NATIONAL TOXICOLOGY PROGRAM Technical Report Series No. 426



# COMPARATIVE TOXICOLOGY

# STUDIES OF

CORN OIL, SAFFLOWER OIL, AND TRICAPRYLIN

(CAS NOs. 8001-30-7, 8001-23-8, and 538-23-8)

IN MALE F344/N RATS

AS VEHICLES FOR GAVAGE

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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# ABSTRACT

Corn Oil

CAS No. 8001-30-7 Synonyms: Maize oil, Maydol Tricaprylin

CAS No. 538-23-8 Chemical Formula: C<sub>27</sub>H<sub>50</sub>O<sub>6</sub> Molecular Weight: 470.69 Synonyms: Trioctanoin; 1,2,3-trioctanoyl glycerol; Glycerol trioctanoate Safflower Oil

CAS No. 8001-23-8

The types and levels of fats in the diet are known to affect the incidence of certain neoplasms in humans and rodents. In long-term toxicity and carcinogenicity studies in rodents, the level of dietary fat is altered by using oil as a vehicle to administer unpalatable or volatile chemicals. Control male rats receiving a corn oil vehicle have a higher incidence of pancreatic proliferative lesions and a lower incidence of mononuclear cell leukemia than untreated control males. Therefore, the National Toxicology Program (NTP) designed studies to evaluate the role of several oils in altering cancer rates in male rats. The NTP study reported here was part of a larger program that included cooperative agreements with Dartmouth Medical School, Northwestern Medical School, and the University of Missouri. The program was designed to study the mechanisms by which corn oil induces pancreatic cancer. To evaluate corn oil as well as two other gavage vehicles for potential toxicity, corn oil, safflower oil, and tricaprylin were administered by gavage to male F344/N rats for 2 years. The rats that received corn oil were also made available to the university investigators for study of the corn oil-induced pancreatic lesions. Each vehicle was administered by gavage at volumes of 2.5, 5, or 10 mL/kg body weight once daily for 5 days per week. In the corn oil study, a control of 10 mL saline/kg was also included. To evaluate the potential role of corn oil in promoting a pancreatic proliferative effect, 500 mg dichloromethane/kg body weight was administered in 2.5, 5, or 10 mL corn oil/kg body weight for 2 years to male F344/N rats. Dichloromethane was chosen because the chemical appeared to cause pancreatic proliferative lesions when administered by gavage in a corn oil vehicle but not when the exposure was by inhalation. In each of these studies, the term "dose" refers to the volume of gavage vehicle administered.

# 2-YEAR STUDIES OF CORN OIL, SAFFLOWER OIL, AND TRICAPRYLIN

# Survival and Body Weights

Two-year survival was increased in male rats receiving corn oil (untreated control, 26/50; saline control, 32/50; 2.5 mL/kg, 33/50; 5 mL/kg, 38/50; 10 mL/kg, 40/50) primarily due to a dose-related decreased incidence of mononuclear cell leukemia. The mean body weights of all dosed groups were at least 5%

higher than those of the untreated and saline controls by week 48, but the mean body weights of groups receiving 2.5 or 5 mL corn oil/kg decreased during the final weeks of the study (after week 89) and were similar to those of the controls at the end of the study.

Two-year survival was slightly increased in male rats receiving safflower oil relative to that of the controls (untreated control, 30/50; 2.5 mL/kg, 33/50; 5 mL/kg, 40/50; 10 mL/kg, 36/50). The mean body weight of male rats receiving 10 mL safflower oil/kg was at least 5% greater than that of the controls after week 45 and was 16% greater by the end of the study.

Two-year survival of high-dose tricaprylin males was lower than that of the controls (untreated control, 31/50; 2.5 mL/kg, 30/50; 5 mL/kg, 31/50; 10 mL/kg, 23/53) due to moribund kills and deaths that appeared to be related to toxicity. The mean body weight of the high-dose group was lower than that of the controls throughout the study, although the difference was less than 5% after week 61.

## Pathology Findings

In the corn oil study, there were significant dose-related increased incidences of pancreatic exocrine hyperplasia and adenoma (hyperplasia: 8/50, 28/47, 28/50, 35/50; adenoma: 1/50, 8/47, 10/50, 23/50; carcinoma: 0/50, 0/47, 1/50, 0/50 in the untreated control, 2.5, 5, and 10 mL/kg groups, respectively). The incidence and severity of nephropathy decreased with dose (incidence [mean severity grade]: 47/50 [2.1], 43/48 [1.8], 45/50 [1.4], 40/49 [1.2]). The incidences of pheochromocytomas (benign, malignant, or complex) of the adrenal medulla were also decreased in dosed rats (23/49, 21/50, 5/50, 9/50). The incidence of mononuclear cell leukemia was significantly decreased in rats dosed with corn oil (27/50, 16/50, 11/50, 7/50).

In rats receiving safflower oil, the incidences of pancreatic exocrine hyperplasia and adenoma increased significantly with dose (hyperplasia: 8/50, 14/50, 29/49, 30/50; adenoma: 1/50, 7/50, 15/49, 28/50; carcinoma: 0/50, 0/50, 0/49, 1/50 in the untreated control, 2.5, 5, and 10 mL/kg groups, respectively). There was a decrease in the severity, but not in the incidence, of nephropathy, a common lesion in aging F344/N rats (incidence [mean severity grade]: 49/50

[2.0], 50/50 [1.8], 47/50 [1.1], 49/49 [1.1]). There were decreased incidences of mononuclear cell leukemia (33/50, 19/50, 18/50, 7/51).

In the tricaprylin study, there were significant doserelated increased incidences of pancreatic exocrine hyperplasia and adenoma (hyperplasia: 8/49, 9/49, 18/49, 28/50; adenoma: 2/49, 6/49, 13/49, 18/50 in the untreated control, 2.5, 5, and 10 mL/kg groups, respectively). The incidence of proliferative lesions of the forestomach increased significantly with dose (basal cell hyperplasia: 4/50, 7/50, 12/49, 21/52; squamous cell papilloma: 0/50, 0/50, 3/50, 10/53). The incidence of nephropathy was significantly decreased in high-dose rats, and the severity of nephropathy decreased with dose (incidence [mean severity grade]: 46/50 [2.0], 42/50 [1.5], 45/50 [1.7], 27/49 [0.9]). In high-dose rats, the incidence of mononuclear cell leukemia was decreased (23/50, 28/50, 22/50, 9/53).

# 2-YEAR STUDY OF DICHLOROMETHANE IN CORN OIL Survival and Body Weights

Two-year survival increased slightly with dose in the three groups receiving 500 mg dichloromethane/kg in 2.5, 5, or 10 mL corn oil/kg (23/50, 28/50, 31/50) due to a dose-related decrease in the incidence of mononuclear cell leukemia. The rats receiving 500 mg dichloromethane/kg without corn oil were sacrificed within the first 3 weeks of the study due to the severe toxicity of dichloromethane. The final mean body weight of the high-dose rats was greater than the final mean body weights of groups receiving dichloromethane in 2.5 or 5 mL corn oil/kg.

## Pathology Findings

There was a dose-related increase in the incidence of pancreatic proliferative exocrine lesions in rats receiving dichloromethane in 2.5, 5, and 10 mL corn oil/kg (hyperplasia: 28/50, 38/50, 44/50; adenoma: 9/50, 19/50, 41/50; carcinoma: 0/50, 1/50, 3/50). The incidences of pancreatic exocrine hyperplasia and adenoma in rats receiving dichloromethane in 5 or 10 mL, but not 2.5 mL, corn oil were increased compared to the incidences in rats receiving comparable volumes of corn oil alone (hyperplasia: 2.5 mL, 28/47; 5 mL, 28/50; 10 mL, 35/50; adenoma: 8/47, 10/50, 23/50; carcinoma: 0/47, 1/50, 0/50).

There were significantly increased incidences of pituitary gland pars distalis adenoma in rats receiving dichloromethane in corn oil (20/50, 18/49, 16/49) when compared to those in rats receiving comparable volumes of corn oil alone (10/50, 6/49, 7/50). The incidence of mammary gland adenoma and fibroadenoma (combined) was significantly increased in rats receiving dichloromethane in 10 mL corn oil/kg (7/50) when compared to rats receiving dichloromethane in 2.5 mL corn oil/kg (1/50), but was not significantly increased when compared to the group receiving 10 mL of corn oil alone (3/50). The incidences of mammary gland adenoma and fibroadenoma (combined) were 7/50 for the untreated safflower oil controls and 6/50 for the untreated tricaprylin controls. The incidence of mononuclear cell leukemia decreased in the group receiving dichloromethane in 10 mL corn oil/kg (13/50, 14/50, 5/50).

## GENETIC TOXICOLOGY

Neither safflower oil nor corn oil was mutagenic in Salmonella typhimurium strains TA97, TA98, TA100, or TA1535, with or without S9. Tricaprylin, in contrast, was mutagenic in strain TA1535 with, but not without, S9. Tricaprylin did not induce mutations in strains TA97, TA98, or TA100, with or without S9.

### SUMMARY

These studies were designed to evaluate the effects of various concentrations of an oil very high in polyunsaturated fat (safflower oil), an oil containing high levels of polyunsaturated and monounsaturated fats (corn oil), and an oil containing saturated mediumchain fatty acids (tricaprylin) on the incidence and pattern of neoplasms in the F344/N rat. In addition, safflower oil and tricaprylin were evaluated as replacements for the corn oil vehicle.

These studies demonstrate that safflower oil and tricaprylin do not offer significant advantages over corn oil as a gavage vehicle in long-term rodent studies. Corn oil, safflower oil, and tricaprylin each caused hyperplasia and adenoma of the exocrine pancreas, decreased incidences of mononuclear cell leukemia, and reduced incidences or severity of nephropathy in male F344/N rats. There was an increased incidence of squamous cell papillomas of the forestomach in F344/N rats receiving 10 mL tricaprylin/kg. Further, the use of corn oil as a gavage vehicle may have a confounding effect on the interpretation of chemical-induced proliferative lesions of the exocrine pancreas and mononuclear cell leukemia in male F344/N rats.

# NATIONAL TOXICOLOGY PROGRAM BOARD OF SCIENTIFIC COUNSELORS TECHNICAL REPORTS REVIEW SUBCOMMITTEE

The members of the Technical Reports Review Subcommittee who evaluated the draft NTP Technical Report on corn oil, safflower oil, and tricaprylin on December 1, 1992, are listed below. Subcommittee members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, subcommittee members have five major responsibilities in reviewing NTP studies:

- o to ascertain that all relevant literature data have been adequately cited and interpreted,
- · to determine if the design and conditions of the NTP studies were appropriate,
- · to ensure that the Technical Report presents the experimental results and conclusions fully and clearly,
- · to judge the significance of the experimental results by scientific criteria, and
- · to assess the evaluation of the evidence of carcinogenic activity and other observed toxic responses.

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# SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

On December 1, 1992 the draft Technical Report on the comparative toxicology studies of corn oil, saf-flower oil, and tricaprylin received public review by the National Toxicology Program Board of Scientific Counselors Technical Reports Review Subcommittee. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Dr. G.A. Boorman, NIEHS, introduced the comparative toxicology studies of corn oil, safflower oil, and tricaprylin by reporting on the rationale for the studies. Corn oil has been used in the National Toxicology Program as the oil vehicle for gavage studies. NTP studies have shown that control male rats receiving a corn oil vehicle have a higher incidence of proliferative lesions of the exocrine pancreas and a lower incidence of mononuclear cell leukemia than untreated control males. The current NTP studies were designed to evaluate the role of several oils in altering cancer rates in male rats and were part of a larger program that included cooperative agreements with Dartmouth Medical School, Northwestern Medical School, and the University of Missouri. The program was designed to study the mechanisms by which corn oil induces pancreatic cancer. To evaluate the potential role of corn oil in promoting a pancreatic proliferative effect, a parallel study was performed in which dichloromethane in corn oil was administered to groups of animals. Dr. Boorman described the experimental design, reported on survival and body weight effects, and commented on chemical-related neoplastic and nonneoplastic lesions in male F344/N rats.

The results were summarized as: These studies demonstrate that safflower oil and tricaprylin do not offer significant advantages over corn oil as a gavage vehicle in long-term rodent studies. Both safflower oil, which is a polyunsaturated oil like corn oil but with markedly different fatty acid composition, and tricaprylin, which is a saturated medium-chain triglyceride, caused proliferative lesions of the exocrine pancreas and decreased incidences of mononuclear cell leukemia in male F344/N rats. Further, corn oil, used as a gavage vehicle, may have a confounding effect on the interpretation of chemical-induced proliferative lesions of the exocrine pancreas.

Dr. van Zwieten, a principal reviewer, said the rationale for the studies was clear, and they were designed and conducted properly. Because the pancreas was a known target tissue, he thought it would be useful to provide additional descriptive information regarding diagnostic criteria for distinguishing pancreatic acinar adenoma, and hyperplasia, carcinoma. Dr. Boorman agreed. Dr. van Zwieten said brief comments on the possible mechanism for the doserelated decrease in the incidence of mononuclear cell leukemia, even if speculative, would be appropriate. Dr. Boorman said there were in-house studies investigating this phenomenon and if something could be added, it would be.

Dr. Ryan, the second principal reviewer, said that she had difficulty interpreting the comparisons between corn oil alone and the dichloromethane groups and the report should be modified to clarify the fact that the addition of corn oil seems to change the shape of the dose-response curve for effects of dichloromethane. Dr. J.K. Haseman, NIEHS, said a summary table would be added, which would help focus attention on the important pairwise comparisons and would include a test for interaction. Dr. Ryan commented that conclusions regarding lesions of the mammary tissues were unclear, and given the controversy over diet and breast cancer, this issue would be worth further discussion. Dr. Boorman stated that in male rats receiving dichloromethane in corn oil, there were statistically significant increases in mammary gland fibroadenomas when the high-dose group was compared with the low-dose group. However, there was no statistically significant difference between animals receiving dichloromethane and the appropriate corn oil controls.

Drs. Ward and Davis led a discussion as to whether levels of evidence of carcinogenic activity should have been assigned as they are in a typical toxicology and carcinogenesis study. Dr. Boorman commented that this was not designed as a traditional carcinogenicity study in that it was done in a single sex of a single species and for a different purpose. Dr. van Zwieten suggested that there might be data from corn oil controls in previous studies for female rats and for mice.

Dr. van Zwieten moved that the Technical Report on corn oil, safflower oil, and tricaprylin be accepted with the revisions discussed and with the conclusions as stated in the summary. Dr. Ryan seconded the motion. Dr. Ward offered an amendment that levels of evidence of carcinogenicity be assigned for the three oils. He proposed some evidence of carcinogenic activity for corn oil based on increased incidences of pancreatic acinar cell adenomas, some evidence of carcinogenic activity for safflower oil based on increased incidences of pancreatic acinar cell adenomas, and some evidence of carcinogenic activity for tricaprylin based on increased incidences of pancreatic acinar cell adenomas and papillomas of the forestomach. Dr. Davis seconded the amendment. In discussion, Dr. William Allaben, NCTR, questioned applying the standard NTP categories to a study that was specifically designed as a research project. Dr. B.A. Schwetz, NIEHS, cautioned that the study would have been designed differently if the aim was to assess carcinogenicity of the oils per se. For example, controls to match caloric intake would have been included. Dr. Davis said lack of appropriate controls would be a design flaw and would change his viewpoint on assigning levels of evidence. Dr. R.A.

Griesemer, NIEHS, said there would be a summary of this discussion in the report. Dr. Ward's amendment was defeated by one yes vote (Dr. Ward) to nine no votes.

Dr. Davidson offered an amendment that the last part of the second sentence in the summary, which reads "... caused proliferative lesions of the exocrine pancreas ...," be changed to "... caused hyperplasia and adenoma of the exocrine pancreas . . . . " Dr. Boorman suggested that a statement be added noting the forestomach papillomas with tricaprylin as follows: "Tricaprylin also caused an increased incidence of squamous cell papillomas of the fore-Dr. Davidson agreed to the addition. stomach." Dr. Carlson seconded the amendment, which was accepted unanimously with ten votes. Dr. Bailey said that, based on the study design, the data were inadequate to judge carcinogenicity, and asked that his comment be included in the discussion of the review. Dr. Klaassen asked that an introductory sentence be added to the summary that would specifically state the rationale for the study. The original motion by Dr. van Zwieten as amended by Dr. Davidson was then accepted unanimously with ten votes.

# INTRODUCTION

Corm Oil

CAS No. 8001-30-7 Synonyms: Maize oil, Maydol

# Tricaprylin

CAS No. 538-23-8 Chemical Formula: C<sub>27</sub>H<sub>50</sub>O<sub>6</sub> Molecular Weight: 470.69 **Synonyms:** Trioctanoin; 1,2,3-trioctanoyl glycerol; Glycerol trioctanoate Safflower Oil

CAS No. 8001-23-8

Corn oil has been used for years as a vehicle to administer unpalatable or volatile chemicals to rodents during hazard identification studies. High dietary levels of corn oil from gavage administration have been shown to increase the incidence of pancreatic proliferative lesions and decrease the incidence of mononuclear cell leukemia in male F344/N rats (Boorman and Eustis, 1984; Eustis and Boorman, 1985; Haseman et al., 1985) and, thus, gavage vehicles have the potential for being a confounding factor in the interpretation of carcinogenicity studies. Diets rich in polyunsaturated fat, especially those containing corn oil, have a stimulating effect on carcinogeninduced mammary gland neoplasms in rats (El-Ela et al., 1987) while diets supplemented with mediumchain triglycerides do not (Cohen and Thompson, 1987). Safflower oil, containing predominantly a single polyunsaturated fatty acid triglyceride, has also been reported to stimulate chemical-induced mammary gland carcinogenesis in the rat (Lasekan et al., 1990).

Corn oil is derived by pressing the germ of the common corn (*Zea mays*). Many chemicals such as ether, chloroform, and benzene are soluble in corn

oil; therefore, corn oil works well as a gavage vehicle. The main constituents of corn oil are the polyunsaturated linoleic acid (approximately 54%), the monounsaturated oleic acid (approximately 25%), the saturated palmitic acid (approximately 10%), and the saturated stearic acid (less than 2%); the total triglyceride content in corn oil is approximately 95% (Merck Index, 1983). In addition to being one of the most common oil vehicles for the administration of test chemicals to rodents, corn oil is widely used as a salad and cooking oil and appears in a variety of foodstuffs. Corn oil has been recommended as a replacement for saturated fat in the diet of humans because of the relationship between consumption of saturated fats and cardiovascular disease (Mead et al., 1986; Dupont et al., 1990) and colon neoplasms (Giovannucci et al., 1992).

Safflower oil, in which many solvents are soluble, contains the unsaturated linoleic (approximately 80%) and oleic (approximately 12%) acids, with lesser amounts of the saturated palmitic (approximately 7%) and stearic (less than 3%) acids. Safflower oil, which is derived by pressing the seeds of

the safflower (Carthamus tinctorius), is also used as a salad dressing and cooking oil.

Tricaprylin, less frequently used as a vehicle for administering chemicals to rodents, is a synthetic triglyceride containing three chains of the 8-carbon saturated fatty acid, caprylic acid. Tricaprylin has been used as an energy source for burn patients and for patients having difficulty digesting long-chain fatty acids (Greenberger and Skillman, 1969).

The absorption and metabolism of the three vehicles, while similar, have important differences due to the type and degree of saturation of the fatty acid constituents. Corn oil, a highly digestible, high energy nutrient, is emulsified in the small intestine in the presence of bile, where the fat particles can be digested by enzymes (predominantly pancreatic lipase). Corn oil contains almost no free fatty acids; instead, the fatty acids are present in the form of triglycerides consisting of one molecule of glycerol and three molecules of fatty acid. The triglycerides are mixed, containing different fatty acids, and each triglyceride has different physiological and physical properties, depending on both the composition of the fatty acids and the position of each acid on the glycerol molecule. The distribution of the fatty acids in the triglyceride does not occur by chance; about 70% of the linoleic acid occupies the beta, or second, position, while the saturated fatty acids (predominantly palmitic and stearic fatty acids for corn oil) occupy the first and third positions (Brisson, 1981).

In the small intestine, most triglycerides are split into monoglycerides, free fatty acids, and glycerol, which are absorbed by the intestinal mucosa. Within the epithelial cells, resynthesized triglycerides collect into globules along with cholesterol and phospholipids and are encased in a protein coat as chylomicrons. Chylomicrons are transported in the lymph to the thoracic duct and eventually into the venous system. The chylomicrons are removed from the blood as they pass through the capillaries of adipose tissue. Fat is stored in adipose cells until it is transported to other tissues as free fatty acids which are used for cellular energy or incorporated into cell membranes. When <sup>14</sup>C-labeled long-chain triglycerides are administered intravenously, 25% to 30% of the radiolabel is found in the liver within 30 to 60 minutes, with less than 5% remaining after 24 hours (Johnson et al., 1990). Lesser amounts of radiolabel are found in the spleen and lung. After 24 hours, nearly 50%

of the radiolabel has been expired in carbon dioxide, with 1% of the carbon label remaining in the brown fat. The concentration of radioactivity in the epididymal fat is less than half that of the brown fat (Johnson *et al.*, 1990).

The metabolism of safflower oil is very similar to that of corn oil; however, because the different fatty acids have different metabolic rates, some differences in degradation, transport, esterification and hydrolysis result, and the fatty acid composition of the rat tissues reflects the composition of the dietary fatty acids (Lands et al., 1990). It has been suggested that the extremely high level of linoleic acid (80%) in safflower oil, which may act as a precursor of arachidonic acid, may suppress immune function (Alexander et al., 1986; Swenson et al., 1991). Additional discussion of the differential lipid metabolism (primarily in rats) can be found in texts by Brisson (1981) and Vergroesen (1989).

In contrast to the unsaturated corn and safflower oils, tricaprylin is a saturated medium-chain triglyceride with three 8-carbon caprylic acids attached to glycerol. The absorption and metabolism of mediumchain triglycerides is different from that of long-chain triglycerides found in safflower and corn oils. The lymphatic absorption of caprylic acid is lower than that of linoleic acid in rats (Ikeda et al., 1991). Some of the medium-chain fatty acids may be transported without resynthesis as triglycerides and may follow the portal venous system (Bach and Babayan, 1982). The administration of triglycerides clearly influences the size and composition of the chylomicrons. The medium-chain triglycerides rapidly release mediumchain fatty acids which do not easily bind to the fattyacid binding protein, are not significantly incorporated into lipid synthesis by the liver, and are not readily incorporated into adipose tissue (Bach and Babayan, 1982; Swenson et al., 1991). In rats, intravenously administered <sup>14</sup>C-labeled tricaprylin is removed much more rapidly from the plasma than long-chain triglycerides, and more than 90% of the radiolabel is expired in carbon dioxide within 24 hours (Johnson et al., 1990). Fat deposition decreased in rats given diets supplemented with 15% medium-chain triglycerides (caprylic 56%, capric 43%) but body weight effects were varied, with either no changes in body weight (Chanez et al., 1991) or decreased body weight (Baba et al., 1982; Geliebter et al., 1983). The medium-chain triglycerides, including tricaprylin, have also been widely studied in humans because they offer an efficient energy source with less protein catabolism for burn patients (Swenson et al., 1991). Medium-chain triglycerides have also been administered to patients with pancreatic insufficiency, neonatal hepatitis, or fat absorption abnormalities (Harkins and Sarett, 1968).

