National Cancer Institute
CARCINOGENESIS
Technical Report Series
No. 67
1978

BIOASSAY OF A MIXTURE OF ASPIRIN, PHENACETIN, AND CAFFEINE FOR POSSIBLE CARCINOGENICITY

CAS No. 8003-03-0

NCI-CG-TR-67

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
National Institutes of Health
Public Health Service

BIOASSAY OF

A MIXTURE OF ASPIRIN, PHENACETIN, AND CAFFEINE

FOR POSSIBLE CARCINOGENICITY

Carcinogenesis Testing Program
Division of Cancer Cause and Prevention
National Cancer Institute
National Institutes of Health
Bethesda, Maryland 20014

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
National Institutes of Health

DHEW Publication No. (NIH) 78-1317

REPORT ON THE BIOASSAY OF APC
FOR POSSIBLE CARCINOGENICITY

CARCINOGENESIS TESTING PROGRAM
DIVISION OF CANCER CAUSE AND PREVENTION
NATIONAL CANCER INSTITUTE, NATIONAL INSTITUTES OF HEALTH

FOREWORD: This report presents the results of the bioassay of APC conducted for the Carcinogenesis Testing Program, Division of Cancer Cause and Prevention, National Cancer Institute (NCI), National Institutes of Health, Bethesda, Maryland. This is one of a series of experiments designed to determine whether selected chemicals have the capacity to produce cancer in animals. Negative results, in which the test animals do not have a significantly greater incidence of cancer than control animals, do not necessarily mean the test chemical is not a carcinogen because the experiments are conducted under a limited set of circumstances. Positive results demonstrate that the test chemical is carcinogenic for animals under the conditions of the test and indicate a potential risk to man. The actual determination of the risk to man from animal carcinogens requires a wider analysis.

CONTRIBUTORS: This bioassay of APC was conducted by Mason Research Institute, Worcester, Massachusetts, initially under direct contract to the NCI and currently under a subcontract to Tracor Jitco, Inc., prime contractor for the NCI Carcinogenesis Testing Program.

The experimental design was determined by the NCI Project Officers, Dr. J. H. Weisburger (1,2) and Dr. E. K. Weisburger (1). The principal investigators for the contract were Dr. E. Smith (3) and Dr. A. Handler (3). Animal treatment and observation were supervised by Mr. G. Wade (3) and Ms. E. Zepp (3). Chemical analysis was performed by Midwest Research Institute (4) and the analytical results were reviewed by Dr. N. Zimmerman (5).

Histopathologic examinations were performed by Dr. D. W. Hayden (3) and Dr. A. S. Krishna Murthy (3) at the Mason Research Institute, and the diagnoses included in this report represent the interpretation of these pathologists. Histopathology findings and reports were reviewed by Dr. R. L. Schueler (6).

Compilation of individual animal survival, pathology, and summary tables was performed by EG&G Mason Research Institute (7); the statistical analysis was performed by Mr. W. W. Belew (5) and Dr. J. R. Joiner (6), using methods selected for the Bioassay Program by Dr. J. J. Gart (8).

This report was prepared at METREK, a Division of The MITRE Corporation (5) under the direction of the NCI. Those responsible for this report at METREK are the project coordinator, Dr. L. W. Thomas (5), the task leader, Dr. M. R. Kornreich (5), the senior biologist, Ms. P. Walker (5) and the technical editor, Ms. P. A. Miller (5). The final report was reviewed by members of the participating organizations.

The statistical analysis was reviewed by members of the Mathematical Statistics and Applied Mathematics Section of the NCI: Dr. J. J. Gart (8), Mr. J. Nam (8), Dr. H. M. Pettigrew (8), and Dr. R. E. Tarone (8).

The following other scientists at the National Cancer Institute were responsible for evaluating the bioassay experiment, interpreting the results, and reporting the findings: Dr. K. C. Chu (1), Dr. C. Cueto, Jr. (1), Dr. J. F. Douglas (1), Dr. D. G. Goodman (1), Dr. R. A. Griesemer (1), Dr. H. A. Milman (1), Dr. T. W. Orme (1), Dr. R. A. Squire (1,9), Dr. J. M. Ward (1), and Dr. C. E. Whitmire (1).

---

1. Carcinogenesis Testing Program, Division of Cancer Cause and Prevention, National Cancer Institute, National Institutes of Health, Bethesda, Maryland.

2. Now with the Naylor Dana Institute for Disease Prevention, American Health Foundation, Hammon House Road, Valhalla, New York.

3. Mason Research Institute, 57 Union Street, Worcester, Massachusetts.

4. Midwest Research Institute, 425 Volker Boulevard, Kansas City, Missouri.

5. The MITRE Corporation, METREK Division, 1820 Dolley Madison Boulevard, McLean, Virginia.

6. Tracor Jitco, Inc., 1776 East Jefferson Street, Rockville, Maryland.

7. EG&G Mason Research Institute, 1530 East Jefferson Street, Rockville, Maryland.

8. Mathematical Statistics and Applied Mathematics Section, Biometry Branch, Field Studies and Statistics Program, Division of Cancer Cause and Prevention, National Cancer Institute, National Institutes of Health, Bethesda, Maryland.

9. Now with the Division of Comparative Medicine, Johns Hopkins University, School of Medicine, Traylor Building, Baltimore, Maryland.

SUMMARY

A bioassay of a mixture of aspirin, phenacetin, and caffeine (APC) for possible carcinogenicity was conducted using Fischer 344 rats and B6C3F1 mice. APC was administered in the feed, at either of two concentrations, to groups of 50 male and 49 or 50 female animals of each species. For each species, 50 animals of each sex were placed on test as controls. The high dose used in the chronic study for the male and female rats and mice was 1.4 percent. The low dose administered to the male and female rats and mice was 0.7 percent. After a 78-week period of compound administration, observation of the rats continued for up to an additional 35 weeks and observation of the mice continued for an additional 16 weeks.

No significant association was established between administration of APC and mortality in rats or female mice; however, there was a significant positive association between treatment and mortality in male mice. For both species the survival in all groups was adequate for statistical analysis of tumor incidence.

In rats, a variety of endocrine tumors were observed with greater frequency in the male rats treated with APC than in the male control rats. These same tumors were not observed with similar frequencies in the female rats or in the mice of either sex. The endocrine tumors observed most frequently in the treated male rats were adenomas and carcinomas of the pituitary gland. The incidences of these tumors proved to be statistically inconclusive.

In rats, a transitional-cell carcinoma of the bladder was observed in one low dose and one high dose females. A tubular-cell adenocarcinoma of the kidney was seen in one low dose female and one low dose male. A fifth neoplasm, a transitional-cell papilloma of the kidney, was seen in one high dose female. The occurrence of these urinary tumors, although considered important, was not statistically significant.

In mice, there was no statistically significant positive association between APC administration and the incidence of tumors in either sex.

Under the conditions of this bioassay evidence was not sufficient for the carcinogenicity of APC in Fischer 344 rats or in B6C3F1 mice.

TABLE OF CONTENTS

LIST OF ILLUSTRATIONS

LIST OF TABLES

LIST OF TABLES (Concluded)

I. INTRODUCTION

APC (NCI No. C02697), an abbreviation often used for mixtures of aspirin, phenacetin and caffeine, is a nonprescription analgesic preparation sold for relief of headache, muscular aches and pains, arthritis, and other common afflictions. The active constituents of the drug mixture were selected for bioassay by the National Cancer Institute because they have been implicated in the induction of human renal carcinomas through clinical studies performed in Switzerland and Scandinavia (Weisburger, 1975; Juusela, 1973).

The Chemical Abstracts Service (CAS) Ninth Collective Index (1977) name for this preparation is 2-(acetyloxy)-benzoic acid, mixture with N-(4-ethoxy-phenzl) acetamide and 3,7-dihydro-1,3,7-trimethyl-1H-purine-2,6-dione.* Other names for the various components are acetylsalicylic acid and acetol for aspirin; acetophenetidine and p-acetophenetidide for phenacetin; and theine and 1,3,7-trimethylxanthine for caffeine.

Aside from its well-known analgesic properties, APC is antipyretic and anti-inflammatory and also acts as a central stimulant (Windholz, 1976). Thus, for many conditions (such as colds, osteoarthritis, rheumatoid arthritis, and so forth) the drug mixture serves a multifold purpose.

Precise production figures for APC preparations are not available; however, the U.S. International Trade Commission (1976)

*The CAS registry number is 8003-03-0.

reported a production of 25,434 x 10^3 pounds and 9835 x 10^3 pounds of aspirin and acetanilide derivatives, respectively, in 1975.

According to the Handbook of Non-Prescription Drugs (1977), seven products that contain aspirin, phenacetin, and caffeine are presently on the market; two of these products contain acetaminophen (an acetanilide derivative related to phenacetin) in addition to the other ingredients. The preparations are in tablet, capsule, or powder form and usually contain approximately 227 mg of aspirin, 160 mg of phenacetin, and 32 mg of caffeine per unit dose. One preparation contains 455 mg of aspirin and 325 mg of phenacetin while another contains only 15 mg of caffeine.

Exposure to APC is both widespread and extensive because of its efficacy and ease of availability. Use patterns range from an occasional tablet to authorized ingestion of as many as 30 tablets per day in rheumatoid or other conditions requiring large doses of anti-inflammatory and analgesic agents (Barr and Perro, 1973). In the latter instances, as much as 4.6 kg of APC may be ingested annually. Consumption of large quantities of APC also occurs among those who abuse these drugs for relatively minor ailments.

Adverse health effects attributable to aspirin, phenacetin, and caffeine may be expected to occur following excessive exposure to these compounds in APC mixtures (Stecher, 1968). Aspirin has been classified as moderately toxic following acute ingestion and slightly toxic as an allergen, while phenacetin and caffeine are considered

moderately toxic following both acute and chronic ingestion (Sax, 1975).

A variety of gastrointestinal disturbances and/or central nervous system (CNS) effects have been reported following ingestion of average to large doses of all three compounds by humans (Sax, 1975; Stecher, 1968). Excessive ingestion of aspirin may result in gastric ulcer, and abuse of aspirin in the form of APC preparations has reportedly led to a significant increase in the incidence of gastric ulcer among populations where abuse of the drug is rife (Medical Journal of Australia, 1976). Hematological disorders including hemolytic anemias and leucocytosis, among others, are associated with prolonged ingestion of phenacetin (Stecher, 1968). Convulsions, coma, circulatory collapse, respiratory failure, and death may result from overdoses of either aspirin or phenacetin (Stecher, 1968).

Analgesic nephropathy, a form of renal disease characterized by renal papillary necrosis and subsequent renal failure, is part of a wider clinical syndrome associated with the abuse of APC mixtures by humans (Nanra, 1976). Aside from the gastrointestinal, CNS, and hematological disorders mentioned previously, neuropsychiatric disorders, ischemic heart disease, toxemia of pregnancy, and premature aging are also observed as part of this syndrome (Nanra, 1976). Although controversy continues about the relative roles of aspirin and phenacetin in the genesis of this disease, evidence suggests that phenacetin is necessary for the major nephrotoxic effect of APC with aspirin having

an additive effect in the induction of renal damage (Caughay et al., 1974; Macklon et al., 1974; Gault, 1975; Nanra, 1976).

Evidence suggests that APC may be carcinogenic in humans (Juusela, 1973). Three out of seventeen patients with renal pelvic carcinoma were definite abusers of APC preparations while two other patients had also possibly abused the drug. In addition, long-term feeding of phenacetin to female Sprague-Dawley rats (0.535 percent of the diet for 110 weeks) was associated with increased incidences of mammary carcinoma and carcinoma of the ear duct (Johansson and Angervall, 1976).

II. MATERIALS AND METHODS

A. Chemicals

Aspirin, phenacetin, and caffeine (Figure 1) were purchased from J. T. Baker Chemical Company. Analysis was performed by Midwest Research Institute. Melting points were determined and comparisons with the literature values are given below:

Chemical	Melting Point Literature (°C)	Melting Point Tested Compound (°C)
Aspirin	56.7	56.7 - 57.2
Phenacetin	56.7 - 57.2	56.1 - 57.2
Caffeine	80.6 - 81.1[s]	80.6 - 81.1[s]

(s = Sublimes)

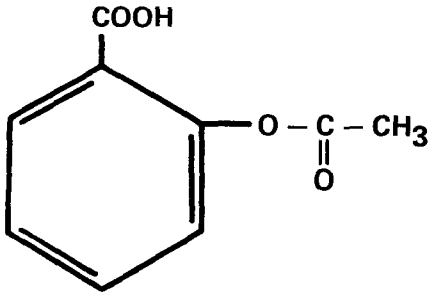
Thin-layer chromatography with ultraviolet visualization showed only one spot for each compound. Results of both melting point determinations and thin-layer chromatography suggested that all compounds were of high purity.

Aspirin, phenacetin and caffeine were combined in the ratio of 50:46:4 percent by weight. For the remainder of this report, this mixture is referred to as APC.

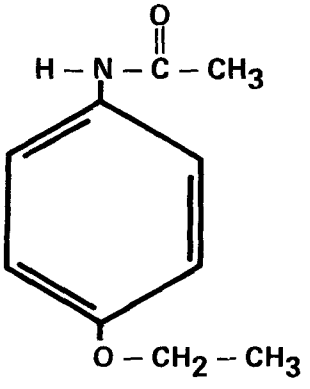
B. Dietary Preparation

The basal laboratory diet for both treated and control animals consisted of Wayne Lab-Blox® (Allied Mills, Inc., Chicago, Illinois). APC was administered to the treated animals as a component of the diet. The chemical was mixed in the diet using a 6 kg capacity

ASPIRIN



PHENACETIN



CAFFEINE

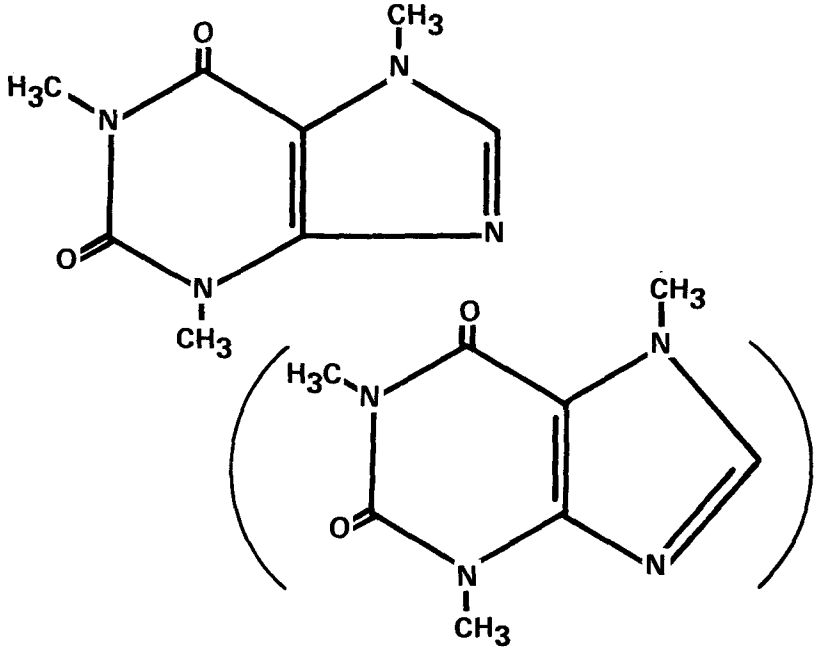


FIGURE 1
CHEMICAL STRUCTURES OF ASPIRIN, PHENACETIN, CAFFEINE

Patterson-Kelly stainless steel twin-shell V-blender. The treated diets were prepared once weekly and stored in double plastic bags in the dark at 4°C.

C. Animals

Two animal species, rats and mice, were used in the carcinogenicity bioassay. The Fischer 344 rats and the B6C3F1 mice were obtained through contracts of the Division of Cancer Treatment, National Cancer Institute. Animals of both species were supplied by Charles River Breeding Laboratories, Inc., Wilmington, Massachusetts. Mice were obtained in one shipment, while rats were received in two (one for treated groups and one for controls).

Upon arrival, a sample of animals was examined for nematode infestation and other signs of disease. The remaining animals were quarantined for 2 weeks prior to initiation of test. Animals were assigned to groups and distributed among cages so that average body weight per cage was approximately equal for a given sex and species.

D. Animal Maintenance

All animals were housed by species in rooms having a temperature range of 23° to 34°C. Incoming air was filtered through Tri-Dek® 15/40 denier Dacron® filters (Tri-Dim Filter Corp., Hawthorne, New Jersey) providing six changes of room air per hour. Fluorescent lighting was provided on a 12-hour-daily cycle.

Rats were housed five per cage by sex in stainless- and galvanized-steel wire-mesh cages suspended above newspapers for the

first 11 months of the bioassay. During this time the newspapers were replaced daily and the racks and cages were washed weekly. For the remainder of the bioassay, rats were housed in suspended polycarbonate cages equipped with disposable nonwoven fiber filter sheets. Corncob bedding, clean cages, and clean stainless steel cage racks were provided twice weekly. Disposable filters were replaced with the same frequency.

