NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 223

CARCINOGENESIS STUDIES OF EUGENOL

(CAS NO. 97-53-0)

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

NATIONAL TOXICOLOGY PROGRAM

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

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

NTP TECHNICAL REPORT
ON THE

CARCINOGENESIS STUDIES OF EUGENOL

(CAS NO. 97-53-0)

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

NATIONAL TOXICOLOGY PROGRAM
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NOTE TO THE READER

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

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

Comments and questions about the National Toxicology Program Technical Reports on Carcinogenesis Studies should be directed to the National Toxicology Program, located at Research Triangle Park, NC 27709 (919-541-3991) or at Room 835B, Westwood Towers, 5401 Westbard Ave., Bethesda, MD 20205 (301-496-1152).

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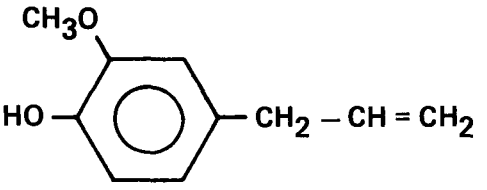
CARCINOGENESIS STUDIES OF EUGENOL



EUGENOL

(1-allyl-3-methoxy-4-hydroxybenzene)

(CAS NO. 97-53-0)

ABSTRACT

Carcinogenesis studies of eugenol (>99% pure), a widely used flavor additive and chemical intermediate, were conducted by feeding diets containing 6,000 or 12,500 ppm of eugenol to groups of 50 female F344/N rats and by feeding diets containing 3,000 or 6,000 ppm to groups of 50 male F344/N rats and B6C3F$_1$ mice of each sex for 103 weeks. Groups of 40 rats and 50 mice of each sex served as controls. Dose levels selected for the two year studies were based on thirteen-week (91-day) studies in which dietary concentrations for the six groups ranged from 0 to 12,500 ppm. Other than a -10% difference from controls in body weights in the 12,500 ppm male rats, no chemically related gross or histopathologic effects were observed.

In the two-year studies, with the exception of the high dose female rats and female mice, final body weights of the treated groups were comparable to their respective controls. No significant differences in survival were apparent for any of the eight groups receiving eugenol and for the appropriate controls. Food consumption among groups was not different in comparison with controls—rats: males ≥97%, females ≥91%; mice: males ≥94%, females ≥90%.

There were no significant observable differences between treated and control groups of rats for either nonneoplastic (toxic) lesions or neoplasms that could be attributed to eugenol. Increases in tumor incidences were diagnosed for low dose male rats with alveolar/bronchiolar adenomas or carcinomas (combined), for C-cell adenomas of the thyroid gland in low dose female rats, and for endometrial stromal polyps of the uterus in high dose female rats. Fibroadenomas of the mammary gland were decreased in dosed groups of female rats compared with controls. None of these differences were considered to be associated with the dietary administration of eugenol.

In male mice, the low dose animals had an increased incidence ($P<0.05$) of both hepatocellular adenomas (control, 4/50; low dose, 13/50; high dose, 10/49) and hepatocellular carcinomas (10/50, 20/50, 9/49) when compared with control animals. A significant increase in hepatic neoplasms was not observed in high dose animals. No single liver tumor type was observed in female mice with a statistically significant increased incidence. When the incidences of female mice with hepatocellular adenoma or carcinoma were combined (2/50, 7/49, 9/49), there was a dose-related positive trend and the incidence of liver neoplasms in high dose animals was higher than in controls ($P<0.05$).

Eugenol was given in the diets of female F344/N rats (0, 0.6, or 1.25%) and of male F344/N rats and male and female B6C3F$_1$ mice (0, 0.3, or 0.6%) for 103 weeks. Under these experimental conditions, there was no evidence of carcinogenicity observed for male or female rats. For mice there was equivocal evidence of carcinogenicity since eugenol caused increased incidences of both carcinomas and adenomas of the liver in male mice at the 3,000 ppm dietary level and because eugenol was associated with an increase in the combined incidences of hepatocellular carcinomas or adenomas in female mice.

CONTRIBUTORS

The carcinogenesis studies of eugenol were conducted at Southern Research Institute under a subcontract to Tracor Jitco, Inc., the prime contractor for the Carcinogenesis Testing Program. The 2-year studies were begun in April and June 1977 for mice and rats, respectively, and ended in April and June 1979.

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SUMMARY OF PEER REVIEW COMMENTS ON THE CARCINOGENESIS STUDIES OF EUGENOL

On 18 February 1981, this carcinogenesis studies technical report on eugenol underwent peer review and was approved by the National Toxicology Program Board of Scientific Counselors' Technical Review Subcommittee and Associated Panel of Experts at an open meeting held in Building 31C, National Institutes of Health, Bethesda, Maryland.

Dr. Schwetz, as a principal reviewer for the report on the carcinogenesis studies of eugenol, agreed with the conclusion that eugenol was not carcinogenic for F344 rats of either sex and that there was some, although equivocal, evidence for increased liver tumors in male and female $B6C3F_1$ mice. He said that the data in the report on the depression in weight gain in females of both species should be more quantitative. In female mice there was a dose-related trend in the incidences of hepatocellular adenomas and carcinomas. He suggested inclusion of the range of these tumors in groups of control mice. Thus, the range of values in historical control groups would be helpful in interpreting the importance of the 6 and 12 percent incidences of hepatocellular carinomas in female mice (see page 124).

Dr. John Doull, on behalf of the Flavoring Extract Manufacturers Association and the Research Institute for Fragrance Materials, said the study was well conducted and the conclusions were supported by the data. He questioned the unknown effects of impurities, particularly in one lot of eugenol; the variation in weight of the rats at the beginning of the two-year studies; and the use of ziram in the same room with the rats being fed eugenol-containing diets.

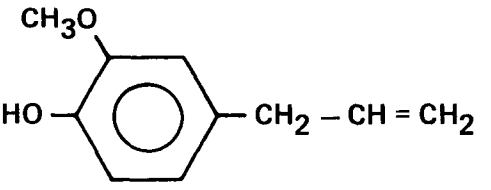
As a second principal reviewer, Dr. Highland disagreed with the conclusion that the findings in mice were equivocal for carcinogenicity. He said the increased liver tumor incidence in male mice supported by the results in female mice were evidence of carcinogenicity. He suggested that the equivocal judgment seems to result from the wide range of control incidences in males for these tumors in the test laboratory. Dr. Haseman, NTP, commented that the mean liver combined tumor rate in male control mice was 32 percent (range 24 to 39 percent) for the nine most recent carcinogenesis studies in the test laboratory where the eugenol studies were performed (data updated as of April 1983). Dr. Highland said he was concerned that we give a consistent evaluation, since, depending on which sets of control data are used, one could arrive at an equivocal result for almost any study. Yet, even using the 32 percent figure, the incidence of liver tumors in the mice receiving the low dose of eugenol was still elevated relative to the controls.

Drs. Swenberg and Hitchcock stated that the important point in support of the conclusion in the report was the lack of dose response. Dr. Williams proposed that the increased incidence in low dose mice might be due to eugenol's acting as a promoter. As support, he cited a study by the Millers (University of Wisconsin) in which eugenol produced no liver tumors in CD-1 male mice while safrole induced a 78 percent incidence. [In 1983, Miller et al. reported a 15 percent liver tumor incidence in untreated male CD-1 mice and 3 percent in females at 12 months.] Dr. Schwetz replied that the result could be interpreted as supporting the equivocal judgment in the current study. Dr. Williams asked that the reference to the Miller's study be cited and, also, a statement be included to note that clove oil, the major ingredient in many mouthwashes, is 85-90 percent eugenol. There was further discussion about the lack of dose response in the results for male mice, and, also, concerning a compromise wording for the conclusion although no unanimity was achieved among the reviewers.

Dr. Schwetz moved that the report on the carcinogenesis studies of eugenol be accepted with the statement that these results are considered equivocal. Dr. Swenberg seconded the motion and the technical report on eugenol was approved by a vote of 6 to 3.

I. INTRODUCTION

I. INTRODUCTION



EUGENOL

(1-allyl-3-methoxy-4-hydroxybenzene)

(CAS NO. 97-53-0)

Eugenol (1-allyl-3-methoxy-4-hydroxybenzene), a colorless or yellowish oily liquid extracted from clove, pimento, bayleaf, and cinnamon oils, is used primarily as a flavoring agent and fragrance (Opdyke, 1975; Balsam and Sagarin, 1972). Oil of clove, containing 85%-95% eugenol, is the major source of this chemical (Kirk-Othmer, 1970). In 1978, 425,000 pounds of eugenol were produced in the United States (USITC, 1979).

Uses

Eugenol is approved for use as a food additive by the U.S. Food and Drug Administration and is on the list of substances "generally recognized as safe" (CFR, 1974). The ADI (acceptable daily intake) for humans has recently been revised to 0-2.5 mg eugenol/kg bw (IPCS, 1982). The average maximum use levels in beverages, ice cream, baked goods, gelatins and puddings, and chewing gums range from 1.4 to 500 ppm, with levels in processed meat products being as high as 2,000 ppm (Furia and Bellanca, 1971). Eugenol is also used as a local anaesthetic in temporary dental fillings and cements (Kirk-Othmer, 1965; U.S. Pharmacopeia, 1975), as a fungicide in pharmaceuticals and cosmetics (Kirk-Othmer, 1966), as an attractant for Japanese beetles (Beroza et al., 1975; Farm Chemicals Handbook, 1977), as a denaturant for alcohol (Kirk-Othmer, 1965), and as a starting material in the synthesis of 3-methyl-4-hydroxybenzaldehyde, commonly known as vanillin (Kirk-Othmer, 1970).

Pharmacologically, eugenol has been reported to exhibit antiseptic properties, analgesic action (local and general), spasmolytic and myorelaxant activities, parasympathetic effects (salivary gland secretion), and direct peripheral vasodilation (Dallmeier and Carlini, 1981).

Acute Toxicity

The oral single dose LD_{50} of eugenol is 2.7 g/kg in Osborne-Mendel rats, 3.0 g/kg in mice (strain and sex not given) (Jenner et al., 1964), and 1.9 g/kg in albino rats (sex not stated) (Sober et al., 1950).

Metabolism

When ^{14}C-eugenol (450 mg/kg) was administered to male Wistar rats by intraperitoneal injection, radioactivity was distributed to most organs (Weinberg et al., 1972). The major portion (percent unstated) of the radioactive material recovered from tissues was unaltered ^{14}C-eugenol. By 24 hours, approximately 1% of the injected ^{14}C had been exhaled as carbon dioxide. Trace radioactivity was found in all tissues examined 100 hours after administration.

Delaforge et al. (1980) have shown that eugenol (as well as other related alkenylbenzenes) undergoes biotransformation through an epoxide-diol metabolic pathway. Eugenol epoxide and allylcatechol epoxide and the corresponding dihydrodiols (dihydrodihydroxy eugenol and dihydrodihydroxy allylcatechol) were detected in the urine of male Wistar rats given a single intraperitoneal injection of 200 mg/kg eugenol in corn oil. The allylcatechol metabolites constitute the major metabolites of eugenol, safrole, and eugenol methyl ether (Delaforge et al., 1980).

Genetic Toxicity

Eugenol was not mutagenic for *Salmonella typhimurium* TA1964, TA1535, TA1532, TA1531, TA1530, TA100, and TA98, with or without metabolic activation (Delaforge et al., 1977; Dorange et al., 1977; Green and Savage, 1978; Swanson et al., 1979; Eder et al., 1980). At concentrations up to 333 μ g/plate eugenol was

not mutagenic in *Salmonella* TA98, TA100, TA1535, or TA1537, with or without exogenous metabolic activation. The 9,000 x g microsomal fraction was obtained from Aroclor 1254®-induced Sprague-Dawley rat or Syrian golden hamster liver (Appendix H, Tables H1 and H2). Samples were preincubated prior to plating in triplicate, and each series was repeated. Leleng et al. (1982) reported slight increases in revertants for *Salmonella* TA98 (32 ± 6.0 versus 22 ± 4.7) at 500 μg eugenol/plate without activation but not for strains TA100, TA1535, TA1537, TA1538. Greater increases were seen with microsomal activation in TA1537 at 10, 50, 150, and 500 μg/plate, but not with TA98, TA100, TA1535, and TA1538. In view of these marginal differences in numbers of revertants and considering other negative findings these reported increases should not be taken as evidence of a mutagenic response.

The 2', 3'-oxide of eugenol was also tested because this chemical was identified following incubation of eugenol with female mouse liver microsomes (Swanson et al., 1978) as well as with epithelial liver cell cultures (Delaforge et al., 1977). Eugenol-2',3'-oxide was mutagenic in *Salmonella* TA1535, with or without activation (Delaforge et al., 1977; Dorange et al., 1977; Swanson et al., 1979). Under the preincubation protocol described above, neither methyl eugenol (93-15-2) (Appendix H) nor isoeugenol (97-51-1) was mutagenic for *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537.

In Chinese hamster ovary cells, eugenol induced both chromosome aberrations and sister chromatid exchanges (Appendix I). The aberrations were observed after activation, whereas exchanges were found with or without microsomal influence.

Carcinogenicity

Eugenol, a known tobacco leaf phenol, was reported to be a weak promoter of skin tumorigenesis initiated by 7,12-dimethylbenz(a)anthracene (DMBA) in female ICR/Ha Swiss mice. After 63 weeks, 3 of 14 mice pretreated with 150 μg DMBA and then painted with 5 mg eugenol three times per week had papillomas, compared with no papillomas in 9 mice pretreated with DMBA alone and followed by 0.1 ml acetone (solvent), and none in 13 mice painted with eugenol alone (Van Duuren et al., 1966).

The structurally related compound safrole (1-allyl-3,4-methylenedioxybenzene) has been found to cause increased incidences of hepatomas in (C57BL/6 × C3H/Anf)F_1 mice of either sex and in female (C57BL/6 × AKR)F_1 mice when administered by gavage or in feed (Innes et al., 1968). When safrole was fed in diets, increased incidences of liver tumors (74% were hepatocellular carcinomas or cholangiocarcinomas) were detected in male and female Osborne-Mendel rats (Long et al., 1963), and increased incidences of hepatocellular carcinomas were observed in male CD-1 mice (Borchert et al., 1973). Safrole has also been found to be a liver carcinogen in Balb/c mice (Lipsky et al., 1979; Lipsky et al., 1980).

In a recent report of a series of publications on the carcinogenic activity of alkenylbenzene derivatives related to safrole and estragole, results on the carcinogenesis testing of eugenol and methyleugenol were described by Miller et al. (1983). In these studies eugenol given during the preweaning period to CD-1 mice by stomach tube (2.5 μmol/g twice weekly for five weeks to male and females) or by intraperitoneal injection (once weekly for four weeks, total dose = 9.45 μmol/g to males) did not cause any hepatocarcinogenic activity after 14 (oral) or 12 (injection) months of observation. The metabolite eugenol-2',3'-oxide was likewise inactive when tested by the intraperitoneal route. These protocols have proved sensitive for the detection of chemically induced hepatic neoplasms (Brochert et al., 1973; Drinkwater et al., 1973; Epstein et al., 1970; Miller et al., 1979; Miller et al., 1983; Roe, 1975).

Two groups of 30 female CD-1 mice ate diets containing 0.5% eugenol (5,000 ppm) for 12 months followed by a grain diet without eugenol for 6 months; one group also received 0.05% phenobarbital in the drinking water for the full 18 months. Neither group developed hepatomas. None of the diet controls and 2 of the phenobarbital controls developed hepatomas (Miller et al., 1983).

In a dermal experiment, eugenol-2',3'-oxide was applied topically to groups of 40 female CD-1 mice 4 days/week for 6 weeks (45 μmol/week) followed by local skin exposure twice weekly to croton oil (0.15 ml of a 0.6% solution in acetone) for another 34 weeks. At the end of the 40-week study, eugenol-2',3'-oxide induced skin tumors in 16/40 (40%) with 0.9 tumors per mouse versus the acetone controls having 3/40 (7%) with 0.1 per mouse. The tumors were epidermal papillomas and keratoacanthomas (Miller et al., 1983).

I. INTRODUCTION

Methyl eugenol and 1'-hydroxymethyleugenol were tested by the intraperitoneal injection route in male $B6C3F_1$ mice. Chemicals were administered on days 1, 8, 15, and 22. At the end of the 18 month study, the number of "hepatomas/bearing mice" for methyl eugenol (total dose = 4.75 μmol) was 56/58 (96%) with 3.2 hepatomas/mouse and for 1'-hydroxymethyleugenol (total dose = 2.85 μmol) was 41/44 (93%) with 3.5/mouse, both compared with trioctanol controls having 24/58 (41%) and 0.5/mouse ($P<0.001$) (Miller et al., 1983).

Miller et al. (1983) concluded that methyl eugenol and 1'-hydroxymethyleugenol appear to be as carcinogenic in the mouse liver as safrole and estragole. Eugenol and eugenol-2',3'-oxide did not cause any hepatocarcinogenic responses in these systems.

Testing Rationale

Eugenol was tested because of widespread use, because of structural similarity to a chemical (safrole) shown to cause neoplasms of the liver in rats and mice, and because previous carcinogenesis studies were considered to be inadequate. Additionally, methyl eugenol has been selected by the NTP for further testing.

II. MATERIALS AND METHODS

CHEMICAL ANALYSES

PREPARATION OF TEST DIETS

SOURCE AND SPECIFICATIONS OF TEST ANIMALS

ANIMAL MAINTENANCE

SHORT-TERM STUDIES

Single-Dose Studies

Fourteen-Day Studies

Thirteen-Week Studies

TWO-YEAR STUDIES

Clinical Examinations and Pathology

Data Recording and Statistical Methods

CHEMICAL ANALYSES

U.S.P. extra grade eugenol (also sold as food grade) was obtained in two batches from Givaudan Corporation (Clifton, NJ). Lot No. 36483 was used for the short-term studies and the first 52 weeks of the two-year studies. Lot No. 26068 was used for the final 52 weeks of the two-year studies. Both lots were >99% pure.

Purity and identity analyses performed at Midwest Research Institute were consistent with the structure (Appendix J). Results of thin-layer chromatography indicated one homogeneous component. Results of vapor-phase chromatography with one system indicated a single homogeneous peak for Lot No. 26068, but two impurities, each with an area 0.1% of the area of the major peak, were observed for Lot No. 36483. When a second vapor-phase chromatography system was used, an impurity with an area 0.09% of the area of the major peak was detected in Lot No. 26068. Four small impurities in Lot No. 36483 were detected by high-pressure liquid chromatography. The impurities were not further characterized (Appendix J).

Both batches of chemical were periodically analyzed throughout the studies by Southern Research Institute using vapor-phase chromatography (Midwest Research Institute, Systems 1 and 2) and infrared spectroscopy. The results from these analyses indicated no change in the composition of the test material during the studies.

The chemical was stored at 20°-24°C during the short-term studies and thereafter at 5°C.

PREPARATION OF TEST DIETS

Sample diet mixtures containing 100,000 ppm eugenol were analyzed at Midwest Research Institute. Eugenol in feed was found to be stable for 2 weeks at temperatures as high as 45°C (Appendix K).

Test diets were prepared by mixing Wayne® Lab Blox meal (Table 1) and eugenol in a Patterson-Kelly® twin-shell laboratory blender for 15 minutes. Eugenol was added to the meal through a liquid dispersion bar. The test diets were stored at 5°C for 1 week followed by no more than 1 week at 21°-23°C.

Dosed feed samples from the short-term and two-year studies were analyzed. In the two-year studies, the mean concentration of eugenol in 26 randomly selected dosed feed samples containing a target level of 6,000 ppm was 6,014±568 ppm. The mean concentration of eugenol in 22 samples containing a target level of 3,000 ppm was 2,799±281 ppm and in eight samples containing a target level of 12,500 ppm was 13,037±947 ppm (Appendix L).

SOURCE AND SPECIFICATIONS OF TEST ANIMALS

The male and female F344/N rats and B6C3F$_1$ mice used in the 14-day, 13-week, and two-year studies were obtained from the NCI Frederick Cancer Research Center (Frederick, Maryland). The F344/N rats and B6C3F$_1$ C57BL/6N × C3H/HeN MTV$^-$) mice used in these studies were produced under strict barrier conditions. Breeding starts for the foundation colony at the production facility originated at the National Institutes of Health Repository. Animals shipped for these studies were progeny of defined microbially associated parents which were transferred from isolators to barrier maintained rooms. Animals were shipped to the testing laboratory at 4-5 weeks of age.

Upon receipt, the animals were isolated for 7-8 days and examined for the presence of parasites or other diseases. In all of the studies, the animals were assigned randomly by species and sex to cages and then the cages were assigned randomly to dosed and control groups. The rats and mice were 6-7 weeks old at the beginning of each study.

ANIMAL MAINTENANCE

The rats and mice were housed five per cage in suspended solid-bottom polycarbonate cages (Table 1) covered with Reemay® spun-bonded polyester filters and Dupont style #2024 filters. Hardwood chip bedding was changed twice per week, and feed hoppers (stainless steel for rats and glazed clay for mice) were changed and washed once per week. Cages were washed twice per week in a tunnel cage dish washer at 82°C.

An automatic watering system supplied tap water. Feed was available *ad libitum*. Animal rooms were maintained at 21°-23°C and humidity was 30%-50%. Incoming air was filtered through fiberglass roughing filters. Room air was changed 15 times per hour. Fluorescent lighting was provided 12 hours per day.

TABLE 1. SPECIFICATIONS AND SOURCES OF MATERIALS USED FOR ANIMAL MAINTENANCE

Item	Specifications	Source
Bedding	Beta® chips	Northeastern Products, Inc. (Warrensburg, NY)
Cages	Solid bottom, polycarbonate	Lab Products, Inc. (Garfield, NJ)
Feed	Wayne Lab Blox® meal	Allied Mills, Inc. (Chicago, IL)
Watering System	Edstrom Automatic	Edstrom Industries (Waterford, WI)
Cage Filters	Reemay® spun-bonded polyester Dupont #2024	Snow Filtration (Cincinnati, OH)
Cage and Rack Washing Compound	MWC Compound	Vestal Laboratories (St. Louis, MO)

SHORT-TERM STUDIES

Single dose oral and 14-day repeated dose feed studies were conducted using F344/N rats and B6C3F$_1$ mice to determine toxicity, potential target organs, and the concentrations of eugenol to be used in the 13-week studies.

Single-Dose Studies

In the single dose oral toxicity study, groups of five males and five females of each species were administered 150 to 3,000 mg/kg eugenol in a 1% solution of carboxymethylcellulose in saline by gavage. Surviving animals were killed on day 16. Deaths occurred in 1/5 female rats receiving 2,000 mg/kg, 1/5 male mice administered 750 mg/kg, and 2/5 male mice and 5/5 female mice administered 3,000 mg/kg. One death occurred in the group of female rats administered 250 mg/kg as a result of gavage error (Tables 2 and 3).

TABLE 2. SURVIVAL AND MEAN BODY WEIGHTS OF RATS ADMINISTERED A SINGLE DOSE OF EUGENOL BY GAVAGE *(a)*

Dose *(b)* (mg/kg)	Survival *(c)* (day of death)	Mean Body Weights (grams)		
		Initial	Final	Change *(d)*
Males				
150	5/5	92 ± 5.8	147 ± 5.4	55 ± 0.8
250	5/5	87 ± 6.5	150 ± 8.1	63 ± 2.2
500	5/5	89 ± 7.6	150 ± 7.9	61 ± 3.5
1,000	5/5	86 ± 8.3	140 ± 12.1	54 ± 4.6
2,000	5/5	75 ± 5.1	131 ± 5.2	56 ± 3.7
Females				
150	5/5	74 ± 3.9	108 ± 3.1	33 ± 1.3
250	4/5 *(e)*	80 ± 3.3	114 ± 2.7	34 ± 2.1
500	5/5	83 ± 5.6	113 ± 6.6	30 ± 2.0
1,000	5/5	73 ± 4.6	114 ± 9.0	41 ± 1.9
2,000	4/5 (2)	78 ± 3.5	107 ± 2.7	29 ± 1.4

(a) Untreated controls were not included in this test.
(b) In 1% solution of carboxymethylcellulose in saline.
(c) Number surviving/number per group.
(d) Mean weight change of the group ± standard error of the mean.
(e) Accidental death by gavage error.

TABLE 3. SURVIVAL AND MEAN BODY WEIGHTS OF MICE ADMINISTERED A SINGLE DOSE OF EUGENOL BY GAVAGE *(a)*

Dose *(b)* (mg/kg)	Survival *(c)* (day of death)	Mean Body Weights (grams)		
		Initial	Final	Change *(d)*
Males				
180	5/5	20 ± 0.9	25 ± 1.0	5 ± 0.4
375	5/5	19 ± 1.0	24 ± 1.3	5 ± 0.5
750	4/5 (6)	21 ± 1.1	26 ± 0.5	5 ± 0.9
1,500	5/5	19 ± 0.9	23 ± 0.8	4 ± 0.4
3,000	3/5 (1,2)	19 ± 1.0	23 ± 0.9	4 ± 1.2
Females				
180	5/5	15 ± 0.5	19 ± 0.4	4 ± 0.5
375	5/5	16 ± 0.6	20 ± 0.4	4 ± 0.4
750	5/5	16 ± 0.7	20 ± 0.5	4 ± 0.7
1,500	5/5	16 ± 0.4	19 ± 0.5	3 ± 0.4
3,000	0/5 (1,1,2,2,2)	16 ± 0.3	—	—

(a) Untreated controls were not included in this test.
(b) In 1% solution of carboxymethylcellulose in saline.
(c) Number surviving/number per group.
(d) Mean weight change of the group ± standard error of the mean.

Fourteen-Day Studies

In the fourteen-day studies, groups of five males and five females of each species were administered 6,000 to 100,000 ppm eugenol in feed for 14 days (Tables 4 and 5). No control group was used. All surviving animals were killed on day 15. One of five male rats and all female rats that received 100,000 ppm died. A dose-associated decrease in mean body weight gain was observed for both male and female rats at or above 25,000 ppm. Male rats that received 100,000 ppm lost weight. Deaths occurred in three of five male mice that received 50,000 ppm eugenol and in all male and female mice that received 100,000 ppm. A dose-associated decrease in mean body weight gain was observed for both male and female mice. Weight loss occurred in male mice that received 12,500 ppm and in all mice that received 25,000 or 50,000 ppm.

TABLE 4. SURVIVAL AND MEAN BODY WEIGHTS OF RATS FED DIETS CONTAINING EUGENOL FOR 14 DAYS *(a)*

Dose (ppm)	Survival *(b)* (day of death)	Mean Body Weights (grams)		
		Initial	Final	Change *(c)*
Males				
6,000	5/5	82 ± 2.3	128 ± 2.6	+46 ± 2.3
12,500	5/5	91 ± 6.6	133 ± 5.0	+42 ± 2.6
25,000	5/5	92 ± 4.5	128 ± 5.9	+36 ± 3.1
50,000	5/5	90 ± 6.5	103 ± 8.2	+13 ± 3.3
100,000	4/5 (9)	98 ± 5.8	72 ± 3.8	-26 ± 5.1
Females				
6,000	5/5	89 ± 3.0	121 ± 3.4	+32 ± 3.1
12,500	5/5	85 ± 3.3	118 ± 1.5	+33 ± 2.7
25,000	5/5	79 ± 4.2	101 ± 3.4	+22 ± 1.2
50,000	5/5	74 ± 1.8	82 ± 3.0	+ 8 ± 2.2
100,000	0/5 (7,8,8,9,10)	77 ± 3.6	—	—

(a) Untreated controls were not included in this test.
(b) Number surviving/number per group.
(c) Mean weight change of the group ± standard error of the mean.

TABLE 5. SURVIVAL AND MEAN BODY WEIGHTS OF MICE FED DIETS CONTAINING EUGENOL FOR 14 DAYS *(a)*

Dose (ppm)	Survival *(b)* (day of death)	Mean Body Weights (grams)		
		Initial	Final	Change *(c)*
Males				
6,000	5/5	19 ± 0.7	22 ± 1.0	+3 ± 1.0
12,500	5/5	21 ± 0.6	20 ± 1.0	−1 ± 0.9
25,000	5/5	20 ± 0.5	17 ± 1.0	−3 ± 1.2
50,000	2/5 (10,10,15)	20 ± 0.4	13 ± 0.9	−7 ± 1.0
100,000	0/5 (11,11,12 12,13)	21 ± 0.5	—	—
Females				
6,000	5/5	17 ± 0.6	18 ± 0.5	+1 ± 0.2
12,500	5/5	17 ± 0.6	18 ± 0.4	+1 ± 0.2
25,000	5/5	17 ± 0.4	15 ± 0.7	−2 ± 1.0
50,000	5/5	17 ± 0.5	12 ± 0.4	−5 ± 0.7
100,000	0/5 (7,7, 7,7,8)	18 ± 0.4	—	—

(a) Untreated controls were not included in this test.
(b) Number surviving/number per group.
(c) Mean weight change of the group ± standard error of the mean.

Thirteen-Week Studies

These studies were conducted to evaluate the cumulative toxicity of the test material, to identify organs affected, and to determine the most appropriate doses for the two-year studies. Weight gain data and results of histopathologic examination were used in determining the concentrations to be used in the two-year studies. Diets containing 0, 800, 1,500, 3,000, 6,000, or 12,500 ppm eugenol were fed for 13 weeks to groups of 10 male and 10 female rats (Table 6), and groups of 10 male and 10 female mice received diets with 0, 400, 800, 1,500, 3,000, or 6,000 ppm (Table 7). Observations for clinical signs or mortality were made twice daily and animals were weighed weekly. At the end of the 91-day study, survivors were killed, necropsies were performed on all animals, and tissues from the controls and the highest dose group were taken for histopathologic analysis.

Final body weights were 10% less for male rats receiving 12,500 ppm when compared to controls; weights of female rats at the 12,500 ppm dietary level were 6% less. No compound-related histopathologic effects were observed. No deaths occurred among the rats. Doses selected for the two-year studies were 3,000 and 6,000 ppm for males and 6,000 and 12,500 ppm for females.

No significant differences in body weights were observed among groups of mice. No deaths occurred among the mice and no dose-related gross or histopathologic effects were observed. Doses for the mice for the chronic study were set at 3,000 and 6,000 ppm for both male and female mice.

TABLE 6. SURVIVAL AND MEAN BODY WEIGHTS OF RATS FED DIETS CONTAINING EUGENOL FOR 13 WEEKS

Dose (ppm)	Survival *(a)*	Mean Body Weights (grams)			Final Body Weights Relative to Controls (Percent) *(c)*
		Initial	Final	Change *(b)*	
Males					
0	10/10	69 ± 3.8	334 ± 5.4	+265 ± 3.4	—
800	9/9	66 ± 2.6	330 ± 4.9	+264 ± 3.6	- 1
1,500	10/10	68 ± 2.6	324 ± 5.2	+256 ± 5.4	- 3
3,000	10/10	68 ± 3.4	324 ± 6.1	+256 ± 5.4	- 3
6,000	10/10	63 ± 2.4	309 ± 3.8	+246 ± 3.4	- 7
12,500	10/10	68 ± 3.1	300 ± 3.9	+232 ± 4.4	-10
Females					
0	10/10	71 ± 1.8	190 ± 1.9	+119 ± 1.8	—
800	10/10	68 ± 2.9	188 ± 2.4	+120 ± 2.5	-1
1,500	10/10	71 ± 2.1	188 ± 3.4	+117 ± 2.3	-1
3,000	10/10	65 ± 1.0	184 ± 2.4	+119 ± 2.5	-3
6,000	9/9	69 ± 1.8	184 ± 2.0	+115 ± 2.7	-3
12,500	10/10	66 ± 1.8	178 ± 2.2	+112 ± 2.5	-6

(a) Number surviving/number per group.
(b) Mean weight change of the group ± standard error of the mean.
(c) Weight relative to controls =

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

TABLE 7. SURVIVAL AND MEAN BODY WEIGHTS OF MICE FED DIETS CONTAINING EUGENOL FOR 13 WEEKS

Dose (ppm)	Survival *(a)*	Mean Body Weights (grams)			Final Body Weights Relative to Controls (Percent) *(c)*
		Initial	Final	Change *(b)*	
Males					
0	10/10	21 ± 0.5	31 ± 0.5	+10 ± 0.5	—
400	10/10	22 ± 0.6	32 ± 0.7	+10 ± 0.9	+3
800	10/10	22 ± 0.6	33 ± 0.5	+11 ± 0.6	+6
1,500	10/10	22 ± 0.7	32 ± 0.5	+10 ± 0.4	+3
3,000	10/10	21 ± 0.4	31 ± 0.5	+10 ± 0.6	0
6,000	10/10	22 ± 0.5	31 ± 0.5	+ 9 ± 0.5	0
Females					
0	10/10	17 ± 0.3	24 ± 0.4	+ 7 ± 0.3	—
400	10/10	18 ± 0.4	24 ± 0.7	+ 6 ± 0.4	0
800	10/10	17 ± 0.4	24 ± 0.5	+ 7 ± 0.4	0
1,500	10/10	17 ± 0.4	23 ± 0.5	+ 6 ± 0.2	-4
3,000	10/10	17 ± 0.4	23 ± 0.5	+ 6 ± 0.3	-4
6,000	10/10	17 ± 0.3	24 ± 0.3	+ 7 ± 0.3	0

(a) Number surviving/number per group.
(b) Mean weight changes of the group ± standard error of the mean.
(c) Weight relative to controls =

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

TWO-YEAR STUDIES

The test groups, doses administered, and durations of the two-year studies are shown in Table 8. For the first 9 months of the two-year studies, rats fed eugenol and the controls were housed in the same room as rats on feeding studies of mannitol (CAS No. 69-65-8) and ziram (CAS No. 137-30-4). For the first year of the two year studies, mice fed eugenol and the controls were housed with mice on feeding studies of mannitol and ziram. Then the mice were moved to the room in which the rats were on test with eugenol. No other chemicals were then on test in that room.