Toxicity has not been reported with corn oil or safflower oil administration, but high levels of medium-chain triglycerides will cause ketonemia in rats (Bach et al., 1977; Chanez et al., 1991). Long-term feeding of high-fat diets is associated with increased body weights and incidences of several neoplasms (Rao et al., 1987). In contrast, tricaprylin may result in less fat deposition in rats (Geliebter et al., 1983). Rats fed tricaprylin (19.5% of the diet) had increased liver weights, apparently caused by increased hepatic protein and not by lipid accumulation (Swenson et al., 1991). Medium-chain triglycerides such as tricaprylin are much more ketogenic than long-chain triglycerides (Yeh and Zee, 1976; Bach et al., 1977).

In liquid incubation assays with Salmonella typhimurium strain TA1537, weak mutagenic activity of several commercially available edible palm and corn oils has been detected (Kensese et al., 1989). In all cases, the mutagenicity was abolished by exogenous catalase, suggesting that the mutagenicity is mediated by hydrogen peroxide. This mutagenicity is not considered to pose a significant health problem (Kensese et al., 1989).

There have been few studies of biological effects of the various oils in humans, but a bolus dose of corn oil has been shown to lead to an increase in the labeling index of human colonic cells, perhaps secondary to increased levels of acidic lipids (Stadler et al., 1988). Tricaprylin, when used as a source of energy in patients, increases blood ketone levels and decreases blood glucose levels (Bach and Babayan, 1982). It is not known whether the pancreatic islets are stimulated by the ketones, the medium-chain triglycerides, or both (Ingebretsen and Wagle, 1974; Bach and Babayan, 1982).

The amount and type of dietary fat have been shown to influence spontaneous and chemical-induced neoplasms in rats (Welsch, 1992). Many of these studies are flawed in that the control groups often receive diets deficient in vitamins, essential amino acids, or energy; these deficient diets result in inhibi-

tion of growth, including neoplasm growth (Vergroesen, 1989). For example, when control rats receive a lard or beef-fat diet for comparison with corn oil studies, the diet is often deficient in linoleic acid, unless this acid has been added. About 4% linoleic acid (18:2n-6) is required for optimal growth and neoplasm promotion (Lasekan et al., 1990). Many recent studies in rats suggest that corn oil will promote chemical-induced mammary gland neoplasms (El-Ela et al., 1987) and azaserine-induced pancreatic neoplasms (O'Connor et al., 1989) and stimulate mammary gland adenocarcinoma metastases (Longnecker et al., 1986; Katz and Boylan, 1989). When the optimal amount of linoleic acid is provided, safflower oil and olive oil have similar promoting effects on mammary gland neoplasms (Lasekan et al., 1990). In contrast, medium-chain triglycerides do not appear to enhance mammary gland neoplasm development in rats (Cohen and Thompson, 1987). Corn oil also increases the incidence of spontaneous pancreatic exocrine adenomas in both male and female rats (Boorman and Eustis, 1984; Haseman et al., 1985; Boorman et al., 1987) while decreasing the incidence of mononuclear cell leukemia in male rats. Female rats given corn oil by gavage also have a lower incidence of pituitary gland adenoma than untreated controls.

Through cooperative agreements with three universities, the physiology and biology of corn oil effects on the rat pancreas were studied in conjunction with the studies reported here. The corn oil induced pancreatic adenomas and hyperplasias that have genotypic and phenotypic characteristics similar to those of the normal pancreas and to azaserine-induced adenomas; these characteristics include nuclear DNA content. lack of growth in soft agar, or growth after transplantation. Specifically, repeated transplantation of corn oil-induced adenomas and hyperplasias either subcutaneously or under the kidney capsule failed to result in the growth of these lesions. Transfection of DNA from corn-oil induced hyperplasias or adenomas into NIH 3T3 cells does not cause increased transformation, whereas transfection of DNA from azaserineinduced carcinomas does cause increased transformation (Longnecker et al., 1986, 1991).

Evaluation of the corn oil-induced pancreatic nodules for mutations in the c-Ki-ras proto-oncogene showed wild-type but not mutated c-Ki-ras. While the gastrointestinal hormone cholecystokinin has been implicated in some pancreatic carcinomas induced by

soybean trypsin inhibitors, there was no evidence that cholecystokinin played a role in the pancreatic lesions induced by diets with a high corn oil content.

A comparison of diets varying in degree of saturated fatty acids for their ability to promote chemicalinduced exocrine pancreatic carcinogenesis suggests that it is the level of fat and not the degree of saturation that is important (Longnecker, 1990). This correlates very well with the NTP studies and is in contrast to earlier findings that suggested that high levels of unsaturated fat caused pancreatic cancer (Roebuck et al., 1981). An analysis of the body fat of rats showed that in rats receiving 20% corn oil, the amount of linoleic acid in the fat increased, while the amount of palmitic acid decreased compared to that in rats receiving 5% corn oil. Diets with intermediate amounts of corn oil had intermediate fatty acid amounts. The scientific publications from the cooperative agreement studies are listed in Appendix L.

Dichloromethane was also selected for inclusion in these studies because of conflicting results in previous studies evaluating the potential of this chemical to induce proliferative lesions of the exocrine pancreas in rats. Dichloromethane given by inhalation caused no effect on the pancreas, while dichloromethane administered by gavage in corn oil was associated with increased incidences of pancreatic exocrine neoplasms (NTP, 1986). In the present studies, one amount of dichloromethane was evaluated using varying volumes of corn oil as a gavage vehicle in order to determine the contributing role of corn oil in the pathogenesis of pancreatic neoplasms.

Increased dietary fat resulting from the use of oil gavage vehicles can alter the incidence of certain spontaneous neoplasms in rats and, thus, acts as a confounding factor in evaluating a chemical for potential toxicity and carcinogenicity. Therefore, these studies were designed to evaluate the effects of various concentrations of an oil very high in polyunsaturated fat (safflower oil), an oil containing high levels of polyunsaturated and monounsaturated fats (corn oil), and an oil containing saturated mediumchain fatty acids (tricaprylin) on the incidence and pattern of neoplasms in the F344/N rat. In addition, safflower oil and tricaprylin were evaluated as replacements for the corn oil vehicle.

# MATERIALS AND METHODS

# PROCUREMENT AND CHARACTERIZATION

## Corn Oil

Corn oil was obtained as a gift from Best Foods (Union, NJ) in two lots (2325 and SFS-L050189) courtesy of Mark Bieber, Ph.D. Characteristics and composition analyses were conducted by Best Foods (Table H1). The supplied corn oil met all specifications for processed corn oil. During the study, corn oil was stored in amber glass bottles at 4° C under an argon headspace. To evaluate stability of the corn oil, the study laboratory monitored the peroxide concentration of each bottle using Official Method Cd 8-53 of the American Oil Chemist Society. The acceptable peroxide concentration was set at 2 mEq/L. A bottle was discarded if the peroxide concentration exceeded this specification.

#### Safflower Oil

R.G. Krishnamurthy, Ph.D., of Kraft, Incorporated (Glenview, IL), arranged a gift of safflower oil. Two suppliers provided the safflower oil - Oilseeds International, Ltd. (lot OISO) and Producers Cotton Oil Company (lot KISO). Both suppliers provided safflower oil that met all specifications for high linoleic acid safflower oil. Specific lot analyses were not provided. During the study, safflower oil was stored in amber glass bottles at 4° C under an argon headspace. Again, to evaluate stability of the safflower oil, the study laboratory determined the peroxide concentration in each bottle prior to use. The acceptable peroxide concentration was set at 2 mEq/L. A bottle was discarded if the peroxide concentration exceeded this specification.

## Tricaprylin

Tricaprylin was obtained from Eastman Kodak (Rochester, NY) in three lots (A15, A11, and 8812-806876). Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute, and confirmed by the study laboratory (Appendix H).

The three lots of the chemical, a clear, colorless to amber liquid, were identified as tricaprylin by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. The purity of all lots of tricaprylin was determined by elemental analyses; Karl Fischer water analysis; United States Pharmacopeia (USP) XX methods of titration for acid and saponification values; thin-layer chromatography (TLC); and gas chromatography.

For lot A15, the purity was determined to be approximately 94%. Elemental analyses for carbon and hydrogen were in agreement with the theoretical values for tricaprylin. Karl Fischer analysis indicated 0.002% water. USP methods of titration indicated an acid value of 1.82 mg KOH/g sample, equivalent to 0.467% octanoic acid, and a saponification value of 345 mg KOH/g sample. The acid and the saponification values indicated that the ester content was 96% of the theoretical ester value. TLC indicated one trace impurity. Gas chromatography indicated one impurity with a peak area of approximately 5%, and up to seven additional impurities, with an additional total area of 1.0%. The largest impurity in lot A15 was identified as dicaprylin by packed column gas chromatography/mass spectrometry/full mass scan at a concentration of approximately 5%. The ratio of the two possible dicaprylin isomers (1,2-dicaprylin and 1,3-dicaprylin) was not determined.

The overall purity of lot A11 was determined to be approximately 97%. Elemental analyses for carbon and hydrogen were in agreement with the theoretical values for tricaprylin. Karl Fischer analysis indicated 0.08% water. USP methods of titration indicated an acid value of 2.27 mg KOH/g sample, equivalent to 0.58% octanoic acid, and a saponification value of 358 mg KOH/g sample. The acid and saponification values indicated that the ester content was 99.5% of the theoretical ester value. TLC indicated a minor impurity and a trace impurity. Gas chromatography indicated up to five impurities with a combined area of 3.6%. Although the presence of dicaprylin was

not confirmed, a peak with an identical retention time was observed and represented approximately 2.3% of the chromatographic peak area.

For lot 8812-806876 the overall purity was determined to be approximately 91%. Elemental analyses for carbon and hydrogen were in agreement with the theoretical values for tricaprylin. Karl Fischer analysis indicated the presence of no more than 0.01% water. USP methods of titration indicated an acid value of 0.60 mg KOH/g sample, equivalent to 0.155% octanoic acid, and a saponification value of 354 mg KOH/g sample. The acid and saponification values indicated that the ester content was 99% of the theoretical ester value. TLC indicated a minor impurity and up to four trace impurities. Gas chromatography indicated up to five impurities with a total area of 8.4%. Again, although the presence of dicaprylin was not confirmed, a peak with an identical retention time was observed and represented approximately 6% of the chromatographic peak area. Because the major impurity was two 8-carbon caprylic acids attached to a glycerol (dicaprylin) instead of three (tricaprylin), further purification steps were not taken.

Accelerated bulk chemical stability studies performed by the analytical chemistry laboratory with gas chromatography indicated that tricaprylin was stable as a bulk chemical for 2 weeks when stored protected from light at temperatures up to 60° C. Throughout the studies, the bulk chemical was stored in amber glass containers at 4° C under an argon headspace. The stability of tricaprylin was monitored periodically by the study laboratory with ultraviolet spectroscopy and gas chromatography. In addition, the peroxide concentration in each bottle was determined prior to use. The acceptable peroxide concentration was set at 2 mEq/L. A bottle was discarded if it exceeded this specification. No significant degradation of the bulk chemical was observed throughout the study.

#### Dichloromethane

Dichloromethane was obtained from Dow Chemical Company (Midland, MI) in one lot (D112480), which was used throughout the study. Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO), and confirmed by the study laboratory (Appendix H).

The chemical, a clear, colorless liquid, was identified as dichloromethane by infrared spectroscopy. The purity of dichloromethane was determined to be approximately 99% by Karl Fischer water analysis, free acid titration, and gas chromatography. Karl Fischer analysis indicated 0.0091% water. Free acid titration indicated less than 0.96 ppm acidic components, expressed as hydrochloric acid. Gas chromatography indicated the presence of two impurities with peak areas greater than 0.01% (0.02% and 0.18%, respectively).

Gas chromatography/mass spectroscopy/full mass scan analyses were conducted to identify and quantitate, if present, vinylidene chloride, trans-1,2-dichloroethylene, 1,3-butadiene, chloroform, carbon tetrachloride, and 1,2-dichloroethane. All of these impurities were detected except 1,2-dichloroethane. In addition, cyclohexane was detected coeluting with vinylidene chloride. The impurities were quantitated using capillary or packed column chromatography. The concentrations found were: less than 100 ppm vinylidene chloride, 100 ppm trans-1,2-dichloroethylene, less than 1 ppm 1,3-butadiene, 18 ppm chloroform (bromochloromethane coeluted), and less than 0.3 ppb carbon tetrachloride.

Accelerated bulk chemical stability studies using gas chromatography indicated that dichloromethane was stable as a bulk chemical for at least 2 weeks at temperatures up to 35° C. Throughout the study, the bulk chemical was stored in amber glass containers in the dark at 20° C. Periodic reanalyses of dichloromethane were performed by the study laboratory using free acid titration and gas chromatography. No degradation of the bulk chemical was observed throughout the study.

# PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

The dose formulations (dichloromethane in corn oil) were prepared by mixing dichloromethane with corn oil (Table H2). Stability studies of the dichloromethane dose formulations performed by the analytical chemical laboratory using gas chromatography indicated that the dose formulations were stable for at least 3 weeks when stored in the dark at room temperature. During the study, the dose formulations were stored at 4° C until use.

Dose formulations of dichloromethane in corn oil were prepared weekly and analyses were performed by the study laboratory approximately every 8 weeks using gas chromatography; 41 of the 42 dose formulations analyzed were within 10% of the target concentrations (Table H3). All animal room samples were within 10% of the target concentrations. Results of periodic referee analyses performed by the analytical chemistry laboratory indicated good agreement with the results obtained by the study laboratory, with the exception of one dose formulation mixed on 18 November 1987 (Table H4). Animal room samples from this dose formulation were analyzed and were within 10% of the target concentrations.

Corn oil, safflower oil, and tricaprylin were dispensed into vials for gavage dosing on a weekly basis and, after dispensing, were stored at 4° C for no more than 3 weeks (oils). Saline solutions were prepared by mixing sodium chloride with deionized water and stored for up to 4 weeks.

## 2-YEAR STUDIES

## Study Design

Corn oil study: Groups of 50 male rats were administered 2.5, 5, or 10 mL corn oil/kg body weight or 10 mL saline/kg body weight by gavage, 5 days a week, for 2 years. Untreated animals served as controls.

Safflower oil and tricaprylin studies: Groups of 60 male rats were administered 2.5, 5, or 10 mL safflower oil or tricaprylin/kg body weight by gavage, 5 days a week, for up to 2 years. Controls were untreated. After 15 months, 10 rats from each group were evaluated.

Dichloromethane in corn oil study: Groups of 50 male rats were administered 500 mg dichloromethane/kg body weight with a dosing volume of 2.5, 5, or 10 mL corn oil/kg by gavage, 5 days a week, for 2 years. A control group receiving only 500 mg/kg neat dichloromethane was initially included in the study; however, these rats were terminated after 3 weeks due to excessive mortality.

Throughout the discussion of these studies in this report, the term "dose" refers to the volume of gavage vehicle used.

# Source and Specification of Animals

Male F344/N rats used in the corn oil, safflower oil, and tricaprylin studies were obtained from Simonsen Laboratories (Gilroy, CA), and male F344/N rats used in the dichloromethane in corn oil study were obtained from Frederick Cancer Research Facility (Frederick, MD). Prior to study start, five rats from each study were randomly selected and killed for parasite evaluation and gross observation of disease. Rats were quarantined for 14 to 22 days and were 7 weeks old at the beginning of the studies. The health of the animals was monitored during the studies according to the protocols of the NTP Sentinel Animal Program (Appendix K).

## Animal Maintenance

Animals were housed five per cage. Cages were rotated within racks and racks were rotated within rooms every 2 weeks. Feed and water were available ad libitum. Further details of animal maintenance are given in Table 1.

## Clinical Examinations and Pathology

All animals were observed twice daily, and findings were recorded at least monthly. With a few exceptions, rats were weighed at study initiation, weekly for 13 weeks, and monthly thereafter (Table 1). Necropsies were performed on all animals except those receiving only dichloromethane.

At 15 months in the safflower oil and tricaprylin studies, rats were randomly selected for interim evaluations. Hematology evaluations were performed on rats from both studies and clinical chemistry evaluations were performed on rats from the safflower oil study. Blood was drawn from the retroorbital sinus of rats in the safflower oil study and from the posterior vena cava of rats in the tricaprylin study to determine the following hematology and clinical chemistry parameters: hematocrit, hemoglobin, erythrocyte count, mean erythrocyte hemoglobin, mean erythrocyte volume, mean erythrocyte hemoglobin concentration, reticulocyte count, total and differential leukocyte counts, potassium, total protein, albumin, cholesterol, alanine aminotransferase, creatine kinase, sorbitol dehydrogenase, and bile acids. The brain, right kidney, and liver of each animal were weighed at necropsy. Further details of the interim evaluations are presented in Table 1.

Animals found in a moribund state, selected for the 15-month interim evaluations, or surviving to the end of the 2-year studies were killed by CO<sub>2</sub> asphyxiation, except those in the tricaprylin study where "Biotol," an ultra fast-acting barbiturate, was used. At necropsy, all organs and tissues were examined for gross lesions, and all major tissues were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin for microscopic examination. Complete histopathologic examinations were performed on all animals except those receiving dichloromethane alone. Tissues examined are listed in Table 1.

Upon completion of the microscopic evaluations by the study laboratory pathologist, the pathology data were entered into the Toxicology Data Management System. The microscope slides, paraffin blocks, and residual wet tissues were sent to the NTP Archives for inventory, slide/block match, and wet-tissue audit. The slides, individual animal data records, and pathology tables were sent to an independent pathology quality assessment laboratory. The individual animal records and pathology tables were compared for accuracy, slide and tissue counts were verified, and histotechnique was evaluated by the quality assessment laboratory. The following organs were reviewed microscopically by the quality assessment pathologist for neoplasms and nonneoplastic lesions: adrenal medulla, kidney, liver, pancreas, spleen, thyroid gland, and tongue in the corn oil study; kidney, liver, pancreas, spleen, and stomach in the safflower oil study; kidney, liver, pancreas, stomach, and spleen in the tricaprylin study; and kidney, liver, mammary gland, pancreas, spleen, and stomach in the dichloromethane in corn oil study.

For each study, the quality assessment report and slides were submitted to the NTP Pathology Working Group (PWG) chair, who reviewed the selected tissues and any other tissues for which there was a disagreement in diagnosis between the laboratory and quality assessment pathologists. Representative histopathology slides containing examples of lesions related to chemical administration, examples of disagreements in diagnosis between the laboratory and quality assessment pathologists, or lesions of general interest were presented by the chair to the PWG for review. These lesions included examples of mononuclear cell leukemia and neoplasms or nonneoplastic lesions of the following organs: adrenal medulla, liver, pancreas, thyroid gland, and tongue

(corn oil study); forestomach, kidney, liver, pancreas, and spleen, (safflower oil study); forestomach, heart, and pancreas (tricaprylin study); and forestomach, liver, mammary gland, and pancreas (dichloromethane in corn oil study). The PWG consisted of the quality assessment pathologist and other pathologists experienced in rodent toxicologic pathology who examined the tissues without knowledge of dose groups or previously rendered diagnoses. When the consensus opinion of the PWG differed from that of the laboratory pathologist, the diagnosis was changed to reflect the PWG consensus. Details of these review procedures have been described by Maronpot and Boorman (1982) and Boorman et al. (1985). For subsequent analyses of pathology data, the diagnosed lesions for each tissue type are evaluated separately or combined according to the guidelines of McConnell et al. (1986).

# Statistical Methods Survival Analyses

The probability of survival was estimated by the product-limit procedure of Kaplan and Meier (1958) and is presented in the form of graphs. Statistical analyses for a possible dose-related effect on survival were performed using the method of Cox (1972) for testing two groups for equality and Tarone's (1975) life table test for a dose-related trend.

## Calculation of Incidence

The incidences of neoplasms or nonneoplastic lesions as presented in Tables A1, A4, B1, B4, C1, C4, D1, and D4 are given as the number of animals bearing such lesions at a specific anatomic site and the number of animals with that site examined microscopically. For calculation of statistical significance, the incidences of most neoplasms (Tables A3, B3, C3, and D3) and all nonneoplastic lesions are given as the ratio of the number of affected animals to the number of animals with the site examined microscopically. However, when macroscopic examination was required to detect neoplasms in certain tissues (e.g., skin, intestine, harderian gland, and mammary gland) before microscopic evaluation, or when neoplasms had multiple potential sites of occurrence (e.g., leukemia or lymphoma), the denominators consist of the number of animals necropsied.

## Analysis of Neoplasm Incidences

The majority of neoplasms in these studies were considered to be incidental to the cause of death or not rapidly lethal. The primary statistical method

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

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

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

#### Analysis of Nonneoplastic Lesion Incidences

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

# Analysis of Continuous Variables

Two approaches were employed to assess the significance of pairwise comparisons between dosed and control groups in the analysis of continuous variables. Organ and body weight data, which have approximately normal distributions, were analyzed using the multiple comparison procedures of Williams (1971, 1972) and Dunnett (1955). Clinical chemistry and hematology data, which have typically skewed distributions, were analyzed using the multiple comparison methods of Shirley (1977) and Dunn (1964). Jonckheere's test (Jonckheere, 1954) was used to assess the significance of dose-response trends and to determine whether a trend-sensitive test was more appropriate for pairwise comparisons than a test that does not assume a monotonic dose response (Dunnett's or Dunn's test). Average severity values were analyzed for significance using the Mann-Whitney U test (Hollander and Wolfe, 1973).

## Historical Control Data

Although the concurrent control group is always the first and most appropriate control group used for evaluation, there are certain instances in which historical control data can be helpful in the overall assessment of neoplasm incidence. Consequently, control neoplasm incidences from the NTP historical control database (Haseman *et al.*, 1984, 1985) are included in the NTP reports for neoplasms appearing to show compound-related effects.

