National Cancer Institute
CARCINOGENESIS
Technical Report Series
No. 196
NTP No. 80-10
1980

BIOASSAY OF CINNAMYL ANTHRANILATE FOR POSSIBLE CARCINOGENICITY

CAS No. 87-29-6

NCI-CG-TR-196

NTP-80-10

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

BIOASSAY OF

CINNAMYL ANTHRANILATE

FOR POSSIBLE CARCINOGENICITY

Carcinogenesis Testing Program
National Cancer Institute
National Institutes of Health
Bethesda, Maryland 10105
and
National Toxicology Program
Research Triangle Park
Box 12233
North Carolina 27709

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

NIH Publication No. 80-1752
August 1980

BIOASSAY OF
CINNAMYL ANTHRANILATE
FOR POSSIBLE CARCINOGENICITY

Carcinogenesis Testing Program
National Cancer Institute/National Toxicology Program

FOREWORD

This report presents the results of the bioassay of cinnamyl anthranilate conducted for the Carcinogenesis Testing Program, National Cancer Institute (NCI)/National Toxicology Program (NTP). This is one of a series of experiments designed to determine whether selected chemicals have the capacity to produce cancer in animals. A negative result, in which the test animals do not have a greater incidence of cancer than control animals, does not necessarily mean that a test chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of circumstances. A positive result demonstrates that a test chemical is carcinogenic for animals under the conditions of the test and indicates that exposure to the chemical is a potential risk to man. The actual determination of the risk to man from chemicals found to be carcinogenic in animals requires a wider analysis.

CONTRIBUTORS

The bioassay of cinnamyl anthranilate was conducted at EG&G Mason Research Institute, Worcester, Massachusetts, initially under direct contract to NCI and currently under a subcontract to Tracor Jitco, Inc., the prime contractor for the NCI Carcinogenesis Testing Program.

The bioassay was conducted under the supervision of Drs. A. Handler (1,2) and E. Smith (1,3), principal investigators, and Mr. G. Wade (1). NCI project officers were Drs. E. K. Weisburger (4), T. Cameron (4), and N. P. Page (4,5). The program manager was Mr. J. Baker (1). Ms. A. Good (1) supervised the technicians in charge of animal care, and Ms. E. Zepp (1) supervised the preparation of the feed mixtures and collected samples of the diets for analysis. Ms. D. Bouthot (1) kept all daily records of the test. Dr. A. Russfield (1), pathologist, directed the necropsies. Histopathologic examinations were performed by Dr. D. A. Willigan (6). The report and selected slides were evaluated by the NCI Pathology Working Group as described by Ward et al. (1978).

Animal pathology tables and survival tables were compiled at EG&G Mason Research Institute, Rockville, Maryland (7). The statistical analyses were performed by Dr. J. R. Joiner (8) and Ms. S. Vatsan (8), using methods selected for the bioassay program by Dr. J. J. Gart (9).

Chemicals used in this bioassay were analyzed under the direction of Dr. E. Murrill (10), dosed feed mixtures were analyzed by Dr. M. Hagopian (1), and all analytical results were reviewed by Dr. C. W. Jameson (8,11).

This report was prepared at Tracor Jitco (8) under the direction of NCI. Those responsible for the report at Tracor Jitco were Dr. C. R. Angel, Director of the Bioassay Program; Dr. S. S. Olin, Deputy Director for Science; Dr. J. F. Robens (12), toxicologist; Dr. R. L. Schueler, pathologist; Dr. A. C. Jacobs, bioscience writer; and Dr. W. D. Theriault and Ms. M. Glasser, technical editors.

The following scientists at NCI (13) were responsible for evaluating the bioassay experiment, interpreting the results, and reporting the findings: Dr. Kenneth C. Chu, Dr. Cipriano Cueto (14), Dr. Michael P. Dieter, Dr. J. Fielding Douglas, Dr. Richard A. Griesemer, Dr. Charles K. Grieshaber, Dr. Thomas E. Hamm, Dr. William V. Hartwell, Dr. J. Young Lee, Dr. Morton H. Levitt, Dr. Harry Mahar, Dr. Harry A. Milman, Dr. Thomas W. Orme, Dr. A. R. Patel (15), Dr. Marcelina B. Powers, Dr. Sherman F. Stinson, Dr. Jerrold M. Ward, and Dr. Carrie E. Whitmire.

---

(1) EG&G Mason Research Institute, 57 Union Street, Worcester, Massachusetts.
(2) Now with Abcor, Inc., 850 Main Street, Wilmington, Massachusetts.
(3) Now with the University of Massachusetts Medical Center, 55 Lake Avenue, Worcester, Massachusetts.
(4) Division of Cancer Cause and Prevention, National Cancer Institute, National Institutes of Health, Bethesda, Maryland.
(5) Now with the Office of Toxic Substances, Environmental Protection Agency, 401 M Street SW, Washington, D.C.
(6) Donald A. Willigan, Inc., 730 Park Avenue, Bound Brook, New Jersey.
(7) EG&G Mason Research Institute, 1530 East Jefferson Street, Rockville, Maryland.
(8) Tracor Jitco, Inc., 1776 East Jefferson Street, Rockville, Maryland.
(9) Mathematical Statistics and Applied Mathematics Section, Biometry Branch, Field Studies and Statistics, Division of Cancer Cause and Prevention, National Cancer Institute, National Institutes of Health, Bethesda, Maryland.
(10) Midwest Research Institute, 425 Volker Boulevard, Kansas City, Missouri.
(11) Now with the Carcinogenesis Testing Program, National Cancer Institute/ National Toxicology Program.
(12) Now with Bureau of Veterinary Medicine, Food and Drug Administration, 5600 Fishers Lane, Rockville, Maryland.
(13) Carcinogenesis Testing Program, National Cancer Institute/National Toxicology Program, Bethesda, Maryland.
(14) Now with Litton Bionetics, Inc., 5516 Nicholson Lane, Kensington, Maryland.
(15) Special Programs, Division of Cancer Cause and Prevention, National Cancer Institute, National Institutes of Health, Bethesda, Maryland.

SUMMARY

A bioassay of cinnamyl anthranilate (a synthetic flavoring agent) for possible carcinogenicity was conducted by administering the test chemical in feed to F344 rats and B6C3F1 mice.

Groups of 50 rats and 50 mice of each sex were fed the test chemical in diets containing 15,000 or 30,000 ppm for 103 weeks and then observed for an additional 2 or 3 weeks. Controls consisted of groups of 50 untreated rats and 50 untreated mice of each sex. All surviving animals were killed and necropsied at 105 to 107 weeks.

Mean body weights of the dosed male and female rats and mice were lower than those of the corresponding controls throughout the bioassay, and weight decrements were dose related. Mortality in rats or mice of either sex was not affected by administration of the test chemical.

In male rats, adenocarcinomas or adenomas of the renal cortex and acinar-cell carcinomas or adenomas of the pancreas were found in low incidences in dosed rats but not in control rats. In direct comparisons with matched control groups, the incidences of these tumors were not significantly increased; however, because these tumors rarely occur spontaneously in aging F344 rats, they were considered to be related to compound administration. Similar pancreatic or renal tumors have not been detected among 634 historical-control male F344 rats at the same laboratory.

In the female rats, no tumors occurred at incidences that could be clearly related to administration of the test chemical.

In both male and female mice, the incidences of hepatocellular carcinomas or adenomas were dose related ($P < 0.001$) and significant ($P \leq 0.001$) in direct comparisons of dosed and control groups.

It was concluded that under the conditions of this bioassay cinnamyl anthranilate was carcinogenic for male and female B6C3F1 mice, inducing increased incidences of hepatocellular carcinomas or adenomas. The test chemical was also carcinogenic for male F344 rats, inducing low incidences of acinar-cell carcinomas or adenomas of the pancreas and adenocarcinomas or adenomas of the renal cortex. Cinnamyl anthranilate was not carcinogenic for female F344 rats.

TABLE OF CONTENTS

APPENDIXES

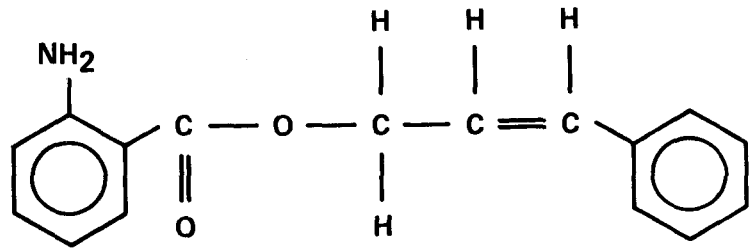
APPENDIXES (Continued)

TABLES

TABLES (Continued)

FIGURES

I. INTRODUCTION



CINNAMYL ANTHRANILATE

Cinnamyl anthranilate (CAS 87-29-6; NCI C03510) is a synthetic flavoring agent in use since the 1940's as an imitation grape or cherry flavor in foods (Meyer, 1960; Swaine, 1972; Opdyke, 1975). It has been approved by the U. S. Food and Drug Administration as a food additive (Code of Federal Regulations, 1977). The Council of Europe listed it as an artificial flavoring substance that may be used at levels up to 25 mg/kg (Opdyke, 1975). The average maximum use levels in beverages, ice cream, candy, baked goods, gelatins, puddings, and chewing gums range from 1.7 to 730 ppm, according to surveys of the industry conducted by the Flavoring Extract Manufacturers' Association (Hall and Oser, 1965).

Cinnamyl anthranilate is also used (0.001 to 0.08 percent) as a fragrance in soaps, detergents, creams, lotions, and perfumes (Opdyke, 1975). U. S. sales of cinnamyl anthranilate for use as a flavoring agent or fragrance were 2,000 pounds in 1976 (USITC, 1977).

The acute oral LD_{50} of cinnamyl anthranilate in rats (strain and sex unspecified) was reported to exceed 5 g/kg body weight (Moreno, 1974). Stoner et al. (1973) reported that cinnamyl anthranilate produced a statistically significant increase in the incidence of lung tumors in strain A/He mice that had received intraperitoneal injections of 500 mg/kg body weight three times a week for 8 weeks and were killed and necropsied 16 weeks after the last injection. Because of its widespread use as a direct food additive and the results of the preliminary study by Stoner et al., cinnamyl anthranilate was selected for study using the protocols of the NCI Carcinogenesis Testing Program.

II. MATERIALS AND METHODS

A. Chemical

Cinnamyl anthranilate (2-aminobenzoic acid, 3-phenyl-2-propenyl ester; anthranilic acid, cinnamyl ester) manufactured by Research Organic Inorganic Chemical Company (Sun Valley, Calif.), was obtained as a single batch (Lot No. A121) from California Aromatics and Flavors (Belleville, N. J.). Elemental analysis, melting point, thin-layer and high-pressure liquid chromatography, nonaqueous titration of the amine group, and spectral analyses (including infrared, ultraviolet, and nuclear magnetic resonance) were performed at Midwest Research Institute, Kansas City, Missouri (Appendix E). Reference data were not found in the literature for the spectral analyses; however, results of the elemental analyses, amine titration, melting point, and infrared and nuclear magnetic resonance spectrometry were consistent with the theoretical composition and structure of the chemical and conformed to specifications (purity not less than 96%) for food-grade cinnamyl anthranilate (Food Chemicals Codex, 1972). Results of thin-layer chromatography indicated the presence of five trace impurities, and results of high-pressure liquid chromatography indicated the presence of two trace impurities. These impurities were not identified or quantitated.

The chemical was stored at 4°C in the original container and transferred to 1-gallon stock bottles as necessary. The test chemical described above is referred to in this report as cinnamyl anthranilate.

B. Dietary Preparation

Test diets were prepared by first mixing the chemical with an aliquot of powdered Wayne® Lab Blox animal feed (Allied Mills, Chicago, Ill.), using a mortar and pestle. This mixture was placed in a Patterson-Kelly® twin-shell blender with the remainder of the feed and mixed for 20 minutes. Test diets were sealed in labeled plastic bags and stored at 4°C for no longer than 1 week.

Analyses of the stability of cinnamyl anthranilate in feed were performed at Midwest Research Institute by assaying samples of diet mixtures containing 3,000 and 30,000 ppm that had been stored at room temperature for 11 days and then extracted with ether. Concentrations of the test chemical in the extracts were determined by spectrophotographic microanalysis at 250 mμ. Cinnamyl anthranilate was found to be stable in feed for 11 days at room temperature with recoveries of 91% and 100% for the diet mixtures containing 3,000 and 30,000 ppm, respectively. Selected batches of the formulated diets administered during the chronic study were analyzed at EG&G Mason Research Institute for homogeneity of preparation. The mean concentration of seven samples containing a theoretical level of 15,000 ppm was 14,900 ppm. The coefficient of variation was 10%, and the range was 2,000 ppm. The mean concentration of seven samples containing a theoretical level of 30,000 ppm was 29,000 ppm. The coefficient of variation was 6.49%, and the range was 3,500 ppm.

Two samples of diet mixtures prepared and analyzed at Mason were shipped to Midwest Research Institute for further analysis of cinnamyl anthranilate by ethanol extraction and high-pressure liquid chromatography (including standards and spiked samples). Results from the two laboratories were similar.

C. Animals

Five-week-old F344 (Fischer) rats and 4-week-old B6C3F1 mice were obtained from the NCI Frederick Cancer Research Center, Frederick, Maryland. After the rats and mice were isolated and maintained in separate quarters for 2 weeks, they were assigned to control or dosed groups in such a way that the mean weight of animals in each cage was approximately the same for each species and sex.

D. Animal Maintenance

Rats were housed four per cage in suspended polycarbonate cages (Lab Products, Inc., Garfield, N.J.) equipped with disposable nonwoven fiber filter sheets. Sanicel® corn cob bedding (Paxton Processing Co.,

Lancaster, Mass.) was used during the first month, and Aspenbed® wood chip bedding (American Excelsior, Summerville, Mass.) for the remainder of the bioassay. Clean bedding and cages were provided twice weekly. Stainless steel cage racks were cleaned every 2 weeks, and disposable filters for the cages were replaced on the same schedule.

Mice were housed five per cage in polycarbonate cages, fitted with perforated stainless steel lids (Lab Products, Inc.). Nonwoven fiber filter bonnets were placed over the cage lids. Bed-o-cobs® corn cob bedding (Anderson Cob Mills, Inc., Maumee, Ohio) was used for the mice during the first 2 months, and Aspen-bed® wood chip bedding (American Excelsior) was used for the remainder of the bioassay. Cages, lids, and bedding were changed twice weekly. Filter bonnets and cage racks were washed every 2 weeks.