Mice were housed by sex, ten per cage for the first 18 months and five per cage thereafter, in shoe box type polycarbonate cages fitted with stainless steel lids and nonwoven fiber filter bonnets. Hardwood chips (Ab-sorb-dri®, Wilner Wood Products Company, Norway, Maine) were supplied as bedding for the first 8 months. SAN-I-CEL® (Paxton Processing Company, Paxton, Illinois) corncob bedding was utilized during months 9 through 20 and was replaced, due to the increasing dust content of SAN-I-CEL®, by Bed-o-Cobs® (The Andersons Cob Division, Maumee, Ohio) for the remainder of the bioassay. Clean cages, lids, and bedding were provided three times per week for the first 18 months and twice weekly thereafter. Reusable filters and pipe racks were sanitized once every 2 weeks throughout the study.

Water was available from 250 ml water bottles fitted with rubber stoppers and stainless steel sipper tubes. Glass water bottles were utilized for the first 4 months for rats and the first 9 months for mice. These were then replaced by polycarbonate bottles for the remainder of the bioassay. Bottles were replaced twice weekly. Wayne

Lab-Blox® was used throughout the bioassay. Water and the treated or untreated food were available ad libitum to both rats and mice.

All rats used in this study were housed in a room with other rats receiving diets containing* 4-nitroanthranilic acid (619-17-0); 5-nitro-o-toluidine (99-55-8); hydrazobenzene (530-50-7); 3-amino-9-ethylcarbazole hydrochloride; 2,4-diaminoanisole sulfate (615-05-4); 2-aminoanthraquinone (117-79-3); 3-amino-4-ethoxyacetanilide (17026-81-2); 6-nitrobenzimidazole (94-52-0); and 1-nitronaphthalene (86-57-7).

All mice in this bioassay were housed with other mice receiving diets containing the following compounds: acetylaminofluorene (53-96-3); amitrole (61-82-5); 2-methyl-1-nitroanthraquinone (129-15-7); N,N-dimethyl-p-nitrosoaniline (138-89-6); 2,4-dinitrotoluene (121-14-2); 3-amino-4-ethoxyacetanilide (17026-81-2); 3-nitro-p-acetophenetide (1777-84-0); 4-nitroanthranilic acid (619-17-0); urea (57-13-6); N-butylurea (592-31-4); sodium nitrite (7632-00-0); dulcin (150-69-6); acetamide (60-35-5); p-tolylurea (622-51-5); and hexanamide (628-02-4).

E. Selection of Initial Concentrations

In order to establish the maximum tolerated concentrations of APC for administration to treated animals in the chronic studies, subchronic toxicity tests were conducted with both rats and mice.

*CAS registry numbers are given in parentheses.

Animals of each species were distributed among six groups, each consisting of five males and five females. APC was incorporated into the basal laboratory diet and fed ad libitum to five of the six rat groups and five of the six mouse groups in concentrations of 0.09, 0.18, 0.36, 0.71, and 1.42 percent. The sixth group of each species served as a control group, receiving only the basal laboratory diet. The dosed dietary preparations were administered for a period of 4 weeks, followed by a 2-week observation period during which all animals were fed the basal diet.

A dosage inducing no mortality or mean body weight depression in either sex was to be selected as the initial high dose in the chronic bioassay. No mortality, compound-related gross abnormalities, or mean body weight depression were reported for any of the treated animals. The initial high concentration selected for use in the chronic bioassay for both rats and mice was 1.4 percent, the highest concentration administered in the subchronic test.

F. Experimental Design

The experimental design parameters for the chronic study (species, sex, group size, concentrations administered, and duration of treated and untreated observation periods) are summarized in Tables 1 and 2.

The low dose, high dose, and control rats were all approximately 6 weeks old at the time they were placed on test. The high and low

TABLE 1

DESIGN SUMMARY FOR FISCHER 344 RATS
APC FEEDING EXPERIMENT

	INITIAL GROUP SIZE	APC CONCENTRATION (PERCENT)	OBSERVATION PERIOD TREATED (WEEKS)	OBSERVATION PERIOD UNTREATED (WEEKS)
MALE				
CONTROL	50	0	0	109
LOW DOSE	50	0.7 0	78	34
HIGH DOSE	50	1.4 0	78	34
FEMALE				
CONTROL	50	0	0	109
LOW DOSE	50	0.7 0	78	34
HIGH DOSE	49	1.4 0	78	35

TABLE 2

DESIGN SUMMARY FOR B6C3F1 MICE
APC FEEDING EXPERIMENT

	INITIAL GROUP SIZE	APC CONCENTRATION (PERCENT)	OBSERVATION PERIOD	
			TREATED (WEEKS)	UNTREATED (WEEKS)
MALE				
CONTROL	50	0	0	96
LOW DOSE	50	0.7	78	
		0		16
HIGH DOSE	50	1.4	78	
		0		16
FEMALE				
CONTROL	50	0	0	96
LOW DOSE	50	0.7	78	
		0		16
HIGH DOSE	50	1.4	78	
		0		16

concentrations of APC administered to males and females were 1.4 and 0.7 percent, respectively. These concentrations were administered in the diet for a total of 78 weeks followed by 34 or 35 weeks of observation during which the untreated diet was available.

The low dose, high dose, and control mice were all approximately 6 weeks old at the time they were placed on test. The high and low concentrations of APC administered to males and females were 1.4 and 0.7 percent, respectively. These concentrations were administered in the diet for a period of 78 weeks followed by an observation period of 16 weeks during which the untreated diet was available.

Both rat and mouse control groups received the untreated basal diet and were maintained and observed in a manner similar to the treated groups.

G. Clinical and Histopathologic Examinations

Animals were weighed immediately prior to initiation of the experiment. Body weights were recorded twice weekly for the first 12 weeks of the study and at monthly intervals thereafter. From the first day, all animals were inspected twice daily for mortality. Food consumption, for two cages from each group, was monitored for seven consecutive days once a month for the first nine months of the bioassay and for three consecutive days each month thereafter. The presence of tissue masses and lesions was determined by monthly observation and palpation of each animal.

A necropsy was performed on each animal regardless of whether it died, was killed when moribund, or was sacrificed at the end of the bioassay. The animals were euthanized by carbon dioxide inhalation, and were immediately necropsied. The histopathologic examination consisted of gross and microscopic examination of major tissues, organs, or gross lesions taken from sacrificed animals and, whenever possible, from animals found dead.

Slides were prepared from the following tissues: skin, subcutaneous tissue, lungs and bronchi, trachea, bone marrow, spleen, lymph nodes, thymus, heart, salivary gland, liver, gallbladder (mice), pancreas, esophagus, stomach, small intestine, large intestine, kidney, urinary bladder, pituitary, adrenal, thyroid, parathyroid, testis, prostate, seminal vesicle, brain, muscle, ear, uterus, mammary gland, and ovary.

Tissues for which slides were prepared were preserved in 10 percent buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin prior to microscopic examination. An occasional section was subjected to special staining techniques for more definitive diagnosis.

A few tissues were not examined for some animals, particularly for those that died early. Also, some animals were missing, cannibalized, or judged to be in such an advanced state of autolysis as to preclude histopathologic interpretation. Thus, the number of animals

for which particular organs, tissues, or lesions were examined microscopically varies and does not necessarily represent the number of animals that were placed on experiment in each group.

H. Data Recording and Statistical Analyses

Pertinent data on this experiment have been recorded in an automatic data processing system, the Carcinogenesis Bioassay Data System (Linhart et al., 1974). The data elements include descriptive information on the chemicals, animals, experimental design, clinical observations, survival, body weight, and individual pathologic results, as recommended by the International Union Against Cancer (Berenblum, 1969). Data tables were generated for verification of data transcription and for statistical review.

These data were analyzed using the statistical techniques described in this section. Those analyses of the experimental results that bear on the possibility of carcinogenicity are discussed in the statistical narrative sections.

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) when testing two groups for equality and used Tarone's (1975) extensions of Cox's methods when

testing a dose-related trend. One-tailed P-values have been reported for all tests except the departure from linearity test, which is only reported 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 was 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 purpose of the statistical analyses of tumor incidence is to determine whether animals receiving the test chemical developed a significantly higher proportion of tumors than did the control animals. As a part of these analyses, the one-tailed Fisher exact test (Cox, 1970, pp. 48-52) was used to compare the tumor incidence of a control group to that of a group of treated animals at each dose level. When results for a number of treated groups, k, are compared simultaneously with those for a control group, a correction to ensure an overall significance level of 0.05 may be made. The Bonferroni inequality (Miller, 1966, pp. 6-10) requires that the P-value for any comparison be less than or equal to 0.05/k. In cases where this correction was

used, it is discussed in the narrative section. It is not, however, presented in the tables, where the Fisher exact P-values are shown.

The Cochran-Armitage test for linear trend in proportions, with continuity correction (Armitage, 1971, pp. 362-365), was also used when appropriate. Under the assumption of a linear trend, this test determined if the slope of the dose-response curve is different from zero at the one-tailed 0.05 level of significance. Unless otherwise noted, the direction of the significant trend was a positive dose relationship. This method also provides a two-tailed test of departure from linear trend.

A time-adjusted analysis was applied when numerous early deaths resulted from causes that were not associated with the formation of tumors. In this analysis, deaths that occurred before the first tumor was observed were excluded by basing the statistical tests on animals that survived at least 52 weeks, unless a tumor was found at the anatomic site of interest before week 52. When such an early tumor was found, comparisons were based exclusively on animals that survived at least as long as the animal in which the first tumor was found. Once this reduced set of data was obtained, the standard procedures for analyses of the incidence of tumors (Fisher exact tests, Cochran-Armitage tests, etc.) were followed.

When appropriate, life-table methods were used to analyze the incidence of tumors. Curves of the proportions surviving without an observed tumor were computed as in Saffiotti et al. (1972). The week

during which animals died naturally or were sacrificed was entered as the time point of tumor observation. Cox's methods of comparing these curves were used for two groups; Tarone's extension to testing for linear trend was used for three groups. The statistical tests for the incidence of tumors which used life-table methods were one-tailed and, unless otherwise noted, in the direction of a positive dose relationship. Significant departures from linearity ($P < 0.05$, two-tailed test) were also noted.

The approximate 95 percent confidence interval for the relative risk of each dosed group compared to its control was calculated from the exact interval on the odds ratio (Gart, 1971). The relative risk is defined as p_t/p_c where p_t is the true binomial probability of the incidence of a specific type of tumor in a treated group of animals and p_c is the true probability of the spontaneous incidence of the same type of tumor in a control group. The hypothesis of equality between the true proportion of a specific tumor in a treated group and the proportion in a control group corresponds to a relative risk of unity. Values in excess of unity represent the condition of a larger proportion in the treated group than in the control.

The lower and upper limits of the confidence interval of the relative risk have been included in the tables of statistical analyses. 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 treated 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 (a $P < 0.025$ one-tailed test when the control incidence is not zero, $P < 0.050$ when the control incidence is zero) has occurred. 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.

III. CHRONIC TESTING RESULTS: RATS

A. Body Weights and Clinical Observations

The mean body weights for both high and low dose male and female rats were consistently lower than those for controls (Figure 2). The only clinical abnormalities observed in the rat groups were a small crusted cutaneous lesion in one control male and three palpable subcutaneous nodules in low dose males.

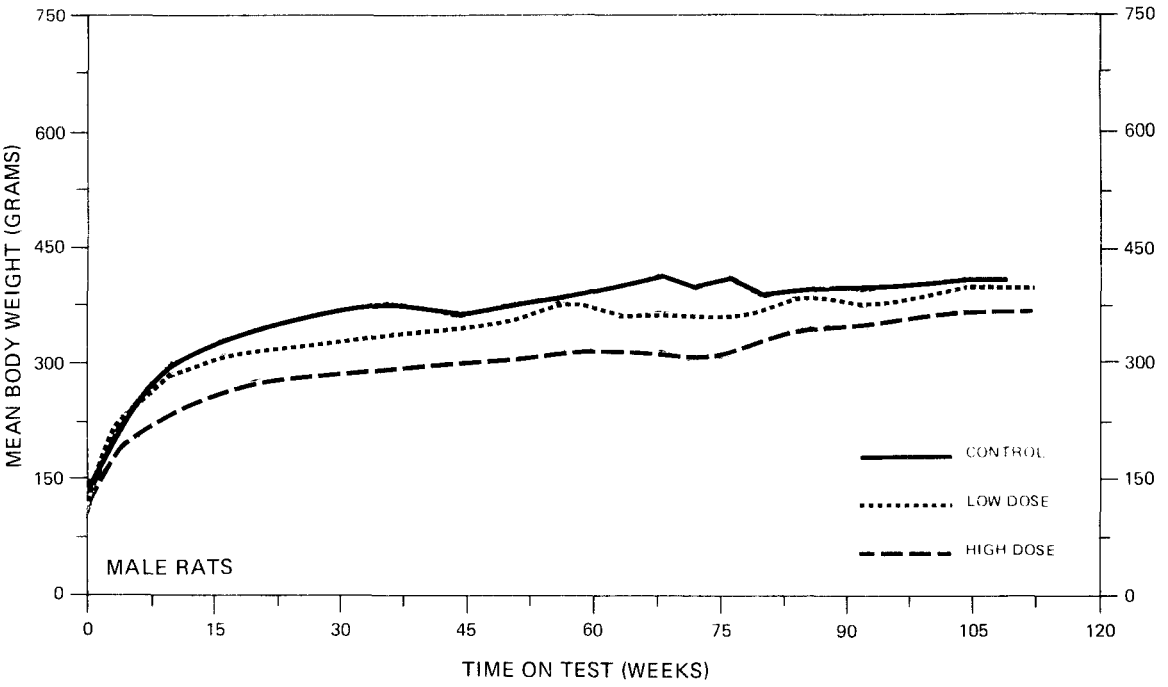
B. Survival

The estimated probabilities of survival for male and female rats in the control and APC-treated groups are shown in Figure 3.

For both male and female rats the Tarone test did not indicate a significant association between dosage and mortality. For males, despite the sacrifice of five rats from each group in week 78, 78 percent (39/50) of the high dose and 66 percent (33/50) of the controls actually survived until the end of the study. Eighty percent (40/50) of the low dose males survived until the end of the study.

For females, despite the sacrifice of five rats from each group in week 78, 78 percent (39/49) of the high dose and 70 percent (35/50) of the controls survived until the end of the study. Seventy-four percent (37/50) of the low dose females survived until the end of the study.

Thus, the actual survival in both sexes was adequate for meaningful statistical analyses of tumor incidence.