TABLE 8. EXPERIMENTAL DESIGN OF TWO-YEAR FEEDING STUDIES WITH EUGENOL IN RATS AND MICE

Test Group	Initial No. of Animals	Dose (ppm)	Weeks on Study	
			Dosed *(a)*	Not dosed
Male Rats				
Control *(b)*	40	0	0	105
Low Dose	50	3,000	103	1
High Dose	50	6,000	103	1
Female Rats				
Control *(b)*	40	0	0	105
Low Dose	50	6,000	103	2
High Dose	50	12,500	103	1
Male Mice				
Control *(b)*	50	0	0	105
Low Dose	50	3,000	103	2
High Dose	50	6,000	103	1
Female Mice				
Control *(b)*	50	0	0	105-106
Low Dose	50	3,000	103	2
High Dose	50	6,000	103	1

(a) The start dates were June 3, 1977, for rats and April 12, 1977, for mice. The kill dates were June 1, 1979, for rats and April 10, 1979, for mice.

(b) Control and dosed groups were of the same strain, sex, and age range and from the same source and shipment. All animals of the same species shared the same room, and all aspects of animal care and maintenance were similar. Animals were randomized to dosed and control groups as described in Section II.C.

Clinical Examinations and Pathology

All animals were observed twice daily for morbidity or mortality. Clinical signs were recorded monthly. Individual animals were weighed weekly for the first 13 weeks, then monthly to week 93, and every 2 weeks thereafter. The mean body weight of each group was calculated by dividing the total weight of all animals in the group by the number of surviving animals in the group. Moribund animals and animals that survived to the end of the bioassay were killed with carbon dioxide.

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

Necropsies were performed on all animals not excessively autolyzed or cannibalized. Thus, the number of animals from which particular organs or tissues were examined microscopically is not necessarily equal to the number of animals that were placed on study in each group.

Neoplastic nodules of the liver were classified according to the recommendations of Squire and Levitt (1975) and the National Academy of Sciences (1980).

When the pathology examination was completed, the slides, individual animal data records, and summary tables were sent to an independent quality assurance laboratory. Individual animal records and tables were compared for accuracy, slides and tissue counts were verified, and histotechniques were evaluated. All tumor diagnoses, all target tissues, and all tissues from a randomly selected 10 percent of the animals were evaluated by an experienced pathologist. Slides of all target tissues and those on which the original and quality assurance pathologists disagreed were submitted to the Chairperson of the Pathology Working Group (PWG) for evaluation. Representative slides selected by the PWG Chairperson were reviewed blindly by the PWG pathologists, who reached a consensus and compared their findings with the original diagnoses. When disagreements occurred, the PWG sent the appropriate slides and their comments to the original pathologist for review. (This procedure has been described, in part, by Ward et al., 1978, and by Maronpot and Boorman, 1982). The final diagnosis represents a consensus of contractor pathologists and the NTP Pathology Working Group.

Data Recording and Statistical Analyses

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

Probabilities of survival were estimated by the product-limit procedure of Kaplan and Meier (1958) and are presented in this report in the form of graphs. Animals were statistically censored as of the time that they died of other than natural causes or were found to be missing; animals dying from natural causes were not statistically censored. Statistical analyses for a possible dose-related effect on survival used the method of Cox (1972) for testing two groups for equality and Tarone's (1975) extensions of Cox's methods for testing for a dose-related trend.

The incidence of neoplastic or nonneoplastic lesions has been given as the ratio of the number of animals bearing such lesions at a specific anatomic site to the number of animals in which that site was examined. In most instances, the denominators included only those animals for which that site was examined microscopically. However, when macroscopic examination was required to detect lesions (e.g., skin or mammary tumors) prior to microscopic sampling or when lesions could have appeared at multiple sites (e.g., lymphomas), the denominators consist of the numbers of animals necropsied.

For the statistical analysis of tumor incidence data, two different methods of adjusting for intercurrent mortality were employed. Each used the classical methods for combining contingency tables developed by Mantel and Haenszel (1959). Tests of significance included pairwise

comparisons of high and low dose groups with controls and tests for overall dose-response trends.

The first method of analysis assumed that all tumors of a given type observed in animals dying before the end of the study were "fatal," i.e., they either directly or indirectly caused the death of the animal. According to this approach, the proportions of tumor-bearing animals in the dosed and control groups were compared at each point in time at which an animal died with a tumor of interest. The denominators of these proportions were the total number of animals at risk in each group. These results, including the data from animals killed at the end of the study, were then combined by the Mantel-Haenszel methods to obtain an overall P-value. This method of adjusting for intercurrent mortality is the life table method of Cox (1972) and of Tarone (1975).

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

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

For studies in which there is little effect of compound administration on survival, the results of the three alternative analyses will generally be similar. When differing results are obtained by the three methods, the final interpretation of the data will depend on the extent to which the tumor under consideration is regarded as being the cause of death.

III. RESULTS

RATS

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

MICE

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

RATS
TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights for male rats and low dose females were comparable among groups. For high dose female rats mean body weights were lower than controls throughout most of the studies (Table 9 and Figure 1). The average daily feed consumption per rat by low dose and high dose male rats was 98% and 97% and for females it was 94% and 91% that of the controls (Appendix E).

Survival

Estimates of the probabilities of survival of male and female rats administered eugenol in the diet at the concentrations used in these carcinogenesis studies and those of the controls are shown by the Kaplan and Meier curves in Figure 2. No significant differences were found between any of the groups of either male or female rats.

In male rats, 23/40 (58%) of the controls, 26/50 (52%) of the low dose, and 37/50 (74%) of the high dose group lived to the end of the study at 105 weeks. In female rats, 30/40 (75%) of the controls, 36/50 (72%) of the low dose, and 44/50 (88%) of the high dose group lived to the end of the study at 105 weeks.

TABLE 9. MEAN BODY WEIGHTS (RELATIVE TO CONTROLS) OF RATS FED DIETS CONTAINING EUGENOL FOR TWO YEARS

Weeks on Study	Vehicle Control		Low Dose			High Dose		
	Av. Wt. (grams)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of controls)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of controls)	No. of Survivors
MALE								
0	94	40	93	98.9	50	90	95.7	50
4	195	40	199	102.1	50	193	99.0	50
8	259	40	260	100.4	50	253	97.7	50
13	307	40	308	100.3	50	306	99.7	50
17	333	40	335	100.6	50	331	99.4	50
21	365	40	365	100.0	50	363	99.5	50
25	377	40	386	102.4	50	375	99.5	50
28	391	40	397	101.5	50	385	98.5	50
34	404	40	405	100.2	50	381	94.3	50
38	411	40	410	99.8	50	399	97.1	50
42	408	40	419	102.7	50	406	99.5	50
46	435	40	430	98.9	50	417	95.9	50
51	428	39	427	99.8	50	415	97.0	49
55	432	39	434	100.5	50	418	96.8	49
59	444	39	439	98.9	50	423	95.3	49
64	439	39	440	100.2	49	413	94.1	49
68	447	39	439	98.2	49	421	94.2	49
72	442	39	439	99.3	49	424	95.9	48
77	453	37	437	96.5	48	430	94.9	48
81	442	36	427	96.6	45	423	95.7	48
86	443	35	430	97.1	42	418	94.4	48
90	438	33	433	98.9	41	417	95.2	46
94	437	32	422	96.6	40	410	93.8	42
98	432	29	418	96.8	38	407	94.2	40
102	422	27	413	97.9	29	402	95.3	37
104	418	25	413	98.8	26	404	96.7	37
FEMALE								
0	83	40	85	102.4	50	85	102.4	50
4	140	40	136	97.1	50	131	93.6	50
8	168	40	167	99.4	50	158	94.0	50
13	188	40	186	98.9	50	175	93.1	50
17	188	40	189	100.5	50	183	97.3	50
21	203	40	199	98.0	50	196	96.6	50
25	205	40	203	99.0	50	196	95.6	50
28	214	40	212	99.1	50	203	94.9	50
34	214	40	208	97.2	50	199	93.0	50
38	218	40	217	99.5	50	207	95.0	50
42	220	40	216	98.2	50	208	94.5	50
46	227	40	221	97.4	50	211	93.0	50
51	232	40	220	94.8	50	208	89.7	50
55	239	40	223	93.3	50	213	89.1	50
59	240	40	226	94.2	50	216	90.0	50
64	244	40	230	94.3	50	221	90.6	50
68	254	40	241	94.9	50	223	87.8	50
72	258	40	244	94.6	49	225	87.2	50
77	269	40	255	94.8	49	235	87.4	50
81	274	39	253	92.3	49	234	85.4	49
86	280	38	266	95.0	48	242	86.4	49
90	281	37	272	96.8	48	247	87.9	48
94	287	36	273	95.1	48	245	85.4	48
98	289	34	274	94.8	45	251	86.9	46
102	291	33	281	96.6	38	253	86.9	45
104	290	30	293	101.0	36	271	93.4	44

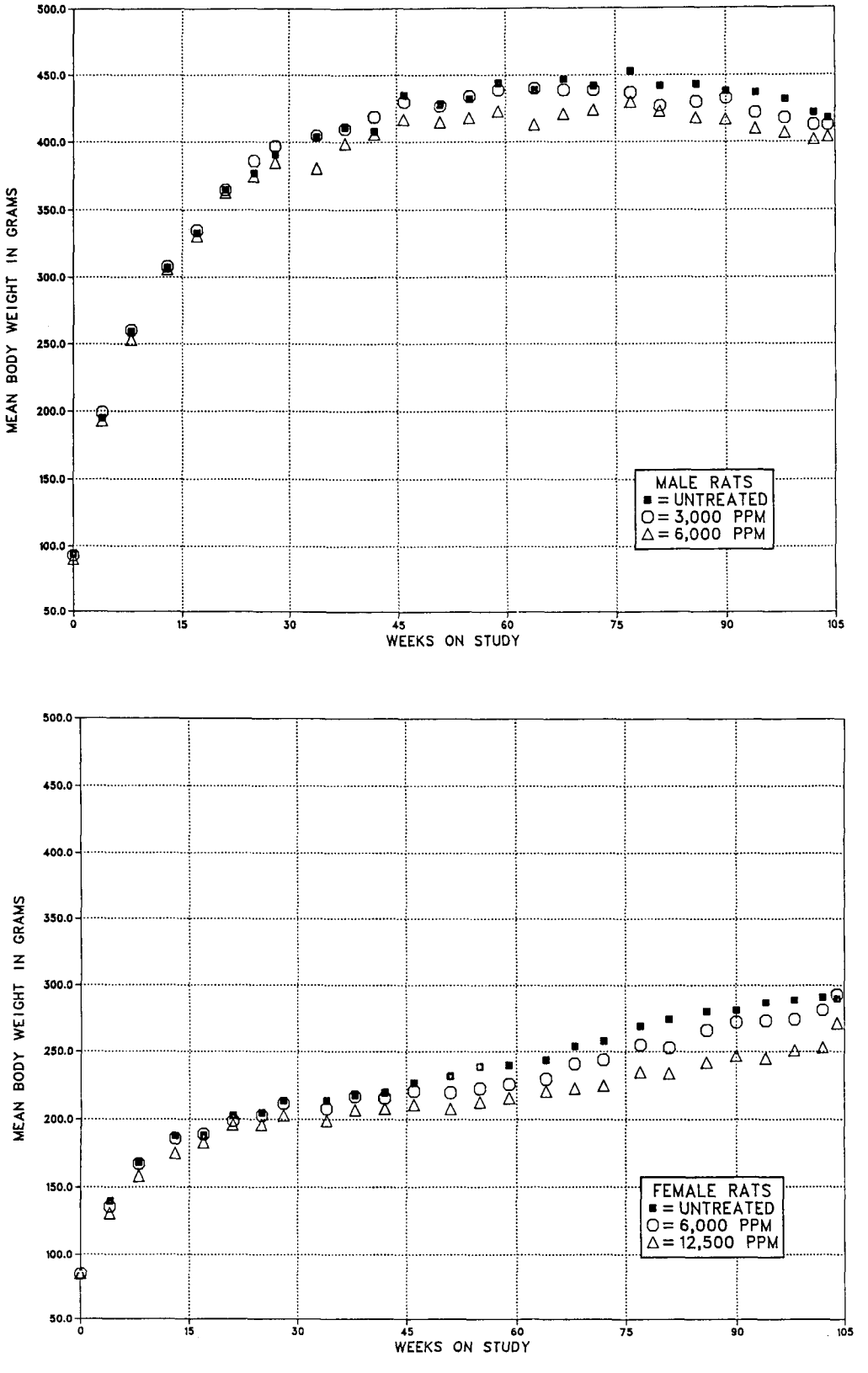
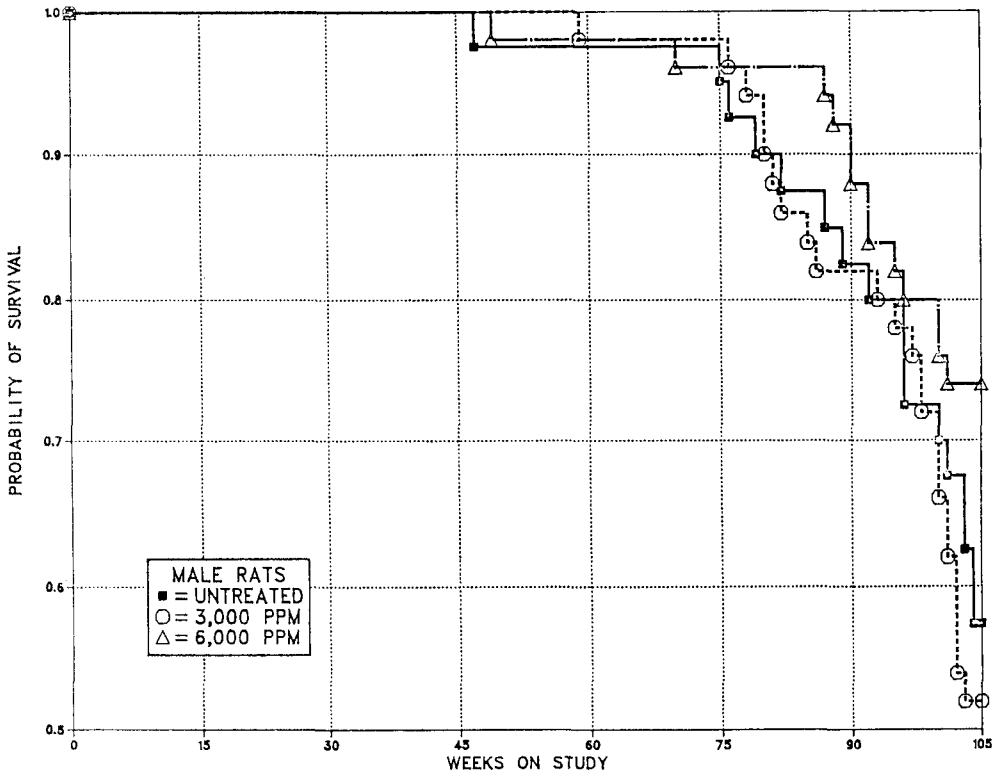


Figure 1. Growth Curves for Rats Fed Diets Containing Eugenol



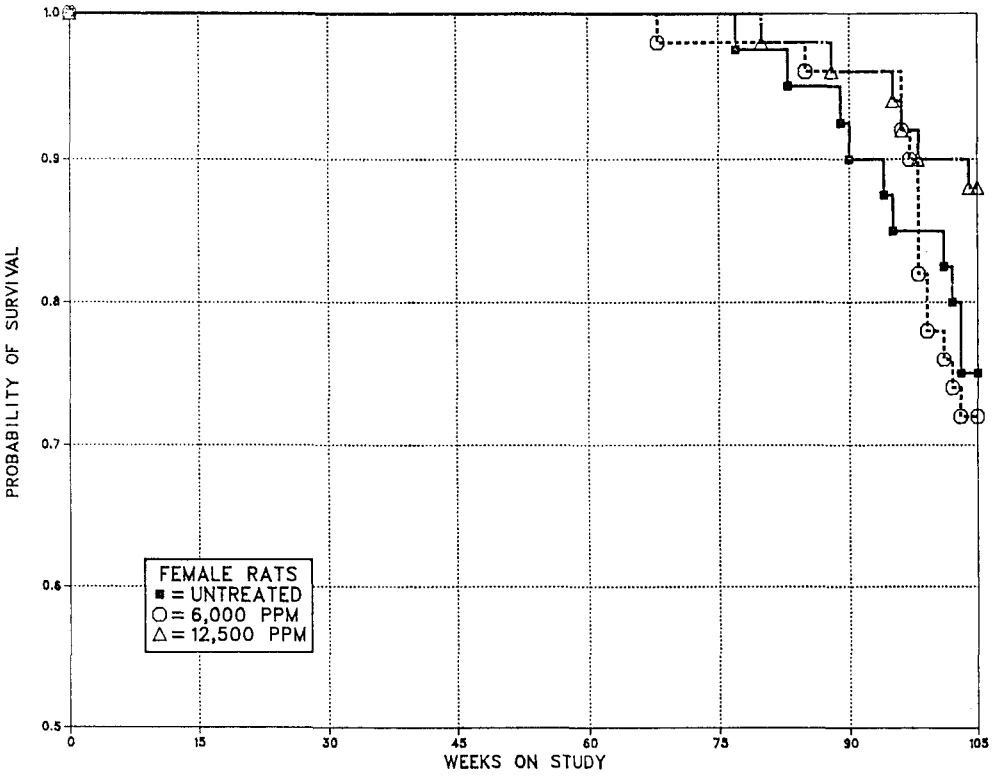


Figure 2. Survival Curves for Rats Fed Diets Containing Eugenol

Pathology and Statistical Analyses of Results

Histopathologic findings on neoplasms in rats are summarized in Appendix A, Tables A1 and A2; Appendix Tables A3 and A4 give the survival and tumor status for individual male and female rats. Findings on nonneoplastic lesions are summarized in Appendix C, Tables C1 and C2. Appendix G, Tables G1 and G2 contain the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the groups. The statistical analyses used are discussed in Chapter II (Data Recording and Statistical Methods). Significant increases or decreases in the occurrence of particular neoplasms are presented below.

Lung: Alveolar/bronchiolar adenomas or carcinomas of the lung in male rats occurred with an increased ($P<0.05$) incidence in the low dose group compared with the other two groups (0/40; 5/49, 10%; 2/50, 4%) (Table 10). The historical incidence of male F344 rats with either alveolar/bronchiolar adenomas or carcinomas (combined) reported at this laboratory is 15/438 (3%). No significant increase was observed in the high dose group. The corresponding rates of these tumors in female rats were 1/39, 1/50, and 0/50.

Thyroid: C-cell adenomas of the thyroid in female rats occurred with an increased incidence ($P<0.05$) in the low dose group compared with the other two groups (3/40, 8%; 11/49, 22%; 2/50, 4%) (Table 11). No significant increase was observed in the high dose group, and when the incidences of female rats with either carcinomas or adenomas were combined, there were no significant results. The incidences of C-cell adenomas of the thyroid in males showed a negative ($P<0.05$) trend: 4/40, 5/50, 0/50. The combined incidence in male rats also showed a negative ($P<0.05$) trend: 7/40, 8/50, 2/50.

TABLE 10. INCIDENCES OF MALE RATS WITH ALVEOLAR/BRONCHIOLAR ADENOMA OR CARCINOMA

	Control	3,000 ppm	6,000 ppm
Alveolar/Bronchiolar Carcinoma			
Overall Incidence	0/40 (0%)	3/49 (6%)	0/50 (0%)
Adjusted Incidence	0.0%	11.5%	0.0%
Terminal Incidence	0/25 (0%)	3/26 (12%)	0/37 (0%)
Life Table Test	P=0.526N	P=0.126	*(a)*
Incidental Tumor Test	P=0.526N	P=0.126	*(a)*
Cochran-Armitage Trend Test	P=0.582N		
Fisher Exact Test		P=0.162	*(a)*
Weeks to First Observed Tumor		104	—
Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Incidence	0/40 (0%)	5/49 (10%)	2/50 (4%)
Adjusted Incidence	0.0%	17.4%	5.4%
Terminal Incidence	0/25 (0%)	4/26 (15%)	2/37 (5%)
Life Table Test	P=0.390	P=0.041	P=0.328
Incidental Tumor Test	P=0.358	P=0.049	P=0.328
Cochran-Armitage Trend Test	P=0.315		
Fisher Exact Test		P=0.046	P=0.306
Weeks to First Observed Tumor		93	104

(a) Statistical comparisons were not done because no tumors were observed in control or dosed groups.

TABLE 11. INCIDENCES OF RATS WITH C-CELL NEOPLASMS OF THE THYROID GLAND

	Control	3,000 ppm	6,000 ppm
Males			
C-Cell Adenoma			
Overall Incidence	4/40 (10%)	5/50 (10%)	0/50 (0%)
Adjusted Incidence	14.5%	15.5%	0.0%
Terminal Incidence	2/25 (8%)	3/26 (12%)	0/37 (0%)
Life Table Test	P=0.030N	P=0.563	P=0.029N
Incidental Tumor Test	P=0.038N	P=0.601N	P=0.055N
Cochran-Armitage Trend Test	P=0.037N		
Fisher Exact Test		P=0.634N	P=0.036N
Weeks to First Observed Tumor	100	80	—
C-Cell Carcinoma			
Overall Incidence	3/40 (8%)	3/50 (6%)	2/50 (4%)
Adjusted Incidence	10.9%	11.5%	5.1%
Terminal Incidence	2/25 (8%)	3/26 (12%)	1/37 (3%)
Life Table Test	P=0.254N	P=0.633N	P=0.346N
Incidental Tumor Test	P=0.295N	P=0.591N	P=0.454N
Cochran-Armitage Trend Test	P=0.313N		
Fisher Exact Test		P=0.550N	P=0.395N
Weeks to First Observed Tumor	96	104	100
C-Cell Adenoma or Carcinoma			
Overall Incidence	7/40 (18%)	8/50 (16%)	2/50 (4%)
Adjusted Incidence	24.3%	26.5%	5.1%
Terminal Incidence	4/25 (16%)	6/26 (23%)	1/37 (3%)
Life Table Test	P=0.021N	P=0.572	P=0.027N
Incidental Tumor Test	P=0.030N	P=0.530N	P=0.056N
Cochran-Armitage Trend Test	P=0.032N		
Fisher Exact Test		P=0.535N	P=0.039N
Weeks to First Observed Tumor	96	80	100

	Control	6,000 ppm	12,500 ppm
Females			
C-Cell Adenoma			
Overall Incidence	3/40 (8%)	11/49 (22%)	2/50 (4%)
Adjusted Incidence	10.0%	28.1%	4.4%
Terminal Incidence	3/30 (10%)	8/35 (23%)	2/45 (4%)
Life Table Test	P=0.187N	P=0.048	P=0.319N
Incidental Tumor Test	P=0.253N	P=0.040	P=0.319N
Cochran-Armitage Trend Test	P=0.271N		
Fisher Exact Test		P=0.049	P=0.395N
Weeks to First Observed Tumor	105	85	104
C-Cell Carcinoma			
Overall Incidence	4/40 (10%)	1/49 (2%)	4/50 (8%)
Adjusted Incidence	12.8%	2.9%	8.9%
Terminal Incidence	3/30 (10%)	1/35 (3%)	4/45 (9%)
Life Table Test	P=0.399N	P=0.138N	P=0.416N
Incidental Tumor Test	P=0.441N	P=0.111N	P=0.490N
Cochran-Armitage Trend Test	P=0.493N		
Fisher Exact Test		P=0.124N	P=0.512N
Weeks to First Observed Tumor	103	105	104
C-Cell Adenoma or Carcinoma			
Overall Incidence	7/40 (18%)	12/49 (24%)	6/50 (12%)
Adjusted Incidence	22.5%	30.7%	13.3%
Terminal Inccidence	6/30 (20%)	9/35 (26%)	6/45 (13%)
Life Table Test	P=0.149N	P=0.269	P=0.217N
Incidental Tumor Test	P=0.215N	P=0.271	P=0.264N
Cochran-Armitage Trend Test	P=0.254N		
Fisher Exact Test		P=0.296	P=0.330N
Weeks to First Observed Tumor	103	85	104

Uterus: There was a positive trend (P*k*0.05) and a marginally (P=0.051) increased incidence of endometrial stromal polyps of the uterus in female rats in the high dose group (6/40, 15%; 6/50, 12%; and 16/50, 32%) (Table 12). The 32% incidence in the high dose group is above the historical average for this laboratory (66/438, 15%).

TABLE 12. INCIDENCES OF FEMALE RATS WITH TUMORS OF THE UTERUS

	Control	6,000 ppm	12,500 ppm
Uterus: Endometrial Stromal Polyp or Sarcoma			
Overall Incidence	6/40 (15%)	6/50 (12%)	16/50 (32%)
Adjusted Incidence	18.3%	15.2%	35.6%
Terminal Inccidence	4/30 (13%)	4/36 (11%)	16/45 (36%)
Life Table Test	P=0.062	P=0.479N	P=0.121
Incidental Tumor Test	P=0.031	P=0.369N	P=0.077
Cochran-Armitage Trend Test	P=0.022		
Fisher Exact Test		P=0.456N	P=0.051
Weeks to First Observed Tumor	94	98	104

Mammary Gland: Fibroadenomas of the mammary gland in female rats were decreased (P<0.05) in the dosed groups compared with the control group (Table 13). The incidence of female F344 rats with fibroadenomas of the mammary gland at this laboratory is 120/439 (27%), which is lower than the 14/40 (35%) reported in the controls in this study. The corresponding rates for this tumor in male rats were 0/40, 3/50, and 2/50.

TABLE 13. INCIDENCES OF FEMALE RATS WITH MAMMARY GLAND FIBROADENOMA

	Control	6,000 ppm	12,500 ppm
Overall Incidence	14/40 (35%)	8/50 (16%)	6/50 (12%)
Adjusted Incidence	40.9%	20.7%	13.3%
Terminal Incidence	10/30 (33%)	6/36 (17%)	5/45 (11%)
Life Table Test	P=0.003N	P=0.050N	P=0.004N
Incidental Tumor Test	P=0.007N	P=0.030N	P=0.014N
Cochran-Armitage Trend Test	P=0.007N		
Fisher Exact Test		P=0.034N	P=0.009N
Weeks to First Observed Tumor	89	98	95

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights were comparable among all groups except the 6,000 ppm female mice, which were 14 and 11 percent lower than controls at weeks 101 and 104, respectively (Table 14 and Figure 3). No compound-related clinical signs were observed. The average daily feed consumption per mouse by low and high dose mice was 97% and 94% that of the controls for males and 95% and 90% for females (Appendix E).

Survival

No significant differences in survival were seen between any of the groups of either sex; survival of the high dose males was somewhat lower than that in the other groups after week 38 and the survival in the low dose female group was lower after week 80. Estimates of the probabilities of survival of male and female mice administered eugenol in the diet at the concentrations of these studies and those of the control group are shown by the Kaplan and Meier curves in Figure 4.

In male mice, 41/50 (82%) of the controls, 35/50 (70%) of the low dose, and 35/50 (70%) of the high dose group lived to the end of the study at 106 weeks. In female mice, 43/50 (86%) of the controls, 40/50 (80%) of the low dose, and 45/50 (90%) of the high dose group lived to the end of the study at 106 weeks. Five of the low dose male mice were accidentally killed during week 13 of the study, at which time they were censored from the statistical analysis of survival.