Water was available ad libitum for both species. Polycarbonate bottles were used for mice for the first month and for rats for the first 14 months, with glass water bottles being used for the remainder of the bioassay. The bottles, rubber stoppers, and stainless steel sipper tubes were washed and refilled twice weekly.

Powdered Wayne® Lab Blox diet for the controls and the test diet described previously for the dosed animals was available ad libitum in stainless-steel, gang-style hoppers (Scientific Cages, Inc., Bryan, Tex.) which were changed once a week and refilled twice a week.

The temperature in animal rooms ranged from 23° to 34°C. Incoming air was filtered through Tri-Dek 15/40 denier Dacron filters and changed six times per hour. Fluorescent lighting was provided 12-hours per day.

Rats and mice fed cinnamyl anthranilate were housed in rooms in which subchronic tests were being conducted on the following chemicals:

Feed Studies

(CAS 101-80-4) 4,4'-oxydianiline (3-week overlap)
(CAS 15481-70-6) 2,6-toluenediamine dihydrochloride (10-week overlap)

E. Subchronic Studies

Subchronic feeding studies were conducted using F344 rats and B6C3F1 mice to determine the concentrations of cinnamyl anthranilate to be used in the chronic studies. Groups of five males and five females of each species were tested at each of four doses, and groups of five males and five females of each species were maintained as untreated controls. Test animals were administered cinnamyl anthranilate for 8 weeks and then killed and necropsied. Doses administered, survival, and mean body weights of dosed groups at week 8 are shown in Table 1.

No deaths occurred in rats or mice at any of the doses tested, and no depression in weight greater than 10% was observed in any group except male mice fed 30,000 ppm. No compound-related lesions were evident at necropsy in either species.

Low and high doses for the chronic studies were set at 15,000 and 30,000 ppm for both rats and mice.

F. Chronic Studies

The number of animals in test groups, doses administered, and times on study of the chronic studies in rats and mice are shown in Table 2.

G. Clinical Examinations and Pathology

All animals were observed twice daily for signs of toxicity. Mean body weights of animals by cage were recorded every 2 weeks for the first 4 to 8 weeks and monthly thereafter. Clinical signs were recorded monthly. Moribund animals and animals that survived to the end of the bioassay were killed using carbon dioxide and necropsied.

Examinations for grossly visible lesions were done 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,

Table 1. Doses, Survival, and Mean Body Weights of Rats and Mice Fed Cinnamyl Anthranilate in the Diet for 8 Weeks

Dose (ppm)	Males		Females	
	Survival(a)	Mean Weight at Week 8 (Percent of Control)	Survival(a)	Mean Weight at Week 8 (Percent of Control)
RATS				
0	5/5	100	5/5	100
1,000	5/5	101	5/5	97
3,000	5/5	96	5/5	98
10,000	5/5	94	5/5	98
30,000	5/5	92	5/5	90
MICE				
0	5/5	100	5/5	100
1,000	5/5	98	5/5	101
3,000	5/5	100	5/5	102
10,000	5/5	98	5/5	97
30,000	5/5	88	5/5	92

(a) Number surviving/number in group.

Table 2. Experimental Design for Chronic Cinnamyl Anthranilate Feeding Studies in Rats and Mice

Sex and Test Group	Initial Number of Animals (a)	Cinnamyl Anthranilate Dose (b) (ppm)	Time on Study	
			Dosed (weeks)	Observed (weeks)
Male				
Matched-Control	50	0		106-107
Low-Dose	50	15,000	103	2-3
High-Dose	50	30,000	103	2
Female				
Matched-Control	50	0		106-107
Low-Dose	50	15,000	103	2
High-Dose	50	30,000	103	2-3

(a) Rats were 7 weeks of age and mice 6 weeks of age at the start of the study.
(b) Test animals received dosed diets ad libitum 7 days per week.

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, ovaries/uterus, nasal tissues, brain, pituitary, eyes, and spinal cord. Special staining techniques were utilized as necessary.

Necropsies were performed on all animals found dead, unless precluded in whole or in part by autolysis or cannibalization. Thus, the number of animals from which particular organs or tissues were examined microscopically varies and does not necessarily represent the number of animals that were placed on study in each group.

H. Data Recording and Statistical Analyses

Data were recorded in the Carcinogenesis Bioassay Data System (Linhart et al., 1974). Data elements used in this report 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. One-tailed P values have been reported for all tests except the departure from linearity test, which is reported only when its two-tailed P value is less than 0.05.

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 (numerator) to the number of animals in which that site is examined (denominator). In most instances, the denominators included only those animals for which that site was examined histologically. However, when macroscopic examination was required to detect lesions prior to

histologic sampling (e.g., skin or mammary tumors), or when lesions could have appeared at multiple sites (e.g., lymphomas), the denominators consist of the numbers of animals necropsied.

The one-tailed Fisher exact test (Cox, 1970) was used to compare the tumor incidence of a control group with that of a group of dosed animals at each dose level. The results of this test are shown in Tables 3,4,6, and 7. Since in this study results for two dosed groups are compared simultaneously with those for a single control group, a correction to ensure an overall significance level of 0.05 is made by use of the Bonferroni inequality (Miller, 1966), which requires that the P value for any comparison be less than or equal to 0.025 to be statistically significant.

The Cochran-Armitage test for linear trend in proportions, with continuity correction (Armitage, 1971), was also used. Under the assumption of a linear trend, this test determines if the slope of the dose-response curve is different from zero at the one-tailed 0.05 level of significance. This method also provides a two-tailed test of departure from linear trend.

Included in the tables are the upper and lower limits of the approximate 95 percent confidence interval for the relative risk of each dosed group compared with its control (Gart, 1971). The interpretation of the limits is that, in approximately 95 percent of a large number of identical experiments, the true ratio of the risk in a dosed group of animals to that in a control group would be within the interval calculated from the experiment. When the lower limit of the confidence interval is greater than one, it can be inferred that a statistically significant result has occurred (P less than 0.025 one-tailed test when the control incidence is not zero, P less than 0.050 when the control incidence is zero). When the lower limit is less than unity, but the upper limit is greater than unity, the lower limit indicates the absence of a significant result while the upper limit indicates that there is a theoretical possibility of the induction of tumors by the test chemical, which could not be detected under the conditions of this test.

The incidence of a particular tumor in a group of control animals may be considered as an instance of the binomial distribution (Fears et al., 1977). The probability of an incidence greater than or equal to that observed in a dosed group is calculated by using the parameters of

distribution derived from historical controls as an estimate. When this probability is small, a probable dose association is indicated. Due to the large variance possible in moderately sized groups as the binomial parameter increases, this method of analysis is applied only when the historical data indicate little or no incidence of the particular tumor under analysis.

III. RESULTS - RATS

A. Body Weights and Clinical Signs (Rats)

Dose-related reductions in mean body weight gain occurred in all groups of dosed male and female rats (Figure 1). Other clinical signs that could be related to administration of the test chemical were not observed.

B. Survival (Rats)

Estimates of the probabilities of survival for male and female rats fed cinnamyl anthranilate at the doses of this bioassay, together with those for the matched controls, are shown by the Kaplan and Meier curves in Figure 2. The result of the Tarone test for dose-related trend in mortality was not significant in either sex.

In male rats, 40/50 (80%) of each dosed group and 32/50 (64%) of the control group lived to the end of the bioassay. In females, 46/50 (92%) of the high-dose, 44/50 (88%) of the low-dose, and 39/50 (78%) of the control groups lived to the end of the bioassay. Dosed animals were killed at weeks 105 or 106; controls were killed at weeks 106 or 107.

C. Pathology (Rats)

Histopathologic findings on neoplasms in rats are summarized in Appendix A, Tables A1 and A2; findings on nonneoplastic lesions are summarized in Appendix C, Tables C1 and C2.

A variety of neoplasms occurred in dosed and control rats. Most of these neoplasms have been encountered previously in control animals of the F344 strain. Their incidences were not clearly related to administration of the test chemical, with the possible exception of adenomas or adenocarcinomas of tubular-cell origin in the renal cortex which rarely occur spontaneously, but were observed in high-dose male rats (adenomas 2/49, adenocarcinomas 2/49). Malignant mesotheliomas of the abdominal cavity/peritoneum occurred in low-and high-dose males (low-dose 1/50,

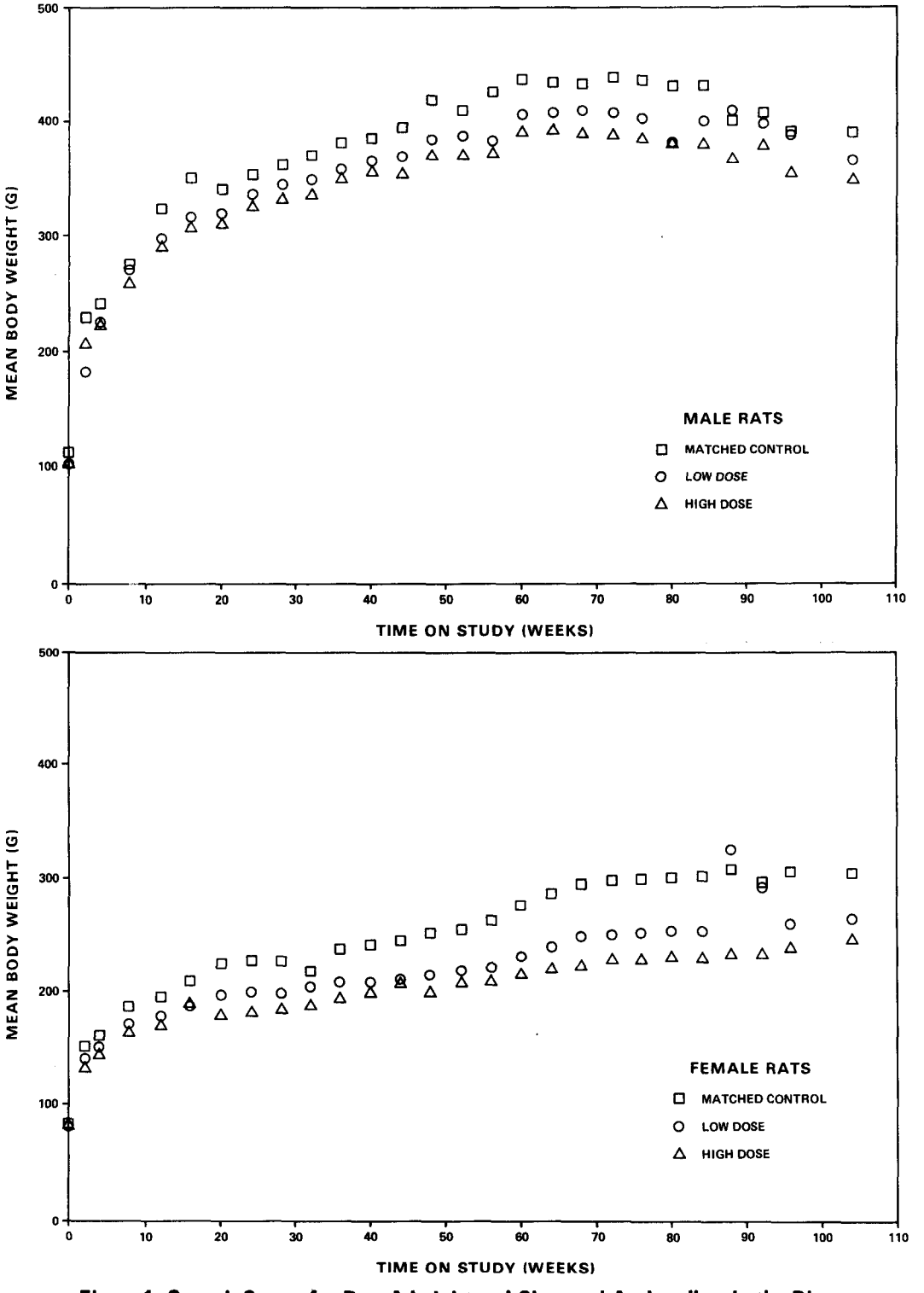


Figure 1. Growth Curves for Rats Administered Cinnamyl Anthranilate in the Diet

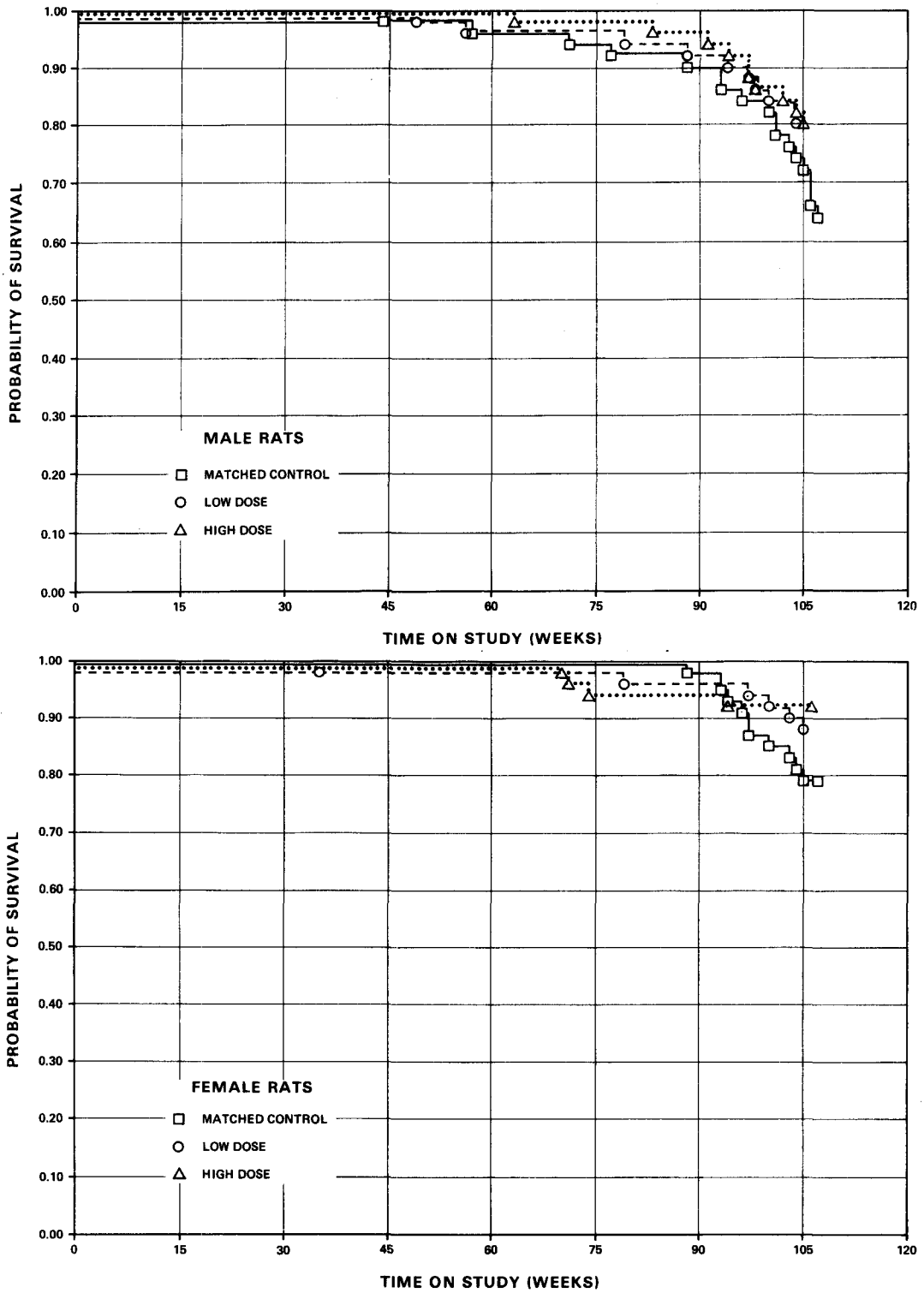


Figure 2. Survival Curves for Rats Administered Cinnamyl Anthranilate in the Diet

high-dose 4/50). Rarely reported acinar-cell tumors of the pancreas occurred in high-dose males (3/45). Two were classified as adenomas and one as a carcinoma.