## Quality Assurance Methods

The 2-year studies of corn oil, safflower oil, and tricaprylin were conducted in compliance with Food and Drug Administration Good Laboratory Practice Regulations (21 CFR, Part 58). As study records for the 2-year studies were submitted to the NTP archives, they were audited retrospectively by an independent quality assurance contractor. Separate audits covering completeness and accuracy of the pathology data, pathology specimens, final pathology tables, and board review draft of the NTP Technical Report were conducted. Audit procedures and findings are presented in the reports, which are on file at the NIEHS. The audit findings were reviewed and assessed by NTP staff so that all discrepancies had been resolved or were otherwise addressed during the preparation of this Technical Report.

# **GENETIC TOXICOLOGY**

The genetic toxicity of corn oil, safflower oil, and tricaprylin was assessed by testing the ability of these materials to induce mutations in Salmonella typhimurium strains TA97, TA98, TA100, and TA1535. The genetic toxicity of dichloromethane was assessed by testing the ability of this material to induce mutations in S. typhimurium strains TA97, TA98, TA100, TA1535, and TA1537; trifluorothymidine resistance in L5178Y mouse lymphoma cells; and sister chromatid exchanges and chromosomal aberrations in cultured Chinese hamster ovary cells. The protocols for these studies and the results are given in Appendix E.

The genetic toxicity studies of these oral gavage vehicles and dichloromethane are part of a larger effort by the NTP to develop a database that would permit the evaluation of carcinogenicity in experimental animals from the structure and responses of the chemical in short-term in vitro and in vivo genetic toxicity tests. These genetic toxicity tests were originally developed to study mechanisms of chemically induced DNA damage and to predict carcinogenicity in animals based on the electrophilic theory of chemical carcinogenesis and the somatic mutation

theory (Miller and Miller, 1977; Straus, 1981; Crawford, 1985).

There is a strong correlation between a chemical's potential electrophilicity (structural alert to DNA reactivity), mutagenicity in Salmonella, and carcinogenicity in rodents. The combination of electrophilicity and Salmonella mutagenicity is highly correlated with the induction of carcinogenicity in rats and mice and/or at multiple tissue sites (Ashby and Tennant, 1991). Other in vitro genetic toxicity tests do not correlate well with rodent carcinogenicity (Tennant et al., 1987; Zeiger et al., 1990), although these other tests can provide information on the types of DNA and chromosome effects that can be induced by the chemical being investigated. Data from NTP studies show that a positive response in Salmonella is currently the most predictive in vitro test for rodent carcinogenicity (89% of the Salmonella mutagens were rodent carcinogens), and that there is no complementarity among the in vitro genetic toxicity tests. That is, no battery of tests that included the Salmonella test improved the predictivity of the Salmonella test alone. The predictivity for carcinogenicity of a positive response in bone marrow chromosome aberration or micronucleus tests is not vet defined.

TABLE 1
Experimental Design and Materials and Methods in the 2-Year Gavage Studies of Corn Oil, Safflower Oil, Tricaprylin, and Dichloromethane in Corn Oil

Corn Oil Study	Safflower Oil Study	Tricaprylin Study	Dichloromethane in Corn Oil Study
Study Laboratory TSI Mason Research Institute (Worcester, MA)	TSI Mason Research Institute (Worcester, MA)	TSI Mason Research Institute (Worcester, MA)	TSI Mason Research Institute (Worcester, MA)
Strain and Species F344/N rats	F344/N rats	F344/N rats	F344/N rats
Animal Source Simonsen Laboratories, Gilroy, CA	Simonsen Laboratories, Gilroy, CA	Simonsen Laboratories, Gilroy, CA	Frederick Cancer Research Facility, Frederick, MD
Size of Study Groups 50 males	60 males	60 males	50 males
Doses 0, 2.5, 5, or 10 mL corn oil/kg body weight or 10 mL saline/kg body weight	0, 2.5, 5, or 10 mL safflower oil/kg body weight	0, 2.5, 5, or 10 mL tricaprylin/kg body weight	500 mg dichloromethane/kg with a dosing volume of 2.5, 5, or 10 mL corn oil/kg body weight
Time Held Before Study 20 days	22 days	20 days	14 days
Average Age When Study Bo 7 weeks	egan 7 weeks	7 weeks	7 weeks
Date of First Dose 1 October 1986	7 November 1986	23 October 1986	22 January 1986
Duration of Dosing 5 days a week for 103 weeks	5 days a week for up to 104 weeks	5 days a week for up to 104 weeks	5 days a week for 104 weeks
Date of Last Dose 20 September 1988	15-month interim: week of 8 February 1988 2-year study: 3 November 1988	15-month interim: week of 25 January 1988 2-year study: 19 October 1988	19 January 1988
Necropsy Dates 28 September - 6 October 1988	4-14 November 1988	20-28 October 1988	20-25 January 1988
Average Age When Killed 111 weeks	111 weeks	111 weeks	111 weeks
Method of Sacrifice 70% CO <sub>2</sub> asphyxiation	70% CO <sub>2</sub> asphyxiation	"Biotol" (an ultra fast-acting barbiturate)	70% CO <sub>2</sub> asphyxiation

TABLE 1

Experimental Design and Materials and Methods in the 2-Year Gavage Studies of Corn Oil, Safflower Oil, Tricaprylin, and Dichloromethane in Corn Oil (continued)

Corn Oil Study	Safflower Oil Study	Tricaprylin Study	Dichloromethane in Corn Oil Study
Animals per Cage	5	5	5
Method of Animal Distribution Animals were assigned to cages and then to groups with tables of random numbers.	ion Same as com oil study	Same as corn oil study	Same as corn oil study
Method of Animal Identifica	tion		
Toe clip	Toe clip	Toe clip	Toe clip
Diet NIH-07 open-stock mash diet (Zeigler Bros., Inc., Gardners, PA), available ad libitum	Same as corn oil study	Same as corn oil study	Same as corn oil study
Water Tap water (Worcester public water supply) via automatic watering system (Edstrom Industries, Waterford, WI), available ad libitum	Same as corn oil study	Same as corn oil study	Same as corn oil study
Cages Polycarbonate (Lab Products, Inc., Garfield, NJ), changed twice weekly	Same as corn oil study	Same as corn oil study	Same as corn oil study
Bedding BetaChips® hardwood chips (Northeastern Products Corp., Warrensburg, NY), changed twice weekly	Same as corn oil study	BetaChips® hardwood chips (Northeastern Products Corp., Warrensburg, NY, or P.J. Murphy Forest Products, Montville, NJ)	Same as corn oil study
Cage Filters Nonwoven fiber filters (Snow Filtration, Cincinnati, OH), changed every 2 weeks	Same as corn oil study	Same as corn oil study	Same as corn oil study
Racks Stainless steel (Lab Products, Inc., Rochelle Park, NJ), changed every 2 weeks	Same as corn oil study	Same as corn oil study	Same as corn oil study
Other Studies in Animal Ro Safflower oil and tricaprylin	om  Corn oil and tricaprylin	Corn oil and safflower oil	Separate corn oil gavage study

TABLE 1
Experimental Design and Materials and Methods in the 2-Year Gavage Studies of Corn Oil,
Safflower Oil, Tricaprylin, and Dichloromethane in Corn Oil (continued)

Corn Oil Study	Safflower Oil Study	Tricaprylin Study	Dichloromethane in Corn Oil Study
Animal Room Environment Average temperature:	Same as corn oil study	Same as corn oil study	Average temperature:
21°-22° C Relative humidity:	<u> </u>	•	22°-23° C Relative humidity:
47.1% ± 4.9%			$47.5\% \pm 3.7\%$
Fluorescent light:			Fluorescent light:
12 hours/day			12 hours/day Room air changes:
Room air changes: At least 10/hour			At least 10/hour
Type and Frequency of Obse			
Observed twice daily; weighed weekly for 13 weeks, except for week 9, at week 16, then monthly; clinical observations recorded weekly for 13 weeks, then monthly	Observed twice daily; weighed weekly for 14 weeks, at week 17, then monthly; clinical observations recorded weekly for 2 weeks and then monthly	Observed twice daily; weighed weekly for 14 weeks, except weeks 6 and 11, at week 17, then monthly; clinical observations recorded monthly	Observed twice daily; weighed weekly for 14 weeks, at week 17, then monthly; clinical observations recorded weekly for first 3 weeks, at week 5, then monthly
Necropsy			
Necropsy was performed on all animals.	Necropsy was performed on all animals. The brain, right kidney, and liver were weighed at 15 months.	Same as safflower oil study	Necropsy was performed on all animals except those receiving dichloromethane only.
Clinical Pathology			
None	Clinical pathology studies were performed on 10 rats from each dose group at 15 months.  Hematology: hematocrit, hemoglobin, erythrocyte count, mean erythrocyte hemoglobin, mean erythrocyte volume, mean erythrocyte hemoglobin concentration, reticulocytes, and leukocyte count and differential  Clinical chemistry: potassium, total protein, albumin, cholesterol, alanine aminotransferase, creatine kinase, sorbitol dehydrogenase, and bile acids	Clinical pathology studies were performed on 10 rats from each dose group at 15 months.  Hematology: hematocrit, hemoglobin, erythrocyte count, mean erythrocyte hemoglobin, mean erythrocyte volume, mean erythrocyte hemoglobin concentration, reticulocytes, and leukocyte count and differential	None

TABLE 1
Experimental Design and Materials and Methods in the 2-Year Gavage Studies of Corn Oil, Safflower Oil, Tricaprylin, and Dichloromethane in Corn Oil (continued)

Safflower Oil Study	Tricaprylin Study	Dichloromethane in Corn Oil Study
Same as corn oil study	Same as corn oil study	Complete histopathology was performed on all rats except those receiving dichloromethane only.  Tissues examined were the same as in corn oil study.

# RESULTS

# CORN OIL, SAFFLOWER OIL, AND TRICAPRYLIN STUDIES

Survival and Clinical Findings

The survival of male rats was similar among the untreated control groups for corn oil (26/50), safflower oil (30/50), and tricaprylin (31/50) and the 10 mL saline/kg group (32/50) (Tables 2, 3, and 4, and Figures 1, 2, and 3). In rats dosed with corn oil, survival increased with dose, and the survival of male rats given 5 or 10 mL/kg was significantly greater than that of the controls, while the survival of rats dosed with safflower oil was slightly, but not significantly, greater than that of the controls. In contrast, the survival of rats receiving 10 mL tricaprylin/kg was significantly lower than that of the controls. Clinical findings of dyspnea, ataxia, and lethargy following dosing were recorded for 50 of the 60 animals receiving 10 mL tricaprylin/kg. However, the animals generally recovered prior to the next daily dosing, and the incidence of clinical findings declined during the second half of the study. No clinical findings of toxicity were noted in the corn oil or safflower oil studies.

Twenty-three rats receiving 10 mL tricaprylin/kg died or were killed between weeks 33 and 85. Ten of these animals were found dead and 13 were killed moribund. Although the cause of death or moribund condition could not be determined in 20 of these animals, clinical findings were noted in all of the moribund animals. Of these, eight rats died or were killed between weeks 45 and 49, when the incidence of clinical findings was highest. The average body weight of these eight animals was 316 g, which was significantly less than the mean group body weight of approximately 360 g for the 10 mL/kg group at 11 months. Only one of the moribund animals had a pulmonary mass that might have explained the dyspnea. Up to four animals in the 10 mL/kg group died or were killed in each subsequent month.

TABLE 2
Survival of Male Rats in the 2-Year Gavage Study of Corn Oil

	Untreated Control	2.5 mL/kg	5 mL/kg	10 mL/kg
Animals initially in study	50	50	50	50
Natural deaths	8	8	6	6
Moribund kills	16	9	6	4
Animals surviving until study termination	26 <sup>a</sup>	33	38	40
Percent probability of survival at end of study <sup>b</sup>	52	66	76	80
Mean survival (days) <sup>c</sup>	689	691	697	715
Survival analysis <sup>d</sup>	P=0.005N	P=0.305N	P=0.029N	P=0.007N

Includes one rat that died during the last week of the study

Kaplan-Meier determinations

<sup>&</sup>lt;sup>c</sup> Mean of all deaths (uncensored, censored, terminal sacrifice)

The result of the life table trend test (Tarone, 1975) is in the control column, and the results of the life table pairwise comparisons (Cox, 1972) with the controls are in the dosed columns. A negative trend or lower mortality in a dose group is indicated by N.

TABLE 3
Survival of Male Rats in the 2-Year Gavage Study of Safflower Oil

;	Untreated Control	2.5 mL/kg	5 mL/kg	10 mL/kg
Animals initially in study	60	60	60	60
5-Month interim evaluation <sup>a</sup>	10	10	10	9
Natural deaths	8	8	3	. 10
Moribund kills	12	9	7	5
Animals surviving until study termination	30	33	40	36
Percent probability of survival at end of study <sup>b</sup>	60	67	81	71
Mean survival (days) <sup>c</sup>	656	650	649	665
Survival analysis <sup>d</sup>	P = 0.252N	P=0.756N	P=0.075N	P=0.341N

<sup>&</sup>lt;sup>a</sup> Censored from survival analyses

TABLE 4
Survival of Male Rats in the 2-Year Gavage Study of Tricaprylin

•	Untreated Control	2.5 mL/kg	5 mL/kg	10 mL/kg
Animals initially in study	60	60	60	60
15-Month interim evaluation <sup>a</sup>	10	10	10	7
Natural deaths	4	7	4	13
Moribund kills	15	13	15	17
Animals surviving until study termination	31 <sup>b</sup>	30	31 <sup>b</sup>	23 <sup>b</sup>
Percent probability of survival at end of study <sup>c</sup>	62	61	63	46
Mean survival (days) <sup>d</sup>	651	639	642	553
Survival analysis <sup>e</sup>	P = 0.004	P=0.944	P=0.969	P=0.014

a Censored from survival analyses

b Kaplan-Meier determinations

Mean of all deaths (uncensored, censored, terminal sacrifice)

The result of the life table trend test (Tarone, 1975) is in the control column, and the results of the life table pairwise comparisons (Cox, 1972) with the controls are in the dosed columns. A negative trend or lower mortality in a dose group is indicated by N.

b Includes one rat (5 and 10 mL/kg groups) or two rats (untreated control group) that died during the last week of the study.

<sup>&</sup>lt;sup>c</sup> Kaplan-Meier determinations

Mean of all deaths (uncensored, censored, terminal sacrifice)

The result of the life table trend test (Tarone, 1975) is in the control column, and the results of the life table pairwise comparisons (Cox, 1972) with the controls are in the dosed columns.

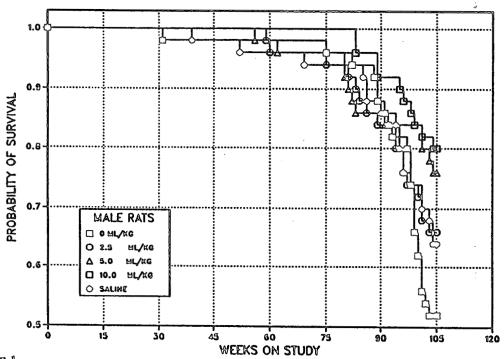


FIGURE 1
Kaplan-Meier Survival Curves for Male Rats Administered Corn Oil by Gavage for 2 Years

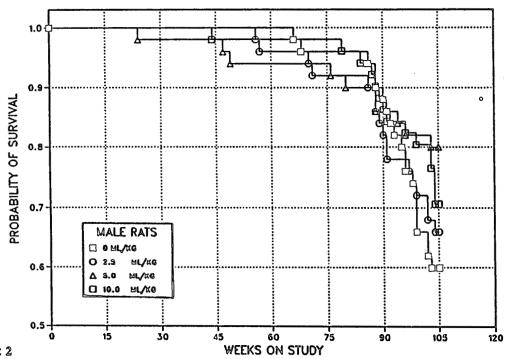


FIGURE 2 WEEKS ON STUDY
Kaplan-Meier Survival Curves for Male Rats Administered Safflower Oil by Gavage for 2 Years

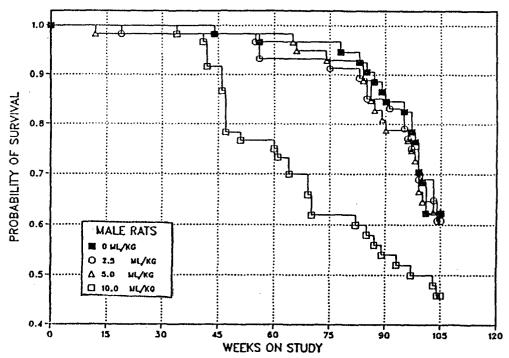


FIGURE 3
Kaplan-Meier Survival Curves for Male Rats Administered Tricaprylin by Gavage for 2 Years

# **Body Weights and Feed Consumption**

The mean body weights of rats receiving 10 mL saline/kg (mean maximum body weight, 428 g; final mean body weight, 383 g) were similar to those of the three untreated control groups (maximum body weight, 414 to 437 g; final mean body weight, 386 to 399 g). The corn oil, tricaprylin, and safflower oil studies were all begun within a 5-week period, and rats were from the same source. Due to slight differences in age, the initial mean body weights varied from 126 to 159 g. The maximum mean body weights did not appear to correlate with the initial mean body weights or the final mean body weights. The mean body weights of rats receiving 2.5 or 5 mL corn oil/kg were 2% to 6% greater than those of

controls, while those of rats receiving tricaprylin or safflower oil in these volumes were similar to those of controls.

Mean body weights of rats receiving 10 mL corn oil/kg (Table 5 and Figure 4) or 10 mL safflower oil/kg (Figure 5 and Table 6) were 10% greater than those of the controls by week 56 and were 16% greater than those of controls at the end of the study. In contrast, the mean body weights of rats receiving 10 mL tricaprylin/kg were lower than those of the controls throughout the study; however, the differences were less than 5% after week 61 (Table 7 and Figure 6).

TABLE 5
Mean Body Weights and Survival of Male Rats in the 2-Year Gavage Study of Corn Oil

Weeks	Untreate	ed Control		2.5 mL/kg			5 mL/kg			10 mL/kg		
on	Av. W1.	No. of	Av. Wt.			Av. Wt.			Av. Wt.	Wt. (% of	No. of	
Study	(g)	Survivors	(g)	-	Survivors	(g)	controls)	Survivors	(g)	controls)	Survivors	
1	126	50	129	102	50	126	100	50	124	98	50	
2	161	50	160	100	50	159	99	50	154	96	50	
3	192	50	192	100	50	190	99	50	185	96	50	
4	210	50	211	101	50	209	100	50	206	98	50	
5	232	50	232	100	50	231	100	50	226	98	50	
6	250	50	251	101	50	248	100	50	243	97	50	
7	265	50	266	101	50	264	100	50	258	97	50	
8	282	50	285	101	50	281	100	50	277	98	50	
10	294	50	300	102	50	297	101	50	292	99	50	
11	303	50	311	103	50	307	101	50	302	100	50	
12	312	50	320	103	50	316	101	50	308	99	50	
13	317	50	324	102	50	318	100	50	316	100	50	
16	332	50	344	104	50	337	102	50	335	101	50	
20	350	50	361	103	50	357	102	50	357	102	50	
24	364	50	368	101	50	368	101	50	369	101	50	
28	378	50	389	103	50	386	102	50	383	101	50	
33	381	49	393	103	50	391	103	50	394	103	50	
37	387	49	406	105	50	395	102	50	403	104	50	
40	392	49	409	104	50	403	103	50	417	106	50	
44	399	49	415	104	50	409	103	50	427	107	50	
48	402	49	427	106	50	420	105	50	438	109	50	
52	402	49	428	107	50	426	106	50	441	110	50	
57	408	49	435	107	50	433	106	49	453	111	50	
61	414	49	439	106	48	438	106	49	460	111	50	
64	414	49	433	105	48	439	106	48	461	111	50	
69	421	49	449	107	48	444	105	48	470	112	50	
73	420	49	445	106	48	443	105	48	471	112	50	
77	423	48	444	105	47	443	105	48	477	113	50	
81	423	48	446	106	47	444	105	46	487	115	50	
85	417	. 47	439	105	44	438	105	43	487	117	48	
89	415	46	432	104	43	434	105	43	484	117	48	
93	418	42	430	103	42	430	103	42	483	116	46	
97	410	41	424	104	38	421	103	42	478	117	44	
101	410	31	419	102	36	409	100	42	473	115	42	
104	399	26	406	102	33	394	99	39	461	116	40	
Terminal	sacrifice	26			33			38			40	
Mean for												
1-13	245		248	101		246	100		241	98		
14-52	379		394	104		389	103		396	104		
53-104	415		434	105		432	104		473	114		

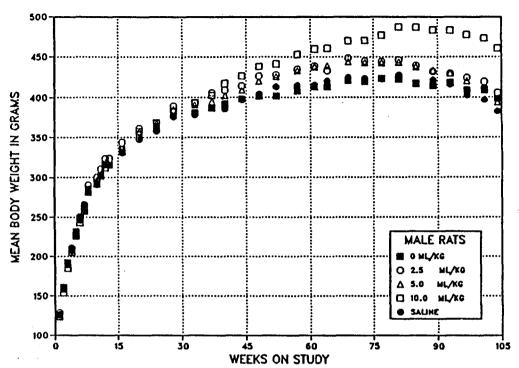


FIGURE 4
Growth Curves for Male Rats Administered Corn Oil by Gavage for 2 Years

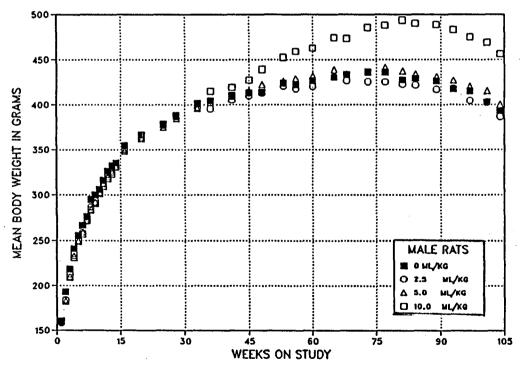


FIGURE 5
Growth Curves for Male Rats Administered Safflower Oil by Gavage for 2 Years

TABLE 6
Mean Body Weights and Survival of Male Rats in the 2-Year Gavage Study of Safflower Oil

Weeks	Untreate	ed Control_		2.5 mL/kg			5 mL/kg			10 mL/kg		
on	Av. Wt.	No. of	Av. Wt.			Av. Wt.			Av. Wt.	Wt. (% of		
Study	(g)	Survivors	(g)	controls)	Survivors	(g)	controls)	Survivors	<b>(g)</b>	controls)	Survivors	
1	159	60	158	99	60	160	101	60	160	101	60	
2	193	60	184	95	60	184	95	60	183	95	60	
3	219	60	213	97	60	212	97	60	210	96	60	
4	242	60	236	98	60	235	97	60	232	96	60	
5	256	60	250	98	60	251	98	60	250	98	60	
6	267	60	259	97	60	261	98	60	257	96	60	
7	276	60	271	98	60	274	99	. 60	274	99	60	
8	295	60	286	97	60	286	97	60	284	96	60	
9	300	60	293	98	60	294	98	. 60	291	97	60	
10	306	60	302	99	60	305	100	60	302	99	60	
11	316	60	312	99	60	314	99	60	310	98	60	
12	326	60	322	99	60	322	99	60	318	98	60	
13	332	60	326	98	60	328	99	60	324	98	60	
14	335	60	331	99	60	333	100	60	331	99	60	
16	355	60	349	98	60	351	99	60	351	99	60	
20	366	60	360	98	60	365	100	60	365	100	60	
25	379	60	374	99	60	378	100	59	379	100	60	
28	389	60	383	99	60	388	100	59	389	100	60	
33	402	60	394	98	60	400	99	59	402	100	60	
36	405	60	393	97	60	406	100	59	417	103	60	
41	410	60	402	98	60	413	101	59	421	103	60	
45	413	60	407	99	60	419	101	59	430	104	59	
48	413	60	409	99	60	425	103	58	443	107	59	
53	423	60	417	99	60	429	101	57	456	108	59	
56	421	60	414	98	59	432	103	57	463	110	59	
60	426	60	416	98	58	435	102	57	467	110	59	
65	429	60	427	99	58	441	103	57	478	111	59	
68 <sup>a</sup>	434	48	427	98	48	435	100	47	473	109	50	
73	437	48	426	97	46	437	100	47	486	111	50	
77	436	48	425	98	46	442	101	46	488	112	50	
81	428	48	423	99	46		102	45	494	116	49	
84	430	48	422	98	46	434	101	45	490	114	48	
89	427	45	417	98	43	432	101	43	489	115	45	
93	418	42	418	100	39	427	102	43	483	116	43	
97	415	38	405	97	39	421	101	41	475	114	42	
101	403	33	403	100	36	415	103	41	469	116	41	
104	393	30	387	98	33	401	102	40	457	116	36	
Terminal	l sacrifice	30			33			40			. 36	
Mean for												
1-13	268		262	98		264	99		261	97		
14-52	387		380	98		388	100		393	102		
53-104	423		416	98		430	102		476	113		

<sup>&</sup>lt;sup>a</sup> Interim evaluation occurred during week 66.