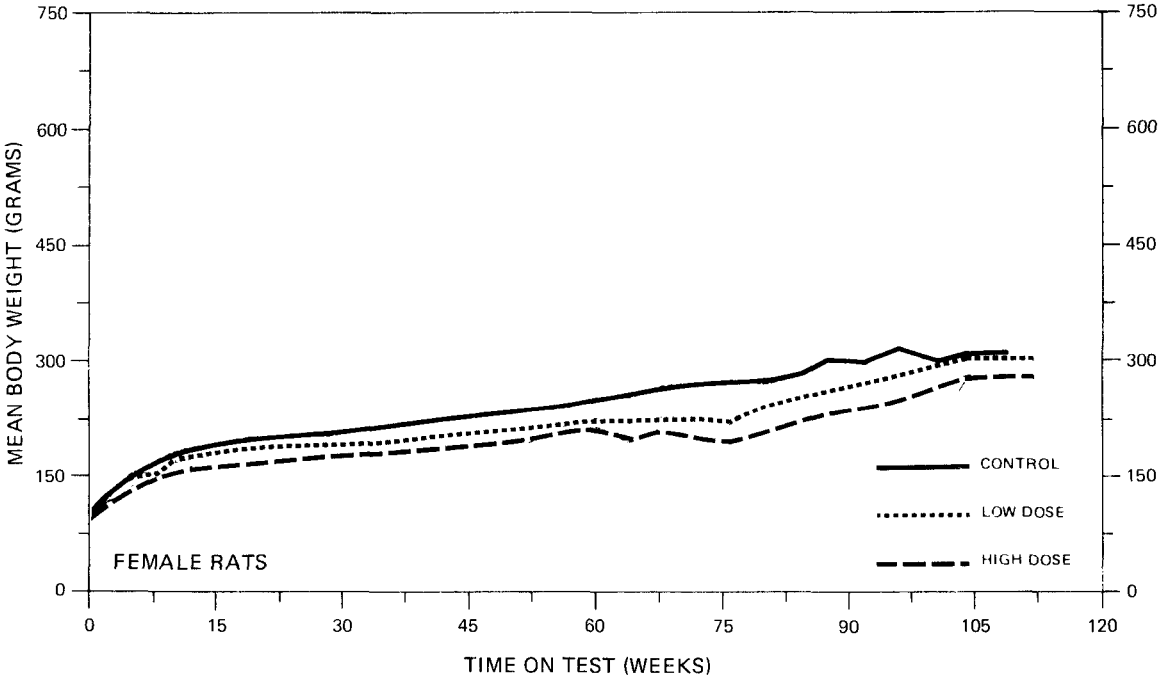
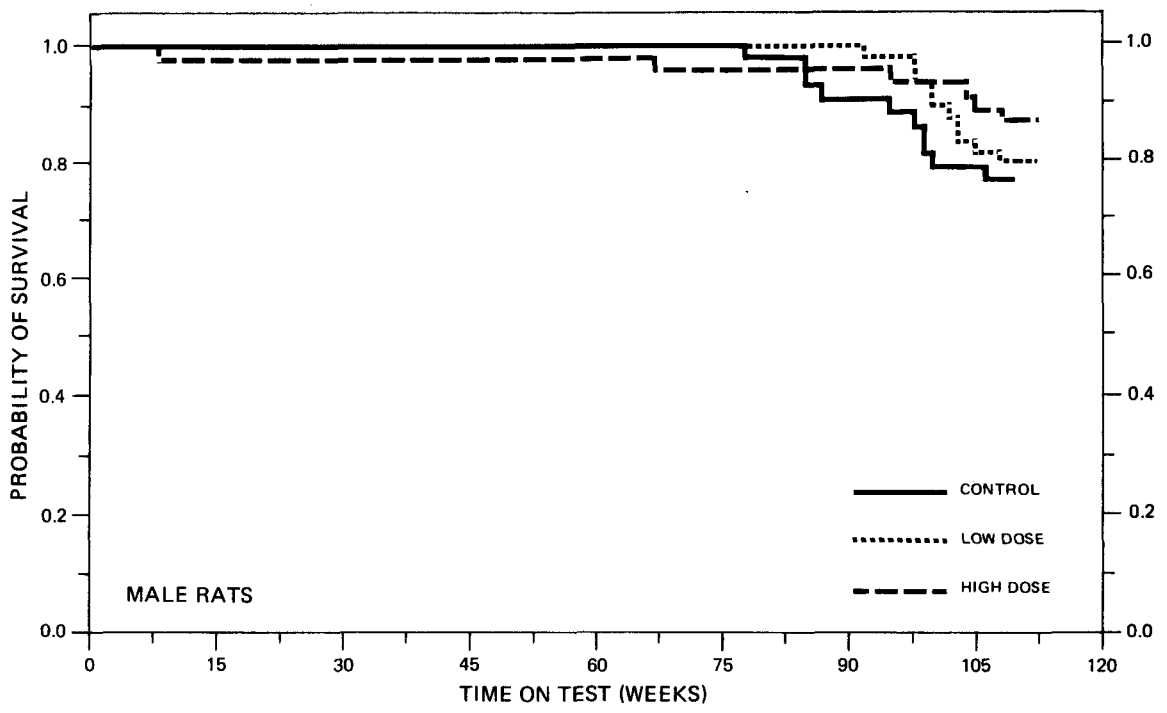


FIGURE 2
GROWTH CURVES FOR APC CHRONIC STUDY RATS



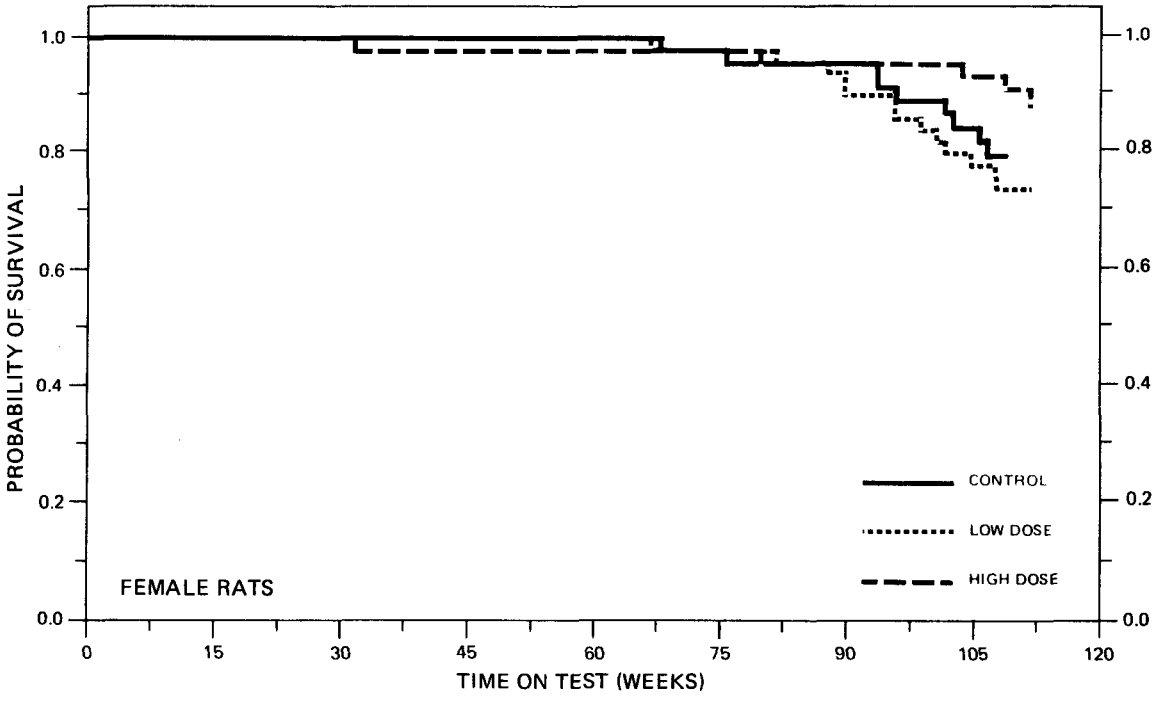


FIGURE 3
SURVIVAL COMPARISONS OF APC CHRONIC STUDY RATS

C. Pathology

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

The only tumors which were observed more frequently in APC-treated rats than in the controls occurred in the endocrine system. Endocrine tumors were found in more low dose males (31/50 or 62 percent) and high dose males (26/49 or 53 percent) than were found in control males (16/47 or 34 percent). Many of these male rats had more than one type of endocrine tumor. In female rats, total endocrine tumor incidence was not affected by APC feeding.

The most common endocrine tumors in both sexes were those of the pituitary gland. These consisted of adenomas defined as well-circumscribed nodules in the anterior lobe composed of a single cell type which compressed adjacent normal tissue and of carcinomas which exhibited nuclear pleomorphism and atypicality and some degree of local invasion. Pituitary tumors were found in 8/47 (17 percent) control males, 18/47 (38 percent) low dose males, and in 12/44 (27 percent) high dose males. In female rats, there were fewer pituitary tumors in the animals that were fed APC (15/43 or 35 percent high dose, 14/44 or 32 percent low dose) than in the controls (20/46 or 43 percent).

Among male rats adrenal tumors were observed more frequently in rats fed APC in their diets than in controls. The tumor found most

frequently in the adrenal was a pheochromocytoma consisting of a rounded nodule of atypical medullary cells which enlarged the medulla, compressed adjacent normal pheochromocytes and frequently distorted the surrounding cortex. Adrenal pheochromocytomas were observed in 7/47 (15 percent) control males, 17/49 (35 percent) low dose males, and 9/48 (19 percent) high dose males. In addition, well-circumscribed adrenal cortical adenomas were observed in 0/47 male controls, 3/49 (6 percent) low dose males, and 1/48 (2 percent) high dose males.

Both follicular-cell and C-cell tumors were found in the thyroid. Treatment with APC did increase the incidence of C-cell tumors in thyroids of male and female rats.

Other endocrine tumors occurred in males only. They consisted of one adenoma of the parathyroid in a control animal and rare islet-cell adenomas (2/47 or 4 percent high dose, 3/47 or 6 percent low dose, 3/45 or 7 percent control) and carcinomas (1/47 or 2 percent high dose, 1/45 or 2 percent control).

Because phenacetin had been linked with the occurrence of renal papillary necrosis and tumors of the urinary tract in man (Johansson et al., 1974), special attention was paid to the urinary system. The chronic renal degenerative disease characteristic of old rats was seen in all groups of animals, being more frequent in males than in females. Its incidence was not affected by APC feeding.

Renal necrosis was not diagnosed in any male rat or in any female of the control and low dose groups. Among the high dose females, there were four rats with renal medullary necrosis, in two cases associated with hyperplasia of the transitional-cell epithelium of the pelvis. One instance of epithelial hyperplasia was noted in the urinary bladder of a control male, another in the bladder of a high dose male. The only nonneoplastic lesion of the bladder observed in the females was a calculus in a high dose female. This was associated with hydronephrosis.

A transitional-cell carcinoma of the bladder was observed in one low dose and one high dose females. A kidney tubular-cell adenocarcinoma was seen in one low dose female and in one low dose male. A transitional-cell papilloma of the kidney was also seen in one high dose female. However, it is concluded that this experiment produced no conclusive evidence that APC induced transitional-cell carcinomas in any portion of the urinary tract. Two of the three high dose female rats exhibiting renal medullary necrosis also showed benign hyperplasia of the renal pelvic epithelium, a much lower incidence of this lesion than that reported by Johansson and Angervall (1976) in Sprague-Dawley females fed phenacetin alone.

The gastrointestinal tract was examined carefully for possible toxic lesions which might be associated with aspirin. No nonneoplastic gastric lesions were noted in either the male or female controls. One instance of acute gastric inflammation was found in a

low dose male rat, and one case of focal gastric inflammation in a high dose female. There were two instances of gastric epithelial hyperplasia in high dose males.

Tumors of the stomach and intestine were only infrequently observed. One mucinous adenocarcinoma of the colon was found in a male control. This had metastasized to the stomach and pancreas. One papillary adenocarcinoma of the ileum was found in a high dose male. No gastric or intestinal tumors were found in any females.

APC was nephrotoxic in less than 10 percent of the high dose female rats. Nephrotoxicity was not apparent in male rats.

D. Statistical Analyses of Results

The results of the statistical analyses of tumor incidence in rats are summarized in Tables 3 and 4. The analysis for every type of tumor that was observed in more than 5 percent of any of the APC-dosed groups of either sex is included.

For male rats both the incidence of pituitary neoplasms and the incidence of pheochromocytomas of the adrenal gland were high in the low dose group. The Fisher exact test was significant both for the pituitary tumors ($P = 0.018$) and the pheochromocytomas ($P = 0.022$) in comparing low dose to control. The Fisher exact tests comparing high dose rats to controls and the Cochran-Armitage tests, however, did not indicate statistically significant results for either the pituitary tumors or the pheochromocytomas. For females no tests showed a positive association between APC administration and tumor incidence.

TABLE 3

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT SPECIFIC SITES IN MALE RATS TREATED WITH APC[a]

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Skin: Fibroma[b]	0/47(0.00)	3/50(0.06)	0/49(0.00)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	---
Lower Limit	---	0.569	---
Upper Limit	---	Infinite	---
Weeks to First Observed Tumor	---	105	---
Hematopoietic System: Malignant Lymphoma or Leukemia[b]	5/47(0.11)	4/50(0.08)	2/49(0.04)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.752	0.389
Lower Limit	---	0.159	0.038
Upper Limit	---	3.285	2.214
Weeks to First Observed Tumor	85	100	112
Liver: Neoplastic Nodule or Hepatocellular Carcinoma[b]	5/47(0.11)	4/50(0.08)	1/49(0.02)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.752	0.192
Lower Limit	---	0.159	0.004
Upper Limit	---	3.285	1.627
Weeks to First Observed Tumor	108	98	112

TABLE 3 (Continued)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Pituitary: Adenoma or Carcinoma NOS[b]	8/47(0.17)	18/47(0.38)	12/44(0.27)
P Values[c]	N.S.	P = 0.018	N.S.
Departure from Linear Trend[e]	P = 0.044	---	---
Relative Risk (Control)[d]	---	2.250	1.602
Lower Limit	---	1.045	0.668
Upper Limit	---	5.337	4.074
Weeks to First Observed Tumor	108	98	78
Adrenal: Cortical Adenoma[b]	0/47(0.00)	3/49(0.06)	1/48(0.02)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.576	0.053
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	112	112
Adrenal: Pheochromocytoma[b]	7/47(0.15)	17/49(0.35)	9/48(0.19)
P Values[c]	N.S.	P = 0.022	N.S.
Departure from Linear Trend[e]	P = 0.016	---	---
Relative Risk (Control)[d]	---	2.329	1.259
Lower Limit	---	1.021	0.457
Upper Limit	---	6.006	3.655
Weeks to First Observed Tumor	108	102	112

TABLE 3 (Continued)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Thyroid: C-Cell Carcinoma[b]	2/46(0.04)	5/48(0.10)	5/46(0.11)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	2.396	2.500
Lower Limit	---	0.414	0.436
Upper Limit	---	24.185	25.197
Weeks to First Observed Tumor	108	98	95
Thyroid: C-Cell Adenoma or C-Cell Carcinoma[b]	4/46(0.09)	9/48(0.19)	8/46(0.17)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	2.156	2.000
Lower Limit	---	0.652	0.580
Upper Limit	---	8.969	8.488
Weeks to First Observed Tumor	108	98	95
Pancreatic Islets: Islet-Cell Adenoma or Islet-Cell Carcinoma[b]	4/45(0.09)	3/47(0.06)	3/47(0.06)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.718	0.718
Lower Limit	---	0.112	0.112
Upper Limit	---	4.010	4.010
Weeks to First Observed Tumor	85	112	112

TABLE 3 (Concluded)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Testis: Interstitial-Cell Tumor[b]	44/47(0.94)	46/49(0.94)	27/49(0.55)
P Values[c]	P < 0.001(N)	N.S.	P < 0.001(N)
Departure from Linear Trend[e]	P = 0.005	---	---
Relative Risk (Control)[d]	---	1.003	0.589
Lower Limit	---	0.907	0.511
Upper Limit	---	1.109	0.756
Weeks to First Observed Tumor	78	100	104

[a]Treated groups received concentrations of 0.7 or 1.4 percent in feed.

[b]Number of tumor-bearing animals/number of animals examined at site (proportion).

[c]The probability level for the Cochran-Armitage test is given beneath the incidence of tumors in the control group when P < 0.05; otherwise, not significant (N.S.) is indicated. The probability level for the Fisher exact test for the comparison of a treated group with the control group is given beneath the incidence of tumors in the treated group when P < 0.05; otherwise, not significant (N.S.) is indicated. For both Cochran-Armitage and Fisher exact tests a negative designation (N) indicates a lower incidence in the treated group(s) than in the control group.

[d]The 95% confidence interval on the relative risk of the treated group to the control group.

[e]The probability level of the test for departure from linear trend is given beneath the control group when P < 0.05.

TABLE 4

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT SPECIFIC SITES IN FEMALE RATS TREATED WITH APC[a]

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Hematopoietic System: Leukemia or Malignant Lymphoma[b]	5/48(0.13)	8/50(0.16)	1/49(0.02)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.536	0.196
Lower Limit	---	0.479	0.004
Upper Limit	---	5.571	1.662
Weeks to First Observed Tumor	96	82	112
Liver: Neoplastic Nodule or Hepatocellular Carcinoma[b]	0/47(0.00)	4/47(0.09)	3/45(0.07)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.929	0.631
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	88	112
Pituitary: Adenoma or Carcinoma NOS[b]	20/46(0.43)	14/44(0.32)	15/43(0.35)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.732	0.802
Lower Limit	---	0.396	0.444
Upper Limit	---	1.319	1.420
Weeks to First Observed Tumor	94	96	112

TABLE 4 (Continued)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Adrenal: Cortical Adenoma or Cortical Carcinoma[b]	4/47(0.09)	4/48(0.08)	2/44(0.05)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.979	0.534
Lower Limit	---	0.193	0.050
Upper Limit	---	4.964	3.523
Weeks to First Observed Tumor	96	112	113
Adrenal: Pheochromocytoma[b]	1/47(0.02)	2/48(0.04)	2/44(0.05)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.958	2.136
Lower Limit	---	0.105	0.115
Upper Limit	---	113.119	123.141
Weeks to First Observed Tumor	109	108	112
Thyroid: Follicular-Cell Adenoma or Follicular-Cell Carcinoma[b]	0/46(0.00)	3/46(0.07)	2/43(0.05)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.602	0.316
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	108	112

TABLE 4 (Continued)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Thyroid: C-Cell Adenoma or C-Cell Carcinoma[b]	3/46(0.07)	8/46(0.17)	4/43(0.09)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	2.667	1.426
Lower Limit	---	0.690	0.255
Upper Limit	---	14.739	9.221
Weeks to First Observed Tumor	109	101	112
Mammary Gland: Fibroadenoma[b]	14/48(0.29)	7/50(0.14)	2/49(0.04)
P Values[c]	P = 0.001(N)	N.S.	P = 0.001(N)
Relative Risk (Control)[d]	---	0.480	0.140
Lower Limit	---	0.180	0.016
Upper Limit	---	1.156	0.563
Weeks to First Observed Tumor	76	105	113
Uterus: Endometrial Stromal Polyp[b]	15/47(0.32)	14/48(0.29)	7/46(0.15)
P Values[c]	P = 0.043(N)	N.S.	N.S.
Relative Risk (Control)[d]	---	0.914	0.477
Lower Limit	---	0.463	0.182
Upper Limit	---	1.796	1.119
Weeks to First Observed Tumor	78	96	78

TABLE 4 (Concluded)

[a]Treated groups received concentrations of 0.7 or 1.4 percent in feed.