Nonneoplastic renal lesions were seen at an increased incidence in dosed rats of each sex. Mineralization of the kidney was dose related in males (control 0/48, low-dose 17/50, high-dose 30/49), and hemosiderosis of the spleen was dose related in females (control 8/47, low-dose 28/50, high-dose 41/50). Chronic inflammatory changes and healed infarcts were seen in the kidneys of high-dose females.

The histopathologic examination provided evidence that, under the conditions of this bioassay, cinnamyl anthranilate induced neoplastic lesions in the pancreas and kidneys of male F344 rats and nonneoplastic lesions in the kidneys of both male and female rats.

D. Statistical Analyses of Results (Rats)

Tables 3 and 4 contain the statistical analyses of the incidences of those primary tumors that occurred in at least two animals of one group and at an incidence of at least 5% in one or more than one group.

The incidence of high-dose male rats with either adenocarcinomas or adenomas in the renal cortex was 4/49 (8%). The result of the Cochran-Armitage test is P=0.015. This tumor was not observed in controls or low-dose groups. The historical incidence among male historical controls at this laboratory is 0/634, and the historical incidence in all laboratories in the Carcinogenesis Testing Program is 8/1,538 (0.37%).

In male rats, acinar-cell neoplasms of the pancreas occurred in the high-dose group (3/45, 7%). Records at this laboratory from two previous bioassay program contracts indicate that neoplasms of this type did not occur in the 634 control male rats. The incidence of acinar-cell adenomas or carcinomas of the pancreas in control groups of all laboratories in the Carcinogenesis Testing Program is 6/1,538 (0.28%). The Fisher exact test does not yield a significant result when the high-dose group is compared with the controls. The Cochran-Armitage test result is P=0.038.

In female rats, the incidence of endometrial stromal polyps of the uterus in the low-dose groups (16/50, 32%) is statistically significant (P

less than 0.001) when compared with that of the controls (2/47, 4%). In the high-dose group, the incidence of 9/50 (18%) results in a value (P=0.032) which is above that required (P=0.025) for statistical significance when using the Bonferroni criterion. Twelve out of 299 (4%) of the bioassay historical-control female rats at this laboratory were reported to have this tumor and one control group had an incidence of 16/52 (31%). Historical records from all laboratories in this bioassay program indicate an incidence of 261/1,574 (17%); therefore, no association of these tumors with administration of the chemical can be made.

Significant results in the negative direction were observed in the incidence of lymphomas in female rats in which a significant decreasing incidence (P=0.010) with increased dosage was determined.

In each of the 95% confidence intervals for relative risk shown in the tables, except for the incidences of tumors in the uterus of female rats, the value of one or less than one is included; this indicates the absence of significant positive results. It should also be noted that each of the intervals except that of the incidence of lymphomas in high-dose female rats has an upper limit greater than one indicating the theoretical possibility of tumor induction by cinnamyl anthranilate, which could not be detected under the conditions of this test.

Table 3. Analyses of the Incidence of Primary Tumors in Male Rats Administered Cinnamyl Anthranilate in the Diet (a)

Topography: Morphology	Matched Control	Low Dose	High Dose
Integumentary System: Fibroma of the Subcutaneous Tissue (b)	0/50 (0)	3/50 (6)	0/50 (0)
P Values (c,d)	N.S.	N.S.	--
Departure from Linear Trend (e)	P=0.013		
Relative Risk (f)		Infinite	--
Lower Limit		0.601	--
Upper Limit		Infinite	--
Weeks to First Observed Tumor (g)	--	97	--
Hematopoietic System: Lymphoma (b)	7/50 (14)	4/50 (8)	2/50 (4)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.571	0.286
Lower Limit		0.130	0.030
Upper Limit		2.099	1.411
Weeks to First Observed Tumor	93	56	104
Liver: Hepatocellular Carcinoma or Neoplastic Nodule (b)	1/48 (2)	4/49 (8)	4/50 (8)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		3.918	3.840
Lower Limit		0.407	0.399
Upper Limit		188.792	185.140
Weeks to First Observed Tumor	106	105	105
Pituitary: Chromophobe Carcinoma or Adenoma (b)	3/41 (7)	3/45 (7)	6/49 (12)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.911	1.673
Lower Limit		0.129	0.384
Upper Limit		6.456	9.806
Weeks to First Observed Tumor	107	100	97

Table 3. Analyses of the Incidence of Primary Tumors in Male Rats Administered Cinnamyl Anthranilate in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Pancreas: Acinar-cell Carcinoma or Adenoma (b)	0/42 (0)	0/49 (0)	3/45 (7)
P Values (c,d)	P=0.038	--	N.S.
Relative Risk (f)		--	Infinite
Lower Limit		--	0.564
Upper Limit		--	Infinite
Weeks to First Observed Tumor	--	--	63
Adrenal: Pheochromocytoma (b)	6/47 (13)	5/50 (10)	8/50 (16)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.783	1.253
Lower Limit		0.202	0.414
Upper Limit		2.876	4.065
Weeks to First Observed Tumor	44	105	97
Thryoid: C-cell Adenoma (b)	2/42 (5)	2/46 (4)	4/46 (9)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.913	1.826
Lower Limit		0.069	0.277
Upper Limit		12.121	19.380
Weeks to First Observed Tumor	100	105	105
Pancreatic Islets: Islet-cell Adenoma (b)	2/42 (5)	0/49 (0)	1/45 (2)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.000	0.467
Lower Limit		0.000	0.008
Upper Limit		2.894	8.634
Weeks to First Observed Tumor	93	--	105

Table 3. Analyses of the Incidence of Primary Tumors in Male Rats Administered Cinnamyl Anthranilate in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Kidney/Cortex: Adenocarcinoma, NOS or Adenoma, NOS (b)	0/48 (0)	0/50 (0)	4/49 (8)
P Values (c,d)	P=0.015	--	N.S.
Relative Risk (f)		--	Infinite
Lower Limit		--	0.909
Upper Limit		--	Infinite
Weeks to First Observed Tumor	--	--	105
Mammary Gland: Fibroadenoma (b)	1/50 (2)	3/50 (6)	0/50 (0)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		3.000	0.000
Lower Limit		0.251	0.000
Upper Limit		154.270	18.658
Weeks To First Observed Tumor	106	79	--
Testis: Interstitial-cell Tumor or Malignant Interstitial-cell Tumor (b)	44/47 (94)	45/50 (90)	48/50 (96)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.961	1.025
Lower Limit		0.867	0.930
Upper Limit		1.098	1.106
Weeks to First Observed Tumor	71	79	83
Abdominal Cavity/Peritoneum: Malignant Mesothelioma (b)	0/50 (0)	1/50 (2)	4/50 (8)
P Values (c,d)	P=0.026	N.S.	N.S.
Relative Risk (f)		Infinite	Infinite
Lower Limit		0.054	0.927
Upper Limit		Infinite	Infinite
Weeks to First Observed Tumor	--	98	83

Table 3. Analyses of the Incidence of Primary Tumors in Male Rats
Administered Cinnamyl Anthranilate in the Diet (a)

(continued)

(a) Dosed groups received 15,000 or 30,000 ppm.
(b) Number of tumor-bearing animals/number of animals examined at site (percent).
(c) Beneath the incidence of tumors in the control group is the probability level for the Cochran-Armitage test when P is less than 0.05; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a dosed group is the probability level for the Fisher exact test for the comparison of that dosed group with the matched-control group when P is less than 0.05; otherwise not significant (N.S.) is indicated.
(d) A negative trend (N) indicates a lower incidence in a dosed group than in a control group.
(e) The probability level for departure from linear trend is given when P is less than 0.05 for any comparison.
(f) The 95% confidence interval of the relative risk between each dosed group and the control group.
(g) Week to first observed tumor is based on time of death with tumor.

Table 4. Analyses of the Incidence of Primary Tumors in Female Rats Administered Cinnamyl Anthranilate in the Diet (a)

Topography: Morphology	Matched Control	Low Dose	High Dose
Hematopoietic System: Lymphoma (b)	5/48 (10)	1/50 (2)	0/50 (0)
P Values (c,d)	P=0.010 (N)	N.S.	P=0.025 (N)
Relative Risk (f)		0.192	0.000
Lower Limit		0.004	0.000
Upper Limit		1.630	0.761
Weeks to First Observed Tumor	93	100	--
Pituitary: Chromophobe Adenoma (b)	20/46 (43)	13/46 (28)	14/45 (31)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.650	0.716
Lower Limit		0.343	0.387
Upper Limit		1.198	1.293
Weeks to First Observed Tumor	94	105	71
Thyroid: C-cell Adenoma (b)	2/46 (4)	3/45 (7)	0/48 (0)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.533	0.000
Lower Limit		0.184	0.000
Upper Limit		17.643	3.236
Weeks to First Observed Tumor	107	103	--
Mammary Gland: Fibroadenoma (b)	8/48 (17)	6/50 (12)	5/50 (10)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.720	0.600
Lower Limit		0.222	0.166
Upper Limit		2.187	1.928
Weeks to First Observed Tumor	94	105	94

Table 4. Analyses of the Incidence of Primary Tumors in Female Rats Administered Cinnamyl Anthranilate in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Uterus: Endometrial Stromal Polyp (b)	2/47 (4)	16/50 (32)	9/50 (18)
P Values (c,d)	N.S.	P is less than 0.001	P=0.032
Departure from Linear Trend (e)	P=0.002		
Relative Risk (f)		7.520	4.230
Lower Limit		1.913	0.938
Upper Limit		64.215	38.600
Weeks to First Observed Tumor	93	103	106

(a) Dosed groups received 15,000 or 30,000 ppm.
(b) Number of tumor-bearing animals/number of animals examined at site (percent).
(c) Beneath the incidence of tumors in the control group is the probability level for the Cochran-Armitage test when P is less than 0.05; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a dosed group is the probability level for the Fisher exact test for the comparison of that dosed group with the matched-control group when P is less than 0.05; otherwise not significant (N.S.) is indicated.
(d) A negative trend (N) indicates a lower incidence in a dosed group than in a control group.
(e) The probability level for departure from linear trend is given when P is less than 0.05 for any comparison.
(f) The 95% confidence interval of the relative risk between each dosed group and the control group.

IV. RESULTS - MICE

A. Body Weights and Clinical Signs (Mice)

Dose-related reductions in mean body weight gain occurred in all groups of dosed male and female mice (Figure 3). Other clinical signs that could clearly be related to administration of the test chemical were not observed.

B. Survival (Mice)

Estimates of the probabilities of survival for male and female mice fed cinnamyl anthranilate at the doses of this bioassay, together with those for the matched controls, are shown by the Kaplan and Meier curves in Figure 4. The result of the Tarone test for dose-related trend in mortality is not significant in either sex.

In male mice, 40/50 (80%) of the high-dose, 41/50 (82%) of the low-dose, and 44/50 (88%) of the control groups lived to the end of the bioassay, and in females, 37/50 (74%) of the high-dose, 41/50 (82%) of the low-dose, and 39/50 (78%) of the control groups lived to the end of the bioassay. Dosed animals were killed at weeks 105 or 106; controls were killed at weeks 106 or 107.

C. Pathology (Mice)

Histopathologic findings on neoplasms in mice are summarized in Appendix B, Tables B1 and B2; findings on nonneoplastic lesions are summarized in Appendix D, Tables D1 and D2. Incidences of hepatocellular carcinomas or adenomas are presented in Table 5.

The hepatocellular carcinomas were usually of the trabecular type; six metastasized to the lung in the females (one low-dose, five high-dose). Four high-dose males and two low-dose females were diagnosed as having both adenomas and carcinomas. In Table 5, they are recorded under carcinomas only. Other neoplastic lesions found were similar to those which occurred in aging B6C3F1 mice not intentionally exposed to the chemical.