TABLE 7
Mean Body Weights and Survival of Male Rats in the 2-Year Gavage Study of Tricaprylin

Weeks	Untreat	ed Control	2.5 mL/kg			5 mL/kg			10 mL/kg		
on	Av. Wt.	No. of	Av. Wt.	Wt. (% of	No. of	Av. Wt.	Wt. (% of	No. of	Av. Wt.	Wt. (% of	No. of
Study	(g)	Survivors	(g)	controls)	Survivors	(g)	controls)	Survivors	(g)	controls)	Survivors
1	146	60	144	98	60	145	99	60	145	99	60
2	172	60	171	100	60	169	98	60	168	97	60
3	199	60	198	99	60	193	97	60	190	95	60
4	219	60	215	98	60	215	98	60	207	94	60
5	243	60	241	99	60	239	98	60	231	95	60
7	263	60	259	98	60	255	97	60	247	94	60
8	266	60	265	100	60	257	97	60	254	96	60
9	283	60	282	100	60	277	98	60	266	94	60
10	300	60	295	98	60	285	95	60	278	93	60
12	306	60	301	98	60	294	96	60	283	92	60
13	306	60	301	98	60	296	97	59	284	93	60
14	317	60	311	98	60	303	96	59	289	91	60
17	332	60	329	99	60	319	96	59	303	91	60
21	351	60	350	100	59	339	97	59	319	91	60
25	363	60	367	101	59	354	98	59	330	91	60
29	376	60	372	99	59	357	95	59	335	89	60
33	381	60	379	99	59	371	97	59	345	90	60
37	386	60	387	100	59	376	97	59	353	92	59
41	388	60	389	100	59	377	97	59	347	90	59
45	389	59	389	100	59	382	98	59	358	92	55
49	388	59	395	102	59	388	100	59	368	95	47
53	401	59	408	102	59	396	99	59	380	95 95	46
57	404	58	411	102	56	394	98	59	380	94	46
61	404	58	416	102	56	400	99	59	390	9 <del>4</del> 97	45
65	403	58	419	103	56	399	98	59	392	97 96	43
69 <sup>a</sup>	406	48	421	103	36 46	400	99	39 47	392	90 97	35
73	408	48	421	104	46 46	403	99	47	392	97 97	33
73 77	414	48	422	103	46 45	406	99 98	46	403	97 98	31
81	413	47	419	102	45	405	98	46	404	98	31
85	405	46	412	102	44	396	98	44	399	99	30
89	402	44	412	102	42	390	97	41	395	98	28
93	400	42	413	103	41	393	98	39	397	99	26
93 97	393	40	406	103	38		98	-	391	99	
						386		38			26 25
101 104	387 386	34 31	404 391	104 101	34 30	379 371	98 96	32 31	379 366	98 95	25 23
104	300	31	391	101	30	3/1	90	31	300	93	23
Terminal	sacrifice	31			30			31			23
Mean for				0.0		222	~=		222		
1-13	246		243	99		239	97		232	94	
14-52	367		367	100		357	97		335	91	
53-104	402		413	103		394	98		390	97	

<sup>&</sup>lt;sup>a</sup> Interim evaluation occurred during week 67.

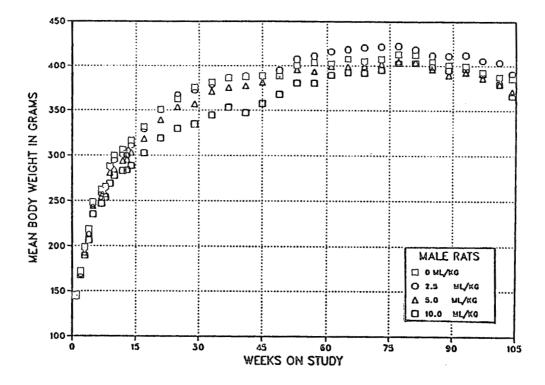


FIGURE 6
Growth Curves for Male Rats Administered Tricaprylin by Gavage for 2 Years

Feed consumption by high-dose rats receiving corn oil, safflower oil, or tricaprylin was decreased (Tables I1, I2, and I3). This resulted in a decrease in the protein consumption per rat. Untreated rats consumed nearly 3.9 g of protein per day while rats

receiving 10 mL of vehicle/kg consumed 2.3 to 2.7 g per day. Rats given 10 mL corn oil or safflower oil/kg received nearly 50% of their caloric intake from the vehicle; in tricaprylin rats, the value was close to 35% (Table 8).

TABLE 8
Energy and Protein Intake Per Rata

Dose (mL/kg)	Source of energy (AEG <sup>b</sup> )			Tricaprylin (Kcal/day (%)) (PFV <sup>c</sup> )	Dichloromethane in corn oil (Kcal/day (%))		
	Diet	58.1 (100)	57.5 (100)	58.1 (100)	NA <sup>d</sup>		
n	Oil gavage	0	0	0	0		
1. 7	Total	58.1	57.5	58.1	NA		
	Protein (g/rat/day)	3.88	3.84	3.88	NA		
,	Trotein (graduay)	5.50	3.04	5.00	The state of the s		
ا د در پا	Diet	50.0 (87.4)	50.3 (87.8)	50.2 (89.6)	47.3 (87.8)		
2.5	Oil gavage	7.2 (12.6)	7.0 (12.2)	5.8 (10.4)	6.6 (12.2)		
	Total	57.2	57.3	56.0	53.9		
tanakan jar Tanakan	Protein (g/rat/day)	3.34	3.36	3.45	3.15		
•	Diet	41.8 (74.4)	42.8 (74.8)	44.9 (80.2)	41.8 (74.1)		
5.0	Oil gavage	14.4 (25.6)	14.4 (25.2)	11.1 (19.8)	14.6 (25.9)		
	Total	56.2	57.2	56.0	56.4		
	Protein (g/rat/day)	2.79	2.86	3.09	2.79		
	Diet	34.0 (53.0)	34.0 (52.7)	39.3 (64.6)	34.3 (51.6)		
10.0	Oil gavage	30.2 (47.0)	30.5 (47.3)	21.5 (35.4)	32.2 (48.4)		
	Total	64.2	64.5 `	60.8	66.5		
	Protein (g/rat/day)	2.27	2.27	2.70	2.29		

<sup>&</sup>lt;sup>a</sup> Gavaged fat intake calculation based on time weighted group mean body weights. Oil gavage was averaged to 7 days/week. Dichloromethane in corn oil study was compensated for dichloromethane at 500 mg/kg body weight. Specific gravity values: corn oil and safflower oil, 0.920; tricaprylin, 0.954; and dichloromethane, 1.326 (Keith and Walter, 1992).

NA = Not available

b AEG = Available Energy for Growth: carbohydrate, 4.0; protein, 4.0; and fat, 11.1 Kcal/g (Donato and Hegsted, 1985).

c PFV = Physiological Fuel Value of 9 Kcal/g of tricaprylin (NRC, 1966).

# Pathology and Statistical Evaluation

This section describes the statistically significant or biologically noteworthy changes in the incidences of mononuclear cell leukemia and neoplasms or nonneoplastic lesions of the exocrine and endocrine pancreas, forestomach, kidney, and adrenal medulla in male rats. Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal neoplasm diagnoses, and statistical analyses of primary neoplasms that occurred with an incidence of at least 5% in at least one animal group are presented in Appendixes A through C.

The neoplastic and nonneoplastic effects of different oral gavage vehicles were determined by comparison of the incidences of lesions in rats exposed to saline, corn oil, safflower oil, or tricaprylin for 2 years. Since the NTP has no previous experience with safflower oil or tricaprylin, 15-month interim evaluations were included for these studies. The organ and body weight data from the interim evaluations are presented in Appendix F. The hematology and clinical chemistry data are in Appendix G.

The criteria for distinguishing proliferative lesions of the pancreas followed a standard format that has been used previously in the NTP studies (Eustis et al., 1990). Acinar cell hyperplasia was a focal lesion less than 3 mm in diameter with little or no compression of the adjacent parenchyma. Acinar cell adenomas were larger discrete masses with compression, often with slight cellular atypia and pleomorphism. Acinar cell carcinomas usually showed a heterogeneity of growth pattern; had marked cellular pleomorphism, cellular atypia, and hemorrhage; and often showed a marked scirrhous reaction. Invasion of the adjacent tissue was common for acinar cell carcinomas while distant metastases were rare.

## Comparison of Control Groups

In comparing the incidences of neoplasms in rats receiving 10 mL saline/kg with the untreated control groups for the corn oil, tricaprylin, and safflower oil studies, there was only one instance where statistically

significant differences occurred. There was a significantly increased incidence of skin neoplasms [papillomas, trichoepitheliomas, keratoacanthomas, squamous cell carcinomas, and basal cell neoplasms (combined)] in the tricaprylin untreated controls (7/50) versus the saline controls (1/50). The incidences of skin neoplasms in the corn oil (5/50) and safflower oil untreated controls (2/50) were not significantly different from the saline controls. Therefore, the increased incidence in neoplasms of the skin was not considered to be biologically significant. The finding of one significant difference in these data is similar to what would be expected by chance alone. The saline controls were included to determine whether 10 mL of gavage fluid/kg could affect the exocrine pancreas. The incidences of exocrine pancreatic hyperplasia (5/50) and adenoma (1/50) in the saline controls were essentially identical to the incidences of hyperplasia (8/50, 8/50, 8/49) and exocrine pancreatic adenoma (1/50, 1/50, 2/49) in the corn oil, safflower oil, and tricaprylin untreated controls, respectively. In other NTP studies, controls receiving water by gavage also had incidences of pancreatic acinar cell neoplasms similar to untreated controls (Haseman and Rao, 1992).

The incidence of benign pheochromocytoma of the adrenal medulla was higher in the corn oil controls (20/49) than in the safflower controls (11/49) or the tricaprylin controls (11/50). However, the incidence of adrenal medulla hyperplasia in the corn oil controls (8/49) was lower than that in the safflower oil controls (23/49) or tricaprylin controls (22/50). Historical incidences of adrenal medulla pheochromocytoma in untreated control rats are given in Table 9. The increased incidence of pheochromocytoma in the corn oil controls is considered to be normal biological variation.

The incidence of mononuclear cell leukemia varied among the control groups (corn oil, 27/50; safflower, 35/60; tricaprylin, 23/60); the incidence of mononuclear cell leukemia has varied between the control groups in other NTP studies.

TABLE 9
Historical Incidence of Adrenal Medulla Pheochromocytomas in Untreated Male F344/N Rats<sup>a</sup>

Study	Incidence in Controls		
	Benign Pheochromocytoma	Malignant Pheochromocytoma	Benign or Malignan Pheochromocytoma
Historical Incidence at EG&G Ma	nson Research Institute (I	Feed and Drinking Water S	tudies)
1-Amino-2,4-dibromoanthraquinone	12/50	1/50	13/50
Acetaminophen	16/44	1/44	17/44
HC Yellow 4	19/50	2/50	19/50
Methylphenidate hydrochloride	17/49	1/49	18/49
Pentaerythritol tetranitrate	19/49	0/49	19/49
Quercetin	12/50	1/50	13/50
Tumeric oleoresin	14/47	0/47	14/47
Barium chloride dihydrate	11/49	2/49	13/49
Overall Historical Incidence (Feed	l, Drinking Water, and In	halation Studies)	
Total	617/1,980 (31.2%)	73/1,980 (3.7%)	673/1,980 <sup>b</sup> (34.0%)
Standard deviation	11.5%	4.1%	10.6%
Range	0%-63%	0%-20%	14%-63%

a Data as of 31 March 1993

## Comparison of Dosed Groups

Pancreas: The exocrine pancreas was expected to contain proliferative lesions because of previous results with oil gavage studies. Therefore the entire pancreas was embedded separately and two or three sections were prepared. The incidences of pancreatic acinar cell hyperplasia and adenoma increased significantly with dose in the corn oil, safflower oil, and tricaprylin studies; the incidences of multiple adenomas were also significantly increased in all studies (Table 10 and Figure 7). Pancreatic acinar cell carcinomas occurred in one mid-dose rat in the corn oil study and in one high-dose rat in the safflower oil study. Multiple carcinomas occurred in one highdose rat in the safflower oil study. No acinar cell carcinomas occurred in the tricaprylin study. The incidences of acinar cell hyperplasia and of adenoma were similar at each dose level in all three gavage vehicle studies (except for hyperplasia at 2.5 mL/kg).

Historical incidences of pancreatic acinar cell neoplasms in controls receiving 5 mL corn oil/kg are given in Table 11. Representative photomicrographs of the proliferative lesions of the exocrine pancreas are presented in Plates 1 through 5.

Pancreatic islets: The incidence of pancreatic islet hyperplasia (6/49, 5/48, 3/49, 1/49) and adenoma or carcinoma (combined) (5/49, 2/48, 3/49, 1/49) decreased, but not significantly, with dose in rats administered tricaprylin (Tables C1 and C4). For corn oil and safflower oil, there was no effect on the incidence of islet cell hyperplasia (corn oil - 1/50, 4/47, 2/50, 3/50; safflower oil - 4/49, 4/50, 4/49, 4/49) or islet cell adenoma (corn oil - 9/50, 3/47, 4/50, 7/50; safflower oil - 7/49, 3/50, 5/49, 3/49) (Tables A1, A4, B1, and B4). Historical incidences of pancreatic islet cell neoplasms in controls receiving 5 mL corn oil/kg are given in Table 12.

b Includes data for complex and unspecified pheochromocytomas

TABLE 10
Incidences of Proliferative Lesions of the Exocrine Pancreas of Male Rats in the 2-Year Gavage Studies of Selected Oral Gavage Vehicles: Comparison of Corn Oil, Safflower Oil, and Tricaprylin

Dose	Untreated Control	2.5 mL/kg	5 mL/kg	10mL/kg
Corn Oil Study				
Hyperplasia			00/50 (5(0))**	05/50 (500)
Overall rate <sup>a</sup>	8/50 (16%)	28/47 (60%)**	28/50 (56%)**	35/50 (70%)**
Adenoma				
Overall rate	1/50 (2%)	8/47 (17%)	10/50 (20%)	23/50 (46%)
Adjusted rate <sup>b</sup>	3.8%	25.0%	24.6%	53.2%
Terminal rate <sup>c</sup>	1/26 (4%)	8/32 (25%)	8/38 (21%)	20/40 (50%)
First incidence (days)	730 (T)	730 (T)	569	576
Logistic regression test <sup>d</sup>	P<0.001	P=0.033	P=0.006	P<0.001
Adenoma, Multiple				
Overall rate	0/50 (0%)	2/47 (4%)	7/50 (14%)*	12/50 (24%)**
Carcinoma				
Overall rate	0/50 (0%)	0/47 (0%)	1/50 (2%)	0/50 (0%)
Adenoma or Carcinoma				
Overall rate	1/50 (2%)	8/47 (17%)	11/50 (22%)	23/50 (46%)
Adjusted rate	3.8%	25.0%	27.2%	53.2%
Terminal rate	1/26 (4%)	8/32 (25%)	9/38 (24%)	20/40 (50%)
First incidence (days)	730 (T)	730 (T)	569	576
Logistic regression test	P<0.001	P = 0.033	P = 0.003	P<0.001
Safflower Oil Study				
Hyperplasia				
Overall rate	8/50 (16%)	14/50 (28%)	29/49 (59%)**	30/50 (60%)**
Adenoma				
Overall rate	1/50 (2%)	7/50 (14%)	15/49 (31%)	28/50 (56%)
Adjusted rate	3.3%	21.2%	36.4%	69.8%
Terminal rate	1/30 (3%)	7/33 (21%)	14/40 (35%)	24/36 (67%)
First incidence (days)	729 (T)	729 (T)	531	672
Logistic regression test	P<0.001	P = 0.041	P<0.001	P<0.001
Adenoma, Multiple				
Overall rate	0/50 (0%)	2/50 (4%)	6/49 (12%)*	19/50 (38%)**
Carcinoma				
Overall rate	0/50 (0%)	0/50 (0%)	0/49 (0%)	1/50 (2%)
Carcinoma, Multiple				
Overall rate	0/50 (0%)	0/50 (0%)	0/49 (0%)	1/50 (2%)
(continued)				

TABLE 10
Incidences of Proliferative Lesions of the Exocrine Pancreas of Male Rats in the 2-Year Gavage Studies of Selected Oral Gavage Vehicles: Comparison of Corn Oil, Safflower Oil, and Tricaprylin (continued)

Dose		# V	Untreated Control	2.5 mL/kg	5 mL/kg	10 mL/kg
Safflower Oil Stu	dy (continued)					
Adenoma or Carcin	oma .					
Overall rate	, .		1/50 (2%)	7/50 (14%)	15/49 (31%)	29/50 (58%)
Adjusted rate	•		3.3%	21.2%	36.4%	70.5%
Terminal rate			1/30 (3%)	7/33 (21%)	14/40 (35%)	24/36 (67%)
First incidence (d			729 (T)	729 (T)	531	633
Logistic regressio	n test		P<0.001	P=0.041	P<0.001	P<0.001
	, · · v					
Tricaprylin Study	,		2			
		* .	· ·			
Hyperplasia		*	040 (160)	040 4000	1040 (000)	00/50 (5(0))**
Overall rate			8/49 (16%)	9/49 (18%)	18/49 (37%)*	28/50 (56%)**
Adenoma			* * * * * * * * * * * * * * * * * * *	,	A Commission	
Overall rate	-		2/49 (4%)	6/49 (12%)	13/49 (27%)	18/50 (36%)
Adjusted rate			6.7%	20.0%	38.2%	71.7%
Terminal rate			2/30 (7%)	6/30 (20%)	11/31 (35%)	16/23 (70%)
First incidence (d	avs)	1 .	729 (T)	729 (T)	518	485
Logistic regressio	• /	* *	P<0.001	P=0.129	P=0.002	P<0.001
Adenoma, Multiple		•		•	et j	
Overall rate	•		0/49 (0%)	1/49 (2%)	2/49 (4%)	11/50 (22%)**

<sup>\*</sup> Significantly different (P≤0.05) from the control group by the logistic regression test

Number of lesion-bearing animals/number of animals examined microscopically

<sup>\*\*</sup> P≤0.01

<sup>(</sup>T)Terminal sacrifice

b Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality

<sup>&</sup>lt;sup>c</sup> Observed incidence at terminal kill

Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The logistic regression test regards neoplasms as nonfatal.

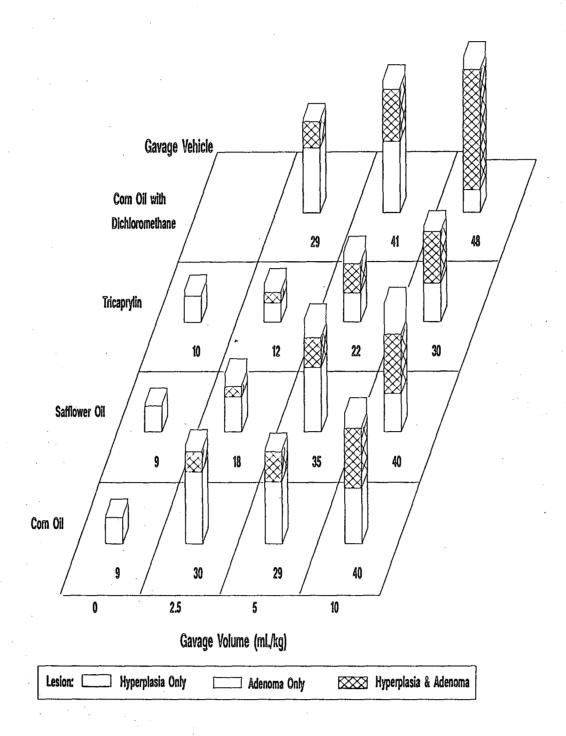


FIGURE 7
Pancreatic Acinar Cell Lesions in Male Rats Administered Corn Oil, Safflower Oil,
Tricaprylin, or Dichloromethane in Corn Oil by Gavage for 2 Years and Total Number
of Male Rats with Proliferative Lesions

TABLE 11
Historical Incidence of Pancreatic Acinar Cell Neoplasms in Male F344/N Rats Administered 5 mL Corn Oil/kg Body Weight by Gavage<sup>a</sup>

· · · · · · · · · · · · · · · · · · ·	Incidence in Controls				
Study	Adenoma	Carcinoma	Adenoma or Carcinoma		
Historical Incidence at EG&G Mas	on Research Institute				
1,2,3-Trichloropropane	5/50	0/50	5/50		
2,4-Diaminophenol dihydrochloride	1/50	0/50	1/50		
Tribromomethane	1/50	0/50	1/50		
Hexachloroethane	0/50	0/50	0/50		
Phenylbutazone	3/50	0/50	3/50		
Probenecid	0/50	0/50	0/50		
Titanocene dichloride	0/59	0/59	0/59		
Overall Historical Incidence					
Total	66/1,010 (6.5%)	0/1,010	66/1,010 (6.5%)		
Standard deviation	8.3%	·	8.3%		
Range	0%-32%		0%–32%		

<sup>&</sup>lt;sup>a</sup> Data as of 31 March 1993; based on single sections

TABLE 12 Historical Incidence of Pancreatic Islet Cell Neoplasms in Male F344/N Rats Administered 5 mL Corn Oil/kg Body Weight by Gavage<sup>a</sup>

_	Incidence in Controls				
Study	Adenoma	Carcinoma	Adenoma or Carcinoma		
Historical Incidence at EG&G Mas	on Research Institute				
1,2,3-Trichloropropane	9/50	1/50	10/50		
2,4-Diaminophenol dihydrochloride	3/50	1/50	4/50		
Tribromomethane	4/48	0/48	4/48		
Hexachloroethane	2/50	0/50	2/50		
Phenylbutazone	2/50	2/50	4/50		
Probenecid	2/49	0/49	2/49		
Titanocene dichloride	5/58	0/58	5/58		
Overall Historical Incidence					
Total	76/1,005 (7.6%)	14/1,005 (1.4%)	90/1,005 (9.0%)		
Standard deviation	4.4%	1.4%	4.6%		
Range	0%-18%	0%-4%	2%-20%		

<sup>&</sup>lt;sup>a</sup> Data as of 31 March 1993; based on single sections

Forestomach: The incidence of squamous cell papilloma in rats receiving 10 mL tricaprylin/kg was significantly greater than that of controls (Table 13). This was accompanied by focal to diffuse basal cell hyperplasia of the forestomach (4/50, 7/50, 12/49, 21/52; Table C4). There were no increased incidences of squamous cell papillomas of the alimentary system related to the administration of corn oil or safflower oil. Historical incidences of squamous cell papilloma in controls receiving 5 mL corn oil/kg are given in Table 14.