TABLE 14. MEAN BODY WEIGHTS (RELATIVE TO CONTROLS) OF MICE FED DIETS CONTAINING EUGENOL FOR TWO YEARS

Weeks on Study	Vehicle Control		Low Dose			High Dose		
	Av. Wt. (grams)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of controls)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of controls)	No. of Survivors
MALE								
0	18	50	19	105.6	50	19	105.6	50
7	28	50	29	103.6	50	28	100.0	50
11	32	50	31	96.9	50	31	96.9	50
15	32	50	32	100.0	45	32	100.0	49
20	34	50	34	100.0	45	33	97.1	49
24	35	49	35	100.0	45	34	97.1	49
28	36	49	36	100.0	45	35	97.2	49
32	36	49	37	102.8	45	36	100.0	49
36	35	49	36	102.9	45	36	102.9	49
41	37	49	36	97.3	45	37	100.0	48
46	37	49	36	97.3	45	36	97.3	47
49	36	49	37	102.8	45	35	97.2	47
53	38	49	37	97.4	45	37	97.4	47
58	39	49	38	97.4	45	37	94.9	47
62	40	49	38	95.0	45	38	95.0	47
66	41	48	39	95.1	44	39	95.1	47
71	40	47	38	95.0	43	37	92.5	44
75	41	47	39	95.1	41	38	92.7	44
79	40	47	39	97.5	41	38	95.0	44
84	40	46	39	97.5	41	39	97.5	43
88	39	45	39	100.0	39	38	97.4	42
93	40	44	38	95.0	39	38	95.0	40
97	39	43	38	97.4	38	38	97.4	37
101	39	43	38	97.4	38	38	97.4	37
104	39	41	38	97.4	36	38	97.4	36
FEMALE								
0	16	50	16	100.0	50	16	100.0	50
7	22	50	22	100.0	50	22	100.0	50
11	25	50	24	96.0	50	24	96.0	50
15	25	50	24	96.0	50	25	100.0	50
20	26	50	25	96.2	50	25	96.2	50
24	27	50	27	100.0	50	26	96.3	50
28	29	50	28	96.6	50	27	93.1	50
32	29	50	28	96.6	50	28	96.6	50
36	28	50	27	96.4	50	28	100.0	50
41	28	50	29	103.6	49	28	100.0	50
46	29	50	29	100.0	49	28	96.6	49
49	30	50	29	96.7	49	28	93.3	49
53	31	50	30	96.8	49	29	93.5	49
58	31	49	31	100.0	49	29	93.5	49
62	32	49	31	96.9	49	30	93.8	49
66	31	49	31	100.0	49	30	96.8	49
71	34	49	34	100.0	48	31	91.2	48
75	34	49	34	100.0	48	31	91.2	48
79	33	49	32	97.0	48	31	93.9	48
84	34	48	33	97.1	47	31	91.2	48
88	33	48	32	97.0	44	31	93.9	48
93	35	47	35	100.0	43	32	91.4	48
97	35	45	34	97.1	43	32	91.4	47
101	36	44	35	97.2	41	31	86.1	46
104	35	43	33	94.3	40	31	88.6	45

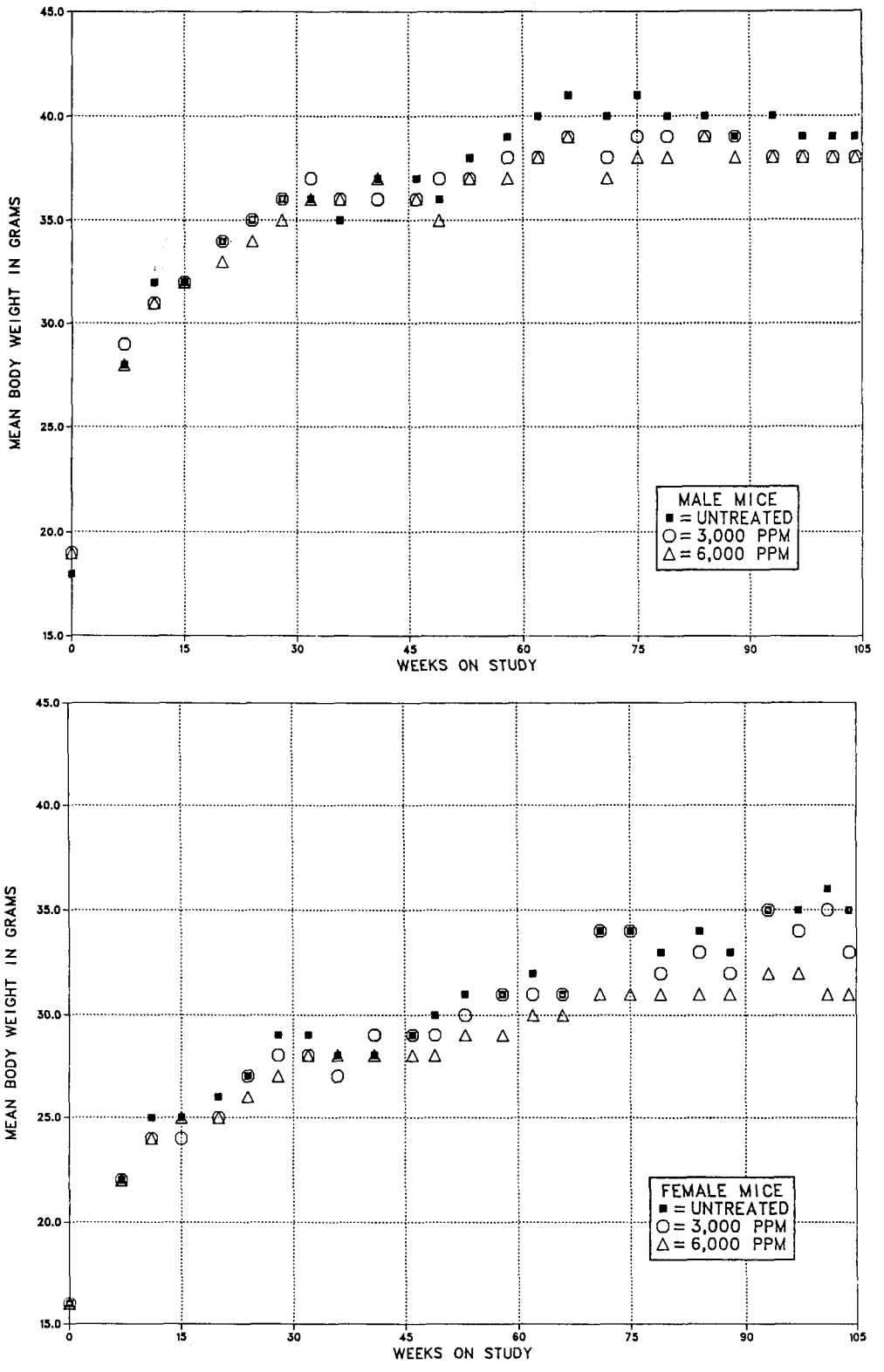


Figure 3. Growth Curves for Mice Fed Diets Containing Eugenol

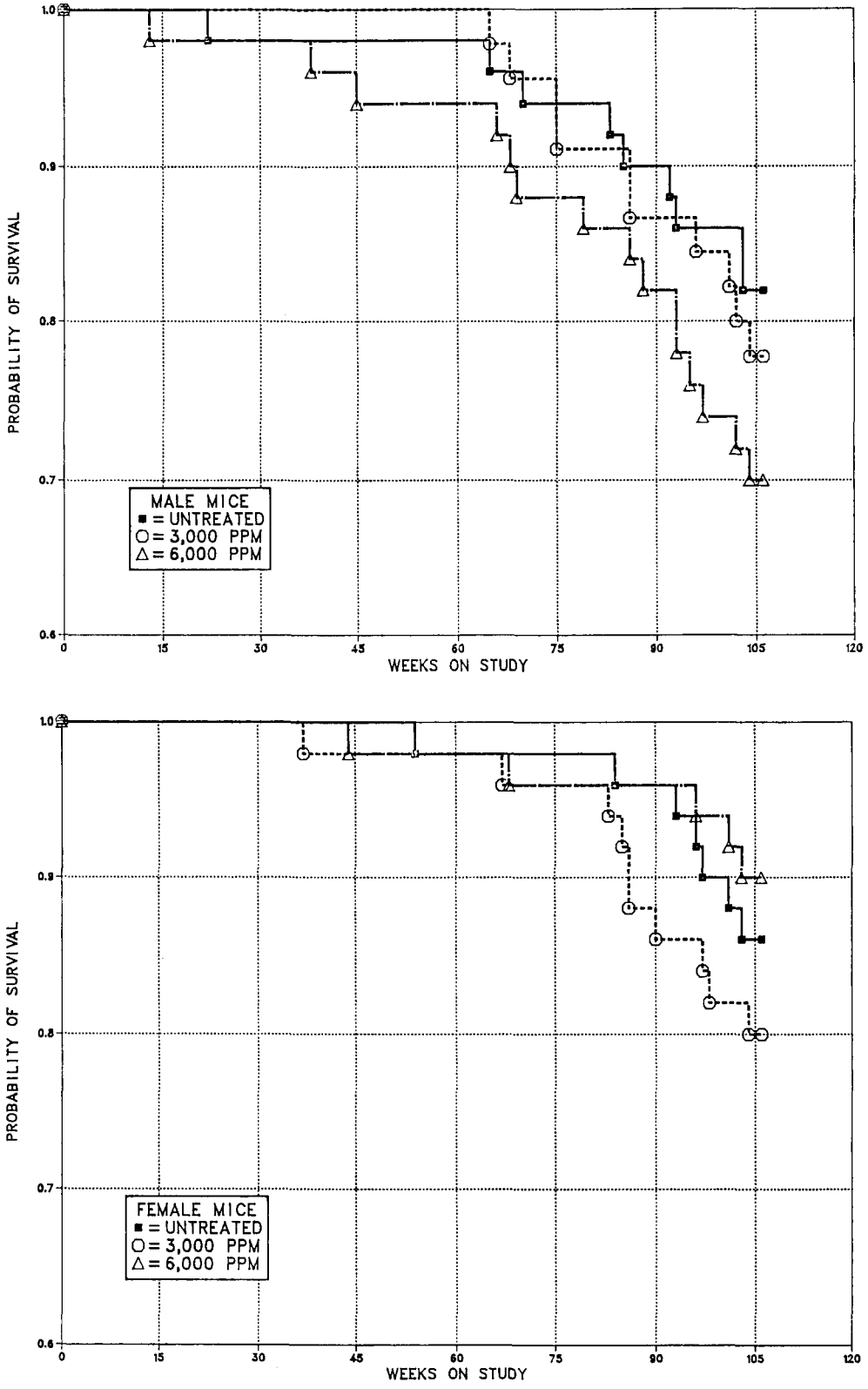


Figure 4. Survival Curves for Mice Fed Diets Containing Eugenol

Pathology and Statistical Analyses of Results

Histopathologic findings on neoplasms in mice are summarized in Appendix B, Tables B1 and B2; Appendix Tables B3 and B4 give the survival and tumor status for individual male and female mice. Findings on nonneoplastic lesions are summarized in Appendix D, Tables D1 and D2. Historical incidences of tumors in control animals are listed in Appendix F, Tables F1 and F2. Appendix G, Tables G3 and G4 contain the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the groups. The statistical analyses used are discussed in Chapter II (Data Recording and Statistical Methods). Significant increases or decreases in the occurrence of particular neoplasms are presented below.

Liver: Adenomas and carcinomas of the liver were increased ($P<0.05$) in low dose male mice; combining male mice with liver tumors strengthened the evidence for an increased ($P<0.005$) incidence in low dose mice. The rates in the high dose group were not different from those observed in controls (Table 15). Comparisons of either hepatocellular adenomas or carcinomas observed in female mice with controls resulted in no significant differences (Table 15). Combining the incidences of these progressive tumor types indicates a compound-associated dose-related increase ($P<0.05$) and the incidence in the high dose group was higher than that in controls ($P<0.05$).

Lesions diagnosed as hepatocellular adenomas consisted of solid nodules of well-differentiated hepatocytes and compressed adjacent hepatic parenchyma. Hepatocytes in these lesions were often larger, with cytoplasm that was more vacuolated and was often basophilic. Compared with hepatocellular adenomas, hepatocellular carcinomas in general had a more disorderly arrangement of hepatocytes, usually with evidence of invasive growth into adjoining hepatic tissue. A key criterion for diagnosing hepatocellular carcinoma was the arrangement of hepatocytes into trabeculae. One male mouse in the low dose group had a liver tumor that had some areas characteristic of hepatocellular carcinoma, as well as areas consisting of a disorderly proliferation of structures resembling bile ducts. That tumor was classified as a mixed hepatocellular/cholangiocarcinoma. A few tumors in each male group metastasized to the lung (control, 2; low dose, 3; high dose, 2). Only one tumor in the females (low dose) metastasized.

TABLE 15. INCIDENCES OF MICE WITH LIVER TUMORS

	Control	3,000 ppm	6,000 ppm
Males			
Hepatocellular Adenoma			
Overall Incidence	4/50 (8%)	13/50 (26%)	10/49 (20%)
Adjusted Incidence	9.8%	36.1%	24.7%
Terminal Incidence	4/41 (10%)	13/36 (36%)	7/36 (19%)
Life Table Test	P=0.044	P=0.006	P=0.051
Incidental Tumor Test	P=0.049	P=0.006	P=0.070
Cochran-Armitage Trend Test	P=0.069		
Fisher Exact Test		P=0.016	P=0.068
Weeks to First Observed Tumor	105	105	45
Hepatocellular Carcinoma			
Overall Incidence	10/50 (20%)	20/50 (40%)	9/49 (18%)
Adjusted Incidence	23.2%	46.3%	20.1%
Terminal Incidence	8/41(20%)	13/36 (36%)	2/36 (6%)
Life Table Test	P=0.502	P=0.014	P=0.591
Incidental Tumor Test	P=0.366N	P=0.015	P=0.371N
Cochran-Armitage Trend Test	P=0.478N		
Fisher Exact Test		P=0.024	P=0.520N
Weeks to First Observed Tumor	93	65	66
Hepatocellular Adenoma or Carcinoma			
Overall Incidence	14/50 (28%)	28/50 (56%)	18/49 (37%)
Adjusted Incidence	32.5%	65.0%	39.3%
Terminal Incidence	12/41 (29%)	21/36 (58%)	9/36 (25%)
Life Table Test	P=0.145	P=0.002	P=0.176
Incidental Tumor Test	P=0.248	P=0.001	P=0.318
Cochran-Armitage Trend Test	P=0.212		
Fisher Exact Test		P=0.004	P=0.238
Weeks to First Observed Tumor	93	65	45
Females			
Hepatocellular Adenoma			
Overall Incidence	0/50 (0%)	4/49 (8%)	3/49 (6%)
Adjusted Incidence	0.0%	9.8%	6.5%
Terminal Incidence	0/43 (0%)	4/41 (10%)	2/45 (4%)
Life Table Test	P=0.133	P=0.057	P=0.131
Incidental Tumor Test	P=0.101	P=0.057	P=0.077
Cochran-Armitage Trend Test	P=0.114		
Fisher Exact Test		P=0.056	P=0.117
Weeks to First Observed Tumor		105	103
Hepatocellular Carcinoma			
Overall Incidence	2/50 (4%)	3/49 (6%)	6/49 (12%)
Adjusted Incidence	4.7%	6.8%	13.3%
Terminal Incidence	2/43(5%)	1/41 (2%)	6/45 (13%)
Life Table Test	P=0.104	P=0.477	P=0.149
Incidental Tumor Test	P=0.066	P=0.532	P=0.149
Cochran-Armitage Trend Test	P=0.085		
Fisher Exact Test		P=0.490	P=0.128
Weeks to First Observed Tumor	105	86	104
Hepatocellular Adenoma or Carcinoma			
Overall Incidence	2/50 (4%)	7/49 (14%)	9/49 (18%)
Adjusted Incidence	4.7%	16.1%	19.6%
Terminal Incidence	2/43 (5%)	5/41 (12%)	8/45 (18%)
Life Table Test	P=0.031	P=0.074	P=0.034
Incidental Tumor Test	P=0.014	P=0.081	P=0.024
Cochran-Armitage Trend Test	P=0.021		
Fisher Exact Test		P=0.075	P=0.023
Weeks to First Observed Tumor	105	86	103

Thyroid: Follicular cell adenomas of the thyroid gland in male mice occurred with an increased ($P<0.05$) trend (control 0/48, 0%; low dose 0/49, 0%; high dose 3/49, 6%) (Table 16). The corresponding rates for this tumor in female mice were 2/48, 0/47, and 1/49.

TABLE 16. INCIDENCES OF MALE MICE WITH FOLLICULAR CELL ADENOMAS OF THE THYROID

	Control	3,000 ppm	6,000 ppm
Follicular Cell Adenoma			
Overall Incidence	0/48 (0%)	0/49 (0%)	3/49 (6%)
Adjusted Incidence	0.0%	0.0%	8.3%
Terminal Incidence	0/41 (0%)	0/36 (0%)	3/36 (8%)
Life Table Test	P=0.031	*(a)*	P=0.099
Incidental Tumor Test	P=0.031	*(a)*	P=0.099
Cochran-Armitage Trend Test	P=0.038		
Fisher Exact Test		*(a)*	P=0.125
Weeks to First Observed Tumor			104

(a) Statistical comparisons were not done because no tumors were observed in control or dosed groups.

IV. DISCUSSION AND CONCLUSIONS

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Overall, placement of eugenol in the diets of rats and mice did not adversely affect food consumption, body weights, or survival; female rats and female mice at the 6,000 ppm level did show reductions in body weights of about 14 percent compared to controls.

The doses chosen for the two-year studies were based on body weights and survival data obtained from the fourteen-day and thirteen-week studies: female rats (0, 6,000, 12,500 ppm) and male rats and male and female mice (0, 3,000, 6,000 ppm). In retrospect and in view of the lack of effects during the two-year studies, the selected doses may have been less than maximal for male rats and male mice. Whether these animals would have eaten (tolerated) higher concentrations remains speculative. Nonetheless, these levels and those for females are considered adequate for testing the potential carcinogenicity of eugenol for these strains of rodents.

Increased incidences of hepatocellular carcinomas and of hepatocellular adenomas were detected in male mice receiving the diet containing 3,000 ppm eugenol. These tumors were not increased significantly in the high dose (6,000 ppm) group when compared to controls. Combining all liver tumors within groups and making the appropriate comparisons further magnified the significantly increased incidence in the low dose males. While the high dose group had a greater incidence than the controls (18/49, 37%, versus 14/50, 28%) this marginal difference was not statistically significant. Neither adenomas nor carcinomas of the liver alone were significantly increased in female mice; yet the combined incidence of liver tumors showed a positive dose-related trend and the neoplasms observed in the high dose group were significantly greater than those found in the controls (2/50, 7/49, 9/49). The adenomatous lesions consisted of solid nodules made up of well differentiated hepatocytes and compressed the adjacent hepatic parenchyma. The hepatocytes were large, vacuolated, and basophilic. Carcinomas were diagnosed as having disordered and poorly differentiated hepatocytes, usually invading surrounding hepatic tissue, and were trabecular in arrangement. These hepatocellular lesions were considered to be associated with the dietary administration of eugenol. Nevertheless the lack of a dose-response effect in male mice and the marginal combined increases in female mice render this interpretation somewhat less than unequivocal evidence of carcinogenicity.

In a series of experiments, Miller et al. (1983) have tested a number of naturally occurring and synthetic alkenylbenzene derivatives for carcinogenicity in the mouse and rat. Findings from their experiments on eugenol and on chemicals structurally similar to eugenol are summarized in the following discussion. To obtain more details about these structure-activity investigations one should begin with the Miller et al. (1983) paper.

Safrole (1-allyl-3,4-methylenedioxybenzene), a major constituent of sassafras oil and a component of certain other essential oils, has induced hepatic neoplasms when fed for long periods in the diets (0.5 to 1%) of rats and mice, and when given to CD-1 mice during the preweaning period; renal carcinomas developed in B6C3F1 mice born to mothers given safrole during pregnancy. Estragole (1-allyl-4-methoxybenzene), a major constituent of tarragon (estragon) oils and sweet basil, and the proximate carcinogenic metabolite 1'-hydroxyestragole, caused hepatic neoplasms in male CD-1 mice given intraperitoneal injections prior to weaning and when offered in the diet of female CD-1 mice for 12 months.

Methyl eugenol (1-allyl-3,4-dimethoxybenzene), and food flavoring agent, is not mutagenic for *Salmonella* and has been selected for further testing by the NTP. Miller et al. (1983) showed that methyl eugenol and the 1'-hydroxy metabolite induced hepatocellular neoplasms in male $B6C3F_1$ mice treated prior to weaning, similar to estragole and 1'-hydroxyestragole. Eugenol (1-allyl-4-hydroxyl-3-methoxybenzene) was inactive in intraperitoneal injection studies using preweaned male CD-1 or male $B6C3F_1$ mice and in a 12-month diet experiment in female CD-1 mice.

The 2',3'-oxide metabolites of safrole, estragole, and eugenol had little or no activity in the preweaning test system; however, those 2',3'-oxides did induce benign skin tumors that could be promoted with croton oil when applied topically to female CD-1 mice. Van Duuren et al. (1966) reported that eugenol was a weak promoter for ICR Swiss mouse skin following initiation by DMBA.

These data show that certain of the alkenylbenzene derivatives related to safrole and estragole produce carcinogenic responses in the systems used and perfected by Miller et al. (1983). Their negative results for eugenol when given at a 0.5% level in the diet of female CD-1

mice for 12 months seem relatively consistent with the NTP findings of equivocal evidence of carcinogenicity in male and female $B6C3F_1$ mice fed diets for 104 weeks containing 0.3 to 0.6% eugenol.

Mutagenesis studies using *Salmonella typhimurium* show that eugenol and methyl eugenol do not induce a mutagenic response (Appendix H). Eugenol induced cytogenetic effects (chromosome aberrations and sister chromatid exchanges) in Chinese hamster ovary cells (Appendix I).

Except for some marginal increases in lung tumors in male rats and in thyroid and endometrial tumors in female rats, no significant eugenol-related toxic or neoplastic effects were observed in this species. These borderline increases are not considered to have been caused by the administration of eugenol in the diet.

For the first nine months of the two-year studies, rats fed eugenol and the controls were housed in the same room as other rats on feeding studies of mannitol (CAS No. 69-65-8) and ziram (CAS No. 137-30-4). Mice fed eugenol and the controls were housed for twelve months with other mice on feeding studies of these same two chemicals. Mannitol (Abdo et al., 1983; NTP, 1982) was not carcinogenic for male and female F344/N rats or for male and female $B6C3F_1$ mice. Ziram (NTP, 1983) caused increased incidences of C-cell carcinomas of the thyroid gland in male F344/N rats. In the eugenol studies marginal increases of C-cell adenomas were observed in female rats in the 6,000 ppm group but not in the 12,500 ppm group. Further, the trend was in the negative direction for the eugenol-exposed male rats. Liver neoplasms were decreased in both male and female mice receiving diets containing ziram. The opposite effect was observed in the mice exposed to eugenol. Although chemical cross contamination among groups cannot be excluded completely, the responses in the separate studies show that any adjacent chemical effect was absent, or minimal.

Conclusions: Eugenol was given in the diets of female F344/N rats (0, 0.6, or 1.25%) and of male F344/N rats and male and female $B6C3F_1$ mice (0, 0.3, or 0.6%) for 103 weeks. Under these experimental conditions, there was no evidence of carcinogenicity observed for male or female rats. For mice there was equivocal evidence of carcinogenicity since eugenol caused increased incidences of both carcinomas and adenomas of the liver in male mice at the 3,000 ppm dietary level and because eugenol was associated with an increase in the combined incidences of hepatocellular carcinomas or adenomas in female mice.

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APPENDIX A

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

TABLE A1.

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

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	40	50	50
ANIMALS NECROPSIED	40	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	40	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(40)	(50)	(50)
SQUAMOUS CELL PAPILLOMA	2 (5%)	1 (2%)	1 (2%)
SQUAMOUS CELL CARCINOMA		1 (2%)	
FIBROMA		1 (2%)	
*SUBCUT TISSUE	(40)	(50)	(50)
BASAL-CELL CARCINOMA	1 (3%)		
SARCOMA, NOS		1 (2%)	
FIBROMA	3 (8%)	1 (2%)	3 (6%)
FIBROUS HISTIOCYTOMA, MALIGNANT		1 (2%)	
LIPOSARCOMA			1 (2%)
RHABDOMYOSARCOMA		1 (2%)	
RESPIRATORY SYSTEM			
*NASAL CAVITY	(40)	(50)	(50)
SQUAMOUS CELL CARCINOMA		1 (2%)	
#LUNG	(40)	(49)	(50)
ALVEOLAR/BRONCHIOLAR ADENOMA		2 (4%)	2 (4%)
ALVEOLAR/BRONCHIOLAR CARCINOMA		3 (6%)	
HEMATOPOIETIC SYSTEM			
#CEREBRUM	(40)	(50)	(49)
MALIGNANT RETICULOSIS			1 (2%)
#BRAIN	(40)	(50)	(49)
MALIGNANT RETICULOSIS	1 (3%)		
*MULTIPLE ORGANS	(40)	(50)	(50)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		1 (2%)	1 (2%)

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		2 (4%)	
UNDIFFERENTIATED LEUKEMIA	13 (33%)	17 (34%)	11 (22%)
#LIVER	(40)	(50)	(50)
UNDIFFERENTIATED LEUKEMIA		1 (2%)	
#THYMUS	(40)	(49)	(48)
THYMOMA			1 (2%)
CIRCULATORY SYSTEM			
#SPLEEN	(40)	(50)	(49)
HEMANGIOSARCOMA			1 (2%)
*MIDDLE MENINGEAL ART	(40)	(50)	(50)
SQUAMOUS CELL CARCINOMA, METASTA		1 (2%)	
DIGESTIVE SYSTEM			
*TONGUE	(40)	(50)	(50)
SQUAMOUS CELL PAPILLOMA		1 (2%)	
#LIVER	(40)	(50)	(50)
NEOPLASTIC NODULE	2 (5%)		
HEPATOCELLULAR CARCINOMA			1 (2%)
#PANCREAS	(40)	(50)	(49)
SARCOMA, NOS			1 (2%)
#STOMACH	(40)	(50)	(49)
SQUAMOUS CELL PAPILLOMA			1 (2%)
#SMALL INTESTINE	(40)	(49)	(46)
MUCINOUS ADENOCARCINOMA			1 (2%)
URINARY SYSTEM			
#KIDNEY	(40)	(50)	(50)
TUBULAR-CELL ADENOCARCINOMA			1 (2%)
#KIDNEY/CORTEX	(40)	(50)	(50)
CARCINOMA,NOS			1 (2%)

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM			
#PITUITARY	(39)	(48)	(49)
CARCINOMA,NOS		1 (2%)	
ADENOMA, NOS	2 (5%)	4 (8%)	4 (8%)
#ADRENAL	(40)	(50)	(50)
ALVEOLAR/BRONCHIOLAR CA, METASTA		1 (2%)	
CORTICAL ADENOMA	1 (3%)	2 (4%)	
PHEOCHROMOCYTOMA	9 (23%)	7 (14%)	8 (16%)
#THYROID	(40)	(50)	(50)
FOLLICULAR-CELL ADENOMA	1 (3%)	1 (2%)	
FOLLICULAR-CELL CARCINOMA			1 (2%)
C-CELL ADENOMA	4 (10%)	5 (10%)	
C-CELL CARCINOMA	3 (8%)	3 (6%)	2 (4%)
#PANCREATIC ISLETS	(40)	(50)	(49)
ISLET-CELL ADENOMA		1 (2%)	3 (6%)
ISLET-CELL CARCINOMA	1 (3%)	2 (4%)	3 (6%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(40)	(50)	(50)
FIBROMA		1 (2%)	
FIBROADENOMA		2 (4%)	2 (4%)
*PREPUTIAL GLAND	(40)	(50)	(50)
CARCINOMA,NOS	2 (5%)	2 (4%)	2 (4%)
#TESTIS	(40)	(50)	(50)
INTERSTITIAL-CELL TUMOR	38 (95%)	47 (94%)	47 (94%)
*VAS DEFERENS	(40)	(50)	(50)
MESOTHELIOMA, NOS			1 (2%)
NERVOUS SYSTEM			
#CEREBRUM	(40)	(50)	(49)
GLIOMA, NOS			1 (2%)
#BRAIN	(40)	(50)	(49)
ASTROCYTOMA			1 (2%)

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
#CEREBELLUM	(40)	(50)	(49)
ASTROCYTOMA		1 (2%)	
*SPINAL CORD	(40)	(50)	(50)
NEUROFIBROSARCOMA	1 (3%)		
SPECIAL SENSE ORGANS			
*EAR CANAL	(40)	(50)	(50)
SQUAMOUS CELL CARCINOMA	1 (3%)		
*ZYMBAL'S GLAND	(40)	(50)	(50)
SQUAMOUS CELL CARCINOMA		1 (2%)	1 (2%)
MUSCULOSKELETAL SYSTEM			
*SKELETAL MUSCLE	(40)	(50)	(50)
NEUROFIBROSARCOMA	1 (3%)		
BODY CAVITIES			
*MESENTERY	(40)	(50)	(50)
LIPOMA		1 (2%)	
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(40)	(50)	(50)
SARCOMA, NOS	1 (3%)		
MESOTHELIOMA, NOS	2 (5%)	1 (2%)	
PERIORBITAL REGION			
SQUAMOUS CELL CARCINOMA, INVASIV		1	

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	40	50	50
NATURAL DEATHa	2	6	6
MORIBUND SACRIFICE	15	18	7
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	23	26	37
ANIMAL MISSING			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	39	50	50
TOTAL PRIMARY TUMORS	89	117	104
TOTAL ANIMALS WITH BENIGN TUMORS	38	48	48
TOTAL BENIGN TUMORS	60	77	72
TOTAL ANIMALS WITH MALIGNANT TUMORS	22	33	24
TOTAL MALIGNANT TUMORS	25	39	31
TOTAL ANIMALS WITH SECONDARY TUMORS#		3	
TOTAL SECONDARY TUMORS		3	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	4	1	1
TOTAL UNCERTAIN TUMORS	4	1	1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

a INCLUDES AUTOLYZED ANIMALS

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

TABLE A2.

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

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	40	50	50
ANIMALS NECROPSIED	40	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	40	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(40)	(50)	(50)
SQUAMOUS CELL PAPILLOMA		1 (2%)	
KERATOACANTHOMA		1 (2%)	
*SUBCUT TISSUE	(40)	(50)	(50)
FIBROMA		1 (2%)	
NEUROFIBROMATOSIS	1 (3%)		
NEURILEMOMA	1 (3%)		
RESPIRATORY SYSTEM			
#LUNG	(39)	(50)	(50)
SQUAMOUS CELL CARCINOMA		1 (2%)	
SQUAMOUS CELL CARCINOMA, METASTA	1 (3%)		
ALVEOLAR/BRONCHIOLAR ADENOMA		1 (2%)	
ALVEOLAR/BRONCHIOLAR CARCINOMA	1 (3%)		
C-CELL CARCINOMA, METASTATIC		1 (2%)	
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(40)	(50)	(50)
UNDIFFERENTIATED LEUKEMIA	5 (13%)	9 (18%)	9 (18%)
#SPLEEN	(40)	(50)	(50)
SARCOMA, NOS	1 (3%)		
#LIVER	(40)	(50)	(50)
UNDIFFERENTIATED LEUKEMIA	2 (5%)	1 (2%)	
CIRCULATORY SYSTEM			
NONE			

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
*TONGUE	(40)	(50)	(50)
SQUAMOUS CELL PAPILLOMA			1 (2%)
SQUAMOUS CELL CARCINOMA		1 (2%)	
URINARY SYSTEM			
#URINARY BLADDER	(40)	(50)	(49)
TRANSITIONAL-CELL PAPILLOMA	1 (3%)		
ENDOCRINE SYSTEM			
#PITUITARY	(39)	(49)	(49)
CARCINOMA,NOS	2 (5%)	1 (2%)	
ADENOMA, NOS	7 (18%)	8 (16%)	9 (18%)
#ADRENAL	(40)	(50)	(50)
CORTICAL ADENOMA	1 (3%)	3 (6%)	1 (2%)
PHEOCHROMOCYTOMA	1 (3%)	5 (10%)	1 (2%)
PHEOCHROMOCYTOMA, MALIGNANT	1 (3%)		
#THYROID	(40)	(49)	(50)
FOLLICULAR-CELL ADENOMA		1 (2%)	1 (2%)
C-CELL ADENOMA	3 (8%)	11 (22%)	2 (4%)
C-CELL CARCINOMA	4 (10%)	1 (2%)	4 (8%)
#PARATHYROID	(33)	(44)	(46)
ADENOMA, NOS		1 (2%)	
#PANCREATIC ISLETS	(40)	(50)	(50)
ISLET-CELL ADENOMA		1 (2%)	
ISLET-CELL CARCINOMA			1 (2%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(40)	(50)	(50)
ADENOCARCINOMA, NOS		1 (2%)	
FIBROADENOMA	14 (35%)	7 (14%)	6 (12%)
*CLITORAL GLAND	(40)	(50)	(50)
CARCINOMA,NOS	1 (3%)		

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
ADENOMA, NOS		1 (2%)	1 (2%)
#UTERUS	(40)	(50)	(50)
LEIOMYOSARCOMA	1 (3%)		
ENDOMETRIAL STROMAL POLYP	6 (15%)	6 (12%)	16 (32%)
ENDOMETRIAL STROMAL SARCOMA			1 (2%)
#UTERUS/ENDOMETRIUM	(40)	(50)	(50)
ADENOCARCINOMA, NOS		2 (4%)	1 (2%)
NERVOUS SYSTEM			
#CEREBRUM	(40)	(50)	(49)
ASTROCYTOMA	1 (3%)		
#BRAIN	(40)	(50)	(49)
CARCINOMA, NOS, INVASIVE	2 (5%)		
SPECIAL SENSE ORGANS			
*EAR CANAL	(40)	(50)	(50)
SQUAMOUS CELL CARCINOMA	1 (3%)		
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*MESENTERY	(40)	(50)	(50)
FIBROMA	1 (3%)		
ALL OTHER SYSTEMS			
NONE			

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	40	50	50
NATURAL DEATH@	1	1	4
MORIBUND SACRIFICE	9	13	2
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	30	36	44
ANIMAL MISSING			

@ INCLUDES AUTOLYZED ANIMALS

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	33	41	38
TOTAL PRIMARY TUMORS	56	65	54
TOTAL ANIMALS WITH BENIGN TUMORS	25	35	29
TOTAL BENIGN TUMORS	35	48	38
TOTAL ANIMALS WITH MALIGNANT TUMORS	16	15	15
TOTAL MALIGNANT TUMORS	20	17	16
TOTAL ANIMALS WITH SECONDARY TUMORS#	3	1	
TOTAL SECONDARY TUMORS	3	1	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	1		
TOTAL UNCERTAIN TUMORS	1		
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

TABLE A3.

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

CONTROL

ANIMAL NUMBER	00011	00023	00031	00045	00061	00071	00085	00091	00101	00115	00121	00133	00141	00155	00161	00173	00185	00193	00201	00211	00221	00233	00241	00255
WEEKS ON STUDY	104	096	100	104	104	104	105	105	105	096	105	103	105	079	105	103	105	075	105	105	089	074	105	087
INTEGUMENTARY SYSTEM																								
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL PAPILLOMA										X														X
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
BASAL-CELL CARCINOMA																								
FIBROMA		X	X																					
RESPIRATORY SYSTEM																								
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																								
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																								
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																								
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NEOPLASTIC NODULE																								
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																								
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																								
PITUITARY	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOMA, NOS																								
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CORTICAL ADENOMA																								
PHEOCHROMOCYTOMA				X	X			X					X		X	X	X	X					X	
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FOLLICULAR-CELL ADENOMA																								
C-CELL ADENOMA			X					X				X									X			
C-CELL CARCINOMA		X		X																			X	
PARATHYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	-	+	+	+	+	+	+	+	+
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ISLET-CELL CARCINOMA																								
REPRODUCTIVE SYSTEM																								
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	N	+	+	+	+	+	+	+
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
INTERSTITIAL-CELL TUMOR	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
CARCINOMA,NOS													X				X							
NERVOUS SYSTEM																								
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MALIGNANT RETICULOSIS																								
SPINAL CORD	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N
NEUROFIBROSARCOMA																								
SPECIAL SENSE ORGANS																								
EAR	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N
SQUAMOUS CELL CARCINOMA																								
MUSCULOSKELETAL SYSTEM																								
MUSCLE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NEUROFIBROSARCOMA																								
ALL OTHER SYSTEMS																								
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
SARCOMA, NOS																								
MESOTHELIOMA, NOS																	X							
UNDIFFERENTIATED LEUKEMIA			X		X						X		X					X			X		X	X

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

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

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

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	TOTAL TISSUES TUMORS
WEEKS ON STUDY	105	092	096	104	105	105	105	101	105	082	047	104	105	105	105	
INTEGUMENTARY SYSTEM																
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40*
SQUAMOUS CELL PAPILLOMA																2
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40*
BASAL-CELL CARCINOMA					X											1
FIBROMA						X										3
RESPIRATORY SYSTEM																
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
HEMATOPOIETIC SYSTEM																
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
THYMUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
CIRCULATORY SYSTEM																
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
DIGESTIVE SYSTEM																
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
NEOPLASTIC NODULE								X				X				2
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	40*
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
URINARY SYSTEM																
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
ENDOCRINE SYSTEM																
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	39
ADENOMA, NOS													X		X	2
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
CORTICAL ADENOMA							X									1
PHEOCHROMOCYTOMA																9
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
FOLLICULAR-CELL ADENOMA										X						1
C-CELL ADENOMA																4
C-CELL CARCINOMA																3
PARATHYROID	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	37
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
ISLET-CELL CARCINOMA								X								1
REPRODUCTIVE SYSTEM																
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40*
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
INTERSTITIAL-CELL TUMOR	X	X	X	X	X	X	X	X	X	X		X	X	X	X	38
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	40*
CARCINOMA,NOS																2
NERVOUS SYSTEM																
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
MALIGNANT RETICULOSIS												X				1
SPINAL CORD	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	40*
NEUROFIBROSARCOMA											X					1
SPECIAL SENSE ORGANS																
EAR	+	N	N	N	N	N	N	N	N	N	N	+	N	N	N	40*
SQUAMOUS CELL CARCINOMA	X															1
MUSCULOSKELETAL SYSTEM																
MUSCLE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40*
NEUROFIBROSARCOMA											X					1
ALL OTHER SYSTEMS																
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	40*
SARCOMA, NOS							X									1
MESOTHELIOMA, NOS				X												2
UNDIFFERENTIATED LEUKEMIA	X	X	X			X				X						13

* ANIMALS NECROPSIED

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

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

TABLE A3.