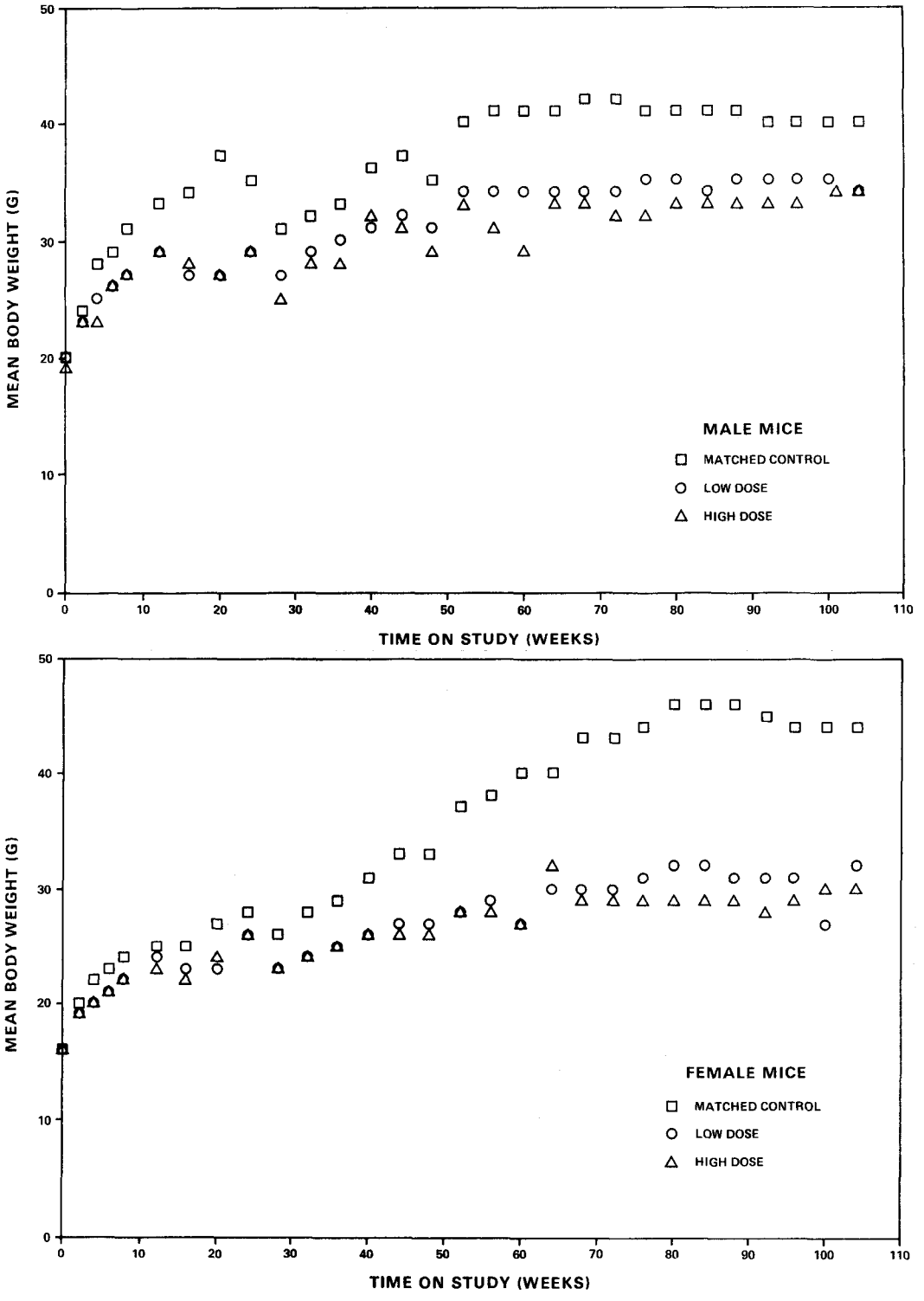


Figure 3. Growth Curves for Mice Administered Cinnamyl Anthranilate in the Diet

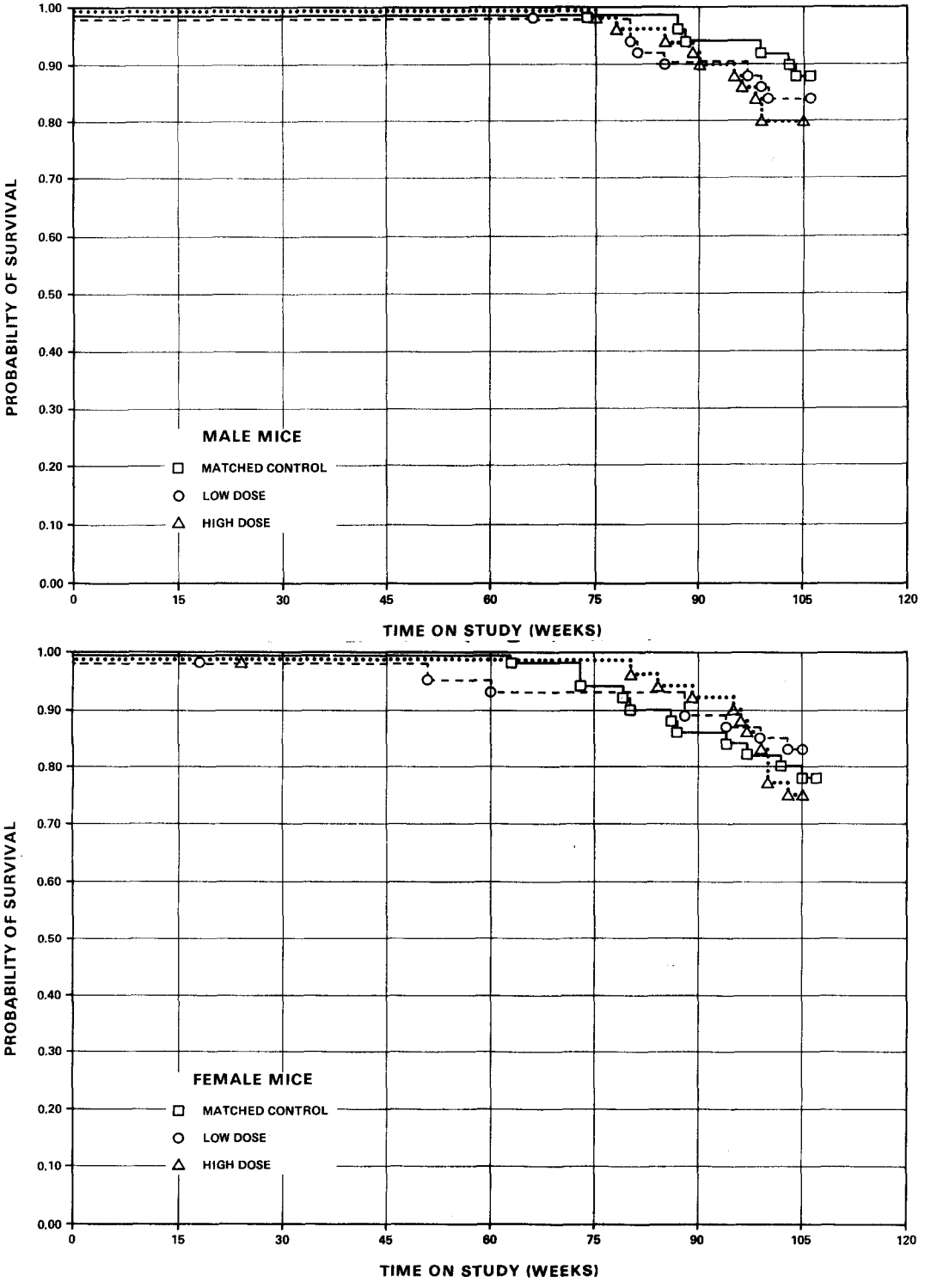


Figure 4. Survival Curves for Mice Administered Cinnamyl Anthranilate in the Diet

Table 5. Incidence of Hepatocellular Carcinomas or Adenomas in Mice Administered Cinnamyl Anthranilate in the Diet

	Males			Females		
Morphology	Control	Low Dose	High Dose	Control	Low Dose	High Dose
Hepatocellular Carcinomas	6/48(13%)	7/50(14%)	12/47(26%)	1/50(2%)	8/49(16%)	14/49(29%)
Hepatocellular Adenomas	8/48(16%)	23/50(46%)	25/47(53%)	2/50(4%)	12/49(25%)	19/49(38%)
Hepatocellular Carcinomas or Adenomas	14/48(29%)	30/50(60%)	37/47(79%)	3/50(6%)	20/49(41%)	33/49(67%)

Pigmentation of hepatocytes and Kupffer's cells occurred primarily in dosed mice. The lesion appeared as bile pigment in hepatocytes and as aging pigment in Kupffer's cells and was recorded as "hemosiderosis"; however, definitive identification by the use of special stains was not accomplished. Other nonneoplastic lesions observed among control and dosed groups of animals were similar to those commonly observed in aging B6C3F1 mice and were without relationship to administration of the test chemical.

The histopathologic examination provided evidence that cinnamyl anthranilate was carcinogenic, causing an increased incidence of hepatocellular carcinomas and adenomas in mice of each sex under the conditions of this bioassay.

D. Statistical Analyses of Results (Mice)

Tables 6 and 7 contain the statistical analyses of the incidences of those primary tumors that occurred in at least two animals of one group and at an incidence of at least 5% in one or more than one group.

In both sexes, the incidence of mice with either hepatocellular carcinomas or adenomas of the liver was found to have a significant (P less than 0.001) linear trend using the Cochran-Armitage test. The Fisher exact test shows that the incidence of these liver tumors in each dosed group is significantly higher than that in the control group (P=0.002 in low-dose males and P less than 0.001 in low-dose females and in high-dose groups of each sex). The incidences of male animals with these tumors in the high-dose (37/47, 79%) and in the low-dose (30/50, 60%) groups are higher than the 112/257 (47%) observed in the male controls in bioassays of 105 to 110 weeks duration at this laboratory. The incidence of this tumor in female control mice over 105 weeks old in these bioassays was 37/273 (14%) as compared with 20/49 (41%) and 33/49 (67%) in the low- and high-dose groups in this study. The statistical conclusion is that the incidence of liver tumors in male and female mice is related to the administration of cinnamyl anthranilate.

Significant results in the negative direction were observed in the incidence of lymphomas in female mice in which a significant decreasing incidence (P less than 0.001) with increased dosage was determined.

Table 6. Analyses of the Incidence of Primary Tumors in Male Mice Administered Cinnamyl Anthranilate in the Diet (a)

Topography: Morphology	Matched Control	Low Dose	High Dose
Lung: Alveolar/Bronchiolar Carcinoma (b)	3/48 (6)	1/50 (2)	0/47 (0)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.320	0.000
Lower Limit		0.006	0.000
Upper Limit		3.823	1.695
Weeks to First Observed Tumor	106	106	--
Lung: Alveolar/Bronchiolar Carcinoma or Adenoma (b)	7/48 (15)	8/50 (16)	4/47 (9)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.097	0.584
Lower Limit		0.378	0.133
Upper Limit		3.283	2.135
Weeks to First Observed Tumor	103	105	85
Hematopoietic System: Lymphoma (b)	4/48 (8)	6/50 (12)	5/48 (10)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.440	1.250
Lower Limit		0.365	0.287
Upper Limit		6.543	5.939
Weeks to First Observed Tumor	88	80	78
All Sites: Hemangioma or Hemangiosarcoma (b)	3/48 (6)	2/50 (4)	4/48 (8)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.640	1.333
Lower Limit		0.055	0.238
Upper Limit		5.345	8.665
Weeks to First Observed Tumor	106	99	85

Table 6. Analyses of the Incidence of Primary Tumors in Male Mice Administered Cinnamyl Anthranilate in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Liver: Hepatocellular Carcinoma (b)	6/48 (13)	7/50 (14)	12/47 (26)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.120	2.043
Lower Limit		0.348	0.779
Upper Limit		3.751	6.082
Weeks to First Observed Tumor	104	80	75
Liver: Hepatocellular Carcinoma or Adenoma (b)	14/48 (29)	30/50 (60)	37/47 (79)
P Values (c,d)	P is less than 0.001	P=0.002	P is less than 0.001
Relative Risk (f)		2.057	2.699
Lower Limit		1.230	1.714
Upper Limit		3.536	4.167
Weeks to First Observed Tumor	104	80	75
Thyroid: Follicular-cell Adenoma (b)	0/41 (0)	2/40 (5)	0/39 (0)
P Values (c,d)	N.S.	N.S.	--
Departure from Linear Trend (e)	P=0.044		
Relative Risk (f)		Infinite	--
Lower Limit		0.305	--
Upper Limit		Infinite	--
Weeks To First Observed Tumor	--	80	--

(a) Dosed groups received 15,000 or 30,000 ppm.
(b) Number of tumor-bearing animals/number of animals examined at site (percent).
(c) Beneath the incidence of tumors in the control group is the probability level for the Cochran-Armitage test when P is less than 0.05; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a dosed group is the probability level for the Fisher exact test for the comparison of that dosed group with the matched-control group when P is less than 0.05; otherwise not significant (N.S.) is indicated.
(d) A negative trend (N) indicates a lower incidence in a dosed group than in a control group.
(e) The probability level for departure from linear trend is given when P is less than 0.05 for any comparison.
(f) The 95% confidence interval of the relative risk between each dosed group and the control group.

Table 7. Analyses of the Incidence of Primary Tumors in Female Mice Administered Cinnamyl Anthranilate in the Diet (a)

Topography: Morphology	Matched Control	Low Dose	High Dose
Lung: Alveolar/Bronchiolar Carcinoma (b)	3/50 (6)	2/49 (4)	1/48 (2)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.680	0.347
Lower Limit		0.059	0.007
Upper Limit		5.680	4.143
Weeks to First Observed Tumor	107	105	105
Lung: Alveolar/Bronchiolar Carcinoma or Adenoma (b)	6/50 (12)	4/49 (8)	2/48 (4)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.680	0.347
Lower Limit		0.150	0.036
Upper Limit		2.686	1.829
Weeks to First Observed Tumor	106	105	105
Hematopoietic System: Lymphoma (b)	18/50 (36)	9/49 (18)	3/49 (6)
P Values (c,d)	P is less than 0.001 (N)	P=0.040 (N)	P is less than 0.001 (N)
Relative Risk (f)		0.510	0.170
Lower Limit		0.225	0.034
Upper Limit		1.070	0.534
Weeks to First Observed Tumor	73	88	97
All Sites: Hemangioma or Hemangiosarcoma (b)	4/50 (8)	4/49 (8)	4/49 (8)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.020	1.020
Lower Limit		0.201	0.201
Upper Limit		5.183	5.183
Weeks to First Observed Tumor	80	99	99

Table 7. Analyses of the Incidence of Primary Tumors in Female Mice Administered Cinnamyl Anthranilate in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Liver: Hepatocellular Carcinoma (b)	1/50 (2)	8/49 (16)	14/49 (29)
P Values (c,d)	P is less than 0.001	P=0.014	P is less than 0.001
Relative Risk (f)		8.163	14.286
Lower Limit		1.160	2.322
Upper Limit		353.685	587.279
Weeks to First Observed Tumor	106	60	84
Liver: Hepatocellular Carcinoma or Adenoma (b)	3/50 (6)	20/49 (41)	33/49 (67)
P Values (c,d)	P is less than 0.001	P is less than 0.001	P is less than 0.001
Relative Risk (f)		6.803	11.224
Lower Limit		2.207	3.958
Upper Limit		33.292	50.694
Weeks to First Observed Tumor	106	60	84
Pituitary: Chromophobe Adenoma (b)	2/44 (5)	0/41 (0)	0/38 (0)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.000	0.000
Lower Limit		0.000	0.000
Upper Limit		3.607	3.883
Weeks to First Observed Tumor	106	--	--

(a) Dosed groups received 15,000 or 30,000 ppm.
(b) Number of tumor-bearing animals/number of animals examined at site (percent).
(c) Beneath the incidence of tumors in the control group is the probability level for the Cochran-Armitage test when P is less than 0.05; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a dosed group is the probability level for the Fisher exact test for the comparison of that dosed group with the matched-control group when P is less than 0.05; otherwise not significant (N.S.) is indicated.
(d) A negative trend (N) indicates a lower incidence in a dosed group than in a control group.
(e) The probability level for departure from linear trend is given when P is less than 0.05 for any comparison.
(f) The 95% confidence interval of the relative risk between each dosed group and the control group.