[b]Number of tumor-bearing animals/number of animals examined at site (proportion).

[c]The probability level for the Cochran-Armitage test is given beneath the incidence of tumors in the control group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. The probability level for the Fisher exact test for the comparison of a treated group with the control group is given beneath the incidence of tumors in the treated group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. For both Cochran-Armitage and Fisher exact tests a negative designation (N) indicates a lower incidence in the treated group(s) than in the control group.

[d]The 95% confidence interval on the relative risk of the treated group to the control group.

Based upon these results the statistical conclusion is that there was not adequate evidence to demonstrate that APC had a carcinogenic effect on Fischer 344 rats.

The possibility of a negative association between treatment and incidence was noted for mammary fibroadenomas in females. Interstitial-cell tumors of the testis were significant in males; these tumors, however, are well known to have a high and variable incidence (Cockrell and Garner, 1976).

Because many of the male rats were observed to have more than one type of endocrine tumor, additional analyses were conducted based upon the combinations of different endocrine tumors shown in Table 5. No significant positive Fisher exact test results were observed when the Bonferroni criterion was applied.

To provide additional insight into the possible carcinogenicity of this compound, 95 percent confidence intervals on the relative risk have been estimated and entered in the tables based upon the observed tumor incidence rates. In many of the intervals shown in Tables 3 and 4, the value one is included; this indicates the absence of statistically significant results. It should also be noted that many of the confidence intervals have an upper limit greater than one, indicating the theoretical possibility of tumor induction in rats by APC that could not be established under the conditions of this test.

TABLE 5

APC-TREATED MALE RATS WITH MORE THAN ONE ENDOCRINE TUMOR

TYPE OF TUMOR	CONTROL[a]	LOW DOSE[a]	HIGH DOSE[a]
Pituitary Adenoma NOS and Adrenal Pheochromocytoma	1/47	5/46	1/43
Pituitary Adenoma NOS and Adrenal Cortical Adenoma	0/47	1/46	0/43
Pituitary Adenoma NOS and Thyroid C-Cell Neoplasm[b]	2/46	1/45	1/41
Pituitary Adenoma NOS and Pancreatic Islets: Islet-Cell Neoplasm[c]	1/45	1/44	0/42
Adrenal Pheochromocytoma and Thyroid C-Cell Neoplasm[b]	1/46	4/47	1/45
Adrenal Pheochromocytoma and Parathyroid Adenoma NOS	1/24	0/26	0/25
Adrenal Pheochromocytoma and Adrenal Cortical Adenoma	0/47	1/49	0/48
Adrenal Cortical Adenoma and Thyroid C-Cell Neoplasm[b]	0/46	0/47	1/45
Thyroid C-Cell Neoplasm[b] and Thyroid Follicular-Cell Adenoma	0/46	0/48	1/46
Pituitary Adenoma NOS and Adrenal Pheochromocytoma and Pancreatic Islet: Islet-Cell Neoplasm[c]	1/45	0/43	1/41
Pituitary Adenoma NOS and Adrenal Pheochromocytoma and Thyroid C-Cell Neoplasm	0/46	1/44	0/40
Pituitary Adenoma NOS and Adrenal Pheochromocytoma and Thyroid C-Cell Neoplasm and Adrenal Cortical Adenoma	0/46	1/44	0/40

[a]Number of animals with these tumors/number of animals with tissues examined from all sites listed.

[b]Thyroid: C-cell adenoma or C-cell carcinoma.

[c]Pancreatic Islets: Islet-cell adenoma or Islet-cell carcinoma.

IV. CHRONIC TESTING RESULTS: MICE

A. Body Weights and Clinical Observations

The mean body weights in treated mice of both sexes were generally depressed in comparison with controls (Figure 4).

No clinical abnormalities were recorded for any treated or control mice.

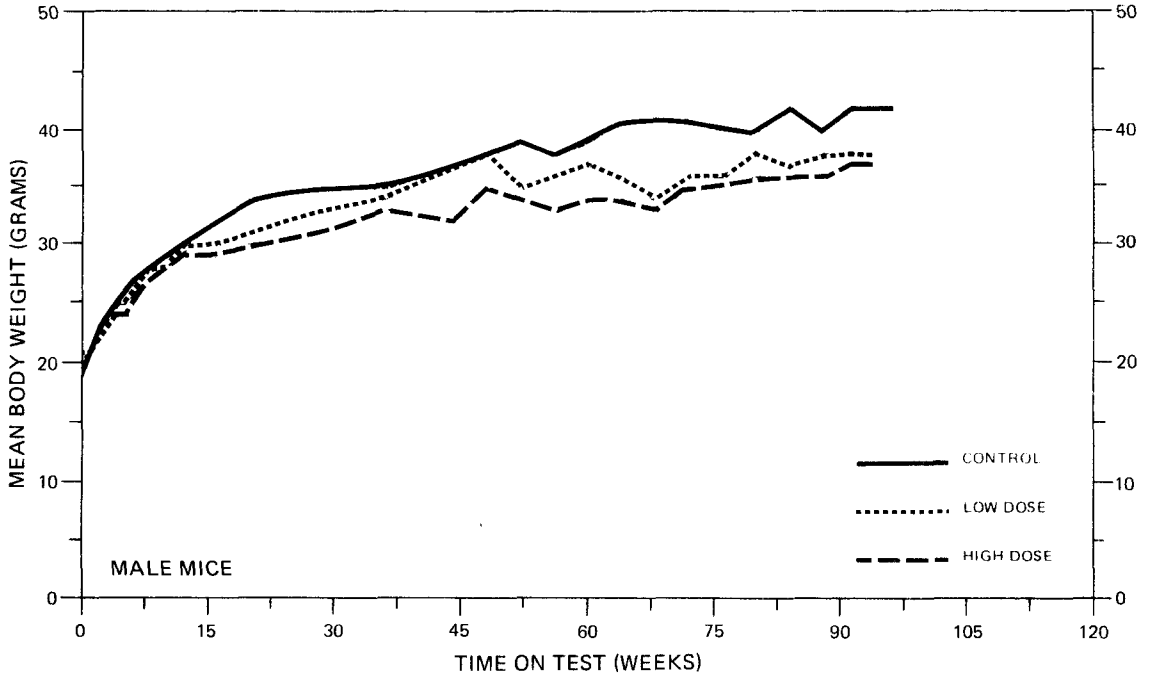
B. Survival

The estimated probabilities of survival for male and female mice in the control and APC-treated groups are shown in Figure 5.

For male mice the Tarone test indicated a significant ($P = 0.013$) positive association between dosage and mortality. The survival was high, however, with 72 percent (36/50) of the high dose group surviving until the end of the study. Five high dose mice were sacrificed in week 78. Eighty-eight percent (44/50) of the low dose and 84 percent (42/50) of the control group survived until the end of the study. Five control group males were sacrificed in week 78.

For female mice there was no significant association between dose and mortality. Eighty-two percent (41/50) of the high dose and 74 percent (37/50) of the control group females survived until the end of the study, despite the sacrifice of five mice from each group in week 78. Eighty-six percent (43/50) of the low dose group survived until the end of the study.

In both sexes survival was adequate for meaningful statistical analysis of tumor incidence.



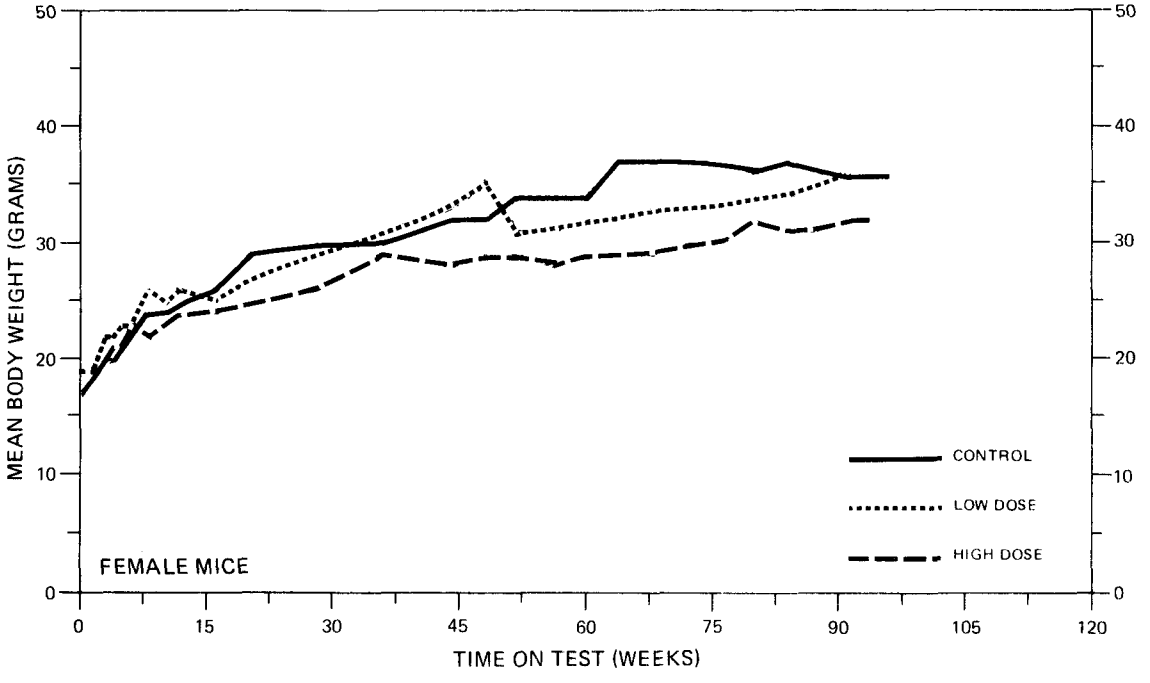
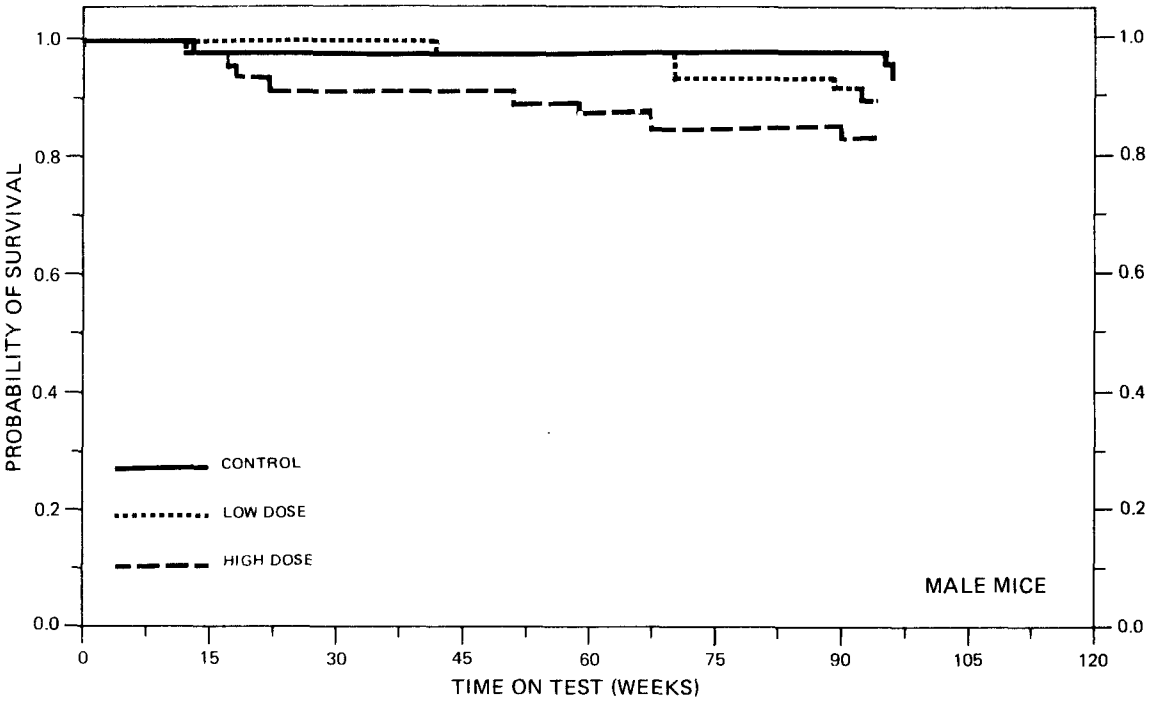


FIGURE 4
GROWTH CURVES FOR APC CHRONIC STUDY MICE



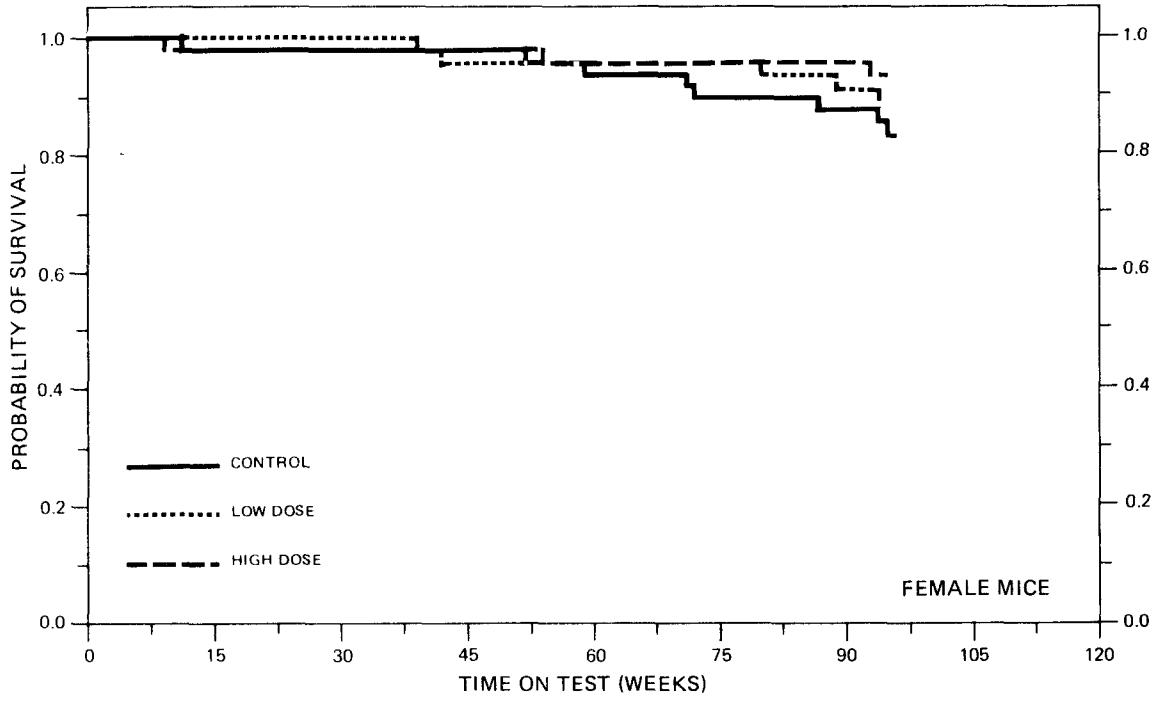


FIGURE 5
SURVIVAL COMPARISONS OF APC CHRONIC STUDY MICE

C. Pathology

Histopathologic findings on neoplasms in mice are tabulated in Appendix B (Tables B1 and B2); findings on nonneoplastic lesions are tabulated in Appendix D (Tables D1 and D2).

Results of this histopatologic examination did not indicate any difference in tumor incidence among mice fed APC in the diet as compared to control animals. In contrast to rats, tumors of the endocrine system were infrequently observed in mice and were not associated with APC administration. No tumors of the kidney or urinary bladder were found in treated or control mice of either sex. The results of the histopathologic examination for nonneoplastic lesions (Appendix D) indicate that APC was not toxic to the kidneys or gastrointestinal tracts of treated mice.

D. Statistical Analyses of Results

The results of the statistical analyses of tumor incidence in mice are summarized in Tables 6 and 7. The analysis for every type of tumor that was observed in more than 5 percent of any of the APC-dosed groups of either sex is included.

For both male and female mice there were no statistically significant positive associations between dosage and tumor incidence. Based upon these results there was no conclusive evidence of the carcinogenicity of APC in mice at the dose levels used in this experiment.