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

LOW DOSE

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	093	104	104	098	104	104	104	100	095	104	104	103	078	104	085	104	104	104	104	100	102	104	104	101	104
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL PAPILLOMA																									
SQUAMOUS CELL CARCINOMA			X																						
FIBROMA	X																								
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SARCOMA, NOS																									
FIBROMA																X									
FIBROUS HISTIOCYTOMA, MALIGNANT																									
RHABDOMYOSARCOMA																									
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALVEOLAR/BRONCHIOLAR ADENOMA	X																X								
ALVEOLAR/BRONCHIOLAR CARCINOMA																		X							
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NASAL CAVITY	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
SQUAMOUS CELL CARCINOMA																									
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
BLOOD VESSELS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
SQUAMOUS CELL CARCINOMA, METASTAT																				X					
DIGESTIVE SYSTEM																									
ORAL CAVITY	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
SQUAMOUS CELL PAPILLOMA																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
UNDIFFERENTIATED LEUKEMIA																									
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+
CARCINOMA,NOS					X																				
ADENOMA, NOS																									
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALVEOLAR/BRONCHIOLAR CA, METASTAT																									
CORTICAL ADENOMA			X									X					X								X
PHEOCHROMOCYTOMA																									
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FOLLICULAR-CELL ADENOMA																	X								
C-CELL ADENOMA	X																	X							
C-CELL CARCINOMA							X																		
PARATHYROID	+	+	–	+	+	+	+	+	+	+	+	+	+	–	–	+	+	+	+	–	+	+	+	+	+
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ISLET-CELL ADENOMA																									
ISLET-CELL CARCINOMA					X							X													
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N
FIBROMA																									
FIBROADENOMA																									
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
INTERSTITIAL-CELL TUMOR	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
CARCINOMA,NOS																				X					
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ASTROCYTOMA																									
SPECIAL SENSE ORGANS																									
ZYMBAL'S GLAND	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
SQUAMOUS CELL CARCINOMA																				X					
BODY CAVITIES																									
MESENTERY	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
LIPOMA																									
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
MESOTHELIOMA, NOS																									
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE									X																
MALIG.LYMPHOMA, HISTIOCYTIC TYPE								X				X													
UNDIFFERENTIATED LEUKEMIA	X			X			X			X			X	X		X			X		X			X	
PERIORBITAL REGION																									
SQUAMOUS CELL CARCINOMA, INVASIVE																									

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

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

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

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL
WEEKS ON STUDY	102	080	076	104	094	094	104	033	041	082	080	095	095	095	095	095	086	095	097	021	095	098	091	100	102	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
SKIN	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SQUAMOUS CELL PAPILLOMA				X																						1
SQUAMOUS CELL CARCINOMA																										1
FIBROMA																										1
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SARCOMA, NOS																								X		1
FIBROMA																										1
FIBROUS HISTIOCYTOMA, MALIGNANT			X																							1
RHABDOMYOSARCOMA								X																		1
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ALVEOLAR/BRONCHIOLAR ADENOMA																										2
ALVEOLAR/BRONCHIOLAR CARCINOMA					X									X												3
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NASAL CAVITY	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50
SQUAMOUS CELL CARCINOMA																	X									1
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
THYMUS	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
BLOOD VESSELS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50
SQUAMOUS CELL CARCINOMA, METASTAT																										1
DIGESTIVE SYSTEM																										
ORAL CAVITY	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50
SQUAMOUS CELL PAPILLOMA																			X							1
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
UNDIFFERENTIATED LEUKEMIA																								X		1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	49
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
CARCINOMA,NOS											X															1
ADENOMA, NOS			X					X																X		4
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALVEOLAR/BRONCHIOLAR CA, METASTAT														X												1
CORTICAL ADENOMA																			X						X	2
PHEOCHROMOCYTOMA								X				X												X		7
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
FOLLICULAR-CELL ADENOMA																										1
C-CELL ADENOMA		X					X	X																		5
C-CELL CARCINOMA					X														X							3
PARATHYROID	+	+	+	+	+	+	-	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	44
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ISLET-CELL ADENOMA								X																		1
ISLET-CELL CARCINOMA																										2
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	+	+	+	+	+	N	+	N	+	+	+	+	+	+	+	+	N	+	+	+	+	N	+	+	+	50
FIBROMA				X																						1
FIBROADENOMA	X																		X							2
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
INTERSTITIAL-CELL TUMOR	X	X		X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	47
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50
CARCINOMA,NOS																			X							2
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ASTROCYTOMA	X																									1
SPECIAL SENSE ORGANS																										
ZYMBAL'S GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50
SQUAMOUS CELL CARCINOMA																										1
BODY CAVITIES																										
MESENTERY	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50
LIPOMA									X																	1
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50
MESOTHELIOMA, NOS																				X						1
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE																										1
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																										2
UNDIFFERENTIATED LEUKEMIA				X					X			X	X									X		X		17
PERIORBITAL REGION																										
SQUAMOUS CELL CARCINOMA, INVASIVE																	X									1

* ANIMALS NECROPSIED

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

TABLE A3.

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

HIGH DOSE

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	104	104	104	104	104	088	104	104	104	104	104	104	104	104	049	104	096	090	090	095	087	104	104	101	104
INTEGUMENTARY SYSTEM																									
SKIN	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+
SQUAMOUS CELL PAPILLOMA																									
SUBCUTANEOUS TISSUE	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+
FIBROMA																									
LIPOSARCOMA	X																								
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALVEOLAR/BRONCHIOLAR ADENOMA			X																						
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+
HEMANGIOSARCOMA					X																				
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	-	+	+	+	+
THYMOMA																									
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR CARCINOMA																									
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+
SARCOMA, NOS															X										
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+
SQUAMOUS CELL PAPILLOMA																									
SMALL INTESTINE	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	-	+	+	-	+	+	-	+
MUCINOUS ADENOCARCINOMA																									
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	-	+	+	-	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARCINOMA,NOS																								X	
TUBULAR-CELL ADENOCARCINOMA																	X								
URINARY BLADDER	+	-	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+
ADENOMA, NOS	X													X											
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PHEOCHROMOCYTOMA		X						X								X			X						
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FOLLICULAR-CELL CARCINOMA																									
C-CELL CARCINOMA																									
PARATHYROID	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+
ISLET-CELL ADENOMA								X				X													
ISLET-CELL CARCINOMA																									
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	N	N	+	N	+	+	+
FIBROADENOMA													X							X					
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
INTERSTITIAL-CELL TUMOR	X	X	X	X	X	X	X	X	X	X	X	X	X			X	X	X	X	X	X	X	X	X	X
PROSTATE	+	-	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
CARCINOMA,NOS																									
VAS DEFERNES, SPERMATIC CORD	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
MESOTHELIOMA, NOS												X													
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+
GLIOMA, NOS																									
ASTROCYTOMA																									
MALIGNANT RETICULOSIS						X																			
SPECIAL SENSE ORGANS																									
ZYMBAL'S GLAND	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N
SQUAMOUS CELL CARCINOMA																			X						
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE																		X							
UNDIFFERENTIATED LEUKEMIA	X															X				X				X	

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

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

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

ANIMAL NUMBER	0246	0278	0291	0308	0311	0320	0335	0341	0355	0361	0371	0381	0391	0401	0411	0421	0431	0441	0455	0461	0471	0481	0491	0501	TOTAL
WEEKS ON STUDY	104	104	104	092	104	070	104	092	004	080	001	004	004	004	104	104	104	104	104	104	104	104	104	104	TISSUES TUMORS
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	+	+	+	+	+	N	+	+	N	+	+	+	N	+	+	+	+	+	50*
SQUAMOUS CELL PAPILLOMA																							X		1
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	N	+	+	N	+	+	+	N	+	+	+	+	+	50*
FIBROMA				X											X					X					3
LIPOSARCOMA																									1
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALVEOLAR/BRONCHIOLAR ADENOMA		X																							2
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMANGIOSARCOMA																									1
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
THYMUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
THYMOMA															X										1
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEPATOCELLULAR CARCINOMA																		X							1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SARCOMA, NOS																									1
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SQUAMOUS CELL PAPILLOMA																			X						1
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
MUCINOUS ADENOCARCINOMA								X																	1
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CARCINOMA,NOS																									1
TUBULAR-CELL ADENOCARCINOMA																									1
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ADENOMA, NOS			X												X										4
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
PHEOCHROMOCYTOMA											X			X		X			X						8
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
FOLLICULAR-CELL CARCINOMA																					X				1
C-CELL CARCINOMA			X							X															2
PARATHYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	47
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ISLET-CELL ADENOMA											X														3
ISLET-CELL CARCINOMA															X	X						X			3
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	N	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	N	+	+	+	+	+	50*
FIBROADENOMA																									2
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
INTERSTITIAL-CELL TUMOR	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	47
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
CARCINOMA,NOS	X		X																						2
VAS DEFERNES, SPERMATIC CORD	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
MESOTHELIOMA, NOS																									1
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
GLIOMA, NOS																							X		1
ASTROCYTOMA										X															1
MALIGNANT RETICULOSIS																									1
SPECIAL SENSE ORGANS																									
ZYMBAL'S GLAND	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
SQUAMOUS CELL CARCINOMA																									1
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE																									1
UNDIFFERENTIATED LEUKEMIA		X			X	X	X				X					X				X					11

* ANIMALS NECROPSIED

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

TABLE A4.

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

CONTROL

ANIMAL NUMBER	0001	0002	0003	0004	0005	0006	0007	0008	0009	0010	0011	0012	0113	0114	0115	0116	0117	0118	0119	0120	0121	0122	0123	0124	0125
WEEKS ON STUDY	104	104	104	104	104	105	104	105	105	103	102	107	101	089	105	103	105	085	095	083	105	105	105	105	105
INTEGUMENTARY SYSTEM																									
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NEUROFIBROMATOSIS																		X							
NEURILEMOMA																		X							
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL CARCINOMA, METASTAT											X														
ALVEOLAR/BRONCHIOLAR CARCINOMA																									
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SARCOMA, NOS																			X						
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
UNDIFFERENTIATED LEUKEMIA																									
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
TRANSITIONAL-CELL PAPILLOMA																									
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARCINOMA,NOS																				X					
ADENOMA, NOS		X											X	X		X			X						
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CORTICAL ADENOMA	X																								
PHEOCHROMOCYTOMA																					X				
PHEOCHROMOCYTOMA, MALIGNANT									X																
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-CELL ADENOMA											X														
C-CELL CARCINOMA																								X	X
PARATHYROID	+	+	+	+	-	+	+	+	+	-	-	+	-	-	+	-	+	+	+	-	+	+	+	+	+
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FIBROADENOMA				X	X		X	X		X			X	X		X	X						X		
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
CARCINOMA,NOS							X																		
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LEIOMYOSARCOMA																									X
ENDOMETRIAL STROMAL POLYP	X					X						X													
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARCINOMA, NOS, INVASIVE																				X					
ASTROCYTOMA												X													
SPECIAL SENSE ORGANS																									
EAR	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N
SQUAMOUS CELL CARCINOMA											X														
BODY CAVITIES																									
MESENTERY	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
FIBROMA																									
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
UNDIFFERENTIATED LEUKEMIA							X			X			X			X									

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

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

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

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	TOTAL TISSUES TUMORS
WEEKS ON STUDY	105	105	105	105	105	105	105	090	105	105	105	105	094	105	105	
INTEGUMENTARY SYSTEM																
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40*
NEUROFIBROMATOSIS																1
NEURILEMOMA																1
RESPIRATORY SYSTEM																
LUNGS AND BRONCHI	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	39
SQUAMOUS CELL CARCINOMA, METASTAT																1
ALVEOLAR/BRONCHIOLAR CARCINOMA												X				1
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
HEMATOPOIETIC SYSTEM																
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	39
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
SARCOMA, NOS																1
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
THYMUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
CIRCULATORY SYSTEM																
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
DIGESTIVE SYSTEM																
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
UNDIFFERENTIATED LEUKEMIA							X		X							2
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	40*
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
URINARY SYSTEM																
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
TRANSITIONAL-CELL PAPILLOMA							X									1
ENDOCRINE SYSTEM																
PITUITARY	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	39
CARCINOMA,NOS													X			2
ADENOMA, NOS	X															7
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
CORTICAL ADENOMA																1
PHEOCHROMOCYTOMA																1
PHEOCHROMOCYTOMA, MALIGNANT																1
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
C-CELL ADENOMA		X	X		X											3
C-CELL CARCINOMA									X							4
PARATHYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	33
REPRODUCTIVE SYSTEM																
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40*
FIBROADENOMA	X		X		X							X				14
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	40*
CARCINOMA,NOS																1
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
LEIOMYOSARCOMA																1
ENDOMETRIAL STROMAL POLYP				X			X						X			6
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
NERVOUS SYSTEM																
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
CARCINOMA, NOS, INVASIVE													X			2
ASTROCYTOMA																1
SPECIAL SENSE ORGANS																
EAR	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	40*
SQUAMOUS CELL CARCINOMA																1
BODY CAVITIES																
MESENTERY	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	40*
FIBROMA		X														1
ALL OTHER SYSTEMS																
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	40*
UNDIFFERENTIATED LEUKEMIA								X								5

* ANIMALS NECROPSIED

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

TABLE A4.

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

LOW DOSE

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	105	101	105	099	068	105	105	105	105	105	105	105	105	105	105	096	098	105	105	098	105	105	105	105	105
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+
SQUAMOUS CELL PAPILLOMA																									
KERATOACANTHOMA																									
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+
FIBROMA																									
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL CARCINOMA																									
ALVEOLAR/BRONCHIOLAR ADENOMA	X																								
C-CELL CARCINOMA, METASTATIC																					X				
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
ORAL CAVITY	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
SQUAMOUS CELL CARCINOMA																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
UNDIFFERENTIATED LEUKEMIA																									
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+
CARCINOMA,NOS																									
ADENOMA, NOS		X	X	X							X											X			
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CORTICAL ADENOMA												X													
PHEOCHROMOCYTOMA						X		X												X					
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FOLLICULAR-CELL ADENOMA												X													
C-CELL ADENOMA						X	X			X				X									X		
C-CELL CARCINOMA																					X				X
PARATHYROID	+	+	+	+	+	-	+	+	+	+	-	+	+	+	+	-	+	+	+	+	+	+	+	+	+
ADENOMA, NOS					X																				
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ISLET-CELL ADENOMA																									
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+
ADENOCARCINOMA, NOS													X	X											
FIBROADENOMA																				X					
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ADENOMA, NOS																									
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOCARCINOMA, NOS															X										
ENDOMETRIAL STROMAL POLYP				X				X			X								X						
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
UNDIFFERENTIATED LEUKEMIA				X		X										X	X	X							

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

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

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

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL
WEEKS ON STUDY	085	105	105	105	105	105	105	105	105	105	105	105	099	098	096	105	098	105	105	105	103	105	097	105	102	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
SQUAMOUS CELL PAPILLOMA																								X		1
KERATOACANTHOMA													X													1
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
FIBROMA			X																							1
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SQUAMOUS CELL CARCINOMA									X																	1
ALVEOLAR/BRONCHIOLAR ADENOMA																										1
C-CELL CARCINOMA, METASTATIC																										1
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
THYMUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
ORAL CAVITY	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
SQUAMOUS CELL CARCINOMA									X																	1
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	48
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
UNDIFFERENTIATED LEUKEMIA																								X		1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
CARCINOMA,NOS																				X						1
ADENOMA, NOS										X					X	X										8
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CORTICAL ADENOMA															X									X		3
PHEOCHROMOCYTOMA														X									X			5
THYROID	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
FOLLICULAR-CELL ADENOMA																										1
C-CELL ADENOMA	X			X										X									X			11
C-CELL CARCINOMA																									X	1
PARATHYROID	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	-	+		44
ADENOMA, NOS																										1
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ISLET-CELL ADENOMA												X														1
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
ADENOCARCINOMA, NOS																						X				1
FIBROADENOMA				X															X	X			X			7
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
ADENOMA, NOS																					X					1
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ADENOCARCINOMA, NOS									X																	2
ENDOMETRIAL STROMAL POLYP		X															X									6
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
UNDIFFERENTIATED LEUKEMIA	X													X									X		X	9

* ANIMALS NECROPSIED

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

TABLE A4.

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

HIGH DOSE

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	108	104	095	104	104	098	104	104	104	104	104	104	104	104
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
ORAL CAVITY SQUAMOUS CELL PAPILLOMA	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY ADENOMA, NOS	+	+	+	+	+	+	+	+	+	+	+	+	+	+ X	+	+	+	+	+	+	+ X	+	+	+ X	+
ADRENAL CORTICAL ADENOMA PHEOCHROMOCYTOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+ X
THYROID FOLLICULAR-CELL ADENOMA C-CELL ADENOMA C-CELL CARCINOMA	+	+	+	+	+	+	+	+	+ X	+	+	+	+	+	+	+	+	+	+	+	+	+ X	+	+ X	+
PARATHYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PANCREATIC ISLETS ISLET-CELL CARCINOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND FIBROADENOMA	+ X	+	+	+	+	+	+	+	+	+	+ X	N	+ X	+ X	+	+	N	+	+	+	+	+	+	+	+ X
PREPUTIAL/CLITORAL GLAND ADENOMA, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
UTERUS ADENOCARCINOMA, NOS ENDOMETRIAL STROMAL POLYP ENDOMETRIAL STROMAL SARCOMA	+	+ X	+	+ X	+	+	+ X	+ X	+	+ X	+	+	+	+	+	+ X	+	+	+	+	+	+ X	+	+	+ X
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS UNDIFFERENTIATED LEUKEMIA	N	N	N X	N	N X	N X	N	N	N	N	N	N	N	N	N	N	N X	N	N	N	N	N	N	N	N X

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

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

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL
WEEKS ON STUDY	101	109	104	104	104	104	101	104	104	104	104	104	096	104	104	104	104	104	104	104	104	104	080	104	104	TISSUES TUMORS
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
THYMUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
ORAL CAVITY	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
SQUAMOUS CELL PAPILLOMA																									X	1
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ADENOMA, NOS							X				X			X						X		X			X	9
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CORTICAL ADENOMA																										1
PHEOCHROMOCYTOMA																						X				1
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
FOLLICULAR-CELL ADENOMA															X											1
C-CELL ADENOMA							X												X							2
C-CELL CARCINOMA														X												4
PARATHYROID	+	+	+	+	+	+	+	–	+	+	+	–	+	–	+	+	+	+	+	+	+	+	+	+	–	46
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ISLET-CELL CARCINOMA																				X						1
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
FIBROADENOMA														X												6
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
ADENOMA, NOS											X															1
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ADENOCARCINOMA, NOS																										1
ENDOMETRIAL STROMAL POLYP				X	X					X					X			X	X					X	X	X	16
ENDOMETRIAL STROMAL SARCOMA				X																						1
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
UNDIFFERENTIATED LEUKEMIA				X										X							X		X			9

* ANIMALS NECROPSIED

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

APPENDIX B

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

TABLE B1.

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

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
FIBROUS HISTIOCYTOMA, MALIGNANT		1 (2%)	
*SKIN	(50)	(50)	(50)
ADNEXAL CARCINOMA			1 (2%)
FIBROMA	2 (4%)	1 (2%)	1 (2%)
FIBROSARCOMA	2 (4%)		
FIBROUS HISTIOCYTOMA, MALIGNANT	1 (2%)		
*SUBCUT TISSUE	(50)	(50)	(50)
FIBROSARCOMA			1 (2%)
RESPIRATORY SYSTEM			
#LUNG	(49)	(49)	(50)
SQUAMOUS CELL CARCINOMA, METASTA			1 (2%)
HEPATOCELLULAR CARCINOMA, METAST	2 (4%)	3 (6%)	2 (4%)
ALVEOLAR/BRONCHIOLAR ADENOMA	9 (18%)	7 (14%)	8 (16%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	5 (10%)	2 (4%)	3 (6%)
OSTEOSARCOMA, METASTATIC	1 (2%)		
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
MALIGNANT LYMPHOMA, NOS		1 (2%)	1 (2%)
MALIG.LYMPHOMA, UNDIFFER-TYPE			1 (2%)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	1 (2%)		
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	3 (6%)	2 (4%)	1 (2%)
MALIGNANT LYMPHOMA, MIXED TYPE	1 (2%)	2 (4%)	4 (8%)
LEUKEMIA,NOS		1 (2%)	
#MESENTERIC L. NODE	(49)	(48)	(50)
MALIGNANT LYMPHOMA, MIXED TYPE			1 (2%)

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
CIRCULATORY SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
HEMANGIOSARCOMA		1 (2%)	
*SKIN	(50)	(50)	(50)
HEMANGIOSARCOMA	1 (2%)		
#SPLEEN	(48)	(49)	(48)
HEMANGIOSARCOMA			1 (2%)
#LIVER	(50)	(50)	(49)
HEMANGIOSARCOMA		1 (2%)	1 (2%)
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(48)	(49)	(49)
ADENOMA, NOS		1 (2%)	
#LIVER	(50)	(50)	(49)
HEPATOCELLULAR ADENOMA	4 (8%)	13 (26%)	10 (20%)
HEPATOCELLULAR CARCINOMA	10 (20%)	20 (40%)	9 (18%)
MIXED HEPATO/CHOLANGIO CARCINOMA		1 (2%)	
#CARDIAC STOMACH	(50)	(50)	(47)
SQUAMOUS CELL CARCINOMA			1 (2%)
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#ADRENAL	(43)	(48)	(47)
CORTICAL ADENOMA			1 (2%)
PHEOCHROMOCYTOMA		1 (2%)	
PHEOCHROMOCYTOMA, MALIGNANT			1 (2%)
#THYROID	(48)	(49)	(49)
FOLLICULAR-CELL ADENOMA			3 (6%)
#PANCREATIC ISLETS	(46)	(49)	(48)
ISLET-CELL ADENOMA		1 (2%)	1 (2%)

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM			
NONE			
NERVOUS SYSTEM			
*TRIGEMINAL GANGLION	(50)	(50)	(50)
NEURILEMOMA		1 (2%)	
SPECIAL SENSE ORGANS			
*HARDERIAN GLAND	(50)	(50)	(50)
ADENOMA, NOS	1 (2%)		1 (2%)
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*MEDIASTINUM	(50)	(50)	(50)
OSTEOSARCOMA, METASTATIC	1 (2%)		
ALL OTHER SYSTEMS			
THORAX			
NEUROFIBROSARCOMA	1		
FOOT			
OSTEOSARCOMA		1	
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	4	3	9
MORIBUND SACRIFICE	5	7	6
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED		5	
TERMINAL SACRIFICE	41	35	35
ANIMAL MISSING			

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	26	36	32
TOTAL PRIMARY TUMORS	41	58	51
TOTAL ANIMALS WITH BENIGN TUMORS	12	20	20
TOTAL BENIGN TUMORS	16	25	25
TOTAL ANIMALS WITH MALIGNANT TUMORS	20	27	20
TOTAL MALIGNANT TUMORS	25	33	26
TOTAL ANIMALS WITH SECONDARY TUMORS#	3	3	2
TOTAL SECONDARY TUMORS	4	3	3
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			
TOTAL UNCERTAIN TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

TABLE B2.

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

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	49	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	49	49
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(49)	(49)
SQUAMOUS CELL PAPILLOMA		1 (2%)	
*SUBCUT TISSUE	(50)	(49)	(49)
FIBROSARCOMA	1 (2%)		
RESPIRATORY SYSTEM			
#PERITRACHEAL TISSUE	(6)	(21)	(27)
HEPATOCELLULAR CARCINOMA, METAST		1 (5%)	
#LUNG	(50)	(49)	(48)
HEPATOCELLULAR CARCINOMA, METAST		1 (2%)	
ALVEOLAR/BRONCHIOLAR ADENOMA	4 (8%)	5 (10%)	4 (8%)
ALVEOLAR/BRONCHIOLAR CARCINOMA		2 (4%)	1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(49)	(49)
MALIGNANT LYMPHOMA, NOS			1 (2%)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	4 (8%)	5 (10%)	3 (6%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	2 (4%)	1 (2%)	
MALIGNANT LYMPHOMA, MIXED TYPE	4 (8%)	4 (8%)	1 (2%)
LYMPHOCYTIC LEUKEMIA	1 (2%)		
#SPLEEN	(50)	(49)	(49)
MALIGNANT LYMPHOMA, MIXED TYPE			1 (2%)
#LIVER	(50)	(49)	(49)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (2%)		
#KIDNEY	(50)	(49)	(49)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE			1 (2%)

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#THYMUS	(46)	(45)	(42)
MALIGNANT LYMPHOMA, MIXED TYPE	1 (2%)		
CIRCULATORY SYSTEM			
*SKIN	(50)	(49)	(49)
HEMANGIOMA	1 (2%)		
#SPLEEN	(50)	(49)	(49)
HEMANGIOSARCOMA			1 (2%)
#LIVER	(50)	(49)	(49)
HEMANGIOSARCOMA	1 (2%)		
*MESENTERY	(50)	(49)	(49)
HEMANGIOSARCOMA			1 (2%)
DIGESTIVE SYSTEM			
*TONGUE	(50)	(49)	(49)
SQUAMOUS CELL PAPILLOMA			1 (2%)
#LIVER	(50)	(49)	(49)
HEPATOCELLULAR ADENOMA		4 (8%)	3 (6%)
HEPATOCELLULAR CARCINOMA	2 (4%)	3 (6%)	6 (12%)
SARCOMA, NOS, METASTATIC	1 (2%)		
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#PITUITARY	(41)	(41)	(39)
ADENOMA, NOS	1 (2%)	1 (2%)	1 (3%)
#ADRENAL	(50)	(48)	(49)
PHEOCHROMOCYTOMA		1 (2%)	
#THYROID	(48)	(47)	(49)
FOLLICULAR-CELL ADENOMA	2 (4%)		1 (2%)

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(49)	(49)
ACINAR-CELL CARCINOMA			1 (2%)
MIXED TUMOR, MALIGNANT	2 (4%)		1 (2%)
*VAGINA	(50)	(49)	(49)
SARCOMA, NOS	1 (2%)		
#UTERUS	(50)	(48)	(49)
LEIOMYOSARCOMA			1 (2%)
#UTERUS/ENDOMETRIUM	(50)	(48)	(49)
ADENOCARCINOMA, NOS		2 (4%)	1 (2%)
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*EYE	(50)	(49)	(49)
MALIGNANT MELANOMA			1 (2%)
*HARDERIAN GLAND	(50)	(49)	(49)
ADENOMA, NOS	1 (2%)		1 (2%)
CYSTADENOMA, NOS	1 (2%)		
MUSCULOSKELETAL SYSTEM			
*MAXILLA	(50)	(49)	(49)
OSTEOMA	1 (2%)		
BODY CAVITIES			
*ABDOMINAL WALL	(50)	(49)	(49)
SARCOMA, NOS		1 (2%)	
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(49)	(49)
ADENOCARCINOMA, NOS, METASTATIC			1 (2%)

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	6	6	4
MORIBUND SACRIFICE	1	4	1
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	43	40	45
ANIMAL MISSING			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	27	22	26
TOTAL PRIMARY TUMORS	31	30	32
TOTAL ANIMALS WITH BENIGN TUMORS	10	11	9
TOTAL BENIGN TUMORS	11	12	11
TOTAL ANIMALS WITH MALIGNANT TUMORS	18	14	21
TOTAL MALIGNANT TUMORS	20	18	21
TOTAL ANIMALS WITH SECONDARY TUMORS#	1	1	1
TOTAL SECONDARY TUMORS	1	2	1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			
TOTAL UNCERTAIN TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE B3.

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

CONTROL

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	105	115	105	070	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	092	065	085	105	105
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	+	+	+	+	+	N	N	N	+	+	+	+	+	+	+	+	+	+	+
FIBROMA									X											X					
FIBROSARCOMA																									
FIBROUS HISTIOCYTOMA, MALIGNANT													X												
HEMANGIOSARCOMA													X												
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR CARCINOMA, METASTA						X												X							
ALVEOLAR/BRONCHIOLAR ADENOMA															X		X							X	
ALVEOLAR/BRONCHIOLAR CARCINOMA																				X					X
OSTEOSARCOMA, METASTATIC																									
TRACHEA	+	-	+	-	+	-	-	-	-	-	+	+	+	-	-	-	-	+	-	+	+	+	+	-	-
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	-	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR ADENOMA																		X			X			X	
HEPATOCELLULAR CARCINOMA	X					X													X						
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	N	+	+	N	N	N	+	+	+	+	+	N	+	+	N	+	+	+	+	+	+	+	N	+	N	+
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYROID	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PARATHYROID	-	+	+	-	-	-	+	-	-	-	-	+	+	+	-	-	-	-	-	-	-	+	-	-	-
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
HARDERIAN GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ADENOMA, NOS								X																	
BODY CAVITIES																									
PLEURA	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
NEUROFIBROSARCOMA																					X				
MEDIASTINUM	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
OSTEOSARCOMA, METASTATIC																									
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE																							X		
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																								X	
MALIGNANT LYMPHOMA, MIXED TYPE																									

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

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

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL
WEEKS ON STUDY	105	105	105	103	083	105	105	105	105	105	105	105	105	105	106	106	093	106	106	106	106	106	106	103	102	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
FIBROMA																										2
FIBROSARCOMA									X																	2
FIBROUS HISTIOCYTOMA, MALIGNANT																										1
HEMANGIOSARCOMA																										1
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	49
HEPATOCELLULAR CARCINOMA, METASTA																										2
ALVEOLAR/BRONCHIOLAR ADENOMA	X		X								X								X		X	X			9
ALVEOLAR/BRONCHIOLAR CARCINOMA	X							X																X		5
OSTEOSARCOMA, METASTATIC					X																					1
TRACHEA	-	-	-	+	+	-	-	-	-	-	-	-	-	-	-	-	+	-	-	+	+	-	-	-	+	17
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	-	+	+	+	+	+	+	48
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	49
THYMUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	-	+	+	+	-	+	+	+	44
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	+	+	+	+	+	+	+	+	+	48
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEPATOCELLULAR ADENOMA	X																									4
HEPATOCELLULAR CARCINOMA						X			X					X			X					X	X		X	10
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	+	+	N	+	+	+	+	+	N	+	+	+	+	+	+	N	+	+	+	+	+	N	+	N	N	50*
PANCREAS	+	+	+	+	-	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	-	46
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	-	+	+	+	+	+	+	+	48
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SMALL INTESTINE	+	+	+	+	-	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	-	46
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	48
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
PITUITARY	+	-	-	+	+	+	+	+	+	-	+	+	+	+	+	+	+	-	+	+	+	+	-	+	+	44
ADRENAL	+	+	+	-	+	+	+	+	-	-	-	+	+	+	-	+	+	+	-	+	-	+	+	+	+	43
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	48
PARATHYROID	-	-	-	+	-	-	+	+	-	-	-	-	-	-	+	-	+	-	-	-	-	-	-	+	-	13
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
HARDERIAN GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
ADENOMA, NOS																										1
BODY CAVITIES																										
PLEURA	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
NEUROFIBROSARCOMA																										1
MEDIASTINUM	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
OSTEOSARCOMA, METASTATIC					X																					1
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE																										1
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			X	X																						3
MALIGNANT LYMPHOMA, MIXED TYPE																										1

* ANIMALS NECROPSIED

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

TABLE B3.