Kidney: The incidence of nephropathy in untreated controls ranged from 92% to 98% with an average severity grade of 2.0 to 2.1 (Table 15). In general, the severity of nephropathy decreased with increasing volume of gavage vehicle. The incidence of nephropathy did not decrease with increasing volumes of safflower oil, but there was a pronounced decrease in the severity of the nephropathy. Both the incidence and severity of nephropathy decreased in high-dose rats receiving tricaprylin. There was also a significantly decreased incidence of nephropathy in rats that received 10 mL corn oil/kg. Incidences of renal neoplasms were similar in the three studies.

TABLE 13
Incidences of Neoplasms of the Forestomach of Male Rats in the 2-Year Gavage Studies of Selected Oral Gavage Vehicles: Comparison of Corn Oil, Safflower Oil, and Tricaprylin

Dose	Untreated Control	2.5 mL/kg	5 mL/kg	10mL/kg
Corn Oil Study			<u> </u>	
Squamous Cell Papilloma Overall rate <sup>a</sup>	0/50 (0%)	0/50 (0%)	1/50 (2%)	0/50 (0%)
Safflower Oil Study				
Squamous Cell Papilloma Overall rate	1/50 (2%)	0/50 (0%)	2/50 (4%)	1/51 (2%)
Tricaprylin Study				
Squamous Cell Papilloma				
Overall rate	0/50 (0%)	0/50 (0%)	3/50 (6%)	10/53 (19%)
Adjusted rate <sup>b</sup> Terminal rate <sup>c</sup>	0.0%	0.0%	8.7%	41.3%
First incidence (days)	0/31 (0%) _e	0/30 (0%)	2/31 (6%) 623	9/23 (39%) 623
Logistic regression test <sup>d</sup>	P<0.001	_	P=0.118	P<0.001

a Number of neoplasm-bearing animals/number of animals examined microscopically

b Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality

Observed incidence at terminal kill

d Beneath the control incidence is the P value associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The logistic regression test regards neoplasms as nonfatal.

e Not applicable; no neoplasms in animal group

TABLE 14
Historical Incidence of Forestomach Squamous Cell Papilloma in Male F344/N Rats
Administered 5 mL Corn Oil/kg Body Weight by Gavage<sup>a</sup>

Study	Incidence in Controls		
Historical Incidence at EG&G Mason Research Institute			
1,2,3-Trichloropropane 2,4-Diaminophenol dihydrochloride Tribromomethane Hexachloroethane Phenylbutazone Probenecid Titanocene dichloride	0/50 0/50 0/50 0/50 0/50 0/50 0/60	Alle Aldrich College	
Overall Historical Incidence  Total Standard deviation Range	· · · · · · · · ·	Proposition of the second of t	i v m

a Data as of 31 March 1993

TABLE 15
Incidences and Severity of Nephropathy in Male Rats in the 2-Year Gavage Studies of Selected Oral Gavage Vehicles: Comparison of Corn Oil, Safflower Oil, and Tricaprylin

Dose	Untreated Control	2.5 mL/kg	5 mL/kg	10 mL/kg
Corn Oil Study			•	
Overall rate <sup>a</sup> Average severity grade <sup>b</sup>	 47/50 (94%) 2.1 ± 0.13	43/48 (90%) 1.8 ± 0.11*	45/50 (90%) 1.4 ± 0.11**	40/49 (82%)** 1.2 ± 0.12**
Safflower Oil Study		•		
Overall rate Average severity grade	 49/50 (98%) 2.0 ± 0.10	50/50 (100%) 1.8 ± 0.10*	47/50 (94%) 1.1 ± 0.07**	49/49 (100%) 1.1 ± 0.04**
Tricaprylin Study	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1			e de la companya de l
Overall rate Average severity grade	46/50 (92%) 2.0 ± 0.12	42/50 (84%) 1.5 ± 0.13**	45/50 (90%) 1.7 ± 0.11*	27/49 (55%)* 0.9 ± 0.13**

Significantly different (P≤0.05) from the control group by the logistic regression test (overall rate) or the Mann-Whitney U test (severity)

<sup>\*\*</sup> P≤0.01

<sup>&</sup>lt;sup>a</sup> Number of lesion-bearing animals/number of animals examined microscopically

Average severity grade is given as mean  $\pm$  standard error: 0 = none, 1 = minimal, 2 = mild, 3 = moderate, and 4 = marked

Adrenal medulla: The incidences of benign or malignant pheochromocytoma (combined) in the 5 and 10 mL corn oil/kg groups were significantly lower than that of the untreated control group (Table 16). The incidences of adrenal medulla hyperplasia in the corn oil groups were similar.

Mononuclear cell leukemia: Significantly decreased incidences of mononuclear cell leukemia occurred in

all groups receiving corn oil or safflower oil (Table 17). The incidence of mononuclear cell leukemia in the 10 mL tricaprylin/kg group was similar to that in the other 10 mL/kg groups and much less than that in the untreated control group. Historical incidences of leukemia in untreated controls from feed and drinking water studies and in vehicle controls receiving 5 mL corn oil/kg in gavage studies are given in Table 18.

Table 16
Incidences of Neoplasms and Nonneoplastic Lesions of the Adrenal Medulla of Male Rats in the 2-Year Gavage Studies of Selected Oral Gavage Vehicles:
Comparison of Corn Oil, Safflower Oil, and Tricaprylin

Dose	Untreated Control	2.5 mL/kg	5 mL/kg	10 mĽ/kg
Corn Oil Study				
Hyperplasia				
Overall rate <sup>a</sup>	8/49 (16%)	12/50 (24%)	11/50 (22%)	9/50 (18%)
Benign Pheochromocytoma				
Overall rate	20/49 (41%)	19/50 (38%)	4/50 (8%)	7/50 (14%)
Adjusted rate <sup>b</sup>	56.3%	48.3%	10.5%	16.8%
Terminal rate <sup>c</sup>	11/25 (44%)	13/33 (39%)	4/38 (11%)	6/40 (15%)
First incidence (days)	610	586	730 (T)	664 ` ´
Logistic regression test <sup>d</sup>	P<0.001N	P = 0.460N	P<0.001N	P = 0.002N
Malignant Pheochromocytoma				
Overall rate	3/49 (6%)	1/50 (2%)	1/50 (2%)	2/50 (4%)
Adjusted rate	9.7%	2.3%	2.6%	4.5%
Terminal rate	1/25 (4%)	0/33 (0%)	1/38 (3%)	1/40 (3%)
First incidence (days)	635	619	730 (T)	576
Logistic regression test	P=0.511N	P = 0.300N	P = 0.292N	P = 0.552N
Benign, Complex, or Malignant Pheoch	romocytoma <sup>e</sup>			
Overall rate	23/49 (47%)	21/50 (42%)	5/50 (10%)	9/50 (18%)
Adjusted rate	61.8%	50.6%	13.2%	20.9%
Terminal rate	12/25 (48%)	13/33 (39%)	5/38 (13%)	7/40 (18%)
First incidence (days)	610	520	730 (T)	576
Logistic regression test	P<0.001N	P = 0.380N	P<0.001N	P = 0.002N

TABLE 16
Incidences of Neoplasms and Nonneoplastic Lesions of the Adrenal Medulla of Male Rats in the 2-Year Gavage Studies of Selected Oral Gavage Vehicles:
Comparison of Corn Oil, Safflower Oil, and Tricaprylin (continued)

Dose	Untreated Control	2.5 mL/kg	5 mL/kg	10 mL/kg
Safflower Oil Study				•
Hyperplasia				
Overall rate	23/49 (47%)	24/48 (50%)	16/49 (33%)	18/49 (37%)
Benign Pheochromocytoma				
Overall rate	11/49 (22%)	12/48 (25%)	10/49 (20%)	7/49 (14%)
Adjusted rate	34.4%	33.8%	25.6%	17.8%
Terminal rate	9/29 (31%)	9/32 (28%)	10/39 (26%)	5/36 (14%)
First incidence (days)	627	634	729 (T)	582
Logistic regression test	P = 0.096N	P = 0.480	P = 0.392N	P = 0.187N
Benign or Malignant Pheochromocytoma	e			
Overall rate	13/49 (27%)	12/48 (25%)	10/49 (20%)	8/49 (16%)
Adjusted rate	41.0%	33.8%	25.6%	19.7%
Terminal rate	11/29 (38%)	9/32 (28%)	10/39 (26%)	5/36 (14%)
First incidence (days)	627	634	729 (T)	582
Logistic regression test	P = 0.077N	P = 0.518N	P = 0.207N	P = 0.136N
Tricaprylin Study				•
Hyperplasia				
Overall rate	22/50 (44%)	18/49 (37%)	22/49 (45%)	18/51 (35%)
Benign Pheochromocytoma				
Overall rate	11/50 (22%)	11/49 (22%)	16/49 (33%)	14/51 (27%)
Adjusted rate	31.9%	30.1%	47.8%	53.6%
Terminal rate	8/31 (26%)	5/29 (17%)	13/30 (43%)	11/23 (48%)
First incidence (days)	678	659	597	623
Logistic regression test	P = 0.019	P = 0.543	P=0.127	P = 0.044
Benign, Complex, or Malignant Pheochro	omocytoma <sup>e</sup>			
Overall rate	14/50 (28%)	11/49 (22%)	17/49 (35%)	14/51 (27%)
Adjusted rate	39.1%	30.1%	49.3%	53.6%
Terminal rate	10/31 (32%)	5/29 (17%)	13/30 (43%)	11/23 (48%)
First incidence (days)	576	659	597	623
Logistic regression test	P = 0.065	P = 0.375N	P = 0.257	P = 0.148

<sup>(</sup>T)Terminal sacrifice

a Number of lesion-bearing animals/number of animals examined microscopically

b Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality

Observed incidence at terminal kill

Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The logistic regression test regards neoplasms as nonfatal. A negative trend or lower incidence in a dose group is indicated by N.

Combined historical incidence for NTP 2-year feed, drinking water, and inhalation studies with untreated control groups (mean ± standard deviation): 673/1,980 (34.0% ± 10.6%); range 14%-63% (includes 8 complex and 7 unspecified pheochromocytomas)

TABLE 17
Incidences of Mononuclear Cell Leukemia in Male Rats in the 2-Year Gavage Studies of Selected Oral Gavage Vehicles: Comparison of Corn Oil, Safflower Oil, and Tricaprylin

Dose	Untreated Control	2.5 mL/kg	5 mL/kg	10 mL/kg
Corn Oil Study				
Overall rate <sup>a</sup>	27/50 (54%)	16/50 (32%)	11/50 (22%)	7/50 (14%)
Adjusted rate <sup>b</sup>	62.6%	39.6%	25.4%	15.9%
Terminal rate <sup>c</sup>	11/26 (42%)	9/33 (27%)	6/38 (16%)	4/40 (10%)
First incidence (days)	523	586	555	623
Life table test <sup>d</sup>	P<0.001N	P = 0.016N	P<0.001N	P<0.001N
Safflower Oil Study				
Overall rate	33/50 (66%)	19/50 (38%)	18/50 (36%)	7/51 (14%)
Adjusted rate	74.1%	48.8%	42.8%	16.5%
Terminal rate	19/30 (63%)	14/33 (42%)	16/40 (40%)	3/36 (8%)
First incidence (days)	457	491	655	613
Life table test	P<0.001N	P = 0.008N	P<0.001N	P<0.001N
Tricaprylin Study				
Overall rate	23/50 (46%)	28/50 (56%)	22/50 (44%)	9/53 (17%)
Adjusted rate	54.9%	71.2%	55.1%	30.9%
Terminal rate	13/31 (42%)	19/30 (63%)	14/31 (45%)	4/23 (17%)
First incidence (days)	593	524	454	446 ` ´
Life table test	P=0.029N	P = 0.205	P = 0.525N	P = 0.071N

<sup>&</sup>lt;sup>a</sup> Number of neoplasm-bearing animals/number of animals with any tissue examined microscopically

b Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality

C Observed incidence at terminal kill

d Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table test regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. A negative trend or lower incidence in a dose group is indicated by N.

TABLE 18
Historical Incidence of Leukemia in Untreated Male F344/N Rats
and in Male F344/N Rats Administered 5 mL Corn Oil/kg Body Weight by Gavage<sup>a</sup>

Study	Incidence in Controls	
Historical Incidence in Untreated Controls (Fee	d and Drinking Water Studies) at EG&G	G Mason Research Institut
1-Amino-2,4-dibromoanthraquinone	25/50	
Acetaminophen	27/50	* •
HC Yellow 4	19/50	
Methylphenidate hydrochloride	29/50	•
Pentaerythritol tetranitrate	29/50	
Quercetin	16/50	
Turmeric oleoresin	27/50	•
Barium chloride dihydrate	35/50	
Overall Historical Incidence		
Total	825/1,634 (50.5%)	
Standard deviation	9.8%	
Range	32%-70%	
,		
Historical Incidence in Vehicle Controls (Gavago	e Studies) at EG&G Mason Research Ins	stitute
1,2,3-Trichloropropane	16/50	·
2,4-Diaminophenol dihydrochloride	7/50	
Tribromomethane	14/50	
Hexachloroethane	13/50	
Phenylbutazone	2/50	
Probenecid	6/50	
Titanocene dichloride	15/60	
Overall Historical Incidence		
Total	231/1,020 (22.6%)	
Total Standard deviation	231/1,020 (22.6%) 9.5%	

<sup>&</sup>lt;sup>a</sup> Data as of 31 March 1993; includes lymphocytic, monocytic, mononuclear, or undifferentiated cell type

# DICHLOROMETHANE IN CORN OIL STUDY

The ability of corn oil to alter the incidence of pancreatic acinar cell proliferative lesions and mononuclear cell leukemia was evaluated by comparing the incidences of neoplasms and nonneoplastic lesions in rats exposed to corn oil alone to those in rats exposed to 500 mg dichloromethane/kg in comparable volumes of corn oil for 2 years. The effect of varying amounts of oil vehicle on the incidence of lesions in rats was determined by comparing the results of exposure to 500 mg dichloromethane/kg in 0, 2.5, 5, or 10 mL corn oil/kg.

### Survival and Clinical Findings

The survival of rats receiving dichloromethane increased slightly with increasing volume of corn oil (Table 19 and Figure 8) due to the decreasing incidence of mononuclear cell leukemia. There were no clinical findings of toxicity in animals receiving 500 mg dichloromethane/kg in 2.5, 5, or 10 mL corn

oil/kg. Rats receiving dichloromethane without the corn oil vehicle showed severe toxicity and high mortality, and this group was terminated at 3 weeks.

### Body Weights and Feed Consumption

The mean body weights of groups receiving dichloromethane in 2.5 and 5 mL corn oil/kg were similar throughout the study. The mean body weight of the dichloromethane in 10 mL corn oil/kg group was at least 10% greater than the mean body weights of the dichloromethane in 2.5 and 5 mL corn oil/kg groups from week 61 through the end of the study (Figure 9 and Table 20). The final mean body weight of the dichloromethane in 10 mL corn oil/kg group was 23% greater than that of the dichloromethane in 2.5 mL corn oil/kg group and 19% greater than that of the dichloromethane in 5 mL corn oil/kg group. As in the corn oil only study, feed consumption in the dichloromethane in corn oil study decreased with dose (Table I4) and high-dose rats received approximately 50% of their caloric intake from the gavage vehicle (Table 8).

TABLE 19 Survival of Male Rats in the 2-Year Gavage Study of Dichloromethane in Corn Oil

	Untreated Control <sup>a</sup>	2.5 mL/kg	5 mL/kg	10 mL/kg
Animals initially in study	50	50	50	50
Accidental deaths <sup>b</sup>		4	1	2
Natural deaths	8	4	8	5
Moribund kills	16	19	13	12
Animals surviving until study termination	$26^{c}$	23	28	31
Percent probability of survival at end of study <sup>d</sup>	52	51	57	66
Mean survival (days) <sup>e</sup>	689	653	669	674
Survival analysis <sup>f</sup>		P=0.810	P=0.807N	P=0.402N

Untreated control from corn oil study

b Censored from survival analyses

c Includes one rat that died during the last week of the study

Kaplan-Meier determinations

e Mean of all deaths (uncensored, censored, terminal sacrifice)

f The results of the life table pairwise comparisons (Cox, 1972) with the corn oil controls are in the dichloromethane in corn oil columns. A lower mortality in a dose group is indicated by N.

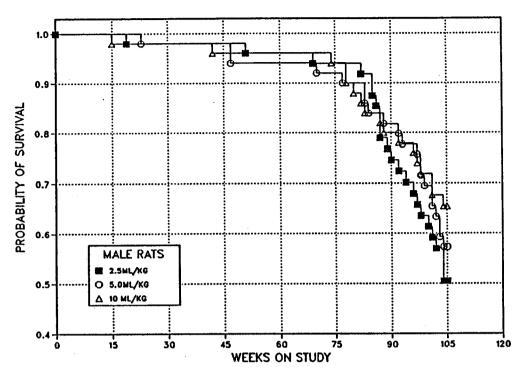


FIGURE 8
Kaplan-Meier Survival Curves for Male Rats Administered Dichloromethane in Corn Oil by Gavage for 2 Years

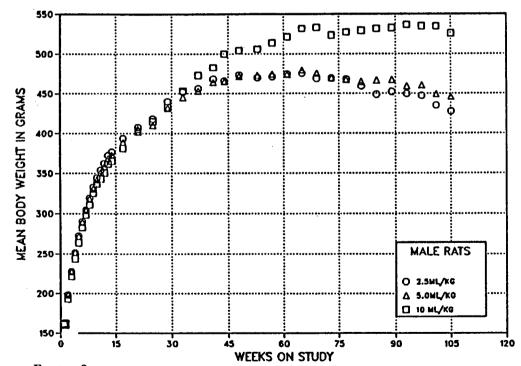


FIGURE 9
Growth Curves for Male Rats Administered Dichloromethane in Corn Oil by Gavage for 2 Years

TABLE 20 Mean Body Weights and Survival of Male Rats in the 2-Year Gavage Study of Dichloromethane in Corn Oil

Weeks	2.5 mL/kg		5 mI/kg			10 mL/kg		
on Study	Av. Wt. (g)	Number of Survivors	Av. Wt.	Wt. (% of 2.5 mL/kg group)	Number of Survivors	Av. Wt.	Wt. (% of 2.5 mL/kg group)	Number of Survivors
1	166	50	166	100	50	161	97	50
2	198	50	199	100	50	193	. 97	50
3	228	50	228	100	50	221	97	50
4	252	50	252	100	50	244	97	50
5	273	50	272	100	50	264	97	50
6	290	50	289	100	50	283	98	50
7	305	50	304	100	50	299	98	50
8	320	50	318	100	50	311	97	50
9	333	50	331	100	50	326	98	50
10	344	50	343	100	50	337	98	50
11	354	50	351	99	50	344	97	50
12	362	50	359	99	50	351	97	50
13	372	50	369	99	50	362	97	50
14	377	50	373	99	50	365	97	50
17	394	50	389	99	50	381	97	49
21	407	49	405	100	50	402	99	49
25	418	49	410	98	49	415	99	49
29	440	49	432	98	49	433	98	49
33	452	49	446	99	49	453	100	49
37	456	. 49	454	99	49	473	104	49
41	468	49	464	99	49	483	103	49
44	466	49	465	100	49	500	107	48
48	473	48	472	100	47	504	107	48
53	470	47	473	101	47	506	108	48
57	471	46	474	101	47	514	109	48
61	475	46	474	100	47	521	110	48
65	476	46	480	101	47	532	112	48
69	469	46	476	101	47	533	114	48
73	469	45	470	100	46	524	112	48
77	468	45	468	100	46	527	113	. 47
81	459	45	465	101	45	529	115	44
85	449	43	467	104	41	532	118	42
89	452	36	468	103	40	533	118	40
93	450	33	459	102	39	537	119	39
97	447	30	461	103	37	535	120	38
101	435	27	449	103	33	535	123	33
Terminal s	ncrifice	23			28			31
Mean for w	eeks							
1-13	292		291	100		284	97	
14-52	435		431	99		441	101	
53-101	461		468	102		528	115	

### Pathology and Statistical Evaluation

This section describes the statistically significant or biologically noteworthy changes in the incidences of mononuclear cell leukemia and neoplasms or nonneoplastic lesions of the exocrine and endocrine pancreas, pituitary gland, mammary gland, and adrenal medulla. Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal neoplasm diagnoses, and statistical analyses of primary neoplasms that occurred with an incidence of at least 5% in at least one animal group are presented in Appendix D. The dichloromethane studies compared the effect of one dose of dichloromethane in increasing volumes of the corn oil gavage vehicle. Because dichloromethane alone proved toxic and this group was terminated, comparisons are made between dichloromethane in increasing volumes of corn oil and comparable volumes of corn oil alone.