TABLE 6

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT SPECIFIC SITES IN MALE MICE TREATED WITH APC[a]

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Lung: Alveolar/Bronchiolar Adenoma or Alveolar/Bronchiolar Carcinoma[b]	6/48(0.13)	9/46(0.20)	12/47(0.26)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.565	2.043
Lower Limit	---	0.542	0.778
Upper Limit	---	4.924	6.082
Weeks to First Observed Tumor	96	94	94
Hematopoietic System: Leukemia or Malignant Lymphoma[b]	4/48(0.08)	7/48(0.15)	4/48(0.08)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.750	1.000
Lower Limit	---	0.477	0.196
Upper Limit	---	7.660	5.071
Weeks to First Observed Tumor	96	93	94
Liver: Hepatocellular Carcinoma[b]	7/48(0.15)	11/46(0.24)	6/47(0.13)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.640	0.875
Lower Limit	---	0.637	0.261
Upper Limit	---	4.551	2.813
Weeks to First Observed Tumor	78	94	94

TABLE 6 (Concluded)

[a]Treated groups received concentrations of 0.7 or 1.4 percent in feed.

[b]Number of tumor-bearing animals/number of animals examined at site (proportion).

[c]The probability level for the Cochran-Armitage test is given beneath the incidence of tumors in the control group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. The probability level for the Fisher exact test for the comparison of a treated group with the control group is given beneath the incidence of tumors in the treated group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. For both Cochran-Armitage and Fisher exact tests a negative designation (N) indicates a lower incidence in the treated group(s) than in the control group.

[d]The 95% confidence interval on the relative risk of the treated group to the control group.

TABLE 7

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT SPECIFIC SITES IN FEMALE MICE TREATED WITH APC[a]

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Lung: Alveolar/Bronchiolar Adenoma or Alveolar/Bronchiolar Carcinoma[b]	4/46(0.09)	7/45(0.16)	4/47(0.09)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.789	0.979
Lower Limit	---	0.491	0.193
Upper Limit	---	7.797	4.955
Weeks to First Observed Tumor	96	94	94
Hematopoietic System: Leukemia or Malignant Lymphoma[b]	5/48(0.10)	6/45(0.13)	5/47(0.11)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.280	1.021
Lower Limit	---	0.350	0.251
Upper Limit	---	4.939	4.153
Weeks to First Observed Tumor	96	94	94
Liver: Hepatocellular Carcinoma[b]	1/47(0.02)	2/45(0.04)	3/47(0.06)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	2.089	3.000
Lower Limit	---	0.113	0.251
Upper Limit	---	120.488	154.014
Weeks to First Observed Tumor	96	94	93

TABLE 7 (Concluded)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Pituitary: Adenoma NOS[b]	2/42(0.05)	4/38(0.11)	2/41(0.05)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	2.211	1.024
Lower Limit	---	0.336	0.078
Upper Limit	---	23.279	13.545
Weeks to First Observed Tumor	96	94	94

[a]Treated groups received concentrations of 0.7 or 1.4 percent in feed.

[b]Number of tumor-bearing animals/number of animals examined at site (proportion).

[c]The probability level for the Cochran-Armitage test is given beneath the incidence of tumors in the control group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. The probability level for the Fisher exact test for the comparison of a treated group with the control group is given beneath the incidence of tumors in the treated group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. For both Cochran-Armitage and Fisher exact tests a negative designation (N) indicates a lower incidence in the treated group(s) than in the control group.

[d]The 95% confidence interval on the relative risk of the treated group to the control group.

To provide additional insight into the possible carcinogenicity of this compound, 95 percent confidence intervals on the relative risk have been estimated and entered in the tables based upon the observed tumor incidence rates. In all of the intervals shown in Tables 6 and 7, the value one is included; this indicates the absence of statistically significant results. It should also be noted that all of the confidence intervals have an upper limit greater than one, indicating the theoretical possibility of tumor induction in mice by APC that could not be established under the conditions of this test.

V. DISCUSSION

In both sexes of rats and in female mice there were no significant associations between administration of APC and mortality; however, there was a significant positive association between compound administration and mortality in male mice. In both species, adequate numbers of APC-treated animals survived sufficiently long for meaningful statistical analysis of tumor incidence.

In rats tumors of the endocrine system were observed almost twice as often in treated males as in controls (i.e., 16/47 [34 percent], 31/50 [62 percent], and 26/49 [53 percent] in the control, low dose, and high dose groups, respectively). The endocrine tumors most frequently observed were adenomas and carcinomas of the pituitary gland (8/47 [17 percent], 18/47 [38 percent], and 12/44 [27 percent] in the control, low dose, and high dose groups, respectively). Only one of the Fisher exact tests, the one comparing low dose and controls, provided a statistically significant result and it was not supported by significance from either the other male rat Fisher exact test or the Cochran-Armitage test.

Pheochromocytomas of the adrenal were also a major contributor to the frequency with which endocrine tumors were observed in male rats. In the control, low dose, and high dose groups the incidences of this tumor were 7/47 (15 percent), 17/49 (35 percent), and 9/48 (19 percent), respectively. The Fisher exact test for the comparison of the incidence of adrenal pheochromocytomas in the low dose to that

in the control group was significant. The high dose to control Fisher exact comparison, however, was not.

Johansson et al. (1974) indicated a relationship between phenacetin exposure and papillary necrosis and tumors of the urinary tract in man. Renal medullary necrosis was observed in only four high dose females. The presence of five neoplasms in the urinary system of rats receiving APC was not considered sufficient evidence to incriminate APC, since similar tumors occasionally appear in control animals in this program.

The gastrointestinal tract was examined for the toxic lesions which might have been expected to be associated with ingestion of aspirin. One case of acute gastric inflammation was observed in a low dose male rat and one case of focal gastric inflammation in a high dose female rat.

Although adequate numbers of animals survived sufficiently long for meaningful statistical analysis of tumor incidence, no effect of APC administration on tumor incidence was observed and no conclusive evidence was provided for APC-induced toxic lesions in the kidney, stomach, or intestine.

Johansson and Angervall (1976) reported that long-term feeding of phenacetin (0.535 percent of the diet for 110 weeks) to female Sprague-Dawley rats produced mammary carcinoma in 5/30 test animals (1/30 controls) and carcinoma of the ear duct in 4/30 test animals (0/30 controls). Johansson and Angervall concluded that phenacetin

had weak carcinogenic activity in Sprague-Dawley rats. In the chronic bioassay of APC performed at Mason Research Institute, Fischer 344 rats were fed phenacetin for 78 weeks, at levels of 0.644 percent of the diet for the high dose groups and 0.322 percent of the diet for low dose groups. No mammary gland carcinomas or carcinomas of the ear duct were reported in rats fed APC in this bioassay, although one mammary adenocarcinoma was observed in a female control rat. Johansson and Angervall also observed urothelial hyperplasia of the renal papillae in 26/30 rats and dilation of the vasa recta in 28/30 rats. In this APC bioassay, renal pelvic epithelial hyperplasias were reported in 2/46 high dose female rats but no renal pelvic epithelial hyperplasias were observed in other female rat groups or in male rat groups. No vascular dilation was reported among rats in this APC bioassay. Differences between histopathologic results of Johansson and Angervall's phenacetin bioassay and results of this APC bioassay could have been due to the different strains of rats used, to the presence of aspirin and caffeine, or to expected variability in spontaneous tumor incidence.

Under the conditions of this bioassay sufficient evidence was not provided for the carcinogenicity of APC in Fischer 344 rats or in B6C3F1 mice.

VI. BIBLIOGRAPHY

Armitage, P., Statistical Methods in Medical Research, Chapter 14. J. Wiley & Sons, New York, 1971.

Barr, W.H. and R.P. Perro, "Internal Analysis." Handbook of Non-Prescription Drugs. The American Pharmaceutical Association, Washington, D.C., pp. 36-50, 1973.

Berenblum, I., editor, Carcinogenicity Testing. International Union Against Cancer, Technical Report Series, Vol. 2. International Union Against Cancer, Geneva, 1969.

Caughay, D.E., I.C. Isdale, J.M. Tweed, B.L.J. Tresdwell, J.K. Laing, and J. Kirk, "Aspirin and the Kidney." British Medical Journal I:593-596, 1974.

Chemical Abstracts Service, The Chemical Abstracts Service (CAS) Ninth Collective Index, Volumes 76-85, 1972-1976. American Chemical Society, Washington, D.C., 1977.

Cockrell, B. and F.M. Garner, "Interstitial-Cell Tumor of the Testis in Rats." Comparative Pathology Bulletin 8(2):2-4, 1976.

Cox, D.R., Analysis of Binary Data, Chapters 4 and 5. Methuen and Co., Ltd., London, 1970.

Cox, D.R., "Regression Models and Life-Tables." Journal of the Royal Statistical Society, Series "B" 34:187-220, 1972.

Gart, J.J., "The Comparison of Proportions: A Review of Significance Tests, Confidence Limits, and Adjustments for Stratification." International Statistical Institute Review 39:148-169, 1971.

Gault, M.H., "The Clinical Course of Patients with Analgesic Nephropathy." Canadian Medical Association Journal I:204-207, 1975.

Handbook of Non-Prescription Drugs, Fifth edition. "Products 10 Internal Analgesic." The American Pharmaceutical Association, Washington, D.C., pp. 129-133, 1977.

Johansson, S. and L. Angervall, "Urothelial Changes in the Renal Papillae in Sprague-Dawley Rats Induced by Long Term Feeding of Phenacetin." Astor Pathologico et Microbiologico Scandinavia Section A 84:375-383, 1976.

Johansson, S., L. Angervall, U. Bengtsson, and L. Wahlqvist, "Urothelial Tumors of the Renal Pelvis Associated with Abuse of Phenacetin-containing Analgesics." Cancer 33:743-753, 1974.

Juusela, H., "Carcinoma of the Renal Pelvis and its Relationship to Analgesic Abuse." Annales Chirurgiae et Gynaecologiae Fenmiae 63:386-390, 1973.

Kaplan, E.L., and P. Meier, "Nonparametric Estimation from Incomplete Observations." Journal of the American Statistical Association 53:457-481, 1958.

Linhart, M.S., J.A. Cooper, R.L. Martin, N.P. Page, and J.A. Peters, "Carcinogenesis Bioassay Data System." Computers and Biomedical Research 7:230-248, 1974.

Macklon, A.F., A.W. Craft, M. Thomson, and D.N. Kerr, "Aspirin and Analgesic Nephropathy." British Medical Journal I:597-600, 1974.

Medical Journal of Australia, "Aspirin and Chronic Gastric Ulcer." Vol. I, pp. 104-105, 1976.

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

Nanra, R.S., "Analgesic Nephropathy." Medical Journal of Australia I:745-748, 1976.

Saffiotti, U., R. Montesano, A.R. Sellakumar, F. Cefis, and D.G. Kaufman, "Respiratory Tract Carcinogenesis in Hamsters Induced by Different Numbers of Administration of Benzo (a) Pyrene and Ferric Oxide." Cancer Research 32:1073-1079, 1972.

Sax, N.I., Dangerous Properties of Industrial Materials. Van Nostrand Reinhold Company, New York, 1975.

Stecher, P.G., editor, The Merck Index: An Encyclopedia of Chemicals and Drugs, Eighth edition. Merck and Company, Inc., Rahway, New Jersey, 1968.

Tarone, R.E., "Tests for Trend in Life-Table Analysis." Biometrika 62:679-682, 1975.

U.S International Trade Commission, Synthetic Organic Chemicals. United States Production and Sales, 1975. USITC Publication 804, Washington, D.C., 1977.

Weisburger, E., Chief, Carcinogen and Toxicology Branch, National Cancer Institute, Bethesda, Maryland. Personal communication, 1975.

Windholz, M., editor, The Merck Index: An Encyclopedia of Chemicals and Drugs, Ninth edition. Merck and Company, Inc., Rahway, New Jersey, 1976.

Review of the Bioassay of a Mixture of
Aspirin, Phenacetin, and Caffeine (APC)* for Carcinogenicity
by the Data Evaluation/Risk Assessment Subgroup of the
Clearinghouse on Environmental Carcinogens

March 7, 1978

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 a mixture of Aspirin, Phenacetin, and Caffeine (APC) for carcinogenicity.

The primary reviewer noted the higher incidence of endocrine tumors in treated male rats than in the associated controls, although the incidence was not statistically significant. After briefly describing the experimental design and conditions of test, he raised the question as to whether the increased incidence of endocrine tumors was sufficient cause to consider a retest of APC.

The secondary reviewer said that APCs are still commonly used. He questioned the significance of the five urinary tract transitional-cell neoplasms in the treated rats. In reviewing the historical controls, a Program staff member said that the incidence of renal papillomas in male rats was 0 out of 255 and in females 1 out of 235. It was noted that a statement in the report summary is needed in regard to the urinary tract tumors. It was suggested that the

report summary conclusion be rewritten to indicate that the evidence was insufficient to assess the carcinogenicity of APC.

It was moved that the report on the bioassay of APC be accepted with the appropriate modifications in the report summary section. It was further moved that the APC be considered for retest. The motion was seconded and approved unanimously.

Members present were:

Gerald N. Wogan (Chairman), Massachusetts Institute of Technology
Arnold Brown, Mayo Clinic
E. Cuyler Hammond, American Cancer Society
Joseph Highland, Environmental Defense Fund
Henry Pitot, University of Wisconsin Medical Center
George Roush, Jr., Monsanto Company
Michael Shimkin, University of California at San Diego

---

* 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:1978 260-899/3109 1-3

APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS TREATED WITH APC

TABLE A1
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS TREATED WITH APC

	CONTROL (UNTR) 01-0055	LOW DOSE 01-0058	HIGH DOSE 01-0059
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS MISSING	2		
ANIMALS NECROPSIED	47	50	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	47	50	49
INTEGUMENTARY SYSTEM			
*SKIN	(47)	(50)	(49)
SQUAMOUS CELL PAPILLOMA	1 (2%)	1 (2%)	
SQUAMOUS CELL CARCINOMA			1 (2%)
BASAL-CELL CARCINOMA			1 (2%)
SARCOMA, NOS		1 (2%)	
FIBROMA		3 (6%)	
FIBROSARCOMA			1 (2%)
LIPOMA		1 (2%)	
LEIOMYOSARCOMA	1 (2%)		
GRANULAR-CELL TUMOR, BENIGN		1 (2%)	
*SUBCUT TISSUE	(47)	(50)	(49)
BASAL-CELL CARCINOMA	1 (2%)		
FIBROMA	7 (15%)		
RESPIRATORY SYSTEM			
#TRACHEA	(46)	(48)	(48)
SQUAMOUS CELL CARCINOMA		1 (2%)	
#LUNG	(47)	(50)	(49)
HEPATOCELLULAR CARCINOMA, METAST		1 (2%)	
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (2%)		
ALVEOLAR/BRONCHIOLAR CARCINOMA			2 (4%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(47)	(50)	(49)
MALIGNANT LYMPHOMA, NOS	1 (2%)		
LEUKEMIA,NOS	1 (2%)		
UNDIFFERENTIATED LEUKEMIA	1 (2%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
**EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE A1 (CONTINUED)

	CONTROL (UNTR) 01-0055	LOW DOSE 01-0058	HIGH DOSE 01-0059
MYELOMONOCYTIC LEUKEMIA	1 (2%)	3 (6%)	
LYMPHOCYTIC LEUKEMIA			1 (2%)
#SPLEEN	(47)	(50)	(49)
MUCINOUS ADENOCARCINOMA, METASTA	1 (2%)		
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	1 (2%)		
LEUKEMIA,NOS		1 (2%)	
#MEDIASTINAL L.NODE	(42)	(41)	(42)
MUCINOUS ADENOCARCINOMA, METASTA	1 (2%)		
#PEYERS PATCH	(47)	(49)	(47)
MALIGNANT LYMPHOMA, NOS			1 (2%)
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
*ORAL CAVITY	(47)	(50)	(49)
FIBROSARCOMA	1 (2%)		
#LIVER	(47)	(50)	(49)
NEOPLASTIC NODULE	5 (11%)	3 (6%)	1 (2%)
HEPATOCELLULAR CARCINOMA		1 (2%)	
#PANCREAS	(45)	(47)	(47)
MUCINOUS ADENOCARCINOMA, METASTA	1 (2%)		
#STOMACH	(47)	(49)	(47)
MUCINOUS ADENOCARCINOMA, METASTA	1 (2%)		
#ILEUM	(47)	(49)	(47)
PAPILLARY ADENOCARCINOMA			1 (2%)
#COLON	(46)	(46)	(43)
MUCINOUS ADENOCARCINOMA	1 (2%)		
URINARY SYSTEM			
#KIDNEY	(47)	(50)	(49)
TUBULAR-CELL ADENOCARCINOMA		1 (2%)	

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

TABLE A1 (CONTINUED)