V. DISCUSSION

Dose-related reductions in mean body weight gain occurred, but mortality was not affected by administration of the test chemical to the test groups of both species. Sufficient numbers of rats and mice in the dosed and control groups were at risk for the development of late-appearing tumors.

In male rats, renal adenomas or carcinomas occurred in the high-dose group at an incidence (4/49, 8%) that was dose-related (P=0.015), but this incidence was not statistically significant. No renal neoplasms were found in the matched controls or low-dose male rats. In addition, acinar-cell tumors of the pancreas occurred in high-dose males (3/45, 7%). It is to be noted that acinar-cell adenomas or carcinomas of the pancreas are considered to be rare tumors, and therefore the incidences are considered to be related to the administration of the test chemical.

The renal neoplasms in male rats and the nephrotoxicity noted in female and male rats receiving cinnamyl anthranilate are similar to the results obtained after exposure of Osborne-Mendel rats to chloroform (NCI, 1976) and chlorothalonil (NCI, TR 41 1978). Renal tubular-cell tumors were observed in 12/50 high-dose chloroform-treated males and in 4/49 high-dose chlorothalonil-treated males, while none was seen in controls. In addition, nephrotoxicity was demonstrated after acute or chronic exposure to each of the chemicals. Other chemicals, primarily heavy metals, are known to induce toxic and neoplastic renal lesions (Payne and Saunders, 1978).

Hepatocellular carcinomas or adenomas occurred in both male and female mice at incidences that were dose related (P less than 0.001) and significantly higher than controls (P less than or equal to 0.001). When compared with historical-control mice which were on study for 105 to 110 weeks at the same laboratory, the incidences of liver tumors in dosed mice were still higher (male mice: historical-control, 112/257 (47%); low-dose, 30/50 (60%); high-dose, 37/47 (79%); and female mice: historical-control, 37/273 (14%); low-dose, 20/49 (41%); high-dose, 33/49 (67%). The presence of pulmonary metastases indicated the malignancy of some of the liver tumors.

Other chemicals, including chloroform (NCI, 1976) and tris(2,3-dibromopropyl) phosphate (NCI, TR 76 1978), cause liver tumors in mice. Similar pigmentation of Kupffer's cells detected in mice receiving cinnamyl anthranilate has been observed in livers of mice exposed to other carcinogens and toxins, including dioxins (McConnell et al., 1978).

Tumor induction has been related to administration of cinnamyl anthranilate by intraperitoneal injection to mice. Increased incidences of pulmonary adenomas have been reported in A/He mice following injections of anthranilate in tricaprylin three times per week for 8 weeks (Stoner et al., 1973). Pulmonary tumors were not induced in B6C3F1 mice in the feeding study described here.

It was concluded that, under the conditions of this bioassay, cinnamyl anthranilate was carcinogenic for male and female B6C3F1 mice, inducing increased incidences of hepatocellular adenomas or carcinomas. The test chemical was carcinogenic for male F344 rats, inducing rare tumors such as acinar-cell carcinomas or adenomas of the pancreas and adenomas or adenocarcinomas of the renal cortex. Cinnamyl anthranilate was not carcinogenic for female F344 rats.

VI. BIBLIOGRAPHY

Armitage, P., Statistical Methods in Medical Research, John Wiley & Sons, Inc., New York, 1971, pp. 362-365.

Berenblum, I., ed., Carcinogenicity Testing: A Report of the Panel of Carcinogenicity of the Cancer Research Commission of UICC, Vol. 2, International Union Against Cancer, Geneva, 1969.

Code of Federal Regulations, 21 CFR 172.515, 1977.

Cox, D. R., Analysis of Binary Data, Methuen & Co., Ltd., London, 1970, pp. 48-52.

Cox, D. R., Regression models and life tables. J. R. Statist. Soc. B34:187-220, 1972.

Fears, T. R., Tarone, R. E., and Chu, K. C., False-positive and false-negative rates for carcinogenicity screens. Cancer Res. 37:1941-1945, 1977.

Food Chemicals Codex, 2nd Edition, National Academy of Sciences, Washington, D. C., 1972.

Furia, T. E. and Bellanca, N., eds., CRC Fenaroli's Handbook of Flavor Ingredients, Chemical Rubber Co., Cleveland, Ohio, 1971, p. 332.

Gart, J. J., The comparison of proportions: a review of significance tests, confidence limits and adjustments for stratification., Rev. Int. Stat. Inst. 39:148-169, 1971.

Hall, R. L. and Oser, B. L., Recent progress in the consideration of flavoring ingredients under the food additives amendment. III GRAS substances. Food Technology 19:151-155, 1965.

Kaplan, E. L. and Meier, P., Nonparametric estimation from incomplete observations. J. Amer. Statist. Assoc. 53:457-481, 1958.

Linhart, M. S., Cooper, J. A., Martin, R. L., Page, N. P., and Peters, J. A., Carcinogenesis bioassay data system. Comp. and Biomed. Res. 7:230-248, 1974.

McConnell, E. E., Moore, J. A., Haseman, J. K., and Harris, M. W., The comparative toxicity of chlorinated dibenzo-p-dioxins in mice and guinea pigs. Toxicol. Appl. Pharmacol. 44:335-356, 1978.

Meyer, L., Food Chemistry, Reinhold Publishing Co., New York, 1960, p. 164.

Miller, R. G., Jr., Simultaneous Statistical Inference, McGraw-Hill Book Co., New York, 1966, pp. 6-10.

Moreno, O. M., Report to RIFM, 22 August 1974. Cited in Opdyke, D.L.J., Cinnamyl anthranilate. Fd. Cosmet. Toxicol. 13:751-752, 1975.

NCI, National Cancer Institute, Report on Carcinogenesis Bioassay of Chloroform, NTIS PB No. 264018/AS, 1976.

NCI, National Cancer Institute, Bioassay of Chlorothalonil, Technical Report No. 41, DHEW Publication No. (NIH) 78-841, U. S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, Bethesda, Md., 1978.

NCI, National Cancer Institute, Bioassay of Tris(2,3-dibromopropyl) phosphate, Technical Report No. 76, DHEW Publication No. (NIH) 78-1326, U. S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, Bethesda, Md., 1978.

Opdyke, D. L. J., Cinnamyl anthranilate. Fd. Cosmet. Toxicol. 13:751-752, 1975.

Payne, B. J. and Saunders, L. Z., Heavy metal nephropathy of rodents. Vet. Path. 15 (Suppl. 5):51-87, 1978.

Stoner, G. D., Shimkin, M. B., Kniazeff, A. J., Weisburger, J. H., Weisburger, E. K., Gori, G. B., Test for carcinogenicity of food additives and chemotherapeutic agents by the pulmonary tumor response in strain A mice. Cancer Res. 33:3069-3085, 1973.

Swaine, R. L., Natural and synthetic flavorings. In: CRC Handbook of Food Additives, Furia, T. E., ed., CRC Press, Cleveland, Ohio, 1972, pp. 460-461, 474, and 492.

Tarone, R. E., Tests for trend in life table analysis. Biometrika 62:679-682, 1975.

United States International Trade Commission, Synthetic Organic Chemicals-United States Production and Sales, 1976, USITC Publication 833, U.S. Government Printing Office, Washington D.C., 1977.

Ward, J. M., Goodman, D. G., Griesemer, R. A., Hardisty, J. F., Schueler, R. L., Squire, R. A., and Strandberg, J. D., Quality assurance for pathology in rodent carcinogenesis tests. J. Environ. Pathol. Toxicol. 2:371-378, 1978.

APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS ADMINISTERED CINNAMYL ANTHRANILATE IN THE DIET

TABLE A1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS ADMINISTERED CINNAMYL ANTHRANILATE IN THE DIET

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	48	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA	1 (2%)		
KERATOACANTHOMA		1 (2%)	1 (2%)
*SUBCUT TISSUE	(50)	(50)	(50)
FIBROMA		3 (6%)	
RESPIRATORY SYSTEM			
#LUNG	(48)	(50)	(50)
ALVEOLAR/BRONCHIOLAR ADENOMA		1 (2%)	1 (2%)
ALVEOLAR/BRONCHIOLAR CARCINOMA		1 (2%)	
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
MALIGNANT LYMPHOMA, NOS	6 (12%)	4 (8%)	2 (4%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (2%)		
#SPLEEN	(48)	(49)	(49)
FIBROMA			1 (2%)
CIRCULATORY SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
HEMANGIOSARCOMA, METASTATIC			1 (2%)
#LUNG	(48)	(50)	(50)
HEMANGIOSARCOMA	1 (2%)		
#KIDNEY	(48)	(50)	(49)
HEMANGIOSARCOMA			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
DIGESTIVE SYSTEM			
#LIVER	(48)	(49)	(50)
NEOPLASTIC NODULE	1 (2%)	2 (4%)	2 (4%)
HEPATOCELLULAR CARCINOMA		2 (4%)	2 (4%)
#PANCREAS	(42)	(49)	(45)
ACINAR-CELL ADENOMA			2 (4%)
ACINAR-CELL CARCINOMA			1 (2%)
#STOMACH	(47)	(49)	(50)
MESOTHELIOMA, METASTATIC			1 (2%)
URINARY SYSTEM			
#KIDNEY/CORTEX	(48)	(50)	(49)
ADENOMA, NOS			2 (4%)
ADENOCARCINOMA, NOS			2 (4%)
ENDOCRINE SYSTEM			
#PITUITARY	(41)	(45)	(49)
ADENOMA, NOS		1 (2%)	
ADENOCARCINOMA, NOS			1 (2%)
CHROMOPHOBE ADENOMA	3 (7%)	3 (7%)	4 (8%)
CHROMOPHOBE CARCINOMA			2 (4%)
#ADRENAL	(47)	(50)	(50)
ADENOCARCINOMA, NOS		1 (2%)	
CORTICAL ADENOMA	1 (2%)		
CORTICAL CARCINOMA	1 (2%)	1 (2%)	
PHEOCHROMOCYTOMA	6 (13%)	5 (10%)	8 (16%)
#ADRENAL MEDULLA	(47)	(50)	(50)
CARCINOMA,NOS			1 (2%)
ADENOCARCINOMA, NOS			1 (2%)
#THYROID	(42)	(46)	(46)
FOLLICULAR-CELL CARCINOMA	1 (2%)		
C-CELL ADENOMA	2 (5%)	2 (4%)	4 (9%)
#THYROID FOLLICLE	(42)	(46)	(46)
CYSTADENOCARCINOMA, NOS			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
PAPILLARY CYSTADENOCARCINOMA,NOS			1 (2%)
#PANCREATIC ISLETS	(42)	(49)	(45)
ISLET-CELL ADENOMA	2 (5%)		1 (2%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
FIBROADENOMA	1 (2%)	3 (6%)	
*PREPUTIAL GLAND	(50)	(50)	(50)
CARCINOMA,NOS	1 (2%)		
ADENOMA, NOS			1 (2%)
#PROSTATE	(45)	(49)	(48)
ACINAR-CELL ADENOMA		1 (2%)	
#TESTIS	(47)	(50)	(50)
INTERSTITIAL-CELL TUMOR		2 (4%)	
INTERSTITIAL-CELL TUMOR, MALIGNA	44 (94%)	43 (86%)	48 (96%)
#TUNICA ALBUGINEA	(47)	(50)	(50)
ACINAR-CELL CARCINOMA, METASTATI			1 (2%)
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*ABDOMINAL CAVITY	(50)	(50)	(50)
ADENOCARCINOMA, NOS		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
MESOTHELIOMA, MALIGNANT			4 (8%)
*PERITONEUM	(50)	(50)	(50)
MESOTHELIOMA, MALIGNANT		1 (2%)	
*TUNICA VAGINALIS	(50)	(50)	(50)
MESOTHELIOMA, METASTATIC			1 (2%)
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
ADENOCARCINOMA, NOS, METASTATIC		1 (2%)	
ACINAR-CELL CARCINOMA, METASTATI			1 (2%)
MESOTHELIOMA, METASTATIC		1 (2%)	3 (6%)
ADIPOSE TISSUE			
LIPOMA	1	1	
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	12	2	6
MORIBUND SACRIFICE	6	8	4
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	32	40	40
ANIMAL MISSING			

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	47	50	50
TOTAL PRIMARY TUMORS	73	79	94
TOTAL ANIMALS WITH BENIGN TUMORS	15	20	19
TOTAL BENIGN TUMORS	16	23	25
TOTAL ANIMALS WITH MALIGNANT TUMORS	45	46	50
TOTAL MALIGNANT TUMORS	56	54	67
TOTAL ANIMALS WITH SECONDARY TUMORS#		2	6
TOTAL SECONDARY TUMORS		2	8
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	1	2	2
TOTAL UNCERTAIN TUMORS	1	2	2
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 A2.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS ADMINISTERED CINNAMYL ANTHRANILATE IN THE DIET

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	48	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	48	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(48)	(50)	(50)
SQUAMOUS CELL CARCINOMA		1 (2%)	
KERATOACANTHOMA	1 (2%)		
FIBROMA	1 (2%)		
*SUBCUT TISSUE	(48)	(50)	(50)
FIBROMA		1 (2%)	
LIPOSARCOMA	1 (2%)		
RESPIRATORY SYSTEM			
#LUNG	(47)	(50)	(50)
ALVEOLAR/BRONCHIOLAR ADENOMA			2 (4%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(48)	(50)	(50)
MALIGNANT LYMPHOMA, NOS	4 (8%)	1 (2%)	
#SPLEEN	(47)	(50)	(50)
MALIGNANT LYMPHOMA, NOS	1 (2%)		
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(46)	(50)	(50)
HEPATOCELLULAR ADENOMA	1 (2%)	2 (4%)	