Pancreas: There was a dose-related increase in the incidence of pancreatic proliferative exocrine lesions in rats receiving dichloromethane in increasing

volumes of corn oil (Table 21). The incidence of multiple pancreatic exocrine adenomas in rats receiving dichloromethane increased markedly with increasing volumes of corn oil.

The incidences of acinar cell hyperplasia and acinar cell adenoma were similar in rats receiving dichloromethane in 2.5 mL corn oil/kg and rats receiving 2.5 mL corn oil/kg alone (Table 21). Rats receiving dichloromethane in 5 or 10 mL corn oil/kg had significantly higher incidences of hyperplasia, adenoma, and adenoma or carcinoma (combined) than those receiving comparable volumes of corn oil alone (Table 22 and Figure 7). Representative photomicrographs of the proliferative lesions of the exocrine pancreas are presented in Plates 6 and 7.

Pancreatic islets: Rats receiving dichloromethane in 10 mL corn oil/kg had significantly higher incidences of islet cell adenoma or islet cell carcinoma (combined) than those of rats receiving a comparable volume of corn oil alone (Table 23).

TABLE 21
Incidences of Proliferative Lesions of the Exocrine Pancreas
in Male Rats Receiving Corn Oil or 500 mg Dichloromethane in Corn Oil

Dose .	Untreated Control	2.5 mL/kg	5 mL/kg	10 mL/kg
Corn Oil Study				
Hyperplasia				•
Overall rate <sup>a</sup>	8/50 (16%)	28/47 (60%)**	28/50 (56%)**	35/50 (70%)**
Adenoma				
Overall rate	1/50 (2%)	8/47 (17%)	10/50 (20%)	23/50 (46%)
Adjusted rate <sup>b</sup>	3.8%	25.0%	24.6%	53.2%
Terminal rate <sup>c</sup>	1/26 (4%)	8/32 (25%)	8/38 (21%)	20/40 (50%)
First incidence (days)	730 (T)	730 (T)	569	576 ` ´
Logistic regression test <sup>d</sup>	P<0.001	P = 0.033	P = 0.006	P<0.001
Adenoma, Multiple				4, 5
Overall rate	0/50 (0%)	2/47 (4%)	7/50 (14%)*	12/50 (24%)**
Carcinoma				
Overall rate	0/50 (0%)	0/47 (0%)	1/50 (2%)	0/50 (0%)
Adenoma or Carcinoma				
Overall rate	1/50 (2%)	8/47 (17%)	11/50 (22%)	23/50 (46%)
Adjusted rate	3.8%	25.0%	27.2%	53.2%
Terminal rate	1/26 (4%)	8/32 (25%)	9/38 (24%)	20/40 (50%)
First incidence (days)	730 (T)	730 (T)	569	576
Logistic regression test	P<0.001	P≈0.033	P = 0.003	P<0.001

TABLE 21 Incidences of Proliferative Lesions of the Exocrine Pancreas in Male Rats Receiving Corn Oil or 500 mg Dichloromethane in Corn Oil (continued)

Dose	2.5 mL/kg	5 mL/kg	10 mL/kg
Dichloromethane in Corn Oil Study			
Hyperplasia			
Overall rate	28/50 (56%)	38/50 (76%)∆	44/50 (88%) <sup>ΔΔ</sup>
Adenoma			
Overall rate	9/50 (18%)	19/50 (38%)	41/50 (82%)
Adjusted rate	35.2%	60.8%	97.6%
Terminal rate	7/23 (30%)	16/28 (57%)	30/31 (97%)
First incidence (days)	622	682	545
Logistic regression test <sup>e</sup>	P<0.001	P = 0.047	P<0.001
Adenoma, Multiple			
Overall rate	2/50 (4%)	13/50 (26%)△	34/50 (68%)
Carcinoma			
Overall rate	0/50 (0%)	1/50 (2%)	3/50 (6%)
Adjusted rate	0.0%	2.9%	9.7%
Terminal rate	0/23 (0%)	0/28 (0%)	3/31 (10%)
First incidence (days)	_f ` `	701	729 (T)
Logistic regression test	P = 0.104	P=0.514	P=0.177
Adenoma or Carcinoma			
Overall rate	9/50 (18%)	20/50 (40%)	41/50 (82%)
Adjusted rate	35.2%	62.0%	97.6%
Terminal rate	7/23 (30%)	16/28 (57%)	30/31 (97%)
First incidence (days)	622	682	545
Logistic regression test	P<0.001	P = 0.029	P<0.001

Significantly different (P≤0.05) from the control group by the logistic regression test

Significantly different (P≤0.05) from the low-dose group by the logistic regression test

ΔΔ P≤0.01

<sup>(</sup>T) Terminal sacrifice

Number of lesion-bearing animals/number of animals examined microscopically

Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality

Observed incidence at terminal kill

Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The logistic regression test regards neoplasms as nonfatal.

Beneath the low-dose incidence are the P values associated with the trend test. Beneath the mid- and high-dose group incidences are the P values corresponding to pairwise comparisons between the low-dose group and that dosed group.

Not applicable; no neoplasms in animal group

TABLE 22
Statistical Comparison of Incidences of Proliferative Lesions of the Exocrine Pancreas in Male Rats Receiving Corn Oil or 500 mg Dichloromethane in Corn Oil

Dose	4.	Corn Oil	Dichloromethane in Corn Oil
2.5 mL/kg			
Hyperplasia		v.	
Overall rate <sup>a</sup>		28/47 (60%)	28/50 (56%)
Adjusted rate <sup>b</sup>		73.0%	81.5%
Terminal rate <sup>c</sup>		22/32 (69%)	17/23 (74%)
First incidence (days)		409 ` ´	572
Logistic regression test <sup>d</sup>			P = 0.484
Adenoma			
Overall rate		8/47 (17%)	9/50 (18%)
Adjusted rate		25.0%	35.2%
Terminal rate		8/32 (25%)	7/23 (30%)
First incidence (days)		731 (T)	622
Logistic regression test			P=0.327
5 mL∕kg			
Hyperplasia			
Overall rate		28/50 (56%)	38/50 (76%)
Adjusted rate	*	61.9%	97.3%
Terminal rate		21/38 (55%)	27/28 (96%)
First incidence (days)		555	484 ` ′
Logistic regression test			P=0.011
Adenoma			
Overall rate		10/50 (20%)	19/50 (38%)
Adjusted rate		24.6%	60.8%
Terminal rate		8/38 (21%)	16/28 (57%)
First incidence (days)		569	682
Logistic regression test			P=0.014
Adenoma or Carcinoma			
Overall rate		11/50 (22%)	20/50 (40%)
Adjusted rate		27.2%	62.0%
Terminal rate		9/38 (24%)	16/28 (57%)
First incidence (days)		569	682
Logistic regression test			P = 0.014
(continued)			•

TABLE 22
Statistical Comparison of Incidences of Proliferative Lesions of the Exocrine Pancreas in Male Rats Receiving Corn Oil or 500 mg Dichloromethane in Corn Oil (continued)

Dose	Corn Oil	Dichloromethane in Corn Oil
10 mL/kg		
Hyperplasia		
Overall rate	35/50 (70%)	44/50 (88%)
Adjusted rate	77.6%	91.6%
Terminal rate	30/40 (75%)	27/31 (87%)
First incidence (days)	575	290
Logistic regression test		P=0.016
Adenoma		
Overall rate	23/50 (46%)	41/50 (82%)
Adjusted rate	53.2%	97.6%
Terminal rate	20/40 (50%)	30/31 (97%)
First incidence (days)	576	545
Logistic regression test		P=0.001
Carcinoma		
Overall rate	0/50 (0%)	3/50 (6%)
Adjusted rate	0.0%	9.7%
Terminal rate	0/40 (0%)	3/31 (10%)
First incidence (days)	_e	729 (T)
Logistic regression test		P = 0.080
Adenoma or Carcinoma	•	
Overall rate	23/50 (46%)	41/50 (82%)
Adjusted rate	53.2%	97.6%
Terminal rate	20/40 (50%)	30/31 (97%)
First incidence (days)	576	545
Logistic regression test		P = 0.001

# (T)Terminal sacrifice

Number of lesion-bearing animals/number of animals examined microscopically

<sup>c</sup> Observed incidence in animals surviving until the end of the study

e Not applicable; no lesions in animal group

b Kaplan-Meier estimated lesion incidence at the end of the study after adjustment for intercurrent mortality

d In the dichloromethane in corn oil column are the P values corresponding to pairwise comparisons of dichloromethane in corn oil and corn oil alone. The logistic regression test regards these lesions as nonfatal.

TABLE 23
Statistical Comparison of Incidences of Pancreatic Islet Lesions in Male Rats Receiving Corn Oil or 500 mg Dichloromethane in Corn Oil

Islet Cell Hyperplasia	Dose	Corn Oil	Dichloromethane in Corn Oil	
Overall rate <sup>4</sup> 4/47 (9%)         7/50 (14%)           Adjusted rate <sup>b</sup> 10.0%         25.7%           Terminal rate <sup>c</sup> 1/32 (3%)         4/23 (17%)           First incidence (days)         653         626           Logistic regression test <sup>d</sup> P=0.274           Islet Cell Adenoma         Overall rate         5/50 (10%)           Overall rate         8.4%         14.3%           Adjusted rate         8.4%         1/23 (4%)           First incidence (days)         599         595           Logistic regression test         P=0.413           5 mL/kg           Islet Cell Hyperplasia           Overall rate         2/50 (4%)         5/50 (10%)           Adjusted rate         4.6%         16.4%           First incidence (days)         560         615           Logistic regression test         P=0.209           Islet Cell Adenoma         Verall rate         4/50 (8%)         8/50 (16%)           Adjusted rate         10.5%         24.5%           Terminal rate         4/38 (11%)         5/28 (18%)           First incidence (days)         730 (T)         643           Logistic regression test         P=0.130	2.5 mL/kg	· · · · · · · · · · · · · · · · · · ·		
Overall rate <sup>4</sup>	Islet Cell Hyperplasia			
Terminal rate <sup>c</sup> 1/32 (3%) 4/23 (17%) First incidence (days) 653 626	Overall rate <sup>a</sup>	4/47 (9%)	7/50 (14%)	
Terminal rate <sup>c</sup> 1/32 (3%) 4/23 (17%) First incidence (days) 653 626 Logistic regression test <sup>d</sup> P=0.274  Islet Cell Adenoma Overall rate 3/47 (6%) 5/50 (10%) Adjusted rate 8.4% 14.3% Terminal rate 2/32 (6%) 1/23 (4%) First incidence (days) 599 595 Logistic regression test P=0.413  S mL/kg  Islet Cell Hyperplasia Overall rate 4/50 (8%) 5/50 (10%) Adjusted rate 4.6% 16.4% Terminal rate 9/38 (0%) 4/28 (14%) First incidence (days) 560 615 Logistic regression test P=0.209  Islet Cell Adenoma Overall rate 4/50 (8%) 8/50 (16%) Adjusted rate 10.5% 24.5% Terminal rate 4/38 (11%) 5/28 (18%) First incidence (days) 730 (T) 643  Overall rate 4/50 (8%) 9/50 (18%) Adjusted rate 10.5% 27.8% Adjusted rate 4/58 (11%) 6/28 (21%) First incidence (days) 730 (T) 643  First incidence (days) 730 (T) 643  First incidence (days) 730 (T) 643	Adjusted rate <sup>b</sup>	10.0%	25.7%	
Logistic regression test d P=0.274  Islet Cell Adenoma  Overall rate 3/47 (6%) 5/50 (10%)  Adjusted rate 8.4% 14.3%  Terminal rate 2/32 (6%) 1/23 (4%)  First incidence (days) 599 595  Logistic regression test P=0.413  SmL/kg  Islet Cell Hyperplasia  Overall rate 2/50 (4%) 5/50 (10%)  Adjusted rate 4,6% 16.4%  Terminal rate 0/38 (0%) 4/28 (14%)  First incidence (days) 560 615  Logistic regression test P=0.209  Islet Cell Adenoma  Overall rate 4/50 (8%) 8/50 (16%)  Adjusted rate 10.5% 24.5%  Terminal rate 4/38 (11%) 5/28 (18%)  First incidence (days) 730 (T) 643  Overall rate 4/38 (11%) 6/28 (21%)  First incidence (days) 730 (T) 643  First incidence (days) 9/50 (18%)  Adjusted rate 4/38 (11%) 6/28 (21%)  First incidence (days) 730 (T) 643		1/32 (3%)	4/23 (17%)	
Logistic regression test d P=0.274  Islet Cell Adenoma  Overall rate 3/47 (6%) 5/50 (10%)  Adjusted rate 8.4% 14.3%  Terminal rate 2/32 (6%) 1/23 (4%)  First incidence (days) 599 595  Logistic regression test P=0.413  SmL/kg  Islet Cell Hyperplasia  Overall rate 2/50 (4%) 5/50 (10%)  Adjusted rate 4,6% 16.4%  Terminal rate 0/38 (0%) 4/28 (14%)  First incidence (days) 560 615  Logistic regression test P=0.209  Islet Cell Adenoma  Overall rate 4/50 (8%) 8/50 (16%)  Adjusted rate 10.5% 24.5%  Terminal rate 4/38 (11%) 5/28 (18%)  First incidence (days) 730 (T) 643  Overall rate 4/38 (11%) 6/28 (21%)  First incidence (days) 730 (T) 643  First incidence (days) 9/50 (18%)  Adjusted rate 4/38 (11%) 6/28 (21%)  First incidence (days) 730 (T) 643	First incidence (days)	653	626	
Overall rate       3/47 (6%)       5/50 (10%)         Adjusted rate       8.4%       14.3%         Terminal rate       2/32 (6%)       1/23 (4%)         First incidence (days)       599       595         Logistic regression test       P=0.413     SmL/kg  Islet Cell Hyperplasia  Overall rate  Overall rate  Overall rate  Overall rate  O/38 (0%)  Adjusted rate  O/38 (0%)  First incidence (days)  Logistic regression test  First incidence (days)  Solution (days)  First incidence (days)  Adjusted rate  Incidence  Overall rate  Adjusted rate  Incidence  Adjusted rate  Incidence  Adjusted rate  Incidence  Adjusted rate  Incidence (days)  Adjusted rate  Adjus	Logistic regression test <sup>d</sup>		P=0.274	
Adjusted rate	Islet Cell Adenoma		·	
Adjusted rate	Overall rate	3/47 (6%)	5/50 (10%)	
First incidence (days) 599 595 Logistic regression test P=0.413  5 mL/kg  Islet Cell Hyperplasia Overall rate 2/50 (4%) 5/50 (10%) Adjusted rate 4.6% 16.4% Terminal rate 0/38 (0%) 4/28 (14%) First incidence (days) 560 615 Logistic regression test P=0.209  Islet Cell Adenoma Overall rate 4/50 (8%) 8/50 (16%) Adjusted rate 10.5% 24.5% Terminal rate 4/38 (11%) 5/28 (18%) First incidence (days) 730 (T) 643  Logistic regression test P=0.130  Islet Cell Adenoma or Carcinoma Overall rate 4/50 (8%) 9/50 (18%) Adjusted rate 10.5% 27.8% Terminal rate 4/50 (8%) 9/50 (18%) Terminal rate 4/58 (11%) 6/28 (21%) First incidence (days) 730 (T) 643	Adjusted rate			• •
First incidence (days) Logistic regression test  599  595  P=0.413  5 mL/kg  Islet Cell Hyperplasia Overall rate 2/50 (4%) Adjusted rate 4.6% 16.4% Terminal rate 0/38 (0%) 4/28 (14%) First incidence (days) 560 615 Logistic regression test P=0.209  Islet Cell Adenoma Overall rate 4/50 (8%) Adjusted rate 10.5% 24.5% Terminal rate 4/38 (11%) First incidence (days) Logistic regression test P=0.130  Islet Cell Adenoma or Carcinoma Overall rate 4/50 (8%) 9/50 (16%) Adjusted rate 10.5% 24.5% Terminal rate 4/38 (11%) 5/28 (18%) First incidence (days) Adjusted rate 10.5% 27.8% Terminal rate 4/38 (11%) 6/28 (21%) First incidence (days) 730 (T) 643	Terminal rate	2/32 (6%)	1/23 (4%)	· . ·
SmL/kg   SmL/kg	First incidence (days)			i
Islet Cell Hyperplasia   2/50 (4%)   5/50 (10%)   Adjusted rate   4.6%   16.4%   16.4%   Terminal rate   0/38 (0%)   4/28 (14%)   First incidence (days)   560   615   Logistic regression test   P=0.209      Islet Cell Adenoma   Overall rate   4/50 (8%)   8/50 (16%)   Adjusted rate   10.5%   24.5%   Terminal rate   4/38 (11%)   5/28 (18%)   First incidence (days)   730 (T)   643   Logistic regression test   P=0.130      Islet Cell Adenoma or Carcinoma   Overall rate   4/50 (8%)   9/50 (18%)   Adjusted rate   10.5%   27.8%   10.5%   27.8%   10.5%   27.8%   10.5%   27.8%   10.5%   27.8%   10.5%   10.5%   27.8%   10.5%   10.	Logistic regression test		P=0.413	* * * * * * * * * * * * * * * * * * * *
Overall rate       2/50 (4%)       5/50 (10%)         Adjusted rate       4.6%       16.4%         Terminal rate       0/38 (0%)       4/28 (14%)         First incidence (days)       560       615         Logistic regression test       P=0.209         Islet Cell Adenoma       Verall rate       4/50 (8%)       8/50 (16%)         Adjusted rate       10.5%       24.5%         Terminal rate       4/38 (11%)       5/28 (18%)         First incidence (days)       730 (T)       643         Logistic regression test       P=0.130         Islet Cell Adenoma or Carcinoma       Verall rate       4/50 (8%)       9/50 (18%)         Adjusted rate       10.5%       27.8%         Terminal rate       4/38 (11%)       6/28 (21%)         First incidence (days)       730 (T)       643	5 mL/kg			
Overall rate       2/50 (4%)       5/50 (10%)         Adjusted rate       4.6%       16.4%         Terminal rate       0/38 (0%)       4/28 (14%)         First incidence (days)       560       615         Logistic regression test       P=0.209         Islet Cell Adenoma       Verall rate       4/50 (8%)       8/50 (16%)         Adjusted rate       10.5%       24.5%         Terminal rate       4/38 (11%)       5/28 (18%)         First incidence (days)       730 (T)       643         Logistic regression test       P=0.130         Islet Cell Adenoma or Carcinoma       Verall rate       4/50 (8%)       9/50 (18%)         Adjusted rate       10.5%       27.8%         Terminal rate       4/38 (11%)       6/28 (21%)         First incidence (days)       730 (T)       643	Islet Cell Hyperplasia	•		*,
Adjusted rate 4.6% 16.4%  Terminal rate 0/38 (0%) 4/28 (14%)  First incidence (days) 560 615  Logistic regression test P=0.209  Islet Cell Adenoma  Overall rate 4/50 (8%) 8/50 (16%)  Adjusted rate 10.5% 24.5%  Terminal rate 4/38 (11%) 5/28 (18%)  First incidence (days) 730 (T) 643  Logistic regression test P=0.130  Islet Cell Adenoma or Carcinoma  Overall rate 4/50 (8%) 9/50 (18%)  Adjusted rate 10.5% 27.8%  Terminal rate 4/38 (11%) 6/28 (21%)  First incidence (days) 730 (T) 643		2/50 (4%)	5/50 (10%)	•
Terminal rate       0/38 (0%)       4/28 (14%)         First incidence (days)       560       615         Logistic regression test       P=0.209         Islet Cell Adenoma       Overall rate       4/50 (8%)       8/50 (16%)         Adjusted rate       10.5%       24.5%         Terminal rate       4/38 (11%)       5/28 (18%)         First incidence (days)       730 (T)       643         Logistic regression test       P=0.130         Islet Cell Adenoma or Carcinoma       Overall rate       4/50 (8%)       9/50 (18%)         Adjusted rate       10.5%       27.8%         Terminal rate       4/38 (11%)       6/28 (21%)         First incidence (days)       730 (T)       643	Adjusted rate			•
First incidence (days) 560 615 Logistic regression test P=0.209  Islet Cell Adenoma Overall rate 4/50 (8%) 8/50 (16%) Adjusted rate 10.5% 24.5%  Terminal rate 4/38 (11%) 5/28 (18%) First incidence (days) 730 (T) 643 Logistic regression test P=0.130  Islet Cell Adenoma or Carcinoma Overall rate 4/50 (8%) 9/50 (18%) Adjusted rate 10.5% 27.8% Terminal rate 4/38 (11%) 6/28 (21%) First incidence (days) 730 (T) 643	Terminal rate	0/38 (0%)		
Logistic regression test   P=0.209	First incidence (days)			•
Overall rate       4/50 (8%)       8/50 (16%)         Adjusted rate       10.5%       24.5%         Terminal rate       4/38 (11%)       5/28 (18%)         First incidence (days)       730 (T)       643         Logistic regression test       P=0.130         Islet Cell Adenoma or Carcinoma       Overall rate       4/50 (8%)       9/50 (18%)         Adjusted rate       10.5%       27.8%         Terminal rate       4/38 (11%)       6/28 (21%)         First incidence (days)       730 (T)       643				
Adjusted rate 10.5% 24.5%  Terminal rate 4/38 (11%) 5/28 (18%)  First incidence (days) 730 (T) 643  Logistic regression test P=0.130  Islet Cell Adenoma or Carcinoma  Overall rate 4/50 (8%) 9/50 (18%)  Adjusted rate 10.5% 27.8%  Terminal rate 4/38 (11%) 6/28 (21%)  First incidence (days) 730 (T) 643	Islet Cell Adenoma			
Terminal rate       4/38 (11%)       5/28 (18%)         First incidence (days)       730 (T)       643         Logistic regression test       P=0.130         Islet Cell Adenoma or Carcinoma       Verall rate       9/50 (18%)         Overall rate       10.5%       27.8%         Terminal rate       4/38 (11%)       6/28 (21%)         First incidence (days)       730 (T)       643	Overall rate	4/50 (8%)	8/50 (16%)	
First incidence (days) 730 (T) 643 Logistic regression test P=0.130  Islet Cell Adenoma or Carcinoma Overall rate 4/50 (8%) 9/50 (18%) Adjusted rate 10.5% 27.8% Terminal rate 4/38 (11%) 6/28 (21%) First incidence (days) 730 (T) 643	Adjusted rate	10.5%	24.5%	
Logistic regression test       P=0.130         Islet Cell Adenoma or Carcinoma       9/50 (18%)         Overall rate       4/50 (8%)       9/50 (18%)         Adjusted rate       10.5%       27.8%         Terminal rate       4/38 (11%)       6/28 (21%)         First incidence (days)       730 (T)       643	Terminal rate	4/38 (11%)	5/28 (18%)	
Islet Cell Adenoma or Carcinoma       4/50 (8%)       9/50 (18%)         Overall rate       10.5%       27.8%         Terminal rate       4/38 (11%)       6/28 (21%)         First incidence (days)       730 (T)       643		730 (T)	643	
Overall rate       4/50 (8%)       9/50 (18%)         Adjusted rate       10.5%       27.8%         Terminal rate       4/38 (11%)       6/28 (21%)         First incidence (days)       730 (T)       643	Logistic regression test		P=0.130	
Adjusted rate       10.5%       27.8%         Terminal rate       4/38 (11%)       6/28 (21%)         First incidence (days)       730 (T)       643	Islet Cell Adenoma or Carcinoma	• .		•
Terminal rate       4/38 (11%)       6/28 (21%)         First incidence (days)       730 (T)       643	Overall rate	4/50 (8%)	9/50 (18%)	
First incidence (days) 730 (T) 643	•			. •
		4/38 (11%)	6/28 (21%)	
Logistic regression test P=0.078		730 (T)	643	
	Logistic regression test		P=0.078	

TABLE 23
Statistical Comparison of Incidences of Pancreatic Islet Lesions
in Male Rats Receiving Corn Oil or 500 mg Dichloromethane in Corn Oil (continued)

Dose	Corn Oil	Dichloromethane in Corn Oil
10 mal/kg		
slet Cell Hyperplasia		
Overall rate	3/50 (6%)	7/50 (14%)
Adjusted rate	7.2%	17.9%
Terminal rate	2/40 (5%)	3/31 (10%)
First incidence (days)	692	290
Logistic regression test		P=0.243
Islet Cell Adenoma		
Overall rate	7/50 (14%)	12/50 (24%)
Adjusted rate	16.6%	34.7%
Terminal rate	5/40 (13%)	9/31 (29%)
First incidence (days)	680	670
Logistic regression test		P=0.081
Islet Cell Carcinoma		
Overall rate	0/50 (0%)	3/50 (6%)
Adjusted rate	0.0%	8.5%
Terminal rate	0/40 (0%)	2/31 (6%)
First incidence (days)	_e	546
Logistic regression test		P=0.132
Islet Cell Adenoma or Carcinoma		
Overall rate	7/50 (14%)	15/50 (30%)
Adjusted rate	16.6%	41.9%
Terminal rate	5/40 (13%)	11/31 (35%)
First incidence (days)	680	546
Logistic regression test		P=0.023

# (T)Terminal sacrifice

à Number of lesion-bearing animals/number of animals examined microscopically

<sup>c</sup> Observed incidence in animals surviving until the end of the study

Not applicable; no lesions in animal group

b Kaplan-Meier estimated lesion incidence at the end of the study after adjustment for intercurrent mortality

In the dichloromethane in corn oil column are the P values corresponding to pairwise comparisons between dichloromethane in corn oil and corn oil alone. The logistic regression test regards these lesions as nonfatal.