	CONTROL (UNTR) 01-0055	LOW DOSE 01-0058	HIGH DOSE 01-0059
LIPOMA	1 (2%)		1 (2%)
NEPHROBLASTOMA		1 (2%)	
ENDOCRINE SYSTEM			
#PITUITARY	(47)	(47)	(44)
CARCINOMA, NOS		2 (4%)	1 (2%)
ADENOMA, NOS	8 (17%)	16 (34%)	11 (25%)
#ADRENAL	(47)	(49)	(48)
CORTICAL ADENOMA		3 (6%)	1 (2%)
PHEOCHROMOCYTOMA	7 (15%)	17 (35%)	9 (19%)
#THYROID	(46)	(48)	(46)
FOLLICULAR-CELL ADENOMA			1 (2%)
C-CELL ADENOMA	2 (4%)	4 (8%)	3 (7%)
C-CELL CARCINOMA	2 (4%)	5 (10%)	5 (11%)
#PARATHYROID	(24)	(27)	(25)
ADENOMA, NOS	1 (4%)		
#PANCREATIC ISLETS	(45)	(47)	(47)
ISLET-CELL ADENOMA	3 (7%)	3 (6%)	2 (4%)
ISLET-CELL CARCINOMA	1 (2%)		1 (2%)
REPRODUCTIVE SYSTEM			
*PREPUTIAL GLAND	(47)	(50)	(49)
ADENOMA, NOS	1 (2%)	1 (2%)	
*SEMINAL VESICLE	(47)	(50)	(49)
MUCINOUS ADENOCARCINOMA, METASTA	1 (2%)		
#TESTIS	(47)	(49)	(49)
INTERSTITIAL-CELL TUMOR	44 (94%)	46 (94%)	27 (55%)
NERVOUS SYSTEM			
#BRAIN/MENINGES	(45)	(50)	(48)
SQUAMOUS CELL CARCINOMA, METASTA		1 (2%)	
#BRAIN	(45)	(50)	(48)
ASTROCYTOMA		1 (2%)	

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

TABLE A1 (CONTINUED)

	CONTROL (UNTR) 01-0055	LOW DOSE 01-0058	HIGH DOSE 01-0059
SPECIAL SENSE ORGANS			
*EAR CANAL	(47)	(50)	(49)
SQUAMOUS CELL CARCINOMA	1 (2%)	1 (2%)	
CERUMINOUS CARCINOMA		1 (2%)	
MUSCULOSKEIETAL SYSTEM			
*STERNUM	(47)	(50)	(49)
MUCINOUS ADENOCARCINOMA, METASTA	1 (2%)		
BODY CAVITIES			
*BODY CAVITIES	(47)	(50)	(49)
MESOTHELIOMA, MALIGNANT	2 (4%)		
*MEDIASTINUM	(47)	(50)	(49)
ALVEOLAR/BRONCHIOLAR CA, METASTA			1 (2%)
*ABDOMINAL CAVITY	(47)	(50)	(49)
LEIOMYOSARCOMA			1 (2%)
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	2	4	3
MORIBUND SACRIFICE	8	6	3
SCHEDULED SACRIFICE	5		5
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	33	40	39
ANIMAL MISSING	2		

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE A1 (CONCLUDED)

	CONTROL (UNTR) 01-0055	LOW DOSE 01-0058	HIGH DOSE 01-0059
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	47	50	38
TOTAL PRIMARY TUMORS	96	118	72
TOTAL ANIMALS WITH BENIGN TUMORS	47	47	36
TOTAL BENIGN TUMORS	76	96	55
TOTAL ANIMALS WITH MALIGNANT TUMORS	11	17	14
TOTAL MALIGNANT TUMORS	15	19	16
TOTAL ANIMALS WITH SECONDARY TUMORS#	1	2	1
TOTAL SECONDARY TUMORS	6	2	1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	5	3	1
TOTAL UNCERTAIN TUMORS	5	3	1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

TABLE A2
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS TREATED WITH APC

	CONTROL (UNTR) 02-0055	LOW DOSE 02-0058	HIGH DOSE 02-0059
ANIMALS INITIALLY IN STUDY	50	50	@50
ANIMALS MISSING	2		
ANIMALS NECROPSIED	48	50	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	47	50	49
INTEGUMENTARY SYSTEM			
*SKIN	(48)	(50)	(49)
SQUAMOUS CELL PAPILLOMA			1 (2%)
SQUAMOUS CELL CARCINOMA			1 (2%)
FIBROMA			1 (2%)
FIBROSARCOMA		1 (2%)	
LIPOMA		1 (2%)	
*SUBCUT TISSUE	(48)	(50)	(49)
SQUAMOUS CELL CARCINOMA		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(47)	(48)	(45)
HEPATOCELLULAR CARCINOMA, METAST		1 (2%)	
TUBULAR-CELL ADENOCARCINOMA, MET		1 (2%)	
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(48)	(50)	(49)
MALIGNANT LYMPHOMA, NOS	2 (4%)		
LEUKEMIA,NOS		1 (2%)	1 (2%)
MYELOMONOCYTIC LEUKEMIA	3 (6%)	4 (8%)	
#SPLEEN	(47)	(48)	(45)
LEUKEMIA,NOS		1 (2%)	
MYELOMONOCYTIC LEUKEMIA		1 (2%)	
#LYMPH NODE	(40)	(46)	(44)
HEPATOCELLULAR CARCINOMA, METAST		1 (2%)	
#SMALL INTESTINE	(46)	(46)	(45)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
**EXCLUDES PARTIALLY AUTOLYZED ANIMALS
@ 50 ANIMAL WERE INITIALLY IN THE STUDY, BUT 1 ANIMAL WAS FOUND TO BE A MALE ANIMAL

TABLE A2 (CONTINUED)

	CONTROL (UNTR) 02-0055	LOW DOSE 02-0058	HIGH DOSE 02-0059
#THYMUS	(39)	(30)	(33)
THYMOMA	1 (3%)		
CIRCULATORY SYSTEM			
#HEART	(47)	(48)	(46)
HEPATOCELLULAR CARCINOMA, METAST		1 (2%)	
DIGESTIVE SYSTEM			
#LIVER	(47)	(47)	(45)
NEOPLASTIC NODULE		3 (6%)	3 (7%)
HEPATOCELLULAR CARCINOMA		1 (2%)	
TUBULAR-CELL ADENOCARCINOMA, MET		1 (2%)	
#PANCREAS	(46)	(46)	(44)
TUBULAR-CELL ADENOCARCINOMA, MET		1 (2%)	
URINARY SYSTEM			
#KIDNEY	(47)	(47)	(46)
TRANSITIONAL-CELL PAPILLOMA			1 (2%)
TUBULAR-CELL ADENOCARCINOMA		1 (2%)	
#URINARY BLADDER	(47)	(47)	(46)
TRANSITIONAL-CELL CARCINOMA		1 (2%)	1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(46)	(44)	(43)
CARCINOMA,NOS	2 (4%)		1 (2%)
ADENOMA, NOS	18 (39%)	14 (32%)	14 (33%)
#ADRENAL	(47)	(48)	(44)
CORTICAL ADENOMA	3 (6%)	4 (8%)	1 (2%)
CORTICAL CARCINOMA	1 (2%)		1 (2%)
PHEOCHROMOCYTOMA	1 (2%)	2 (4%)	2 (5%)
LIPOMA		1 (2%)	
#ADRENAL MEDULLA	(47)	(48)	(44)
GANGLIONEUROMA			1 (2%)

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

TABLE A2 (CONTINUED)

	CONTROL (UNTR) 02-0055	LOW DOSE 02-0058	HIGH DOSE 02-0059
#THYROID	(46)	(46)	(43)
FOLLICULAR-CELL ADENOMA		1 (2%)	
FOLLICULAR-CELL CARCINOMA		2 (4%)	2 (5%)
C-CELL ADENOMA		4 (9%)	2 (5%)
C-CELL CARCINOMA	3 (7%)	4 (9%)	2 (5%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(48)	(50)	(49)
ADENOCARCINOMA, NOS	1 (2%)		
PAPILLARY CYSTADENOMA, NOS	1 (2%)		
FIBROADENOMA	14 (29%)	7 (14%)	2 (4%)
*VAGINA	(48)	(50)	(49)
SARCOMA, NOS	1 (2%)		
#UTERUS	(47)	(48)	(46)
ADENOCARCINOMA, NOS	2 (4%)	3 (6%)	
ADENOCA IN ADENOMATOUS POLYP		1 (2%)	
ENDOMETRIAL STROMAL POLYP	15 (32%)	14 (29%)	7 (15%)
#CERVIX UTERI	(47)	(48)	(46)
LEIOMYOMA		1 (2%)	
#OVARY	(46)	(48)	(45)
HEPATOCELLULAR CARCINOMA, METAST		1 (2%)	
GRANULOSA-CELL TUMOR			1 (2%)
GRANULOSA-CELL CARCINOMA	1 (2%)		
NERVOUS SYSTEM			
#BRAIN	(47)	(48)	(46)
ASTROCYTOMA	1 (2%)		
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			

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

TABLE A2 (CONCLUDED)

	CONTROL (UNTR) 02-0055	LOW DOSE 02-0058	HIGH DOSE 02-0059
BODY CAVITIES			
*MEDIASTINUM	(48)	(50)	(49)
TUBULAR-CELL ADENOCARCINOMA, MET		1 (2%)	
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	3	9	4
MORIBUND SACRIFICE	6	4	1
SCHEDULED SACRIFICE	5		5
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	34	37	39
ANIMAL MISSING	2		
ANIMAL DELETED			1
@ INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	42	41	32
TOTAL PRIMARY TUMORS	70	75	45
TOTAL ANIMALS WITH BENIGN TUMORS	38	28	26
TOTAL BENIGN TUMORS	53	49	32
TOTAL ANIMALS WITH MALIGNANT TUMORS	14	20	7
TOTAL MALIGNANT TUMORS	17	23	9
TOTAL ANIMALS WITH SECONDARY TUMORS#		2	
TOTAL SECONDARY TUMORS		8	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT		3	4
TOTAL UNCERTAIN TUMORS		3	4
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 TREATED WITH APC

TABLE B1
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE TREATED WITH APC

	CONTROL (UNTR) 05-0037	LOW DOSE 05-0058	HIGH DOSE 05-0059
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS MISSING		1	1
ANIMALS NECROPSIED	48	48	48
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	48	47	48
INTEGUMENTARY SYSTEM			
*SKIN	(48)	(48)	(48)
FIBROSARCOMA		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(48)	(46)	(47)
ALVEOLAR/BRONCHIOLAR ADENOMA		6 (13%)	7 (15%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	6 (13%)	3 (7%)	5 (11%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(48)	(48)	(48)
MALIGNANT LYMPHOMA, NOS	2 (4%)		
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	2 (4%)	4 (8%)	2 (4%)
#SPLEEN	(47)	(46)	(46)
HEMANGIOMA	1 (2%)		
HEMANGIOSARCOMA			1 (2%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)	
#LYMPH NODE	(44)	(44)	(41)
PLASMA-CELL TUMOR			1 (2%)
#MANDIBULAR L. NODE	(44)	(44)	(41)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)	
#MESENTERIC L. NODE	(44)	(44)	(41)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)
#PEYERS PATCH	(48)	(45)	(45)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)	1 (2%)
CIRCULATORY SYSTEM			
NONE			

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
**EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE B1 (CONTINUED)

	CONTROL (UNTR) 05-0037	LOW DOSE 05-0058	HIGH DOSE 05-0059
DIGESTIVE SYSTEM			
*LIVER	(48)	(46)	(47)
HEPATOCELLULAR CARCINOMA	7 (15%)	11 (24%)	6 (13%)
HEMANGIOMA	1 (2%)		1 (2%)
HEMANGIOSARCOMA		1 (2%)	2 (4%)
*STOMACH	(47)	(43)	(46)
SQUAMOUS CELL CARCINOMA	1 (2%)		
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#THYROID	(47)	(42)	(42)
FOLLICULAR-CELL ADENOMA	1 (2%)	1 (2%)	
#PANCREATIC ISLETS	(48)	(45)	(45)
ISLET-CELL ADENOMA			1 (2%)
REPRODUCTIVE SYSTEM			
NONE			
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*EXTERNAL EAR	(48)	(48)	(48)
FIBROSARCOMA			1 (2%)
MUSCULOSKELETAL SYSTEM			
*MUSCLE HIP/THIGH	(48)	(48)	(48)
RHABDOMYOSARCOMA			1 (2%)
BODY CAVITIES			
NONE			

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

TABLE B1 (CONCLUDED)

	CONTROL (UNTR) 05-0037	LOW DOSE 05-0058	HIGH DOSE 05-0059
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	3	4	6
MORIBUND SACRIFICE		1	2
SCHEDULED SACRIFICE	5		5
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	42	44	36
ANIMAL MISSING		1	1
@ INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	17	24	21
TOTAL PRIMARY TUMORS	21	30	30
TOTAL ANIMALS WITH BENIGN TUMORS	2	7	8
TOTAL BENIGN TUMORS	3	7	9
TOTAL ANIMALS WITH MALIGNANT TUMORS	15	21	17
TOTAL MALIGNANT TUMORS	18	23	20
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			

TABLE B2
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE TREATED WITH APC

	CONTROL (UNTR) 06-0037	LOW DOSE 06-0058	HIGH DOSE 06-0059
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS MISSING		1	1
ANIMALS NECROPSIED	48	45	47
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	47	45	47
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE	(48)	(45)	(47)
LEIOMYOSARCOMA	1 (2%)		
RESPIRATORY SYSTEM			
#LUNG	(46)	(45)	(47)
HEPATOCELLULAR CARCINOMA, METAST		1 (2%)	1 (2%)
ALVEOLAR/BRONCHIOLAR ADENOMA	3 (7%)	7 (16%)	2 (4%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	1 (2%)		3 (6%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(48)	(45)	(47)
MALIGNANT LYMPHOMA, NOS	1 (2%)		
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	2 (4%)	4 (9%)	1 (2%)
#SPLEEN	(46)	(44)	(47)
HEMANGIOMA		1 (2%)	
HEMANGIOSARCOMA	1 (2%)		
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (2%)		
#SUBMANDIBULAR L.NODE	(39)	(34)	(38)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (3%)
#MESENTERIC L. NODE	(39)	(34)	(38)
MALIGNANT LYMPHOMA, NOS			1 (3%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (3%)	1 (3%)
#LIVER	(47)	(45)	(47)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)	
#PEYERS PATCH	(44)	(45)	(46)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
**EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE B2 (CONTINUED)

	CONTROL (UNTR) 06-0037	LOW DOSE 06-0058	HIGH DOSE 06-0059
#THYMUS	(31)	(39)	(42)
MALIGNANT LYMPHOMA, NOS	1 (3%)		
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(47)	(45)	(47)
HEPATOCELLULAR CARCINOMA	1 (2%)	2 (4%)	3 (6%)
FIBROSARCOMA	1 (2%)		
#STOMACH	(44)	(43)	(45)
SQUAMOUS CELL PAPILLOMA	1 (2%)		
#COLON	(40)	(44)	(43)
LEIOMYOSARCOMA	1 (3%)		
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#PITUITARY	(42)	(38)	(41)
CARCINOMA,NOS	1 (2%)		
ADENOMA, NOS	2 (5%)	4 (11%)	2 (5%)
#ADRENAL	(45)	(42)	(46)
PHEOCHROMOCYTOMA	1 (2%)		
#THYROID	(43)	(31)	(45)
FOLLICULAR-CELL ADENOMA			1 (2%)
FOLLICULAR-CELL CARCINOMA			1 (2%)
REPRODUCTIVE SYSTEM			
#UTERUS	(45)	(43)	(46)
LEIOMYOSARCOMA	1 (2%)		

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

TABLE B2 (CONTINUED)

	CONTROL (UNTR) 06-0037	LOW DOSE 06-0058	HIGH DOSE 06-0059
ENDOMETRIAL STROMAL POLYP	3 (7%)		
HEMANGIOMA			1 (2%)
#OVARY	(45)	(45)	(42)
TUBULAR ADENOMA	1 (2%)		
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*HARDERIAN GLAND	(48)	(45)	(47)
PAPILLARY ADENOMA			1 (2%)
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	6	5	3
MORIBUND SACRIFICE	2		
SCHEDULED SACRIFICE	5		5
ACCIDENTALLY KILLED		1	
TERMINAL SACRIFICE	37	43	41
ANIMAL MISSING		1	1

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE B2 (CONCLUDED)

	CONTROL (UNTR) 06-0037	LOW DOSE 06-0058	HIGH DOSE 06-0059
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	20	17	14
TOTAL PRIMARY TUMORS	24	20	19
TOTAL ANIMALS WITH BENIGN TUMORS	11	11	6
TOTAL BENIGN TUMORS	11	12	7
TOTAL ANIMALS WITH MALIGNANT TUMORS	11	8	11
TOTAL MALIGNANT TUMORS	13	8	12
TOTAL ANIMALS WITH SECONDARY TUMORS#		1	1
TOTAL SECONDARY TUMORS		1	1
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