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
NEOPLASTIC NODULE	1 (2%)		
URINARY SYSTEM			
#URINARY BLADDER	(46)	(49)	(49)
ADENOCARCINOMA, NOS			1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(46)	(46)	(45)
ADENOMA, NOS		1 (2%)	1 (2%)
ADENOCARCINOMA, NOS		2 (4%)	
CHROMOPHOBE ADENOMA	20 (43%)	13 (28%)	14 (31%)
#ADRENAL	(47)	(50)	(49)
CORTICAL ADENOMA	1 (2%)	1 (2%)	
PHEOCHROMOCYTOMA	1 (2%)	1 (2%)	1 (2%)
GANGLIONEUROMA			1 (2%)
#THYROID	(46)	(45)	(48)
C-CELL ADENOMA	2 (4%)	3 (7%)	
#THYROID FOLLICLE	(46)	(45)	(48)
PAPILLARY CYSTADENOMA, NOS			1 (2%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(48)	(50)	(50)
ADENOMA, NOS	1 (2%)		
CYSTADENOMA, NOS	1 (2%)		
FIBROADENOMA	8 (17%)	6 (12%)	5 (10%)
*CLITORAL GLAND	(48)	(50)	(50)
CARCINOMA,NOS		1 (2%)	
PAPILLOMA, NOS		1 (2%)	
SQUAMOUS CELL CARCINOMA		1 (2%)	
ADENOMA, NOS	2 (4%)		
#UTERUS	(47)	(50)	(50)
FIBROSARCOMA	1 (2%)		
LEIOMYOMA		1 (2%)	
ENDOMETRIAL STROMAL POLYP	2 (4%)	16 (32%)	9 (18%)
NERVOUS SYSTEM			
NONE			

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
*SKELETAL MUSCLE	(48)	(50)	(50)
RHABDOMYOSARCOMA		1 (2%)	
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	4	1	1
MORIBUND SACRIFICE	6	5	3
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	39	44	46
ANIMAL MISSING			

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	34	37	28
TOTAL PRIMARY TUMORS	49	53	35
TOTAL ANIMALS WITH BENIGN TUMORS	33	31	28
TOTAL BENIGN TUMORS	41	46	34
TOTAL ANIMALS WITH MALIGNANT TUMORS	7	7	1
TOTAL MALIGNANT TUMORS	7	7	1
TOTAL ANIMALS WITH SECONDARY TUMORS#			
TOTAL SECONDARY TUMORS			
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

APPENDIX B

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE ADMINISTERED CINNAMYL ANTHRANILATE IN THE DIET

TABLE B1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE ADMINISTERED CINNAMYL ANTHRANILATE IN THE DIET

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	48	50	48
ANIMALS EXAMINED HISTOPATHOLOGICALLY	48	50	47
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE	(48)	(50)	(48)
FIBROMA			1 (2%)
RESPIRATORY SYSTEM			
#LUNG	(48)	(50)	(47)
ALVEOLAR/BRONCHIOLAR ADENOMA	4 (8%)	7 (14%)	4 (9%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	3 (6%)	1 (2%)	
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(48)	(50)	(48)
MALIGNANT LYMPHOMA, NOS	3 (6%)	2 (4%)	1 (2%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)	
#SPLEEN	(47)	(46)	(44)
MALIGNANT LYMPHOMA, NOS	1 (2%)		
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)
#MESENTERIC L. NODE	(44)	(40)	(45)
MALIGNANT LYMPHOMA, NOS		2 (5%)	1 (2%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)
#LIVER	(48)	(50)	(47)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)	
#PEYERS PATCH	(46)	(47)	(45)
MALIGNANT LYMPHOMA, NOS			1 (2%)
CIRCULATORY SYSTEM			
*MULTIPLE ORGANS	(48)	(50)	(48)
HEMANGIOSARCOMA			1 (2%)

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
*SUBCUT TISSUE	(48)	(50)	(48)
HEMANGIOSARCOMA	1 (2%)		
#SPLEEN	(47)	(46)	(44)
HEMANGIOMA	1 (2%)		
HEMANGIOSARCOMA	1 (2%)	1 (2%)	
#MESENTERIC L. NODE	(44)	(40)	(45)
HEMANGIOSARCOMA			1 (2%)
#HEART	(48)	(50)	(47)
HEMANGIOMA	1 (2%)		
#LIVER	(48)	(50)	(47)
HEMANGIOMA		1 (2%)	1 (2%)
HEMANGIOSARCOMA		1 (2%)	1 (2%)
DIGESTIVE SYSTEM			
#LIVER	(48)	(50)	(47)
HEPATOCELLULAR ADENOMA	8 (17%)	23 (46%)	29 (62%)
HEPATOCELLULAR CARCINOMA	6 (13%)	7 (14%)	12 (26%)
FIBROMA		1 (2%)	
FIBROSARCOMA		1 (2%)	
#CARDIAC STOMACH	(46)	(47)	(44)
PAPILLOMA, NOS	1 (2%)		
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#THYROID	(41)	(40)	(39)
FOLLICULAR-CELL ADENOMA		2 (5%)	
PAPILLARY CYSTADENOMA, NOS			1 (3%)
REPRODUCTIVE SYSTEM			
*SEMINAL VESICLE	(48)	(50)	(48)
PAPILLARY ADENOMA	1 (2%)		

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*EYE/LACRIMAL GLAND	(48)	(50)	(48)
PAPILLARY ADENOMA		1 (2%)	
*HARDERIAN GLAND	(48)	(50)	(48)
PAPILLARY CYSTADENOMA, NOS		1 (2%)	
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATHa	6	3	8
MORIBUND SACRIFICE		6	2
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	44	41	40
ANIMAL MISSING			

a INCLUDES AUTOLYZED ANIMALS

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	22	39	40
TOTAL PRIMARY TUMORS	31	53	56
TOTAL ANIMALS WITH BENIGN TUMORS	13	29	32
TOTAL BENIGN TUMORS	16	36	36
TOTAL ANIMALS WITH MALIGNANT TUMORS	13	15	18
TOTAL MALIGNANT TUMORS	15	17	20
TOTAL ANIMALS WITH SECONDARY TUMORS#			
TOTAL SECONDARY TUMORS			
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 ADMINISTERED CINNAMYL ANTHRANILATE IN THE DIET

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS MISSING		1	1
ANIMALS NECROPSIED	50	49	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	49	49
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(49)	(49)
FIBROSARCOMA	1 (2%)		
*SUBCUT TISSUE	(50)	(49)	(49)
FIBROSARCOMA	2 (4%)		
LIPOSARCOMA	1 (2%)		
RESPIRATORY SYSTEM			
#LUNG	(50)	(49)	(48)
HEPATOCELLULAR CARCINOMA, METAST		1 (2%)	5 (10%)
ALVEOLAR/BRONCHIOLAR ADENOMA	3 (6%)	2 (4%)	1 (2%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	3 (6%)	2 (4%)	1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(49)	(49)
MALIGNANT LYMPHOMA, NOS	11 (22%)	6 (12%)	3 (6%)
#SPLEEN	(50)	(49)	(49)
MALIGNANT LYMPHOMA, NOS	5 (10%)		
#MESENTERIC L. NODE	(45)	(46)	(39)
MALIGNANT LYMPHOMA, NOS	1 (2%)	2 (4%)	
#THYMUS	(25)	(27)	(30)
MALIGNANT LYMPHOMA, NOS	1 (4%)	1 (4%)	
CIRCULATORY SYSTEM			
*SKIN	(50)	(49)	(49)
HEMANGIOMA		1 (2%)	

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
HEMANGIOSARCOMA	2 (4%)		
#SPLEEN	(50)	(49)	(49)
HEMANGIOSARCOMA	2 (4%)		
#MESENTERIC L. NODE	(45)	(46)	(39)
HEMANGIOSARCOMA			1 (3%)
#LIVER	(50)	(49)	(49)
HEMANGIOMA			1 (2%)
HEMANGIOSARCOMA, METASTATIC		1 (2%)	
#ILEUM	(48)	(48)	(48)
HEMANGIOSARCOMA		1 (2%)	
#URINARY BLADDER	(47)	(46)	(48)
HEMANGIOMA		1 (2%)	
#UTERUS	(50)	(48)	(47)
HEMANGIOMA			1 (2%)
HEMANGIOSARCOMA		1 (2%)	
#OVARY	(44)	(46)	(36)
HEMANGIOMA	1 (2%)		1 (3%)
DIGESTIVE SYSTEM			
#LIVER	(50)	(49)	(49)
HEPATOCELLULAR ADENOMA	2 (4%)	14 (29%)	19 (39%)
HEPATOCELLULAR CARCINOMA	1 (2%)	8 (16%)	14 (29%)
#PANCREATIC DUCT	(48)	(46)	(45)
ADENOCARCINOMA, NOS	1 (2%)		
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#PITUITARY	(44)	(41)	(38)
ADENOMA, NOS	1 (2%)		

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
CHROMOPHOBE ADENOMA	2 (5%)		
#THYROID	(43)	(40)	(43)
FOLLICULAR-CELL ADENOMA	1 (2%)		
#THYROID FOLLICLE	(43)	(40)	(43)
PAPILLARY CYSTADENOMA, NOS	1 (2%)		
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(49)	(49)
ADENOCARCINOMA, NOS	2 (4%)		
FIBROADENOMA		1 (2%)	
#UTERUS	(50)	(48)	(47)
FIBROSARCOMA		1 (2%)	
LEIOMYOSARCOMA	1 (2%)		
ENDOMETRIAL STROMAL POLYP		1 (2%)	
#OVARY	(44)	(46)	(36)
PAPILLARY ADENOMA			1 (3%)
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*HARDERIAN GLAND	(50)	(49)	(49)
PAPILLARY ADENOMA	1 (2%)		
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	7	5	6
MORIBUND SACRIFICE	4	3	6
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	39	41	37
ANIMAL MISSING		1	1
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	32	30	36
TOTAL PRIMARY TUMORS	46	42	43
TOTAL ANIMALS WITH BENIGN TUMORS	11	18	22
TOTAL BENIGN TUMORS	12	20	24
TOTAL ANIMALS WITH MALIGNANT TUMORS	25	19	16
TOTAL MALIGNANT TUMORS	34	22	19
TOTAL ANIMALS WITH SECONDARY TUMORS#		2	5
TOTAL SECONDARY TUMORS		2	5
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

APPENDIX C

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS ADMINISTERED CINNAMYL ANTHRANILATE IN THE DIET

TABLE C1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS ADMINISTERED CINNAMYL ANTHRANILATE IN THE DIET

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	48	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
CYST, NOS	1 (2%)		
EPIDERMAL INCLUSION CYST	1 (2%)	1 (2%)	
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)		
ABSCESS, CHRONIC	1 (2%)		
RESPIRATORY SYSTEM			
#TRACHEA	(46)	(49)	(48)
INFLAMMATION, CHRONIC	8 (17%)		1 (2%)
#LUNG	(48)	(50)	(50)
HEMORRHAGE		1 (2%)	
PNEUMONIA, CHRONIC MURINE	8 (17%)	5 (10%)	4 (8%)
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(38)	(45)	(48)
APLASIA, HEMATOPOIETIC	1 (3%)	1 (2%)	2 (4%)
#SPLEEN	(48)	(49)	(49)
CONGESTION, NOS	4 (8%)	1 (2%)	
INFLAMMATION, ACUTE	1 (2%)		
INFARCT, NOS		1 (2%)	
PIGMENTATION, NOS			1 (2%)
HEMOSIDEROSIS	1 (2%)	1 (2%)	1 (2%)
ATROPHY, NOS		1 (2%)	3 (6%)
HYPERPLASIA, RETICULUM CELL		1 (2%)	
HYPERPLASIA, LYMPHOID	2 (4%)		
HEMATOPOIESIS	1 (2%)	1 (2%)	
MYELOID METAPLASIA	1 (2%)		

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
#LYMPH NODE	(43)	(45)	(48)
HYPERPLASIA, RETICULUM CELL	1 (2%)		
HYPERPLASIA, LYMPHOID	2 (5%)		
#MANDIBULAR L. NODE	(43)	(45)	(48)
HYPERPLASIA, LYMPHOID	3 (7%)		
#MESENTERIC L. NODE	(43)	(45)	(48)
CONGESTION, NOS		1 (2%)	
HEMORRHAGE			3 (6%)
HEMOSIDEROSIS		1 (2%)	
ATROPHY, NOS	1 (2%)	1 (2%)	4 (8%)
ERYTHROPHAGOCYTOSIS		2 (4%)	
HYPERPLASIA, RETICULUM CELL		1 (2%)	
HYPERPLASIA, LYMPHOID			1 (2%)
#LUNG/BRONCHUS	(48)	(50)	(50)
HYPERPLASIA, LYMPHOID			1 (2%)
#LIVER	(48)	(49)	(50)
LEUKOCYTOSIS, NOS	1 (2%)		
HEMATOPOIESIS	4 (8%)		
#THYMUS	(31)	(30)	(25)
ATROPHY, NOS	31 (100%)	30 (100%)	25 (100%)
CIRCULATORY SYSTEM			
#MANDIBULAR L. NODE	(43)	(45)	(48)
LYMPHANGIECTASIS	2 (5%)	1 (2%)	
#MESENTERIC L. NODE	(43)	(45)	(48)
LYMPHANGIECTASIS	2 (5%)	1 (2%)	6 (13%)
#HEART	(48)	(50)	(50)
THROMBOSIS, NOS			1 (2%)
#HEART/ATRIUM	(48)	(50)	(50)
THROMBOSIS, NOS			2 (4%)
#MYOCARDIUM	(48)	(50)	(50)
INFLAMMATION, CHRONIC	45 (94%)	29 (58%)	34 (68%)
#PANCREAS	(42)	(49)	(45)
PERIARTERITIS	2 (5%)	1 (2%)	

