1 (2%)	2 (4%)		1 (2%)
Mesentery	(9)	(9)	(7)	(5)
Adenocarcinoma, metastatic, pancreas				1 (20%)
Fibrosarcoma		1 (11%)		
Hemangioma		1 (11%)		
Pancreas	(50)	(51)	(51)	(50)
Histiocytic sarcoma				1 (2%)
Acinar cell, adenocarcinoma				1 (2%)
Salivary glands	(50)	(50)	(51)	(50)
Stomach, forestomach	(50)	(51)	(51)	(50)
Squamous cell carcinoma				1 (2%)
Stomach, glandular	(50)	(51)	(51)	(49)
Cardiovascular System				
Blood vessel	(50)	(51)	(50)	(49)
Heart	(50)	(51)	(51)	(50)
Osteosarcoma, metastatic, skin		1 (2%)		
Endocrine System				
Adrenal cortex	(50)	(51)	(50)	(50)
Adenoma			1 (2%)	
Extra adrenal tissue, adenocarcinoma, metastatic, pancreas				1 (2%)
Islets, pancreatic	(50)	(51)	(51)	(50)
Adenoma	1 (2%)	2 (4%)	1 (2%)	
Pituitary gland	(48)	(47)	(49)	(46)
Pars distalis, adenoma	11 (23%)	9 (19%)	17 (35%)	10 (22%)
Pars distalis, carcinoma			1 (2%)	
Pars intermedia, adenoma	1 (2%)	1 (2%)	3 (6%)	1 (2%)
Thyroid gland	(48)	(51)	(51)	(50)
Histiocytic sarcoma				1 (2%)
Follicular cell, adenoma		4 (8%)	3 (6%)	2 (4%)
General Body System				
None				

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of Codeine (continued)

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
2-Year Study (continued)				
Genital System				
Ovary	(49)	(51)	(50)	(50)
Adenocarcinoma, metastatic, pancreas				1 (2%)
Adenoma	2 (4%)	3 (6%)		2 (4%)
Cystadenoma				1 (2%)
Granulosa cell tumor benign	1 (2%)			
Histiocytic sarcoma		1 (2%)		1 (2%)
Teratoma malignant				1 (2%)
Uterus	(50)	(51)	(50)	(50)
Adenocarcinoma, metastatic, pancreas				1 (2%)
Hemangioma			1 (2%)	
Hemangiosarcoma		1 (2%)		
Histiocytic sarcoma	1 (2%)	1 (2%)		1 (2%)
Leiomyosarcoma		1 (2%)		
Polyp stromal	4 (8%)		2 (4%)	
Squamous cell carcinoma, metastatic, uncertain primary site		1 (2%)		
Hematopoietic System				
Bone marrow	(50)	(51)	(51)	(50)
Histiocytic sarcoma	1 (2%)			
Lymph node	(4)	(2)	(2)	(9)
Histiocytic sarcoma	1 (25%)			
Teratoma malignant, metastatic				1 (11%)
Mediastinal, histiocytic sarcoma		1 (50%)		1 (11%)
Lymph node, mandibular	(45)	(46)	(49)	(49)
Histiocytic sarcoma		1 (2%)		1 (2%)
Lymph node, mesenteric	(49)	(48)	(47)	(48)
Adenocarcinoma, metastatic, pancreas				1 (2%)
Histiocytic sarcoma	1 (2%)	2 (4%)		1 (2%)
Squamous cell carcinoma, metastatic, uncertain primary site		1 (2%)		
Spleen	(50)	(51)	(51)	(50)
Hemangiosarcoma			1 (2%)	
Histiocytic sarcoma	1 (2%)	1 (2%)		1 (2%)
Thymus	(38)	(41)	(47)	(42)
Integumentary System				
Mammary gland	(45)	(51)	(50)	(50)
Carcinoma			2 (4%)	2 (4%)
Skin	(50)	(51)	(51)	(50)
Subcutaneous tissue, fibrosarcoma		2 (4%)		
Subcutaneous tissue, hemangiosarcoma	1 (2%)			1 (2%)
Subcutaneous tissue, liposarcoma		1 (2%)		
Subcutaneous tissue, osteosarcoma		1 (2%)		
Subcutaneous tissue, sarcoma	1 (2%)	2 (4%)	1 (2%)	2 (4%)

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of Codeine (continued)

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
2-Year Study (continued)				
Musculoskeletal System				
Bone	(50)	(51)	(51)	(50)
Chondrosarcoma			1 (2%)	
Osteosarcoma		1 (2%)		
Skeletal muscle	(1)		(1)	(1)
Adenocarcinoma, metastatic, pancreas				1 (100%)
Hemangiosarcoma			1 (100%)	
Nervous System				
None				
Respiratory System				
Lung	(50)	(51)	(51)	(50)
Adenocarcinoma, metastatic, pancreas				1 (2%)
Alveolar/bronchiolar adenoma	1 (2%)	2 (4%)	5 (10%)	4 (8%)
Alveolar/bronchiolar adenoma, multiple			1 (2%)	
Alveolar/bronchiolar carcinoma	1 (2%)	1 (2%)	1 (2%)	
Carcinoma, metastatic, harderian gland		1 (2%)		
Hepatocellular carcinoma, metastatic, liver				3 (6%)
Histiocytic sarcoma	1 (2%)	2 (4%)		1 (2%)
Osteosarcoma, metastatic, skin		1 (2%)		
Mediastinum, osteosarcoma, metastatic, skin		1 (2%)		
Nose	(50)	(51)	(50)	(50)
Trachea	(50)	(51)	(51)	(50)
Special Senses System				
Harderian gland	(2)	(4)	(3)	(3)
Adenoma	1 (50%)	2 (50%)	1 (33%)	2 (67%)
Carcinoma		1 (25%)		
Bilateral, adenoma		1 (25%)		
Urinary System				
Kidney	(50)	(51)	(51)	(50)
Adenocarcinoma, metastatic, pancreas				1 (2%)
Histiocytic sarcoma		1 (2%)		1 (2%)
Squamous cell carcinoma, metastatic, uncertain primary site		1 (2%)		
Urinary bladder	(50)	(50)	(51)	(50)
Adenocarcinoma, metastatic, pancreas				1 (2%)
Systemic Lesions				
Multiple organs	(50)	(51)	(51)	(50)
Histiocytic sarcoma	2 (4%)	2 (4%)		1 (2%)
Lymphoma malignant lymphocytic	2 (4%)	1 (2%)		
Lymphoma malignant mixed	5 (10%)	4 (8%)	6 (12%)	8 (16%)

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of Codeine (continued)

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
Neoplasm Summary				
Total animals with primary neoplasms[c]				
15-Month interim evaluation	4	3		
2-Year study	34	36	38	31
Total primary neoplasms				
15-Month interim evaluation	6	3		
2-Year study	51	60	69	48
Total animals with benign neoplasms				
15-Month interim evaluation	4	2		
2-Year study	26	25	33	19
Total benign neoplasms				
15-Month interim evaluation	5	2		
2-Year study	34	35	48	27
Total animals with malignant neoplasms				
15-Month interim evaluation	1	1		
2-Year study	15	23	17	19
Total malignant neoplasms				
15-Month interim evaluation	1	1		
2-Year study	17	25	21	21
Total animals with metastatic neoplasms				
2-Year study		3		5
Total metastatic neoplasms				
2-Year study		7		14
Total animals with malignant neoplasms of uncertain primary site				
2-Year study		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 D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Codeine: 0 ppm

Number of Days on Study	0	2	4	5	5	5	5	5	5	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7
	0	7	9	3	4	6	7	8	9	5	5	9	1	2	3	3	3	3	3	3	3	3	3	3	3
	9	2	7	0	4	5	0	2	1	1	9	5	3	2	1	2	4	4	4	4	4	4	4	4	4
Carcass ID Number	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
	5	9	9	5	6	7	8	8	5	8	5	4	4	5	7	8	4	4	4	4	6	6	7	8	9
	7	3	0	0	6	5	8	3	9	5	1	9	3	6	8	6	2	5	6	8	4	9	0	4	1
Alimentary System																									
Esophagus	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	A	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	A	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma						X		X																	
Hepatocellular adenoma			X														X	X							
Hepatocellular adenoma, multiple																						X			
Histiocytic sarcoma				X																					
Mesentery											+		+			+		+						+	
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma			X																						
Parathyroid gland	+	+	M	+	M	+	M	+	+	M	+	+	M	+	M	+	+	+	+	+	M	+	+	+	+
Pituitary gland	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma														X	X	X		X		X					X
Pars intermedia, adenoma							X																		
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	M	+	+	+	+	+	+	+	+	M	M	+	+	M	M	M	+	+	+	+	M	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Granulosa cell tumor benign																									
Oviduct								+			+	+													
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma				X																					
Polyp stromal										X									X						

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Codeine: 0 ppm (continued)

Number of Days on Study	735	735	735	735	735	735	735	735	735	735	735	735	735	735	735	736	736	736	736	736	736	736	736	736	736	
Carcass ID Number	244	255	258	267	271	274	276	279	281	282	287	296	297	298	299	241	252	253	261	262	268	280	289	294	290	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Gallbladder	+	+	+	M	M	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	43
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma	X													X	X											5
Hepatocellular adenoma		X								X								X	X							7
Hepatocellular adenoma, multiple	X							X													X			X		5
Histiocytic sarcoma																										1
Mesentery	+						+						+								+					9
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Parathyroid gland	+	M	M	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	M	+	M	+	+	M	36
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pars distalis, adenoma		X				X							X			X	X									11
Pars intermedia, adenoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	48
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	41
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma												X					X									2
Granulosa cell tumor benign																X										1
Oviduct																										3
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Polyp stromal						X	X																			4

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Codeine: 0 ppm (continued)

Number of Days on Study	0	2	4	5	5	5	5	5	5	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7
	0	7	9	3	4	6	7	8	9	5	5	9	1	2	3	3	3	3	3	3	3	3	4	4	3
	9	2	7	0	4	5	0	2	1	1	9	5	3	2	1	2	4	4	4	4	4	4	4	4	4
Carcass ID Number	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
	5	9	9	5	6	7	8	8	5	8	5	4	4	5	7	8	4	4	4	4	6	6	7	8	9
	7	3	0	0	6	5	8	3	9	5	1	9	3	6	8	6	2	5	6	8	4	9	0	4	1
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma				X																					
Lymph node				+					+	+						+									
Histiocytic sarcoma				X																					
Lymph node, mandibular	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma				X																					
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									X
Thymus	M	+	+	M	M	+	+	+	+	+	I	M	+	M	+	+	M	+	+	M	+	+	+	M	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, hemangiosarcoma													X												
Subcutaneous tissue, sarcoma																	X								
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle									+																
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																	X								
Alveolar/bronchiolar carcinoma																									
Histiocytic sarcoma				X																					
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland																						+			
Adenoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma				X																					X
Lymphoma malignant lymphocytic					X				X																
Lymphoma malignant mixed														X		X	X								

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Codeine: 0 ppm (continued)

Number of Days on Study	735	735	735	735	735	735	735	735	735	735	735	735	735	735	735	736	736	736	736	736	736	736	736	736	736	
Carcass ID Number	244	245	258	267	271	274	276	279	281	282	287	296	297	298	299	241	252	253	261	262	268	280	289	294	290	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Lymph node																										4
Histiocytic sarcoma																										1
Lymph node, mandibular	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	45
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Thymus	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	38
Integumentary System																										
Mammary gland	+	+	M	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	M	+	+	+	+	+	45
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, hemangiosarcoma																										1
Subcutaneous tissue, sarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										1
Alveolar/bronchiolar carcinoma																		X								1
Histiocytic sarcoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Harderian gland																			+							2
Adenoma																			X							1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										2
Lymphoma malignant lymphocytic																										2
Lymphoma malignant mixed	X												X													5

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Codeine: 750 ppm

Number of Days on Study	0	0	3	3	3	4	5	5	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7
	0	0	4	5	8	7	1	3	1	2	3	4	6	7	7	3	3	3	3	3	3	3	3	3	3
	8	8	8	9	8	9	2	9	6	5	3	7	4	2	7	1	4	4	4	4	4	4	4	4	4
Carcass ID Number	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	4	4	5	3	4	2	4	3	3	5	2	2	4	1	2	0	0	0	0	1	1	1	2	2	3
	6	8	0	4	3	3	5	2	9	2	5	7	2	1	8	4	1	2	8	2	6	7	2	4	1
Alimentary System																									
Esophagus	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	A	+	+	+	+	+	M	+	+	M	+	+	A	+	+	M	+	+	M	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	M	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	M	+	+	+	+	+	+	+	+
Intestine small, ileum	A	+	A	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma												X			X						X				
Hepatocellular adenoma									X			X	X						X						
Hepatocellular adenoma, multiple																									X
Histiocytic sarcoma										X				X											
Mesentery																		+						+	
Fibrosarcoma																									
Hemangioma																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, skin				X																					
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	M	+	+	M	+	+	+	M	+	+	M	+	+	M	+	+	+	M	+	+	M	+	+	+	M
Pituitary gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma							X												X						X
Pars intermedia, adenoma															X										
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																X									
General Body System																									
Tissue NOS													+												
Genital System																									
Clitoral gland	M	M	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																X		X							
Histiocytic sarcoma														X											
Oviduct													+												

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Codeine: 750 ppm (continued)

Number of Days on Study	734	734	734	734	734	734	734	734	735	735	735	735	735	735	735	735	735	735	735	735	735	735	735	736	736		
Carcass ID Number	335	336	337	340	347	349	351	354	303	305	306	309	310	313	314	318	319	321	326	329	357	358	359	360	320	344	Total Tissues/ Tumors
Alimentary System																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	42
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Hepatocellular carcinoma						X															X					X	6
Hepatocellular adenoma					X			X				X				X		X									9
Hepatocellular adenoma, multiple																											1
Histiocytic sarcoma																											2
Mesentery	+	+		+																+	+	+			+		9
Fibrosarcoma		X																									1
Hemangioma																					X						1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Salivary glands	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Cardiovascular System																											
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Osteosarcoma, metastatic, skin																											1
Endocrine System																											
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adrenal medulla	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adenoma						X																		X			2
Parathyroid gland	M	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	39
Pituitary gland	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	47
Pars distalis, adenoma			X		X			X				X			X							X					9
Pars intermedia, adenoma																											1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Follicular cell, adenoma								X			X	X															4
General Body System																											
Tissue NOS																											1
Genital System																											
Clitoral gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	43
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adenoma																										X	3
Histiocytic sarcoma																											1
Oviduct																											1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Codeine: 750 ppm (continued)

Number of Days on Study	0	0	3	3	3	4	5	5	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7
	0	0	4	5	8	7	1	3	1	2	3	4	6	7	7	3	3	3	3	3	3	3	3	3	3
	8	8	8	9	8	9	2	9	6	5	3	7	4	2	7	1	4	4	4	4	4	4	4	4	4
Carcass ID Number	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	4	4	5	3	4	2	4	3	3	5	2	2	4	1	2	0	0	0	0	1	1	1	2	2	3
	6	8	0	4	3	3	5	2	9	2	5	7	2	1	8	4	1	2	8	2	6	7	2	4	1
Genital System (continued)																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma													X												
Histiocytic sarcoma														X											
Leiomyosarcoma																									
Squamous cell carcinoma, metastatic, uncertain primary site																									
Hematopoietic System																									
Blood																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node											+			+											
Mediastinal, histiocytic sarcoma														X											
Lymph node, mandibular	M	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Histiocytic sarcoma														X											
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M
Histiocytic sarcoma										X				X											
Squamous cell carcinoma, metastatic, uncertain primary site																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma														X											
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	M	+	+	+	M	M	M
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma												X													X
Subcutaneous tissue, liposarcoma					X																				
Subcutaneous tissue, osteosarcoma				X																					
Subcutaneous tissue, sarcoma																	X								
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																		X				X			
Alveolar/bronchiolar carcinoma																									
Carcinoma, metastatic, harderian gland									X																
Histiocytic sarcoma										X				X											
Osteosarcoma, metastatic, skin				X																					
Mediastinum, osteosarcoma, metastatic, skin				X																					
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Codeine: 750 ppm (continued)

Number of Days on Study	734	734	734	734	734	734	734	734	735	735	735	735	735	735	735	735	735	735	735	735	735	735	735	735	736	736		
Carcass ID Number	335	336	337	340	347	349	351	354	303	305	306	309	310	313	314	318	319	321	326	329	357	358	359	360	320	344	Total Tissues/ Tumors	
Genital System (continued)																												
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51	
Hemangiosarcoma																											1	
Histiocytic sarcoma																											1	
Leiomyosarcoma																X											1	
Squamous cell carcinoma, metastatic, uncertain primary site									X																		1	
Hematopoietic System																												
Blood																										+	1	
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51	
Lymph node																											2	
Mediastinal, histiocytic sarcoma																											1	
Lymph node, mandibular	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46	
Histiocytic sarcoma																											1	
Lymph node, mesenteric	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48	
Histiocytic sarcoma																											2	
Squamous cell carcinoma, metastatic, uncertain primary site									X																		1	
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51	
Histiocytic sarcoma																											1	
Thymus	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	41	
Integumentary System																												
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51	
Subcutaneous tissue, fibrosarcoma																											2	
Subcutaneous tissue, liposarcoma																											1	
Subcutaneous tissue, osteosarcoma																											1	
Subcutaneous tissue, sarcoma																			X								2	
Musculoskeletal System																												
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51	
Osteosarcoma																								X			1	
Nervous System																												
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51	
Respiratory System																												
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51	
Alveolar/bronchiolar adenoma																											2	
Alveolar/bronchiolar carcinoma			X																								1	
Carcinoma, metastatic, harderian gland																											1	
Histiocytic sarcoma																											2	
Osteosarcoma, metastatic, skin																											1	
Mediastinum, osteosarcoma, metastatic, skin																											1	
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51	
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51	

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Codeine: 750 ppm (continued)

Number of Days on Study	0	0	3	3	3	4	5	5	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7
	0	0	4	5	8	7	1	3	1	2	3	4	6	7	7	3	3	3	3	3	3	3	3	3	3
	8	8	8	9	8	9	2	9	6	5	3	7	4	2	7	1	4	4	4	4	4	4	4	4	4
Carcass ID Number	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	4	4	5	3	4	2	4	3	3	5	2	2	4	1	2	0	0	0	0	1	1	1	2	2	3
	6	8	0	4	3	3	5	2	9	2	5	7	2	1	8	4	1	2	8	2	6	7	2	4	1
Special Senses System																									
Eye									+																
Harderian gland									+													+			
Adenoma																									
Carcinoma									X																
Bilateral, adenoma																						X			
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma														X											
Squamous cell carcinoma, metastatic, uncertain primary site																									
Urinary bladder	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma										X				X											
Lymphoma malignant lymphocytic			X																						
Lymphoma malignant mixed											X														

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Codeine: 750 ppm (continued)

Number of Days on Study	734	734	734	734	734	734	734	734	735	735	735	735	735	735	735	735	735	735	735	735	735	735	735	735	736	736	
Carcass ID Number	335	336	337	340	347	349	351	354	303	305	306	309	310	313	314	318	319	321	326	329	357	358	359	360	320	344	Total Tissues/ Tumors
Special Senses System																											
Eye																											1
Harderian gland									+											+							4
Adenoma									X											X							2
Carcinoma																											1
Bilateral, adenoma																											1
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Histiocytic sarcoma																											1
Squamous cell carcinoma, metastatic, uncertain primary site									X																		1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Histiocytic sarcoma																											2
Lymphoma malignant lymphocytic																											1
Lymphoma malignant mixed														X	X	X											4

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Codeine: 1,500 ppm

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Codeine: 1,500 ppm (continued)

Number of Days on Study	735	735	735	735	735	735	735	735	735	735	735	735	735	735	735	735	735	736	736	736	736	736	736	736	736	736	
Carcass ID Number	371	372	377	380	381	387	391	393	395	399	404	406	407	408	409	413	417	363	366	369	375	379	398	410	415	420	Total Tissues/ Tumors
Alimentary System																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	49
Gallbladder	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	47
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Hemangiosarcoma																						X					1
Hepatocellular carcinoma					X			X				X								X							6
Hepatocellular adenoma			X	X	X			X				X	X				X					X					11
Hepatocellular adenoma, multiple							X									X											2
Mesentery		+							+	+						+											7
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Cardiovascular System																											
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Endocrine System																											
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																											1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adenoma																											1
Parathyroid gland	+	M	+	+	+	M	+	+	M	M	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	40
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma									X					X			X			X				X	X	X	17
Pars distalis, carcinoma																											1
Pars intermedia, adenoma						X																					3
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Follicular cell, adenoma				X																	X						3
General Body System																											
None																											
Genital System																											
Clitoral gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	M	+	M	+	+	+	+	45
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma																											1
Polyp stromal															X												2

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Codeine: 1,500 ppm (continued)

Number of Days on Study	0	3	3	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	0	2	2	4	0	2	2	2	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	8	3	9	3	3	4	7	7	1	4	4	4	4	4	4	4	4	4	4	4	4	4	4	5	5	5
Carcass ID Number	4	3	3	3	3	3	3	4	4	3	3	3	3	3	3	3	3	3	4	4	4	4	4	3	3	
	0	9	9	8	9	8	9	0	1	6	6	7	7	7	8	8	8	8	0	0	1	1	1	6	6	
	2	0	6	6	7	3	2	5	2	1	5	3	4	8	2	4	5	9	0	3	1	6	8	4	8	
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Lymph node		+						+																		
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Lymph node, mesenteric	M	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Hemangiosarcoma					X																					
Thymus	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Carcinoma				X					X																	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Subcutaneous tissue, sarcoma							X																			
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Chondrosarcoma			X																							
Skeletal muscle					+																					
Hemangiosarcoma					X																					
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Spinal cord					+																					
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Alveolar/bronchiolar adenoma						X											X									
Alveolar/bronchiolar adenoma, multiple																										
Alveolar/bronchiolar carcinoma																							X			
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Special Senses System																										
Ear		+																								
Eye														+												
Harderian gland														+												
Adenoma																										
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Ureter																										
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Lymphoma malignant mixed					X	X	X	X								X										

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Codeine: 1,500 ppm (continued)

Number of Days on Study	735	735	735	735	735	735	735	735	735	735	735	735	735	735	735	735	735	736	736	736	736	736	736	736	736	736	
Carcass ID Number	371	372	377	380	381	387	391	393	395	399	404	406	407	408	409	413	417	363	366	369	375	379	398	410	415	420	Total Tissues/ Tumors
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Lymph node																											2
Lymph node, mandibular	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Hemangiosarcoma																											1
Thymus	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Integumentary System																											
Mammary gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																											2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Subcutaneous tissue, sarcoma																											1
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Chondrosarcoma																											1
Skeletal muscle																											1
Hemangiosarcoma																											1
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Spinal cord																											1
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Alveolar/bronchiolar adenoma				X		X								X													5
Alveolar/bronchiolar adenoma, multiple								X																			1
Alveolar/bronchiolar carcinoma																											1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Special Senses System																											
Ear																											1
Eye														+													2
Harderian gland												+		+													3
Adenoma										X																	1
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Ureter		+																									1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Lymphoma malignant mixed															X												6

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Codeine: 3,000 ppm

Number of Days on Study	0	0	3	5	5	5	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	0	0	9	0	5	9	1	3	8	1	1	2	2	2	2	3	3	3	3	3	3	3	3	3
	8	8	7	6	6	8	9	1	0	1	1	0	2	7	8	1	4	4	4	4	4	4	4	4
Carcass ID Number	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
	5	7	6	3	2	3	2	4	2	2	3	5	6	5	5	6	3	3	3	3	4	4	4	4
	8	2	6	4	8	0	4	4	3	1	9	1	3	4	2	7	3	5	6	8	1	3	6	9
Alimentary System																								
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	A	+	+	+	M	+	+	+	+	M	+	+	M	M	+	+	+	M	+	+	+	M	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, pancreas															X									
Intestine large, cecum	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma						X																		
Intestine small, ileum	A	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma												X	X					X						
Hepatocellular carcinoma, multiple																						X		
Hepatocellular adenoma																						X		
Hepatocellular adenoma, multiple																					X			
Histiocytic sarcoma						X																		
Mesentery							+								+	+								
Adenocarcinoma, metastatic, pancreas															X									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma						X																		
Acinar cell, adenocarcinoma															X									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																								
Stomach, glandular	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																								
Blood vessel	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																								
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Extra adrenal tissue, adenocarcinoma, metastatic, pancreas															X									
Adrenal medulla	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	M	+	M	+	M	M	M	M	M	M	+	+	+	+	+	+	+	+	+	M	M	+	+
Pituitary gland	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma																	X		X					X
Pars intermedia, adenoma																						X		
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma						X																		
Follicular cell, adenoma																								
General Body System																								
None																								

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Codeine: 3,000 ppm (continued)

Number of Days on Study	734	734	734	734	734	734	734	734	734	734	734	735	735	735	735	735	735	735	735	735	735	736	736	736	736		
Carcass ID Number	450	455	461	462	469	470	471	474	476	477	478	479	425	429	431	442	448	453	456	459	468	473	422	426	440	464	Total Tissues/ Tumors
Alimentary System																											
Esophagus	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	48
Gallbladder	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	41
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma, metastatic, pancreas																											1
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																											1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma																											3
Hepatocellular carcinoma, multiple																											1
Hepatocellular adenoma												X	X		X												4
Hepatocellular adenoma, multiple																											1
Histiocytic sarcoma																											1
Mesentery			+																	+							5
Adenocarcinoma, metastatic, pancreas																											1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																											1
Acinar cell, adenocarcinoma																											1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma					X																						1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cardiovascular System																											
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																											
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Extra adrenal tissue, adenocarcinoma, metastatic, pancreas																											1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	M	M	M	M	M	+	33
Pituitary gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	46
Pars distalis, adenoma					X	X		X				X			X						X			X			10
Pars intermedia, adenoma																											1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																											1
Follicular cell, adenoma												X												X			2
General Body System																											
None																											

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Codeine: 3,000 ppm (continued)

Number of Days on Study	0	0	3	5	5	5	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	0	0	9	0	5	9	1	3	8	1	1	2	2	2	2	3	3	3	3	3	3	3	3	3
	8	8	7	6	6	8	9	1	0	1	1	0	2	7	8	1	4	4	4	4	4	4	4	4
Carcass ID Number	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
	5	7	6	3	2	3	2	4	2	2	3	5	6	5	5	6	3	3	3	3	4	4	4	4
	8	2	6	4	8	0	4	4	3	1	9	1	3	4	2	7	3	5	6	8	1	3	6	9
Genital System																								
Clitoral gland	+	+	M	M	+	+	M	+	+	+	+	M	+	M	+	M	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, pancreas															X									
Adenoma																								
Cystadenoma										X														
Histiocytic sarcoma						X																		
Teratoma malignant			X																					
Oviduct				+																				
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, pancreas															X									
Histiocytic sarcoma						X																		
Vagina			+																					
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node			+		+	+			+		+						+							
Teratoma malignant, metastatic			X																					
Mediastinal, histiocytic sarcoma						X																		
Lymph node, mandibular	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma						X																		
Lymph node, mesenteric	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, pancreas															X									
Histiocytic sarcoma						X																		
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma						X																		
Thymus	+	+	+	+	+	M	+	+	+	M	M	+	M	M	+	M	+	+	+	+	+	+	+	+
Integumentary System																								
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																								
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, hemangiosarcoma				X																				
Subcutaneous tissue, sarcoma																							X	
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle															+									
Adenocarcinoma, metastatic, pancreas															X									
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																								
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, pancreas															X									
Alveolar/bronchiolar adenoma										X			X											
Hepatocellular carcinoma, metastatic, liver													X					X				X		
Histiocytic sarcoma						X																		
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Codeine: 3,000 ppm (continued)