APPENDIX C

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS TREATED WITH APC

TABLE C1
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS TREATED WITH APC

	CONTROL (UNTR) 01-0055	LOW DOSE 01-0058	HIGH DOSE 01-0059
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS MISSING	2		
ANIMALS NECROPSIED	47	50	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	47	50	49
INTEGUMENTARY SYSTEM			
*SKIN	(47)	(50)	(49)
EPIDERMAL INCLUSION CYST	1 (2%)		
INFLAMMATION, NECROTIZING	1 (2%)		
INFLAMMATION, ACUTE FOCAL	1 (2%)		
ABSCESS, NOS		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG/BRONCHUS	(47)	(50)	(49)
ABSCESS, NOS	1 (2%)		
#LUNG	(47)	(50)	(49)
BRONCHOPNEUMONIA, NOS		1 (2%)	
HYPERPLASIA, ALVEOLAR EPITHELIUM		2 (4%)	
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(46)	(49)	(47)
MYELOFIBROSIS		1 (2%)	
#SPLEEN	(47)	(50)	(49)
INFARCT HEMORRHAGIC	1 (2%)		
HYPERPLASIA, NOS			1 (2%)
HEMATOPOIESIS		1 (2%)	
#LYMPH NODE	(42)	(41)	(42)
FIBROSIS		1 (2%)	
#PANCREATIC L.NODE	(42)	(41)	(42)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)		
#ILEOCOLIC LYMPH NODE	(42)	(41)	(42)
LYMPHADENOPATHY	1 (2%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
**EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE C1 (CONTINUED)

	CONTROL (UNTR) 01-0055	LOW DOSE 01-0058	HIGH DOSE 01-0059
CIRCULATORY SYSTEM			
#HEART	(47)	(50)	(49)
PERIARTERITIS		1 (2%)	
#MYOCARDIUM	(47)	(50)	(49)
DEGENERATION, NOS	10 (21%)	17 (34%)	14 (29%)
#CARDIAC VALVE	(47)	(50)	(49)
INFLAMMATION, CHRONIC			1 (2%)
*PULMONARY ARTERY	(47)	(50)	(49)
MINERALIZATION	1 (2%)		
DIGESTIVE SYSTEM			
#LIVER	(47)	(50)	(49)
INFLAMMATION, NECROTIZING		1 (2%)	1 (2%)
DEGENERATION, HYALINE	1 (2%)		
NECROSIS, FOCAL	1 (2%)		
METAMORPHOSIS FATTY	3 (6%)		
FOCAL CELLULAR CHANGE	12 (26%)	1 (2%)	3 (6%)
HYPERPLASIA, FOCAL		1 (2%)	
#LIVER/CENTRILOBULAR	(47)	(50)	(49)
NECROSIS, NOS		3 (6%)	1 (2%)
*BILE DUCT	(47)	(50)	(49)
HYPERPLASIA, NOS	4 (9%)		
#PANCREAS	(45)	(47)	(47)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)		
FIBROSIS		1 (2%)	
#PANCREATIC ACINUS	(45)	(47)	(47)
ATROPHY, NOS	3 (7%)		2 (4%)
ATROPHY, FOCAL	1 (2%)		
HYPERPLASIA, NOS	1 (2%)		
#STOMACH	(47)	(49)	(47)
ULCER, NOS		1 (2%)	
INFLAMMATION, ACUTE		1 (2%)	
HYPERPLASIA, EPITHELIAL		1 (2%)	2 (4%)

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

TABLE C1 (CONTINUED)

	CONTROL (UNTR) 01-0055	LOW DOSE 01-0058	HIGH DOSE 01-0059
URINARY SYSTEM			
#KIDNEY	(47)	(50)	(49)
CYST, NOS	1 (2%)		
GLOMERULONEPHRITIS, NOS		1 (2%)	
INFLAMMATION, CHRONIC	39 (83%)	42 (84%)	40 (82%)
#URINARY BLADDER	(47)	(49)	(48)
HYPERPLASIA, EPITHELIAL	1 (2%)		1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(47)	(47)	(44)
COLLOID CYST			1 (2%)
HYPERPLASIA, NOS		1 (2%)	
HYPERPLASIA, FOCAL	3 (6%)	3 (6%)	5 (11%)
#ADRENAL	(47)	(49)	(48)
HYPERPLASIA, FOCAL	1 (2%)		
#ADRENAL CORTEX	(47)	(49)	(48)
HYPERPLASIA, FOCAL		6 (12%)	5 (10%)
#ADRENAL MEDULLA	(47)	(49)	(48)
HYPERPLASIA, NODULAR	3 (6%)	1 (2%)	2 (4%)
HYPERPLASIA, NOS			1 (2%)
HYPERPLASIA, FOCAL		2 (4%)	
#THYROID	(46)	(48)	(46)
FOLLICULAR CYST, NOS			1 (2%)
HYPERPLASIA, C-CELL	4 (9%)	1 (2%)	1 (2%)
#PARATHYROID	(24)	(27)	(25)
HYPERPLASIA, NOS	1 (4%)		
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(47)	(50)	(49)
GALACTOCELE	1 (2%)		
HYPERPLASIA, NOS	1 (2%)		
HYPERPLASIA, FOCAL			1 (2%)
*PENIS	(47)	(50)	(49)
INFLAMMATION, ACUTE NECROTIZING			1 (2%)

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

TABLE C1 (CONTINUED)

	CONTROL (UNTR) 01-0055	LOW DOSE 01-0058	HIGH DOSE 01-0059
*PREPUTIAL GLAND	(47)	(50)	(49)
INFLAMMATION, ACUTE	1 (2%)		
#PROSTATE	(46)	(44)	(49)
INFLAMMATION, ACUTE	7 (15%)	5 (11%)	1 (2%)
INFLAMMATION, ACUTE FOCAL	3 (7%)		1 (2%)
INFLAMMATION, ACUTE/CHRONIC	2 (4%)		
INFLAMMATION, CHRONIC		1 (2%)	1 (2%)
#TESTIS	(47)	(49)	(49)
DEGENERATION, NOS	1 (2%)		
NECROSIS, DIFFUSE			1 (2%)
#TESTIS/TUBULE	(47)	(49)	(49)
DEGENERATION, NOS	1 (2%)	11 (22%)	10 (20%)
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*EYE	(47)	(50)	(49)
INFLAMMATION, CHRONIC			1 (2%)
CATARACT			3 (6%)
*EYE/RETINA	(47)	(50)	(49)
DEGENERATION, NOS		1 (2%)	2 (4%)
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*MESENTERY	(47)	(50)	(49)
PERIARTERITIS			1 (2%)
ALL OTHER SYSTEMS			
NONE			

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

TABLE C1 (CONCLUDED)

	CONTROL (UNTR) 01-0055	LOW DOSE 01-0058	HIGH DOSE 01-0059
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED			2
ANIMAL MISSING/NO NECROPSY	2		
AUTOLYSIS/NO NECROPSY	1		1

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

TABLE C2
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS TREATED WITH APC

	CONTROL (UNTR) 02-0055	LOW DOSE 02-0058	HIGH DOSE 02-0059
ANIMALS INITIALLY IN STUDY	50	50	@50
ANIMALS MISSING	2		
ANIMALS NECROPSIED	48	50	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	47	50	49
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG/BRONCHUS	(47)	(48)	(45)
BRONCHIECTASIS			1 (2%)
#LUNG	(47)	(48)	(45)
BRONCHOPNEUMONIA SUPPURATIVE			1 (2%)
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(45)	(46)	(46)
MYELOSCLEROSIS		1 (2%)	
HYPERPLASIA, HEMATOPOIETIC		2 (4%)	1 (2%)
#SPLEEN	(47)	(48)	(45)
HYPERPLASIA, NOS		1 (2%)	
HYPERPLASIA, HEMATOPOIETIC		1 (2%)	
HEMATOPOIESIS	1 (2%)	2 (4%)	
CIRCULATORY SYSTEM			
#HEART	(47)	(48)	(46)
THROMBUS, MURAL			1 (2%)
#MYOCARDIUM	(47)	(48)	(46)
DEGENERATION, NOS	7 (15%)	5 (10%)	5 (11%)
#ENDOCARDIUM	(47)	(48)	(46)
INFLAMMATION, CHRONIC		1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
**EXCLUDES PARTIALLY AUTOLYZED ANIMALS
@ 50 ANIMAL WERE INITIALLY IN THE STUDY, BUT 1 ANIMAL WAS FOUND TO BE A MALE ANIMAL

TABLE C2 (CONTINUED)

	CONTROL (UNTR) 02-0055	LOW DOSE 02-0058	HIGH DOSE 02-0059
DIGESTIVE SYSTEM			
#LIVER	(47)	(47)	(45)
DEGENERATION, NOS	1 (2%)		
METAMORPHOSIS FATTY	2 (4%)		
FOCAL CELLULAR CHANGE	25 (53%)	26 (55%)	22 (49%)
HEPATOCYTOMEGALY		2 (4%)	
HYPERPLASIA, FOCAL			1 (2%)
ANGIECTASIS		1 (2%)	
#LIVER/CENTRILOBULAR	(47)	(47)	(45)
NECROSIS, NOS		1 (2%)	
#LIVER/PERIPORTAL	(47)	(47)	(45)
INFLAMMATION, CHRONIC			1 (2%)
*BILE DUCT	(48)	(50)	(49)
INFLAMMATION, CHRONIC		1 (2%)	
HYPERPLASIA, NOS	2 (4%)	1 (2%)	
#PANCREAS	(46)	(46)	(44)
INFLAMMATION, CHRONIC		1 (2%)	
#PANCREATIC ACINUS	(46)	(46)	(44)
ATROPHY, NOS	8 (17%)		
#STOMACH	(46)	(46)	(45)
INFLAMMATION, FOCAL			1 (2%)
URINARY SYSTEM			
#KIDNEY	(47)	(47)	(46)
HYDRONEPHROSIS			1 (2%)
INFLAMMATION, CHRONIC	29 (62%)	14 (30%)	20 (43%)
POSTMORTEM CHANGE	1 (2%)		
NECROSIS, MEDULLARY			1 (2%)
#KIDNEY/CORTEX	(47)	(47)	(46)
CYST, NOS		1 (2%)	
#KIDNEY/PELVIS	(47)	(47)	(46)
NECROSIS, MEDULLARY			3 (7%)
HYPERPLASIA, EPITHELIAL			2 (4%)

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

TABLE C2 (CONTINUED)

	CONTROL (UNTR) 02-0055	LOW DOSE 02-0058	HIGH DOSE 02-0059
#URINARY BLADDER	(47)	(47)	(46)
CALCULUS, NOS			1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(46)	(44)	(43)
COLLOID CYST			1 (2%)
HYPERPLASIA, NOS			1 (2%)
HYPERPLASIA, FOCAL	1 (2%)		1 (2%)
#ADRENAL CORTEX	(47)	(48)	(44)
CYST, NOS	1 (2%)		
HEMORRHAGIC CYST			1 (2%)
DEGENERATION, NOS	3 (6%)		
METAMORPHOSIS FATTY	1 (2%)		2 (5%)
HYPERPLASIA, NODULAR	2 (4%)		
HYPERPLASIA, FOCAL	3 (6%)	3 (6%)	7 (16%)
#ADRENAL MEDULLA	(47)	(48)	(44)
THROMBOSIS, NOS	1 (2%)		
HYPERPLASIA, FOCAL	1 (2%)	1 (2%)	
#THYROID	(46)	(46)	(43)
HYPERPLASIA, C-CELL	4 (9%)	2 (4%)	2 (5%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(48)	(50)	(49)
DILATATION/DUCTS	3 (6%)		
GALACTOCELE	7 (15%)		
HYPERPLASIA, NOS	4 (8%)		
*MAMMARY DUCT	(48)	(50)	(49)
FIBROSIS	2 (4%)		
*CLITORAL GLAND	(48)	(50)	(49)
CYSTIC DUCTS			1 (2%)
*VAGINA	(48)	(50)	(49)
INFLAMMATION, ACUTE		1 (2%)	
#UTERUS	(47)	(48)	(46)
HYDROMETRA	2 (4%)	8 (17%)	4 (9%)

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

TABLE C2 (CONTINUED)

	CONTROL (UNTR) 02-0055	LOW DOSE 02-0058	HIGH DOSE 02-0059
PYOMETRA			1 (2%)
#UTERUS/ENDOMETRIUM	(47)	(48)	(46)
INFLAMMATION, ACUTE	9 (19%)	3 (6%)	2 (4%)
INFLAMMATION, CHRONIC	1 (2%)		
HYPERPLASIA, CYSTIC	3 (6%)	8 (17%)	1 (2%)
HYPERPLASIA, STROMAL	1 (2%)		
#OVARY/OVIDUCT	(47)	(48)	(46)
INFLAMMATION, ACUTE	3 (6%)		1 (2%)
INFLAMMATION ACTIVE CHRONIC	1 (2%)		
INFLAMMATION, CHRONIC	1 (2%)		
#OVARY	(46)	(48)	(45)
INFLAMMATION, CHRONIC	1 (2%)		
#OVARY/FOLLICLE	(46)	(48)	(45)
HYPERPLASIA, NOS	1 (2%)		
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*EYE	(48)	(50)	(49)
CATARACT		1 (2%)	7 (14%)
*EYE/CORNEA	(48)	(50)	(49)
INFLAMMATION, ACUTE			1 (2%)
*EYE/RETINA	(48)	(50)	(49)
DEGENERATION, NOS		1 (2%)	7 (14%)
MUSCULOSKELETAL SYSTEM			
*BONE	(48)	(50)	(49)
OSTEOSCLEROSIS	1 (2%)		
*ABDOMINAL MUSCLE	(48)	(50)	(49)
DEGENERATION, NOS			1 (2%)
BODY CAVITIES			
*PLEURA	(48)	(50)	(49)
INFLAMMATION, CHRONIC	1 (2%)		

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

TABLE C2 (CONCLUDED)

	CONTROL(UNTR) 02-0055	LOW DOSE 02-0058	HIGH DOSE 02-0059
*EPICARDIUM	(48)	(50)	(49)
INFLAMMATION, CHRONIC	1 (2%)		
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED		1	3
ANIMAL MISSING/NO NECROPSY	2		
AUTO/NECROPSY/HISTO PERF			1
AUTO/NECROPSY/NO HISTO	1		

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

APPENDIX D

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE TREATED WITH APC

TABLE D1
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE TREATED WITH APC

	CONTROL (UNTR) 05-0037	LOW DOSE 05-0058	HIGH DOSE 05-0059
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS MISSING		1	1
ANIMALS NECROPSIED	48	48	48
ANIMALS EXAMINED HISTOPATHOLOGICALLY **	48	47	48
INTEGUMENTARY SYSTEM			
*SKIN	(48)	(48)	(48)
INFLAMMATION, NOS			1 (2%)
ABSCESS, NOS		1 (2%)	
FIBROSIS	1 (2%)		
ALOPECIA	1 (2%)		
*SUBCUT TISSUE	(48)	(48)	(48)
INFLAMMATION, CHRONIC			1 (2%)
NECROSIS, NOS	1 (2%)		
RESPIRATORY SYSTEM			
#LUNG/BRONCHUS	(48)	(46)	(47)
INFLAMMATION, NOS	1 (2%)		
INFLAMMATION, FOCAL	1 (2%)		
#LUNG	(48)	(46)	(47)
INFLAMMATION, NOS	1 (2%)		
INFLAMMATION, INTERSTITIAL	14 (29%)	1 (2%)	1 (2%)
HYPERPLASIA, EPITHELIAL	2 (4%)		
#LUNG/ALVEOLI	(48)	(46)	(47)
INFLAMMATION, FOCAL	2 (4%)		
FIBROSIS, FOCAL	1 (2%)		
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(47)	(45)	(45)
HYPERPLASIA, HEMATOPOIETIC			1 (2%)
#SPLEEN	(47)	(46)	(46)
HEMORRHAGIC CYST			1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
**EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE D1 (CONTINUED)