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
*MESENTERY	(50)	(50)	(50)
PERIARTERITIS			1 (2%)
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(43)	(50)	(48)
INFLAMMATION, CHRONIC	6 (14%)		
#LIVER	(48)	(49)	(50)
CHOLANGIOFIBROSIS	1 (2%)	1 (2%)	
NECROSIS, NOS	6 (13%)	1 (2%)	1 (2%)
METAMORPHOSIS FATTY	2 (4%)		
LIPOIDOSIS	2 (4%)	1 (2%)	1 (2%)
FOCAL CELLULAR CHANGE	4 (8%)		2 (4%)
HYPERTROPHY, NOS	1 (2%)		
HYPERPLASIA, NOS	3 (6%)	1 (2%)	1 (2%)
ANGIECTASIS	3 (6%)	1 (2%)	
#LIVER/CENTRILOBULAR	(48)	(49)	(50)
CONGESTION, NOS	1 (2%)		1 (2%)
DEGENERATION, NOS			1 (2%)
NECROSIS, NOS	1 (2%)		1 (2%)
#LIVER/HEPATOCYTES	(48)	(49)	(50)
ATROPHY, NOS			1 (2%)
#BILE DUCT	(48)	(49)	(50)
CYST, NOS		1 (2%)	
HYPERPLASIA, NOS	27 (56%)	18 (37%)	16 (32%)
#PANCREAS	(42)	(49)	(45)
INFLAMMATION, CHRONIC	5 (12%)	2 (4%)	
ATROPHY, NOS			1 (2%)
#PANCREATIC ACINUS	(42)	(49)	(45)
ATROPHY, NOS	2 (5%)	9 (18%)	2 (4%)
#STOMACH	(47)	(49)	(50)
ULCER, ACUTE	1 (2%)	2 (4%)	1 (2%)
#GASTRIC MUCOSA	(47)	(49)	(50)
EROSION			1 (2%)
#CARDIAC STOMACH	(47)	(49)	(50)
ULCER, ACUTE			1 (2%)

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
#PEYERS PATCH	(47)	(50)	(50)
INFLAMMATION, CHRONIC		1 (2%)	
#ILEUM	(47)	(50)	(50)
ULCER, NOS	1 (2%)		
URINARY SYSTEM			
#KIDNEY	(48)	(50)	(49)
MINERALIZATION		17 (34%)	30 (61%)
INFLAMMATION, CHRONIC	35 (73%)	47 (94%)	44 (90%)
INFARCT, HEALED	1 (2%)		
HEMOSIDEROSIS	2 (4%)		
#KIDNEY/CORTEX	(48)	(50)	(49)
HEMOSIDEROSIS			1 (2%)
#KIDNEY/TUBULE	(48)	(50)	(49)
HEMOSIDEROSIS		1 (2%)	
#KIDNEY/PELVIS	(48)	(50)	(49)
MINERALIZATION	1 (2%)		
ENDOCRINE SYSTEM			
#PITUITARY	(41)	(45)	(49)
CYST, NOS	3 (7%)		
#ADRENAL	(47)	(50)	(50)
ANGIECTASIS			2 (4%)
#ADRENAL CORTEX	(47)	(50)	(50)
LIPOIDOSIS	2 (4%)	1 (2%)	2 (4%)
#ADRENAL MEDULLA	(47)	(50)	(50)
HEMORRHAGIC CYST		1 (2%)	
#THYROID	(42)	(46)	(46)
FOLLICULAR CYST, NOS			1 (2%)
HYPERPLASIA, C-CELL	1 (2%)	2 (4%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
GALACTOCELE			1 (2%)

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
*PREPUTIAL GLAND	(50)	(50)	(50)
EPIDERMAL INCLUSION CYST	2 (4%)		
#PROSTATE	(45)	(49)	(48)
INFLAMMATION, ACUTE	6 (13%)	3 (6%)	1 (2%)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)		
INFLAMMATION, CHRONIC	3 (7%)	4 (8%)	1 (2%)
*SEMINAL VESICLE	(50)	(50)	(50)
ATROPHY, NOS			1 (2%)
#TESTIS	(47)	(50)	(50)
ATROPHY, NOS	45 (96%)	46 (92%)	46 (92%)
ASPERMATOGENESIS			2 (4%)
NERVOUS SYSTEM			
#BRAIN	(45)	(50)	(49)
HEMORRHAGE	1 (2%)	1 (2%)	
SPECIAL SENSE ORGANS			
*EYE/CONJUNCTIVA	(50)	(50)	(50)
INFLAMMATION, CHRONIC	1 (2%)		
*EAR	(50)	(50)	(50)
ACANTHOSIS			1 (2%)
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*EPICARDIUM	(50)	(50)	(50)
INFLAMMATION, ACUTE	1 (2%)		
*MESENTERY	(50)	(50)	(50)
INFLAMMATION, NOS			1 (2%)

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ALL OTHER SYSTEMS			
ADIPOSE TISSUE			
LIPOGRANULOMA	7	5	4
SPECIAL MORPHOLOGY SUMMARY			
AUTO/NECROPSY/NO HISTO	2		

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

TABLE C2.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS ADMINISTERED CINNAMYL ANTHRANILATE IN THE DIET

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	48	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	48	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(48)	(50)	(50)
EPIDERMAL INCLUSION CYST	2 (4%)		
RESPIRATORY SYSTEM			
#TRACHEA	(46)	(49)	(50)
INFLAMMATION, CHRONIC	3 (7%)		
#LUNG	(47)	(50)	(50)
PNEUMONIA, CHRONIC MURINE	18 (38%)	1 (2%)	
HYPERPLASIA, ALVEOLAR EPITHELIUM	1 (2%)		
HEMATOPOIETIC SYSTEM			
#SPLEEN	(47)	(50)	(50)
INFLAMMATION, CHRONIC		1 (2%)	
NECROSIS, NOS	1 (2%)		
PIGMENTATION, NOS	1 (2%)		
HEMOSIDEROSIS	8 (17%)	28 (56%)	41 (82%)
HEMATOPOIESIS	2 (4%)		
#MANDIBULAR L. NODE	(43)	(47)	(50)
ATROPHY, NOS	1 (2%)		
PLASMACYTOSIS	2 (5%)		
HYPERPLASIA, LYMPHOID	2 (5%)		
#MESENTERIC L. NODE	(43)	(47)	(50)
HEMORRHAGE		1 (2%)	1 (2%)
ATROPHY, NOS	1 (2%)		
HYPERPLASIA, RETICULUM CELL			1 (2%)
#THYMUS	(38)	(34)	(33)
ATROPHY, NOS	38 (100%)	33 (97%)	33 (100%)

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
CIRCULATORY SYSTEM			
#MANDIBULAR L. NODE	(43)	(47)	(50)
LYMPHANGIECTASIS	1 (2%)		
#HEART/ATRIUM	(47)	(50)	(50)
THROMBOSIS, NOS			1 (2%)
#MYOCARDIUM	(47)	(50)	(50)
INFLAMMATION, CHRONIC	23 (49%)	23 (46%)	15 (30%)
*HEPATIC VEIN	(48)	(50)	(50)
THROMBUS, ORGANIZED	1 (2%)		
#PANCREAS	(43)	(49)	(50)
PERIARTERITIS		1 (2%)	
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(44)	(48)	(47)
INFLAMMATION, ACUTE	3 (7%)		
INFLAMMATION, CHRONIC	10 (23%)	1 (2%)	
#LIVER	(46)	(50)	(50)
CONGESTION, NOS	1 (2%)		
NECROSIS, NOS	2 (4%)	2 (4%)	2 (4%)
NECROSIS, FOCAL			1 (2%)
METAMORPHOSIS FATTY	3 (7%)		
FOCAL CELLULAR CHANGE	31 (67%)	21 (42%)	3 (6%)
HYPERTROPHY, NOS	1 (2%)		
HYPERPLASIA, NOS	1 (2%)	14 (28%)	8 (16%)
#LIVER/CENTRILOBULAR	(46)	(50)	(50)
DEGENERATION, NOS	1 (2%)		1 (2%)
NECROSIS, NOS	1 (2%)		
#BILE DUCT	(46)	(50)	(50)
INFLAMMATION, CHRONIC	1 (2%)		
HYPERPLASIA, NOS	16 (35%)	21 (42%)	24 (48%)
#PANCREAS	(43)	(49)	(50)
DILATATION/DUCTS	1 (2%)	1 (2%)	
ATROPHY, FOCAL		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
#PANCREATIC ACINUS	(43)	(49)	(50)
ATROPHY, NOS	6 (14%)	5 (10%)	5 (10%)
ATROPHY, FOCAL	1 (2%)		
#STOMACH	(47)	(50)	(50)
EDEMA, NOS		1 (2%)	
ULCER, ACUTE	1 (2%)		
INFLAMMATION, ACUTE/CHRONIC			1 (2%)
#CARDIAC STOMACH	(47)	(50)	(50)
CYST, NOS			1 (2%)
ULCER, ACUTE	1 (2%)		
#LARGE INTESTINE	(47)	(49)	(50)
MUCOCELE	1 (2%)		
URINARY SYSTEM			
#KIDNEY	(48)	(50)	(50)
MINERALIZATION	2 (4%)		3 (6%)
PYELONEPHRITIS, ACUTE		1 (2%)	
INFLAMMATION, CHRONIC	9 (19%)	9 (18%)	16 (32%)
INFARCT, HEALED			11 (22%)
#KIDNEY/CORTEX	(48)	(50)	(50)
CYST, NOS			2 (4%)
ATROPHY, NOS			2 (4%)
#KIDNEY/TUBULE	(48)	(50)	(50)
NECROSIS, NOS	3 (6%)		
HEMOSIDEROSIS	1 (2%)		
ATROPHY, NOS	1 (2%)		4 (8%)
#URINARY BLADDER	(46)	(49)	(49)
HYPERPLASIA, EPITHELIAL			1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(46)	(46)	(45)
CYST, NOS	3 (7%)	3 (7%)	4 (9%)
HEMORRHAGIC CYST			1 (2%)
#ADRENAL	(47)	(50)	(49)
HEMORRHAGIC CYST	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
ANGIECTASIS	6 (13%)	6 (12%)	11 (22%)
#ADRENAL CORTEX	(47)	(50)	(49)
LIPOIDOSIS	5 (11%)	3 (6%)	2 (4%)
#THYROID	(46)	(45)	(48)
FOLLICULAR CYST, NOS		1 (2%)	
HYPERPLASIA, C-CELL	1 (2%)		1 (2%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(48)	(50)	(50)
GALACTOCELE	2 (4%)	1 (2%)	2 (4%)
EPIDERMAL INCLUSION CYST	1 (2%)		
#UTERUS	(47)	(50)	(50)
HYDROMETRA	3 (6%)	2 (4%)	2 (4%)
HEMORRHAGE			1 (2%)
#UTERUS/ENDOMETRIUM	(47)	(50)	(50)
CYST, NOS	7 (15%)	2 (4%)	5 (10%)
INFLAMMATION, VESICULAR	1 (2%)		
INFLAMMATION, ACUTE	1 (2%)		
INFLAMMATION, ACUTE VESICULAR	1 (2%)		
INFLAMMATION, CHRONIC	2 (4%)		
HYPERPLASIA, NOS	1 (2%)	1 (2%)	
#OVARY/OVIDUCT	(47)	(50)	(50)
INFLAMMATION, ACUTE		2 (4%)	1 (2%)
#OVARY	(47)	(49)	(49)
CYST, NOS	3 (6%)		
FOLLICULAR CYST, NOS	3 (6%)	4 (8%)	2 (4%)
NERVOUS SYSTEM			
#BRAIN	(47)	(49)	(50)
ATROPHY, PRESSURE	1 (2%)	1 (2%)	1 (2%)
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
ADIPOSE TISSUE			
LIPOGRANULOMA	5	3	
SPECIAL MORPHOLOGY SUMMARY			
AUTOLYSIS/NO NECROPSY	1		

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

APPENDIX D

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE ADMINISTERED CINNAMYL ANTHRANILATE IN THE DIET

TABLE D1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE ADMINISTERED CINNAMYL ANTHRANILATE IN THE DIET

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	48	50	48
ANIMALS EXAMINED HISTOPATHOLOGICALLY	48	50	47
INTEGUMENTARY SYSTEM			
*SKIN	(48)	(50)	(48)
EDEMA, NOS			1 (2%)
ULCER, NOS	1 (2%)		
INFLAMMATION, ACUTE			1 (2%)
ABSCESS, NOS		1 (2%)	
ACANTHOSIS			1 (2%)
RESPIRATORY SYSTEM			
#LUNG	(48)	(50)	(47)
EDEMA, NOS			1 (2%)
PNEUMONIA, CHRONIC MURINE		3 (6%)	
HEMATOPOIETIC SYSTEM			
*SKIN	(48)	(50)	(48)
PARAKERATOSIS		1 (2%)	1 (2%)
#BONE MARROW	(44)	(48)	(41)
HYPERPLASIA, GRANULOCYTIC			1 (2%)
#SPLEEN	(47)	(46)	(44)
INFLAMMATION, ACUTE		1 (2%)	
ATROPHY, NOS			2 (5%)
HYPERPLASIA, LYMPHOID	1 (2%)	2 (4%)	3 (7%)
HEMATOPOIESIS		1 (2%)	
#MANDIBULAR L. NODE	(44)	(40)	(45)
HYPERPLASIA, LYMPHOID		1 (3%)	
#MESENTERIC L. NODE	(44)	(40)	(45)
CONGESTION, NOS	4 (9%)	1 (3%)	

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
HEMORRHAGE	10 (23%)	2 (5%)	
ATROPHY, NOS	3 (7%)	2 (5%)	
PLASMACYTOSIS	1 (2%)		
HYPERPLASIA, RETICULUM CELL	1 (2%)		
HYPERPLASIA, LYMPHOID	4 (9%)	1 (3%)	3 (7%)
#LIVER	(48)	(50)	(47)
RETICULOCYTOSIS		1 (2%)	
#PEYERS PATCH	(46)	(47)	(45)
HYPERPLASIA, LYMPHOID	1 (2%)	1 (2%)	
#KIDNEY	(47)	(50)	(46)
HYPERPLASIA, LYMPHOID		1 (2%)	2 (4%)
CIRCULATORY SYSTEM			
#MESENTERIC L. NODE	(44)	(40)	(45)
LYMPHANGIECTASIS			1 (2%)
#MYOCARDIUM	(48)	(50)	(47)
INFLAMMATION, ACUTE		1 (2%)	
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(48)	(49)	(45)
LYMPHOCYTIC INFLAMMATORY INFILTR		1 (2%)	
ATROPHY, NOS			1 (2%)
#LIVER	(48)	(50)	(47)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)		
INFLAMMATION, ACUTE			1 (2%)
NECROSIS, NOS		2 (4%)	1 (2%)
LIPOIDOSIS	1 (2%)	1 (2%)	3 (6%)
HEMOSIDEROSIS		6 (12%)	15 (32%)
HYPERPLASIA, NOS		6 (12%)	2 (4%)
#LIVER/KUPFFER CELL	(48)	(50)	(47)
HEMOSIDEROSIS		3 (6%)	
#PANCREAS	(46)	(46)	(41)
CYSTIC DUCTS		1 (2%)	
INFLAMMATION, CHRONIC		1 (2%)	