Number of Days on Study	734	734	734	734	734	734	734	734	734	734	734	734	735	735	735	735	735	735	735	735	735	735	736	736	736	736	
Carcass ID Number	450	455	461	462	469	470	471	474	476	477	478	479	425	429	431	442	448	453	456	459	468	473	422	426	440	464	Total Tissues/ Tumors
Genital System																											
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, metastatic, pancreas																											1
Adenoma			X																	X							2
Cystadenoma																											1
Histiocytic sarcoma																											1
Teratoma malignant																											1
Oviduct																											1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, metastatic, pancreas																											1
Histiocytic sarcoma																											1
Vagina																											1
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node								+			+								+								9
Teratoma malignant, metastatic																											1
Mediastinal, histiocytic sarcoma																											1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																											1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenocarcinoma, metastatic, pancreas																											1
Histiocytic sarcoma																											1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																											1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	42
Integumentary System																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma										X	X																2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, hemangiosarcoma																											1
Subcutaneous tissue, sarcoma		X																									2
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																											1
Adenocarcinoma, metastatic, pancreas																											1
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, metastatic, pancreas																											1
Alveolar/bronchiolar adenoma					X						X																4
Hepatocellular carcinoma, metastatic, liver																											3
Histiocytic sarcoma																											1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Codeine: 3,000 ppm (continued)

Number of Days on Study	0	0	3	5	5	5	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	0	0	9	0	5	9	1	3	8	1	1	2	2	2	2	3	3	3	3	3	3	3	3	3	3
	8	8	7	6	6	8	9	1	0	1	1	0	2	7	8	1	4	4	4	4	4	4	4	4	4
Carcass ID Number	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
	5	7	6	3	2	3	2	4	2	2	3	5	6	5	5	6	3	3	3	3	4	4	4	4
	8	2	6	4	8	0	4	4	3	1	9	1	3	4	2	7	3	5	6	8	1	3	6	9
Special Senses System																									
Eye																		+							
Harderian gland																		+							
Adenoma																		X							
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, pancreas															X										
Histiocytic sarcoma						X																			
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, pancreas															X										
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma						X																			
Lymphoma malignant mixed					X		X		X					X			X								

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Codeine: 3,000 ppm (continued)

Number of Days on Study	734	734	734	734	734	734	734	734	734	734	734	734	735	735	735	735	735	735	735	735	735	736	736	736	736		
Carcass ID Number	450	455	461	462	469	470	471	474	476	477	478	479	425	429	431	442	448	453	456	459	468	473	422	426	440	464	Total Tissues/ Tumors
Special Senses System																											
Eye				+											+												3
Harderian gland								+							+												3
Adenoma								X																			2
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, metastatic, pancreas																											1
Histiocytic sarcoma																											1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, metastatic, pancreas																											1
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																											1
Lymphoma malignant mixed					X			X			X																8

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

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
Harderian Gland: Adenoma				
Overall rate[a]	1/50 (2%)	3/51 (6%)	1/51 (2%)	2/50 (4%)
Adjusted rate[b]	2.8%	8.3%	2.3%	5.7%
Terminal rate[c]	1/36 (3%)	3/36 (8%)	1/43 (2%)	2/35 (6%)
First incidence (days)	731	731	731	731
Life table test[d]	P=0.524	P=0.305	P=0.722N	P=0.490
Logistic regression test[d]	P=0.524	P=0.305	P=0.722N	P=0.490
Cochran-Armitage test[d]	P=0.524			
Fisher exact test[d]		P=0.316	P=0.748N	P=0.500
Harderian Gland: Adenoma or Carcinoma				
Overall rate	1/50 (2%)	4/51 (8%)	1/51 (2%)	2/50 (4%)
Adjusted rate	2.8%	10.5%	2.3%	5.7%
Terminal rate	1/36 (3%)	3/36 (8%)	1/43 (2%)	2/35 (6%)
First incidence (days)	731	616	731	731
Life table test	P=0.597N	P=0.184	P=0.722N	P=0.490
Logistic regression test	P=0.581N	P=0.173	P=0.722N	P=0.490
Cochran-Armitage test	P=0.595			
Fisher exact test		P=0.187	P=0.748N	P=0.500
Liver: Hepatocellular Adenoma				
Overall rate	12/50 (24%)	10/51 (20%)	13/51 (25%)	5/50 (10%)
Adjusted rate	32.0%	25.3%	30.2%	14.3%
Terminal rate	11/36 (31%)	7/36 (19%)	13/43 (30%)	5/35 (14%)
First incidence (days)	497	616	731	731
Life table test	P=0.054N	P=0.408N	P=0.488N	P=0.059N
Logistic regression test	P=0.045N	P=0.424N	P=0.565N	P=0.047N
Cochran-Armitage test	P=0.061N			
Fisher exact test		P=0.385N	P=0.523	P=0.054N
Liver: Hepatocellular Carcinoma				
Overall rate	5/50 (10%)	6/51 (12%)	6/51 (12%)	4/50 (8%)
Adjusted rate	12.5%	15.7%	14.0%	10.5%
Terminal rate	3/36 (8%)	4/36 (11%)	6/43 (14%)	2/35 (6%)
First incidence (days)	565	647	731	720
Life table test	P=0.382N	P=0.492	P=0.610	P=0.501N
Logistic regression test	P=0.376N	P=0.499	P=0.529	P=0.499N
Cochran-Armitage test	P=0.395N			
Fisher exact test		P=0.514	P=0.514	P=0.500N
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	16/50 (32%)	15/51 (29%)	15/51 (29%)	8/50 (16%)
Adjusted rate	40.3%	37.3%	34.9%	21.4%
Terminal rate	13/36 (36%)	11/36 (31%)	15/43 (35%)	6/35 (17%)
First incidence (days)	497	616	731	720
Life table test	P=0.035N	P=0.506N	P=0.288N	P=0.060N
Logistic regression test	P=0.028N	P=0.520N	P=0.413N	P=0.047N
Cochran-Armitage test	P=0.039N			
Fisher exact test		P=0.474N	P=0.474N	P=0.050N

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Feed Study of Codeine (continued)

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	1/50 (2%)	2/51 (4%)	6/51 (12%)	4/50 (8%)
Adjusted rate	2.8%	5.6%	13.5%	10.4%
Terminal rate	1/36 (3%)	2/36 (6%)	5/43 (12%)	2/35 (6%)
First incidence (days)	731	731	724	711
Life table test	P=0.113	P=0.500	P=0.096	P=0.185
Logistic regression test	P=0.130	P=0.500	P=0.094	P=0.191
Cochran-Armitage test	P=0.111			
Fisher exact test		P=0.508	P=0.059	P=0.181
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	2/50 (4%)	3/51 (6%)	7/51 (14%)	4/50 (8%)
Adjusted rate	5.6%	8.3%	15.8%	10.4%
Terminal rate	2/36 (6%)	3/36 (8%)	6/43 (14%)	2/35 (6%)
First incidence (days)	731	731	724	711
Life table test	P=0.241	P=0.500	P=0.134	P=0.339
Logistic regression test	P=0.276	P=0.500	P=0.135	P=0.357
Cochran-Armitage test	P=0.237			
Fisher exact test		P=0.509	P=0.085	P=0.339
Ovary: Adenoma				
Overall rate	2/49 (4%)	3/51 (6%)	0/50 (0%)	2/50 (4%)
Adjusted rate	5.6%	8.3%	0.0%	5.7%
Terminal rate	2/36 (6%)	3/36 (8%)	0/43 (0%)	2/35 (6%)
First incidence (days)	731	731	—[e]	731
Life table test	P=0.476N	P=0.500	P=0.200N	P=0.685
Logistic regression test	P=0.476N	P=0.500	P=0.200N	P=0.685
Cochran-Armitage test	P=0.470N			
Fisher exact test		P=0.519	P=0.242N	P=0.684N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	11/48 (23%)	9/47 (19%)	17/49 (35%)	10/46 (22%)
Adjusted rate	29.7%	25.9%	39.4%	30.3%
Terminal rate	10/36 (28%)	8/33 (24%)	16/42 (38%)	10/33 (30%)
First incidence (days)	722	512	703	731
Life table test	P=0.473	P=0.482N	P=0.264	P=0.586N
Logistic regression test	P=0.539N	P=0.498N	P=0.269	P=0.528N
Cochran-Armitage test	P=0.472			
Fisher exact test		P=0.422N	P=0.146	P=0.544N
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma				
Overall rate	11/48 (23%)	9/47 (19%)	18/49 (37%)	10/46 (22%)
Adjusted rate	29.7%	25.9%	41.7%	30.3%
Terminal rate	10/36 (28%)	8/33 (24%)	17/42 (40%)	10/33 (30%)
First incidence (days)	722	512	703	731
Life table test	P=0.460	P=0.482N	P=0.202	P=0.586N
Logistic regression test	P=0.544	P=0.498N	P=0.206	P=0.528N
Cochran-Armitage test	P=0.460			
Fisher exact test		P=0.422N	P=0.103	P=0.544N

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Feed Study of Codeine (continued)

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
Pituitary Gland (Pars Intermedia): Adenoma				
Overall rate	1/48 (2%)	1/47 (2%)	3/49 (6%)	1/46 (2%)
Adjusted rate	2.3%	2.7%	7.1%	3.0%
Terminal rate	0/36 (0%)	0/33 (0%)	3/42 (7%)	1/33 (3%)
First incidence (days)	570	677	731	731
Life table test	P=0.556	P=0.752	P=0.357	P=0.753
Logistic regression test	P=0.545	P=0.744N	P=0.303	P=0.765
Cochran-Armitage test	P=0.544			
Fisher exact test		P=0.747	P=0.316	P=0.742
Skin (Subcutaneous Tissue): Fibrosarcoma or Sarcoma				
Overall rate	1/50 (2%)	4/51 (8%)	1/51 (2%)	2/50 (4%)
Adjusted rate	2.8%	10.6%	2.2%	5.7%
Terminal rate	1/36 (3%)	3/36 (8%)	0/43 (0%)	2/35 (6%)
First incidence (days)	731	647	727	731
Life table test	P=0.595N	P=0.180	P=0.715N	P=0.490
Logistic regression test	P=0.577N	P=0.172	P=0.723N	P=0.490
Cochran-Armitage test	P=0.595			
Fisher exact test		P=0.187	P=0.748N	P=0.500
Thyroid Gland (Follicular Cell): Adenoma				
Overall rate	0/48 (0%)	4/51 (8%)	3/51 (6%)	2/50 (4%)
Adjusted rate	0.0%	11.1%	7.0%	5.7%
Terminal rate	0/34 (0%)	4/36 (11%)	3/43 (7%)	2/35 (6%)
First incidence (days)	—	731	731	731
Life table test	P=0.399	P=0.070	P=0.166	P=0.245
Logistic regression test	P=0.399	P=0.070	P=0.166	P=0.245
Cochran-Armitage test	P=0.398			
Fisher exact test		P=0.066	P=0.133	P=0.258
Uterus: Stromal Polyp				
Overall rate	4/50 (8%)	0/51 (0%)	2/51 (4%)	0/50 (0%)
Adjusted rate	10.6%	0.0%	4.7%	0.0%
Terminal rate	3/36 (8%)	0/36 (0%)	2/43 (5%)	0/35 (0%)
First incidence (days)	651	—	731	—
Life table test	P=0.057N	P=0.066N	P=0.263N	P=0.067N
Logistic regression test	P=0.055N	P=0.065N	P=0.296N	P=0.061N
Cochran-Armitage test	P=0.061N			
Fisher exact test		P=0.056N	P=0.329N	P=0.059N
All Organs: Hemangioma or Hemangiosarcoma				
Overall rate	1/50 (2%)	2/51 (4%)	3/51 (6%)	1/50 (2%)
Adjusted rate	2.6%	5.3%	6.7%	2.1%
Terminal rate	0/36 (0%)	1/36 (3%)	2/43 (5%)	0/35 (0%)
First incidence (days)	713	664	703	506
Life table test	P=0.562N	P=0.494	P=0.377	P=0.757N
Logistic regression test	P=0.579N	P=0.495	P=0.338	P=0.759N
Cochran-Armitage test	P=0.579N			
Fisher exact test		P=0.508	P=0.316	P=0.753N

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Feed Study of Codeine (continued)

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
All Organs: Malignant Lymphoma (Lymphocytic or Mixed)				
Overall rate	7/50 (14%)	5/51 (10%)	6/51 (12%)	8/50 (16%)
Adjusted rate	17.4%	12.4%	12.8%	19.6%
Terminal rate	4/36 (11%)	3/36 (8%)	2/43 (5%)	4/35 (11%)
First incidence (days)	544	348	703	556
Life table test	P=0.385	P=0.386N	P=0.369N	P=0.503
Logistic regression test	P=0.360	P=0.362N	P=0.469N	P=0.500
Cochran-Armitage test	P=0.357			
Fisher exact test		P=0.366N	P=0.485N	P=0.500
All Organs: Benign Neoplasms				
Overall rate	26/50 (52%)	25/51 (49%)	33/51 (65%)	19/50 (38%)
Adjusted rate	64.7%	60.8%	73.3%	51.1%
Terminal rate	22/36 (61%)	20/36 (56%)	31/43 (72%)	17/35 (49%)
First incidence (days)	497	512	703	711
Life table test	P=0.110N	P=0.509N	P=0.430	P=0.129N
Logistic regression test	P=0.065N	P=0.547N	P=0.257	P=0.080N
Cochran-Armitage test	P=0.126N			
Fisher exact test		P=0.460N	P=0.137	P=0.114N
All Organs: Malignant Neoplasms				
Overall rate	15/50 (30%)	24/51 (47%)	17/51 (33%)	19/50 (38%)
Adjusted rate	34.2%	52.0%	34.7%	41.7%
Terminal rate	8/36 (22%)	14/36 (39%)	11/43 (26%)	9/35 (26%)
First incidence (days)	530	348	329	397
Life table test	P=0.468	P=0.077	P=0.530N	P=0.293
Logistic regression test	P=0.269	P=0.060	P=0.187	P=0.162
Cochran-Armitage test	P=0.424			
Fisher exact test		P=0.060	P=0.442	P=0.263
All Organs: Benign or Malignant Neoplasms				
Overall rate	34/50 (68%)	36/51 (71%)	38/51 (75%)	31/50 (62%)
Adjusted rate	73.7%	76.5%	77.6%	67.2%
Terminal rate	24/36 (67%)	25/36 (69%)	32/43 (74%)	20/35 (57%)
First incidence (days)	497	348	329	397
Life table test	P=0.284N	P=0.420	P=0.430N	P=0.392N
Logistic regression test	P=0.332N	P=0.421	P=0.358	P=0.336N
Cochran-Armitage test	P=0.271N			
Fisher exact test		P=0.474	P=0.308	P=0.338N

[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for liver, lung, ovary, 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 exposure group is indicated by N.
[e] Not applicable; no neoplasms in animal group

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

	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Microbiological Associates, Inc.			
C.I. Direct Blue 218	7/49	5/49	10/49
dl-Amphetamine Sulfate	5/50	0/50	5/50
Overall Historical Incidence			
Total	194/1,312 (14.8%)	90/1,312 (6.9%)	260/1,312 (19.8%)
Standard deviation	10.5%	6.1%	12.8%
Range	2%-50%	0%-20%	3%-56%

[a] Data as of 17 June 1994

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

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	10	9	9	9
Early deaths				
Moribund	7	9	6	4
Natural deaths	7	6	2	11
Survivors				
Died last week of study	1			1
Terminal sacrifice	35	36	43	34
Missing				1
Animals examined microscopically	60	60	60	59
15-Month Interim Evaluation				
Alimentary System				
Liver	(10)	(9)	(9)	(9)
Basophilic focus	1 (10%)			
Inflammation, chronic active	4 (40%)	3 (33%)	2 (22%)	2 (22%)
Mixed cell focus			1 (11%)	
Mesentery	(1)			
Fat, necrosis	1 (100%)			
Pancreas	(10)	(9)	(9)	(9)
Inflammation, chronic	4 (40%)	4 (44%)	4 (44%)	
Salivary glands	(10)	(9)	(9)	(9)
Inflammation, chronic	6 (60%)	6 (67%)	7 (78%)	4 (44%)
Stomach, glandular	(10)	(9)	(9)	(9)
Dilatation	1 (10%)			
Inflammation, chronic active		1 (11%)		
Endocrine System				
Adrenal cortex	(10)	(9)	(9)	(9)
Subcapsular, hyperplasia	10 (100%)	9 (100%)	9 (100%)	9 (100%)
Adrenal medulla	(10)	(9)	(9)	(9)
Hyperplasia		1 (11%)		
Pituitary gland	(10)	(9)	(9)	(9)
Pars distalis, hyperplasia	1 (10%)		2 (22%)	1 (11%)
Thyroid gland	(10)	(9)	(9)	(9)
Follicular cell, hyperplasia, focal			1 (11%)	1 (11%)
Genital System				
Clitoral gland	(10)	(8)	(8)	(8)
Dilatation	8 (80%)	7 (88%)	7 (88%)	6 (75%)
Ovary	(9)	(9)	(9)	(9)
Cyst	1 (11%)	1 (11%)	2 (22%)	1 (11%)
Uterus	(10)	(9)	(9)	(9)
Dilatation	2 (20%)	4 (44%)	1 (11%)	2 (22%)
Hyperplasia, cystic	10 (100%)	8 (89%)	8 (89%)	8 (89%)

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

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of Codeine (continued)

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
15-Month Interim Evaluation (continued)				
Hematopoietic System				
Lymph node, mandibular	(9)	(9)	(9)	(7)
Hyperplasia, lymphoid			1 (11%)	
Thymus	(10)	(9)	(9)	(9)
Hyperplasia, lymphoid		2 (22%)	1 (11%)	1 (11%)
Integumentary System				
Mammary gland	(10)	(9)	(9)	(9)
Infiltration cellular, lymphocyte		1 (11%)		
Skin	(10)	(9)	(9)	(9)
Inflammation, chronic active	2 (20%)	1 (11%)	1 (11%)	
Musculoskeletal System				
Bone	(10)	(9)	(9)	(9)
Dysplasia	1 (10%)	1 (11%)		
Nervous System				
Brain	(10)	(9)	(9)	(9)
Mineralization	4 (40%)	3 (33%)	1 (11%)	2 (22%)
Respiratory System				
Lung	(10)	(9)	(9)	(9)
Infiltration cellular, lymphocyte	9 (90%)	6 (67%)	9 (100%)	4 (44%)
Nose	(10)	(9)	(9)	(9)
Olfactory epithelium, degeneration, hyaline	9 (90%)	7 (78%)	8 (89%)	9 (100%)
Respiratory epithelium, degeneration, hyaline	7 (70%)	6 (67%)	8 (89%)	8 (89%)
Respiratory epithelium, inflammation, chronic active	1 (10%)	1 (11%)	1 (11%)	1 (11%)
Urinary System				
Kidney	(10)	(9)	(9)	(9)
Cyst		1 (11%)		
Inflammation, chronic	5 (50%)	7 (78%)	7 (78%)	5 (56%)
Renal tubule, regeneration	2 (20%)	1 (11%)		
Urinary bladder	(10)	(9)	(9)	(9)
Infiltration cellular, lymphocyte	8 (80%)	7 (78%)	9 (100%)	6 (67%)
Systems Examined With No Lesions Observed				
Cardiovascular System				
General Body System				
Special Senses System				

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of Codeine (continued)

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
2-Year Study				
Alimentary System				
Gallbladder	(43)	(42)	(47)	(41)
Inflammation, chronic active	1 (2%)			1 (2%)
Intestine small, duodenum	(48)	(49)	(48)	(48)
Ulcer			1 (2%)	
Intestine small, jejunum	(50)	(48)	(50)	(50)
Hemorrhage				1 (2%)
Hyperplasia, lymphoid		1 (2%)	1 (2%)	1 (2%)
Liver	(50)	(51)	(51)	(50)
Angiectasis	1 (2%)			1 (2%)
Atrophy			1 (2%)	
Basophilic focus			1 (2%)	1 (2%)
Clear cell focus			1 (2%)	
Congestion				1 (2%)
Cyst		1 (2%)	2 (4%)	
Eosinophilic focus	6 (12%)	7 (14%)	9 (18%)	2 (4%)
Fatty change, focal			1 (2%)	
Hematopoietic cell proliferation	3 (6%)	5 (10%)		3 (6%)
Infarct			2 (4%)	1 (2%)
Inflammation, chronic active	7 (14%)	7 (14%)	12 (24%)	4 (8%)
Mineralization			1 (2%)	
Mitotic alteration		1 (2%)		1 (2%)
Mixed cell focus			2 (4%)	1 (2%)
Necrosis	2 (4%)	2 (4%)	2 (4%)	2 (4%)
Bile duct, hyperplasia			1 (2%)	
Centrilobular, inflammation, chronic			1 (2%)	
Centrilobular, necrosis	1 (2%)			
Centrilobular, pigmentation			1 (2%)	
Hepatocyte, necrosis		1 (2%)		
Kupffer cell, hypertrophy				1 (2%)
Mesentery	(9)	(9)	(7)	(5)
Inflammation, chronic active	2 (22%)			1 (20%)
Artery, inflammation, chronic active			1 (14%)	
Fat, necrosis	5 (56%)	8 (89%)	6 (86%)	2 (40%)
Pancreas	(50)	(51)	(51)	(50)
Inflammation, chronic	1 (2%)			
Inflammation, chronic active	2 (4%)		1 (2%)	2 (4%)
Acinar cell, atrophy	2 (4%)	1 (2%)	1 (2%)	2 (4%)
Acinar cell, depletion secretory	1 (2%)			
Duct, cyst	1 (2%)	1 (2%)		2 (4%)
Salivary glands	(50)	(50)	(51)	(50)
Inflammation, chronic	28 (56%)	28 (56%)	27 (53%)	23 (46%)
Stomach, forestomach	(50)	(51)	(51)	(50)
Hyperplasia	1 (2%)	1 (2%)	2 (4%)	1 (2%)
Inflammation, acute				1 (2%)
Inflammation, chronic active	2 (4%)		2 (4%)	3 (6%)
Stomach, glandular	(50)	(51)	(51)	(49)
Cyst				1 (2%)
Dysplasia	1 (2%)			
Inflammation, chronic active	3 (6%)	9 (18%)		6 (12%)
Necrosis	2 (4%)	1 (2%)	1 (2%)	

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of Codeine (continued)

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
2-Year Study (continued)				
Cardiovascular System				
Blood vessel	(50)	(51)	(50)	(49)
Aorta, inflammation, chronic active			1 (2%)	
Heart	(50)	(51)	(51)	(50)
Fibrosis		2 (4%)		
Inflammation, chronic active	2 (4%)			
Mineralization		1 (2%)		
Thrombosis		2 (4%)		
Artery, inflammation, chronic active		1 (2%)	1 (2%)	
Endocrine System				
Adrenal cortex	(50)	(51)	(50)	(50)
Angiectasis		1 (2%)		1 (2%)
Cyst			1 (2%)	
Cytoplasmic alteration, focal	1 (2%)			
Hematopoietic cell proliferation		2 (4%)		
Hypertrophy, focal			1 (2%)	
Inflammation, chronic active				3 (6%)
Subcapsular, hyperplasia	47 (94%)	46 (90%)	49 (98%)	45 (90%)
Adrenal medulla	(49)	(50)	(50)	(48)
Hyperplasia			2 (4%)	2 (4%)
Pituitary gland	(48)	(47)	(49)	(46)
Craniopharyngeal duct, hyperplasia			1 (2%)	
Pars distalis, angiectasis	2 (4%)	1 (2%)		2 (4%)
Pars distalis, cyst		1 (2%)		2 (4%)
Pars distalis, hyperplasia	11 (23%)	12 (26%)	11 (22%)	10 (22%)
Pars intermedia, hyperplasia	1 (2%)			1 (2%)
Thyroid gland	(48)	(51)	(51)	(50)
Inflammation, chronic active	2 (4%)	6 (12%)	10 (20%)	4 (8%)
Follicle, cyst	3 (6%)	1 (2%)	5 (10%)	3 (6%)
Follicular cell, hyperplasia, diffuse			1 (2%)	
Follicular cell, hyperplasia, focal	14 (29%)	29 (57%)	42 (82%)	44 (88%)
General Body System				
None				
Genital System				
Clitoral gland	(41)	(43)	(45)	(44)
Dilatation	34 (83%)	39 (91%)	40 (89%)	41 (93%)
Inflammation, chronic active	3 (7%)	4 (9%)	5 (11%)	10 (23%)
Pigmentation	3 (7%)	2 (5%)	2 (4%)	1 (2%)
Ovary	(49)	(51)	(50)	(50)
Abscess	1 (2%)			3 (6%)
Cyst	5 (10%)	11 (22%)	12 (24%)	6 (12%)
Hemorrhage			1 (2%)	
Infiltration cellular, histiocyte			2 (4%)	
Inflammation, chronic active	2 (4%)			2 (4%)
Periovarian tissue, infiltration cellular, lymphocyte			1 (2%)	1 (2%)

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of Codeine (continued)

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
2-Year Study (continued)				
Genital System (continued)				
Oviduct	(3)	(1)		(1)
Cyst	1 (33%)			
Dilatation		1 (100%)		
Inflammation, chronic active	1 (33%)	1 (100%)		
Uterus	(50)	(51)	(50)	(50)
Atrophy			1 (2%)	
Dilatation	10 (20%)	10 (20%)	9 (18%)	7 (14%)
Hemorrhage		2 (4%)		
Hyperplasia, cystic	36 (72%)	41 (80%)	38 (76%)	38 (76%)
Inflammation, chronic active		1 (2%)		
Cervix, inflammation, chronic active			1 (2%)	
Lymphatic, ectasia		1 (2%)		
Hematopoietic System				
Bone marrow	(50)	(51)	(51)	(50)
Atrophy		1 (2%)		
Congestion		1 (2%)	1 (2%)	
Myeloid cell, hyperplasia	4 (8%)	2 (4%)	1 (2%)	1 (2%)
Lymph node	(4)	(2)	(2)	(9)
Iliac, hyperplasia, lymphoid			1 (50%)	
Iliac, inflammation, chronic active	1 (25%)			
Inguinal, pigmentation			1 (50%)	
Mediastinal, hyperplasia, plasma cell				1 (11%)
Lymph node, mandibular	(45)	(46)	(49)	(49)
Hemorrhage	2 (4%)	1 (2%)		
Hyperplasia, lymphoid		1 (2%)	3 (6%)	4 (8%)
Lymph node, mesenteric	(49)	(48)	(47)	(48)
Cyst		2 (4%)		
Fibrosis		1 (2%)		
Hematopoietic cell proliferation	1 (2%)	1 (2%)	2 (4%)	
Hemorrhage	4 (8%)	2 (4%)	1 (2%)	
Hyperplasia, lymphoid	1 (2%)			
Infiltration cellular, histiocyte			1 (2%)	
Inflammation, chronic active				1 (2%)
Spleen	(50)	(51)	(51)	(50)
Atrophy			1 (2%)	
Fibrosis		1 (2%)	1 (2%)	
Hematopoietic cell proliferation	17 (34%)	19 (37%)	18 (35%)	14 (28%)
Hyperplasia, lymphoid	1 (2%)	4 (8%)	6 (12%)	3 (6%)
Infiltration cellular, plasma cell		1 (2%)		
Pigmentation, hemosiderin	1 (2%)		2 (4%)	1 (2%)
Capsule, inflammation, chronic active	1 (2%)			1 (2%)
Thymus	(38)	(41)	(47)	(42)
Atrophy	5 (13%)	9 (22%)	4 (9%)	6 (14%)
Ectopic parathyroid gland		1 (2%)		1 (2%)
Ectopic thyroid			1 (2%)	
Hyperplasia, lymphoid	2 (5%)	5 (12%)	7 (15%)	4 (10%)