Pituitary gland: There were significantly increased incidences of adenoma of the pars distalis in rats receiving dichloromethane in corn oil compared to rats receiving equal volumes of corn oil alone (Table 24). The incidences of pituitary gland adenoma were also greater in groups receiving dichloromethane than in untreated control groups and in groups receiving comparable volumes of safflower oil (10/48, 4/49, 8/50) or tricaprylin (8/47, 5/49, 4/51). Historical incidences of pars distalis neoplasms in untreated controls and in controls receiving 5 mL corn oil/kg are given in Table 25. The incidence of hyperplasia of the pars distalis was similar between rats given only corn oil and rats given dichloromethane in corn oil (Table 24).

Mammary gland: The incidence of mammary gland adenoma or fibroadenoma (combined) was significantly greater in rats receiving dichloromethane in 10 mL corn oil/kg than in those receiving dichloromethane in 2.5 mL corn oil/kg (1/50, 2/50, 7/50;

Table D3). The incidences of fibroadenoma of the mammary gland in rats receiving dichloromethane in corn oil (1/50, 2/50, 6/50; Table D3) and those of rats receiving corn oil alone (1/50, 1/50, 3/50; Table A3) were similar. The slight increased incidences of mammary gland adenoma or fibroadenoma (combined) in animals receiving 10 mL corn oil/kg (with and without dichloromethane) were considered to be within the range of normal variability (i.e., the safflower oil and tricaprylin control rates were 7/50 and 6/50 respectively). The historical incidence of mammary gland fibroadenoma or adenoma (combined) in controls receiving 5 mL corn oil/kg is 68/1,020 (6.7%), with a range of 2% to 14%; the range in untreated controls is 0% to 12% (Table 26). Thus, this response was not considered to be chemical related.

Mononuclear cell leukemia: There were similar doserelated decreased incidences of mononuclear cell leukemia in rats receiving corn oil alone and rats receiving dichloromethane in corn oil (Table 27).

TABLE 24
Statistical Comparison of Incidences of Neoplasms and Nonneoplastic Lesions of the Pituitary Gland in Male Rats Receiving Corn Oil or 500 mg Dichloromethane in Corn Oil

Dose	Corn Oil	Dichloromethane in Corn Oil
2.5 mL/kg		
Pars Distalis Hyperplasia		•
Overall rate <sup>a</sup>	13/50 (26%)	9/50 (18%)
Adjusted rate <sup>b</sup>	37.9%	36.4%
Terminal rate <sup>c</sup>	12/33 (36%)	8/23 (35%)
First incidence (days)	656	605
Logistic regression test <sup>d</sup>		P = 0.428N
Pars Distalis Adenoma		
Overall rate	10/50 (20%)	20/50 (40%)
Adjusted rate	25.0%	58.2%
Terminal rate	5/33 (15%)	10/23 (43%)
First incidence (days)	409	352
Logistic regression test		P=0.022

TABLE 24
Statistical Comparison of Incidences of Neoplasms and Nonneoplastic Lesions of the Pituitary Gland im Male Rats Receiving Corn Oil or 500 mg Dichloromethane in Corn Oil (continued)

Dose	Corn Oil	Dichloromethane in Corn Oil
5 mL/kg		
Pars Distalis Hyperplasia		
Overall rate	9/49 (18%)	10/49 (20%)
Adjusted rate	22.5%	30.1%
Terminal rate	7/37 (19%)	7/28 (25%)
First incidence (days)	432	327
Logistic regression test		P=0.510
Pars Distalis Adenoma		
Overall rate	6/49 (12%)	18/49 (37%)
Adjusted rate	15.4%	47.9%
Terminal rate	5/37 (14%)	10/28 (36%)
First incidence (days)	562 `	580 ` ´
Logistic regression test		P = 0.004
10 mL/kg		
Pars Distalis Hyperplasia		
Overall rate	9/50 (18%)	7/49 (14%)
Adjusted rate	21.3%	21.4%
Terminal rate	7/40 (18%)	5/30 (17%)
First incidence (days)	672	678
Logistic regression test		P = 0.566N
Pars Distalis Adenoma		
Overall rate	7/50 (14%)	16/49 (33%)
Adjusted rate	16.3%	41.2%
Terminal rate	5/40 (13%)	9/30 (30%)
First incidence (days)	575	545
Logistic regression test		P=0.027

<sup>&</sup>lt;sup>a</sup> Number of lesion-bearing animals/number of animals examined microscopically

b Kaplan-Meier estimated lesion incidence at the end of the study after adjustment for intercurrent mortality

C Observed incidence in animals surviving until the end of the study

In the dichloromethane in corn oil column are the P values corresponding to pairwise comparisons between dichloromethane in corn oil and corn oil alone. The logistic regression test regards these lesions as nonfatal. A lower incidence in the dichloromethane in corn oil group is indicated by N.

TABLE 25
Historical Incidence of Pituitary Gland (Pars Distalis) Neoplasms in Untreated Male F344/N Rats and in Male F344/N Rats Administered 5 mL Corn Oil/kg Body Weight by Gavage<sup>a</sup>

•	Incidence in Controls					
Study	Adenoma	Carcinoma	Adenoma or Carcinoma			
listorical Incidence in Untreated	Controls (Feed and Drinki	ng Water Studies) at EG&	&G Mason Research Institut			
-Amino-2,4-dibromoanthraquinone	21/48	0/48	21/48			
Acetaminophen	16/48	1/48	17/48			
IC Yellow 4	17/45	0/45	17/45			
Methylphenidate hydrochloride	11/48	1/48	12/48			
entaerythritol tetranitrate	13/49	0/49	13/49			
Quercetin	14/46	0/46	14/46			
Turmeric oleoresin	23/50	0/50	23/50			
Sarium chloride dihydrate	21/48	1/48	22/48			
Overall Historical Incidence			,			
Total	483/1,609 (30.0%)	8/1,609 (0.5%)	490/1,609 (30.5%)			
Standard deviation	12.8%	1.0%	12.8%			
Range	12%-67%	0%–4%	12%–67%			
listorical Incidence in Vehicle Co	ntrols (Gavage Studies) at	EG&G Mason Research	Institute			
,2,3-Trichloropropane	9/48	0/48	9/48			
,2,3-Trichloropropane ,4-Diaminophenol dihydrochloride	9/48 23/50	0/48 1/50	9/48 24/50			
,4-Diaminophenol dihydrochloride		·	• =			
,4-Diaminophenol dihydrochloride Pribromomethane	23/50	1/50	24/50			
	23/50 12/50	1/50 0/50	24/50 12/50			
,4-Diaminophenol dihydrochloride ribromomethane łexachloroethane rhenylbutazone	23/50 12/50 24/49	1/50 0/50 0/49	24/50 12/50 24/49			
,4-Diaminophenol dihydrochloride Fribromomethane Hexachloroethane	23/50 12/50 24/49 16/48	1/50 0/50 0/49 0/48	24/50 12/50 24/49 16/48			
4-Diaminophenol dihydrochloride Pribromomethane Hexachloroethane Phenylbutazone Probenecid	23/50 12/50 24/49 16/48 15/50	1/50 0/50 0/49 0/48 0/50	24/50 12/50 24/49 16/48 15/50			
4.4-Diaminophenol dihydrochloride Pribromomethane Hexachloroethane Phenylbutazone Probenecid Pitanocene dichloride	23/50 12/50 24/49 16/48 15/50	1/50 0/50 0/49 0/48 0/50	24/50 12/50 24/49 16/48 15/50 23/56			
A-Diaminophenol dihydrochloride Pribromomethane Hexachloroethane Phenylbutazone Probenecid Pitanocene dichloride  Deverall Historical Incidence	23/50 12/50 24/49 16/48 15/50 23/56	1/50 0/50 0/49 0/48 0/50 0/56	24/50 12/50 24/49 16/48 15/50			

a Data as of 31 March 1993

TABLE 26
Historical Incidence of Mammary Gland Neoplasms in Untreated Male F344/N Rats and in Male F344/N Rats Administered 5 mL Corn Oil/kg Body Weight by Gavage<sup>a</sup>

	Incidence in Controls					
Study			Fibroadenoma or			
•	Fibroadenoma	Adenoma	Adenoma			
Historical Incidence in Untreated (	Controls (Feed and Drinki	ng Water Studies) at EG&	&G Mason Research Institute			
-Amino-2,4-dibromoanthraquinone	1/50	0/50	1/50			
Acetaminophen	4/50	0/50	4/50			
HC Yellow 4	3/50	1/50	4/50			
Methylphenidate hydrochloride	1/50	0/50	1/50			
Pentaerythritol tetranitrate	4/50	0/50	4/50			
Quercetin	5/50	0/50	5/50			
Furmeric oleoresin	0/50	1/50	1/50			
Barium chloride dihydrate	2/50	0/50	2/50			
Overall Historical Incidence						
Total	73/1,634 (4.5%)	4/1,634 (0.2%)	77/1,634 (4.7%)			
Standard deviation	3.0%	0.7%	3.0%			
Range	0%-12%	0%–2%	0%–12%			
Historical Incidence in Vehicle Con	ntrols (Gavage Studies) at	EG&G Mason Research	Institute			
1,2,3-Trichloropropane	2/50	0/50	2/50			
2,4-Diaminophenol dihydrochloride	4/50	0/50	4/50			
<b>Fribromomethane</b>	5/50	0/50	5/50			
Hexachloroethane	7/50	0/50	7/50			
Phenylbutazone	2/50	0/50	2/50			
Probenecid	3/50	0/50	3/50			
Titanocene dichloride	4/60	0/60	4/60			
Overall Historical Incidence						
Overall Historical Incidence  Total	66/1,020 (6.5%)	2/1,020 (0.2%)	68/1,020 (6.7%)			
	66/1,020 (6.5%) 3.3%	2/1,020 (0.2%) 0.6%	68/1,020 (6.7%) 3.3%			

a Data as of 31 March 1993

TABLE 27
Incidences of Mononuclear Cell Leukemia
in Male Rats Receiving Corn Oil or 500 mg Dichloromethane in Corn Oil

Dose	Untreated Control <sup>a</sup>	2.5 mL/kg	5 mL/kg	10 mL/kg
Corn Oil Study				
Overall rate <sup>b</sup>	27/50 (54%)	16/50 (32%)	11/50 (22%)	7/50 (14%)
Adjusted rate <sup>c</sup>	62.6%	39.6%	25.4%	15.9%
Terminal rated	11/26 (42%)	9/33 (27%)	6/38 (16%)	4/40 (10%)
First incidence (days)	523	586	555	623
Life table test <sup>e</sup>	P<0.001N	P = 0.016N	P<0.001N	P<0.001N
Dichloromethane in Corn Oil Stu	dy			
Overall rate		13/50 (26%)	14/50 (28%)	5/50 (10%)
Adjusted rate		43.0%	37.4%	12.4%
Terminal rate		7/23 (30%)	6/28 (21%)	1/31 (3%)
First incidence (days)		605	580	574
Life table test <sup>f</sup>		P = 0.025N	P = 0.468N	P=0.015N

a Control rats in the dichloromethane in corn oil study were terminated early and were not examined microscopically.

Number of neoplasm-bearing animals/number of animals examined microscopically

c Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality

d Observed incidence at terminal kill

Beneath the control incidence is the P value associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table test regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. A negative trend or lower incidence in a dose group is indicated by N.

Beneath the 2.5 mL/kg incidence is the P value associated with the trend test. Beneath the 5 and 10 mL/kg incidences are the P values corresponding to pairwise comparisons between the 2.5 mL/kg group and that dosed group. A negative trend or lower incidence in the 5 or 10 mL/kg group is indicated by N.

Interaction of dichloromethane and corn oil: One objective of this study was to determine if the effect of dichloromethane was dependent on the volume of corn oil used, and Table 28 summarizes these comparisons for the four neoplasms reported in Tables 22, 23, 24, and 27. Logistic regression analyses (life table analysis for mononuclear cell leukemia) were carried out to evaluate the consistency of the neoplasm response (i.e., to determine whether or not there is an interaction between dichloromethane and corn oil). These analyses revealed that the interaction was statistically significant only for pancreatic acinar cell adenoma or carcinoma (combined) (P<0.01; Table 28).

This interaction implies that the carcinogenic effect of dichloromethane depends on the volume of corn oil used. In 2.5 mL corn oil/kg, dichloromethane has no effect on the incidence of pancreatic acinar cell adenoma; when given in 5 mL corn oil/kg, the increased incidence is marginally significant; when given in 10 mL corn oil/kg, the incidence is markedly increased (Table 22).

For the other three neoplasms in Table 28, there is no significant interaction, although there are consistent dichloromethane effects on pituitary gland and pancreatic islet cell neoplasms and corn oil effects on pancreatic islet cell neoplasms and mononuclear cell leukemia (Table 28). These effects have been discussed previously.

TABLE 28
Interaction of Dichloromethane and Corn Oil for Selected Neoplasms

Dose (mL/kg)	Corn Oil	Dichloromethane in Corn Oil	Significance of Interaction
ancreatic acinar cell adenoma	or carcinoma		
2.5	17% (8/47)	18% (9/50)	
5	22% (11/50)	40% (20/50)	P<0.01
10	46% (23/50)	82% (41/50)	
ncreatic islet cell adenoma or	carcinoma* <sup>△</sup>		
2.5	6% (3/47)	10% (5/50)	
5	8% (4/50)	18% (9/50)	Not significant
10	14% (7/50)	30% (15/50)	· ·
tuitary gland adenoma^			
2.5	20% (10/50)	40% (20/50)	
5	12% (6/49)	37% (18/49)	Not significant
10	14% (7/50)	33% (16/49)	
ononuclear cell leukemía <sup>v</sup>			
2.5	32% (16/50)	26% (13/50)	
5	22% (11/50)	28% (14/50)	Not significant
10	14% (7/50)	10% (5/50)	ŭ

Significant (P<0.01) corn oil effect by the logistic regression test</li>

Significant (P<0.01) dichloromethane effect by the logistic regression test

<sup>∇</sup> Significant (P<0.01) corn oil effect by the life table test
</p>

### **GENETIC TOXICOLOGY**

Corn oil and safflower oil (100 to 10,000  $\mu$ g/plate) were tested for mutagenicity in Salmonella typhimurium strains TA97, TA98, TA100, and TA1535, using a preincubation protocol with and without hamster or rat S9 liver activation enzymes (Table E1a,b). Neither oil produced an increase in revertants. Corn oil is used routinely as a solvent for in vivo bone marrow chromosome studies with mice. A comparison of saline- and corn oil-treated control groups showed no differences between these groups in frequencies of sister chromatid exchanges, chromosomal aberrations, or micronuclei (NTP, unpublished data). Tricaprylin (Table E1c), however, was mutagenic in S. typhimurium strain TA1535 in the presence of hamster or rat S9, but only at very high concentrations (6,666 to 16,666 µg/plate). No mutagenic activity was detected in strains TA97, TA98, or TA100, when treated with tricaprylin with or without **S9.** 

Dichloromethane was tested in two separate studies for induction of mutations in *S. typhimurium* (Table E1d; Zeiger *et al.*, 1990). With a preincubation protocol that did not control for volatility,

dichloromethane (100 to 10,000  $\mu$ g/plate) did not induce mutations in strains TA97, TA98, TA100, TA1535, or TA1537, with or without S9 activation enzymes. However, when exposure occurred within the closed environment of a desiccator, dichloromethane (up to 1.0 mL/chamber) produced a positive response in strain TA100, with and without S9, and in TA98, but only in the presence of hamster liver S9.

Dichloromethane was tested for mutagenicity in L5178Y mouse lymphoma cells with and without S9 (Table E2; Myhr et al., 1990). Both with and without S9, the first of the three trials was positive, the second was judged equivocal, and the third trial in each case was negative. Therefore, the overall results for the test were considered equivocal. Although a significant increase in mutant colonies was observed at the highest dose tested in the third trial without S9, the presence of a precipitate at this concentration invalidated the data and the trial was judged negative.

No increase in sister chromatid exchanges (Table E3) or chromosomal aberrations (Table E4) was observed in cultured Chinese hamster ovary cells treated with dichloromethane (up to  $5,000 \mu g/mL$ ) in the presence or the absence of S9 (Anderson *et al.*, 1990).

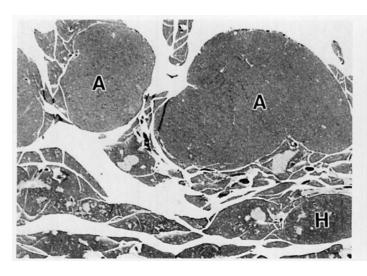


PLATE 1 Multiple pancreatic exocrine adenomas (A) and pancreatic exocrine hyperplasia (H) in a male F344/N rat exposed to 10 mL/kg corn oil in the 2-year gavage study. H&E, 10×.

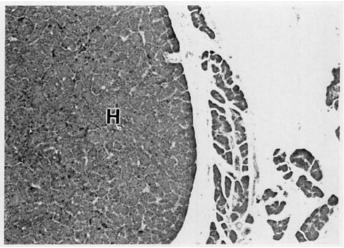


PLATE 2
Pancreatic exocrine adenoma (H) in a male F344/N rat exposed to 10 mL/kg tricaprylin in the 2-year gavage study. The loose lobular arrangement of the pancreas makes it difficult to judge compression at the margin of the lesions H&E, 45×.

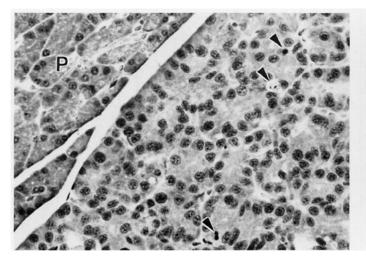


PLATE 3
Pancreatic exocrine adenoma in a male F344/N rat exposed to 10 mL/kg corn oil in the 2-year gavage study. The normal pancreas (P) shows an acinar arrangement while within the adenoma there is apoptosis (arrows), less organized acinar pattern, and more variation in size and shape of nuclei. H&E, 250×

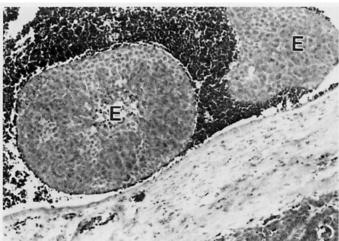
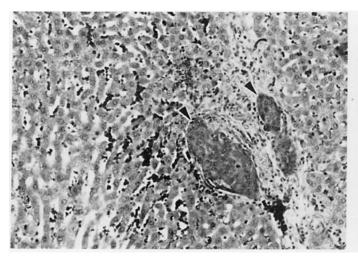


PLATE 4 Pancreatic exocrine carcinoma emboli (E) in the pancreas of a male F344/N rat exposed to 10 mL/kg safflower oil in the 2-year gavage study. H&E,  $100\times$ .



A

PLATE 5
Pancreatic exocrine carcinoma metastases (arrows) in the liver of a male F344/N rat exposed to 10 mL/kg safflower oil in the 2-year gavage study. H&E, 120×.

PLATE 6
Pancreatic exocrine carcinoma in a male F344/N rat exposed to 500 mg/kg dichloromethane in 10 mL/kg corn oil in the 2-year gavage study. There are numerous dilated blood filled vessels (arrows) within the carcinoma plus an area that shows increased atypia (A). H&E, 10×.

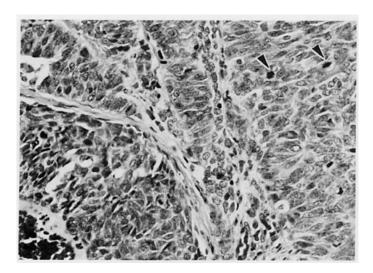


PLATE 7
Pancreatic exocrine carcinoma in a male F344/N rat exposed to 500 mg/kg dichloromethane in 10 mL/kg corn oil in the 2-year gavage study (detail of Plate 6). There are numerous mitotic figures (arrows). There tends to be solid growth with moderate cellular atypia. H&E, 200×.