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

LOW DOSE

ANIMAL NUMBER	0012	0023	0046	0055	0067	0078	0091	0110	0114	0125	0132	0145	0155	0167	0178	0191	0201	0221	0233	0244	0255
WEEKS ON STUDY	105	105	105	105	105	105	105	104	105	086	102	105	105	086	065	105	105	075	105	105	105
INTEGUMENTARY SYSTEM																					
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FIBROMA																					
RESPIRATORY SYSTEM																					
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR CARCINOMA, METASTA											X		X								
ALVEOLAR/BRONCHIOLAR ADENOMA		X		X		X													X		
ALVEOLAR/BRONCHIOLAR CARCINOMA				X									X								
TRACHEA	+	-	+	-	+	-	+	+	+	-	-	+	+	+	-	+	+	+	-	-	+
HEMATOPOIETIC SYSTEM																					
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	+	+	-	+	+	+	-	+	+	+	+	+	+	+	+	+
THYMUS	+	+	+	+	+	+	+	-	-	-	-	+	+	+	+	+	-	-	+	+	+
CIRCULATORY SYSTEM																					
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																					
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+
ADENOMA, NOS																					
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR ADENOMA	X			X		X					X								X		X
HEPATOCELLULAR CARCINOMA		X		X	X	X		X		X	X	X	X		X	X	X	X		X	
MIXED HEPATO/CHOLANGIO CARCINOMA																					
HEMANGIOSARCOMA																					
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	+	+	+	N	+	N	+	N	+	+	N	N	N	+	+	N	+	N	+	+	N
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+
ESOPHAGUS	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	-	+	+	-	+	+	+	+	+	+
URINARY SYSTEM																					
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																					
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	-	+
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	-	+	+
PHEOCHROMOCYTOMA		X																			
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+
PARATHYROID	+	-	+	-	-	-	+	+	-	-	-	-	+	-	-	+	-	+	-	+	+
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+
ISLET-CELL ADENOMA					X																
REPRODUCTIVE SYSTEM																					
MAMMARY GLAND	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																					
NERVES	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
NEURILEMOMA									X												
ALL OTHER SYSTEMS																					
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
FIBROUS HISTIOCYTOMA, MALIGNANT																					
HEMANGIOSARCOMA																					X
MALIGNANT LYMPHOMA, NOS												X									
MALIG.LYMPHOMA, HISTIOCYTIC TYPE														X							
MALIGNANT LYMPHOMA, MIXED TYPE															X						
LEUKEMIA,NOS																					
FOOT NOS																					
OSTEOSARCOMA						X															

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

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

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

ANIMAL NUMBER	0261	0271	0281	0291	0301	0312	0323	0334	0345	0356	0367	0381	0391	0401	0411	0423	0434	0445	0469	0475	0488	0491	0501	TOTAL
WEEKS ON STUDY	105	105	105	105	105	103	103	103	103	105	105	105	068	105	101	105	105	105	096	105	075	105	105	TISSUES TUMORS
INTEGUMENTARY SYSTEM																								
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	50*
FIBROMA				X																				1
RESPIRATORY SYSTEM																								
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	49
HEPATOCELLULAR CARCINOMA, METASTA															X									3
ALVEOLAR/BRONCHIOLAR ADENOMA				X						X			X											7
ALVEOLAR/BRONCHIOLAR CARCINOMA																								2
TRACHEA	-	-	+	-	+	+	+	+	+	+	-	+	-	+	-	-	+	+	+	-	+	-	+	+	30
HEMATOPOIETIC SYSTEM																								
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	49
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
THYMUS	-	+	-	+	-	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	40
CIRCULATORY SYSTEM																								
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																								
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ADENOMA, NOS										X														1
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEPATOCELLULAR ADENOMA		X	X									X	X							X				13
HEPATOCELLULAR CARCINOMA												X	X		X							X		20
MIXED HEPATO/CHOLANGIO CARCINOMA														X										1
HEMANGIOSARCOMA				X																				1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	+	N	+	+	+	+	+	+	N	+	N	+	+	N	+	+	+	+	+	50*
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
URINARY SYSTEM																								
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																								
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	-	+	-	+	+	+	+	+	-	+	+	+	45
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
PHEOCHROMOCYTOMA																								1
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
PARATHYROID	-	-	-	-	+	+	-	-	-	-	+	+	+	-	-	-	+	+	-	+	+	+	-	+	22
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ISLET-CELL ADENOMA																								1
REPRODUCTIVE SYSTEM																								
MAMMARY GLAND	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	50*
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																								
NERVES	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
NEURILEMOMA																								1
ALL OTHER SYSTEMS																								
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
FIBROUS HISTIOCYTOMA, MALIGNANT													X											1
HEMANGIOSARCOMA																								1
MALIGNANT LYMPHOMA, NOS																								1
MALIG.LYMPHOMA, HISTIOCYTIC TYPE				X																				2
MALIGNANT LYMPHOMA, MIXED TYPE			X							X														2
LEUKEMIA,NOS																								1
FOOT NOS																								
OSTEOSARCOMA																								1

* ANIMALS NECROPSIED

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

TABLE B3.

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

HIGH DOSE

ANIMAL NUMBER	0011	0012	0013	0014	0015	0016	0017	0018	0019	0110	0111	0112	0113	0114	0115	0116	0117	0118	0119	0120	0121	0122	0123	0124	0125
WEEKS ON STUDY	104	045	104	041	044	044	044	044	044	044	044	041	086	046	052	038	044	041	044	066	013	044	079	068	095
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+
ADNEXAL CARCINOMA																									
FIBROMA																									
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+
FIBROSARCOMA													X												
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL CARCINOMA, METASTAT																							X		
HEPATOCELLULAR CARCINOMA, METASTA																							X	X	
ALVEOLAR/BRONCHIOLAR ADENOMA			X		X	X	X				X							X							
ALVEOLAR/BRONCHIOLAR CARCINOMA				X	X						X														
TRACHEA	+	+	-	-	+	+	-	+	+	-	-	-	+	-	+	+	+	+	+	+	+	-	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	-	-	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	-	+	+	+	+	+
HEMANGIOSARCOMA					X																				
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MALIGNANT LYMPHOMA, MIXED TYPE																									
THYMUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR ADENOMA		X										X	X					X							
HEPATOCELLULAR CARCINOMA															X					X			X	X	X
HEMANGIOSARCOMA																									
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	+	N	+	+	N	+	+	+	+	+	N	N	+	+	+	N	+	+	+	N	+
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	-	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	-	+	+	+	+	+
SQUAMOUS CELL CARCINOMA																							X		
SMALL INTESTINE	+	+	+	-	+	+	+	+	+	+	+	+	+	+	-	-	+	+	+	-	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	+	+	+	-	+	+	+	+	-
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	-	+	+	+	-	+	+	+	+	+
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	-	+	+	+	-	+	+	+	+	+
CORTICAL ADENOMA		X			X																				
PHEOCHROMOCYTOMA, MALIGNANT																									
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+
FOLLICULAR-CELL ADENOMA												X						X							
PARATHYROID	-	+	-	+	-	+	+	-	+	-	-	+	-	-	-	-	-	+	+	+	-	-	-	+	+
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	-	+	+	+	+	+
ISLET-CELL ADENOMA																									
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PROSTATE	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
HARDERIAN GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ADENOMA, NOS																							X		
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
MALIGNANT LYMPHOMA, NOS															X										
MALIG.LYMPHOMA, UNDIFFER-TYPE																									
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																									
MALIGNANT LYMPHOMA, MIXED TYPE																									

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

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

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

ANIMAL NUMBER	0246	0271	0289	0293	0301	0311	0312	0331	0334	0335	0336	0337	0338	0339	0401	0411	0412	0413	0414	0415	0416	0417	0418	0419	0501	TOTAL
WEEKS ON STUDY	1104	1104	0693	0104	0104	0104	0104	0104	0934	0104	0104	0104	0104	0104	0104	0104	0104	0104	0104	0104	0104	0104	0104	0884	0971	0104	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
ADNEXAL CARCINOMA							X																			1
FIBROMA																									X	1
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
FIBROSARCOMA																										1
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SQUAMOUS CELL CARCINOMA, METASTAT																										1
HEPATOCELLULAR CARCINOMA, METASTA																										2
ALVEOLAR/BRONCHIOLAR ADENOMA					X															X						8
ALVEOLAR/BRONCHIOLAR CARCINOMA																										3
TRACHEA	-	+	+	-	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-	+	-	-	-	+	-	22
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
HEMANGIOSARCOMA																										1
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
MALIGNANT LYMPHOMA, MIXED TYPE							X																			1
THYMUS	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEPATOCELLULAR ADENOMA			X		X	X		X				X			X											10
HEPATOCELLULAR CARCINOMA			X				X		X				X													9
HEMANGIOSARCOMA		X																								1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
GALLBLADDER & COMMON BILE DUCT	+	+	N	N	+	+	+	+	N	+	+	+	N	N	+	N	+	N	+	+	+	+	N	N	+	50*
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
STOMACH	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
SQUAMOUS CELL CARCINOMA																										1
SMALL INTESTINE	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
LARGE INTESTINE	+	+	+	-	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	43
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	+	+	+	+	45
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
CORTICAL ADENOMA																										1
PHEOCHROMOCYTOMA, MALIGNANT																										1
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
FOLLICULAR-CELL ADENOMA							X																			3
PARATHYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	+	+	+	+	+	+	+	-	+	+	33
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ISLET-CELL ADENOMA										X																1
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
PROSTATE	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
SPECIAL SENSE ORGANS																										
HARDERIAN GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
ADENOMA, NOS																										1
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
MALIGNANT LYMPHOMA, NOS				X																						1
MALIG.LYMPHOMA, UNDIFFER-TYPE																										1
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																							X			1
MALIGNANT LYMPHOMA, MIXED TYPE					X								X											X	X	4

* ANIMALS *NECROPSIED*

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

TABLE B4.

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

CONTROL

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	105	105	105	105	105	054	105	105	105	105	105	096	101	105	084	105	105	103	105	105	105	105	105	061	106
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMANGIOMA																								X	
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FIBROSARCOMA																X									
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALVEOLAR/BRONCHIOLAR ADENOMA			X											X											
TRACHEA	-	-	-	-	-	+	-	+	-	-	-	+	-	-	+	-	-	-	-	-	-	-	-	-	-
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	+	+	+	+	+	-	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MALIGNANT LYMPHOMA, MIXED TYPE																						X			
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR CARCINOMA																									
SARCOMA, NOS, METASTATIC																									
HEMANGIOSARCOMA				X																					
MALIG.LYMPHOMA, HISTIOCYTIC TYPE															X										
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	+	N	+	+	+	+	+	+	N	+	N	+	+	+	+	+	+	+	N	+	+
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	-	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	-	+	+	+
ADENOMA, NOS																	X								
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYROID	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	
FOLLICULAR-CELL ADENOMA																						X			
PARATHYROID	-	+	+	-	-	-	-	-	-	+	-	-	+	-	-	+	-	-	-	-	-	-	+	-	+
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MIXED TUMOR, MALIGNANT																								X	
VAGINA	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
SARCOMA, NOS																									
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
HARDERIAN GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ADENOMA, NOS		X																					X		
CYSTADENOMA, NOS																									
MUSCULOSKELETAL SYSTEM																									
BONE	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
OSTEOMA						X																			
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE									X									X							
MALIG.LYMPHOMA, HISTIOCYTIC TYPE													X												
MALIGNANT LYMPHOMA, MIXED TYPE							X					X				X									
LYMPHOCYTIC LEUKEMIA																									

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

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

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

ANIMAL NUMBER	0261	0271	0281	0291	0301	0311	0321	0335	0341	0351	0361	0371	0381	0391	0401	0419	0422	0431	0445	0461	0477	0488	0493	0501	TOTAL
WEEKS ON STUDY	106	105	106	106	106	106	106	106	106	106	106	106	106	106	106	107	106	106	106	106	106	106	093	106	TISSUES TUMORS
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	50*
HEMANGIOMA																									1
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	50*
FIBROSARCOMA																									1
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALVEOLAR/BRONCHIOLAR ADENOMA					X															X					4
TRACHEA	-	-	-	-	-	-	-	-	+	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	6
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
THYMUS	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	46
MALIGNANT LYMPHOMA, MIXED TYPE																									1
CIRCULATORY SYSTEM																									
HEART	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEPATOCELLULAR CARCINOMA		X																	X						2
SARCOMA, NOS, METASTATIC																	X								1
HEMANGIOSARCOMA																									1
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																									1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	+	+	N	+	+	N	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	N	+	50*
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	47
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																									
PITUITARY	-	+	+	+	+	+	+	-	+	+	+	+	-	-	+	+	+	+	+	+	+	+	-	+	41
ADENOMA, NOS																									1
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
FOLLICULAR-CELL ADENOMA																				X					2
PARATHYROID	-	-	+	-	-	+	-	-	+	-	-	+	-	+	+	-	+	+	-	-	+	-	+	+	18
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
MIXED TUMOR, MALIGNANT								X																	2
VAGINA	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
SARCOMA, NOS																	X								1
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																									
HARDERIAN GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
ADENOMA, NOS																									1
CYSTADENOMA, NOS																									1
MUSCULOSKELETAL SYSTEM																									
BONE	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
OSTEOMA																									1
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		X																	X						4
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																				X					2
MALIGNANT LYMPHOMA, MIXED TYPE										X															4
LYMPHOCYTIC LEUKEMIA																X									1

* ANIMALS NECROPSIED

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

TABLE B4.

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

LOW DOSE

ANIMAL NUMBER	0011	0021	0031	0041	0051	0061	0071	0081	0091	0101	0111	0121	0131	0141	0151	0161	0171	0181	0191	0201	0211	0221	0231	0241	0251
WEEKS ON STUDY	105	090	104	105	051	037	105	105	105	105	105	105	105	067	105	051	051	086	051	105	105	105	105	105	105
INTEGUMENTARY SYSTEM																									
SKIN	+	+	N	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N
SQUAMOUS CELL PAPILLOMA																					X				
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR CARCINOMA, METASTA																									
ALVEOLAR/BRONCHIOLAR ADENOMA			X	X			X																		
ALVEOLAR/BRONCHIOLAR CARCINOMA							X																		
TRACHEA	-	+	+	-	+	A	-	+	-	-	-	-	-	+	-	-	-	+	+	-	-	-	+	-	+
HEPATOCELLULAR CARCINOMA, METASTA																									
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	+	+	+	+	+	A	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	-	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR ADENOMA									X		X										X				X
HEPATOCELLULAR CARCINOMA																									
BILE DUCT	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	+	N	N	+	N	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+
PANCREAS	+	+	-	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	-	+	+	A	+	+	+	+	+	+	+	+	+	+	-	+	-	+	+	+	+	+	+
STOMACH	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	-	-	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	-	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	-	+	+	A	+	-	+	+	+	+	+	+	+	-	+	+	+	+	+	-	+	+	
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	-	+	-	+
ADENOMA, NOS								X																	
ADRENAL	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+
PHEOCHROMOCYTOMA												X													
THYROID	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	-	-	+	+	+	+	+	+	+	+
PARATHYROID	-	+	+	-	+	A	-	+	-	-	+	-	-	+	+	-	-	+	-	+	-	+	+	-	-
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	+	N	+	+	A	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	N	+	N
UTERUS	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+
ADENOCARCINOMA, NOS																									
OVARY	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	-
BODY CAVITIES																									
PERITONEUM	N	N	N	N	N	A	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
SARCOMA, NOS		X																							
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	A	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		X																X					X	X	X
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			X																						
MALIGNANT LYMPHOMA, MIXED TYPE																								X	

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

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

ANIMAL NUMBER	02	02	02	02	03	03	03	03	03	03	03	03	03	03	04	04	04	04	04	04	04	04	05	TOTAL
WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	086	085	085	085	105	085	097	083	105	105	098	105	105	TISSUES TUMORS
INTEGUMENTARY SYSTEM																								
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	N	+	+	+	+	N	49*
SQUAMOUS CELL PAPILLOMA																								1
RESPIRATORY SYSTEM																								
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEPATOCELLULAR CARCINOMA, METASTA																	X							1
ALVEOLAR/BRONCHIOLAR ADENOMA					X				X															5
ALVEOLAR/BRONCHIOLAR CARCINOMA											X													2
TRACHEA	-	+	-	-	-	+	-	-	-	+	+	+	+	-	-	+	+	+	+	-	+	-	+	21
HEPATOCELLULAR CARCINOMA, METASTA																	X							1
HEMATOPOIETIC SYSTEM																								
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	48
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
THYMUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	-	45
CIRCULATORY SYSTEM																								
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																								
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEPATOCELLULAR ADENOMA																								4
HEPATOCELLULAR CARCINOMA											X				X		X							3
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	+	+	+	+	+	N	N	+	N	N	+	N	N	+	+	+	+	+	N	49*
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	47
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	-	+	+	+	+	+	+	47
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	46
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	46
URINARY SYSTEM																								
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	44
ENDOCRINE SYSTEM																								
PITUITARY	+	+	-	+	+	+	-	+	+	+	+	-	+	+	+	+	+	+	+	+	+	-	-	41
ADENOMA, NOS																								1
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
PHEOCHROMOCYTOMA																								1
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
PARATHYROID	+	-	+	-	-	-	-	-	-	+	+	+	-	+	-	-	+	+	-	+	-	-	-	21
REPRODUCTIVE SYSTEM																								
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	N	+	49*
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ADENOCARCINOMA, NOS			X																			X		2
OVARY	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	-	+	+	+	+	+	+	+	45
BODY CAVITIES																								
PERITONEUM	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	49*
SARCOMA, NOS																								1
ALL OTHER SYSTEMS																								
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	49*
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE																								5
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																								1
MALIGNANT LYMPHOMA, MIXED TYPE											X				X									4

* ANIMALS NECROPSIED

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

TABLE B4.

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

HIGH DOSE

ANIMAL NUMBER	0011	0012	0013	0014	0015	0016	0017	0018	0019	0020	0111	0112	0113	0114	0115	0116	0117	0118	0119	0120	0121	0122	0123	0124	0125
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	103	104	111	104	104
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+
ALVEOLAR/BRONCHIOLAR ADENOMA							X		X				X												
ALVEOLAR/BRONCHIOLAR CARCINOMA																									
TRACHEA	+	+	+	−	+	−	−	+	−	−	−	−	−	−	+	−	+	+	−	−	+	+	+	A	−	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+
HEMANGIOSARCOMA																									
MALIGNANT LYMPHOMA, MIXED TYPE																									
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+
THYMUS	−	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+
DIGESTIVE SYSTEM																									
ORAL CAVITY	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	A	N	N
SQUAMOUS CELL PAPILLOMA																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+
HEPATOCELLULAR ADENOMA																				X	X				
HEPATOCELLULAR CARCINOMA					X	X								X				X							
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	N	+	+	+	N	+	A	+	+
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	−	+	+	A	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	A	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	A	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	X																								
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	A	+	+
ENDOCRINE SYSTEM																									
PITUITARY	−	−	+	+	+	+	−	+	+	+	−	+	+	+	+	+	−	+	+	+	−	−	A	+	+
ADENOMA, NOS																									
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+
FOLLICULAR-CELL ADENOMA																					X				
PARATHYROID	+	+	−	+	+	+	−	+	−	+	+	−	+	+	+	+	+	+	+	−	+	+	A	−	−
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	N	+	N	+	N	+	N	+	+	+	N	+	A	+	+
ACINAR-CELL CARCINOMA																									
MIXED TUMOR, MALIGNANT																									
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+
ADENOCARCINOMA, NOS																								X	
LEIOMYOSARCOMA																									
OVARY	+	+	+	+	+	+	+	+	+	+	−	+	+	−	+	+	+	+	+	+	+	+	A	+	+
SPECIAL SENSE ORGANS																									
EYE	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	X	N	N	A	N	N
MALIGNANT MELANOMA																									
HARDERIAN GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	X	N	N	A	N	N
ADENOMA, NOS																									
BODY CAVITIES																									
MESENTERY	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	A	N	N
HEMANGIOSARCOMA																									
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	A	N	N
ADENOCARCINOMA, NOS, METASTATIC																									
MALIGNANT LYMPHOMA, NOS																					X				
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE															X										X
MALIGNANT LYMPHOMA, MIXED TYPE																									

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

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

ANIMAL NUMBER	0216	0227	0228	0229	0310	0311	0312	0313	0314	0315	0316	0317	0318	0319	0410	0411	0412	0413	0414	0415	0416	0417	0418	0419	0510	TOTAL
WEEKS ON STUDY	1041	1068	1041	1041	1041	1041	1041	0961	1041	1041	1041	1041	1041	1041	1041	1041	1041	1041	1041	1041	1041	1041	1041	1041	1041	TISSUES TUMORS
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	48
ALVEOLAR/BRONCHIOLAR ADENOMA				X																						4
ALVEOLAR/BRONCHIOLAR CARCINOMA														X												1
TRACHEA	+	+	+	-	+	-	+	+	-	+	-	-	+	-	-	-	-	+	-	+	+	+	+	+	+	27
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	48
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMANGIOSARCOMA			X																							1
MALIGNANT LYMPHOMA, MIXED TYPE																							X			1
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
THYMUS	+	+	+	+	+	+	+	+	-	+	+	+	-	+	+	+	-	+	+	+	+	-	-	+	+	42
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
ORAL CAVITY	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	49*
SQUAMOUS CELL PAPILLOMA			X																							1
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEPATOCELLULAR ADENOMA														X												3
HEPATOCELLULAR CARCINOMA												X													X	6
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
GALLBLADDER & COMMON BILE DUCT	+	N	+	+	+	+	+	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49*
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	47
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE																										1
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	+	+	+	+	-	-	+	+	+	+	+	+	+	+	-	+	+	+	+	39
ADENOMA, NOS				X																						1
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
FOLLICULAR-CELL ADENOMA																										1
PARATHYROID	-	+	-	-	-	+	+	+	-	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	36
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	+	+	+	+	+	+	+	N	+	+	+	+	N	+	+	N	+	+	+	+	+	+	+	+	+	49*
ACINAR-CELL CARCINOMA								X																		1
MIXED TUMOR, MALIGNANT													X													1
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ADENOCARCINOMA, NOS																X										1
LEIOMYOSARCOMA																										1
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	46
SPECIAL SENSE ORGANS																										
EYE	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	49*
MALIGNANT MELANOMA																										1
HARDERIAN GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	49*
ADENOMA, NOS																										1
BODY CAVITIES																										
MESENTERY	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	49*
HEMANGIOSARCOMA																				X						1
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	49*
ADENOCARCINOMA, NOS, METASTATIC																X										1
MALIGNANT LYMPHOMA, NOS																										1
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE											X															3
MALIGNANT LYMPHOMA, MIXED TYPE					X																					1

* ANIMALS NECROPSIED

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

APPENDIX C

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

TABLE C1.

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

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	40	50	50
ANIMALS NECROPSIED	40	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	40	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(40)	(50)	(50)
EPIDERMAL INCLUSION CYST	2 (5%)	1 (2%)	2 (4%)
ULCER, FOCAL			1 (2%)
INFLAMMATION, ACUTE/CHRONIC		1 (2%)	
INFLAMMATION, CHRONIC FOCAL		1 (2%)	
REACTION, FOREIGN BODY		1 (2%)	
FIBROSIS			1 (2%)
HYPERPLASIA, FOCAL		1 (2%)	
*SUBCUT TISSUE	(40)	(50)	(50)
EDEMA, NOS			1 (2%)
HEMORRHAGIC CYST	1 (3%)		
INFLAMMATION, ACUTE/CHRONIC		1 (2%)	1 (2%)
RESPIRATORY SYSTEM			
NONE			
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(40)	(50)	(50)
HYPERPLASIA, LYMPHOID		3 (6%)	
#BONE MARROW	(40)	(50)	(49)
ATROPHY, NOS		1 (2%)	
#SPLEEN	(40)	(50)	(49)
INFARCT, NOS			1 (2%)
ATROPHY, NOS		1 (2%)	
HYPERPLASIA, LYMPHOID	1 (3%)		
HEMATOPOIESIS	2 (5%)	1 (2%)	

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#PEYER'S PATCH	(40)	(49)	(46)
HYPERPLASIA, LYMPHOID	1 (3%)		
CIRCULATORY SYSTEM			
#MESENTERIC L. NODE	(40)	(50)	(50)
LYMPHANGIECTASIS			1 (2%)
#AURICULAR APPENDAGE	(40)	(50)	(50)
THROMBUS, MURAL	1 (3%)		
#MYOCARDIUM	(40)	(50)	(50)
INFLAMMATION, ACUTE/CHRONIC			1 (2%)
INFLAMMATION, CHRONIC	27 (68%)	39 (78%)	32 (64%)
INFLAMMATION, CHRONIC FOCAL	1 (3%)		1 (2%)
*ARTERIOLE	(40)	(50)	(50)
NECROSIS, FIBRINOID	1 (3%)		
#PANCREAS	(40)	(50)	(49)
PERIARTERITIS	1 (3%)	1 (2%)	
*MESENTERY	(40)	(50)	(50)
THROMBOSIS, NOS	1 (3%)		
#KIDNEY	(40)	(50)	(50)
PERIARTERITIS	1 (3%)		
#THYROID	(40)	(50)	(50)
PERIARTERITIS	1 (3%)		
DIGESTIVE SYSTEM			
#LIVER	(40)	(50)	(50)
NECROSIS, COAGULATIVE	1 (3%)		
CYTOPLASMIC CHANGE, NOS		1 (2%)	
CYTOPLASMIC VACUOLIZATION		1 (2%)	2 (4%)
BASOPHILIC CYTO CHANGE		1 (2%)	1 (2%)
FOCAL CELLULAR CHANGE	1 (3%)		
ANGIECTASIS		1 (2%)	
#LIVER/CENTRILOBULAR	(40)	(50)	(50)
CYTOPLASMIC VACUOLIZATION	1 (3%)		

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#BILE DUCT	(40)	(50)	(50)
HYPERPLASIA, NOS	2 (5%)		
#PANCREAS	(40)	(50)	(49)
EDEMA, NOS			1 (2%)
INFLAMMATION, CHRONIC	2 (5%)	1 (2%)	
#PANCREATIC ACINUS	(40)	(50)	(49)
ATROPHY, NOS		1 (2%)	1 (2%)
#GASTRIC SUBMUCOSA	(40)	(50)	(49)
EDEMA, NOS		2 (4%)	
#COLON	(40)	(50)	(47)
NEMATODIASIS	2 (5%)	1 (2%)	
#COLONIC SUBMUCOSA	(40)	(50)	(47)
EDEMA, NOS	1 (3%)		
URINARY SYSTEM			
#KIDNEY	(40)	(50)	(50)
HYDRONEPHROSIS			1 (2%)
INFLAMMATION, CHRONIC	29 (73%)	46 (92%)	43 (86%)
INFARCT, FOCAL	1 (3%)	1 (2%)	
HEMOSIDEROSIS		1 (2%)	
#KIDNEY/CORTEX	(40)	(50)	(50)
CYST, NOS			1 (2%)
#URINARY BLADDER	(40)	(50)	(46)
INFLAMMATION, HEMORRHAGIC			1 (2%)
#U.BLADDER/SUBMUCOSA	(40)	(50)	(46)
INFLAMMATION, CHRONIC FOCAL			1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(39)	(48)	(49)
COLLOID CYST		1 (2%)	
GLIOSIS			1 (2%)
HYPERPLASIA, NOS	1 (3%)		

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#ADRENAL	(40)	(50)	(50)
NECROSIS, ISCHEMIC	1 (3%)		
ANGIECTASIS		1 (2%)	
#ADRENAL CORTEX	(40)	(50)	(50)
CYTOPLASMIC VACUOLIZATION	1 (3%)		
CYTOPLASMIC LIPID AGGREGATE	1 (3%)		
HYPERPLASIA, FOCAL		1 (2%)	
#ADRENAL MEDULLA	(40)	(50)	(50)
HYPERPLASIA, NOS	2 (5%)		
HYPERPLASIA, FOCAL	3 (8%)		
#THYROID	(40)	(50)	(50)
HYPERPLASIA, C-CELL	1 (3%)	1 (2%)	4 (8%)
#THYROID FOLLICLE	(40)	(50)	(50)
ATROPHY, NOS	1 (3%)		
#PARATHYROID	(37)	(44)	(47)
HYPERPLASIA, NOS	1 (3%)		
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(40)	(50)	(50)
CYSTIC DUCTS	1 (3%)	3 (6%)	3 (6%)
*PREPUTIAL GLAND	(40)	(50)	(50)
INFLAMMATION, CHRONIC SUPPURATIV		1 (2%)	2 (4%)
HYPERPLASIA, CYSTIC			1 (2%)
#PROSTATE	(40)	(50)	(47)
INFLAMMATION, SUPPURATIVE	3 (8%)	9 (18%)	5 (11%)
INFLAMMATION, CHRONIC			1 (2%)
INFLAMMATION, CHRONIC SUPPURATIV		5 (10%)	2 (4%)
HYPERPLASIA, CYSTIC			1 (2%)
#TESTIS	(40)	(50)	(50)
HYPERPLASIA, INTERSTITIAL CELL	3 (8%)	4 (8%)	2 (4%)
NERVOUS SYSTEM			
#CEREBRUM	(40)	(50)	(49)
MALACIA			1 (2%)

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#BRAIN	(40)	(50)	(49)
HEMORRHAGE			1 (2%)
MALACIA			1 (2%)
#CEREBRAL HEMISPHERE	(40)	(50)	(49)
STATUS SPONGIOSUS	1 (3%)		
#CEREBELLUM	(40)	(50)	(49)
STATUS SPONGIOSUS		1 (2%)	
SPECIAL SENSE ORGANS			
*EYE	(40)	(50)	(50)
PHTHISIS BULBI		1 (2%)	
*EYE/CORNEA	(40)	(50)	(50)
ULCER, NOS		1 (2%)	
INFLAMMATION, CHRONIC SUPPURATIV		1 (2%)	
*EYE/RETINA	(40)	(50)	(50)
DEGENERATION, NOS		1 (2%)	
MUSCULOSKELETAL SYSTEM			
*SKULL	(40)	(50)	(50)
EXOSTOSIS			1 (2%)
*FEMUR	(40)	(50)	(50)
FIBROUS OSTEODYSTROPHY	1 (3%)		
BODY CAVITIES			
*MESENTERY	(40)	(50)	(50)
STEATITIS	3 (8%)	3 (6%)	6 (12%)
NECROSIS, FAT		1 (2%)	
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(40)	(50)	(50)
INFLAMMATION, SUPPURATIVE	1 (3%)		
SPECIAL MORPHOLOGY SUMMARY			
NONE			

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

TABLE C2.