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of Codeine (continued)

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
2-Year Study (continued)				
Integumentary System				
Mammary gland	(45)	(51)	(50)	(50)
Hyperplasia			2 (4%)	
Inflammation, chronic active	1 (2%)			1 (2%)
Skin	(50)	(51)	(51)	(50)
Developmental malformation	1 (2%)			
Inflammation, chronic active	3 (6%)	2 (4%)	6 (12%)	5 (10%)
Ulcer	1 (2%)			
Epidermis, hyperplasia	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Subcutaneous tissue, abscess	1 (2%)			
Subcutaneous tissue, inflammation, chronic active	1 (2%)			1 (2%)
Subcutaneous tissue, pigmentation	1 (2%)			
Subcutaneous tissue, fat, atrophy	1 (2%)		1 (2%)	1 (2%)
Musculoskeletal System				
Bone	(50)	(51)	(51)	(50)
Dysplasia	11 (22%)	5 (10%)	8 (16%)	6 (12%)
Fracture			1 (2%)	
Artery, inflammation, chronic active			1 (2%)	
Nervous System				
Brain	(50)	(51)	(51)	(50)
Compression	3 (6%)	1 (2%)	3 (6%)	1 (2%)
Degeneration		1 (2%)		
Hemorrhage	1 (2%)			
Infiltration cellular, histiocyte			1 (2%)	
Mineralization	23 (46%)	18 (35%)	21 (41%)	10 (20%)
Artery, inflammation, chronic active			1 (2%)	
Meninges, inflammation, chronic	1 (2%)			
Respiratory System				
Lung	(50)	(51)	(51)	(50)
Congestion		1 (2%)		
Hemorrhage		1 (2%)		
Infiltration cellular, lymphocyte	29 (58%)	22 (43%)	24 (47%)	20 (40%)
Infiltration cellular, histiocyte	1 (2%)			
Pigmentation, hemosiderin	1 (2%)			
Alveolar epithelium, hyperplasia	1 (2%)	1 (2%)	2 (4%)	1 (2%)
Nose	(50)	(51)	(50)	(50)
Olfactory epithelium, degeneration, hyaline	27 (54%)	32 (63%)	27 (54%)	41 (82%)
Respiratory epithelium, hyperplasia, glandular	2 (4%)			

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of Codeine (continued)

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
2-Year Study (continued)				
Special Senses System				
Eye		(1)	(2)	(3)
Atrophy			1 (50%)	
Inflammation, chronic active			1 (50%)	2 (67%)
Cornea, inflammation, chronic active				1 (33%)
Harderian gland	(2)	(4)	(3)	(3)
Hyperplasia, focal	1 (50%)			
Inflammation, chronic active			2 (67%)	1 (33%)
Urinary System				
Kidney	(50)	(51)	(51)	(50)
Amyloid deposition	1 (2%)			
Atrophy				1 (2%)
Glomerulosclerosis	1 (2%)			
Hemorrhage				1 (2%)
Hydronephrosis				1 (2%)
Infarct	1 (2%)		2 (4%)	2 (4%)
Inflammation, chronic	9 (18%)	12 (24%)	8 (16%)	13 (26%)
Metaplasia, osseous	1 (2%)			
Nephropathy		3 (6%)	2 (4%)	1 (2%)
Capsule, inflammation, chronic active				1 (2%)
Glomerulus, inflammation, chronic				1 (2%)
Perirenal tissue, inflammation, chronic active				1 (2%)
Renal tubule, degeneration, hyaline	1 (2%)			1 (2%)
Renal tubule, karyomegaly			1 (2%)	
Renal tubule, pigmentation				1 (2%)
Renal tubule, regeneration	19 (38%)	27 (53%)	31 (61%)	19 (38%)
Ureter			(1)	
Infiltration cellular, lymphocyte			1 (100%)	
Urinary bladder	(50)	(50)	(51)	(50)
Dilatation	1 (2%)			
Infiltration cellular, lymphocyte	30 (60%)	38 (76%)	37 (73%)	36 (72%)
Inflammation, chronic active				1 (2%)
Artery, inflammation, chronic active			1 (2%)	

APPENDIX E
GENETIC TOXICOLOGY

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GENETIC TOXICOLOGY

SALMONELLA MUTAGENICITY TEST PROTOCOL

Testing was performed as reported by Zeiger *et al.* (1992). Codeine phosphate was sent to the laboratory as a coded aliquot from Radian Corporation (Austin, TX). It was incubated with the *Salmonella typhimurium* tester strains (TA97, TA98, TA100, or 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 five doses of codeine phosphate. In the absence of toxicity, 10,000 μg/plate was selected as the high dose. All trials were repeated.

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

CHINESE HAMSTER OVARY CELL CYTOGENETICS PROTOCOLS

Testing was performed as reported by Galloway *et al.* (1987). Codeine phosphate was sent to the laboratory as a coded aliquot by Radian Corporation. It was tested in cultured Chinese hamster ovary (CHO) cells for induction of sister chromatid exchanges (SCEs) and chromosomal aberrations (Abs), both in the presence and absence of Aroclor 1254-induced male Sprague-Dawley rat liver S9 and cofactor mix. Cultures were handled under gold lights to prevent photolysis of bromodeoxyuridine-substituted DNA. Each test consisted of concurrent solvent and positive controls and of at least three doses of codeine phosphate; the high dose in the absence of S9 was limited by toxicity. In the presense of S9, the high dose was limited to 10,000 mg/mL. A single flask per dose was used, and tests yielding equivocal or positive results were repeated. In both the SCE and Abs tests, higher doses of codeine phosphate produced an acidic pH shift in the cultures; some experiments employed *N*-(2-hydroxyethyl)piperazine-*N'*-(2-ethanesulfonic acid) (HEPES) buffer to counter this effect.

Sister Chromatid Exchange Test: In the SCE test without S9, CHO cells were incubated for a minimum of 25.6 hours with codeine phosphate in McCoy's 5A medium supplemented with fetal bovine serum, *l*-glutamine, and antibiotics. Bromodeoxyuridine (BrdU) was added 2 hours after culture initiation. After approximately 26 hours, the medium containing codeine phosphate 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 codeine phosphate, serum-free medium, and S9 for 2 hours. The medium was then removed and replaced with medium containing serum and BrdU and no codeine phosphate and incubation proceeded for an additional 25.4 hours or more, 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. For trial 1, both with and without S9, fifty second-division metaphase cells were scored for frequency of SCEs/cell from each dose level. Because of the positive

response, 20 second-division metaphase cells were scored in trials 2 and 3. Because significant chemical-induced cell cycle delay was seen, incubation time was lengthened to ensure a sufficient number of scorable (second-division metaphase) cells.

Statistical analyses were conducted on the slopes of the dose-response curves and the individual dose points (Galloway *et al.*, 1987). An SCE frequency 20% above the concurrent solvent control value was chosen as a statistically conservative positive response. The probability of this level of difference occurring by chance at one dose point is less than 0.01; the probability for such a chance occurrence at two dose points is less than 0.001. An increase of 20% or greater at any single dose was considered weak evidence of activity; increases at two or more doses resulted in a determination that the trial was positive. A statistically significant trend ($P<0.005$) in the absence of any responses reaching 20% above background led to a call of equivocal.

Chromosomal Aberrations Test: In the Abs test without S9, cells were incubated in McCoy's 5A medium with codeine phosphate for 18.5 or 18.6 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 codeine phosphate and S9 for 2 hours, after which the treatment medium was removed and the cells were incubated for 18.5 hours in fresh medium, with Colcemid present for the final 2 hours. Cells were harvested in the same manner as for the treatment without S9. The harvest time for the Abs test was based on the cell cycle information obtained in the SCE test; cell cycle delay was anticipated, and the incubation period was extended.

Cells were selected for scoring on the basis of good morphology and completeness of karyotype (21 ± 2 chromosomes). All slides were scored blind and those from a single test were read by the same person. One 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.

RESULTS

Codeine phosphate (100 to 10,000 μg/plate) was not mutagenic in *Salmonella typhimurium* strains TA97, TA98, TA100, or TA1535, with or without induced liver S9 enzymes (Table E1; Zeiger *et al.*, 1992). Dose-related increases in the frequency of SCEs were induced by codeine phosphate in cultured CHO cells, with and without S9 (Table E2), but these significantly increased frequencies were noted only at doses that caused marked cell cycle delay, indicative of a high level of cytotoxicity. The role of confounding factors, such as toxicity-related changes in DNA metabolism, needs to be considered in the evaluation of cytogenetic data. Slowly cycling cells undergo prolonged exposure to 5-bromodeoxyuridine, which can also result in an increased level of SCEs. A clear association between cytotoxicity and SCE frequencies has not been shown. There are numerous examples of chemicals that induce cell cycle delay without inducing SCEs (Galloway *et al.*, 1987). Acidic pH shifts were noted in cultures exposed to higher concentrations of codeine phosphate; addition of HEPES buffer in some of the trials stabilized the pH.

SCE frequencies did not appear to be affected by the pH shifts; increases were noted both in acidic and neutral cultures. No increases in the frequency of Abs were noted in cultured CHO cells treated with codeine phosphate at doses similar to those used in the SCE test (Table E3); codeine phosphate-induced cell cycle delay was also observed in these cultures.

TABLE E1
Mutagenicity of Codeine Phosphate in *Salmonella typhimurium*[a]

Strain	Dose (μg/plate)	Revertants/plate[b] -S9 Trial 1	-S9 Trial 2	+hamster S9 10%	+hamster S9 30%	+rat S9 10%	+rat S9 30%
TA100	0	102 ± 5.7	98 ± 6.7	110 ± 8.7	120 ± 6.1	107 ± 4.0	115 ± 8.1
	100	100 ± 6.1	97 ± 5.6	102 ± 9.9	120 ± 5.1	89 ± 8.3	101 ± 5.9
	333	87 ± 3.0	90 ± 7.0	112 ± 10.9	113 ± 7.2	95 ± 3.3	116 ± 3.8
	1,000	89 ± 7.6	104 ± 13.9	111 ± 5.8	119 ± 10.6	86 ± 5.0	121 ± 9.2
	3,333	97 ± 1.7	92 ± 4.4	97 ± 2.4	115 ± 1.5	100 ± 2.6	110 ± 3.8
	10,000	107 ± 3.2	93 ± 3.5	114 ± 11.3	114 ± 7.1	104 ± 8.7	107 ± 13.1
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control[c]		558 ± 19.2	365 ± 14.2	1,649 ± 10.3	549 ± 4.8	1,260 ± 14.2	380 ± 18.7
TA1535	0	23 ± 2.0	8 ± 2.0	7 ± 0.7	10 ± 1.9	10 ± 1.2	12 ± 1.2
	100	19 ± 3.5	5 ± 0.9	8 ± 1.0	6 ± 1.2	10 ± 0.3	8 ± 0.9
	333	24 ± 3.0	7 ± 1.5	9 ± 2.3	9 ± 1.7	5 ± 0.3	10 ± 1.5
	1,000	26 ± 1.2	4 ± 0.3	8 ± 1.5	10 ± 3.2	10 ± 2.3	10 ± 0.3
	3,333	26 ± 2.3	4 ± 1.5	5 ± 1.5	8 ± 1.2	8 ± 0.7	7 ± 1.5
	10,000	30 ± 0.9	8 ± 1.0	8 ± 2.2	7 ± 0.3	6 ± 0.9	7 ± 0.3
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		485 ± 17.1	274 ± 5.5	407 ± 16.7	132 ± 4.5	281 ± 3.8	155 ± 3.5
TA97							
	0	136 ± 6.6	124 ± 14.5	175 ± 6.0	160 ± 10.2	180 ± 18.7	170 ± 16.3
	100	137 ± 2.6	121 ± 8.5	149 ± 15.5	154 ± 5.6	176 ± 7.4	215 ± 10.4
	333	115 ± 8.6	110 ± 8.0	141 ± 3.6	174 ± 25.4	190 ± 14.9	199 ± 6.5
	1,000	138 ± 6.4	134 ± 10.4	146 ± 16.0	194 ± 22.8	198 ± 12.1	192 ± 9.0
	3,333	128 ± 0.9	121 ± 15.9	152 ± 2.3	170 ± 14.5	193 ± 10.3	194 ± 18.4
	10,000	148 ± 12.5	141 ± 14.8	153 ± 16.5	173 ± 25.5	196 ± 6.0	199 ± 7.6
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		1,931 ± 109.1	2,102 ± 134.1	1,346 ± 93.5	1,302 ± 28.0	1,070 ± 28.0	558 ± 19.4
TA98	0	13 ± 1.9	18 ± 3.5	27 ± 5.5	19 ± 2.6	28 ± 3.2	18 ± 1.2
	100	13 ± 1.0	15 ± 1.3	30 ± 2.3	22 ± 3.4	32 ± 0.6	20 ± 2.8
	333	19 ± 3.8	12 ± 3.5	28 ± 2.6	21 ± 6.6	32 ± 2.5	23 ± 1.3
	1,000	19 ± 1.2	15 ± 1.5	36 ± 0.9	21 ± 1.5	30 ± 5.3	16 ± 5.7
	3,333	17 ± 3.8	17 ± 0.9	32 ± 3.0	26 ± 2.7	32 ± 1.7	27 ± 5.5
	10,000	26 ± 1.2	17 ± 3.7	39 ± 2.0	18 ± 5.9	36 ± 2.0	20 ± 4.6
Trial summary		Equivocal	Negative	Negative	Negative	Negative	Negative
Positive control		1,278 ± 52.0	1,824 ± 19.1	1,029 ± 20.0	338 ± 7.9	823 ± 16.7	142 ± 10.5

[a] Study performed at SRI, International. The detailed protocol and these data are presented in Zeiger *et al.* (1992).
[b] Revertants are presented as mean ± standard error from three plates.
[c] The positive controls in the absence of metabolic activation were sodium azide (TA100 and TA1535), 9-aminoacridine (TA97), and 4-nitro-*o*-phenylenediamine (TA98). The positive control for metabolic activation with all strains was 2-aminoanthracine.

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

Compound	Dose (μg/mL)	Total Cells	No. of Chromosomes	No. of SCEs	SCEs/ Chromosome	SCEs/ Cell	Hrs in BrdU	Relative Change of SCEs/ Chromosome[b] (%)
-S9								
Trial 1								
Summary: Positive								
Dimethylsulfoxide		50	1,023	435	0.42	8.7	25.7	
Mitomycin-C	0.0015	50	1,027	753	0.73	15.1	25.7	72.43
	0.0100	5	103	265	2.57	53.0	25.7	505.07
Codeine phosphate	1,000	50	1,031	541	0.52	10.8	30.9[c]	23.40*
	1,500	50	1,029	560	0.54	11.2	30.9[c]	27.99*
	2,000	50	1,012	574	0.56	11.5	30.9[c]	33.39*
	2,500	0						
					P<0.001[d]			
Trial 2								
Summary: Positive								
Dimethylsulfoxide		20	409	163	0.39	8.2	25.6	
Mitomycin-C	0.0015	20	404	289	0.71	14.5	25.6	79.49
	0.0100	5	105	252	2.40	50.4	25.6	502.21
Codeine phosphate	1,000	20	400	173	0.43	8.7	25.6	8.52
	1,500	20	409	224	0.54	11.2	32.3[c]	37.42*
	2,000	20	417	236	0.56	11,8	32.3[c]	42.01*
	2,500	0						
					P<0.001			
Trial 3								
Summary: Positive								
Dimethylsulfoxide		20	405	173	0.42	8.7	25.6	
Mitomycin-C	0.0015	20	412	301	0.73	15.1	25.6	71.03
	0.0100	5	103	217	2.10	43.4	25.6	393.21
Codeine phosphate	1,000	20	408	178	0.43	8.9	25.6	2.13
	1,500	20	402	278	0.69	13.9	32.2[c]	61.89*
	2,000	20	414	305	0.73	15.3	32.2[c]	72.47*
	2,500	0						
					P<0.001			

* Positive response (≥20% increase over solvent control)
[a] Study performed at Litton Bionetics, Inc. 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 codeine phosphate induced a delay in the cell division cycle, harvest time was extended to maximize the number of second-division cells available for analysis.

TABLE E2
Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by Codeine Phosphate (continued)

Compound	Dose (μg/mL)	Total Cells	No. of Chromo-somes	No. of SCEs	SCEs/ Chromo-some	SCEs/ Cell	Hrs in BrdU	Relative Change of SCEs/ Chromosome (%)
+S9								
Trial 1								
Summary: Positive								
Dimethylsulfoxide		50	1,029	462	0.44	9.2	25.4	
Cyclophosphamide								
	0.4	50	1,028	733	0.71	14.7	25.4	58.81
	2.0	5	103	177	1.71	35.4	25.4	282.75
Codeine phosphate								
	500	50	1,033	553	0.53	11.1	25.4	19.24
	1,700	50	1,008	603	0.59	12.1	33.9[c]	33.24*
	5,000[e]	50	1,015	742	0.73	14.8	33.9[c]	62.82*
					P<0.001			
Trial 2								
Summary: Positive								
Dimethylsulfoxide		20	403	188	0.46	9.4	25.8	
Cyclophosphamide								
	0.4	20	415	295	0.71	14.8	25.8	52.38
	2.0	5	102	208	2.03	41.6	25.8	337.13
Codeine phosphate[e]								
	8,000	20	413	248	0.60	12.4	31.0[c]	28.72*
	9,000	20	414	269	0.64	13.5	31.0[c]	39.28*
	10,000	20	410	280	0.68	14.0	31.0[c]	46.39*
					P<0.001			
Trial 3								
Summary: Weakly positive								
Dimethylsulfoxide		20	401	232	0.57	11.6	25.6	
Cyclophosphamide								
	0.4	20	401	267	0.66	13.4	25.6	15.09
	2.0	5	103	192	1.86	38.4	25.6	222.20
Codeine phosphate[f]								
	9,000	20	402	269	0.66	13.5	25.6	15.66
	9,500	20	407	279	0.68	14.0	25.6	18.49
	10,000	20	401	309	0.77	15.5	32.2	33.19*
					P<0.001			

[d] Significance of relative SCEs/chromosome tested by the linear regression trend test vs. log of the dose
[e] Acidic pH shift
[f] HEPES buffer used; no acidic pH shift noted at any of the doses tested

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

-S9					+S9				
Dose (μg/mL)	Total Cells	No. of Abs	Abs/ Cell	Cells with Abs (%)	Dose (μg/mL)	Total Cells	No. of Abs	Abs/ Cell	Cells with Abs (%)
Trial 1 - Harvest time: 20.5 hours[b] Summary: Negative					**Trial 1** - Harvest time: 20.5 hours Summary: Negative				
Dimethylsulfoxide					Dimethylsulfoxide				
	100	3	0.03	3.0		100	1	0.01	1.0
Mitomycin-C					Cyclophosphamide				
0.0026	100	15	0.15	14.0	2.5	100	7	0.07	7.0
0.0620	25	13	0.52	40.0	12.5	25	8	0.32	24.0
Codeine phosphate					Codeine phosphate				
2,000	100	0	0.00	0.0	9,000[c]	100	4	0.04	4.0
2,500	100	4	0.04	4.0	9,500	100	3	0.03	3.0
3,000[c]	100	4	0.04	3.0	10,000	100	3	0.03	3.0
				P=0.271[d]					P=0.247
Trial 2 - Harvest time: 20.6 hours Summary: Negative					**Trial 2** - Harvest time: 20.5 hours Summary: Negative				
Dimethylsulfoxide					Dimethylsulfoxide				
	100	3	0.03	3.0		100	0	0.00	0.0
Mitomycin-C					Cyclophosphamide				
0.0250	100	16	0.16	14.0	2.5	100	1	0.01	1.0
0.0625	25	6	0.24	24.0	12.5	25	6	0.24	24.0
Codeine phosphate					Codeine phosphate[e]				
2,500	100	1	0.01	1.0	9,000	100	2	0.02	2.0
3,000[c]	100	2	0.02	2.0	9,500	100	2	0.02	2.0
3,500	0				10,000	100	1	0.01	1.0
				P=0.693					P=0.271

TABLE E3
Induction of Chromosomal Aberrations in Chinese Hamster Ovary Cells by Codeine Phosphate (continued)

	-S9			
Dose (μg/mL)	Total Cells	No. of Abs	Abs/ Cell	Cells with Abs (%)
Trial 3 - Harvest time: 20.6 hours Summary: Negative				
Dimethylsulfoxide				
	100	3	0.03	3.0
Mitomycin-C				
0.0250	100	9	0.09	9.0
0.0625	25	5	0.20	20.0
Codeine phosphate				
3,500	100	3	0.03	3.0
4,000	100	4	0.04	2.0
4,500	100	4	0.04	4.0
5,000	0			
				P=0.404

[a] Study performed at Litton Bionetics, Inc. The detailed protocol is presented in Galloway *et al.* (1987). Abs=aberrations.
[b] Because of significant chemical-induced cell cycle delay, incubation time prior to addition of Colcemid was lengthened to provide sufficient metaphase cells at harvest.
[c] Acidic pH shift at doses of 3,000 μg/mL and higher
[d] Significance of percent cells with aberrations tested by the linear regression trend test vs. log of the dose
[e] HEPES buffer used; no pH shift noted at any doses in this trial

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

TABLE F1 Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 14-Day Feed Study of Codeine 228

TABLE F2 Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 13-Week Feed Study of Codeine 230

TABLE F3 Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats at the 15-Month Interim Evaluation in the 2-Year Feed Study of Codeine 232

TABLE F4 Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 14-Day Feed Study of Codeine 233

TABLE F5 Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 13-Week Feed Study of Codeine 235

TABLE F6 Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice at the 15-Month Interim Evaluation in the 2-Year Feed Study of Codeine 237

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

	0 ppm	1,562 ppm	3,125 ppm	6,250 ppm	12,500 ppm	25,000 ppm
Male						
n	5	5	5	5	4	0
Necropsy body wt	193 ± 5	172 ± 3**	171 ± 4**	151 ± 2**	119 ± 4**	—[b]
Brain						
Absolute	1.719 ± 0.017	1.802 ± 0.111	1.724 ± 0.030	1.654 ± 0.028	1.618 ± 0.017	—
Relative	8.92 ± 0.18	10.53 ± 0.74*	10.13 ± 0.30*	10.93 ± 0.11**	13.64 ± 0.42**	—
Heart						
Absolute	0.633 ± 0.018	0.598 ± 0.021	0.570 ± 0.015**	0.511 ± 0.004**	0.415 ± 0.012**	—
Relative	3.28 ± 0.07	3.49 ± 0.11	3.36 ± 0.15	3.38 ± 0.05	3.49 ± 0.08	—
R. Kidney						
Absolute	0.691 ± 0.022	0.727 ± 0.110	0.594 ± 0.011	0.571 ± 0.016	0.456 ± 0.014**	—
Relative	3.58 ± 0.07	4.26 ± 0.68	3.49 ± 0.12	3.77 ± 0.09	3.84 ± 0.15	—
Liver						
Absolute	8.199 ± 0.258	6.679 ± 0.234**	6.596 ± 0.152**	6.336 ± 0.153**	5.163 ± 0.276**	—
Relative	42.46 ± 0.42	38.90 ± 0.95*	38.79 ± 1.42*	41.87 ± 0.68	43.29 ± 0.78	—
Lung						
Absolute	1.033 ± 0.098	1.527 ± 0.415	0.831 ± 0.015	0.827 ± 0.008	0.658 ± 0.020	—
Relative	5.35 ± 0.50	8.78 ± 2.28	4.89 ± 0.15	5.47 ± 0.13	5.53 ± 0.07	—
R. Testis						
Absolute	1.007 ± 0.062	0.813 ± 0.064*[c]	0.743 ± 0.040**	0.814 ± 0.049**	0.398 ± 0.062**	—
Relative	5.22 ± 0.32	4.81 ± 0.41[c]	4.35 ± 0.18	5.37 ± 0.26	3.31 ± 0.44**	—
Thymus						
Absolute	0.383 ± 0.024	0.420 ± 0.011	0.411 ± 0.012	0.322 ± 0.030	0.096 ± 0.016**	—
Relative	1.98 ± 0.11	2.45 ± 0.07	2.41 ± 0.11	2.13 ± 0.20	0.80 ± 0.11**	—

TABLE F1
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 14-Day Feed Study of Codeine (continued)

	0 ppm	1,562 ppm	3,125 ppm	6,250 ppm	12,500 ppm	25,000 ppm
Female						
n	5	5	5	4	2	0
Necropsy body wt	141 ± 3	140 ± 4	126 ± 5**	128 ± 3*	112 ± 7**	—
Brain						
Absolute	1.627 ± 0.019	1.655 ± 0.021	1.584 ± 0.037	1.605 ± 0.009	1.568 ± 0.138	—
Relative	11.53 ± 0.12	11.86 ± 0.15	12.67 ± 0.56*	12.61 ± 0.29*	13.94 ± 0.40**	—
Heart						
Absolute	0.461 ± 0.012	0.492 ± 0.015	0.448 ± 0.027	0.449 ± 0.009	0.410 ± 0.026	—
Relative	3.27 ± 0.06	3.52 ± 0.07	3.55 ± 0.11	3.53 ± 0.11	3.65 ± 0.02	—
R. Kidney						
Absolute	0.501 ± 0.020	0.512 ± 0.025	0.459 ± 0.019	0.476 ± 0.012	0.480 ± 0.033	—
Relative	3.54 ± 0.08	3.66 ± 0.11	3.66 ± 0.09	3.74 ± 0.03	4.27 ± 0.04**	—
Liver						
Absolute	5.572 ± 0.194	5.915 ± 0.217	4.981 ± 0.292	5.593 ± 0.123	5.338 ± 0.059	—
Relative	39.43 ± 0.79	42.32 ± 0.68	39.54 ± 1.31	43.88 ± 0.61**	47.68 ± 2.32**	—
Lung						
Absolute	0.723 ± 0.035	0.761 ± 0.026	0.709 ± 0.029[c]	0.731 ± 0.033	0.663 ± 0.066	—
Relative	5.12 ± 0.19	5.45 ± 0.14	5.76 ± 0.19[c]	5.74 ± 0.24	5.89 ± 0.23	—
Thymus						
Absolute	0.350 ± 0.015	0.340 ± 0.011	0.265 ± 0.061	0.259 ± 0.016	0.124 ± 0.044**	—
Relative	2.48 ± 0.10	2.44 ± 0.07	2.05 ± 0.42	2.04 ± 0.15	1.08 ± 0.32*	—

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error).
[b] No data calculated due to 100% mortality in this exposure group
[c] n=4

TABLE F2
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 13-Week Feed Study of Codeine[a]