	CONTROL (UNTR) 05-0037	LOW DOSE 05-0058	HIGH DOSE 05-0059
INFLAMMATION, NOS	1 (2%)		
HYPERPLASIA, NOS	2 (4%)		1 (2%)
HYPERPLASIA, HEMATOPOIETIC	2 (4%)	3 (7%)	3 (7%)
HYPERPLASIA, ERYTHROID	2 (4%)		
HYPERPLASIA, RETICULUM CELL		1 (2%)	
HYPERPLASIA, LYMPHOID	2 (4%)		
HEMATOPOIESIS			1 (2%)
#LYMPH NODE	(44)	(44)	(41)
HEMORRHAGIC CYST	1 (2%)		
INFLAMMATION, NOS	13 (30%)		
DEGENERATION, CYSTIC	1 (2%)		
HYPERPLASIA, NOS	2 (5%)		
HYPERPLASIA, HEMATOPOIETIC	1 (2%)		
HYPERPLASIA, LYMPHOID	2 (5%)		
MYELOID METAPLASIA	2 (5%)		
#MEDIASTINAL L.NODE	(44)	(44)	(41)
NECROSIS, NOS	1 (2%)		
#ABDOMINAL LYMPH NODE	(44)	(44)	(41)
HYPERPLASIA, LYMPHOID		1 (2%)	
#PANCREATIC L.NODE	(44)	(44)	(41)
INFLAMMATION, NOS	1 (2%)		
#MESENTERIC L. NODE	(44)	(44)	(41)
HEMORRHAGE	1 (2%)		
INFLAMMATION, NOS	9 (20%)		1 (2%)
LYMPHADENOPATHY		26 (59%)	18 (44%)
HYPERPLASIA, LYMPHOID		1 (2%)	
#THYMUS	(34)	(35)	(31)
NECROSIS, NOS	1 (3%)		
CIRCULATORY SYSTEM			
#HEART/VENTRICLE	(48)	(47)	(47)
MELANIN	2 (4%)		
#MYOCARDIUM	(48)	(47)	(47)
INFLAMMATION, INTERSTITIAL	2 (4%)		
FIBROSIS	5 (10%)		
*BLOOD VESSEL	(48)	(48)	(48)
INFLAMMATION, NOS	2 (4%)		

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

TABLE D1 (CONTINUED)

	CONTROL (UNTR) 05-0037	LOW DOSE 05-0058	HIGH DOSE 05-0059
*PULMONARY ARTERY	(48)	(48)	(48)
MINERALIZATION	2 (4%)		
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(47)	(46)	(45)
INFLAMMATION, NOS	2 (4%)		
PERIVASCULAR CUFFING	1 (2%)		
#LIVER	(48)	(46)	(47)
NECROSIS, FOCAL	13 (27%)		
METAMORPHOSIS FATTY	3 (6%)	1 (2%)	
HYPERPLASIA, NODULAR	2 (4%)		
HYPERPLASTIC NODULE		1 (2%)	
HYPERPLASIA, FOCAL	1 (2%)	1 (2%)	
HYPERPLASIA, DIFFUSE		1 (2%)	
ANGIECTASIS	1 (2%)		1 (2%)
MYELOID METAPLASIA	1 (2%)		
#LIVER/HEPATOCYTES	(48)	(46)	(47)
DEGENERATION, NOS	1 (2%)		
*GALLBLADDER	(48)	(48)	(48)
INFLAMMATION, FOCAL	1 (2%)		
#PANCREAS	(48)	(45)	(45)
CYSTIC DUCTS		1 (2%)	
INFLAMMATION, NOS	7 (15%)		
INFLAMMATION, FOCAL	1 (2%)		
INFLAMMATION, ACUTE/CHRONIC		1 (2%)	
DEGENERATION, CYSTIC	1 (2%)		
METAMORPHOSIS FATTY	1 (2%)		
#PANCREATIC DUCT	(48)	(45)	(45)
HYPERPLASIA, NOS	1 (2%)		
#PANCREATIC ACINUS	(48)	(45)	(45)
ATROPHY, NOS		1 (2%)	
HYPERTROPHY, FOCAL	1 (2%)		
HYPERPLASIA, FOCAL	1 (2%)		
#STOMACH	(47)	(43)	(46)
INFLAMMATION, NOS	13 (28%)		

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

TABLE D1 (CONTINUED)

	CONTROL (UNTR) 05-0037	LOW DOSE 05-0058	HIGH DOSE 05-0059
ULCER, NOS	1 (2%)		
INFLAMMATION, FOCAL	1 (2%)		
INFLAMMATION, INTERSTITIAL	1 (2%)		
HYPERPLASIA, NOS	1 (2%)		
HYPERPLASIA, FOCAL	1 (2%)		
HYPERKERATOSIS	3 (6%)		
ACANTHOSIS	3 (6%)		
#GASTRIC MUCOSA	(47)	(43)	(46)
HYPERPLASIA, FOCAL	1 (2%)		
#PEYERS PATCH	(48)	(45)	(45)
HYPERPLASIA, NOS	2 (4%)	1 (2%)	
HYPERPLASIA, LYMPHOID		2 (4%)	
#ILEUM	(48)	(45)	(45)
HEMORRHAGE	1 (2%)		
INFLAMMATION, NOS	2 (4%)		
#COLON	(45)	(45)	(38)
PARASITISM	1 (2%)		
URINARY SYSTEM			
#KIDNEY	(47)	(47)	(46)
CYST, NOS		1 (2%)	1 (2%)
GLOMERULONEPHRITIS, NOS	6 (13%)	9 (19%)	7 (15%)
INFLAMMATION, NOS	1 (2%)		
INFLAMMATION, INTERSTITIAL	23 (49%)	1 (2%)	
FIBROSIS, DIFFUSE		1 (2%)	
#KIDNEY/TUBULE	(47)	(47)	(46)
NECROSIS, FOCAL	1 (2%)		
#KIDNEY/PELVIS	(47)	(47)	(46)
INFLAMMATION, ACUTE/CHRONIC		1 (2%)	
#URINARY BLADDER	(48)	(47)	(44)
INFLAMMATION, NOS	4 (8%)		
HYPERPLASIA, EPITHELIAL	9 (19%)		
ENDOCRINE SYSTEM			
#PITUITARY	(42)	(30)	(35)
HYPERPLASIA, NOS	3 (7%)		1 (3%)

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

TABLE D1 (CONTINUED)

	CONTROL (UNTR) 05-0037	LOW DOSE 05-0058	HIGH DOSE 05-0059
HYPERPLASIA, FOCAL	3 (7%)		
*ADRENAL CORTEX	(45)	(46)	(46)
NODULE	1 (2%)		
HYPERTROPHY, FOCAL	1 (2%)		
HYPERPLASIA, NOS	1 (2%)		
*ADRENAL MEDULLA	(45)	(46)	(46)
DEGENERATION, NOS	1 (2%)		
HYPERPLASIA, NODULAR			1 (2%)
*THYROID	(47)	(42)	(42)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)		
HYPERPLASIA, PAPILLARY	1 (2%)		
HYPERPLASIA, FOLLICULAR-CELL	1 (2%)		
*PANCREATIC ISLETS	(48)	(45)	(45)
HYPERPLASIA, NOS	2 (4%)		
REPRODUCTIVE SYSTEM			
*PREPUTIAL GLAND	(48)	(48)	(48)
ABSCESS, NOS	2 (4%)		
*TESTIS	(47)	(47)	(46)
FIBROSIS		1 (2%)	
DEGENERATION, NOS			1 (2%)
*TESTIS/TUBULE	(47)	(47)	(46)
DEGENERATION, NOS	4 (9%)	11 (23%)	1 (2%)
NERVOUS SYSTEM			
*CEREBRAL CORTEX	(48)	(46)	(47)
MINERALIZATION	3 (6%)		
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			

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

TABLE D1 (CONCLUDED)

	CONTROL(UNTR) 05-0037	LOW DOSE 05-0058	HIGH DOSE 05-0059
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED		6	13
ANIMAL MISSING/NO NECROPSY		1	1
AUTO/NECROPSY/NO HISTO		1	
AUTOLYSIS/NO NECROPSY	2	1	1

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

TABLE D2
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE TREATED WITH APC

	CONTROL (UNTR) 06-0037	LOW DOSE 06-0058	HIGH DOSE 06-0059
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS MISSING		1	1
ANIMALS NECROPSIED	48	45	47
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	47	45	47
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE	(48)	(45)	(47)
MINERALIZATION	1 (2%)		
FIBROSIS	1 (2%)		
RESPIRATORY SYSTEM			
#LUNG/BRONCHUS	(46)	(45)	(47)
INFLAMMATION, FOCAL	1 (2%)		
#LUNG	(46)	(45)	(47)
INFLAMMATION, INTERSTITIAL	10 (22%)		
HYPERPLASIA, EPITHELIAL	3 (7%)		
HYPERPLASIA, ADENOMATOUS			1 (2%)
HYPERPLASIA, ALVEOLAR EPITHELIUM		1 (2%)	
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(45)	(44)	(47)
MYELOFIBROSIS	1 (2%)	2 (5%)	
MYELOSCLEROSIS		3 (7%)	
#SPLEEN	(46)	(44)	(47)
HEMORRHAGIC CYST			1 (2%)
HYPERPLASIA, HEMATOPOIETIC	16 (35%)	7 (16%)	2 (4%)
HYPERPLASIA, ERYTHROID	6 (13%)		
HYPERPLASIA, RETICULUM CELL		1 (2%)	3 (6%)
HYPERPLASIA, LYMPHOID	10 (22%)		2 (4%)
HEMATOPOIESIS	1 (2%)		
MYELOPOIESIS	1 (2%)		
#LYMPH NODE	(39)	(34)	(38)
CYST, NOS	1 (3%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
**EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE D2 (CONTINUED)

	CONTROL (UNTR) 06-0037	LOW DOSE 06-0058	HIGH DOSE 06-0059
INFLAMMATION, NOS	15 (38%)		
HYPERPLASIA, NOS	1 (3%)		
RETICULOCYTOSIS	1 (3%)		
HYPERPLASIA, HEMATOPOIETIC	2 (5%)		
MYELOID METAPLASIA	1 (3%)		
*SUBMANDIBULAR L.NODE	(39)	(34)	(38)
HYPERPLASIA, RETICULUM CELL			1 (3%)
*MEDIASTINAL L.NODE	(39)	(34)	(38)
HYPERPLASIA, LYMPHOID		1 (3%)	
*PANCREATIC L.NODE	(39)	(34)	(38)
HYPERPLASIA, LYMPHOID			1 (3%)
*MESENTERIC L. NODE	(39)	(34)	(38)
LYMPHADENOPATHY		3 (9%)	4 (11%)
*THYMUS	(31)	(39)	(42)
HYPERPLASIA, LYMPHOID		1 (3%)	1 (2%)
CIRCULATORY SYSTEM			
*HEART/VENTRICLE	(46)	(45)	(47)
MELANIN	4 (9%)		
DIGESTIVE SYSTEM			
*SALIVARY GLAND	(45)	(43)	(47)
INFLAMMATION, NOS	2 (4%)		
PERIVASCULAR CUFFING	4 (9%)		
*LIVER	(47)	(45)	(47)
INFLAMMATION, NOS	1 (2%)		
DEGENERATION, NOS		1 (2%)	
NECROSIS, FOCAL	22 (47%)		
HEPATOCYTOMEGALY		1 (2%)	2 (4%)
HYPERTROPHY, FOCAL		1 (2%)	
HYPERPLASTIC NODULE	1 (2%)	1 (2%)	
HYPERPLASIA, FOCAL		1 (2%)	1 (2%)
ANGIECTASIS	1 (2%)	2 (4%)	3 (6%)
HEMATOPOIESIS	3 (6%)		
*GALLBLADDER	(48)	(45)	(47)
INFLAMMATION, NOS	3 (6%)		

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

TABLE D2 (CONTINUED)

	CONTROL (UNTR) 06-0037	LOW DOSE 06-0058	HIGH DOSE 06-0059
*BILE DUCT	(48)	(45)	(47)
INFLAMMATION, NOS	1 (2%)		
#PANCREAS	(44)	(44)	(47)
DILATATION/DUCTS			1 (2%)
CYSTIC DUCTS			1 (2%)
INFLAMMATION, NOS	5 (11%)		
FIBROSIS			1 (2%)
PERIARTERITIS	1 (2%)		
#PANCREATIC DUCT	(44)	(44)	(47)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)		
#PANCREATIC ACINUS	(44)	(44)	(47)
ATROPHY, NOS			1 (2%)
#STOMACH	(44)	(43)	(45)
INFLAMMATION, NOS	7 (16%)		
ULCER, NOS	1 (2%)		
INFLAMMATION, FOCAL	1 (2%)	1 (2%)	
ULCER, FOCAL		1 (2%)	
INFLAMMATION, ACUTE FOCAL			1 (2%)
GRANULOMA, NOS		1 (2%)	
HYPERPLASIA, NOS	1 (2%)		
HYPERPLASIA, EPITHELIAL	1 (2%)		
HYPERPLASIA, ADENOMATOUS	1 (2%)		
HYPERKERATOSIS	1 (2%)		
ACANTHOSIS	1 (2%)		
#GASTRIC MUCOSA	(44)	(43)	(45)
HYPERPLASIA, FOCAL	1 (2%)		
#PEYERS PATCH	(44)	(45)	(46)
HYPERPLASIA, NOS	1 (2%)		
#ILEUM	(44)	(45)	(46)
AMYLOIDOSIS			1 (2%)
URINARY SYSTEM			
#KIDNEY	(46)	(45)	(47)
CYST, NOS		1 (2%)	
GLOMERULONEPHRITIS, NOS	14 (30%)	3 (7%)	

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

TABLE D2 (CONTINUED)

	CONTROL (UNTR) 06-0037	LOW DOSE 06-0058	HIGH DOSE 06-0059
INFLAMMATION, INTERSTITIAL	16 (35%)	2 (4%)	5 (11%)
NEPHROPATHY		1 (2%)	
#KIDNEY/PELVIS	(46)	(45)	(47)
LYMPHOCYTIC INFLAMMATORY INFILTR			1 (2%)
#URINARY BLADDER	(46)	(44)	(46)
INFLAMMATION, NOS	4 (9%)		
HYPERPLASIA, EPITHELIAL	10 (22%)		
ENDOCRINE SYSTEM			
#PITUITARY	(42)	(38)	(41)
HYPERPLASIA, FOCAL	6 (14%)		
#ADRENAL CORTEX	(45)	(42)	(46)
NODULE	3 (7%)		
METAMORPHOSIS FATTY		1 (2%)	
HYPERPLASIA, FOCAL		1 (2%)	
#THYROID	(43)	(31)	(45)
FOLLICULAR CYST, NOS	1 (2%)		
INFLAMMATION, NOS	1 (2%)		
HYPERPLASIA, FOLLICULAR-CELL			1 (2%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(48)	(45)	(47)
GALACTOCELE	1 (2%)		
HYPERPLASIA, NOS	4 (8%)		
#UTERUS	(45)	(43)	(46)
LYMPHANGIECTASIS			1 (2%)
HYDROMETRA	1 (2%)	7 (16%)	9 (20%)
INFLAMMATION, NOS		1 (2%)	
PYOMETRA		1 (2%)	
INFLAMMATION, ACUTE			1 (2%)
ABSCESS, NOS	3 (7%)		
FIBROSIS	1 (2%)		
#UTERUS/ENDOMETRIUM	(45)	(43)	(46)
INFLAMMATION, NOS	10 (22%)	4 (9%)	
INFLAMMATION, SUPPURATIVE	4 (9%)		

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

TABLE D2 (CONTINUED)

	CONTROL (UNTR) 06-0037	LOW DOSE 06-0058	HIGH DOSE 06-0059
INFLAMMATION, ACUTE			1 (2%)
ABSCESS, NOS			1 (2%)
HYPERPLASIA, NOS	4 (9%)		
HYPERPLASIA, CYSTIC	18 (40%)	33 (77%)	23 (50%)
HYPERPLASIA, ADENOMATOUS	1 (2%)		
HYPERPLASIA, STROMAL			1 (2%)
METAPLASIA, SQUAMOUS		1 (2%)	1 (2%)
#UTERUS/MYOMETRIUM	(45)	(43)	(46)
LYMPHOCYTIC INFLAMMATORY INFILTR		1 (2%)	
#OVARY/OVIDUCT	(45)	(43)	(46)
INFLAMMATION, NOS	5 (11%)		
INFLAMMATION, SUPPURATIVE		2 (5%)	
INFLAMMATION, CHRONIC		1 (2%)	
#OVARY	(45)	(45)	(42)
CYST, NOS	3 (7%)		
INFLAMMATION, NOS	4 (9%)		
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)		
INFLAMMATION, SUPPURATIVE	10 (22%)		
ABSCESS, NOS	4 (9%)		
DEGENERATION, CYSTIC	1 (2%)		
HYPERPLASIA, NOS		1 (2%)	
NERVOUS SYSTEM			
#BRAIN	(44)	(45)	(45)
LYMPHOCYTIC INFLAMMATORY INFILTR			1 (2%)
INFLAMMATION, ACUTE/CHRONIC			1 (2%)
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
*BONE	(48)	(45)	(47)
RESORPTION	3 (6%)		
BODY CAVITIES			
NONE			

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

TABLE D2 (CONCLUDED)

	CONTROL (UNTR) 06-0037	LOW DOSE 06-0058	HIGH DOSE 06-0059
ALL OTHER SYSTEMS			
OMENTUM			
NECROSIS, FAT	1		
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	1	2	6
ANIMAL MISSING/NO NECROPSY		1	1
AUTO/NECROPSY/HISTO PERF	2		
AUTO/NECROPSY/NO HISTO	1		
AUTOLYSIS/NO NECROPSY	2	4	2

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

DHEW Publication No. (NIH) 78-1317