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

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	40	50	50
ANIMALS NECROPSIED	40	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	40	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(40)	(50)	(50)
ULCER, CHRONIC			2 (4%)
INFLAMMATION, CHRONIC FOCAL	1 (3%)		
FIBROSIS, FOCAL		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(39)	(50)	(50)
EDEMA, NOS			1 (2%)
PNEUMONIA INTERSTITIAL CHRONIC		1 (2%)	
PROTEINOSIS, ALVEOLAR		1 (2%)	
HYPERPLASIA, ADENOMATOUS	1 (3%)		1 (2%)
HYPERPLASIA, ALVEOLAR EPITHELIUM		1 (2%)	
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(40)	(50)	(50)
HYPERPLASIA, LYMPHOID		1 (2%)	
#SPLEEN	(40)	(50)	(50)
HEMOSIDEROSIS	1 (3%)	1 (2%)	8 (16%)
#MANDIBULAR L. NODE	(40)	(50)	(50)
HYPERPLASIA, LYMPHOID	1 (3%)		
#PEYER'S PATCH	(40)	(50)	(49)
HYPERPLASIA, LYMPHOID	3 (8%)		1 (2%)
CIRCULATORY SYSTEM			
#HEART/ATRIUM	(40)	(50)	(50)
THROMBUS, MURAL			1 (2%)

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#MYOCARDIUM	(40)	(50)	(50)
INFLAMMATION, ACUTE/CHRONIC	3 (8%)	3 (6%)	2 (4%)
INFLAMMATION, CHRONIC	23 (58%)	21 (42%)	32 (64%)
INFLAMMATION, CHRONIC FOCAL		2 (4%)	
DEGENERATION, NOS			1 (2%)
*PULMONARY VEIN	(40)	(50)	(50)
THROMBUS, ORGANIZED		1 (2%)	
DIGESTIVE SYSTEM			
*TONGUE	(40)	(50)	(50)
ABSCESS, CHRONIC		1 (2%)	
INFLAMMATION, PYOGRANULOMATOUS		1 (2%)	
#LIVER	(40)	(50)	(50)
INFLAMMATION, ACUTE/CHRONIC	1 (3%)		
NECROSIS, COAGULATIVE	1 (3%)	1 (2%)	2 (4%)
CYTOPLASMIC CHANGE, NOS	1 (3%)	1 (2%)	3 (6%)
CYTOPLASMIC VACUOLIZATION	2 (5%)	2 (4%)	2 (4%)
BASOPHILIC CYTO CHANGE			1 (2%)
FOCAL CELLULAR CHANGE		6 (12%)	
ANGIECTASIS		1 (2%)	1 (2%)
#LIVER/CENTRILOBULAR	(40)	(50)	(50)
CONGESTION, NOS			1 (2%)
CYTOPLASMIC VACUOLIZATION			1 (2%)
#LIVER/KUPFFER CELL	(40)	(50)	(50)
HYPERPLASIA, FOCAL		1 (2%)	
#PANCREAS	(40)	(50)	(50)
INFLAMMATION, CHRONIC			2 (4%)
#STOMACH	(40)	(50)	(50)
ULCER, FOCAL		1 (2%)	
#COLON	(40)	(50)	(50)
NEMATODIASIS	2 (5%)	1 (2%)	1 (2%)
URINARY SYSTEM			
#KIDNEY	(40)	(50)	(50)
INFLAMMATION, CHRONIC	4 (10%)	3 (6%)	2 (4%)

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#URINARY BLADDER	(40)	(50)	(49)
INFLAMMATION, ACUTE/CHRONIC		1 (2%)	1 (2%)
#U.BLADDER/SUBMUCOSA	(40)	(50)	(49)
FIBROSIS			1 (2%)
FIBROSIS, FOCAL			1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(39)	(49)	(49)
COLLOID CYST			1 (2%)
HEMORRHAGIC CYST	1 (3%)	2 (4%)	
ANGIECTASIS	1 (3%)	1 (2%)	
#ADRENAL CORTEX	(40)	(50)	(50)
CYST, NOS		1 (2%)	
#ADRENAL MEDULLA	(40)	(50)	(50)
HYPERPLASIA, FOCAL	1 (3%)	3 (6%)	
#THYROID	(40)	(49)	(50)
HYPERPLASIA, C-CELL	6 (15%)	7 (14%)	5 (10%)
#THYROID FOLLICLE	(40)	(49)	(50)
ATROPHY, NOS			3 (6%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(40)	(50)	(50)
CYSTIC DUCTS	8 (20%)	8 (16%)	8 (16%)
*MAMMARY LOBULE	(40)	(50)	(50)
HYPERPLASIA, NOS	1 (3%)		
*PREPUTIAL GLAND	(40)	(50)	(50)
HYPERPLASIA, NOS		1 (2%)	1 (2%)
#UTERUS	(40)	(50)	(50)
INTUSSUSCEPTION		1 (2%)	
EDEMA, NOS		1 (2%)	
INFLAMMATION, NECROTIZING		1 (2%)	
#UTERUS/ENDOMETRIUM	(40)	(50)	(50)
CYST, NOS		1 (2%)	3 (6%)

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
INFLAMMATION, SUPPURATIVE	1 (3%)		
INFLAMMATION, NECROTIZING		1 (2%)	
HYPERPLASIA, NOS	1 (3%)	2 (4%)	1 (2%)
HYPERPLASIA, EPITHELIAL			1 (2%)
HYPERPLASIA, FOCAL			1 (2%)
HYPERPLASIA, CYSTIC	1 (3%)	2 (4%)	11 (22%)
HYPERPLASIA, ADENOMATOUS			1 (2%)
DECIDUAL ALTERATION, NOS			1 (2%)
#OVARY	(40)	(50)	(50)
FOLLICULAR CYST, NOS		1 (2%)	
NERVOUS SYSTEM			
#BRAIN/MENINGES	(40)	(50)	(49)
HEMORRHAGE	1 (3%)		
METAPLASIA, OSSEOUS	1 (3%)		
#CEREBRAL VENTRICLE	(40)	(50)	(49)
HEMORRHAGE			1 (2%)
#BRAIN	(40)	(50)	(49)
HEMORRHAGE			1 (2%)
#CEREBELLUM	(40)	(50)	(49)
HEMORRHAGE		1 (2%)	
SPECIAL SENSE ORGANS			
*EYE	(40)	(50)	(50)
HEMORRHAGE, CHRONIC		1 (2%)	
*EYE/RETINA	(40)	(50)	(50)
DEGENERATION, NOS			1 (2%)
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*MESENTERY	(40)	(50)	(50)
MINERALIZATION		1 (2%)	

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
STEATITIS	1 (3%)		1 (2%)
NECROSIS, FAT		1 (2%)	
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED		3	

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

APPENDIX D

SUMMARY OF THE INCIDENCE OF NONENOPLASTIC LESIONS IN MICE FED DIETS CONTAINING EUGENOL

TABLE D1.

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

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
INFLAMMATION, NOS	1 (2%)		
ULCER, NOS	3 (6%)	1 (2%)	1 (2%)
INFLAMMATION, SUPPURATIVE	1 (2%)		
INFLAMMATION, CHRONIC	7 (14%)	11 (22%)	
ULCER, CHRONIC	2 (4%)	5 (10%)	1 (2%)
INFLAMMATION, CHRONIC SUPPURATIV		1 (2%)	
FIBROSIS	1 (2%)	1 (2%)	2 (4%)
FIBROSIS, FOCAL		1 (2%)	
HYPERPLASIA, EPITHELIAL	1 (2%)		
RESPIRATORY SYSTEM			
*LARYNGEAL GLAND	(50)	(50)	(50)
INFLAMMATION, SUPPURATIVE	1 (2%)		
#LUNG	(49)	(49)	(50)
ASPIRATION, FOREIGN BODY		5 (10%)	
CONGESTION, NOS		1 (2%)	3 (6%)
INFLAMMATION, INTERSTITIAL			1 (2%)
INFLAMMATION, ACUTE/CHRONIC			1 (2%)
LIPOGRANULOMA			1 (2%)
INFLAMMATION, FOCAL GRANULOMATOU	12 (24%)	14 (29%)	
HYPERPLASIA, ADENOMATOUS	17 (35%)	21 (43%)	18 (36%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
HYPERPLASIA, LYMPHOID	2 (4%)		
#BONE MARROW	(48)	(49)	(47)
HYPERPLASIA, GRANULOCYTIC		1 (2%)	1 (2%)

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#SPLEEN	(48)	(49)	(48)
ATROPHY, NOS		1 (2%)	
HYPERPLASIA, RETICULUM CELL		1 (2%)	
HYPERPLASIA, LYMPHOID		1 (2%)	2 (4%)
HEMATOPOIESIS	5 (10%)	7 (14%)	4 (8%)
#LYMPH NODE	(49)	(48)	(50)
ATROPHY, NOS	1 (2%)		
ANGIECTASIS	1 (2%)		
#MESENTERIC L. NODE	(49)	(48)	(50)
CONGESTION, NOS	1 (2%)		4 (8%)
HEMORRHAGE	1 (2%)		1 (2%)
ANGIECTASIS	5 (10%)		
HYPERPLASIA, PLASMA CELL			1 (2%)
HYPERPLASIA, RETICULUM CELL		1 (2%)	
HYPERPLASIA, LYMPHOID	4 (8%)	2 (4%)	1 (2%)
HEMATOPOIESIS	4 (8%)	3 (6%)	
#INGUINAL LYMPH NODE	(49)	(48)	(50)
PIGMENTATION, NOS	1 (2%)		
HYPERPLASIA, LYMPHOID			1 (2%)
#LUNG	(49)	(49)	(50)
HYPERPLASIA, LYMPHOID	1 (2%)		
#LIVER	(50)	(50)	(49)
HEMATOPOIESIS	2 (4%)		
#PEYER'S PATCH	(46)	(49)	(45)
HYPERPLASIA, LYMPHOID		1 (2%)	
CIRCULATORY SYSTEM			
#MYOCARDIUM	(50)	(50)	(50)
INFLAMMATION, INTERSTITIAL			1 (2%)
#PROSTATIC GLAND	(50)	(50)	(48)
PERIARTERITIS	1 (2%)		
DIGESTIVE SYSTEM			
#PAROTID GLAND	(48)	(49)	(49)
INFLAMMATION, NOS			1 (2%)

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#LIVER	(50)	(50)	(49)
HEMORRHAGE			2 (4%)
HEMATOMA, NOS		1 (2%)	
INFLAMMATION, FOCAL	2 (4%)		1 (2%)
INFLAMMATION, MULTIFOCAL	6 (12%)		
PARASITISM			1 (2%)
NECROSIS, NOS			1 (2%)
NECROSIS, FOCAL	1 (2%)		1 (2%)
NECROSIS, COAGULATIVE		1 (2%)	1 (2%)
METAMORPHOSIS FATTY	1 (2%)		1 (2%)
CALCIFICATION, NOS		1 (2%)	
PIGMENTATION, NOS	1 (2%)		1 (2%)
CYTOPLASMIC VACUOLIZATION	3 (6%)	2 (4%)	1 (2%)
BASOPHILIC CYTO CHANGE			1 (2%)
EOSINOPHILIC CYTO CHANGE		1 (2%)	
ANGIECTASIS	1 (2%)		
#LIVER/CENTRILOBULAR	(50)	(50)	(49)
METAMORPHOSIS FATTY	1 (2%)		
*GALLBLADDER	(50)	(50)	(50)
INFLAMMATION, SUPPURATIVE			1 (2%)
#BILE DUCT	(50)	(50)	(49)
CYST, NOS		1 (2%)	
#PANCREAS	(46)	(49)	(48)
ATROPHY, FOCAL			1 (2%)
#ESOPHAGUS	(48)	(49)	(50)
HYPERPLASIA, EPITHELIAL	1 (2%)		
#STOMACH	(50)	(50)	(47)
INFLAMMATION, SUPPURATIVE			1 (2%)
HYPERPLASIA, EPITHELIAL	1 (2%)		
#GASTRIC MUCOSA	(50)	(50)	(47)
HYPERPLASIA, EPITHELIAL	1 (2%)		
HYPERPLASIA, CYSTIC		1 (2%)	
#GASTRIC FUNDAL GLAND	(50)	(50)	(47)
DILATATION, NOS			1 (2%)
URINARY SYSTEM			
#KIDNEY	(49)	(50)	(49)
CONGESTION, NOS			1 (2%)

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
INFLAMMATION, FOCAL			8 (16%)
INFLAMMATION, INTERSTITIAL			1 (2%)
INFLAMMATION, ACUTE SUPPURATIVE		1 (2%)	
INFLAMMATION, ACUTE/CHRONIC		1 (2%)	
INFLAMMATION, CHRONIC			1 (2%)
NEPHROSIS, NOS	30 (61%)	26 (52%)	4 (8%)
INFARCT, ACUTE		1 (2%)	
PIGMENTATION, NOS	1 (2%)		
#KIDNEY/CORTEX	(49)	(50)	(49)
INFLAMMATION, FOCAL			3 (6%)
NEPHROSIS, NOS			1 (2%)
#KIDNEY/TUBULE	(49)	(50)	(49)
REGENERATION, NOS			1 (2%)
#URINARY BLADDER	(49)	(50)	(49)
ULCER, NOS		1 (2%)	
INFLAMMATION, SUPPURATIVE		1 (2%)	
*URETHRA	(50)	(50)	(50)
INFLAMMATION, ACUTE SUPPURATIVE	1 (2%)		
ENDOCRINE SYSTEM			
#THYROID	(48)	(49)	(49)
DEGENERATION, CYSTIC	11 (23%)	3 (6%)	
HYPERPLASIA, FOLLICULAR-CELL	1 (2%)	1 (2%)	
REPRODUCTIVE SYSTEM			
*PREPUTIAL GLAND	(50)	(50)	(50)
DILATATION, NOS	1 (2%)		
CYSTIC DUCTS		5 (10%)	1 (2%)
INFLAMMATION, SUPPURATIVE	2 (4%)	1 (2%)	
ABSCESS, CHRONIC			1 (2%)
#PROSTATE	(50)	(50)	(48)
INFLAMMATION, SUPPURATIVE		1 (2%)	
INFLAMMATION, ACUTE SUPPURATIVE	1 (2%)		
#TESTIS	(50)	(50)	(50)
ATROPHY, NOS	1 (2%)		

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
*EPIDIDYMIS	(50)	(50)	(50)
INFLAMMATION, FOCAL GRANULOMATOU	1 (2%)		
NERVOUS SYSTEM			
#BRAIN/THALAMUS	(50)	(50)	(50)
PSAMMOMA BODIES	22 (44%)	23 (46%)	25 (50%)
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*MESENTERY	(50)	(50)	(50)
INFLAMMATION, CHRONIC FOCAL		1 (2%)	
GRANULATION, TISSUE	1 (2%)		
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
ANGIECTASIS	1 (2%)		
THORAX			
ULCER, NOS			1
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	2		1

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

TABLE D2.

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

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	49	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	49	49
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(49)	(49)
INFLAMMATION, NOS		5 (10%)	
INFLAMMATION, CHRONIC	7 (14%)		
INFLAMMATION, CHRONIC FOCAL			1 (2%)
INFLAMMATION, PYOGRANULOMATOUS			1 (2%)
RESPIRATORY SYSTEM			
*LARYNX	(50)	(49)	(49)
EDEMA, NOS	1 (2%)		
#LUNG	(50)	(49)	(48)
CONGESTION, NOS			3 (6%)
LYMPHOCYTIC INFLAMMATORY INFILTR			1 (2%)
INFLAMMATION, INTERSTITIAL		1 (2%)	
BRONCHOPNEUMONIA ACUTE SUPPURATI		1 (2%)	
LIPOGRANULOMA		1 (2%)	
INFLAMMATION, FOCAL GRANULOMATOU	18 (36%)	19 (39%)	25 (52%)
INFARCT, NOS	1 (2%)		
HYPERPLASIA, ADENOMATOUS	22 (44%)	22 (45%)	26 (54%)
HYPERPLASIA, ALVEOLAR EPITHELIUM			1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(49)	(49)
LEUKOCYTOSIS, EOSINOPHILIC	1 (2%)		
HYPERPLASIA, LYMPHOID			4 (8%)
HEMATOPOIESIS		1 (2%)	
#BONE MARROW	(50)	(48)	(48)
HYPERPLASIA, GRANULOCYTIC		1 (2%)	

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#SPLEEN	(50)	(49)	(49)
NECROSIS, NOS	1 (2%)		
PIGMENTATION, NOS	1 (2%)		1 (2%)
HYPERPLASIA, LYMPHOID	3 (6%)	6 (12%)	1 (2%)
HEMATOPOIESIS	5 (10%)	2 (4%)	4 (8%)
#MANDIBULAR L. NODE	(50)	(49)	(49)
HYPERPLASIA, RETICULUM CELL		1 (2%)	
HYPERPLASIA, LYMPHOID			1 (2%)
#BRONCHIAL LYMPH NODE	(50)	(49)	(49)
HYPERPLASIA, LYMPHOID			1 (2%)
#PANCREATIC L.NODE	(50)	(49)	(49)
HYPERPLASIA, LYMPHOID	1 (2%)	1 (2%)	
HEMATOPOIESIS		1 (2%)	
#MESENTERIC L. NODE	(50)	(49)	(49)
ANGIECTASIS	1 (2%)		
HEMATOPOIESIS	1 (2%)		
#RENAL LYMPH NODE	(50)	(49)	(49)
HYPERPLASIA, NOS		1 (2%)	
#INGUINAL LYMPH NODE	(50)	(49)	(49)
HYPERPLASIA, LYMPHOID		1 (2%)	
MASTOCYTOSIS		1 (2%)	
#LUNG	(50)	(49)	(48)
HYPERPLASIA, LYMPHOID	2 (4%)	1 (2%)	
#LIVER	(50)	(49)	(49)
HYPERPLASIA, RETICULUM CELL			1 (2%)
HYPERPLASIA, LYMPHOID	1 (2%)	3 (6%)	
HEMATOPOIESIS	1 (2%)	1 (2%)	3 (6%)
#PEYER'S PATCH	(50)	(46)	(48)
HYPERPLASIA, LYMPHOID		1 (2%)	2 (4%)
*MESENTERY	(50)	(49)	(49)
HYPERPLASIA, LYMPHOID	1 (2%)		
#KIDNEY	(50)	(49)	(49)
HYPERPLASIA, LYMPHOID	1 (2%)	1 (2%)	

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
#URINARY BLADDER	(49)	(44)	(48)
HYPERPLASIA, LYMPHOID	1 (2%)		
#UTERUS	(50)	(48)	(49)
HYPERPLASIA, LYMPHOID	1 (2%)		
CIRCULATORY SYSTEM			
#LUNG	(50)	(49)	(48)
EMBOLISM, NOS	1 (2%)		
PERIARTERITIS	1 (2%)		
#MYOCARDIUM	(49)	(49)	(49)
INFLAMMATION, SUPPURATIVE			1 (2%)
*RENAL ARTERY	(50)	(49)	(49)
INFLAMMATION, NECROTIZING			1 (2%)
*INTESTINAL TRACT	(50)	(49)	(49)
LYMPHANGIECTASIS		1 (2%)	
*MESENTERY	(50)	(49)	(49)
PERIVASCULITIS			1 (2%)
#URINARY BLADDER	(49)	(44)	(48)
PERIARTERITIS			1 (2%)
#THYROID	(48)	(47)	(49)
PERIARTERITIS			1 (2%)
#THYMUS	(46)	(45)	(42)
LYMPHANGIECTASIS		1 (2%)	
DIGESTIVE SYSTEM			
#LIVER	(50)	(49)	(49)
HEMORRHAGE		1 (2%)	
HEMORRHAGIC CYST		1 (2%)	
INFLAMMATION, FOCAL			2 (4%)
LYMPHOCYTIC INFLAMMATORY INFILTR			1 (2%)
INFLAMMATION, MULTIFOCAL	19 (38%)	20 (41%)	17 (35%)
INFLAMMATION, SUPPURATIVE		1 (2%)	

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
INFLAMMATION, GRANULOMATOUS			1 (2%)
FIBROSIS, FOCAL			1 (2%)
DEGENERATION PIGMENTARY			2 (4%)
NECROSIS, NOS	2 (4%)	1 (2%)	1 (2%)
NECROSIS, FOCAL			2 (4%)
ANISOKARYOSIS	1 (2%)		
CYTOPLASMIC CHANGE, NOS		1 (2%)	
CYTOPLASMIC VACUOLIZATION	1 (2%)		1 (2%)
ANGIECTASIS		2 (4%)	1 (2%)
#PANCREAS	(49)	(47)	(47)
CYSTIC DUCTS	2 (4%)		1 (2%)
EDEMA, NOS		1 (2%)	
INFLAMMATION, NOS			1 (2%)
INFLAMMATION, CHRONIC FOCAL	1 (2%)		
#GASTRIC MUCOSA	(50)	(47)	(49)
CYST, NOS		2 (4%)	
ULCER, NOS			1 (2%)
ABSCESS, NOS			1 (2%)
URINARY SYSTEM			
#KIDNEY	(50)	(49)	(49)
HYDRONEPHROSIS		1 (2%)	1 (2%)
LYMPHOCYTIC INFLAMMATORY INFILTR			4 (8%)
INFLAMMATION, CHRONIC		1 (2%)	
GLOMERULONEPHRITIS, CHRONIC	1 (2%)		
NEPHROSIS, NOS	18 (36%)	16 (33%)	13 (27%)
AMYLOIDOSIS	1 (2%)		
#KIDNEY/PELVIS	(50)	(49)	(49)
HYPERPLASIA, EPITHELIAL	1 (2%)		
#URINARY BLADDER	(49)	(44)	(48)
HYPERPLASIA, EPITHELIAL	1 (2%)		
ENDOCRINE SYSTEM			
#ADRENAL	(50)	(48)	(49)
CYST, NOS	1 (2%)		
#THYROID	(48)	(47)	(49)
ULTIMOBRANCHIAL CYST			1 (2%)

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
INFLAMMATION, FOCAL			1 (2%)
DEGENERATION, CYSTIC	11 (23%)	8 (17%)	7 (14%)
DEGENERATION PIGMENTARY			1 (2%)
HYPERTROPHY, NOS	1 (2%)		
HYPERPLASIA, FOLLICULAR-CELL	1 (2%)	2 (4%)	6 (12%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(49)	(49)
CYSTIC DUCTS	5 (10%)	2 (4%)	2 (4%)
*VAGINAL MUCOUS MEMBR	(50)	(49)	(49)
HYPERPLASIA, CYSTIC			1 (2%)
#UTERUS	(50)	(48)	(49)
EDEMA, NOS			1 (2%)
INFLAMMATION, SUPPURATIVE	3 (6%)	5 (10%)	3 (6%)
PYOMETRA		1 (2%)	1 (2%)
ABSCESS, NOS	1 (2%)		
AMYLOIDOSIS	1 (2%)		
#UTERUS/ENDOMETRIUM	(50)	(48)	(49)
HYDROMETRA	1 (2%)		
INFLAMMATION, SUPPURATIVE		1 (2%)	
HYPERPLASIA, CYSTIC	41 (82%)	39 (81%)	40 (82%)
#UTERUS/MYOMETRIUM	(50)	(48)	(49)
HYPERPLASIA, NOS		1 (2%)	
#OVARY	(50)	(45)	(46)
FOLLICULAR CYST, NOS	11 (22%)	10 (22%)	15 (33%)
ABSCESS, NOS		1 (2%)	
NERVOUS SYSTEM			
#BRAIN/THALAMUS	(50)	(49)	(49)
PSAMMOMA BODIES	24 (48%)	18 (37%)	23 (47%)
SPECIAL SENSE ORGANS			
*EYE	(50)	(49)	(49)
PHTHISIS BULBI			1 (2%)

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
MUSCULOSKELETAL SYSTEM			
*MASSETER MUSCLE	(50)	(49)	(49)
INFLAMMATION, CHRONIC SUPPURATIV		1 (2%)	
*ABDOMINAL MUSCLE	(50)	(49)	(49)
INFLAMMATION, SUPPURATIVE		1 (2%)	
INFLAMMATION, CHRONIC SUPPURATIV		1 (2%)	
*MUSCLE OF LEG	(50)	(49)	(49)
PARASITISM	1 (2%)		
BODY CAVITIES			
*ABDOMINAL WALL	(50)	(49)	(49)
INFLAMMATION, PYOGRANULOMATOUS		1 (2%)	
*PERITONEUM	(50)	(49)	(49)
INFLAMMATION, NOS			1 (2%)
INFLAMMATION, SUPPURATIVE		1 (2%)	
*MESENTERY	(50)	(49)	(49)
NECROSIS, FAT	1 (2%)	2 (4%)	
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(49)	(49)
INFLAMMATION, SUPPURATIVE		1 (2%)	
PLASMA-CELL INFILTRATE	1 (2%)		
SPECIAL MORPHOLOGY SUMMARY			
AUTOLYSIS/NO NECROPSY		1	1

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

APPENDIX E

FEED CONSUMPTION BY RATS AND MICE RECEIVING EUGENOL

TABLE E1. FEED CONSUMPTION BY MALE RATS RECEIVING EUGENOL

Week	Control	3,000 ppm		6,000 ppm	
	Grams Feed/ Day *(a)*	Grams Feed/ Day *(a)*	Low/ Control *(b)*	Grams Feed/ Day *(a)*	High/ Control *(b)*
8	19.0	19.0	1.0	18.0	1.0
13	16.0	18.0	1.1	17.0	1.1
17	20.0	18.0	0.9	19.0	1.0
21	16.0	17.0	1.1	17.0	1.1
25	17.0	18.0	1.1	16.0	0.9
28	21.9	20.6	0.9	23.1	1.1
34	14.6	13.7	0.9	15.4	1.1
38	21.9	19.4	0.9	21.9	1.0
42	13.4	12.6	0.9	12.6	0.9
46	15.0	16.0	1.1	15.0	1.0
51	18.0	18.0	1.0	17.0	0.9
55	23.0	17.0	0.7	17.0	0.7
59	17.0	17.0	1.0	17.0	1.0
64	17.0	17.0	1.0	16.0	0.9
68	17.0	17.0	1.0	16.0	0.9
72	17.0	17.0	1.0	16.0	0.9
77	17.0	16.0	1.0	16.0	0.9
81	17.0	16.0	1.0	16.0	0.9
86	17.0	16.0	1.0	16.0	0.9
90	16.0	16.0	1.0	15.0	0.9
94	16.0	16.0	1.0	15.0	0.9
98	15.0	18.0	1.2	16.0	1.1
102	17.7	17.8	1.0	17.8	1.0
104	14.9	14.9	1.0	14.9	1.0
MEAN	17.3	16.9	1.0	16.7	1.0
SD *(c)*	2.4	1.7	0.1	2.2	0.1
CV *(d)*	13.9	10.1	10.0	13.2	10.0

(a) Grams of feed consumed per animal per day.
(b) Ratio of feed per day for the dosed group to that for the controls.
(c) Standard deviation.
(d) (Standard Deviation/Mean) x 100.

TABLE E2. FEED CONSUMPTION BY FEMALE RATS RECEIVING EUGENOL

Week	Control	6,000 ppm		12,500 ppm	
	Grams Feed/ Day *(a)*	Grams Feed/ Day *(a)*	Low/ Control *(b)*	Grams Feed/ Day *(a)*	High/ Control *(b)*
8	15.0	13.0	0.9	13.0	0.9
13	11.0	13.0	1.2	11.0	1.1
17	14.0	11.0	0.8	10.0	0.7
21	12.0	9.0	0.8	11.0	1.0
25	12.0	10.0	0.8	10.0	0.9
28	14.2	16.8	1.2	11.6	0.9
34	9.4	11.1	1.2	7.7	0.9
38	13.4	12.1	0.9	12.1	1.0
42	8.6	7.9	0.9	8.6	1.1
46	11.0	9.0	0.8	8.0	0.8
51	12.0	11.0	1.0	10.0	0.9
55	12.0	10.0	0.9	10.0	0.8
59	13.0	11.0	0.9	11.0	0.8
64	12.0	12.0	1.1	11.0	0.9
68	12.0	12.0	1.1	11.0	0.9
72	12.0	12.0	1.1	11.0	0.9
77	12.0	11.0	1.0	12.0	1.0
81	12.0	11.0	1.0	12.0	1.0
86	12.0	11.0	1.0	12.0	1.0
90	13.0	12.0	0.9	12.0	0.9
94	13.0	12.0	1.0	12.0	0.9
98	12.0	13.0	1.1	13.0	1.1
102	14.4	13.3	1.0	15.5	1.2
104	12.1	11.1	0.9	13.0	1.1
MEAN	12.3	11.5	0.9	11.2	0.9
SD *(c)*	1.4	1.8	0.1	1.7	0.1
CV *(d)*	11.4	15.7	11.1	15.2	11.1

(a) Grams of feed consumed per animal per day.
(b) Ratio of feed per day for the dosed group to that for the controls.
(c) Standard deviation.
(d) (Standard Deviation/Mean) x 100.

TABLE E3. FEED CONSUMPTION BY MALE MICE RECEIVING EUGENOL

Week	Control	3,000 ppm		6,000 ppm	
	Grams Feed/ Day *(a)*	Grams Feed/ Day *(a)*	Low/ Control *(b)*	Grams Feed/ Day *(a)*	High/ Control *(b)*
7	10.0	10.0	1.0	10.0	1.0
11	8.0	8.0	1.0	7.0	0.9
15	8.0	7.0	0.9	7.0	0.9
20	7.0	8.0	1.1	8.0	1.1
24	8.0	8.0	1.0	9.0	1.1
28	7.7	7.7	1.0	8.7	1.1
32	9.3	8.3	0.9	8.3	0.9
36	9.0	8.0	0.9	8.0	0.9
41	9.0	8.0	0.9	8.0	0.9
46	9.7	7.7	0.8	8.7	0.9
49	8.4	8.4	1.0	8.4	1.0
53	7.7	7.7	1.0	6.8	0.9
58	9.0	8.0	0.9	9.0	1.0
62	9.0	9.0	1.0	9.0	1.0
66	9.0	9.0	1.0	9.0	1.0
71	9.0	9.0	1.0	8.0	0.9
75	9.0	9.0	1.0	9.0	1.0
79	6.0	6.0	1.0	5.0	0.8
84	6.0	6.0	1.0	5.0	0.8
88	6.0	6.0	1.0	5.0	0.8
93	6.0	6.0	1.0	5.0	0.8
97	6.0	6.0	1.0	5.0	0.8
101	6.0	6.0	1.0	5.0	0.8
104	6.0	6.0	1.0	6.0	1.0
MEAN	7.9	7.6	1.0	7.4	1.0
SD *(c)*	1.4	1.2	0.1	1.7	0.1
CV *(d)*	17.7	15.8	10.0	23.0	10.0

(a) Grams of feed consumed per animal per day.
(b) Ratio of feed per day for the dosed group to that for the controls.
(c) Standard deviation.
(d) (Standard Deviation/Mean) x 100.

TABLE E4. FEED CONSUMPTION BY FEMALE MICE RECEIVING EUGENOL

Week	Control	3,000 ppm		6,000 ppm	
	Grams Feed/ Day *(a)*	Grams Feed/ Day *(a)*	Low/ Control *(b)*	Grams Feed/ Day *(a)*	High/ Control *(b)*
7	10.0	10.0	1.0	10.0	1.0
11	10.0	8.0	0.9	9.0	0.9
15	9.0	8.0	1.1	7.0	0.8
20	10.0	8.0	1.0	8.0	0.8
24	9.0	9.0	1.0	9.0	1.0
28	7.7	7.7	1.0	7.7	1.0
32	9.4	8.3	1.0	8.3	0.9
36	8.0	8.0	1.0	8.0	1.0
41	8.0	8.0	1.0	8.0	1.0
46	8.7	9.7	1.1	8.7	1.0
49	9.4	7.3	0.9	8.4	0.9
53	9.6	8.7	1.1	7.7	0.8
58	9.0	8.0	1.0	8.0	0.9
62	9.0	8.0	1.0	8.0	0.9
66	8.0	9.0	1.1	8.0	1.0
71	8.0	8.0	1.1	7.0	0.9
75	8.0	9.0	1.1	8.0	1.0
79	7.0	6.0	1.0	6.0	0.9
84	6.0	6.0	1.2	5.0	0.8
88	6.0	6.0	1.2	5.0	0.8
93	6.0	6.0	1.2	5.0	0.8
97	5.0	5.0	1.3	4.0	0.8
101	5.0	5.0	1.3	4.0	0.8
104	6.0	5.0	1.0	5.0	0.8
MEAN	8.0	7.6	1.0	7.2	0.9
SD *(c)*	1.6	1.5	0.1	1.7	0.1
CV *(d)*	20.0	19.7	10.0	23.6	11.1

(a) Grams of feed consumed per animal per day.
(b) Ratio of feed per day for the dosed group that for the controls.
(c) Standard deviation.
(d) (Standard Deviation/Mean) x 100.