	0 ppm	390 ppm	781 ppm	1,562 ppm	3,125 ppm	6,250 ppm
Male						
n	10	9	10	10	10	10
Necropsy body wt	370 ± 7	343 ± 7*	335 ± 6**	316 ± 7**	300 ± 6**	292 ± 9**
Adrenal Gland						
Absolute	0.045 ± 0.002	0.052 ± 0.002*	0.058 ± 0.002**	0.059 ± 0.002**	0.068 ± 0.002**	0.069 ± 0.003**
Relative	0.12 ± 0.00	0.15 ± 0.01**	0.17 ± 0.01**	0.19 ± 0.00**	0.23 ± 0.00**	0.23 ± 0.01**
Brain						
Absolute	1.992 ± 0.013	1.960 ± 0.027	1.933 ± 0.034	1.946 ± 0.021	1.946 ± 0.026	1.980 ± 0.023
Relative	5.40 ± 0.09	5.74 ± 0.12	5.78 ± 0.10*	6.19 ± 0.12**	6.49 ± 0.11**	6.83 ± 0.17**
Heart						
Absolute	1.063 ± 0.033	0.934 ± 0.020**	0.940 ± 0.015**	0.851 ± 0.020**	0.875 ± 0.031**	0.871 ± 0.035**
Relative	2.88 ± 0.10	2.73 ± 0.08	2.81 ± 0.05	2.70 ± 0.03	2.91 ± 0.06	2.98 ± 0.04
R. Kidney						
Absolute	1.263 ± 0.033	1.103 ± 0.030**	1.043 ± 0.031**	0.968 ± 0.021**	0.990 ± 0.024**	0.963 ± 0.038**
Relative	3.42 ± 0.08	3.22 ± 0.09	3.11 ± 0.06**	3.07 ± 0.04**	3.30 ± 0.06	3.29 ± 0.05
Liver						
Absolute	13.828 ± 0.356	11.453 ± 0.426**	10.466 ± 0.331**	9.306 ± 0.289**	9.538 ± 0.402**	9.537 ± 0.593**
Relative	37.36 ± 0.47	33.36 ± 0.76**	31.22 ± 0.66**	29.44 ± 0.45**	31.65 ± 0.80**	32.45 ± 1.17**
Lung						
Absolute	1.380 ± 0.046	1.273 ± 0.023	1.187 ± 0.044**	1.168 ± 0.049**	1.162 ± 0.035**[b]	1.139 ± 0.044**
Relative	3.73 ± 0.11	3.73 ± 0.10	3.54 ± 0.11	3.70 ± 0.15	3.90 ± 0.08[b]	3.91 ± 0.10
Spleen						
Absolute	0.777 ± 0.016	0.720 ± 0.023	0.709 ± 0.018*	0.636 ± 0.017**	0.611 ± 0.027**	0.568 ± 0.017**
Relative	2.10 ± 0.01	2.10 ± 0.05	2.11 ± 0.02	2.02 ± 0.04	2.03 ± 0.06	1.95 ± 0.03*
R. Testis						
Absolute	1.430 ± 0.020	1.472 ± 0.015	1.431 ± 0.034	1.369 ± 0.039	1.402 ± 0.021	1.416 ± 0.032[b]
Relative	3.87 ± 0.04	4.30 ± 0.07**	4.28 ± 0.11**	4.34 ± 0.11**	4.67 ± 0.06**	4.86 ± 0.12**[b]
Thymus						
Absolute	0.303 ± 0.017	0.287 ± 0.014	0.285 ± 0.014	0.238 ± 0.016**	0.167 ± 0.012**	0.198 ± 0.007**
Relative	0.82 ± 0.05	0.84 ± 0.04	0.85 ± 0.04	0.76 ± 0.06	0.55 ± 0.04**	0.69 ± 0.04**

TABLE F2
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 13-Week Feed Study of Codeine (continued)

	0 ppm	390 ppm	781 ppm	1,562 ppm	3,125 ppm	6,250 ppm
Female						
n	10	10	10	10	10	10
Necropsy body wt	194 ± 5	189 ± 3	192 ± 3	181 ± 3*	175 ± 5**	170 ± 3**
Adrenal Gland						
Absolute	0.051 ± 0.002	0.049 ± 0.002	0.054 ± 0.003	0.055 ± 0.001	0.061 ± 0.003**	0.064 ± 0.002**
Relative	0.26 ± 0.01	0.26 ± 0.01	0.28 ± 0.01	0.31 ± 0.01**	0.35 ± 0.01**	0.38 ± 0.01**
Brain						
Absolute	1.771 ± 0.020[b]	1.790 ± 0.018	1.812 ± 0.023	1.809 ± 0.019	1.810 ± 0.018	1.839 ± 0.015
Relative	9.05 ± 0.16[b]	9.48 ± 0.17	9.44 ± 0.16	10.01 ± 0.16**	10.44 ± 0.27**	10.85 ± 0.16**
Heart						
Absolute	0.585 ± 0.013	0.573 ± 0.011	0.590 ± 0.012	0.571 ± 0.012	0.613 ± 0.019	0.586 ± 0.009
Relative	3.03 ± 0.04	3.03 ± 0.04	3.07 ± 0.06	3.16 ± 0.05	3.52 ± 0.06**	3.46 ± 0.05**
R. Kidney						
Absolute	0.668 ± 0.014	0.636 ± 0.017	0.647 ± 0.009	0.644 ± 0.012	0.649 ± 0.021	0.643 ± 0.009
Relative	3.45 ± 0.04	3.36 ± 0.07	3.37 ± 0.05	3.56 ± 0.06	3.72 ± 0.07**	3.79 ± 0.04**
Liver						
Absolute	6.401 ± 0.212	6.063 ± 0.142	6.337 ± 0.160	5.904 ± 0.187	6.002 ± 0.336	6.325 ± 0.228
Relative	33.00 ± 0.45	32.08 ± 0.71	32.94 ± 0.57	32.55 ± 0.62	34.16 ± 0.97	37.19 ± 0.98**
Lung						
Absolute	0.917 ± 0.030	0.883 ± 0.032[b]	0.889 ± 0.025	0.880 ± 0.011	0.843 ± 0.017[b]	0.881 ± 0.027
Relative	4.74 ± 0.14	4.67 ± 0.17[b]	4.62 ± 0.12	4.87 ± 0.10	4.91 ± 0.10[b]	5.20 ± 0.17
Spleen						
Absolute	0.482 ± 0.016	0.448 ± 0.012	0.477 ± 0.014	0.435 ± 0.010*	0.416 ± 0.016**	0.400 ± 0.017**
Relative	2.48 ± 0.05	2.37 ± 0.05	2.48 ± 0.04	2.40 ± 0.03	2.38 ± 0.02	2.35 ± 0.07
Thymus						
Absolute	0.221 ± 0.003	0.217 ± 0.012	0.214 ± 0.008	0.216 ± 0.006	0.186 ± 0.013**	0.178 ± 0.005**
Relative	1.15 ± 0.03	1.15 ± 0.07	1.11 ± 0.03	1.19 ± 0.03	1.06 ± 0.06	1.05 ± 0.03

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error).
[b] n=9

TABLE F3
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats at the 15-Month Interim Evaluation in the 2-Year Feed Study of Codeine[a]

	0 ppm	400 ppm	800 ppm	1,600 ppm
Male				
n	10	10	10	10
Necropsy body wt	478 ± 6	448 ± 6*	432 ± 9**	392 ± 12**
Adrenal Gland				
Absolute	0.059 ± 0.004	0.061 ± 0.002	0.071 ± 0.003*	0.076 ± 0.005**
Relative	0.12 ± 0.01	0.14 ± 0.00	0.17 ± 0.01**	0.19 ± 0.01**
R. Kidney				
Absolute	1.610 ± 0.042	1.617 ± 0.042	1.560 ± 0.032	1.577 ± 0.042
Relative	3.36 ± 0.07	3.61 ± 0.10	3.62 ± 0.11	4.04 ± 0.09**
Liver				
Absolute	16.732 ± 0.281	14.531 ± 0.442**	13.384 ± 0.384**	12.223 ± 0.568**
Relative	34.98 ± 0.26	32.44 ± 0.99*	31.08 ± 1.05**	31.13 ± 0.96**
Female				
n	10	10	9	9
Necropsy body wt	334 ± 3	313 ± 8*	313 ± 5*	283 ± 7**
Adrenal Gland				
Absolute	0.065 ± 0.003	0.061 ± 0.003	0.066 ± 0.003	0.059 ± 0.004
Relative	0.19 ± 0.01	0.19 ± 0.01	0.21 ± 0.01	0.21 ± 0.01
R. Kidney				
Absolute	1.079 ± 0.027	1.164 ± 0.125	1.077 ± 0.021	0.993 ± 0.029
Relative	3.23 ± 0.07	3.72 ± 0.38	3.45 ± 0.05	3.52 ± 0.05
Liver				
Absolute	9.487 ± 0.159	10.038 ± 0.246	9.790 ± 0.169	8.922 ± 0.419
Relative	28.43 ± 0.48	32.17 ± 0.96**	31.35 ± 0.40*	31.53 ± 1.20*

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

TABLE F4
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 14-Day Feed Study of Codeine[a]

	0 ppm	781 ppm	1,562 ppm	3,125 ppm	6,250 ppm	12,500 ppm
Male						
n	5	5	5	5	5	5
Necropsy body wt	25.2 ± 0.9	25.7 ± 1.0	25.9 ± 1.2	24.4 ± 1.0	24.7 ± 0.8	22.8 ± 0.7
Brain						
Absolute	0.450 ± 0.016	0.448 ± 0.014	0.474 ± 0.006	0.466 ± 0.011	0.457 ± 0.009	0.445 ± 0.010
Relative	17.83 ± 0.20	17.45 ± 0.50	18.41 ± 0.79	19.19 ± 0.44	18.54 ± 0.47	19.62 ± 0.92
Heart						
Absolute	0.114 ± 0.005	0.125 ± 0.008	0.135 ± 0.009	0.121 ± 0.006	0.122 ± 0.006	0.119 ± 0.005
Relative	4.52 ± 0.12	4.88 ± 0.21	5.22 ± 0.17	4.97 ± 0.10	4.93 ± 0.16	5.24 ± 0.28*
R. Kidney						
Absolute	0.202 ± 0.009	0.210 ± 0.009	0.207 ± 0.007	0.203 ± 0.012	0.192 ± 0.010	0.157 ± 0.006**
Relative	8.01 ± 0.22	8.14 ± 0.17	7.99 ± 0.17	8.34 ± 0.34	7.76 ± 0.18	6.94 ± 0.43*
Liver						
Absolute	1.366 ± 0.069	1.299 ± 0.038	1.249 ± 0.059[b]	1.162 ± 0.060**	1.092 ± 0.046**	0.947 ± 0.016**
Relative	54.07 ± 1.31	50.59 ± 0.80*	49.37 ± 0.44**[b]	47.65 ± 0.80**	44.14 ± 0.46**	41.67 ± 1.47**
Lung						
Absolute	0.184 ± 0.016	0.169 ± 0.010	0.189 ± 0.010	0.160 ± 0.003	0.165 ± 0.006	0.153 ± 0.006
Relative	7.25 ± 0.52	6.57 ± 0.32	7.30 ± 0.27	6.62 ± 0.26	6.69 ± 0.03	6.75 ± 0.33
R. Testis						
Absolute	0.097 ± 0.005	0.096 ± 0.005	0.103 ± 0.006	0.098 ± 0.003	0.133 ± 0.031	0.096 ± 0.004
Relative	3.83 ± 0.13	3.74 ± 0.06	3.98 ± 0.09	4.05 ± 0.09	5.47 ± 1.38	4.23 ± 0.27
Thymus						
Absolute	0.038 ± 0.008	0.048 ± 0.009	0.055 ± 0.002	0.045 ± 0.006	0.043 ± 0.003	0.034 ± 0.004
Relative	1.54 ± 0.34	1.88 ± 0.39	2.14 ± 0.18	1.89 ± 0.27	1.76 ± 0.16	1.50 ± 0.19

TABLE F4
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 14-Day Feed Study of Codeine (continued)

	0 ppm	781 ppm	1,562 ppm	3,125 ppm	6,250 ppm	12,500 ppm
Female						
n	5	5	5	5	5	5
Necropsy body wt	18.7 ± 0.3	18.8 ± 0.2	18.2 ± 0.4	20.1 ± 0.5*	19.0 ± 0.2	16.8 ± 0.3**
Brain						
Absolute	0.444 ± 0.006	0.433 ± 0.010	0.450 ± 0.007	0.449 ± 0.011	0.447 ± 0.008	0.450 ± 0.005
Relative	23.78 ± 0.51	23.05 ± 0.59	24.78 ± 0.27	22.37 ± 0.44	23.50 ± 0.15	26.78 ± 0.61**
Heart						
Absolute	0.094 ± 0.003	0.093 ± 0.004	0.093 ± 0.007	0.098 ± 0.004	0.099 ± 0.004	0.084 ± 0.002
Relative	5.01 ± 0.11	4.94 ± 0.16	5.09 ± 0.28	4.86 ± 0.14	5.23 ± 0.19	5.00 ± 0.19
R. Kidney						
Absolute	0.128 ± 0.006	0.138 ± 0.006	0.134 ± 0.006	0.143 ± 0.002	0.134 ± 0.002	0.119 ± 0.002
Relative	6.87 ± 0.29	7.32 ± 0.26	7.36 ± 0.20	7.11 ± 0.12	7.05 ± 0.13	7.05 ± 0.11
Liver						
Absolute	0.941 ± 0.039	0.943 ± 0.026	0.861 ± 0.036	0.954 ± 0.040	0.902 ± 0.030	0.749 ± 0.011**
Relative	50.29 ± 1.33	50.17 ± 1.36	47.33 ± 1.07	47.41 ± 1.29	47.46 ± 1.07	44.55 ± 0.89**
Lung						
Absolute	0.168 ± 0.007	0.154 ± 0.008	0.140 ± 0.004**	0.154 ± 0.004	0.147 ± 0.006	0.147 ± 0.006
Relative	9.00 ± 0.25	8.19 ± 0.45	7.70 ± 0.23*	7.69 ± 0.27*	7.75 ± 0.24*	8.75 ± 0.41
Thymus						
Absolute	0.055 ± 0.006	0.063 ± 0.003	0.062 ± 0.001	0.061 ± 0.002	0.062 ± 0.004	0.056 ± 0.003
Relative	2.98 ± 0.36	3.34 ± 0.15	3.44 ± 0.11	3.06 ± 0.11	3.27 ± 0.19	3.34 ± 0.19

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error).
[b] n=4

TABLE F5
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 13-Week Feed Study of Codeine[a]

	0 ppm	390 ppm	781 ppm	1,562 ppm	3,125 ppm	6,250 ppm
Male						
n	10	10	10	10	8	10
Necropsy body wt	30.8 ± 0.5	31.3 ± 0.4	31.8 ± 0.5	30.9 ± 0.6	30.1 ± 0.5	29.7 ± 0.4
Adrenal Gland						
Absolute	0.005 ± 0.001	0.008 ± 0.001**	0.006 ± 0.000	0.007 ± 0.001	0.006 ± 0.001	0.006 ± 0.000
Relative	0.17 ± 0.02	0.24 ± 0.02*	0.18 ± 0.00	0.21 ± 0.02	0.21 ± 0.02	0.21 ± 0.01
Brain						
Absolute	0.460 ± 0.006	0.464 ± 0.005	0.458 ± 0.005	0.462 ± 0.005	0.466 ± 0.003	0.467 ± 0.004
Relative	14.99 ± 0.24	14.81 ± 0.25	14.44 ± 0.21	14.97 ± 0.25	15.50 ± 0.27	15.74 ± 0.18*
Heart						
Absolute	0.140 ± 0.005	0.143 ± 0.003	0.138 ± 0.004	0.142 ± 0.004	0.145 ± 0.004	0.142 ± 0.003
Relative	4.54 ± 0.11	4.55 ± 0.07	4.36 ± 0.10	4.58 ± 0.08	4.81 ± 0.10	4.78 ± 0.06
R. Kidney						
Absolute	0.273 ± 0.006	0.286 ± 0.008	0.259 ± 0.006	0.257 ± 0.006	0.251 ± 0.007*	0.232 ± 0.005**
Relative	8.89 ± 0.14	9.13 ± 0.23	8.15 ± 0.18*	8.32 ± 0.13*	8.34 ± 0.13*	7.80 ± 0.15**
Liver						
Absolute	1.463 ± 0.041	1.543 ± 0.042	1.549 ± 0.027	1.535 ± 0.029	1.477 ± 0.049	1.461 ± 0.027
Relative	47.51 ± 0.67	49.21 ± 1.08	48.75 ± 0.78	49.71 ± 0.96	49.04 ± 1.17	49.26 ± 0.91
Lung						
Absolute	0.179 ± 0.005	0.182 ± 0.005	0.179 ± 0.004	0.190 ± 0.007	0.183 ± 0.008	0.171 ± 0.003
Relative	5.83 ± 0.15	5.80 ± 0.17	5.63 ± 0.12	6.16 ± 0.20	6.11 ± 0.26	5.77 ± 0.16
Spleen						
Absolute	0.083 ± 0.009	0.098 ± 0.005	0.092 ± 0.003	0.089 ± 0.006	0.099 ± 0.011	0.094 ± 0.005
Relative	2.69 ± 0.26	3.15 ± 0.18	2.89 ± 0.09	2.84 ± 0.16	3.30 ± 0.37	3.15 ± 0.14
R. Testis						
Absolute	0.110 ± 0.002	0.111 ± 0.002	0.114 ± 0.002	0.112 ± 0.005	0.110 ± 0.003	0.104 ± 0.002[b]
Relative	3.58 ± 0.07	3.55 ± 0.08	3.60 ± 0.06	3.60 ± 0.12	3.65 ± 0.09	3.51 ± 0.06[b]
Thymus						
Absolute	0.029 ± 0.003	0.026 ± 0.002	0.020 ± 0.003	0.029 ± 0.003	0.028 ± 0.003	0.033 ± 0.003
Relative	0.96 ± 0.08	0.82 ± 0.07	0.63 ± 0.10*	0.95 ± 0.08	0.93 ± 0.09	1.12 ± 0.08

TABLE F5
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 13-Week Feed Study of Codeine (continued)

	0 ppm	390 ppm	781 ppm	1,562 ppm	3,125 ppm	6,250 ppm
Female						
n	9	10	10	10	10	10
Necropsy body wt	23.9 ± 0.4[c]	25.2 ± 0.4	24.4 ± 0.4	23.8 ± 0.3	24.2 ± 0.3	21.3 ± 0.6**
Adrenal Gland						
Absolute	0.010 ± 0.000	0.011 ± 0.001	0.011 ± 0.001	0.010 ± 0.001	0.010 ± 0.001	0.009 ± 0.001
Relative	0.41 ± 0.02	0.46 ± 0.03	0.44 ± 0.03	0.44 ± 0.03	0.41 ± 0.03	0.43 ± 0.03
Brain						
Absolute	0.472 ± 0.004	0.476 ± 0.004	0.464 ± 0.005	0.468 ± 0.005	0.475 ± 0.007	0.473 ± 0.005
Relative	19.78 ± 0.40	18.94 ± 0.34	19.11 ± 0.45	19.66 ± 0.29	19.64 ± 0.26	22.32 ± 0.57**
Heart						
Absolute	0.109 ± 0.002	0.115 ± 0.002	0.107 ± 0.003	0.112 ± 0.002	0.109 ± 0.002	0.104 ± 0.003
Relative	4.57 ± 0.12	4.59 ± 0.09	4.40 ± 0.08	4.71 ± 0.10	4.51 ± 0.08	4.91 ± 0.13
R. Kidney						
Absolute	0.177 ± 0.003	0.193 ± 0.005	0.180 ± 0.005	0.177 ± 0.004	0.177 ± 0.003	0.166 ± 0.003
Relative	7.42 ± 0.13	7.64 ± 0.14	7.40 ± 0.27	7.40 ± 0.12	7.31 ± 0.13	7.80 ± 0.18
Liver						
Absolute	1.103 ± 0.014	1.217 ± 0.023**	1.152 ± 0.027	1.106 ± 0.030	1.145 ± 0.022	1.065 ± 0.025
Relative	46.19 ± 0.58	48.29 ± 0.66	47.29 ± 1.03	46.34 ± 0.91	47.28 ± 0.66	50.07 ± 0.49**
Lung						
Absolute	0.159 ± 0.005	0.161 ± 0.006	0.164 ± 0.005	0.159 ± 0.006	0.168 ± 0.004	0.163 ± 0.005
Relative	6.64 ± 0.23	6.38 ± 0.17	6.75 ± 0.23	6.66 ± 0.20	6.93 ± 0.14	7.66 ± 0.19**
Spleen						
Absolute	0.073 ± 0.002	0.078 ± 0.003	0.070 ± 0.003	0.070 ± 0.002	0.076 ± 0.003	0.070 ± 0.006
Relative	3.05 ± 0.07	3.09 ± 0.08	2.87 ± 0.11	2.93 ± 0.07	3.12 ± 0.13	3.24 ± 0.22
Thymus						
Absolute	0.031 ± 0.003	0.032 ± 0.003	0.029 ± 0.004	0.025 ± 0.002	0.025 ± 0.003	0.022 ± 0.003
Relative	1.27 ± 0.14	1.25 ± 0.11	1.20 ± 0.15	1.07 ± 0.10	1.03 ± 0.12	1.04 ± 0.14

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error).
[b] n=9
[c] n=10

TABLE F6
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice at the 15-Month Interim Evaluation in the 2-Year Feed Study of Codeine[a]

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
Male				
n	9	10	9	10
Necropsy body wt	51.3 ± 0.6	52.6 ± 0.7	48.1 ± 1.3*	43.9 ± 1.3**
Adrenal Gland				
Absolute	0.008 ± 0.001	0.007 ± 0.001	0.006 ± 0.001	0.009 ± 0.001
Relative	0.16 ± 0.01	0.14 ± 0.02	0.13 ± 0.01	0.20 ± 0.02
R. Kidney				
Absolute	0.448 ± 0.012	0.427 ± 0.011	0.382 ± 0.009**	0.362 ± 0.011**
Relative	8.74 ± 0.23	8.12 ± 0.15	7.97 ± 0.20	8.27 ± 0.27
Liver				
Absolute	2.443 ± 0.093	2.305 ± 0.084	2.230 ± 0.193	2.048 ± 0.181
Relative	47.64 ± 1.78	43.82 ± 1.41	46.20 ± 3.38	46.37 ± 3.35
Female				
n	10	9	9	9
Necropsy body wt	55.1 ± 1.8	56.0 ± 1.5	50.9 ± 2.8	45.8 ± 1.8**
Adrenal Gland				
Absolute	0.011 ± 0.001	0.015 ± 0.001	0.013 ± 0.001	0.013 ± 0.001
Relative	0.21 ± 0.02	0.26 ± 0.03	0.27 ± 0.03	0.29 ± 0.02
R. Kidney				
Absolute	0.302 ± 0.010	0.316 ± 0.007	0.296 ± 0.007	0.274 ± 0.007*
Relative	5.51 ± 0.17	5.66 ± 0.15	5.92 ± 0.24	6.04 ± 0.21
Liver				
Absolute	2.110 ± 0.227	2.079 ± 0.062	1.987 ± 0.081	1.886 ± 0.089
Relative	38.14 ± 3.60	37.15 ± 0.97	39.34 ± 1.00	41.32 ± 1.48

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

APPENDIX G
HEMATOLOGY, CLINICAL CHEMISTRY, AND URINALYSIS RESULTS

TABLE G1 Hematology, Clinical Chemistry, and Urinalysis Data for Rats in the 13-Week Feed Study of Codeine 240
TABLE G2 Hematology, Clinical Chemistry, and Urinalysis Data for Mice in the 13-Week Feed Study of Codeine 242

TABLE G1
Hematology, Clinical Chemistry, and Urinalysis Data for Rats in the 13-Week Feed Study of Codeine[a]

	0 ppm	390 ppm	781 ppm	1,562 ppm	3,125 ppm	6,250 ppm
Male						
Hematology						
n	10	9	10	10	10	9
Hematocrit (%)	44.8 ± 0.6	45.3 ± 0.4	45.5 ± 0.7	45.9 ± 0.2	45.4 ± 1.2	45.7 ± 0.5
Hemoglobin (g/dL)	16.2 ± 0.1	16.5 ± 0.1	16.5 ± 0.1	16.6 ± 0.1**	16.2 ± 0.4	16.3 ± 0.2
Erythrocytes ($10^6/\mu L$)	8.92 ± 0.13	8.51 ± 0.08*	8.41 ± 0.10**	8.41 ± 0.05**	8.24 ± 0.24**	8.31 ± 0.09**
Reticulocytes ($10^6/\mu L$)	0.27 ± 0.02	0.24 ± 0.02	0.20 ± 0.01*	0.19 ± 0.02*	0.22 ± 0.03*	0.20 ± 0.01**
Nucleated erythrocytes ($10^3/\mu L$)	0.01 ± 0.01	0.04 ± 0.02	0.07 ± 0.02	0.04 ± 0.02	0.05 ± 0.02	0.05 ± 0.03
Mean cell volume (fL)	50.3 ± 0.3	53.1 ± 0.4**	54.0 ± 0.4**	54.6 ± 0.2**	55.1 ± 0.2**	55.0 ± 0.2**
Mean cell hemoglobin (pg)	18.1 ± 0.2	19.4 ± 0.2**	19.6 ± 0.2**	19.8 ± 0.1**	19.7 ± 0.1**	19.6 ± 0.2**
Mean cell hemoglobin concentration (g/dL)	36.1 ± 0.4	36.4 ± 0.4	36.3 ± 0.6	36.2 ± 0.3	35.7 ± 0.2	35.7 ± 0.3
Platelets ($10^3/\mu L$)	540.5 ± 14.8	531.4 ± 13.8	503.8 ± 10.9[b]	498.0 ± 9.5*	487.4 ± 9.6**	471.7 ± 14.9**
Leukocytes ($10^3/\mu L$)	6.78 ± 0.34	6.66 ± 0.33	6.29 ± 0.24	6.05 ± 0.37	6.56 ± 0.16	5.44 ± 0.27**
Segmented neutrophils ($10^3/\mu L$)	1.16 ± 0.11	1.11 ± 0.12	0.96 ± 0.05	1.14 ± 0.16	1.31 ± 0.13	0.91 ± 0.08
Lymphocytes ($10^3/\mu L$)	5.24 ± 0.23	5.11 ± 0.24	4.89 ± 0.20	4.62 ± 0.23	4.86 ± 0.21	4.20 ± 0.32**
Monocytes ($10^3/\mu L$)	0.25 ± 0.06	0.36 ± 0.05	0.30 ± 0.04	0.21 ± 0.03	0.29 ± 0.04	0.26 ± 0.04
Eosinophils ($10^3/\mu L$)	0.13 ± 0.03	0.07 ± 0.01	0.12 ± 0.04	0.07 ± 0.02	0.09 ± 0.03	0.06 ± 0.02
Clinical Chemistry						
n	5	4	5	5	5	5
Urea nitrogen (mg/dL)	20.4 ± 1.3	21.5 ± 0.9	21.0 ± 1.5	20.0 ± 1.8	20.2 ± 1.8	23.4 ± 1.5
Creatinine (mg/dL)	0.56 ± 0.02	0.63 ± 0.06	0.50 ± 0.06	0.58 ± 0.04	0.54 ± 0.02	0.56 ± 0.02
Glucose (mg/dL)	185 ± 1	186 ± 13	168 ± 4*	178 ± 9	156 ± 4**	157 ± 5**
Total protein (g/dL)	6.3 ± 0.1	6.9 ± 0.2	6.3 ± 0.1	6.3 ± 0.2	6.4 ± 0.2	6.2 ± 0.3
Albumin (g/dL)	4.5 ± 0.1	4.8 ± 0.1	4.7 ± 0.0	4.7 ± 0.1	4.6 ± 0.1	4.7 ± 0.1
Alanine aminotransferase (IU/L)	73 ± 6	65 ± 3	57 ± 3*	52 ± 6*	56 ± 4*	39 ± 3**
Alkaline phosphatase (IU/L)	248 ± 14	258 ± 24	210 ± 11	192 ± 13*	203 ± 14*	167 ± 16**
Aspartate aminotransferase (IU/L)	143 ± 12	102 ± 13	103 ± 7	102 ± 6*	117 ± 7	97 ± 8*
Urinalysis						
n	10	9	10	10	10	10
Volume (mL/16 hr)	5.1 ± 0.9	3.4 ± 0.9	5.1 ± 0.5	4.2 ± 0.4	5.0 ± 0.7	4.9 ± 0.7
Specific gravity	1.036 ± 0.006	1.048 ± 0.005	1.030 ± 0.002	1.040 ± 0.002	1.043 ± 0.003	1.043 ± 0.003