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
#PANCREATIC ACINUS	(46)	(46)	(41)
ATROPHY, NOS		1 (2%)	
#STOMACH	(46)	(47)	(44)
CYST, NOS	1 (2%)		
ULCER, ACUTE			1 (2%)
URINARY SYSTEM			
#KIDNEY	(47)	(50)	(46)
HYDRONEPHROSIS	1 (2%)		
LYMPHOCYTIC INFLAMMATORY INFILTR			2 (4%)
PYELONEPHRITIS, ACUTE	1 (2%)		
INFLAMMATION, CHRONIC	1 (2%)		1 (2%)
PYELONEPHRITIS, CHRONIC		1 (2%)	
GLOMERULOSCLEROSIS, NOS		1 (2%)	
#KIDNEY/CORTEX	(47)	(50)	(46)
CYST, NOS			1 (2%)
#U.BLADDER/SUBMUCOSA	(48)	(48)	(45)
EDEMA, NOS	1 (2%)		
ENDOCRINE SYSTEM			
#PITUITARY	(39)	(35)	(38)
CYST, NOS	1 (3%)		
#THYROID	(41)	(40)	(39)
CYSTIC FOLLICLES			1 (3%)
REPRODUCTIVE SYSTEM			
#PROSTATE	(44)	(43)	(41)
INFLAMMATION, ACUTE		1 (2%)	
*SEMINAL VESICLE	(48)	(50)	(48)
ATROPHY, NOS			2 (4%)
#TESTIS	(48)	(49)	(46)
ATROPHY, NOS	1 (2%)		1 (2%)

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ASPERMATOGENESIS			1 (2%)
*EPIDIDYMIS	(48)	(50)	(48)
ABSCESS, NOS		1 (2%)	
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*ABDOMINAL WALL	(48)	(50)	(48)
CYST, NOS	1 (2%)		
*PERITONEUM	(48)	(50)	(48)
INFLAMMATION, CHRONIC	1 (2%)		
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	11	1	1
AUTO/NECROPSY/HISTO PERF	1	2	
AUTO/NECROPSY/NO HISTO			1
AUTOLYSIS/NO NECROPSY	2		2

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

TABLE D2.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE ADMINISTERED CINNAMYL ANTHRANILATE IN THE DIET

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS MISSING		1	1
ANIMALS NECROPSIED	50	49	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	49	49
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(49)	(49)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)		
ABSCESS, CHRONIC		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(50)	(49)	(48)
PNEUMONIA, CHRONIC MURINE	7 (14%)	1 (2%)	2 (4%)
METAPLASIA, OSSEOUS	1 (2%)		
#LUNG/ALVEOLI	(50)	(49)	(48)
INFLAMMATION, DIFFUSE			1 (2%)
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(49)	(44)	(45)
HYPERPLASIA, GRANULOCYTIC			1 (2%)
#SPLEEN	(50)	(49)	(49)
INFLAMMATION, ACUTE	1 (2%)		
ATROPHY, NOS			1 (2%)
HYPERPLASIA, LYMPHOID	9 (18%)	1 (2%)	2 (4%)
HEMATOPOIESIS	1 (2%)	2 (4%)	4 (8%)
#MANDIBULAR L. NODE	(45)	(46)	(39)
HYPERPLASIA, LYMPHOID		1 (2%)	1 (3%)
#LUMBAR LYMPH NODE	(45)	(46)	(39)
HYPERPLASIA, LYMPHOID	1 (2%)		
#MESENTERIC L. NODE	(45)	(46)	(39)
CONGESTION, NOS	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
HEMORRHAGE	4 (9%)		1 (3%)
INFLAMMATION, CHRONIC	2 (4%)		
ATROPHY, NOS	4 (9%)		1 (3%)
PLASMACYTOSIS			1 (3%)
HYPERPLASIA, LYMPHOID	2 (4%)		5 (13%)
#RENAL LYMPH NODE	(45)	(46)	(39)
INFLAMMATION, CHRONIC			1 (3%)
AMYLOIDOSIS			1 (3%)
HYPERPLASIA, LYMPHOID	1 (2%)		
#LIVER	(50)	(49)	(49)
HYPERPLASIA, LYMPHOID	1 (2%)	1 (2%)	1 (2%)
HEMATOPOIESIS		1 (2%)	1 (2%)
#ILEUM	(48)	(48)	(48)
HYPERPLASIA, LYMPHOID			1 (2%)
#KIDNEY	(50)	(49)	(49)
HYPERPLASIA, LYMPHOID	4 (8%)	5 (10%)	3 (6%)
CIRCULATORY SYSTEM			
*HEPATIC VEIN	(50)	(49)	(49)
EMBOLISM, NOS			1 (2%)
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(48)	(49)	(47)
ATROPHY, NOS			3 (6%)
#LIVER	(50)	(49)	(49)
CYST, NOS	1 (2%)		
INFLAMMATION, ACUTE	1 (2%)		
INFLAMMATION, CHRONIC	1 (2%)		
FIBROSIS	1 (2%)		
NECROSIS, NOS	2 (4%)		3 (6%)
NECROSIS, FOCAL			1 (2%)
NECROSIS, COAGULATIVE	1 (2%)		
HEMOSIDEROSIS			6 (12%)
HYPERPLASIA, NOS		3 (6%)	1 (2%)
*GALLBLADDER	(50)	(49)	(49)
HYPERPLASIA, PAPILLARY	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
#BILE DUCT	(50)	(49)	(49)
INFLAMMATION, CHRONIC	1 (2%)		
HYPERPLASIA, PAPILLARY	1 (2%)		
#PANCREAS	(48)	(46)	(45)
DILATATION/DUCTS			1 (2%)
INFLAMMATION, CHRONIC	1 (2%)		1 (2%)
#STOMACH	(47)	(47)	(47)
ULCER, ACUTE		1 (2%)	
#CARDIAC STOMACH	(47)	(47)	(47)
ULCER, ACUTE			1 (2%)
URINARY SYSTEM			
#KIDNEY	(50)	(49)	(49)
MINERALIZATION		1 (2%)	
HYDRONEPHROSIS	1 (2%)	1 (2%)	
FIBROSIS, DIFFUSE			1 (2%)
#KIDNEY/TUBULE	(50)	(49)	(49)
ATROPHY, NOS			3 (6%)
ENDOCRINE SYSTEM			
#THYROID	(43)	(40)	(43)
FOLLICULAR CYST, NOS	1 (2%)		
REPRODUCTIVE SYSTEM			
*VAGINA	(50)	(49)	(49)
HYPERKERATOSIS		1 (2%)	
ACANTHOSIS		1 (2%)	
#UTERUS	(50)	(48)	(47)
HYDROMETRA			4 (9%)
ATROPHY, NOS		2 (4%)	5 (11%)
#UTERUS/ENDOMETRIUM	(50)	(48)	(47)
CYST, NOS	4 (8%)	3 (6%)	9 (19%)

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, ACUTE VESICULAR	1 (2%)	1 (2%)	
INFLAMMATION, CHRONIC SUPPURATIV	1 (2%)		
HYPERPLASIA, CYSTIC	36 (72%)	36 (75%)	27 (57%)
#OVARY	(44)	(46)	(36)
MINERALIZATION			1 (3%)
CYST, NOS	6 (14%)		5 (14%)
FOLLICULAR CYST, NOS	2 (5%)	2 (4%)	2 (6%)
INFLAMMATION, CHRONIC	1 (2%)		
AMYLOIDOSIS		1 (2%)	
#OVARY/FOLLICLE	(44)	(46)	(36)
HEMORRHAGIC CYST			1 (3%)
NERVOUS SYSTEM			
#BRAIN	(49)	(48)	(49)
LYMPHOCYTIC INFLAMMATORY INFILTR		1 (2%)	
SPECIAL SENSE ORGANS			
*HARDERIAN GLAND	(50)	(49)	(49)
ABSCESS, CHRONIC			1 (2%)
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*ABDOMINAL WALL	(50)	(49)	(49)
ABSCESS, CHRONIC			1 (2%)
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED			1

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMAL MISSING/NO NECROPSY		1	1
AUTO/NECROPSY/HISTO PERF		1	

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

APPENDIX E

ANALYSIS OF CINNAMYL ANTHRANILATE

APPPENDIX E

Analysis of Cinnamyl Anthranilate
Midwest Research Institute

A. Elemental Analysis

Element:	C	H	N
Theory:	75.87	5.97	5.53
Found:	75.77	6.04	5.37
	75.52	6.16	5.32

B. Melting Point

Literature: A melting point of greater than 60°C is specified for the commercial product (Furia and Bellanca, 1971).
Found: 63°-64.5°C

C. Thin-Layer Chromatography

Plates: Silica gel F-254
Amount Spotted: 100 and 300μg
Visualization: 254 and 366 nm light and furfural
Results:

System I:	Ethyl acetate	R_f 0.86 (major), traces at 0.72, 0.68, 0.07, and origin
System II:	Benzene	R_f 0.32 (major), traces at 0.77, 0.63, 0.05, and origin

D. High-Pressure Liquid Chromatography

Apparatus: Waters ALC 202 with 660 Programmer
Column: Porasil, 30 cm x 0.4 cm
Solvent: (a) chloroform; (b) 50% chloroform/hexane to 100% chloroform
Program: (a) 2 ml/min; (b) No. 6, 4 ml/min
Detection: Ultraviolet 254 nm
Results: (a) major peak, with two trace impurities; (b) one homogeneous peak
Retention times: (a) 10 min (major), 3 and 26.5 min (trace) impurities; (b) 6.4 min

E. Spectral Data

1. Infrared (Beckman IR-12; 1.5% KBr pellet)
   Literature: No literature reference found; spectrum consistent with structure.
   Found: vs 1242 cm^{-1}
   s 3483, 3380, 1689, 1618, 1585, 1557, 1297, 1164, 1099, 973, 950, 751, 694, cm^{-1}
   m 1488, 1455, 1379, 529 cm^{-1}
   μ 3055, 2963, 1028, 959, 800 cm^{-1}

2. Ultraviolet/Visible (Cary 115; solvent, 95% alcohol)
   Literature: No literature reference found
   Found: ϵmax 339.5 = 572.2 $\pm$ 0.9 (δ) x 10^1
   ϵmax 292 = 15.1 $\pm$ 0.2 (δ) x 10^2
   ϵmax 282.5 = 16.8 $\pm$ 0.1 (δ) x 10^2
   ϵmax 252 = 260.3 $\pm$ 0.7 (δ) x 10^2

3. Nuclear Magnetic Resonance (Varian HA-100; solvent, $CDCl_3$ with internal TMS)
   Literature: No literature reference found; spectrum consistent with structure
   Found: Assignments (a) 4.77δ, (b) 5.56δ, (c) 6.05 - 6.68δ, (d) 6.98 - 7.338δ, (e) 7.82δ
   Integration ratios: (a) 2.15, (b) 1.77, (c) 4.48, (d) 5.83, (e) 0.73

Review of the Bioassay of Cinnamyl Anthranilite* for Carcinogenicity by the Data Evaluation/Risk Assessment Subgroup of the Clearinghouse on Environmental Carcinogens

February 15, 1980

The Clearinghouse on Environmental Carcinogens was established in May, 1976, in compliance with DHEW Committee Regulations and the Provisions of the Federal Advisory Committee Act. The purpose of the Clearinghouse is to advise the Director of the National Cancer Institute (NCI) on its bioassay program to identify and to evaluate chemical carcinogens in the environment to which humans may be exposed. The members of the Clearinghouse have been drawn from academia, industry, organized labor, public interest groups, State health officials, and quasi-public health and research organizations. Members have been selected on the basis of their experience in carcinogenesis or related fields and, collectively, provide expertise in chemistry, biochemistry, biostatistics, toxicology, pathology, and epidemiology. Representatives of various Governmental agencies participate as ad hoc members. The Data Evaluation/Risk Assessment Subgroup of the Clearinghouse is charged with the responsibility of providing a peer review of reports prepared on NCI-sponsored bioassays of chemicals studied for carcinogenicity. It is in this context that the below critique is given on the bioassay of Cinnamyl Anthranilite for carcinogenicity.

The primary reviewer for the report on the bioassay of cinnamyl anthranilate said one study of the chemical in the strain A lung adenoma induction showed an increase the incidence of lung tumors. In the NCI bioassay, cinnamyl anthranilate induced significant numbers of hepatocellular tumors in the treated mice. The reviewer pointed out that the report also states the chemical was carcinogenic in male rats, based on an elevated but not statistically significant incidence of acinar-cell tumors of the pancreas and other tumors of the renal cortex. Based on the findings, he said cinnamyl anthranilate must be regarded as a potential carcinogen for man, even though it is consumed at but a small fraction of the dosages tested.

The secondary reviewer opined that the maximum tolerated dose may not have been tested in rats. He noted certain structural features of cinnamyl anthranilate which supports the finding of its carcinogenicity. He also noted the peculiar species sensitivity to aromatic amines. The reviewer suggested that a further evaluation of its carcinogenicity might be warranted.

In further discussion, a program staff pathologist noted that spontaneous pancreatic tumors in rats are very rare. A Clearinghouse member indicated that such tumors are easy to overlook unless special efforts are taken to examine the pancreas. He suggested that it would be worthwhile to review the slides to check if all the pancreatic tumors were identified. The staff pathologist responded that the review of slides were carefully controlled, although the thoroughness of autopsies may be a different problem.

The primary reviewer moved that the report on the bioassay of cinnamyl anthranilate be accepted as written. The motion was seconded and approved unanimously.

Members present were:

Arnold L. Brown (Chairman), University of Wisconsin Medical School
David B. Clayson, Eppley Institute for Research in Cancer
Joseph Highland, Environmental Defense Fund
William Lijinsky, Federick Cancer Research Center
Henry C. Pitot, University of Wisconsin Medical Center
Verne A. Ray, Pfizer Medical Research Laboratory
Louise Strong, University of Texas Health Sciences Center

---

* Subsequent to this review, changes may have been made in the bioassay report either as a result of the review or other reasons. Thus, certain comments and criticisms reflected in the review may no longer be appropriate.

*U.S. GOVERNMENT PRINTING OFFICE : 1980 0-311-201/3149

NIH Publication No. 80-1752
August 1980