APPENDIX F

HISTORICAL INCIDENCES OF LIVER NEOPLASMS IN UNTREATED CONTROL B6C3F$_1$ MICE

TABLE F1. HISTORICAL INCIDENCE OF LIVER NEOPLASMS IN UNTREATED MALE B6C3F$_1$ MICE

Chemical	Adenoma	Carcinoma	Adenoma or Carcinoma
RATES AT SOUTHERN RESEARCH INSTITUTE			
Eugenol	4/50 (8%)	10/50 (20%)	14/50 (28%)
Reserpine	7/50 (14%)	6/50 (12%)	12/50 (24%)
Cytembena	4/47 (9%)	13/47 (28%)	17/47 (36%)
Mannitol	3/50 (6%)	11/50 (22%)	14/50 (28%)
Ziram	6/49 (12%)	13/49 (27%)	19/49 (39%)
Propyl Gallate	3/50 (6%)	14/50 (28%)	17/50 (34%)
Zearalenone	4/50 (8%)	15/50 (30%)	19/50 (38%)
HC Blue 1	4/50 (8%)	11/50 (22%)	15/50 (30%)
Stannous Chloride	7/50 (14%)	10/50 (20%)	16/50 (32%)
Total	42/446 (9%)	103/446 (23%)	143/446 (32%)
All NTP Laboratories			
Total	242/2386 (10%)	501/2386 (21%)	730/2386 (31%)
Overall Historical Range			
High	11/50	18/50	29/50
Low	0/49	3/52	5/52

TABLE F2. HISTORICAL INCIDENCE OF LIVER NEOPLASMS IN UNTREATED FEMALE B6C3F$_1$ MICE

Chemical	Adenoma	Carcinoma	Adenoma or Carcinoma
RATES AT SOUTHERN RESEARCH INSTITUTE			
Eugenol	0/50 (0%)	2/50 (4%)	2/50 (4%)
Reserpine	2/50 (4%)	0/50 (0%)	2/50 (4%)
Cytembena	0/48 (0%)	3/48 (6%)	3/48 (6%)
Mannitol	0/48 (0%)	3/48 (6%)	3/48 (6%)
Ziram	7/50 (14%)	2/50 (4%)	9/50 (18%)
Propyl Gallate	0/50 (0%)	3/50 (6%)	3/50 (6%)
Zearalenone	0/50 (0%)	3/50 (6%)	3/50 (6%)
HC Blue 1	2/50 (4%)	1/50 (2%)	3/50 (6%)
Stannous Chloride	3/49 (6%)	0/49 (0%)	3/49 (6%)
Total	14/445 (3%)	16/445 (4%)	30/445 (7%)
All NTP Laboratories			
Total	102/2519 (4%)	106/2519 (4%)	205/2519 (8%)
Overall Historical Range			
High	9/49	7/48	10/49
Low	0/49	0/50	0/50

APPENDIX G

ANALYSIS OF PRIMARY TUMORS IN F344 RATS AND B6C3F$_1$ MICE

TABLE G1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS

	Control	3,000 ppm	6,000 ppm
Subcutaneous Tissue: Fibroma			
Tumor Rates			
Overall *(a)*	3/40 (8%)	1/50 (2%)	3/50 (6%)
Adjusted *(b)*	10.2%	3.8%	7.6%
Terminal *(c)*	1/25 (4%)	1/26 (4%)	2/37 (5%)
Statistical Tests *(d)*			
Life Table Test	P=0.440N	P=0.265N	P=0.499N
Incidental Tumor Test	P=0.509N	P=0.176N	P=0.611N
Cochran-Armitage Trend Test	P=0.500N		
Fisher Exact Test		P=0.230N	P=0.550N
Weeks to First Observed Tumor	96	104	92
Integumentary System: Fibroma			
Tumor Rates			
Overall *(a)*	3/40 (8%)	2/50 (4%)	3/50 (6%)
Adjusted *(b)*	10.2%	6.2%	7.6%
Terminal *(c)*	1/25 (4%)	1/26 (4%)	2/37 (5%)
Statistical Tests *(d)*			
Life Table Test	P=0.429N	P=0.434N	P=0.499N
Incidental Tumor Test	P=0.522N	P=0.293N	P=0.611N
Cochran-Armitage Trend Test	P=0.487N		
Fisher Exact Test		P=0.395N	P=0.550N
Weeks to First Observed Tumor	96	93	92
Lung: Alveolar/Bronchiolar Carcinoma			
Tumor Rates			
Overall *(a)*	0/40 (0%)	3/49 (6%)	0/50 (0%)
Adjusted *(b)*	0.0%	11.5%	0.0%
Terminal *(c)*	0/25 (0%)	3/26 (12%)	0/37 (0%)
Statistical Tests *(d)*			
Life Table Test	P=0.526N	P=0.126	*(e)*
Incidental Tumor Test	P=0.526N	P=0.126	*(e)*
Cochran-Armitage Trend Test	P=0.582N		
Fisher Exact Test		P=0.162	*(e)*
Weeks to First Observed Tumor		104	
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Tumor Rates			
Overall *(a)*	0/40 (0%)	5/49 (10%)	2/50 (4%)
Adjusted *(b)*	0.0%	17.4%	5.4%
Terminal *(c)*	0/25 (0%)	4/26 (15%)	2/37 (5%)
Statistical Tests *(d)*			
Life Table Test	P=0.390	P=0.041	P=0.328
Incidental Tumor Test	P=0.358	P=0.049	P=0.328
Cochran-Armitage Trend Test	P=0.315		
Fisher Exact Test		P=0.046	P=0.306
Weeks to First Observed Tumor		93	104
Hematopoietic System: All Lymphomas			
Tumor Rates			
Overall *(a)*	0/40 (0%)	3/50 (6%)	1/50 (2%)
Adjusted *(b)*	0.0%	8.7%	2.4%
Terminal *(c)*	0/25 (0%)	0/26 (0%)	0/37 (0%)
Statistical Tests *(d)*			
Life Table Test	P=0.471	P=0.151	P=0.549
Incidental Tumor Test	P=0.261	P=0.277	P=0.433
Cochran-Armitage Trend Test	P=0.446		
Fisher Exact Test		P=0.167	P=0.555
Weeks to First Observed Tumor		95	96

TABLE G1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS (Continued)

	Control	3,000 ppm	6,000 ppm
Hematopoietic System: Undifferentiated Leukemia			
Tumor Rates			
Overall *(a)*	13/40 (33%)	18/50 (36%)	11/50 (22%)
Adjusted *(b)*	41.8%	46.0%	25.7%
Terminal *(c)*	8/25 (32%)	7/26 (27%)	6/37 (16%)
Statistical Tests *(d)*			
Life Table Test	P=0.100N	P=0.344	P=0.127N
Incidental Tumor Test	P=0.222N	P=0.562	P=0.243N
Cochran-Armitage Trend Test	P=0.149N		
Fisher Exact Test		P=0.452	P=0.190N
Weeks to First Observed Tumor	82	59	70
Hematopoietic System: All Lymphomas/All Leukemias			
Tumor Rates			
Overall *(a)*	13/40 (33%)	21/50 (42%)	12/50 (24%)
Adjusted *(b)*	41.8%	50.8%	27.5%
Terminal *(c)*	8/25 (32%)	7/26 (27%)	6/37 (16%)
Statistical Tests *(d)*			
Life Table Test	P=0.135N	P=0.186	P=0.178N
Incidental Tumor Test	P=0.324N	P=0.393	P=0.339N
Cochran-Armitage Trend Test	P=0.197N		
Fisher Exact Test		P=0.241	P=0.255N
Weeks to First Observed Tumor	82	59	70
Pituitary: Adenoma			
Tumor Rates			
Overall *(a)*	2/39 (5%)	4/48 (8%)	4/49 (8%)
Adjusted *(b)*	8.3%	12.7%	10.8%
Terminal *(c)*	2/24 (8%)	2/25 (8%)	4/37 (11%)
Statistical Tests *(d)*			
Life Table Test	P=0.482	P=0.381	P=0.548
Incidental Tumor Test	P=0.413	P=0.435	P=0.548
Cochran-Armitage Trend Test	P=0.377		
Fisher Exact Test		P=0.442	P=0.453
Weeks to First Observed Tumor	105	76	104
Pituitary: Adenoma or Carcinoma			
Tumor Rates			
Overall *(a)*	2/39 (5%)	5/48 (10%)	4/49 (8%)
Adjusted *(b)*	8.3%	14.6%	10.8%
Terminal *(c)*	2/24 (8%)	2/25 (8%)	4/37 (11%)
Statistical Tests *(d)*			
Life Table Test	P=0.497	P=0.269	P=0.548
Incidental Tumor Test	P=0.418	P=0.307	P=0.548
Cochran-Armitage Trend Test	P=0.393		
Fisher Exact Test		P=0.312	P=0.453
Weeks to First Observed Tumor	105	76	104
Adrenal: Pheochromocytoma			
Tumor Rates			
Overall *(a)*	9/40 (23%)	7/50 (14%)	8/50 (16%)
Adjusted *(b)*	32.4%	25.4%	20.1%
Terminal *(c)*	7/25 (28%)	6/26 (23%)	6/37 (16%)
Statistical Tests *(d)*			
Life Table Test	P=0.166N	P=0.343N	P=0.203N
Incidental Tumor Test	P=0.219N	P=0.268N	P=0.300N
Cochran-Armitage Trend Test	P=0.267N		
Fisher Exact Test		P=0.220N	P=0.303N
Weeks to First Observed Tumor	75	101	90

TABLE G1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS (Continued)

	Control	3,000 ppm	6,000 ppm
Thyroid: C-Cell Adenoma			
Tumor Rates			
Overall *(a)*	4/40 (10%)	5/50 (10%)	0/50 (0%)
Adjusted *(b)*	14.5%	15.5%	0.0%
Terminal *(c)*	2/25 (8%)	3/26 (12%)	0/37 (0%)
Statistical Tests *(d)*			
Life Table Test	P=0.030N	P=0.563	P=0.029N
Incidental Tumor Test	P=0.038N	P=0.601N	P=0.055N
Cochran-Armitage Trend Test	P=0.037N		
Fisher Exact Test		P=0.634N	P=0.036N
Weeks to First Observed Tumor	100	80	
Thyroid: C-Cell Carcinoma			
Tumor Rates			
Overall *(a)*	3/40 (8%)	3/50 (6%)	2/50 (4%)
Adjusted *(b)*	10.9%	11.5%	5.1%
Terminal *(c)*	2/25 (8%)	3/26 (12%)	1/37 (3%)
Statistical Tests *(d)*			
Life Table Test	P=0.254N	P=0.633N	P=0.346N
Incidental Tumor Test	P=0.295N	P=0.591N	P=0.454N
Cochran-Armitage Trend Test	P=0.313N		
Fisher Exact Test		P=0.550N	P=0.395N
Weeks to First Observed Tumor	96	104	100
Thyroid: C-Cell Adenoma or Carcinoma			
Tumor Rates			
Overall *(a)*	7/40 (18%)	8/50 (16%)	2/50 (4%)
Adjusted *(b)*	24.3%	26.5%	5.1%
Terminal *(c)*	4/25 (16%)	6/26 (23%)	1/37 (3%)
Statistical Tests *(d)*			
Life Table Test	P=0.021N	P=0.572	P=0.027N
Incidental Tumor Test	P=0.030N	P=0.530N	P=0.056N
Cochran-Armitage Trend Test	P=0.032N		
Fisher Exact Test		P=0.535N	P=0.039N
Weeks to First Observed Tumor	96	80	100
Pancreatic Islets: Islet Cell Adenoma			
Tumor Rates			
Overall *(a)*	0/40 (0%)	1/50 (2%)	3/49 (6%)
Adjusted *(b)*	0.0%	3.8%	7.8%
Terminal *(c)*	0/25 (0%)	1/26 (4%)	2/37 (5%)
Statistical Tests *(d)*			
Life Table Test	P=0.112	P=0.508	P=0.195
Incidental Tumor Test	P=0.083	P=0.508	P=0.147
Cochran-Armitage Trend Test	P=0.077		
Fisher Exact Test		P=0.555	P=0.162
Weeks to First Observed Tumor		104	100
Pancreatic Islets: Islet Cell Carcinoma			
Tumor Rates			
Overall *(a)*	1/40 (3%)	2/50 (4%)	3/49 (6%)
Adjusted *(b)*	3.6%	7.4%	8.1%
Terminal *(c)*	0/25 (0%)	1/26 (4%)	3/37 (8%)
Statistical Tests *(d)*			
Life Table Test	P=0.355	P=0.523	P=0.445
Incidental Tumor Test	P=0.278	P=0.677	P=0.381
Cochran-Armitage Trend Test	P=0.280		
Fisher Exact Test		P=0.584	P=0.389
Weeks to First Observed Tumor	101	103	104

TABLE G1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS (Continued)

	Control	3,000 ppm	6,000 ppm
Pancreatic Islets: Islet Cell Adenoma/Islet Cell Carcinoma			
Tumor Rates			
Overall *(a)*	1/40 (3%)	3/50 (6%)	6/49 (12%)
Adjusted *(b)*	3.6%	11.1%	15.7%
Terminal *(c)*	0/25 (0%)	2/26 (8%)	5/37 (14%)
Statistical Tests *(d)*			
Life Table Test	P=0.102	P=0.329	P=0.142
Incidental Tumor Test	P=0.057	P=0.451	P=0.089
Cochran-Armitage Trend Test	P=0.056		
Fisher Exact Test		P=0.397	P=0.094
Weeks to First Observed Tumor	101	103	100
Testis: Interstitial Cell Tumor			
Tumor Rates			
Overall *(a)*	38/40 (95%)	47/50 (94%)	47/50 (94%)
Adjusted *(b)*	100.0%	100.0%	97.9%
Terminal *(c)*	25/25 (100%)	26/26 (100%)	36/37 (97%)
Statistical Tests *(d)*			
Life Table Test	P=0.106N	P=0.254	P=0.140N
Incidental Tumor Test P=0.162	P=0.210N	P=0.490N	P=0.364N
Cochran-Armitage Trend Test	P=0.513N		
Fisher Exact Test		P=0.606N	P=0.606N
Weeks to First Observed Tumor	75	78	87

(a) Number of tumor bearing animals/number of animals examined at the site.

(b) Kaplan-Meier estimated lifetime tumor incidence after adjusting for intercurrent mortality.

(c) Observed tumor incidence at terminal kill.

(d) Beneath the control incidence are the P-values associated with the trend test. Beneath the dosed group incidence are the P-values corresponding to pairwise comparisons between that dosed group and the controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as non-fatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend is indicated by (N).

(e) Statistical comparisons were not done since no tumors were observed in control or dosed groups.

TABLE G2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS

	Control	6,000 ppm	12,500 ppm
Hematopoietic System: All Leukemias			
Tumor Rates			
Overall *(a)*	7/40 (18%)	10/50 (20%)	9/50 (18%)
Adjusted *(b)*	20.3%	21.9%	19.1%
Terminal *(c)*	3/30 (10%)	3/36 (8%)	7/45 (16%)
Statistical Tests *(d)*			
Life Table Test	P=0.445N	P=0.478	P=0.509N
Incidental Tumor Test	P=0.309	P=0.566	P=0.400
Cochran-Armitage Trend Test	P=0.544		
Fisher Exact Test		P=0.490	P=0.587
Weeks to First Observed Tumor	90	85	96
Pituitary: Adenoma			
Tumor Rates			
Overall *(a)*	7/39 (18%)	8/49 (16%)	9/49 (18%)
Adjusted *(b)*	20.0%	19.9%	19.3%
Terminal *(c)*	3/30 (10%)	5/36 (14%)	7/44 (16%)
Statistical Tests *(d)*			
Life Table Test	P=0.475N	P=0.557N	P=0.526N
Incidental Tumor Test	P=0.423	P=0.482N	P=0.449
Cochran-Armitage Trend Test	P=0.528		
Fisher Exact Test		P=0.531N	P=0.592
Weeks to First Observed Tumor	89	96	80
Pituitary: Adenoma/Carcinoma			
Tumor Rates			
Overall *(a)*	9/39 (23%)	9/49 (18%)	9/49 (18%)
Adjusted *(b)*	24.2%	22.1%	19.3%
Terminal *(c)*	3/30 (10%)	5/36 (14%)	7/44 (16%)
Statistical Tests *(d)*			
Life Table Test	P=0.267N	P=0.424N	P=0.309N
Incidental Tumor Test	P=0.502N	P=0.342N	P=0.590N
Cochran-Armitage Trend Test	P=0.351N		
Fisher Exact Test		P=0.389N	P=0.389N
Weeks to First Observed Tumor	83	96	80
Adrenal: Cortical Adenoma			
Tumor Rates			
Overall *(a)*	1/40 (3%)	3/50 (6%)	1/50 (2%)
Adjusted *(b)*	3.3%	6.9%	2.2%
Terminal *(c)*	1/30 (3%)	1/36 (3%)	1/45 (2%)
Statistical Tests *(d)*			
Life Table Test	P=0.470N	P=0.401	P=0.669N
Incidental Tumor Test	P=0.588N	P=0.468	P=0.669N
Cochran-Armitage Trend Test	P=0.526N		
Fisher Exact Test		P=0.397	P=0.694N
Weeks to First Observed Tumor	104	96	104
Adrenal: Pheochromocytoma			
Tumor Rates			
Overall *(a)*	1/40 (3%)	5/50 (10%)	1/50 (2%)
Adjusted *(b)*	3.3%	12.4%	2.0%
Terminal *(c)*	1/30 (3%)	3/36 (8%)	0/45 (0%)
Statistical Tests *(d)*			
Life Table Test	P=0.425N	P=0.162	P=0.686N
Incidental Tumor Test	P=0.566N	P=0.200	P=0.765
Cochran-Armitage Trend Test	P=0.485N		
Fisher Exact Test		P=0.162	P=0.694N
Weeks to First Observed Tumor	105	98	80

TABLE G2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS (Continued)

	Control	6,000 ppm	12,500 ppm
Thyroid: C-Cell Adenoma			
Tumor Rates			
Overall *(a)*	3/40 (8%)	11/49 (22%)	2/50 (4%)
Adjusted *(b)*	10.0%	28.1%	4.4%
Terminal *(c)*	3/30 (10%)	8/35 (23%)	2/45 (4%)
Statistical Tests *(d)*			
Life Table Test	P=0.187N	P=0.048	P=0.319N
Incidental Tumor Test	P=0.253N	P=0.040	P=0.319N
Cochran-Armitage Trend Test	P=0.271N		
Fisher Exact Test		P=0.049	P=0.395N
Weeks to First Observed Tumor	105	85	104
Thyroid: C-Cell Carcinoma			
Tumor Rates			
Overall *(a)*	4/40 (10%)	1/49 (2%)	4/50 (8%)
Adjusted *(b)*	12.8%	2.9%	8.9%
Terminal *(c)*	3/30 (10%)	1/35 (3%)	4/45 (9%)
Statistical Tests *(d)*			
Life Table Test	P=0.399N	P=0.138N	P=0.416N
Incidental Tumor Test	P=0.441N	P=0.111N	P=0.490N
Cochran-Armitage Trend Test	P=0.493N		
Fisher Exact Test		P=0.124N	P=0.512N
Weeks to First Observed Tumor	103	105	104
Thyroid: C-Cell Adenoma/C-Cell Carcinoma			
Tumor Rates			
Overall *(a)*	7/40 (18%)	12/49 (24%)	6/50 (12%)
Adjusted *(b)*	22.5%	30.7%	13.3%
Terminal *(c)*	6/30 (20%)	9/35 (26%)	6/45 (13%)
Statistical Tests *(d)*			
Life Table Test	P=0.149N	P=0.269	P=0.217N
Incidental Tumor Test	P=0.215N	P=0.271	P=0.264N
Cochran-Armitage Trend Test	P=0.254N		
Fisher Exact Test		P=0.296	P=0.330N
Weeks to First Observed Tumor	103	85	104
Mammary Gland: Fibroadenoma			
Tumor Rates			
Overall *(a)*	14/40 (35%)	7/50 (14%)	6/50 (12%)
Adjusted *(b)*	40.9%	18.1%	13.0%
Terminal *(c)*	10/30 (33%)	5/36 (14%)	5/45 (11%)
Statistical Tests *(d)*			
Life Table Test	P=0.003N	P=0.030N	P=0.004N
Incidental Tumor Test	P=0.007N	P=0.016N	P=0.014N
Cochran-Armitage Trend Test	P=0.006N		
Fisher Exact Test		P=0.019N	P=0.009N
Weeks to First Observed Tumor	89	98	95
Uterus: Endometrial Stromal Polyp or Sarcoma			
Tumor Rates			
Overall *(a)*	6/40 (15%)	6/50 (12%)	16/50 (32%)
Adjusted *(b)*	18.3%	15.2%	35.6%
Terminal *(c)*	4/30 (13%)	4/36 (11%)	16/45 (36%)
Statistical Tests *(d)*			
Life Table Test	P=0.062	P=0.479N	P=0.121
Incidental Tumor Test	P=0.031	P=0.369N	P=0.077
Cochran-Armitage Trend Test	P=0.022		
Fisher Exact Test		P=0.456N	P=0.051
Weeks to First Observed Tumor	94	98	104

(a) Number of tumor bearing animals/number of animals examined at the site.
(b) Kaplan-Meier estimated lifetime tumor incidence after adjusting for intercurrent mortality.
(c) Observed tumor incidence at terminal kill.
(d) Beneath the control incidence are the P-values associated with the trend test. Beneath the dosed group incidence are the P-values corresponding to pairwise comparisons between that dosed group and the controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as non-fatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend is indicated by (N).

TABLE G3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE

	Control	3,000 ppm	6,000 ppm
Integumentary System: Fibroma or Fibrosarcoma			
Tumor Rates			
Overall *(a)*	4/50 (8%)	1/50 (2%)	2/50 (4%)
Adjusted *(b)*	9.5%	2.8%	5.0%
Terminal *(c)*	3/41 (7%)	1/36 (3%)	1/36 (3%)
Statistical Tests *(d)*			
Life Table Test	P=0.288N	P=0.226N	P=0.397N
Incidental Tumor Test	P=0.251N	P=0.214N	P=0.340N
Cochran-Armitage Trend Test	P=0.238N		
Fisher Exact Test		P=0.181N	P=0.339N
Weeks to First Observed Tumor	103	105	86
Lung: Alveolar/Bronchiolar Carcinoma			
Tumor Rates			
Overall *(a)*	5/49 (10%)	2/49 (4%)	3/50 (6%)
Adjusted *(b)*	12.1%	5.6%	8.3%
Terminal *(c)*	4/40 (10%)	2/36 (6%)	3/36 (8%)
Statistical Tests *(d)*			
Life Table Test	P=0.329N	P=0.267N	P=0.421N
Incidental Tumor Test	P=0.293N	P=0.281N	P=0.373N
Cochran-Armitage Trend Test	P=0.265N		
Fisher Exact Test		P=0.218N	P=0.346N
Weeks to First Observed Tumor	103	105	104
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Tumor Rates			
Overall *(a)*	13/49 (27%)	8/49 (16%)	9/50 (18%)
Adjusted *(b)*	31.6%	21.3%	25.0%
Terminal *(c)*	12/40 (30%)	7/36 (19%)	9/36 (25%)
Statistical Tests *(d)*			
Life Table Test	P=0.270N	P=0.239N	P=0.328N
Incidental Tumor Test	P=0.239N	P=0.218N	P=0.298N
Cochran-Armitage Trend Test	P=0.177N		
Fisher Exact Test		P=0.163N	P=0.218N
Weeks to First Observed Tumor	103	68	104
Hematopoietic System: Malignant Lymphoma, Histiocytic Type			
Tumor Rates			
Overall *(a)*	3/50 (6%)	2/50 (4%)	1/50 (2%)
Adjusted *(b)*	7.1%	5.6%	2.4%
Terminal *(c)*	2/41 (5%)	2/36 (6%)	0/36 (0%)
Statistical Tests *(d)*			
Life Table Test	P=0.268N	P=0.563N	P=0.354N
Incidental Tumor Test	P=0.228N	P=0.547N	P=0.285N
Cochran-Armitage Trend Test	P=0.222N		
Fisher Exact Test		P=0.500N	P=0.309N
Weeks to First Observed Tumor	103	105	88
Hematopoietic System: Malignant Lymphoma, Mixed Type			
Tumor Rates			
Overall *(a)*	1/50 (2%)	2/50 (4%)	5/50 (10%)
Adjusted *(b)*	2.2%	5.6%	13.5%
Terminal *(c)*	0/41 (0%)	2/36 (6%)	4/36 (11%)
Statistical Tests *(d)*			
Life Table Test	P=0.047	P=0.457	P=0.082
Incidental Tumor Test	P=0.060	P=0.424	P=0.105
Cochran-Armitage Trend Test	P=0.060		
Fisher Exact Test		P=0.500	P=0.102
Weeks to First Observed Tumor	85	105	97

TABLE G3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE (Continued)

	Control	3,000 ppm	6,000 ppm
Hematopoietic System: All Lymphomas			
Tumor Rates			
Overall *(a)*	5/50 (10%)	5/50 (10%)	8/50 (16%)
Adjusted *(b)*	11.4%	13.5%	19.8%
Terminal *(c)*	3/41 (7%)	4/36 (11%)	4/36 (11%)
Statistical Tests *(d)*			
Life Table Test	P=0.169	P=0.542	P=0.215
Incidental Tumor Test	P=0.257	P=0.546	P=0.324
Cochran-Armitage Trend Test	P=0.221		
Fisher Exact Test		P=0.630N	P=0.277
Weeks to First Observed Tumor	85	102	88
Liver: Hepatocellular Adenoma			
Tumor Rates			
Overall *(a)*	4/50 (8%)	13/50 (26%)	10/49 (20%)
Adjusted *(b)*	9.8%	36.1%	24.7%
Terminal *(c)*	4/41 (10%)	13/36 (36%)	7/36 (19%)
Statistical Tests *(d)*			
Life Table Test	P=0.044	P=0.006	P=0.051
Incidental Tumor Test	P=0.049	P=0.006	P=0.070
Cochran-Armitage Trend Test	P=0.069		
Fisher Exact Test		P=0.016	P=0.068
Weeks to First Observed Tumor	105	105	45
Liver: Hepatocellular Carcinoma			
Tumor Rates			
Overall *(a)*	10/50 (20%)	20/50 (40%)	9/49 (18%)
Adjusted *(b)*	23.2%	46.3%	20.1%
Terminal *(c)*	8/41(20%)	13/36 (36%)	2/36 (6%)
Statistical Tests *(d)*			
Life Table Test	P=0.502	P=0.014	P=0.591
Incidental Tumor Test	P=0.366N	P=0.015	P=0.371N
Cochran-Armitage Trend Test	P=0.478N		
Fisher Exact Test		P=0.024	P=0.520N
Weeks to First Observed Tumor	93	65	66
Liver: Hepatocellular Adenoma or Carcinoma			
Tumor Rates			
Overall *(a)*	14/50 (28%)	28/50 (56%)	18/49 (37%)
Adjusted *(b)*	32.5%	65.0%	39.3%
Terminal *(c)*	12/41 (29%)	21/36 (58%)	9/36 (25%)
Statistical Tests *(d)*			
Life Table Test	P=0.145	P=0.002	P=0.176
Incidental Tumor Test	P=0.248	P=0.001	P=0.318
Cochran-Armitage Trend Test	P=0.212		
Fisher Exact Test		P=0.004	P=0.238
Weeks to First Observed Tumor	93	65	45
Thyroid: Follicular Cell Adenoma			
Tumor Rates			
Overall *(a)*	0/48 (0%)	0/49 (0%)	3/49 (6%)
Adjusted *(b)*	0.0%	0.0%	8.3%
Terminal *(c)*	0/41 (0%)	0/36 (0%)	3/36 (8%)
Statistical Tests *(d)*			
Life Table Test	P=0.031	*(e)*	P=0.099
Incidental Tumor Test	P=0.031	*(e)*	P=0.099
Cochran-Armitage Trend Test	P=0.038		
Fisher Exact Test		*(e)*	P=0.125
Weeks to First Observed Tumor			104

(a) Number of tumor bearing animals/number of animals examined at the site.
(b) Kaplan-Meier estimated lifetime tumor incidence after adjusting for intercurrent mortality.
(c) Observed tumor incidence at terminal kill.
(d) Beneath the control incidence are the P-values associated with the trend test. Beneath the dosed group incidence are the P-values corresponding to pairwise comparisons between that dosed group and the controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as non-fatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend is indicated by (N).
(e) Not significant; no tumors were observed in dosed or control groups.

TABLE G4. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE

	Control	3,000 ppm	6,000 ppm
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Tumor Rates			
Overall *(a)*	4/50 (8%)	6/49 (12%)	5/48 (10%)
Adjusted *(b)*	9.3%	14.1%	11.4%
Terminal *(c)*	4/43 (9%)	5/41 (12%)	5/44 (11%)
Statistical Tests *(d)*			
Life Table Test	P=0.449	P=0.341	P=0.514
Incidental Tumor Test	P=0.425	P=0.426	P=0.514
Cochran-Armitage Trend Test	P=0.407		
Fisher Exact Test		P=0.357	P=0.474
Weeks to First Observed Tumor	105	86	104
Hematopoietic System: Malignant Lymphoma, Lymphocytic Type			
Tumor Rates			
Overall *(a)*	4/50 (8%)	5/49 (10%)	4/49 (8%)
Adjusted *(b)*	9.1%	11.4%	8.9%
Terminal *(c)*	3/43 (7%)	3/41 (7%)	4/45 (9%)
Statistical Tests *(d)*			
Life Table Test	P=0.545N	P=0.467	P=0.617N
Incidental Tumor Test	P=0.498	P=0.611	P=0.606
Cochran-Armitage Trend Test	P=0.558		
Fisher Exact Test		P=0.487	P=0.631
Weeks to First Observed Tumor	103	86	104
Hematopoietic System: Malignant Lymphoma, Histiocytic Type			
Tumor Rates			
Overall *(a)*	3/50 (6%)	1/49 (2%)	0/49 (0%)
Adjusted *(b)*	6.4%	2.4%	0.0%
Terminal *(c)*	1/43 (2%)	1/41 (2%)	0/45 (0%)
Statistical Tests *(d)*			
Life Table Test	P=0.062N	P=0.328N	P=0.121N
Incidental Tumor Test	P=0.083N	P=0.258N	P=0.330N
Cochran-Armitage Trend Test	P=0.063N		
Fisher Exact Test		P=0.316N	P=0.125N
Weeks to First Observed Tumor	84	104	
Hematopoietic System: Malignant Lymphoma, Mixed Type			
Tumor Rates			
Overall *(a)*	5/50 (10%)	4/49 (8%)	2/49 (4%)
Adjusted *(b)*	11.2%	9.3%	4.4%
Terminal *(c)*	4/43 (9%)	3/41 (7%)	2/45 (4%)
Statistical Tests *(d)*			
Life Table Test	P=0.161N	P=0.532N	P=0.203N
Incidental Tumor Test	P=0.202N	P=0.490N	P=0.251N
Cochran-Armitage Trend Test	P=0.176N		
Fisher Exact Test		P=0.513N	P=0.227N
Weeks to First Observed Tumor	96	86	104
Hematopoietic System: All Lymphomas			
Tumor Rates			
Overall *(a)*	12/50 (24%)	10/49 (20%)	7/49 (14%)
Adjusted *(b)*	25.4%	22.5%	15.2%
Terminal *(c)*	8/43 (19%)	7/41 (17%)	6/45 (13%)
Statistical Tests *(d)*			
Life Table Test	P=0.123N	P=0.463N	P=0.144N
Incidental Tumor Test	P=0.225N	P=0.301N	P=0.331N
Cochran-Armitage Trend Test	P=0.138N		
Fisher Exact Test		P=0.426N	P=0.166N
Weeks to First Observed Tumor	84	86	103

TABLE G4. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE (Continued)

	Control	3,000 ppm	6,000 ppm
Liver: Hepatocellular Adenoma			
Tumor Rates			
Overall *(a)*	0/50 (0%)	4/49 (8%)	3/49 (6%)
Adjusted *(b)*	0.0%	9.8%	6.5%
Terminal *(c)*	0/43 (0%)	4/41 (10%)	2/45 (4%)
Statistical Tests *(d)*			
Life Table Test	P=0.133	P=0.057	P=0.131
Incidental Tumor Test	P=0.101	P=0.057	P=0.077
Cochran-Armitage Trend Test	P=0.114		
Fisher Exact Test		P=0.056	P=0.117
Weeks to First Observed Tumor	105	103	
Liver: Hepatocellular Carcinoma			
Tumor Rates			
Overall *(a)*	2/50 (4%)	3/49 (6%)	6/49 (12%)
Adjusted *(b)*	4.7%	6.8%	13.3%
Terminal *(c)*	2/43(5%)	1/41 (2%)	6/45 (13%)
Statistical Tests *(d)*			
Life Table Test	P=0.104	P=0.477	P=0.149
Incidental Tumor Test	P=0.066	P=0.532	P=0.149
Cochran-Armitage Trend Test	P=0.085		
Fisher Exact Test		P=0.490	P=0.128
Weeks to First Observed Tumor	105	86	104
Liver: Hepatocellular Adenoma or Carcinoma			
Tumor Rates			
Overall *(a)*	2/50 (4%)	7/49 (14%)	9/49 (18%)
Adjusted *(b)*	4.7%	16.1%	19.6%
Terminal *(c)*	2/43 (5%)	5/41 (12%)	8/45 (18%)
Statistical Tests *(d)*			
Life Table Test	P=0.031	P=0.074	P=0.034
Incidental Tumor Test	P=0.014	P=0.081	P=0.024
Cochran-Armitage Trend Test	P=0.021		
Fisher Exact Test		P=0.075	P=0.023
Weeks to First Observed Tumor	105	86	103

(a) Number of tumor bearing animals/number of animals examined at the site.
(b) Kaplan-Meier estimated lifetime tumor incidence after adjusting for intercurrent mortality.
(c) Observed tumor incidence at terminal kill.
(d) Beneath the control incidence are the P-values associated with the trend test. Beneath the dosed group incidence are the P-values corresponding to pairwise comparisons between that dosed group and the controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as non-fatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend is indicated by (N).