TABLE G1
Hematology, Clinical Chemistry, and Urinalysis Data for Rats in the 13-Week Feed Study of Codeine (continued)

	0 ppm	390 ppm	781 ppm	1,562 ppm	3,125 ppm	6,250 ppm
Female						
Hematology						
n	10	9	10	10	10	10
Hematocrit (%)	43.6 ± 0.6	45.3 ± 0.7	43.9 ± 0.6	44.3 ± 0.6	43.4 ± 0.6	44.2 ± 0.5
Hemoglobin (g/dL)	16.1 ± 0.1	16.5 ± 0.2	16.1 ± 0.1	16.1 ± 0.2	15.9 ± 0.1	16.0 ± 0.1
Erythrocytes ($10^6/\mu L$)	8.01 ± 0.10	8.26 ± 0.16	7.96 ± 0.12	8.06 ± 0.11	7.80 ± 0.13	7.85 ± 0.10
Reticulocytes ($10^6/\mu L$)	0.20 ± 0.02	0.22 ± 0.01	0.23 ± 0.02	0.19 ± 0.01	0.21 ± 0.02	0.16 ± 0.01
Nucleated erythrocytes ($10^3/\mu L$)	0.01 ± 0.01	0.01 ± 0.01	0.00 ± 0.00	0.01 ± 0.01	0.02 ± 0.01	0.04 ± 0.02[b]
Mean cell volume (fL)	54.5 ± 0.2	55.0 ± 0.3	55.3 ± 0.3*	54.9 ± 0.3	55.5 ± 0.4*	56.4 ± 0.3**
Mean cell hemoglobin (pg)	20.2 ± 0.3	20.1 ± 0.2	20.3 ± 0.3	20.0 ± 0.3	20.4 ± 0.3	20.4 ± 0.2
Mean cell hemoglobin concentration (g/dL)	37.0 ± 0.6	36.5 ± 0.3	36.8 ± 0.5	36.4 ± 0.5	36.7 ± 0.4	36.3 ± 0.3
Platelets ($10^3/\mu L$)	562.4 ± 28.5	591.0 ± 17.8	589.0 ± 13.8	553.4 ± 12.4	515.5 ± 12.1	578.8 ± 18.5
Leukocytes ($10^3/\mu L$)	5.64 ± 0.29	5.50 ± 0.32	5.94 ± 0.42	4.64 ± 0.21*	4.41 ± 0.22**	3.76 ± 0.26**[b]
Segmented neutrophils ($10^3/\mu L$)	1.13 ± 0.12	1.03 ± 0.07	1.33 ± 0.14	0.79 ± 0.11	0.71 ± 0.07*	0.64 ± 0.06**[b]
Lymphocytes ($10^3/\mu L$)	4.32 ± 0.24	4.18 ± 0.30	4.36 ± 0.33	3.65 ± 0.13	3.53 ± 0.20*	2.95 ± 0.25**[b]
Monocytes ($10^3/\mu L$)	0.15 ± 0.03	0.20 ± 0.03	0.22 ± 0.04	0.14 ± 0.02	0.12 ± 0.02	0.12 ± 0.02[b]
Eosinophils ($10^3/\mu L$)	0.05 ± 0.01	0.07 ± 0.02	0.03 ± 0.01	0.07 ± 0.02	0.05 ± 0.01	0.05 ± 0.01[b]
Clinical Chemistry						
n	5	5	5	5	5	5
Urea nitrogen (mg/dL)	18.4 ± 0.7	20.2 ± 1.2	21.8 ± 1.5	19.4 ± 1.6	17.8 ± 0.7	21.8 ± 0.6
Creatinine (mg/dL)	0.40 ± 0.04[c]	0.46 ± 0.08	0.42 ± 0.05	0.46 ± 0.05	0.44 ± 0.02	0.48 ± 0.02
Glucose (mg/dL)	169 ± 4	159 ± 4	147 ± 4*	154 ± 6	168 ± 6	156 ± 5
Total protein (g/dL)	5.6 ± 0.1[c]	5.5 ± 0.1	5.8 ± 0.2	5.7 ± 0.2	5.6 ± 0.1	5.9 ± 0.1
Albumin (g/dL)	4.4 ± 0.1[c]	4.3 ± 0.0	4.5 ± 0.1	4.6 ± 0.1	4.4 ± 0.1	4.8 ± 0.1
Alanine aminotransferase (IU/L)	52 ± 4	58 ± 5	53 ± 3	49 ± 5	50 ± 3	42 ± 4
Alkaline phosphatase (IU/L)	216 ± 18	197 ± 12	191 ± 11	216 ± 10	260 ± 21	215 ± 14
Aspartate aminotransferase (IU/L)	97 ± 7	103 ± 2	88 ± 4	93 ± 4	104 ± 4	83 ± 7
Urinalysis						
n	9	10	10	10	10	10
Volume (mL/16 hr)	3.1 ± 0.6	2.5 ± 0.4	1.9 ± 0.2	1.8 ± 0.4	3.3 ± 1.4	2.7 ± 0.6
Specific gravity	1.027 ± 0.004	1.035 ± 0.003	1.039 ± 0.003*[b]	1.050 ± 0.005**	1.045 ± 0.005**	1.044 ± 0.003**

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error. Statistical tests were performed on unrounded data.
[b] n=9
[c] n=4

TABLE G2
Hematology, Clinical Chemistry, and Urinalysis Data for Mice in the 13-Week Feed Study of Codeine[a]

	0 ppm	390 ppm	781 ppm	1,562 ppm	3,125 ppm	6,250 ppm
Male						
n	9	10	10	10	8	10
Hematology						
Hematocrit (%)	46.8 ± 0.8	46.2 ± 0.9	45.8 ± 0.6	48.1 ± 1.0	45.7 ± 1.1	46.0 ± 0.8
Hemoglobin (g/dL)	15.7 ± 0.2	15.7 ± 0.3	15.5 ± 0.3	16.2 ± 0.4	15.7 ± 0.4	15.6 ± 0.3
Erythrocytes ($10^6/\mu L$)	9.32 ± 0.15	9.20 ± 0.19	9.18 ± 0.12	9.36 ± 0.14	9.10 ± 0.14	8.98 ± 0.12
Reticulocytes ($10^6/\mu L$)	0.24 ± 0.02	0.25 ± 0.02[b]	0.18 ± 0.03	0.29 ± 0.03	0.27 ± 0.04	0.29 ± 0.03
Nucleated erythrocytes ($10^3/\mu L$)	0.01 ± 0.01	0.01 ± 0.01	0.02 ± 0.01	0.00 ± 0.00	0.04 ± 0.04	0.01 ± 0.01
Mean cell volume (fL)	50.3 ± 0.3	50.3 ± 0.5	50.0 ± 0.3	51.3 ± 0.5	50.1 ± 0.7	51.3 ± 0.3
Mean cell hemoglobin (pg)	16.8 ± 0.2	17.1 ± 0.2	16.9 ± 0.2	17.3 ± 0.2	17.2 ± 0.2	17.4 ± 0.2
Mean cell hemoglobin concentration (g/dL)	33.5 ± 0.3	34.1 ± 0.2	33.7 ± 0.3	33.7 ± 0.2	34.4 ± 0.3	33.9 ± 0.2
Platelets ($10^3/\mu L$)	893.6 ± 35.5	964.1 ± 45.4	873.0 ± 61.2	976.9 ± 40.9	904.6 ± 39.1	939.7 ± 46.1
Leukocytes ($10^3/\mu L$)	4.06 ± 0.41	3.97 ± 0.42	4.74 ± 0.99	4.68 ± 0.59	4.60 ± 0.83	3.09 ± 0.22
Segmented neutrophils ($10^3/\mu L$)	1.01 ± 0.23	1.31 ± 0.18[b]	2.58 ± 1.00	1.34 ± 0.24[b]	1.74 ± 0.66	0.86 ± 0.08
Lymphocytes ($10^3/\mu L$)	2.84 ± 0.24	2.15 ± 0.23	1.92 ± 0.34	2.64 ± 0.27	2.65 ± 0.50	2.09 ± 0.20
Monocytes ($10^3/\mu L$)	0.08 ± 0.03	0.10 ± 0.03	0.10 ± 0.03	0.09 ± 0.03	0.05 ± 0.03	0.03 ± 0.01
Eosinophils ($10^3/\mu L$)	0.12 ± 0.03	0.13 ± 0.03	0.09 ± 0.02[b]	0.12 ± 0.03	0.16 ± 0.05	0.11 ± 0.02
Clinical Chemistry						
Urea nitrogen (mg/dL)	20.6 ± 1.1	22.1 ± 1.1[b]	22.0 ± 1.9	19.1 ± 2.2	18.1 ± 2.0	26.8 ± 1.1*
Creatinine (mg/dL)	0.31 ± 0.03	0.28 ± 0.02[b]	0.29 ± 0.03	0.28 ± 0.03	0.27 ± 0.04[c]	0.34 ± 0.04
Glucose (mg/dL)	193 ± 4	178 ± 7	192 ± 9	190 ± 5	197 ± 7	160 ± 8*
Total protein (g/dL)	4.7 ± 0.1	4.8 ± 0.1	4.8 ± 0.1	4.7 ± 0.1	4.8 ± 0.2	4.8 ± 0.2
Albumin (g/dL)	3.4 ± 0.1	3.3 ± 0.1	3.7 ± 0.2	3.3 ± 0.1	3.6 ± 0.1	3.5 ± 0.1
Alanine aminotransferase (IU/L)	45 ± 4	38 ± 5	53 ± 8	40 ± 2	32 ± 2	42 ± 6
Alkaline phosphatase (IU/L)	61 ± 2	59 ± 3	59 ± 3	67 ± 3	67 ± 7	74 ± 2**
Aspartate aminotransferase (IU/L)	134 ± 28	89 ± 24	109 ± 20	94 ± 17	63 ± 11*	69 ± 9
Urinalysis						
n	9	10	10	10	6	8
Volume (mL/16 hr)	1.0 ± 0.1	1.2 ± 0.1	1.3 ± 0.1	0.7 ± 0.2	0.9 ± 0.2	0.8 ± 0.2
Specific gravity	1.045 ± 0.004	1.045 ± 0.002	1.032 ± 0.003	1.045 ± 0.006[c]	1.046 ± 0.007	1.035 ± 0.004[c]

TABLE G2
Hematology, Clinical Chemistry, and Urinalysis Data for Mice in the 13-Week Feed Study of Codeine (continued)

	0 ppm	390 ppm	781 ppm	1,562 ppm	3,125 ppm	6,250 ppm
Female						
n	9	10	10	10	10	10
Hematology						
Hematocrit (%)	49.1 ± 1.1	49.3 ± 1.0	51.8 ± 1.0	49.8 ± 0.7	51.3 ± 0.8[b]	47.9 ± 0.8
Hemoglobin (g/dL)	16.7 ± 0.2	17.0 ± 0.2	17.4 ± 0.3	17.1 ± 0.2	17.4 ± 0.3	16.0 ± 0.3
Erythrocytes ($10^6/\mu L$)	9.81 ± 0.16	9.68 ± 0.21	10.14 ± 0.17	9.77 ± 0.07	9.87 ± 0.11[b]	9.45 ± 0.13
Reticulocytes ($10^6/\mu L$)	0.19 ± 0.03	0.25 ± 0.05	0.26 ± 0.03	0.23 ± 0.03	0.24 ± 0.03[b]	0.30 ± 0.06
Nucleated erythrocytes ($10^3/\mu L$)	0.00 ± 0.00	0.01 ± 0.01[b]	0.02 ± 0.02	0.00 ± 0.00	0.01 ± 0.01	0.00 ± 0.00
Mean cell volume (fL)	50.2 ± 0.5	51.0 ± 0.3	50.9 ± 0.5	51.1 ± 0.6	51.9 ± 0.4[b]	50.7 ± 0.3
Mean cell hemoglobin (pg)	17.0 ± 0.2	17.7 ± 0.4	17.2 ± 0.3	17.5 ± 0.2	17.4 ± 0.2[b]	16.9 ± 0.1
Mean cell hemoglobin concentration (g/dL)	34.0 ± 0.5	34.6 ± 0.7	33.6 ± 0.5	34.4 ± 0.4	33.5 ± 0.3[b]	33.3 ± 0.2
Platelets ($10^3/\mu L$)	720.3 ± 22.6[d]	782.4 ± 19.1	799.9 ± 10.1*[b]	767.6 ± 12.2[b]	786.8 ± 16.4[b]	801.4 ± 20.7
Leukocytes ($10^3/\mu L$)	2.88 ± 0.17	4.19 ± 0.59[b]	3.08 ± 0.54	3.26 ± 0.32	3.63 ± 0.47	3.25 ± 0.36
Segmented neutrophils ($10^3/\mu L$)	0.37 ± 0.06	0.69 ± 0.13[b]	0.31 ± 0.04	0.50 ± 0.10	0.85 ± 0.12*	0.61 ± 0.12
Lymphocytes ($10^3/\mu L$)	2.41 ± 0.15	3.35 ± 0.47[b]	2.65 ± 0.51	2.60 ± 0.30	2.67 ± 0.36	2.50 ± 0.29
Monocytes ($10^3/\mu L$)	0.03 ± 0.01	0.08 ± 0.03[b]	0.06 ± 0.01	0.06 ± 0.01	0.05 ± 0.02	0.07 ± 0.03
Eosinophils ($10^3/\mu L$)	0.06 ± 0.02	0.07 ± 0.02[b]	0.07 ± 0.02	0.10 ± 0.02	0.06 ± 0.02	0.07 ± 0.02
Clinical Chemistry						
Urea nitrogen (mg/dL)	19.0 ± 1.8	15.0 ± 0.8	17.3 ± 1.8[b]	13.3 ± 1.0*	13.8 ± 1.0*	16.6 ± 3.9*[c]
Creatinine (mg/dL)	0.31 ± 0.02	0.28 ± 0.02	0.25 ± 0.03[d]	0.29 ± 0.01[b]	0.34 ± 0.02	0.26 ± 0.02[c]
Glucose (mg/dL)	191 ± 3	194 ± 4	187 ± 8	194 ± 10	188 ± 6	199 ± 6[d]
Total protein (g/dL)	4.77 ± 0.05	4.60 ± 0.07	4.53 ± 0.16	4.74 ± 0.13	4.63 ± 0.10	4.90 ± 0.09[e]
Albumin (g/dL)	3.7 ± 0.1	3.8 ± 0.1	3.6 ± 0.2	3.9 ± 0.1	3.9 ± 0.1	4.1 ± 0.1**[c]
Alanine aminotransferase (IU/L)	44 ± 6	52 ± 12	42 ± 10[b]	27 ± 3	29 ± 3	42 ± 10
Alkaline phosphatase (IU/L)	80 ± 3	72 ± 3	73 ± 7	84 ± 6	74 ± 3	89 ± 6[b]
Aspartate aminotransferase (IU/L)	98 ± 12	75 ± 11	80 ± 14[b]	67 ± 5	71 ± 14	72 ± 8[d]
Urinalysis						
n	10	10	10	8	9	8
Volume (mL/16 hr)	0.4 ± 0.1	0.5 ± 0.1	0.3 ± 0.0	0.5 ± 0.1	0.4 ± 0.1	0.4 ± 0.1
Specific gravity	1.036 ± 0.005[d]	1.033 ± 0.004[b]	1.036 ± 0.004[d]	1.027 ± 0.003	1.034 ± 0.004[c]	1.028 ± 0.006

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error. Statistical tests were performed on unrounded data.
[b] n=9
[c] n=7
[d] n=8
[e] n=6

APPENDIX H
REPRODUCTIVE TISSUE EVALUATIONS AND ESTROUS CYCLE CHARACTERIZATION

TABLE H1 Summary of Reproductive Tissue Evaluations and Estrous Cycle Characterization for Rats in the 13-Week Feed Study of Codeine 246
TABLE H2 Summary of Reproductive Tissue Evaluations and Estrous Cycle Characterization for Mice in the 13-Week Feed Study of Codeine 247

TABLE H1
Summary of Reproductive Tissue Evaluations and Estrous Cycle Characterization for Rats in the 13-Week Feed Study of Codeine[a]

	0 ppm	1,562 ppm	3,125 ppm	6,250 ppm
Male				
n	10	10	10	10
Weights (g)				
Necropsy body wt	370 ± 7	316 ± 7**	300 ± 6**	292 ± 9**
R. cauda	0.211 ± 0.005	0.204 ± 0.006	0.208 ± 0.005	0.190 ± 0.008
R. epididymis	0.458 ± 0.008	0.436 ± 0.013	0.453 ± 0.007	0.439 ± 0.008
R. testis	1.430 ± 0.020	1.369 ± 0.039	1.402 ± 0.021	1.416 ± 0.032[b]
Concentration				
(10^6/g cauda epididymal tissue)	628.9 ± 55.3	629.1 ± 40.8	552.6 ± 43.8	566.3 ± 61.1
Motility (%)	74.16 ± 3.20	83.94 ± 1.75	70.89 ± 4.32	51.58 ± 6.62
Epididymal spermatozoal parameters (per 500 sperm)				
Normal	495.5 ± 1.0	495.9 ± 0.5	495.1 ± 0.9	493.7 ± 0.8
Amorphous	0.500 ± 0.307	0.200 ± 0.133	0.700 ± 0.213	0.600 ± 0.221
Excessive hook	0.800 ± 0.249	0.500 ± 0.224	1.000 ± 0.333	0.800 ± 0.327
No hook	2.40 ± 0.54	2.50 ± 0.50	2.90 ± 0.66	3.90 ± 0.67
Pin-head	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Short-headed	0.800 ± 0.291	0.900 ± 0.277	0.200 ± 0.133	1.000 ± 0.258
Two tails or heads	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Abnormal (%)	0.900 ± 0.209	0.820 ± 0.092	0.980 ± 0.180	1.260 ± 0.161
Female				
n	10	10	10	10
Necropsy body wt (g)	194 ± 5	181 ± 3*	175 ± 5**	170 ± 3**
Estrous cycle length (days)	4.88 ± 0.30[c]	4.71 ± 0.42[d]	4.60 ± 0.24[e]	4.20 ± 0.49[e]
Estrous stage (% of cycle)				
Diestrus	32.9	34.3	40.0	32.9
Proestrus	22.9	21.4	20.0	28.6
Estrus	30.0	28.6	22.9	27.1
Metestrus	14.3	15.7	14.3	11.4
Uncertain diagnoses	0.0	0.0	2.9	0.0

* Significantly different ($P \leq 0.05$) from the control group by Williams' test (body weight)
** $P \leq 0.01$
[a] Data are presented as mean ± standard error.
[b] n=9
[c] Estrous cycle longer than 7 days or unclear in 2 of 10 animals
[d] Estrous cycle longer than 7 days or unclear in 3 of 10 animals
[e] Estrous cycle longer than 7 days or unclear in 5 of 10 animals

TABLE H2
Summary of Reproductive Tissue Evaluations and Estrous Cycle Characterization for Mice in the 13-Week Feed Study of Codeine[a]

	0 ppm	1,562 ppm	3,125 ppm	6,250 ppm
Male				
n	9	10	7	9
Weights (g)				
Necropsy body wt	30.7 ± 0.6	30.9 ± 0.6	30.1 ± 0.5[b]	29.7 ± 0.4[c]
R. cauda	0.015 ± 0.001	0.015 ± 0.001	0.016 ± 0.001[b]	0.014 ± 0.001[c]
R. epididymis	0.041 ± 0.002	0.042 ± 0.002	0.040 ± 0.002[b]	0.040 ± 0.002[c]
R. testis	0.110 ± 0.002[c]	0.112 ± 0.005	0.110 ± 0.003[b]	0.104 ± 0.002
Concentration				
(10^6/g cauda epididymal tissue)	1,221 ± 121	1,122 ± 84	1,164 ± 161	1,202 ± 81[c]
Motility (%)	78.44 ± 5.94	65.34 ± 5.19**	79.63 ± 1.43[b]	66.20 ± 6.55[c]
Epididymal spermatozoal parameters (per 500 sperm)				
Normal	494.4 ± 1.0	493.6 ± 1.1[d]	494.0 ± 1.0	493.4 ± 1.0
Amorphous	2.11 ± 0.42	1.67 ± 0.33[d]	2.29 ± 0.29	2.22 ± 0.62
Blunt hook	0.667 ± 0.289	0.556 ± 0.377[d]	0.429 ± 0.297	0.778 ± 0.465
Banana	2.33 ± 0.65	3.33 ± 0.41[d]	2.43 ± 0.69	2.44 ± 0.50
Pin-head	0.111 ± 0.111	0.000 ± 0.000[d]	0.000 ± 0.000	0.000 ± 0.000
Short-headed	0.222 ± 0.147	0.778 ± 0.364[d]	0.857 ± 0.553	1.000 ± 0.289
Two tails or heads	0.000 ± 0.000	0.111 ± 0.111[d]	0.000 ± 0.000	0.000 ± 0.000
Abnormal (%)	1.11 ± 0.20	1.37 ± 0.21	1.20 ± 0.21	1.32 ± 0.17[c]
Female				
n	10	10	10	10
Necropsy body wt (g)	23.9 ± 0.4[d]	23.8 ± 0.3	24.2 ± 0.3	21.3 ± 0.6**
Estrous cycle length (days)	4.70 ± 0.26	5.57 ± 0.20[e]	5.33 ± 0.42[f]	5.43 ± 0.20[e]
Estrous stage (% of cycle)				
Diestrus	17.1	31.4	41.4	34.3
Proestrus	30.0	15.7	15.7	18.6
Estrus	35.7	34.3	27.1	32.9
Metestrus	17.7	14.3	15.7	14.3
Uncertain diagnoses	0.0	4.3	0.0	0.0

** Significantly different ($P \leq 0.01$) from the control group by Williams' (body weight) or Dunn's test (motility)
[a] Data are presented as mean ± standard error.
[b] n=8
[c] n=10
[d] n=9
[e] Estrous cycle longer than 7 days or unclear in 3 of 10 animals
[f] Estrous cycle longer than 7 days or unclear in 4 of 10 animals

APPENDIX I
CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

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CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

PROCUREMENT AND CHARACTERIZATION OF CODEINE

Codeine was obtained from Penick Corporation (Newark, NJ) in two lots (471NFN003 and 471NIN001/A). Lot 471NFN003 was used during the 14-day and 13-week studies, and lot 471NIN001/A was used during the 2-year studies. 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 codeine studies are on file at the National Institute of Environmental Health Sciences (NIEHS).

Both lots of the chemical, a white powder, were identified as codeine by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. All spectra were consistent with those expected for the structure and with the literature spectra (*Sadtler Standard Spectra*; Jacobson *et al.*, 1972; CRC, 1975) of codeine (Figures I1 and I2). The observed melting point ranges, 155.4° to 156.8° C for lot 471NIN001/A and 154° to 158° C for lot 471NFN003, and the specific optical activities, $[\alpha]_D^{27} = -117.1 \pm 0.1°$ for lot 471NIN001/A and $[\alpha]_D^{32} = -120.0 \pm 0.6°$ for lot 471NFN003, were consistent with the literature reference (*Merck Index*, 1983).

The purity of each lot was determined by elemental analyses, Karl Fischer water analysis, functional group titration, thin-layer chromatography (TLC), and gas chromatography. For functional group titration, samples of codeine were dissolved in 25 mL glacial acetic acid and titrated with 0.1 N perchloric acid in glacial acetic acid and monitored potentiometrically using a combination pH/mV electrode filled with 4 M potassium chloride. TLC was performed on Silica Gel 60 F-254 plates with two solvent systems: 1) methanol and 2) carbon tetrachloride:*n*-butanol:methanol:6 N ammonium hydroxide (40:30:30:2). Caffeine was used as a reference standard. Plates were examined with visible and ultraviolet light (254 and 366 nm) and with a spray of iodoplatinate reagent. Gas chromatography was performed using a flame ionization detector with a nitrogen carrier gas at a flow rate of 70 mL/minute. Two systems were used:

A) 1% SP-2100 on 100/120 Supelcoport (1.8 m × 4 mm ID) glass column, with an oven temperature program of 100° C for 5 minutes, then 100° to 250° C at 10° C per minute, and

B) 1% Dexsil 300 on 100/120 Supelcoport (1.8 m × 4 mm ID) glass column, with an oven temperature program of 100° C for 5 minutes, then 100° to 350° C at 10° C per minute.

Generally, elemental analyses for carbon, hydrogen, and nitrogen were in agreement with the theoretical values for codeine; however, the hydrogen value for lot 471NFN003 was higher than the theoretical value and the carbon value was slightly lower. Karl Fischer water analysis indicated 1.98% ± 0.07% water in lot 471NFN003 and 4.66% ± 0.05% water in lot 471NIN001/A. Functional group titration indicated a purity (anhydrous basis) of 100.0% ± 0.5% for lot 471NFN003 and 99.8% ± 0.8% for lot 471NIN001/A. For both lots, TLC by system 1 indicated one major spot and no impurities, and TLC by system 2 indicated one major spot and one slight trace impurity. Gas chromatography using system A indicated one major peak and one impurity with an area greater than 0.1% relative to the major peak for both lots, and system B indicated one major peak and no impurities. Concomitant gas chromatography with a reference sample of lot 471NFN003 using system A with an oven temperature of 170° C to 250° C at 10° C per minute indicated that lot 471NIN001/A had a purity of 97.4% ± 0.4% relative to lot 471NFN003. The overall purity of each lot was determined to be at least 99% on an anhydrous basis.

The analytical chemistry laboratory analyzed lot 471NFN003 to determine if it met United States Pharmacopeia XX (USP) purity requirements. The complete battery of USP analyses was performed as a supplement to the chemical characterization of codeine. The chemical met the USP requirements for the identification tests, which included ultraviolet/visible absorption spectroscopy, a selenious acid color test, and an organic nitrogenous bases test. The melting range was determined to be 154.1° to 156.1° C. Weight loss on drying was 1.90% ± 0.01%. The residue on ignition was 0.022% ± 0.006%. Test for readily carbonizable substances and morphine met USP specifications. The titrimetric purity assay indicated that lot 471NFN003 contained 100.0% ± 0.6% codeine, which met USP requirements for purity.

Stability studies of the bulk chemical (lot 471NFN003) were performed by the analytical chemistry laboratory. Gas chromatography was performed using system A for the purity analysis except with an oven temperature program of 170° to 250° C at 10° C per minute. These studies indicated that codeine was stable as a bulk chemical for 2 weeks when stored protected from light at temperatures up to 25° C. To ensure stability, the bulk chemical was stored at approximately 20° C, in the dark, in sealed amber glass bottles in a secure cabinet. The stability of the bulk chemical was monitored by the study laboratories prior to the start of the 14-day and 13-week studies, once during the 13-week studies, and at least every 4 months during the 2-year studies using functional group titration and/or gas chromatography. No degradation of the bulk chemical was observed.

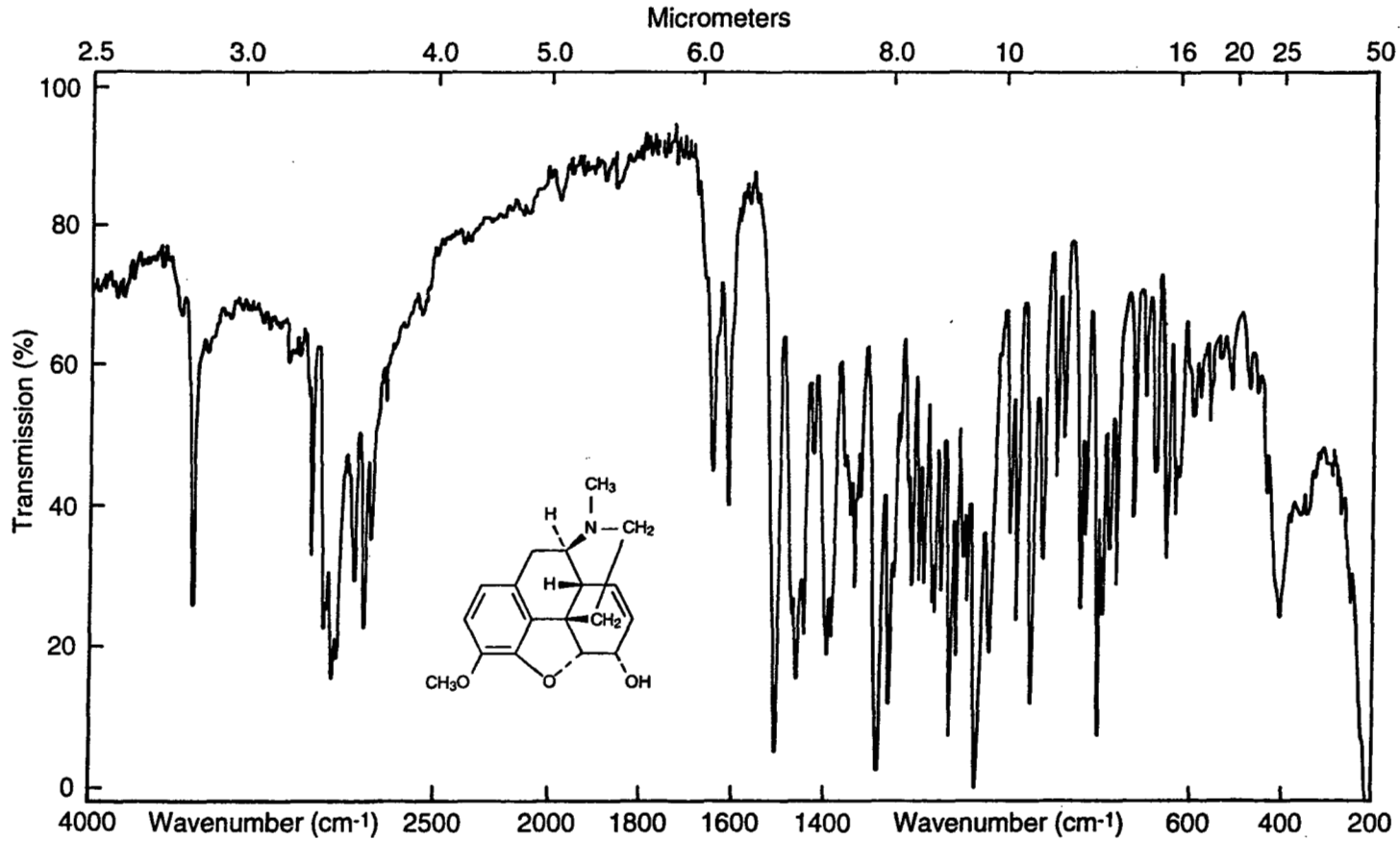
Preparation and Analysis of Dose Formulations

The dose formulations were prepared weekly by mixing codeine with feed (Table I1). Mixtures were made by preparing a codeine/feed premix by hand, which was then blended with feed for 15 minutes using an intensifier bar. Formulations were stored in double plastic bags at 4° C (14-day, 13-week, and beginning of the 2-year studies) or at room temperature (end of 2-year study) for up to 3 weeks. Bags in use were transferred to the study room in covered plastic buckets.

Homogeneity and stability studies of a 160 and a 30,000 ppm (homogeneity only) formulation were performed by the analytical chemistry laboratory. Extracts were prepared by mixing samples in a methanol:water solution (70:30) containing 0.9% hydrochloric acid and clarified by centrifugation. For the 30,000 ppm dose formulation, aliquots of the extracts were mixed with 4 mL of internal standard solution (3 mg propiophenone/mL methanol) and diluted with a water:methanol solution (37:63) containing 1% glacial acetic acid and 0.005 M sodium heptane sulfonate. High-performance liquid chromatography (HPLC) was performed with a Brownlee RP-18 (10 μ, 100 mm × 4.6 mm ID) column using ultraviolet detection (280 nm) and a mobile phase solvent system of water:methanol (63:37) containing 1% glacial acetic acid and 0.005 M sodium heptane sulfonate. The flow rate was 1.0 mL/minute. For the 160 ppm dose formulation, 20 mL aliquots of the extracts were mixed with 20 mL water and 20 mL methylene chloride and centrifuged to separate the phases. Aliquots (25 mL) of the top layers were mixed with 2 mL portions of 1 N sodium hydroxide and 20 mL methylene chloride and centrifuged after which the top layers were removed by aspiration. Aliquots of the methylene chloride layers were evaporated. The residues were dissolved in 3 mL of internal standard solution (0.12 mg propiophenone/mL methanol) and mixed with 7 mL of water:glacial acetic acid solution (99:1) containing 0.005 M sodium heptane sulfonate. The solutions were then analyzed using the HPLC system described previously. Homogeneity was confirmed, and the stability of the dose formulations was confirmed for up to 3 weeks when stored in the dark at room temperature.

Periodic analyses of the dose formulations of codeine were conducted at the study laboratory and analytical chemistry laboratory using HPLC. Dose formulations were analyzed at the beginning of the 14-day studies (Table I2) and at the beginning, midpoint, and end of the 13-week studies (Table I3). All

dose formulations for the 14-day and 13-week studies were within 10% of the target concentrations. During the 2-year studies, dose formulations were analyzed every 6 to 10 weeks (Table I4). Of the dose formulations analyzed for the 2-year rat study, 97% (86/89) were within 10% of the target concentration. Two dose formulations were remixed, and no dose formulation more than 10% from the target concentration was used. Of the dose formulations analyzed for the 2-year mouse study, 100% (40/40) were within 10% of the target concentration. Results of periodic referee analyses performed by the analytical chemistry laboratory indicated good agreement with the results obtained by the study laboratory (Table I5).

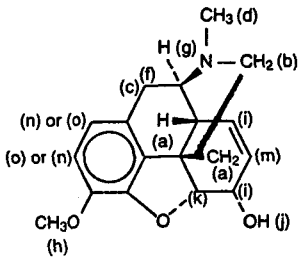


ABSCISSA	ORDINATE	SCAN TIME 12 min	REP. SCAN — SINGLE BEAM —
EXPANSION 1	EXPANSION 1	RESPONSE 1	TIME DRIVE — PRE SAMPLE CHOP —
SUPPRESSION Off	% T 0-100% ABS —	SLIT PROGRAM Normal (6)	OPERATOR T. Pederson DATE 7/9/86
SAMPLE Codeine	REMARKS Reference beam attenuated with IR die	SOLVENT —	CELL PATH KBr Disc
Batch No.: 03			
Lot No.: 471 NIN 001/A		CONCENTRATION 2% (w/w) in KBr	REFERENCE 250 N
Task No.: RE-1768			
Project No.: 8403-68			

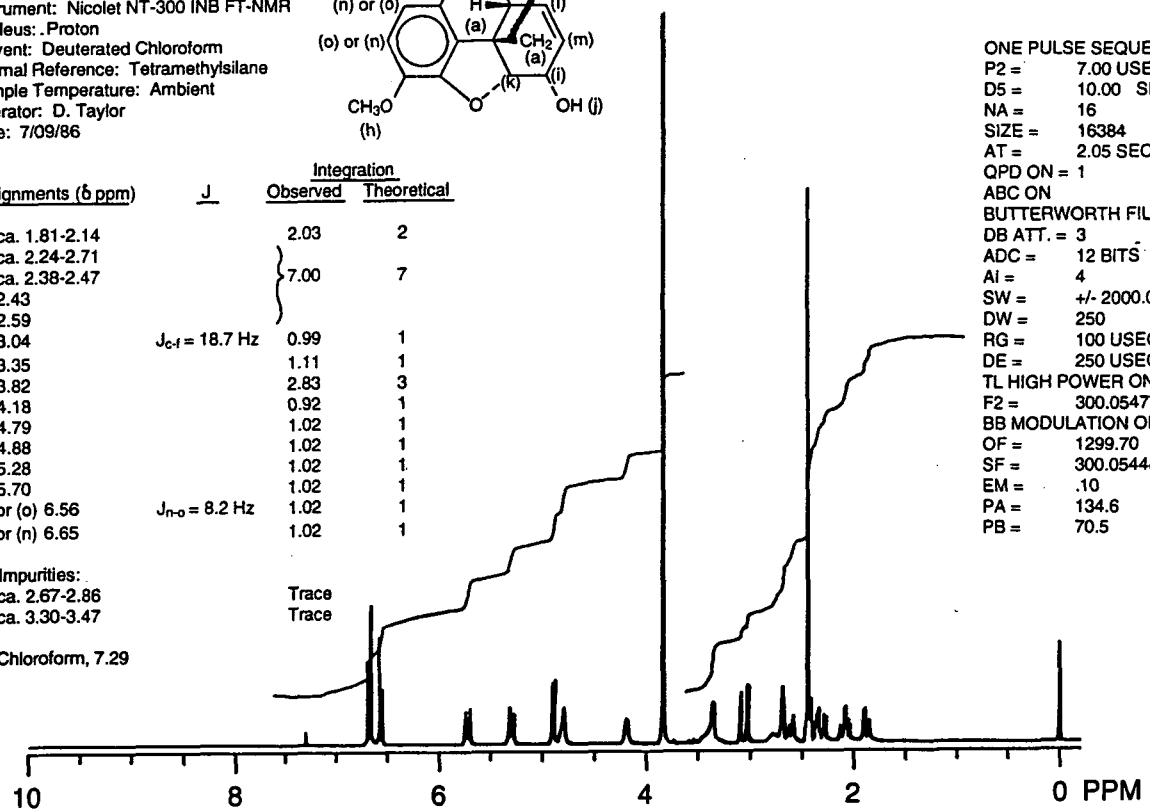
FIGURE 11
Infrared Absorption Spectrum of Codeine

Codeine
Lot No.: 471 NIN 001/A
Batch No.: 03
Project No.: 8403-68

Instrument: Nicolet NT-300 INB FT-NMR
Nucleus: Proton
Solvent: Deuterated Chloroform
Internal Reference: Tetramethylsilane
Sample Temperature: Ambient
Operator: D. Taylor
Date: 7/09/86



Assignments (δ ppm)	J	Integration Observed	Integration Theoretical
(a) ca. 1.81-2.14		2.03	2
(b) ca. 2.24-2.71		7.00	7
(c) ca. 2.38-2.47			
(d) 2.43			
(e) 2.59			
(f) 3.04	$J_{c\text{-}f}$ = 18.7 Hz	0.99	1
(g) 3.35		1.11	1
(h) 3.82		2.83	3
(i) 4.18		0.92	1
(j) 4.79		1.02	1
(k) 4.88		1.02	1
(l) 5.28		1.02	1
(m) 5.70		1.02	1
(n) or (o) 6.56	$J_{n\text{-}o}$ = 8.2 Hz	1.02	1
(o) or (n) 6.65		1.02	1
Impurities:			
(p) ca. 2.67-2.86		Trace	
(q) ca. 3.30-3.47		Trace	
(r) Chloroform, 7.29			



ONE PULSE SEQUENCE
P2 = 7.00 USEC
D5 = 10.00 SEC
NA = 16
SIZE = 16384
AT = 2.05 SEC
QPD ON = 1
ABC ON
BUTTERWORTH FILTER ON
DB ATT. = 3
ADC = 12 BITS
AI = 4
SW = +/- 2000.00
DW = 250
RG = 100 USEC
DE = 250 USEC
TL HIGH POWER ON
F2 = 300.054777
BB MODULATION ON
OF = 1299.70
SF = 300.054484
EM = .10
PA = 134.6
PB = 70.5

FIGURE I2
Nuclear Magnetic Resonance Spectrum of Codeine

TABLE I1
Preparation and Storage of Dose Formulations in the Feed Studies of Codeine

14-Day Studies	13-Week Studies	2-Year Studies
Preparation		
A premix of feed and codeine was prepared, then layered into the remaining feed and blended in a Patterson-Kelly V-blender with the intensifier bar on for 15 minutes. Doses were prepared weekly.	Same as 14-day studies	A premix of feed and codeine was prepared, then layered into the remaining feed and blended in a Patterson-Kelly twin-shell blender with the intensifier bar on for 15 minutes. Doses were prepared weekly.
Chemical Lot Number		
471NFN003	471NFN003	471NIN001/A
Maximum Storage Time		
3 weeks	3 weeks	3 weeks
Storage Conditions		
Stored in double plastic bags at 4° C	Stored in double plastic bags at 4° C	Stored in double plastic bags at 4° C or at room temperature. Bags in use stored in covered plastic buckets in the study room.
Study Laboratory		
EG&G Mason Research Institute (Worcester, MA)	EG&G Mason Research Institute (Worcester, MA)	Microbiological Associates, Inc. (Bethesda, MD)
Referee Laboratory		
Midwest Research Institute (Kansas City, MO)	Midwest Research Institute (Kansas City, MO)	Midwest Research Institute (Kansas City, MO)

TABLE I2
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 14-Day Feed Studies of Codeine

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration[a] (ppm)	% Difference from Target
Rats				
26 March 1984	29 March 1984	1,562	1,564	0
		3,125	3,170	+1
	30 March 1984	6,250	6,310	+1
		12,500	12,000	−4
		25,000	24,700	−1
Mice				
26 March 1984	29 March 1984	781	740	−5
		1,562	1,564	0
		3,125	3,170	+1
	30 March 1984	6,250	6,310	+1
		12,500	12,000	−4

[a] Results of duplicate analyses

TABLE I3
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 13-Week Feed Studies of Codeine

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration[a] (ppm)	% Difference from Target
10 October 1984	12 October 1984	390	399[b]	+2
		390	418[c]	+7
		390	368[d]	−6
		781	780	0
		1,562	1,490	−5
	17 October 1984	3,125	3,020	−3
		6,250	6,230[b]	0
		6,250	6,520[c]	+4
		6,250	6,010[d]	−4
5 December 1984	6 December 1984	390	384	−2
		781	773	−1
		1,562	1,550	−1
	10 December 1984	3,125	3,050	−2
		6,250	6,210	−1
30 January 1985	31 January 1985	390	394	+1
		781	789	+1
		1,562	1,480	−5
	5 February 1985	3,125	3,100	−1
		6,250	6,070	−3

[a] Results of duplicate analyses
[b] Sample selection from top left of V-blender
[c] Sample selection from top right of V-blender
[d] Sample selection from bottom of V-blender

TABLE I4
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 2-Year Feed Studies of Codeine

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration[a] (ppm)	% Difference from Target
Rats				
3 April 1989	5-7 April 1989	400	381	−5
		400	409	+2
		800	772	−3
		800	760	−5
		1,600	1,490	−7
		1,600	1,620	+1
15 May 1989	16-18 May 1989	400	408	+2
		400	–[b]	
		400	375[c]	−6
		800	776	−3
		800	751	−6
		1,600	1,530	−4
		1,600	1,560	−2
10 July 1989	10-14 July 1989	400	–[b]	
		400	470	+18
		800	811	+1
		800	839	+5
		1,600	1,760	+10
		1,600	1,770	+11
	18 July 1989	400	378[c,d]	−5
17 July 1989	18 July 1989	400	404[e]	+1
		1,600	1,480	−7
5 September 1989	6-8 September 1989	400	406	+2
		400	422	+6
		800	855	+7
		800	820	+3
		1,600	1,660	+4
		1,600	1,690	+6
30 October 1989	1-4 November 1989	400	424	+6
		400	419	+5
		800	789	-1
		800	737	-8
		1,600	–[b]	
		1,600	1,700	+6
	7 November 1989	1,600	1,770	+11
	8 November 1989	400	422[c,d]	+6
8 November 1989[e]	9 November 1989	1,600	1,670	+4

TABLE I4
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 2-Year Feed Studies of Codeine (continued)

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration (ppm)	% Difference from Target
Rats (continued)				
18 December 1989	19-21 December 1989	400	398	0
		400	-[b]	
		800	813[b]	+2
		800	743	−7
		1,600	-[b]	
		1,600	1,490	−7
	21-22 December 1989	400	390[c]	−2
		800	787[c,d]	−2
		1,600	1,520[c]	−5
26 February 1990	27 February - 3 March 1990	400	379	−5
		400	375	−6
		800	771	−4
		800	769	−4
		1,600	1,560	−2
		1,600	1,500	−6
16 April 1990	17-19 April 1990	400	381	−5
		400	406	+2
		800	799	0
		800	780	−2
		1,600	1,540	−4
		1,600	1,560	−2
11 June 1990	12-14 June 1990	400	397	−1
		400	380	−5
		800	792	−1
		800	776	−3
		1,600	1,620	+1
		1,600	1,540	−4
20 August 1990	21-23 August 1990	400	416	+4
		400	407	+2
		800	792	−1
		800	801	0
		1,600	1,590	−1
		1,600	1,600	0
1 October 1990	2-4 October 1990	400	381	−5
		400	405	+1
		800	855	+7
		800	841	+5
		1,600	1,540	−4
		1,600	1,570	−2

TABLE I4
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 2-Year Feed Studies of Codeine (continued)

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration (ppm)	% Difference from Target
Rats (continued)				
26 November 1990	27-30 November 1990	400	402	+1
		400	399	0
		800	793	−1
		800	782	−2
		1,600	1,570	−2
		1,600	1,630	+2
21 January 1991	22-24 January 1991	400	386	−3
		400	368	−8
		800	804	+1
		800	–[b]	
		1,600	1,530	−4
		1,600	1,570	−2
	25 January 1991	800	788[c]	−1
25 March 1991	26-28 March 1991	400	373	−7
		400	362	−9
		800	742	−7
		800	748	−6
		1,600	1,480	−7
		1,600	1,440	−10
Mice				
20 March 1989	21-27 March 1989	750	706	−6
		1,500	1,460	−3
		3,000	2,930	−2
15 May 1989	16-18 May 1989	750	778	+4
		1,500	1,470	−2
		3,000	2,980	−1
10 July 1989	10-14 July 1989	750	724	−3
		1,500	1,560	+4
		3,000	3,100	+3
5 September 1989	6-8 September 1989	750	807	+8
		1,500	1,640	+9
		3,000	3,010	0
30 October 1989	1-4 November 1989	750	711	-5
		1,500	1490	-1
		3,000	2940	-2

TABLE I4
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 2-Year Feed Studies of Codeine (continued)

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration (ppm)	% Difference from Target
Mice (continued)				
18 December 1989	19-21 December 1989	750	792[b]	+6
		1,500	-[b]	
		3,000	-[b]	
18 December 1989	21-22 December 1989	750	771[c,d]	+3
		1,500	1,500[c]	0
		3,000	3,000[c]	0
26 February 1990	27 February - 3 March 1990	750	721	−4
		1,500	1,400	−7
		3,000	2,880	−4
16 April 1990	17-19 April 1990	750	790	+5
		1,500	1,430	−5
		3,000	2,830	−6
11 June 1990	12-14 June 1990	750	708	−6
		1,500	1,510	+1
		3,000	2,890	−4
20 August 1990	21-23 August 1990	750	701	+1
		1,500	1,490	−1
		3,000	2,990	0
1 October 1990	2-4 October 1990	750	771	+3
		1,500	1,480	−1
		3,000	2,990	0
26 November 1990	27-30 November 1990	750	738	−2
		1,500	1,500	0
		3,000	3,220	+7
21 January 1991	22-24 January 1990	750	718	−4
		1,500	1,440	−4
		3,000	2,950	−2

[a] Results of duplicate analyses
[b] Repeat analysis required
[c] Results of reanalysis
[d] Results of triplicate analyses
[e] Results of remix

TABLE I5
Results of Referee Analysis of Dose Formulations Administered to Rats and Mice in the 13-Week and 2-Year Feed Studies of Codeine

Date Prepared	Target Concentration (ppm)	Determined Concentration (ppm) Study Laboratory[a]	Determined Concentration (ppm) Referee Laboratory[b]
13-Week Studies (EG&G Mason Research Institute)			
10 October 1984	781	780	774 ± 1.2
2-Year Studies (Microbiological Associates, Inc.)			
Rats			
3 April 1989	800	772	808 ± 14
Mice			
20 March 1989	3,000	2,930	3,050 ± 220
5 September 1989	1,500	1,640	1,610 ± 70
26 February 1990	750	721	762 ± 22

[a] Results of duplicate analyses
[b] Results of triplicate analyses (mean ± standard error)

APPENDIX J
FEED AND COMPOUND CONSUMPTION IN THE 2-YEAR FEED STUDIES OF CODEINE

TABLE J1 Feed and Compound Consumption by Male Rats in the 2-Year Feed Study of Codeine 264
TABLE J2 Feed and Compound Consumption by Female Rats in the 2-Year Feed Study of Codeine 265
TABLE J3 Feed and Compound Consumption by Male Mice in the 2-Year Feed Study of Codeine 266
TABLE J4 Feed and Compound Consumption by Female Mice in the 2-Year Feed Study of Codeine 267

TABLE J1
Feed and Compound Consumption by Male Rats in the 2-Year Feed Study of Codeine

	0 ppm		400 ppm			800 ppm			1,600 ppm		
Week	Feed (g/day)[a]	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose/ Day[b] (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)
2	16.7	199	14.9	187	32	14.9	182	66	14.8	179	132
6	16.9	292	17.2	279	25	17.2	272	50	18.1	268	108
10	18.1	341	17.2	327	21	16.7	320	42	17.6	315	89
14	16.5	368	16.4	355	18	16.9	348	39	17.0	346	79
17	15.8	392	16.5	370	18	16.1	363	36	18.1	354	82
21	16.9	407	16.5	396	17	16.5	382	34	17.3	366	76
25	16.6	430	17.0	414	16	16.9	398	34	16.9	387	70
29	14.4	438	14.1	426	13	15.3	408	30	17.1	397	69
33	17.1	444	16.9	429	16	16.0	414	31	16.3	394	66
37	14.7	452	14.3	437	13	15.3	420	29	16.9	402	67
41	16.8	458	17.1	442	16	16.5	428	31	15.7	405	62
45	14.6	465	15.4	452	14	15.7	434	29	17.1	408	67
49	16.4	466	15.7	452	14	15.5	435	28	16.2	405	64
53	16.5	478	16.4	465	14	16.8	444	30	18.5	407	73
57	15.0	477	14.9	468	13	15.3	450	27	16.4	409	64
61	15.0	470	14.4	459	13	15.2	443	28	17.8	404	71
65	15.0	471	15.5	458	14	15.2	444	27	15.8	400	63
69	13.6	463	13.6	454	12	13.6	439	25	17.6	403	70
73	14.7	459	14.3	453	13	13.8	435	25	16.4	397	66
77	14.0	458	13.4	448	12	13.9	429	26	16.9	395	68
81	13.7	453	13.9	444	12	14.3	423	27	16.1	393	65
85	13.8	444	13.3	439	12	14.3	423	27	15.8	393	64
89	12.7	447	13.1	434	12	14.9	424	28	15.1	396	61
93	12.7	437	12.4	428	12	13.8	415	27	14.0	390	57
97	13.0	427	11.9	412	12	13.3	408	26	13.9	382	58
101	13.0	433	12.3	418	12	12.0	401	24	11.9	376	51
Means for weeks											
1-13	17.2	277	16.4	264	26	16.3	258	53	16.8	254	110
14-52	16.0	432	16.0	417	15	16.1	403	32	16.9	386	70
53-101	14.0	455	13.8	445	12	14.3	429	27	15.8	396	64

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

TABLE J2
Feed and Compound Consumption by Female Rats in the 2-Year Feed Study of Codeine

	0 ppm		400 ppm			800 ppm			1,600 ppm		
Week	Feed (g/day)[a]	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose/ Day[b] (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)
2	12.0	140	10.8	136	32	11.0	136	65	10.6	133	128
6	11.5	182	11.3	175	26	12.2	171	57	12.3	173	114
10	12.4	201	11.1	192	23	12.0	191	50	11.8	188	101
14	11.4	215	12.6	205	25	12.0	203	47	11.6	198	94
17	11.6	224	10.9	211	21	12.0	206	47	12.2	204	96
21	10.8	233	10.8	223	19	11.8	221	43	12.3	217	91
25	10.5	242	11.0	228	19	11.0	227	39	11.1	223	79
29	11.1	244	10.3	233	18	11.3	232	39	11.1	232	77
33	11.0	255	10.3	237	17	10.7	235	36	11.4	234	78
37	11.4	260	10.8	240	18	11.0	243	36	10.7	245	70
41	11.5	273	10.7	251	17	10.9	251	35	11.5	249	74
45	11.8	286	11.6	259	18	11.7	258	36	10.6	255	66
49	12.0	297	11.0	266	17	11.1	262	34	11.6	256	72
53	12.1	310	12.2	277	18	13.1	270	39	11.5	264	70
57	12.2	320	12.0	288	17	12.3	284	35	12.0	271	71
61	12.6	328	12.5	295	17	12.6	292	34	11.2	279	64
65	11.1	336	11.9	306	16	12.0	302	32	11.8	283	67
69	11.4	331	11.4	308	15	12.0	304	32	11.1	284	62
73	12.1	339	11.9	312	15	12.6	307	33	12.0	290	66
77	11.4	342	11.1	317	14	12.1	315	31	11.1	297	60
81	11.8	342	11.7	319	15	12.0	317	30	11.7	298	63
85	10.9	341	11.3	325	14	11.6	323	29	11.2	307	59
89	10.8	338	11.6	326	14	11.7	325	29	11.0	304	58
93	11.5	343	12.3	333	15	12.1	327	30	11.4	309	59
97	12.5	345	11.5	334	14	10.8	324	27	11.1	307	58
101	11.6	349	11.2	336	13	10.4	324	26	11.4	303	60
Means for weeks											
1-13	12.0	175	11.1	167	27	11.7	166	57	11.6	164	114
14-52	11.3	253	11.0	235	19	11.4	234	39	11.4	231	80
53-101	11.7	336	11.7	313	15	11.9	309	31	11.4	292	63

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

TABLE J3
Feed and Compound Consumption by Male Mice in the 2-Year Feed Study of Codeine