APPENDIX H

MUTAGENESIS RESULTS FOR EUGENOL AND METHYL EUGENOL IN *SALMONELLA*

TABLE H1. RESULTS OF MUTAGENICITY TESTS OF EUGENOL IN *SALMONELLA*

Strain	Dose (μg/plate)	Revertants/plate *(a)*		
		-S9	+S9 (rat)	+S9 (hamster)
TA100	0.0	99 ± 5.2	113 ± 2.0	115 ± 8.7
	3.3	85 ± 3.2	105 ± 3.7	124 ± 11.3
	10.0	80 ± 5.8	104 ± 4.0	111 ± 11.0
	33.3	85 ± 5.3	108 ± 2.6	111 ± 10.5
	100.0	73 ± 3.6	107 ± 2.6	103 ± 8.5
	333.3	77 ± 2.2	109 ± 3.0	107 ± 10.3
TA1535	0.0	20 ± 1.0	13 ± 3.0	13 ± 0.6
	3.3	18 ± 3.8	9 ± 1.0	17 ± 3.5
	10.0	16 ± 1.8	10 ± 1.0	10 ± 1.2
	33.3	21 ± 1.5	7 ± 0.3	12 ± 2.3
	100.0	22 ± 4.3	11 ± 1.0	13 ± 2.6
	333.3	21 ± 1.5	9 ± 1.9	13 ± 2.9
TA1537	0.0	8 ± 1.0	14 ± 1.9	12 ± 2.7
	3.3	10 ± 0.9	9 ± 0.9	11 ± 2.0
	10.0	7 ± 1.5	13 ± 1.5	11 ± 0.7
	33.3	8 ± 1.8	9 ± 3.2	14 ± 3.3
	100.0	6 ± 0.9	11 ± 1.8	11 ± 2.2
	333.3	4 ± 1.2	9 ± 1.7	14 ± 1.7
TA98	0.0	27 ± 3.1	35 ± 2.3	37 ± 4.7
	3.3	21 ± 2.3	37 ± 2.3	34 ± 3.3
	10.0	20 ± 2.6	33 ± 6.2	44 ± 1.7
	33.3	17 ± 1.2	46 ± 2.2	36 ± 2.1
	100.0	19 ± 4.2	36 ± 1.9	37 ± 2.0
	333.3	13 ± 2.3	36 ± 4.0	41 ± 1.5

(a) The S9 fractions were prepared from the livers of Aroclor 1254®-induced animals (male Sprague-Dawley rats and male Syrian hamsters). Cells and test compound or solvent (DMSO) were incubated for 20 min at 37° C in the presence of either S9 or buffer (Yahagi et al., 1975). After the addition of soft agar, the contents of each tube were poured onto minimal medium, and the plates were incubated at 37° C for 48 hr (Ames et al., 1975). The experiment was performed twice, each time in triplicate; because the results were similar; data from only one experiment are shown.

TABLE H2. RESULTS OF MUTAGENICITY TESTS OF METHYL EUGENOL IN *SALMONELLA*

Strain	Dose (μg/plate)	Revertants/plate *(a)*		
		-S9	+S9 (rat)	+S9 (hamster)
TA100	0.0	90 ± 6.4	98 ± 8.1	103 ± 8.7
	3.3	86 ± 3.5	95 ± 5.3	90 ± 8.0
	10.0	93 ± 4.0	94 ± 2.7	89 ± 6.1
	33.3	93 ± 10.7	92 ± 4.3	90 ± 6.8
	100.0	96 ± 2.7	91 ± 7.6	80 ± 14.4
	333.3	16 ± 13.7	97 ± 2.6	78 ± 1.0
TA1535	0.0	20 ± 3.5	9 ± 0.6	12 ± 2.1
	3.3	20 ± 2.3	6 ± 0.3	8 ± 0.9
	10.0	21 ± 3.3	7 ± 2.6	8 ± 2.3
	33.3	22 ± 2.7	9 ± 1.0	9 ± 2.8
	100.0	26 ± 0.7	7 ± 0.9	10 ± 3.7
	333.3	2 ± 1.5	8 ± 1.9	9 ± 2.3
TA1537	0.0	5 ± 0.3	6 ± 0.9	5 ± 0.3
	3.3	3 ± 0.9	8 ± 2.1	9 ± 1.5
	10.0	3 ± 0.9	4 ± 1.0	6 ± 0.9
	33.3	4 ± 1.2	9 ± 1.5	5 ± 1.2
	100.0	4 ± 0.6	7 ± 1.2	5 ± 1.0
	333.3	3 ± 0.3	5 ± 2.2	4 ± 1.3
TA98	0.0	16 ± 1.7	20 ± 4.1	31 ± 3.7
	3.3	13 ± 2.2	27 ± 0.9	31 ± 4.0
	10.0	14 ± 0.9	23 ± 2.6	28 ± 2.3
	33.3	13 ± 1.8	20 ± 2.3	26 ± 1.2
	100.0	13 ± 0.9	29 ± 5.5	29 ± 6.0
	333.3	3 ± 3.0	19 ± 0.3	21 ± 2.7

(a) The S9 fractions were prepared from the livers of Aroclor 1254®-induced animals (male Sprague-Dawley rats and male Syrian hamsters). Cells and test compound or solvent (DMSO) were incubated for 20 min at 37° C in the presence of either S9 or buffer (Yahagi et al., 1975). After the addition of soft agar, the contents of each tube were poured onto minimal medium, and the plates were incubated at 37° C for 48 hr (Ames et al., 1975). The experiment was performed twice, each time in triplicate; because the results were similar; data from only one experiment are shown.

APPENDIX I

CYTOGENETIC RESULTS FOR EUGENOL IN CHINESE HAMSTER OVARY (CHO) CELLS

TABLE I1. CYTOGENETIC EFFECTS OF EUGENOL IN CHINESE HAMSTER OVARY (CHO) CELLS

Sister-Chromatid Exchanges *(a)*				Chromosome Aberrations *(b)*			
-S9		+S9 *(c)*		-S9		+S9 *(c)*	
Dose (μg/ml)	SCE/Cell	Dose (μg/ml)	SCE/Cell	Dose (μg/ml)	Abs/100 Cells (% cells w/abs)	Dose (μg/ml)	Abs/100 Cells (% cells w/abs)
DMSO (10 μl)	8.8	DMSO (10 μl)	8.4	DMSO (10 μl)	0 (0)	DMSO (10 μl)	0 (0)
75	11.5	273	11.6	198	0 (0)	274	0 (0)
99	11.0	300	11.1	251	3 (3)	299	4 (3)
123	12.9	326	12.2	300	0 (0)	324	55 (28)
Mitomycin C (0.01)	44.2	Cyclophos-phamide (2.0)	39.6	Mitomycin C (0.065)	>32 (32)	Cyclophos-phamide (15)	10 (18)

(a) In the absence of S9, CHO cells were incubated with test compound or solvent for 2 hr at 37°C. Then BrdU was added and incubation continued for 24 hr. Cells were washed, fresh medium containing BrdU (10 μM) and colcemid (0.1 μg/ml) was added, and incubation was continued for 2-3 hr. Cells were then collected by mitotic shake-off, treated for 3 min. with KCl (75 mM), washed twice with fixative, and dropped onto slides and air-dried. Staining was by a modified technique (after Perry and Wolff, 1974; Goto et al., 1978). In the presence of S9, cells were incubated with test compound or solvent for 2 hr at 37°C. Then cells were washed, and medium containing 10 μM BrdU was added. Cells were incubated for a further 26 hr , with colcemid (0.1 μg/ml) present for the final 2-3 hr.

(b) In the absence of S9, CHO cells were incubated with test compound or solvent for 8-10 hr at 37°C. Cells were then washed, and fresh medium containing colcemid (0.1 μg/ml) was added. After a further 2-3 hr of incubation, cells were harvested by mitotic shake-off, fixed, and stained in 6% Giemsa. In the presence of S9, cells were incubated with test compound or solvent for 2 hr at 37°C. Cells were then washed, medium was added, and incubation continued for 8-10 hr. Colcemid (0.1 μg/ml) was added for the last 2-3 hr of incubation, then cells were harvested and fixed as above.

(c) S9 from the livers of Aroclor 1254®-induced male Sprague-Dawley rats.

Conclusions:

	-S9	+S9
SCE	+w	+w
CA	-	+

APPENDIX J

ANALYSIS OF EUGENOL
(Lot Nos. 36483 and 26068)

MIDWEST RESEARCH INSTITUTE

APPENDIX J

A. ELEMENTAL ANALYSIS

Batch 01 (Lot No. 36483)

Element	C	H
Theory	73.16	7.37
Determined	73.42	7.44
	73.20	7.35

Batch 02 (Lot No. 26068)

Element	C	H
Theory	73.14	7.37
Determined	72.80	7.27
	72.91	7.29

B. BOILING POINT

Batch 01

Determined	Literature Values
b.p. (746 mm Hg) 249° to 255°C (Dupont 900 DTA)	b.p. (760 mm Hg) 254°C (Kremers, 1919)
b.p. (746 mm Hg) 255°C (visual micro)	

C. REFRACTIVE INDEX

Batch 01

Determined	Literature Values
n_D^{20} 1.5424 ± 0.0005 (δ)	n_D^{20} 1.5413 (Mel'kanovitskaya and Rashkes, 1967)

D. DENSITY

Batch 01

Determined	Literature Values
d_{23} 1.052 ± 0.0001 (δ)	d_{20} 1.066 (Mel'kanovitskaya and Rashkes, 1967)

E. THIN-LAYER CHROMATOGRAPHY

Batch 01

Plates: Silica Gel 60 F254 0.25 mm layer precoated	Ref. Standard: Phenol
Amount Spotted: 100 and 300 μg	Visualization: Ultraviolet (254 nm) and iodine vapor
System 1: Methanol, 100%	System 2: Benzene, 100%
R_f : 0.85 (major)	R_f : 0.27 (major)
R_{st} : 1.00	R_{st} : 1.9

Batch 02

Plates: Silica Gel 60 F254
Amount Spotted: 100 and 300 μg (10 μg/μl in methanol)
R_f: 0.91

R_{st} : 1.00

Ref. Standard: Phenol
Visualization: Ultraviolet (254 and 366 nm) and Fast Blue B salt (aqueous solution) followed by 0.1N NaOH. (Stahl, 1969)

R_f : 0.39

R_{st} : 1.86

F. VAPOR-PHASE CHROMATOGRAPHY

Batch 01

System 1

Instrument: Tracor MT 220
Detector: Flame ionization
Column: 5% Carbowax 20M TPA, 1.8 m x 4 mm I.D.
Oven Temperature Program: 5 minutes at 75°C, then 75° to 125°C at 10°C/min
Results: One homogeneous peak, retention time 30 minutes

System 2

Instrument: Tracor MT 220
Detector: Flame ionization
Column: 3% OV-17, 1.8 m x 4 mm I.D.
Oven Temperature Program: 5 minutes held at 100°C, then 100° to 250°C at 10°C/minute
Results: Major peak and two impurities

Peak	Retention Time (min)	Retention Time (Relative to Eugenol)	Area (Relative to Eugenol)
1	8.0	0.84	0.1
2	9.5	1.00	100
3	21.8	2.3	0.1

Batch 02

System 1

Instrument: Varian Aerograph VA 3740
Detector: Flame ionization
Column: 3% OV-17 on 80/100 Supelcoport, 1.8 m x 4 mm I.D., glass
Oven temperature program: 100°C, 5 min; 100° to 250°C, 10°C/min
Inlet temperature: 220°C
Detector temperature: 260°C
Carrier gas: Nitrogen
Carrier gas flow rate: 40 cc/min
Sample injected: 5 μl of a 1% v/v solution in chloroform
Results: Single homogeneous peak, retention time 11.6 minutes

System 2

Instrument: Varian Aerograph VA 2400
Detector: Flame ionization
Column: 10% Carbowax 20 M TPA on 80/100 Chromosorb W AW, 1.8 m x 2 mm I.D., glass
Oven temperature program: 75°C, 3 min; 75° to 200°C, 10°C/min
Inlet temperature: 140°C
Detector temperature: 230°C
Carrier gas: Nitrogen
Carrier gas flow rate: 38 cc/min
Sample injected: 4 μl of a 1% v/v solution in chloroform diluted to 0.5% to check for overloading
Results: Major peak and one impurity with an area 0.09% of the area of the major peak

Peak	Retention Time (min)	Retention Time (Relative to Eugenol)	Area (Relative to Eugenol)
1	16.1	1.00	100
2	18.0	1.12	0.09

G. HIGH-PRESSURE LIQUID CHROMATOGRAPHY

Batch 01

Instrument: Waters ALC202 with Model 660 Solvent Programmer
System 1
Column: μPorasil - 300 x 4 mm I.D.
Detector: Ultraviolet, 282 nm
Solvent: Hexane, 100% to tetrahydrofuran, 100%
Program No.: 6
Program Time: 10 minutes
Flow: 2 ml/min
Results: One homogeneous peak, retention time 5.3 minutes

System 2

Column: μBondapak C18
Detector: Ultraviolet, 229 nm
Solvent: 5% to 100% methanol in water
Program No.: 6
Program Time: 10 minutes
Flow: 2 ml/min
Results: Major peak and 4 minor peaks

Peak	Retention Time (min)	Retention Time (Relative to Eugenol)	Area (Relative to Eugenol)
Minor	5.8	0.67	0.21
Minor	6.5	0.75	0.11
Minor	7.6	0.87	0.21
Major	8.7	1.00	100.00
Minor	11.2	1.29	0.85

H. SPECTRAL DATA

(1) Infrared

Instrument: Beckman IR-12
Cell: Neat, NaCl plates
Results: See Figure 5 (01) and Figure 6 (02)

Consistent with literature spectrum (Sadtler Standard Spectra)

(2) Ultraviolet/Visible

Instrument: Cary 118

Batch 01

Determined		Literature Values (Savari, 1928)	
λ max (nm)	$\epsilon \times 10^{-3}$	λ max (nm)	$\epsilon \times 10^{-3}$
281	3.03 ± 0.04 (δ)	280.7	3.73
229	6.46 ± 0.02 (δ)	228.8	7.41

No absorbance between 350 and 800 nm (visible range) at a concentration of 0.2 mg/ml
Solvent: 95% Ethanol

Solvent: Hexane

Batch 02

Determined	
λ max (nm)	ϵ
340 shoulder	0.00776 ± 0.00004 (δ)
281	3.20 ± .06 (δ)
230	6.35 ± .64 (δ)

Solvent: 95% Ethanol

(3) Nuclear Magnetic Resonance

Batch 01

Instrument: Varian HA-100
Solvent: $CDCl_3$ with internal tetramethylsilane
Assignments (See Figure 7)

Consistent with literature spectrum (Sadtler Standard Spectra).

(a) d, δ 3.24 ppm, J_{ad} = Hz
(b) s, δ 3.67 ppm
(c) m, δ 4.97 ppm
(d) m, δ 5.10 ppm
(e) s, δ 5.97 ppm
(f) m, δ 5.72 to 6.18 ppm
(g) m, δ 6.65 ppm, J_{gi} = 9 Hz
(h) m, δ 6.67 ppm
(i) d, δ 6.89 ppm
(j) Impurity, s, δ 0.39 ppm

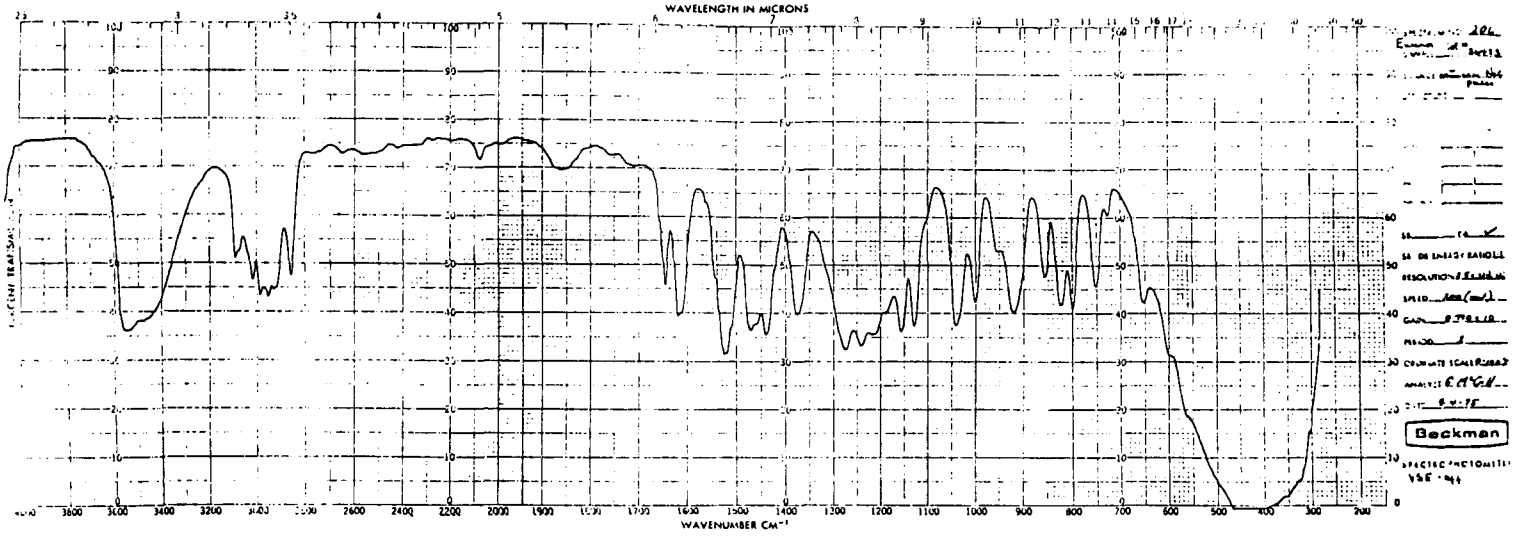

Figure 5. Infrared Absorption Spectrum Eugenol (Lot No. 36483)

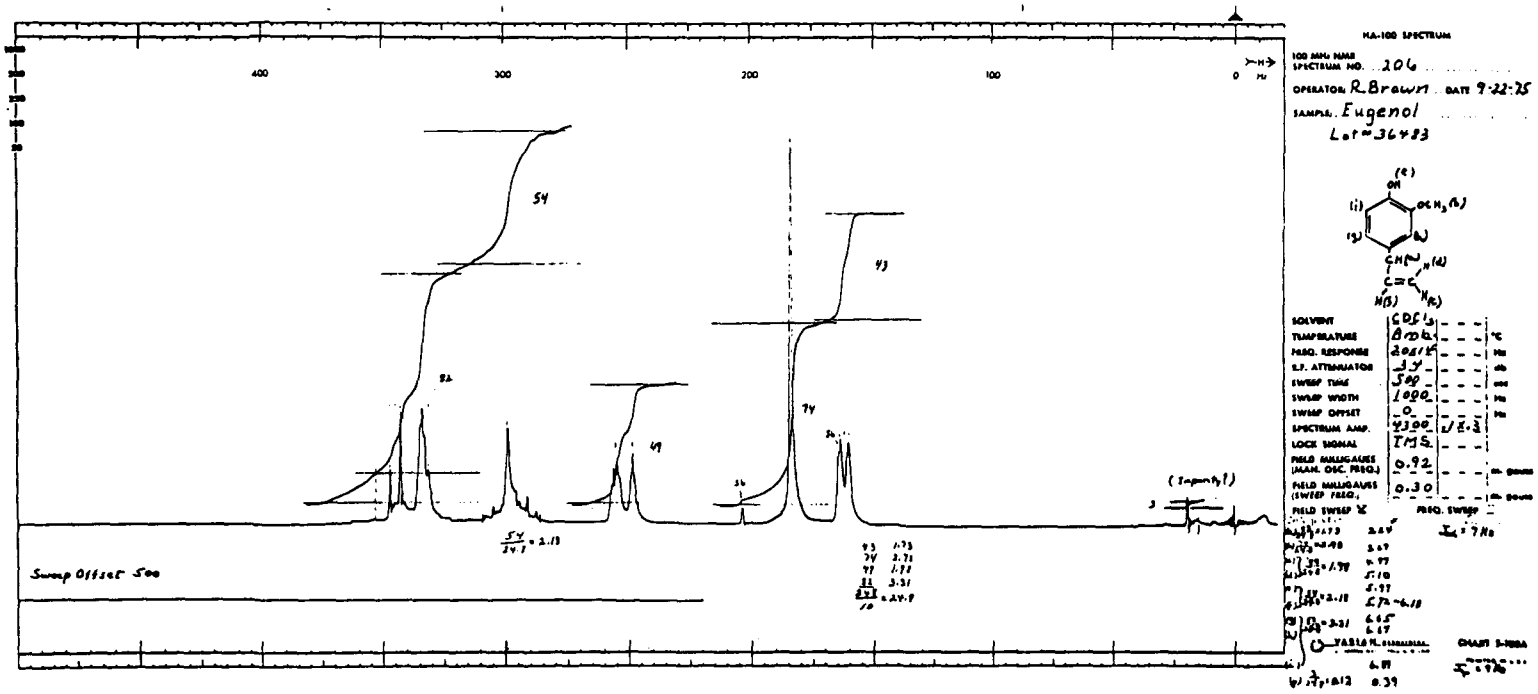

Figure 6. Nuclear Magnetic Resonance Spectrum Eugenol (Lot No. 36483)

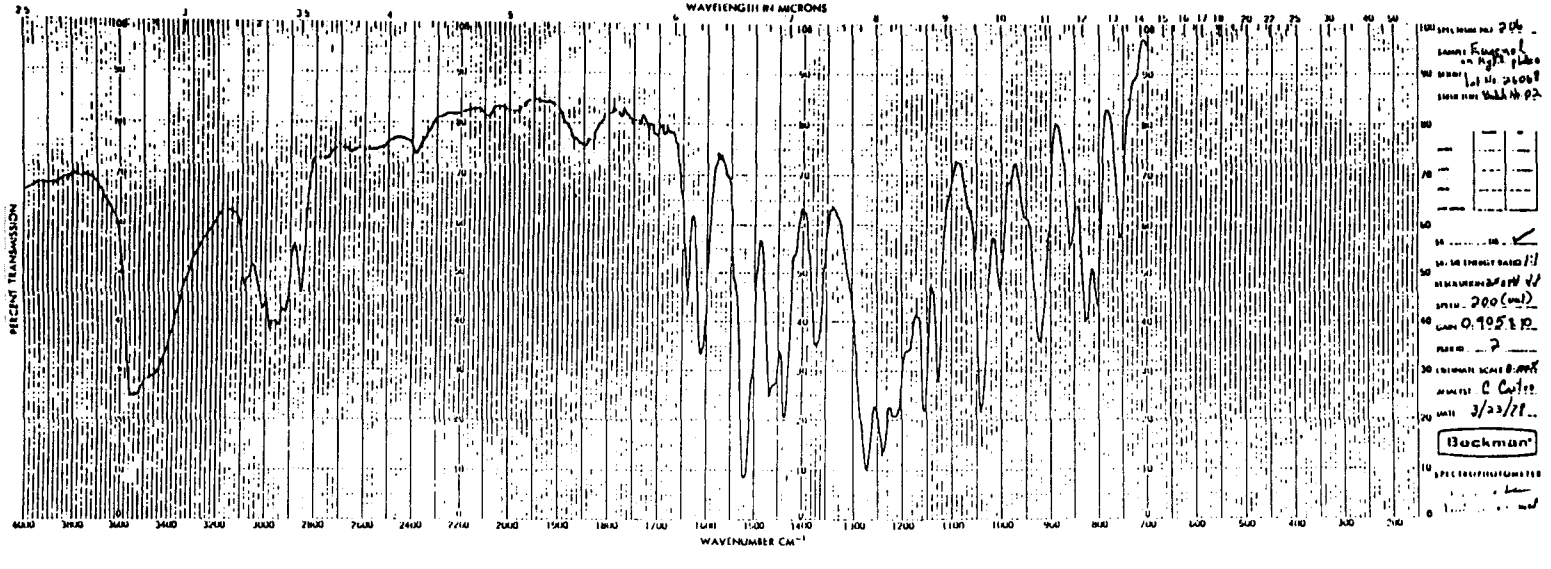

Figure 7. Infrared Absorption Spectrum Eugenol (Lot No. 26068)

Integration Ratios:

(a) 1.73
(b) 2.98
(c) 1.98
(d) 1.98
(e) 2.18
(f) 2.18
(g) 3.31
(h) 3.31
(i) 3.31
(j) 0 12

Batch 02

Instrument: Varian E M 360 A
Solvent: Chloroform-d with tetramethylsilane added
Assignments: (See Figure 8)

Consistent with literature spectrum (Sadtler Standard Spectra).

(a) d, δ 3.26 ppm, J_{ad} = 6 Hz
(b) s, δ 3.66 ppm
(c) m, δ 4.80-5.23 ppm
(d) m, δ 5.60-6.20 ppm
(e) s, δ 5.93 ppm
(f) m, δ 6.50-6.73 ppm
(g) m, δ 6.50-6.73 ppm
(h) d, δ 6.85 ppm, J_{hf} = 9 Hz

Integration Ratios:

(a) 1.94
(b) 2.97
(c) 2.00
(d) 2.00
(e) 2.00
(f) 3.00
(g) 3.00
(h) 3.00

I. CHARACTERIZATION AND IDENTIFICATION OF IMPURITIES

Minor components in the test chemicals normally are characterized chromatographically but no attempt is made to identify them, since the intent of the studies, in most cases, is to test a commercial product. For example, if a chemical selected because of its use as a drug met USP specifications, it would be acceptable for carcinogenesis study purposes whether or not it contained minor impurities. The chromatographic pattern of impurities is used for a semi-quantitative purity determination and for monitoring the test chemical for possible degradation during the studies.

Eugenol was procured as food grade material, and no attempt was made to identify minor components detected chromatographically.

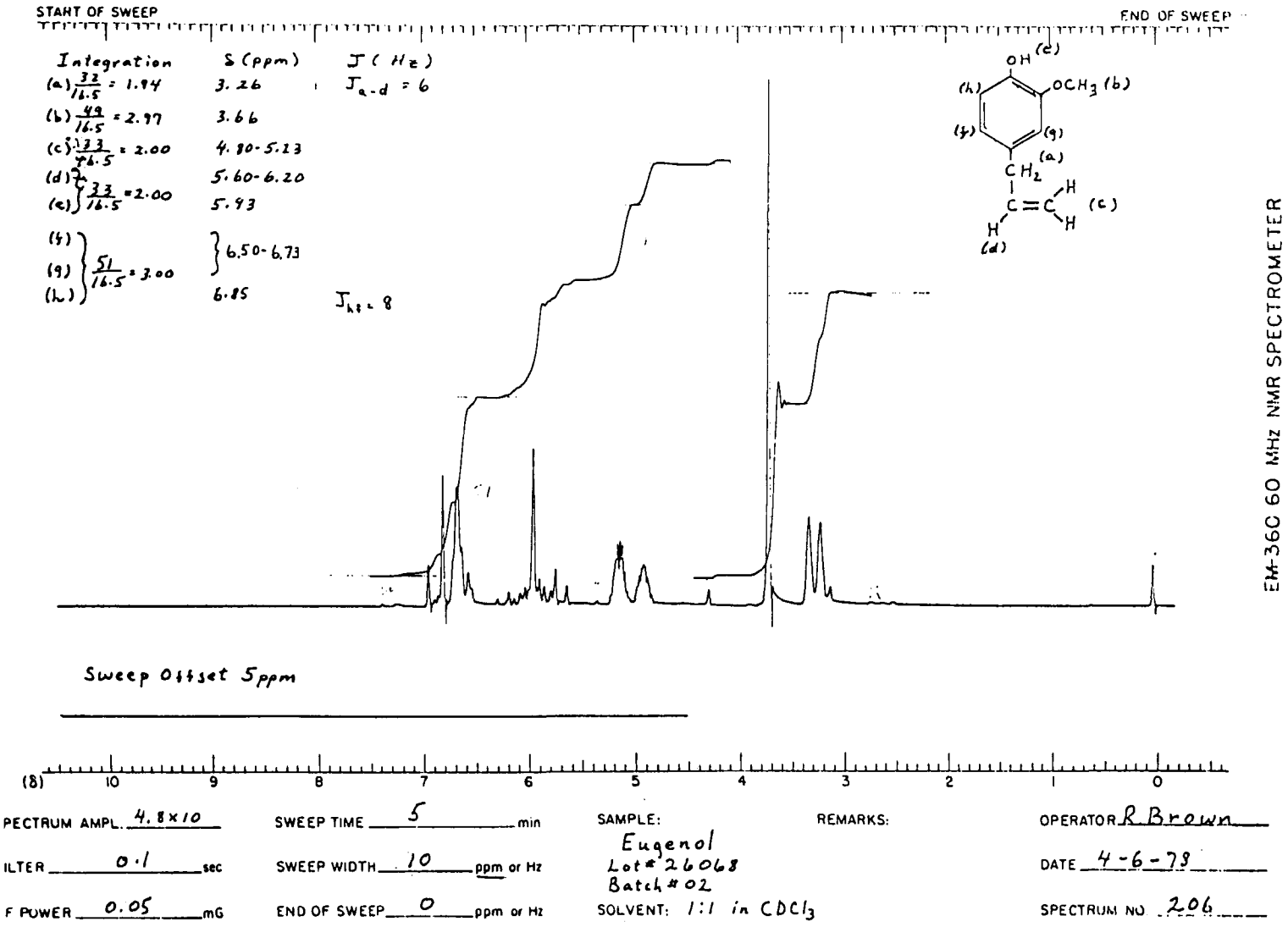

Figure 8. Nuclear Magnetic Resonance Spectrum (Lot No. 26068)

APPENDIX K

STABILITY ANALYSIS OF EUGENOL IN FORMULATED DIETS

MIDWEST RESEARCH INSTITUTE

APPENDIX K

A. MIXING AND STORAGE

Eugenol (20 g) and Wayne Lab-Blox® Rodent Feed (180 g) were mixed using a mortar and pestle. Samples of the mix were then removed and stored for 2 weeks at -20°, 5°, 25°, and 45°C, respectively.

B. EXTRACTION AND ANALYSIS PROCEDURES

The samples were mixed with methanol in an ultrasonic vibratory bath and subsequently triturated with the methanol using a Polytron® mixer. The resulting mixture was centrifuged and the supernatant solution decanted. The extraction was repeated with fresh methanol, and the supernatant solutions were combined and diluted to working volume for analysis by vapor-phase chromatography as described below:

Instrument: Tracor MT-220
Column: 3% OV-1 on Supelcoport, 80/100 mesh, glass, 1.8 m x 4 nm I.D.
Oven Temperature: 130°C, isothermal
Detector: Flame ionization
Retention Time of Test Compound: 1.5 minutes

C. RESULTS

Temperature (°C)	Average (%)
-20	10.5 ± 0.4
5	10.2 ± 0.4
25	10.2 ± 0.4
45	9.8 ± 0.4

D. CONCLUSION

Eugenol mixed with feed is stable for 2 weeks at temperatures up to 45°C.

APPENDIX L

ANALYSES OF FORMULATED DIETS FOR CONCENTRATIONS OF EUGENOL

SOUTHERN RESEARCH INSTITUTE

A 5.000-g sample of feed was triturated with 20 ml of chloroform using a Polytron® high speed blender for 2 minutes. The mixture was filtered and the extraction procedure repeated with 20 ml of chloroform. The extracts were combined and diluted to 50 ml with chloroform. The chloroform extract was analyzed by vapor-phase chromatography.

Gas Chromatography Specifications:

Column: 3% OV-1 on 80/100 mesh Supelcoport, glass column
Detector: Flame ionization
Injection Port Temperature: 200°C
Oven Temperature: 130°C
Detector Temperature: 200°C
Sample Size: 2 μl
Retention Time-Eugenol: 4.8 minutes

The average percent recovery for the plain feed samples spiked with 0.6% eugenol that were analyzed by the above procedure is approximately 95%.

TABLE L1. ANALYSES OF FORMULATED DIETS

Date Mixed *(a)*	Date Used (Weeks of)	Concentration *(b)* of Eugenol in Feed for Target concentration of		
		3,000 ppm	6,000 ppm	12,500 ppm
5/02/77	5/4 and 5/11		6,600	
5/16/77	5/16 and 5/23		6,200	
7/12/77	7/15 and 7/22	2,590	5,220	12,000
9/01/77	9/7 and 9/14	2,480	4,580	
9/26/77	9/29 and 10/5	3,300	6,070	12,400
10/25/77	10/26 and 11/2	3,000	6,100	13,500
11/29/77	12/1 and 12/7		6,200	
12/20/77	12/22 and 12/29	2,800	4,700	
			5,200	
1/24/78	1/26 and 2/1	3,500	6,100	
2/23/78	2/27 and 3/5	3,000	6,600	
3/16/78	3/20 and 3/27	2,900	6,000	13,000
4/20/78	4/23 and 4/30	2,900	6,600	
5/24/78	5/28 and 6/4	3,000	6,500	15,000
6/22/78	7/2 and 7/9	2,600	6,200	12,200
7/13/78	7/16 and 7/23	3,200	6,800	13,000
8/10/78	8/13 and 8/20	2,800	6,300	
9/07/78	9/10 and 9/17	2,500	5,800	13,200
10/09/78	10/12 and 10/19	2,800	6,000	
11/02/78	11/5 and 11/12	2,800	6,000	
12/15/78	12/10 and 12/17	2,600	6,000	
			5,800	
1/04/79	1/7 and 1/14	2,600	6,500	
1/08/79	1/14 and 1/21	2,500		
1/25/79	1/28 and 2/4	2,600	6,500	
2/22/79	3/3 and 3/10	2,500	5,500	
3/15/79	3/17 and 3/24	2,600	6,300	
Mean (ppm)		2,799	6,014	13,037
Standard deviation		281	568	947
Coefficient of Variation (%)		10.0	9.4	7.3
Range (ppm)		2,480–3,500	4,580–6,800	12,000–15,000
Number of Samples		22	26	8

(a) 4/17/77 was the start date for mice and 6/3/77 was the start date for rats.
(b) The data presented are the average of duplicate analyses.

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