	0 ppm		750 ppm			1,500 ppm			3,000 ppm		
Week	Feed (g/day)[a]	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose/ Day[b] (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)
2	4.4	23.8	3.8	23.6	121	3.9	23.4	251	4.1	22.8	537
6	4.7	28.1	4.5	27.7	123	4.4	27.2	245	4.5	26.9	498
10	5.0	32.4	5.1	31.1	122	5.1	30.5	251	4.9	29.8	497
14	5.1	35.2	5.5	34.0	121	5.4	32.8	246	5.2	31.7	492
17	5.0	38.1	5.1	36.9	104	5.2	35.0	223	5.1	33.3	460
21	4.6	41.6	4.8	40.0	90	4.9	37.2	196	4.8	34.9	414
25	4.7	42.3	5.0	41.1	91	5.1	39.3	196	5.2	36.6	422
29	4.7	44.9	4.7	44.8	79	4.8	42.3	169	4.7	38.9	360
33	4.9	46.1	5.0	45.1	83	5.1	42.5	180	5.2	38.5	404
37	4.4	48.3	4.7	46.8	76	4.9	44.2	165	4.7	40.4	348
41	4.6	48.9	4.8	48.9	73	4.8	45.7	156	5.0	41.7	357
45	4.5	49.5	4.6	49.9	69	5.0	47.0	160	5.0	43.3	345
49	4.6	49.4	4.8	50.0	72	5.1	47.4	161	5.0	43.8	341
53	4.7	50.0	4.9	51.3	72	5.1	48.7	156	5.0	44.6	337
57	4.9	50.4	5.1	51.6	74	5.0	49.2	153	5.2	45.2	342
61	4.9	50.7	5.0	51.7	72	5.1	49.4	155	5.1	45.4	339
65	5.0	50.3	5.0	51.5	72	5.1	49.0	156	4.9	45.0	326
69	4.7	50.6	4.7	51.3	69	4.7	49.5	143	4.7	44.7	313
73	4.8	49.4	4.9	50.5	73	5.1	48.6	157	4.9	43.4	337
77	4.7	49.2	4.9	50.4	72	5.0	48.5	156	5.0	43.4	343
81	5.1	49.9	5.0	50.6	74	5.4	47.5	169	5.1	43.7	353
85	4.7	49.5	4.9	50.3	73	5.0	47.5	157	5.0	43.8	344
89	4.6	50.2	4.7	51.4	69	5.1	48.1	160	5.0	44.2	338
93	4.9	48.5	5.1	50.3	76	5.2	45.9	171	5.1	41.8	368
97	4.9	49.0	4.8	51.0	71	5.0	46.0	163	4.9	42.2	348
101	4.8	49.0	4.9	50.3	74	5.2	45.1	173	5.1	41.7	365
Means for weeks											
1-13	4.7	28.1	4.5	27.5	122	4.5	27.0	249	4.5	26.5	511
14-52	4.7	44.4	4.9	43.8	86	5.0	41.3	185	5.0	38.3	394
53-101	4.8	49.7	4.9	50.9	72	5.1	47.9	159	5.0	43.8	342

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

TABLE J4
Feed and Compound Consumption by Female Mice in the 2-Year Feed Study of Codeine

	0 ppm		750 ppm			1,500 ppm			3,000 ppm		
Week	Feed (g/day)[a]	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose/ Day[b] (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)
2	4.3	19.5	4.5	19.6	174	4.4	19.2	345	4.1	18.9	651
6	4.6	24.5	4.5	24.5	138	4.5	24.1	277	4.4	23.6	564
10	5.0	28.3	5.0	27.7	137	5.1	27.3	282	5.0	26.6	568
14	5.2	31.1	5.5	30.0	137	5.5	29.0	283	5.2	28.1	560
17	5.4	34.5	5.3	33.3	119	5.4	31.2	258	5.2	29.5	528
21	4.8	39.1	5.1	36.9	103	5.1	34.0	223	5.0	31.7	470
25	5.2	40.7	5.3	38.8	103	5.2	36.6	214	5.2	33.6	469
29	5.2	42.5	5.1	41.7	93	5.2	38.9	201	5.0	35.1	432
33	5.0	44.6	5.4	42.4	95	5.4	39.8	205	5.6	35.5	474
37	5.0	46.2	5.5	44.6	92	5.5	41.4	199	5.6	36.5	457
41	5.1	47.5	5.3	47.2	84	5.3	43.8	183	5.3	38.5	415
45	5.1	48.9	5.3	49.0	80	5.2	45.3	174	5.4	39.9	403
49	5.2	48.7	5.4	49.5	82	5.5	46.5	177	5.6	40.4	412
53	5.2	50.2	5.5	51.0	81	5.6	48.3	174	5.5	42.2	389
57	5.3	51.2	5.5	52.7	78	5.5	50.4	163	5.6	43.6	384
61	5.2	52.5	5.5	54.3	75	5.5	51.7	159	5.6	44.4	376
65	5.4	52.4	5.6	54.0	77	5.4	51.3	157	5.5	44.2	370
69	5.4	52.6	5.5	53.5	78	5.7	52.5	163	5.6	44.2	377
73	5.2	50.9	5.5	53.2	78	5.7	52.4	164	5.7	44.3	385
77	5.2	49.8	5.4	53.2	76	5.5	52.3	158	5.4	43.7	372
81	5.2	51.4	5.5	53.9	77	5.5	53.2	155	5.6	44.3	376
85	5.1	53.0	5.2	54.2	72	5.4	54.1	150	5.5	44.1	371
89	5.2	53.2	5.3	53.5	75	5.6	53.7	157	5.8	43.6	397
93	5.3	51.3	5.4	52.1	77	5.4	52.4	155	5.6	41.7	404
97	4.8	52.5	5.2	53.2	73	5.3	52.5	152	5.4	42.4	384
101	5.1	51.6	5.5	53.5	77	5.5	51.3	162	5.7	41.4	411
Means for weeks											
1-13	4.6	24.1	4.7	23.9	150	4.7	23.5	301	4.5	23.0	595
14-52	5.1	42.4	5.3	41.3	99	5.3	38.7	212	5.3	34.9	462
53-101	5.2	51.7	5.4	53.3	77	5.5	52.0	159	5.6	43.4	384

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

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

TABLE K1 Ingredients of NIH-07 Rat and Mouse Ration 270
TABLE K2 Vitamins and Minerals in NIH-07 Rat and Mouse Ration 270
TABLE K3 Nutrient Composition of NIH-07 Rat and Mouse Ration 271
TABLE K4 Contaminant Levels in NIH-07 Rat and Mouse Ration 272

TABLE K1
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 K2
Vitamins and Minerals in NIH-07 Rat and Mouse Ration[a]

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

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

TABLE K3
Nutrient Composition of NIH-07 Rat and Mouse Ration

Nutrient	Mean ± Standard Deviation	Range	Number of Samples
Protein (% by weight)	23.46 ± 0.78	21.30 - 25.20	26
Crude fat (% by weight)	5.23 ± 0.23	4.80 - 5.80	26
Crude fiber (% by weight)	3.64 ± 0.51	2.60 - 4.80	26
Ash (% by weight)	6.52 ± 0.18	6.12 - 6.97	26
Amino Acids (% of total diet)			
Arginine	1.287 ± 0.084	1.100 - 1.390	10
Cystine	0.306 ± 0.075	0.181 - 0.400	10
Glycine	1.160 ± 0.050	1.060 - 1.220	10
Histidine	0.580 ± 0.024	0.531 - 0.608	10
Isoleucine	0.917 ± 0.034	0.867 - 0.965	10
Leucine	1.972 ± 0.052	1.850 - 2.040	10
Lysine	1.273 ± 0.051	1.200 - 1.370	10
Methionine	0.437 ± 0.115	0.306 - 0.699	10
Phenylalanine	0.994 ± 0.125	0.665 - 1.110	10
Threonine	0.896 ± 0.055	0.824 - 0.985	10
Tryptophan	0.223 ± 0.160	0.107 - 0.671	10
Tyrosine	0.677 ± 0.105	0.564 - 0.794	10
Valine	1.089 ± 0.057	0.962 - 1.170	10
Essential Fatty Acids (% of total diet)			
Linoleic	2.389 ± 0.233	1.830 - 2.570	9
Linolenic	0.277 ± 0.036	0.210 - 0.320	9
Vitamins			
Vitamin A (IU/kg)	7,084 ± 1,650	4,290 - 12,540	26
Vitamin D (IU/kg)	4,450 ± 1,382	3,000 - 6,300	4
α-Tocopherol (ppm)	36.92 ± 9.32	22.5 - 48.9	9
Thiamine (ppm)	18.29 ± 1.59	15.0 - 22.0	26
Riboflavin (ppm)	7.92 ± 0.93	6.10 - 9.00	10
Niacin (ppm)	100.95 ± 25.92	65.0 - 150.0	9
Pantothenic acid (ppm)	30.30 ± 3.60	23.0 - 34.6	10
Pyridoxine (ppm)	9.25 ± 2.62	5.60 - 14.0	10
Folic acid (ppm)	2.51 ± 0.64	1.80 - 3.70	10
Biotin (ppm)	0.267 ± 0.049	0.19 - 0.35	10
Vitamin B_{12} (ppb)	40.14 ± 20.04	10.6 - 65.0	10
Choline (ppm)	3,068 ± 314	2,400 - 3,430	9
Minerals			
Calcium (%)	1.21 ± 0.10	0.90 - 1.37	26
Phosphorus (%)	0.95 ± 0.04	0.88 - 1.03	26
Potassium (%)	0.887 ± 0.067	0.772 - 0.971	8
Chloride (%)	0.526 ± 0.092	0.380 - 0.635	8
Sodium (%)	0.315 ± 0.034	0.258 - 0.370	10
Magnesium (%)	0.168 ± 0.008	0.151 - 0.180	10
Sulfur (%)	0.274 ± 0.063	0.208 - 0.420	10
Iron (ppm)	356.2 ± 90.0	255.0 - 523.0	10
Manganese (ppm)	92.24 ± 5.35	81.70 - 99.40	10
Zinc (ppm)	58.14 ± 9.91	46.10 - 81.60	10
Copper (ppm)	11.50 ± 2.40	8.090 - 15.39	10
Iodine (ppm)	3.70 ± 1.14	1.52 - 5.83	10
Chromium (ppm)	1.71 ± 0.45	0.85 - 2.09	9
Cobalt (ppm)	0.797 ± 0.23	0.490 - 1.150	6

TABLE K4
Contaminant Levels in NIH-07 Rat and Mouse Ration[a]

	Mean ± Standard Deviation[b]	Range	Number of Samples
Contaminants			
Arsenic (ppm)	0.34 ± 0.17	0.06 - 0.60	26
Cadmium (ppm)	0.07 ± 0.03	0.05 - 0.12	26
Lead (ppm)	0.25 ± 0.18	0.10 - 0.90	26
Mercury (ppm)	0.03 ± 0.02	0.02 - 0.08	26
Selenium (ppm)	0.33 ± 0.10	0.10 - 0.52	26
Aflatoxins (ppb)[c]	<5.0		25
Nitrate nitrogen (ppm)[d]	14.10 ± 4.40	5.90 - 21.0	26
Nitrite nitrogen (ppm)[d]	0.23 ± 0.21	0.10 - 1.00	26
BHA (ppm)[e]	1.44 ± 0.87	1.00 - 4.00	26
BHT (ppm)[e]	1.44 ± 1.23	1.00 - 7.00	26
Aerobic plate count (CFU/g)	10,802 ± 83,872	4,700 - 380,000	26
Coliform (MPN/g)	25.64 ± 27.5	3.00 - 93.00	26
Escherichia coli (MPN/g)	3.31 ± 1.20	3.00 - 9.0	26
Total nitrosoamines (ppb)[f]	7.20 ± 2.48	2.00 - 13.70	26
N-Nitrosodimethylamine (ppb)[f]	5.45 ± 2.00	1.00 - 11.00	26
N-Nitrosopyrrolidine (ppb)[f]	1.75 ± 1.02	1.00 - 4.30	26
Pesticides (ppm)			
α-BHC	<0.01		31
β-BHC	<0.02		31
γ-BHC	<0.01		31
δ-BHC	<0.01		31
Heptachlor	<0.01		31
Aldrin	<0.01		31
Heptachlor epoxide	<0.01		31
DDE	<0.01		31
DDD	<0.01		31
DDT	<0.01		31
HCB	<0.01		31
Mirex	<0.01		31
Methoxychlor	<0.05		31
Dieldrin	<0.01		31
Endrin	<0.01		31
Telodrin	<0.01		31
Chlordane	<0.05		31
Toxaphene	<0.1		31
Estimated PCBs	<0.2		31
Ronnel	<0.01		31
Ethion	<0.02		31
Trithion	<0.05		31
Diazinon	<0.1		31
Methyl parathion	<0.02		31
Ethyl parathion	<0.02		31
Malathion	0.28 ± 0.26	<0.05 - 1.00	26
Endosulfan I	<0.01		31
Endosulfan II	<0.01		31
Endosulfan sulfate	<0.03		31

[a] CFU = colony forming units, MPN = most probable number, BHC is hexachlorocyclohexane or benzene hexachloride.
[b] For values less than the limit of detection, the detection limit is given as the mean.
[c] No aflatoxin measurement was recorded for the lot milled 2 October 1989.
[d] Sources of contamination: alfalfa, grains, and fish meal.
[e] Sources of contamination: soy oil and fish meal; no BHA or BHT measurements were recorded for the lot milled 1 November 1989.
[f] All values were corrected for percent recovery.

APPENDIX L
SENTINEL ANIMAL PROGRAM

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SENTINEL ANIMAL PROGRAM

METHODS

Rodents used in the Carcinogenesis Program of the National Toxicology Program are produced in optimally clean facilities to eliminate potential pathogens that may affect study results. The Sentinel Animal Program is part of the periodic monitoring of animal health that occurs during the toxicologic evaluation of chemical compounds. Under this program, the disease state of the rodents is monitored via serology on sera from extra (sentinel) animals in the study rooms. These animals and the study animals are subject to identical environmental conditions. The sentinel animals come from the same production source and weanling groups as the animals used for the studies of chemical compounds.

Serum samples were collected from randomly selected rats and mice during the 13-week and 2-year studies. Blood from each animal was collected and allowed to clot, and the serum was separated. The samples were processed appropriately and sent to Microbiological Associates, Inc. (Bethesda, MD), for determination of antibody titers. The laboratory serology methods and viral agents for which testing was performed are tabulated below; the times at which blood was collected during the studies are also listed.

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

MICE

13-Week Study

Complement Fixation	
LCM (lymphocytic choriomeningitis virus)	Study termination
ELISA	
Ectromelia virus	Study termination
GDVII (mouse encephalomyelitis virus)	Study termination
Mouse adenoma virus	Study termination
MHV (mouse hepatitis virus)	Study termination
M. arthritidis	Study termination
M. pulmonis	Study termination
PVM	Study termination
Reovirus 3	Study termination
Sendai	Study termination
Immunofluorescence Assay	
EDIM (epizootic diarrhea of infant mice)	Study termination
Hemagglutination Inhibition	
K (papovavirus)	Study termination
MVM (minute virus of mice)	Study termination
Polyoma virus	Study termination

2-Year Study

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

2-Year Study (continued)

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

RESULTS

For the 13-week feed studies with rats and mice, all serology test results were negative. One rat and one mouse had positive titers to *M. arthritidis* at the end of the 2-year studies.

Further evaluation of serum positive for *M. arthritidis* by immunoblot and Western blot procedures indicated that the positive titers may be 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, sporadic *M. arthritidis*-positive titers were considered to be false positives.

APPENDIX M
CODEINE TOXICOKINETICS IN RATS DURING A TWO-YEAR DOSED FEED STUDY

Jinhua Yuan, June K. Dunnick, Evelyn R. Barnes, and John W.A. Findlay

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CODEINE TOXICOKINETICS IN RATS DURING A TWO-YEAR DOSED FEED STUDY

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ABSTRACT:

Codeine toxicokinetics in F344 rats of both sexes were determined during a 2-year chronic toxicology study using dosed feed as the exposure route with a 12-hr light/dark cycle starting at 7:00 a.m. Rats were allowed to access to dosed feed formulations *ad libitum* with codeine concentrations at 0, 400, 800, and 1600 ppm. Blood samples were collected from individual rat on days 7, 21, and 90 at 7:00 p.m., 11:00 p.m., 3:00 a.m., and 7:00 a.m. Additional samples were collected at 16 and 24 months between 6:00–8:00 a.m. Plasma concentrations of codeine and morphine were determined directly by radioimmunoassay. Concentrations of their conjugates were determined indirectly by measuring the total amount of free codeine and morphine released after samples were treated with β-glucuronidase. Results indicated that plasma concentrations of both codeine and morphine steadily decreased from day 7 to 16 months and then rebounded at 24 months. Results also indicated that plasma concentrations of both codeine and morphine correlated well with the amounts of codeine added to the feed. Bioavailability of codeine using the dosed feed route increased with dose, varying from 10% to 25%, which was somewhat higher than the previously reported ~8% bioavailability using the gavage route. Concentrations of conjugated codeine were very low, whereas concentrations of conjugated morphine were very high. These results suggested that demethylation of codeine to morphine in rats is the main metabolic pathway and was maintained over the course of the study.

Codeine is one of the opioid alkaloids that has been used as an effective analgesic and antitussive drug for centuries (1–3). However, little is known about the carcinogenic potential of codeine and the related morphine group of chemicals. Because of the widespread use of codeine and the lack of knowledge of its carcinogenic potential, the National Toxicology Program has conducted long-term rodent studies of codeine. In the 2-year chronic rodent studies, codeine was administered in the feed to F344 rats of both sexes at concentrations of 0, 400, 800, and 1600 ppm. (This dose range was selected to include a low dose with little or no toxic effects and a high dose that was ~100 times the human dose on a mg/kg basis and was considered the maximum dose that animals could tolerate over the 2-year dosing period.) Because humans may ingest codeine-containing drugs 3–4 times/day, the feed route was chosen for the rodent bioassay.

Comparison of the metabolism and toxicokinetics in the experimental studies and humans serves as one basis for extrapolating the results from animal studies to humans. This study reports the findings on the resulting plasma concentrations of codeine and its various metabolites in rats during 2 years of dosed-feed exposure and compares the results to those obtained in human pharmokinetic studies.

Materials and Methods

Chemicals. Codeine (lot 471-NIN-001/A, purity > 99%) was manufactured by Penick Corporation (Newark, NJ). [1-^{3}H]Codeine (specific activity, 20 Ci/mmol) and [1,6,7-^{3}H]dihydromorphine (specific activity, 81 Ci/mmol) were purchased from Amersham Corp. (Arlington Heights, IL). Details of antisera production and of other necessary chemicals can be found elsewhere (5).

Formulations. Dosed feed formulations were prepared by blending codeine with NIH-07 feed (Zeigler Brothers, Gardners, PA) to concentrations of 0, 400, 800, and 1600 ppm. Stability and homogeneity of the prepared formulations, as well as the concentrations of codeine in feed, were confirmed by taking samples from the feed formulations and analyzing the codeine content prior to use. Feed samples (10 g) were extracted for 15 min with 50 ml of acidified aqueous methanol solution (18 ml concentrated HCl and 1387 ml methanol in 595 ml water). The extract was clarified by centrifugation for 5 min at 1500 rpm. An aliquot of the supernatant (15 ml) was first diluted with water (15 ml), then washed with methylene chloride (15 ml). After discarding the organic phase, the upper aqueous layer (25 ml) was made basic by adding 1 N NaOH (2 ml) and was reextracted with methylene chloride (20 ml). The resulting organic phase (10 ml) was evaporated to dryness, and the residue was reconstituted in 3 ml of methanol containing propiophenone (200 μg/ml) as internal standard, and 7 ml of a diluting solution (1.01 g sodium heptane sulfonate and 5 ml acetic acid in 495 ml water). The reconstituted solution was filtrated and then injected (23 μl) into the HPLC system. The HPLC system contained a UV detector operated at 280 nm and a Brownlee RP-18 column (10 μm, 100 mm × 4.6 i.d., Alltech Associates, Inc., Deerfield, IL) preceded by a guard column (Brownlee RP-18, 30 mm × 4.6 i.d.). The mobile phase (1 ml/min) was water:methanol (63:37, v/v) containing glacial acetic acid (1%, v/v) and sodium heptane sulfonate (0.005 M). The standard curve was obtained by analyzing spiked feed samples.

Animals. Groups of male and female Fischer 344 rats (4-week old) were obtained from Taconic Farms (Germantown, NY) and were quarantined for 15 days before the start of the study. A light cycle of 7:00 a.m.–7:00 p.m. was used in the animal facility. Rats of both sexes were randomized by body weight and were assigned to a specific blood collection period: days 7, 21, 90, and months 16 (65 weeks) and months 24 (104 weeks). Rats were exposed to codeine *via* the dosed feed *ad libitum*. Concentrations of codeine (free base) in feed were 0, 400, 800, and 1600 ppm. Body weights and feed consumption were recorded during the study. On days 7, 21, and 90, groups of 5 male and 5 female rats from each of the codeine-treated groups were bled *via* the orbital sinus, under CO_2 anesthesia (70% CO_2, 30% O_2), at 7:00 p.m., 11:00 p.m., 3:00 a.m. (next day), and 7:00 a.m. (next day) of the dark cycle of the animal facility (7:00 p.m.–7:00 a.m.). Control animals were bled only at 11:00 p.m. on days 7, 21, and 90. At 16 and 24 months, blood samples were collected using the same procedure from 5 rats of each of the codeine-

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TABLE I

Daily feed and codeine consumption of rats in chronic codeine dosed feed studies[a]

Dose	Male					Female				
	Day 7	Day 21	Day 90	16 Month	24 Month	Day 7	Day 21	Day 90	16 Month	24 Month
ppm										
					Body Weight (g)					
0	151 ± 28	232 ± 22	361 ± 13	471 ± 24	411 ± 43	124 ± 13	148 ± 2	217 ± 15	336 ± 19	342 ± 33
400	153 ± 24	230 ± 21	361 ± 24	458 ± 22	405 ± 36	120 ± 13	144 ± 9	201 ± 12	306 ± 22	335 ± 40
800	155 ± 23	212 ± 26	355 ± 16	444 ± 24	390 ± 29	119 ± 13	147 ± 9	204 ± 11	302 ± 22	315 ± 40
1600	146 ± 23	203 ± 20	330 ± 18	400 ± 24	362 ± 33	110 ± 14	142 ± 10	198 ± 13	283 ± 20	303 ± 23
					Food Consumption (g/animal/day)[b]					
0	14.4 ± 1.3	18.1 ± 2.8	18.5 ± 1.2	15.0 ± 0.7	9.8 ± 2.3	11.6 ± 1.5	10.8 ± 0.8	11.3 ± 1.4	11.1 ± 0.6	10.2 ± 0.5
400	13.0 ± 2.5	18.2 ± 4.3	18.6 ± 2.6	15.5 ± 1.2	9.2 ± 1.9	10.7 ± 1.3	11.7 ± 2.6	11.7 ± 1.6	11.9 ± 0.4	9.7 ± 2.0
800	13.4 ± 1.7	17.0 ± 3.7	17.7 ± 2.8	15.2 ± 1.6	11.6 ± 1.3	10.0 ± 1.3	11.7 ± 3.2	11.3 ± 2.1	12.0 ± 0.7	10.0 ± 0.8
1600	12.3 ± 1.3	17.2 ± 4.0	17.7 ± 3.8	15.7 ± 1.0	10.3 ± 1.3	9.0 ± 1.4	12.2 ± 2.9	12.3 ± 2.0	11.8 ± 0.6	10.8 ± 1.5
					Codeine Intake (mg/day/kg body weight)					
0	—	—	—	—	—	—	—	—	—	
400	34.0 ± 8.4	31.7 ± 8.0	20.7 ± 3.2	10.8 ± 1.0	7.3 ± 1.6	35.6 ± 5.6	32.4 ± 7.5	23.2 ± 3.5	12.4 ± 1.0	9.3 ± 2.2
800	69.1 ± 13.5	64.0 ± 15.8	40.1 ± 6.7	21.9 ± 2.6	19.0 ± 2.6	68.6 ± 11.3	63.5 ± 18.0	44.2 ± 8.6	25.0 ± 2.4	20.3 ± 3.0
1600	133.9 ± 25.0	135.1 ± 34.0	86.0 ± 19.0	50.2 ± 4.4	36.4 ± 5.7	130.2 ± 26.9	137.2 ± 34.4	99.5 ± 17.6	53.4 ± 4.6	45.6 ± 7.2

[a] Values are expressed as the mean ± SD of 5 rats (0 ppm) and 20 rats (400, 800, and 1600 ppm) for day 7 to day 90; and of 60 rats for 16 months and of 30 rats for 24 months.

[b] Rats were housed 5/cage and feed consumption for an individual rat was calculated based on the feed consumption of per cage.

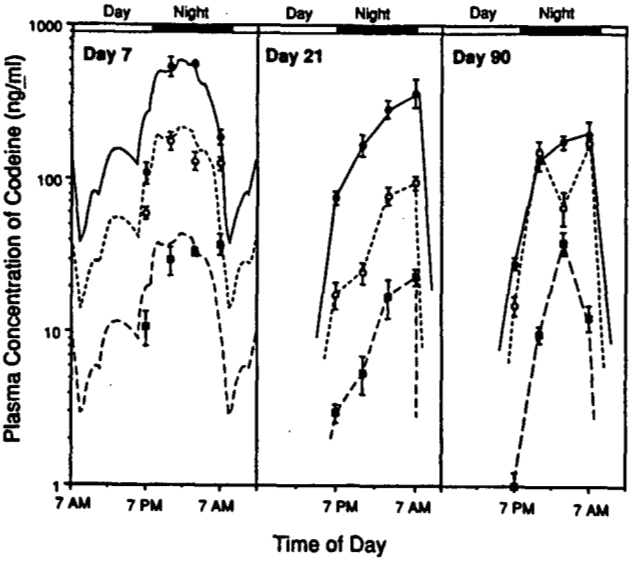

FIG. 1. *Plasma concentration profiles of unconjugated codeine in male F344 rats during the dark cycle on days 7, 21, and 90 in a codeine dosed feed study.*

Curves for day 7 were generated using a dosed feed model. ■, 400 ppm; O, 800 ppm; and ●, 1600 ppm.

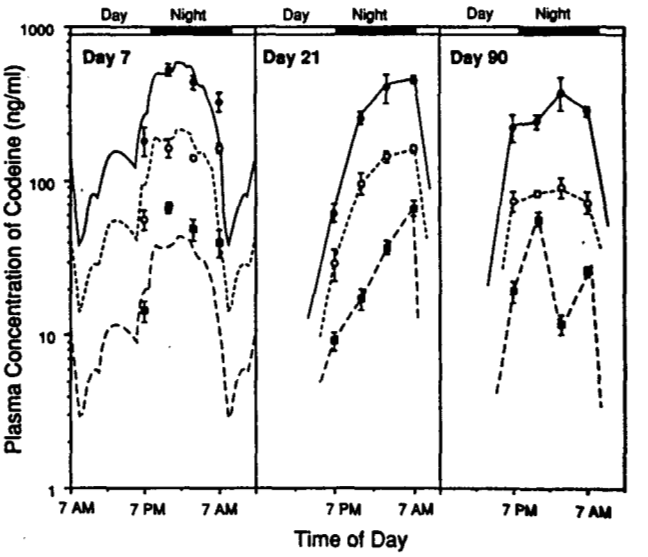

FIG. 2. *Plasma concentration profiles of unconjugated codeine in female F344 rats during the dark cycle on days 7, 21, and 90 in a codeine dosed feed study.*

Curves for day 7 were generated using a dosed feed model. ■, 400 ppm; O, 800 ppm; and ●, 1600 ppm.

treated groups at 6:00–8:00 a.m. Each rat was sampled only once. All blood samples were drawn through heparinized microhematocrit tubes into EDTA-treated 5-ml Venoject blood collection tubes, and were centrifuged under refrigerated conditions to separate the plasma. The harvested plasma samples were stored at ~70°C until they were analyzed.

Analyzing Plasma Samples. Plasma samples were analyzed for codeine and morphine by radioimmunoassay procedures as previously described (5). The concentrations of their conjugates were determined indirectly by measuring the total amount of free codeine and morphine released after samples were treated with β-glucuronidase using the same radioimmunoassay procedures (5). Results are expressed as total codeine and total morphine concentrations, which are the plasma concentrations of codeine and morphine after samples being treated with β-glucuronidase.

Modeling. Plasma concentrations of unconjugated codeine on day 7 were fit to a dosed feed model assuming linear pharmacokinetics as previously described by Yuan (4). Briefly, the model treats a dosed feed study as a series of consecutive gavage studies, with variable doses repeated at a small time interval such as 0.5 hr. The theoretical gavage dose at each time interval was determined from the daily total chemical intake (experimentally determined), as well as the percentage of the daily feeding activity occurring during the same time interval. The plasma concentrations of test chemical from each theoretical small gavage dose at each time interval were calculated based on the small gavage dose and

TABLE 2

Estimated AUC values for codeine in rat dosed feed codeine studies[a]

Sex	Dose in Feed	Day 7		Day 21		Day 90	
		Codeine[b]	Total Codeine[c]	Codeine	Total Codeine	Codeine	Total Codeine
	ppm	*ng·hr/ml*	*ng·hr/ml*	*ng·hr/ml*	*ng·hr/ml*	*ng·hr/ml*	*ng·hr/ml*
Male	400	350 ± 30	358 ± 33	143 ± 21	175 ± 37	224 ± 26	289 ± 26
	800	1,566 ± 117	1,567 ± 120	635 ± 49	632 ± 46	1,237 ± 118	1,492 ± 144
	1600	4,894 ± 336	4,958 ± 387	2,668 ± 236	2,689 ± 234	1,681 ± 136	3,042 ± 150
Female	400	572 ± 41	581 ± 35	368 ± 24	395 ± 26	394 ± 29	639 ± 48
	800	1,633 ± 90	1,676 ± 104	1,319 ± 77	1,380 ± 84	985 ± 65	1,547 ± 101
	1600	4,820 ± 292	4,870 ± 270	3,631 ± 353	3,727 ± 380	3,350 ± 391	3,876 ± 395

[a] AUC values are expressed as mean ± SD for the 12-hr dark cycle period.
[b] Unconjugated codeine.
[c] Unconjugated and conjugated codeine.

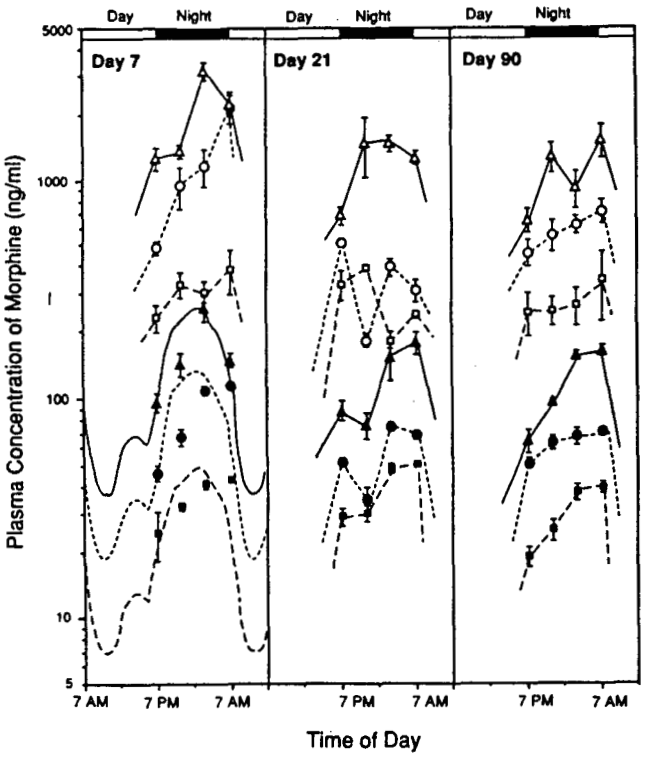

FIG. 3. *Plasma concentration profiles of unconjugated and conjugated morphine in male F344 rats during the dark cycle on days 7, 21, and 90 in a codeine dosed feed study.*

Curves for day 7 of unconjugated morphine were generated using a dosed feed model. *Filled symbols* represent unconjugated morphine, and *open symbols* represent total morphine. ■, 400 ppm; ●, 800 ppm; and ▲, 1600 ppm.

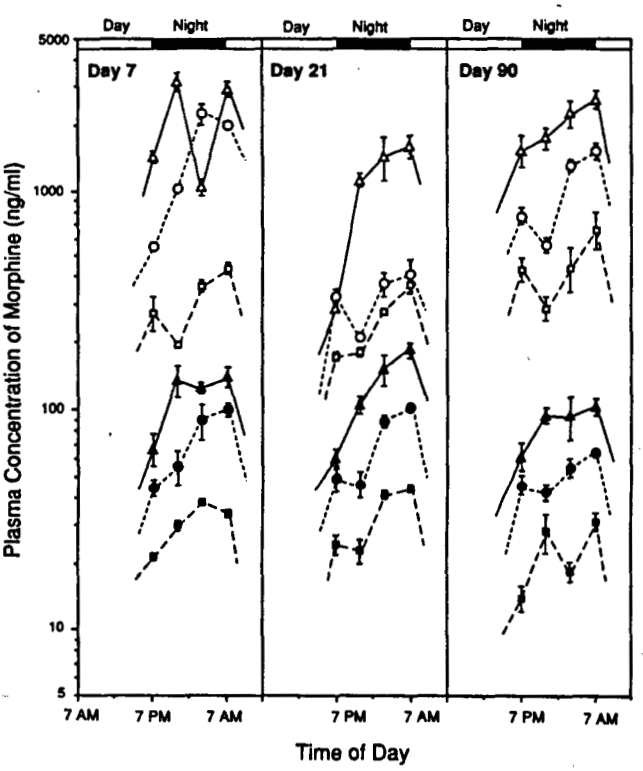

FIG. 4. *Plasma concentration of unconjugated and conjugated morphine profiles in female F344 rats during the dark cycle on days 7, 21, and 90 in a codeine dosed feed study.*

Filled symbols represent unconjugated morphine, and *open symbols* represent total morphine. ■, 400 ppm; ●, 800 ppm; and ▲, 1600 ppm.

the unit impulse response function, then summed to yield the plasma concentrations of test chemical profiles in a dosed feed study. The unit impulse response function, defined as the plasma concentration profiles obtained after a bolus gavage dose of 1 unit of test chemical, can be experimentally determined after bolus gavage doses. Specifically, the unit impulse response function for codeine is based on the following equation:

$$C\delta(t)\ (\text{ng/ml}) = \frac{FD_0K_a}{V_d(K_a - K_e)}\cdot(e^{-K_e t} - e^{-K_a t})$$

with $D_0 = 1\ \mu\text{g/kg}$, (1)

where K_e and K_a are the elimination and absorption rate constants and are equal to 1.26 and 33 hr^{-1}, respectively; V_d is the apparent volume of distribution and is equal to 3.8 liters/kg, assuming codeine is evenly distributed between plasma and red blood cells (6). The value for bioavailability (F) was initially set to be 8% and was finally determined by the model. The dose unit (μg/kg) was necessary to express $C\delta(t)$ in ng/ml, a concentration unit used throughout this study.

As previously stated, the model used a daily feeding activity curve to calculate the theoretical gavage dose at each time interval (input function) that assumes that feeding activity was directly proportional to the amount of feed consumed. Ideally, the feeding activity curve should be obtained from the treated animals. However, because of the experimental difficulty, the feeding activity curve collected from control animals (4, 7) was

TABLE 3

Estimated AUC values for morphine in rat dosed feed codeine studies[a]

Sex	Dose in Feed	Day 7		Day 21		Day 90	
		Morphine[b]	Total Morphine[c]	Morphine	Total Morphine	Morphine	Total Morphine
	ppm	*ng·hr/ml*	*ng·hr/ml*	*mg·hr/ml*	*ng·hr/ml*	*ng·hr/ml*	*ng·hr/ml*
Male	400	427 ± 17	3,752 ± 296	472 ± 15	3,422 ± 122	368 ± 18	3,206 ± 368
	800	1,018 ± 32	13,728 ± 1,427	676 ± 22	3,944 ± 180	764 ± 30	7,050 ± 491
	1600	2,069 ± 155	24,970 ± 1,357	1,429 ± 135	15,692 ± 1,883	1,449 ± 35	13,102 ± 1,195
Female	400	382 ± 8	3,638 ± 143	394 ± 16	2,900 ± 87	275 ± 25	5,084 ± 514
	800	867 ± 76	18,236 ± 1,014	840 ± 36	3,778 ± 238	609 ± 27	12,002 ± 470
	1600	1,447 ± 97	22,506 ± 1,325	1,508 ± 105	13,944 ± 1,362	1,079 ± 89	24,254 ± 1,647

[a] AUC values are expressed as mean ± SD for the 12-hr dark cycle period.
[b] Unconjugated morphine.
[c] Unconjugated and conjugated morphine.

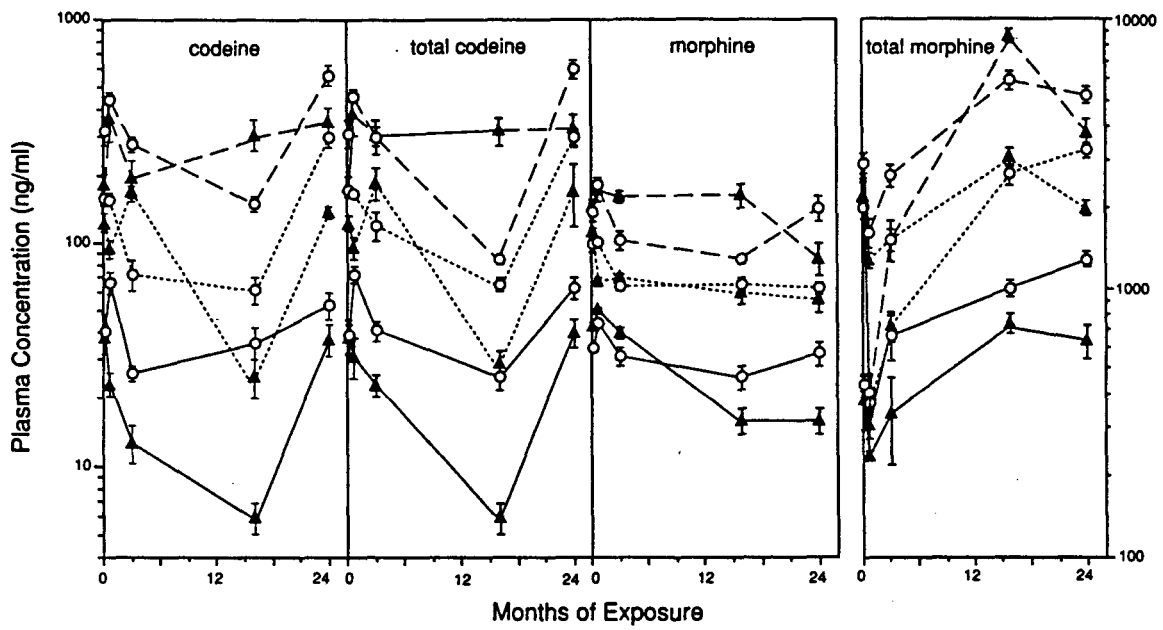

FIG. 5. *Plasma concentrations of codeine and morphine over the 2-year rat codeine dosed feed study.*

Samples were collected at 6:00–8:00 a.m. ▲, male rat; O, female rat; ——, 400 ppm; . . . . ., 800 ppm; - - -, 1600 ppm.

actually used in the model. This is justified because concentration of codeine in diet was low and the presence of codeine had little impact on the feed palatability at early stages (table 1). Moreover, model simulation indicated that slight changes in the feeding activity curve or even the absorption half-life had little effect toward the achievable plasma concentrations (4).

Choosing a unit impulse response function for unconjugated morphine was more difficult than for codeine, because morphine is a metabolite of codeine. From a theoretical point of view, the unit impulse response function for unconjugated morphine should at least contain three exponential terms representing absorption of codeine, conversion of codeine to morphine, and elimination of morphine, respectively. However, the experimentally obtained plasma concentrations of metabolites rarely allow these three exponential components to be separated. Because codeine is rapidly absorbed and metabolized, these two processes can be mathematically expressed as one exponential term. Hence, eq. 1 can also be used as the unit impulse response function for unconjugated morphine except that K_a should be viewed as the apparent absorption-formation rate constant. The values of K_e, K_a, and V_d used in the model were 0.77 hr^{-1}, 1.26 hr^{-1}, and 10.8 liters/kg based on literature (5, 8), respectively. The bioavailability was initially set to be 10% and was finally determined from the model. Again, the feed activity curve from control animals (4, 7) was used in the model.

Data Analysis. AUC[1] values of codeine, morphine, and their conjugates over the 12-hr blood sampling period were determined by the trapezoidal rule. The standard deviation of AUC was estimated based again on the trapezoidal rule (9). T_{max} and C_{max} were directly determined from the plasma concentration data. *F*-test was used to determine if the calculated AUC values were sex- or dose-dependent. Plasma concentrations of codeine and morphine were evaluated by four-way ANOVA as a function of dose, sex, the day of sampling, and the time of sampling using the program Data Desk® (Odesta Corp., Northbrook, IL).

Results

Some dose-related decreases in body weight gain were observed on days 7, 21, and 90 and were more obvious at 24 months (table 1), which might be related to opiate dependence. Based on the feed consumption data in table 1, codeine at the doses used had very minor impact on the palatability of the dosed feed. The daily intake of codeine increased proportionally with the codeine concentration in feed. Daily intake/body weight was sex-independent (ANOVA, $p > 0.05$) and was gradually decreased over

[1] Abbreviations used are: AUC, area under the curve; T_{max}, time to reach peak concentration; C_{max}, maximum concentration; ANOVA, analysis of variance.

TABLE 4

Comparing C_{max} of plasma concentrations of unconjugated and conjugated codeine and morphine achieved in rats and humans after codeine oral administration

Species	Route	Dose[a]	Codeine		Morphine		Conjugated Codeine		Conjugated Morphine		Sources
			T_{max}	C_{max}	T_{max}	C_{max}	T_{max}	C_{max}	T_{max}	C_{max}	
		mg/kg	hr	ng/ml	hr	ng/ml	hr	ng/ml	hr	ng/ml	
Man	bolus oral	0.6[b]	1.2 ± 0.6	88 ± 25.1	1.2 ± 0.6	2.7 ± 0.6	—	—	—	—	(12)
Man	bolus oral	0.7[c]	0.6 ± 0.2	179 ± 100	1.3 ± 0.9	9.8 ± 5	1.0 ± 0.5	2052 ± 890	1.9 ± 0.7	27.5 ± 31.7	(15)
Sprague-Dawley rat	bolus gavage	3.8[d]	0.1 ± 0.07	101 ± 42	0.1 ± 0.07	69 ± 33	—	—	—	—	(6)
Sprague-Dawley rat	bolus gavage	10	~0.17	~120	~0.19	~75	—	~0	~2.1	~283	(5)
Fischer 344 rat	feed[e]	34 (400 ppm)[f]	11:00 p.m.	37.7 ± 13.2	7:00 a.m.	42.9 ± 2.5	—	~0	7:00 a.m.	339 ± 90	current study
	feed	69 (800 ppm)[f]	11:00 p.m.	128 ± 36	7:00 a.m.	113 ± 6.7	—	~0	7:00 a.m.	2057 ± 370	current study
	feed	134 (1600 ppm)[f]	11:00 p.m.	549 ± 55	3:00 a.m.	254 ± 76.3	—	~0	3:00 a.m.	2905 ± 302	current study

[a] Doses are expressed as codeine free base.
[b] Dose used in the study was 60 mg codeine phosphate per person. Standard body weight (75kg) was used in calculation.
[c] Dose used in the study was 60 mg codeine sulfate per person with average body weight of 73.1 ± 1.6 kg.
[d] Dose used in the study was 5 mg codeine phosphate per kilogram body weight.
[e] Rats were allowed access to dosed-feed 24 hr per day *ad libitum*. Values were obtained on day 7.
[f] Total daily intake of codeine base in feed on day 7 expressed as ng/kg.

the course of study because of the increase in the body weight of the animal.

Plasma concentrations of unconjugated codeine increased with the daily amount of codeine consumed and fluctuated over the course of the study. The peak plasma concentrations of codeine occurred at 11:00 p.m. on day 7 (figs. 1 and 2). Overall, plasma concentration profiles of unconjugated codeine were similar in both sexes. ANOVA analysis indicated that codeine plasma concentrations were dose-dependent ($p < 0.01$). In most cases, female rats had higher plasma concentrations of codeine and its metabolites than males. Plasma concentrations of unconjugated codeine consistently decreased from day 7 to day 90 (ANOVA, $p < 0.01$), which may be related to the decrease of codeine intake over the course of the study (table 1). However, because the drug intake on day 7 and day 21 were comparable, the reduction in plasma codeine concentrations may also have resulted from enzyme induction.

The calculated AUC values of unconjugated codeine are listed in table 2. AUC values increased with dose (F-test, $p < 0.01$) and varied considerably throughout the study. However, the calculated AUC values generally decreased as the study progressed, which indicated that codeine did not accumulate during the study (table 2). Female rats tended to have larger AUC values (ANOVA, $p < 0.01$).

Theoretical plasma concentration profiles on day 7 predicted by the model are also shown in figs. 1 and 2. The prediction was reasonably consistent with the study results. Based on the model results from day 7, bioavailability of codeine from the diet was estimated to be 10, 24, and 25% for 400, 800, and 1,600 ppm dose groups, respectively.

Plasma concentrations of conjugated codeine (presumably codeine-6-glucuronide) were also determined. Results indicated that most codeine was present in plasma as the unconjugated form, and the concentrations of conjugated codeine were very low. Plasma concentrations of total codeine (unconjugated and conjugated) were generally higher in females than in males, but the difference was less consistent than for free codeine. The time courses of plasma concentrations of total codeine (data not presented) were very similar to those shown in fig. 1. As expected, the estimated AUC values of total codeine were slightly higher than the AUC values of unconjugated codeine (table 2) and also increased with dose (F-test, $p < 0.01$).

Unconjugated morphine plasma concentration data are summarized in figs. 3 and 4. Plasma concentrations of unconjugated morphine were generally higher than those of unconjugated codeine in the 400 ppm dose group, but lower than the free codeine concentrations at the two higher dose groups. This finding is also in agreement with earlier observations that morphine was a major metabolite of codeine in the rat. Peak concentrations of unconjugated morphine in the 1600 ppm dose group reached 254 ng/ml on day 7. Plasma concentrations of unconjugated morphine decreased from day 7 to day 90, although the extent of the reduction was less dramatic than for those of the parent drug. The unconjugated morphine AUC data (table 3) indicated that exposure to morphine in the plasma of these rats was generally somewhat less that to codeine (table 2). Unconjugated morphine AUC values approximately increased linearly with dose from 400 to 1600 ppm.

For male rats, morphine plasma concentration profiles on day 7 were also predicted by the model. Again, the prediction was reasonably close to the experimentally determined concentrations (fig. 3, day 7). Based on the modeling results, the bioavail-

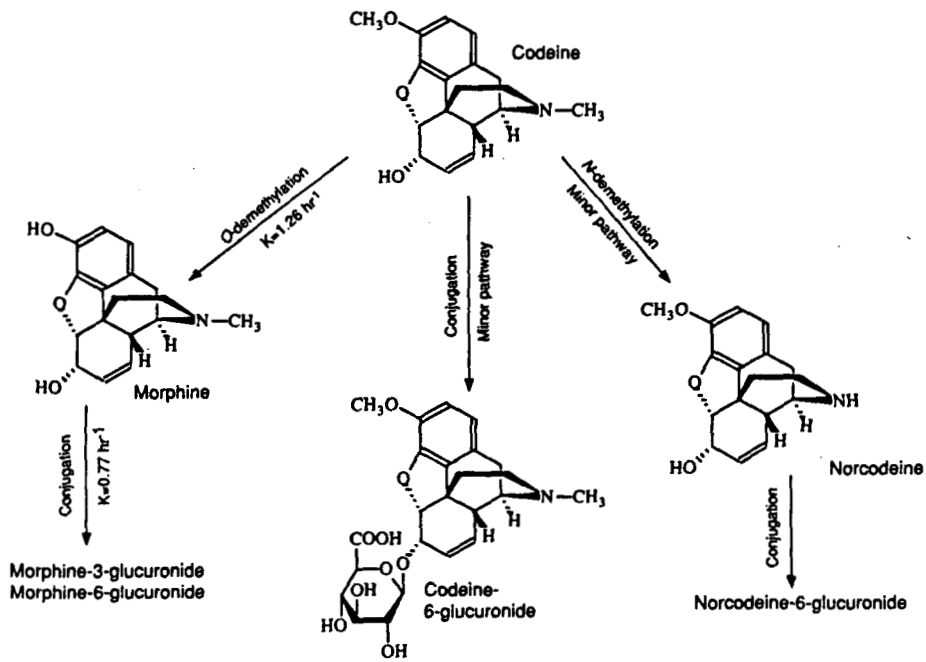

FIG. 6. *Metabolic pathways of codeine in rats (14).*

ability of morphine from codeine diet was estimated to be 15, 20, and 20% for 400, 800, and 1600 ppm dose groups, respectively. For female rats, the prediction was not conducted because of unavailability of the estimated values for K_a, K_e, and V_d (5).

Total morphine plasma concentrations are also summarized in figs. 3 and 4. It is immediately clear that conjugated morphine (presumably morphine-3-glucuronide) circulated in rat plasma at much higher concentrations than either codeine or the primary metabolite, morphine, in their unconjugated forms. This was also consistent with earlier studies. Mean total morphine concentrations frequently exceeded the corresponding unconjugated morphine concentrations by 10- to 20-fold or more. Peak concentrations of total morphine ranged up to 3162 ng/ml, indicating considerably greater exposure of rats to conjugated morphine.

Total morphine AUC data are also presented in table 3. These values were much higher than the AUC values for any other compound measured in the study, again confirming that exposure of these rats to morphine and its conjugated metabolite was much greater than to the parent drug, codeine. Thus, total morphine AUC values were all multiples of the corresponding data for total codeine with the higher multiples being noted at the lower dose groups.

The distribution of codeine and codeine-derived metabolites in plasma (mean ± SE, $N = 360$) based on data from day 7 to day 90 was as follows: free codeine (11.8 ± 0.47%), conjugated codeine (1.42 ± 0.16%), free morphine (9.56 ± 0.30%), and conjugated morphine (77.19 ± 0.63%). These data further indicated a high exposure to conjugated morphine in rats.

Plasma concentrations of codeine and its metabolites between 7:00–8:00 a.m. over the course of the 2-year study are shown in fig. 5. Plasma concentrations of codeine and total codeine steadily decreased from day 7 to 16 months and then rebounded at 24 months. Plasma concentration of morphine showed a steady decrease from day 7 to 16 months then held relatively constant between 16 and 24 months. In contrast, plasma concentrations of total morphine peaked at 16 months and were still relatively high at 24 months. In most cases, female rats showed higher plasma concentrations of codeine and its metabolites than males.

Discussion

Pharmacokinetic studies of codeine in rats and humans have been reported (5, 6, 10–13), and the main metabolic pathways of codeine in rats and humans were also identified (14). Based on the literature and the current findings, the metabolic pathways of codeine in rats are summarized in fig. 6. The rate constants assigned for various pathways were based on the published data (5, 6). A comparison of C_{max} and T_{max} of plasma codeine and morphine in various studies in humans and rats are shown in table 4. The differences of C_{max} in reported human and Sprague–Dawley rat studies might be related to the different analytical methods used in the studies [*i.e.* HPLC with electrochemical detection (6, 12) *vs.* radioimmunoassay (5, 15)]. It can be seen that C_{max} for codeine in rats receiving 800 ppm codeine in the feed is comparable with the mean of C_{max} achieved in humans receiving an oral dose of 60 mg codeine phosphate or codeine sulfate. On the other hand, because the C_{max} values of the codeine metabolite, morphine, obtained in the rat study are much higher than the values obtained in the human study, *O*-demethylation must be the main metabolic pathway in rats but only a minor route in humans (15, 16). This difference may further suggest that the rate of *O*-demethylation of codeine in humans is much slower than in rats. Exposure of rats to codeine-6-glucuronide (indicated by the minor differences in codeine measured before and after enzyme treatment of plasma samples) was much less than that in humans. In contrast, exposure of rats to morphine and its conjugates was much greater than that in humans (table 4).

The higher plasma concentrations of conjugated morphine may be attributed to its smaller V_d because of its enhanced aqueous solubility. Like other glucuronide conjugates, it is also

possible that conjugated morphine may be subject to enterohepatic circulation (17). The presence of high plasma concentrations of morphine conjugates might have a significant impact on the interpretation of the rat codeine chronic study results, because it has been demonstrated that morphine conjugates also possess opioid pharmacological effects in humans (2).

Study results also indicate that the bioavailability of codeine in feed is greater than the ~8% bioavailability of codeine obtained after gavage administration of codeine phosphate (6). This is especially true when the concentration of codeine in the diet is high (*e.g.* the estimated bioavailability of codeine is ~25% at 1600 ppm). This enhanced bioavailability of codeine might be explained by the increase in hepatic perfusion rate as the results of the presence of food in the gastrointestinal tract. It is well known that an increase in hepatic perfusion rate will decrease hepatic transit time, which in turn reduces the time available for *O*-demethylation of codeine in liver during the first pass (18). Therefore, the bioavailability of codeine at higher doses was improved.

The changes of plasma concentration of codeine and its metabolites over the course of this study (fig. 5) suggest that metabolism of codeine and morphine might be increased between day 7 and 16 months. This is evident, because plasma concentrations of codeine and total codeine were lowest at 16 months, whereas the total morphine concentrations were highest despite the decreased intake of chemical on a unit body weight basis (table 1). At 24 months, the metabolic rate for rats is expected to be slower because of the effects of aging on the metabolism of many compounds. This is also consistent with the observation of the rebound of plasma concentrations of codeine and morphine at 24 months.

In conclusion, exposure of rats to codeine through the dosed feed route did not change the metabolic pathways, with *O*-demethylation of codeine remaining the main metabolic pathway. At 800 ppm, the C_{max} of codeine in rats is comparable with the C_{max} of codeine in humans observed after a therapeutic dose of codeine. Accumulation of codeine or its metabolites was not observed over the course of the study. Administering codeine *via* the diet improved the bioavailability of codeine and bioavailability increased with the concentration of codeine in the diet. Plasma concentrations of codeine and its metabolites increased with the codeine concentration in dosed feed. Peak concentrations of codeine and its metabolites occurred between 11 p.m. and 7:00 a.m. Prolonged exposure of rats to codeine resulted in decreased plasma concentrations of codeine and increased total morphine concentrations.

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