### DISCUSSION

Unsaturated fats, especially polyunsaturated fats, have generally been considered beneficial to humans when substituted for saturated fats in the diet (Dupont et al., 1990), but increased dietary fat has been implicated as a possible risk factor for cancer in humans (Mead et al., 1986; Giovannucci et al., 1992). High dietary fat levels will also promote cancer in numerous animal models (Longnecker et al., 1986; Perino et al., 1988; Reddy and Sugie, 1988; Locniskar et al., 1991; Nelson and Holian, 1991; Reddy et al., 1991; Zhao et al., 1991; Birt et al., 1992; Welsch, 1992). Increased dietary fat resulting from the use of oil gavage vehicles can alter the incidence of spontaneous neoplasms in rats and, thus, acts as a confounding factor in evaluating chemicals for potential toxicity and carcinogenicity (Boorman and Eustis, 1984; Haseman et al., 1985). The NTP decided to evaluate the effect of different oils on the pattern of neoplasm development and to determine whether any of the vehicles evaluated could serve as a replacement The male F344/N rat was chosen because the effects of corn oil on the pancreas and on the incidence rates of mononuclear cell leukemia were well documented in this sex and species. The volumes used in the study, 2.5, 5, and 10 mL/kg, were the minimum, standard, and maximum volumes of oils that could be reasonably administered to rats over a 2-year period.

Three oils (corn oil, safflower oil, and tricaprylin) that vary widely in type and composition of fatty acids were chosen. Corn oil contains 58% polyunsaturated fatty acids (mostly linoleic) and 28% monounsaturated fatty acids (mostly oleic). Safflower oil contains approximately 80% of the polyunsaturated linoleic acid and approximately 10% of the monounsaturated oleic acid. In both oils, the main saturated fatty acids are palmitic (about 8%) and stearic (about 3%). Tricaprylin, in contrast, is a triglyceride made up of three short, saturated fatty acids (the 8-carbon caprylic acid). Thus the oils chosen allow the comparison of vehicles containing mostly polyunsaturated fatty acids (safflower oil), mixed polyunsaturated and monounsaturated fatty acids (corn oil), and saturated fatty acids (tricaprylin).

The evaluation of one amount of dichloromethane in various volumes of corn oil was an attempt to determine for one chemical the potential confounding effect of corn oil. Dichloromethane is a widely used solvent; its effect on the exocrine pancreas in male rats or in humans is controversial and, in an inhalation study, the potential of dichloromethane to increase the incidence of mononuclear cell leukemia in female rats was considered equivocal (NTP, 1986). Thus, dichloromethane was included in the studies because of its widespread use and also because of its uncertain role as a promoter of two neoplasms that have rates that are also affected by corn oil gavage.

There was no toxicity associated with corn oil or safflower oil, but decreased feed consumption and elevated body weights were seen at 10 mL/kg. Tricaprylin at 10 mL/kg was toxic, with the animals showing lethargy, ataxia, dyspnea, decreased weight gain, and increased mortality. The toxicity may have been due to the large volume of triglycerides in each dose and is consistent with severe ketosis. medium-chain fatty acids from the triglyceride are transported directly to the liver and are promptly oxidized by hepatocytes (Geliebter et al., 1983). Clinical findings in patients given medium-chain triglycerides can be minimized by administering the triglycerides several times a day or feeding medium-chain triglyceride diets slowly (Harkins and Sarett, 1968). Rats given approximately 6 g of medium-chain triglycerides/kg by gavage show ketonemia (Bach et al., 1977) and decreased body weight (Geliebter et al., 1983); however, rats given 15% medium-chain triglycerides in the diet did not show ketonemia or decreased weight gains (Chanez et al., 1991). In both studies, the rats receiving medium-chain triglycerides had decreased body fat.

In the present study, rats receiving 10 mL tricaprylin/kg had lower mean body weights than the controls or other groups receiving tricaprylin. The oxidation of medium-chain fatty acids from tricaprylin does not result in fat deposition and much of the energy is probably dissipated as heat with little incorporation into tissues (Baba et al., 1982; Geliebter et al., 1983; Swenson et al., 1991). This would explain the lower mean body weights in the rats receiving the high volume of tricaprylin.

The administration of corn oil, safflower oil, and tricaprylin to male rats by gavage was associated with similar increased incidences of pancreatic proliferative lesions despite the marked difference in the amount, type and degree of saturation of the fatty Further, the magnitude of the acids in each. response was similar for corn oil, safflower oil, and tricaprylin at each dose level. Increased incidences of exocrine pancreatic hyperplasia and adenoma occurred in the 2.5 mL/kg groups, with more marked responses occurring in the 5 and 10 mL/kg groups. In the 10 mL/kg groups, 60% to 80% of the animals had pancreatic proliferative lesions. One mid-dose rat receiving corn oil had a carcinoma and two highdose rats in the safflower oil study had carcinomas. No pancreatic carcinomas were observed in the rats given tricaprylin. When rats receiving diets with six fats having varying degrees of saturation/unsaturation were compared for azaserine-induced pancreatic cancer, each fat had a similar stimulatory activity (Roebuck, 1986). This is similar to the results of the current studies and in contrast to earlier findings that suggested that unsaturated fats were more stimulatory than saturated fats (Roebuck et al., 1981). However, in the Roebuck et al. (1981) study, the controls received only saturated fat and would have had a linoleic acid deficiency, which limits animal (and neoplasm) growth (Vergroesen, 1989).

The mechanism by which these dietary fats or triglycerides stimulate proliferation of the exocrine pancreas is unknown. Several mechanisms have been proposed. Chronic administration of the gastrointestinal hormone, cholecystokinin, increases pancreatic weight and DNA synthesis (Solomon et al., 1987). Cholecystokinin also will promote chemical-induced pancreatic cancer in the rat (Douglas et al., 1989). Mediumchain triglycerides (58% octanoic acid) and corn oil were reported to stimulate cholecystokinin secretion in the rat, with corn oil administered by gavage causing only a moderate response (Douglas et al., 1990). However, another study showed no increase in cholecystokinin in rats fed 20% corn oil in their diet (Roebuck et al., 1987). The rats in both studies were cannulated and blood samples were drawn repeatedly. Thus the role of cholecystokinin in the promotion of pancreatic lesions by dietary oils is not clear. Douglas et al. (1989) have shown that exogenous cholecystokinin enhances azaserine-induced lesions, an effect that can be blocked by a specific cholecystokinin receptor antagonist. Further, bombesin, an amphibian analogue of the gastrin-releasing hormone in mammals, also promotes chemical-induced pancreatic carcinogenesis in the rat (Douglas et al., 1989). In the studies supported by the NTP cooperative agreements, there was no evidence that cholecystokinin played a role in the oil-induced pancreatic neoplasms in male F344/N rats (Dr. Travis Solomon, unpublished data).

The evaluation of chemicals for potential toxicity and carcinogenicity, and especially for their role in the induction of proliferative lesions of the exocrine pancreas, may be obscured by the use of corn oil as the gavage vehicle. Since dichloromethane appeared to cause exocrine pancreatic lesions when given by gavage (unpublished NTP data) but did not cause pancreatic lesions in a subsequent inhalation study (NTP, 1986a), a single amount of dichloromethane in varying volumes of corn oil was included in this study. There was no significant difference in the incidence of exocrine adenoma in rats receiving 500 mg dichloromethane/kg in 2.5 mL corn oil/kg and that in rats receiving only 2.5 mL corn oil/kg. When this same amount of dichloromethane was given in either 5 or 10 mL corn oil/kg, the incidence of pancreatic adenoma was significantly greater than that of rats receiving corn oil alone. In addition, at 10 mL/kg, the dichloromethane-treated rats had three pancreatic carcinomas and rats receiving 10 mL corn oil/kg alone had none. Thus, our interpretation of the effect of 500 mg dichloromethane/kg would differ depending on the volume of corn oil in which the chemical was given. Benzyl acetate at 500 mg/kg caused acinar cell adenomas in male rats, but the corn oil gavage vehicle was considered a possible contributing factor (NTP, 1986b). This conclusion is supported by the results of a later study in which an increase in pancreatic lesions did not occur when a comparable dose of benzyl acetate was administered in feed (NTP, 1993). These data clearly indicate that use of a corn oil gavage vehicle is a confounding factor for lesions of the exocrine pancreas.

The NTP studies on gavage vehicle effects on the pancreas were augmented by studies arranged through cooperative agreements with three universities. These cooperative studies showed that the corn oil-induced pancreatic adenomas and hyperplasias have genotypic and phenotypic characteristics similar to those of the normal pancreas and differ

from transplantable exocrine carcinomas (Longnecker et al., 1991). Explants from corn oil-induced nodules did not grow in soft agar, whereas explants from several carcinomas did. Transfection of DNA from adenomas into NIH 3T3 cells yielded a low frequency of transformed colonies that did not differ from background. Repeated transplantation of corn oil-induced adenomas and hyperplasias either subcutaneously or under the kidney capsule failed to result in growth of the adenomas. The recipients were necropsied after 3 months, and no growth of the transplant was observed in the 96 recipients (Longnecker et al., 1991). This suggests that the pancreatic nodules are not very transplantable.

Evaluation of the corn oil-induced pancreatic nodules for mutations in the c-Ki-ras proto-oncogene showed wild-type, but not mutated, c-Ki-ras. A majority of human adenocarcinomas of the exocrine pancreas contain c-Ki-ras genes with mutations at codon 12 (Almoguera et al., 1988; Grünewald et al., 1989). Azaserine-induced pancreatic carcinomas in the rat show increased expression of C-myc, c-raf-1, and c-Ki-ras (Silverman et al., 1990). In contrast, adenomas in rats that had received corn oil by gavage for 2 years during the NTP studies did not show expression of c-Ki-ras (Schaeffer et al., 1990). The results of these studies show that the corn oil-induced pancreatic adenomas differ from the majority of human pancreatic carcinomas or chemical-induced rat exocrine carcinomas in that the c-Ki-ras in the rat exocrine adenomas is not mutated at codon 12.

While the gastrointestinal hormone cholecystokinin has been implicated in some pancreatic carcinomas induced by soybean trypsin inhibitors, there was no evidence that cholecystokinin played a role in the pancreatic lesions induced by diets with a high corn oil content (Roebuck et al., 1987). A comparison of diets varying in degree of saturated fatty acids suggests that it is the level of fat and not the degree of saturation that is important (Longnecker, 1990). This correlates very well with the NTP studies and is in contrast to earlier findings that suggested that high levels of unsaturated fat caused pancreatic cancer (Roebuck et al., 1981). An analysis of the body fat of rats showed that approximately 80% of the body fat consisted of three fatty acids (linoleic, oleic, and palmitic acid). In rats receiving 20% corn oil, the amount of linoleic acid in the fat increased, and the amount of palmitic acid decreased compared to that in rats receiving 5% corn oil (Appendix L).

At the time these studies started, corn oil-induced exocrine pancreatic lesions were believed to be restricted to the male F344/N rat. Subsequent evaluation of multiple sections of the pancreas from control rats administered corn oil by gavage showed that while the response was most pronounced in the male rat, exocrine pancreatic lesions also occurred in the female rat (Boorman et al., 1987). studies have shown that testosterone appears to promote the growth of carcinogen-induced pancreatic foci (Lhoste et al., 1987), while estrogen appears to have an inhibitory effect (Sumi et al., 1989). This provides an explanation for the higher incidence of spontaneous neoplasms in the male historical controls receiving corn oil compared to the incidence in the female controls.

In all four of the current studies (corn oil, safflower oil, tricaprylin, and dichloromethane in corn oil), there was a marked dose-related decrease in the incidence of mononuclear cell leukemia. This effect was also noted in a survey of the controls from numerous feed and corn oil gavage studies conducted by the NTP (Haseman et al., 1985, Haseman and Rao, 1992). There was no difference in the rates of mononuclear cell leukemia in rats receiving dichloromethane in corn oil and those of controls receiving a comparable volume of corn oil alone. Mononuclear cell leukemia is a disease that commonly arises in the spleen of the F344/N rat but is rare in other rat strains. Since the amount of dietary oil affects the incidence rates, this is another cancer endpoint that is confounded by the use of an oil gavage vehicle.

While cross-cultural comparisons generally support the role of dietary fat in the etiology of breast cancer in women, the results of epidemiology studies are less clear (Kushi et al., 1992; Richardson et al., 1992; Yu et al., 1992). In this NTP study, the combined incidence of mammary gland fibroadenomas in the three untreated control groups was 11% while the incidence in the 10 mL corn oil/kg group was 6%, and the incidences in the 10 mL safflower oil/kg and the 10 mL tricaprylin/kg groups were 4%. dichloromethane in 10 mL corn oil/kg group had the highest incidence of mammary gland fibroadenomas (12%), but it was not significantly different from the incidence in the dichloromethane in 2.5 mL corn oil/kg group. Thus, even in the high-dose groups that received nearly 50% of their energy from the gavage oil, there was no evidence for an effect of the oil. Zevenbergen et al. (1992) concluded that low fat levels can influence the incidence of mammary gland neoplasms in mice but levels above 22% of the diet have little effect.

Nephropathy is an important age-related spontaneous renal disease of F344/N rats. The pathogenesis appears to be an increase in thickness and porosity of the basement membrane leading to protein leakage (Montgomery and Seely, 1990). The severity of the disease is related to the amount and type of protein in the diet; less protein results in lower incidence of, or less severe, nephropathy. In this study the severity of the nephropathy decreased with increasing volumes of gavage vehicle, and the decrease was most pronounced in rats receiving tricaprylin and safflower oil; however, less marked effects were also seen in rats receiving corn oil. The incidence of nephropathy was also decreased in rats administered 10 mL corn oil or tricaprylin/kg. In the present studies, administration of the oils resulted in greater body weights although feed consumption decreased. The decreased consumption of dietary protein appears to explain the decreased nephropathy found in these studies.

There was a clear increase in the incidence of squamous cell papillomas of the forestomach in rats receiving 10 mL tricaprylin/kg (19%) with multiple papillomas occurring in two rats. All except one of the papillomas were found at the end of the study. There was a pronounced increased incidence of basal cell hyperplasia (38%) in the 10 mL tricaprylin/kg group, which did not appear to be in response to irritation of the forestomach as there was very little evidence of inflammation or other toxicity. Tricaprylin is mutagenic, and the forestomach response may be directly related its effect on the forestomach epithelium.

There were significantly increased incidences of pituitary gland adenomas in rats receiving dichloromethane in any volume of corn oil when compared to rats receiving comparable volumes of corn oil alone, safflower oil, or tricaprylin. In three previous 2-year studies (two inhalation: Burek et al., 1984, and NTP, 1986; and one drinking water: Serota et al., 1986), dichloromethane did not cause an increase in pituitary gland adenomas in male rats, suggesting that the effect in this study is not related to the dichloromethane exposure. In the NTP (1986) inhalation study, the exposure concentrations were as high as 4,000 ppm, while in the Burek et al. (1984) study, the

exposure concentration was 3,500 ppm. drinking water study, the exposure was only 232 mg/kg as compared to 500 mg/kg in this study. None of these studies suggested an increase in pituitary gland neoplasms and, in the Burek et al. (1984) study, the incidence of pituitary gland neoplasms in females rats significantly decreased with increasing exposure concentrations. The current NTP studies were conducted at one contract laboratory, and the corn oil, safflower oil, and tricaprylin studies started within one month; however, the dichloromethane study began approximately 9 months prior to the initiation of the other three studies. Also, rats for the dichloromethane exposures were obtained from the Frederick Cancer Research Facility, while rats for the other three studies came from Simonsen Laboratories. A comparison of the pituitary lesions from the four studies suggested that similar diagnostic criteria were used in each study. It is unlikely that the increased incidence of pituitary gland adenomas was caused by the dichloromethane exposure; rather the increase probably represents the normal biologic variation within populations of rats from different sources.

#### Summary

These studies were designed to evaluate the effects of various concentrations of an oil very high in polyunsaturated fat (safflower oil), an oil containing high levels of polyunsaturated and monounsaturated fats (corn oil), and an oil containing saturated medium-chain fatty acids (tricaprylin) on the incidence and pattern of neoplasms in the F344/N rat. In addition, safflower oil and tricaprylin were evaluated as replacements for the corn oil vehicle.

These studies demonstrate that safflower oil and tricaprylin do not offer significant advantages over corn oil as a gavage vehicle in long-term rodent studies. Corn oil, safflower oil, and tricaprylin each caused hyperplasia and adenomas of the exocrine pancreas, decreased incidences of mononuclear cell leukemia, and reduced incidences or severity of nephropathy in male F344/N rats. There was an increased incidence of squamous cell papillomas of the forestomach in F344/N rats receiving 10 mL tricaprylin/kg. Further, use of corn oil as a gavage vehicle may have a confounding effect on the interpretation of chemical-induced proliferative lesions of the exocrine pancreas and mononuclear cell leukemia in male F344/N rats.

# REFERENCES

Alexander, J.W., Saito, H., Trocki, O., and Ogle, C.K. (1986). The importance of lipid type in the diet after burn injury. *Ann. Surg.* 204, 1-8.

Almoguera, C., Shibata, D., Forrester, K., Martin, J., Arnheim, N., and Perucho, M. (1988). Most human carcinomas of the exocrine pancreas contain mutant c-K-ras genes. *Cell* 53, 549-554.

Anderson, B.E., Zeiger, E., Shelby, M.D., Resnick, M.A., Gulati, D.K., Ivett, J.L., and Loveday, K.S. (1990). Chromosome aberration and sister chromatid exchange test results with 42 chemicals. *Environ. Mol. Mutagen.* 16 (Suppl. 18), 55-137.

Armitage, P. (1971). Statistical Methods in Medical Research, pp. 362-365. John Wiley and Sons, New York.

Ashby, J., and Tennant, R.W. (1991). Definitive relationships among chemical structure, carcinogenicity, and mutagenicity for 301 chemicals tested by the U.S. NTP. *Mutat. Res.* 257, 229-306.

Baba, N., Bracco, E.F., and Hashim, S.A. (1982). Enhanced thermogenesis and diminished deposition of fat in response to overfeeding with diet containing medium chain triglyceride. *Am. J. Clin. Nutr.* 35, 678-682.

Bach, A.C., and Babayan, V.K. (1982). Medium-chain triglycerides: An update. *Am. J. Clin. Nutr.* 36, 950-962.

Bach, A., Schirardin, H., Weryha, A., and Bauer, M. (1977). Ketogenic response to medium-chain triglyceride load in the rat. *J. Nutr.* 107, 1863-1870.

Birt D.F., Kris, E.S., Choe, M., and Pelling, J.C. (1992). Dietary energy and fat effects on tumor promotion. *Cancer Res.* 52 (Suppl.), 2035s-2039s.

Boorman, G.A., and Eustis, S.L. (1984). Proliferative lesions of the exocrine pancreas in male F344/N rats. *Environ. Health Perspect.* 56, 213-217.

Boorman, G.A., Montgomery, C.A., Jr., Eustis, S.L., Wolfe, M.J., McConnell, E.E., and Hardisty, J.F. (1985). Quality assurance in pathology for rodent carcinogenicity studies. In *Handbook of Carcinogen Testing* (H.A. Milman and E.K. Weisburger, Eds.), pp. 345-357. Noyes Publications, Park Ridge, NJ.

Boorman, G.A., Banas, D.A., Eustis, S.L., and Haseman, J.K. (1987). Proliferative exocrine pancreatic lesions in rats. The effect of sample size on the incidence of lesions. *Toxicol. Pathol.* 15, 451-456.

Brisson, G.J. (1981). Lipids in Human Nutrition: An Appraisal of Some Dietary Concepts, pp. 1-13. Jack K. Burgess, Inc., Englewood, NJ.

Burek, J.D., Nitschke, K.D., Bell, T.J., Wackerle, D.L., Childs, R.C., Beyer, J.E., Dittenber, D.A., Rampy, L.W., and McKenna, M.J. (1984). Methylene chloride: A two-year inhalation toxicity and oncogenicity study in rats and hamsters. Fundam. Appl. Toxicol. 4, 30-47.

Caspary, W.J., Lee, Y.J., Poulton, S., Myhr, B.C., Mitchell, A.D., and Rudd, C.J. (1988). Evaluation of the L5178Y mouse lymphoma cell mutagenesis assay: Quality control guidelines and response categories. *Environ. Mol. Mutagen.* 12 (Suppl. 13), 19-36.

Chanez, M., Bois-Joyeux, B., Arnaud, M.J., and Peret, J. (1991). Metabolic effects in rats of a diet with a moderate level of medium-chain triglycerides. *J. Nutr.* 121, 585-594.

Code of Federal Regulations (CFR) 21, Part 58.

Cohen, L.A., and Thompson, D.O. (1987). The influence of dietary medium chain triglycerides on rat mammary tumor development. *Lipids* 22, 455-461.

Cox, D.R. (1972). Regression models and life-tables. J. R. Stat. Soc. B34, 187-220. Crawford, B.D. (1985). Perspectives on the somatic mutation model of carcinogenesis. In Advances in Modern Environmental Toxicology: Mechanisms and Toxicity of Chemical Carcinogens and Mutagens. (M.A. Mehlman, W.G. Flamm, and R.J. Lorentzen, Eds.), pp. 13-59. Princeton Scientific Publishing Co., Inc., Princeton, NJ.

Dinse, G.E., and Haseman, J.K. (1986). Logistic regression analysis of incidental-tumor data from animal carcinogenicity experiments. *Fundam. Appl. Toxicol.* **6**, 44-52.

Dinse, G.E., and Lagakos, S.W. (1983). Regression analysis of tumour prevalence data. *Appl. Statist.* 32, 236-248.

Donato, K., and Hegsted, D.M. (1985). Efficiency of utilization of various sources of energy for growth. *Proc. Natl. Acad. Sci.* **82**, 4866-4870.

Douglas, B.R., Woutersen, R.A., Jansen, J.B.M.J., de Jong, A.J.L., Rovati, L.C., and Lamers, C.B.H.W. (1989). Influence of cholecystokinin antagonist on the effects of cholecystokinin and bombesin on azaserine-induced lesions in rat pancreas. *Gastroenterology* **96**, 462-469.

Douglas, B.R., Jansen, J.B.M.J., de Jong, A.J.L., and Lamers, C.B.H.W. (1990). Effect of various triglycerides on plasma cholecystokinin levels in rats. *J. Nutr.* 120, 686-690.

Dunn, O.J. (1964). Multiple comparisons using rank sums. *Technometrics* 6, 241-252.

Dunnett, C.W. (1955). A multiple comparison procedure for comparing several treatments with a control. *J. Am. Stat. Assoc.* **50**, 1096-1121.

Dupont, J., White, P.J., Carpenter, M.P., Schaefer, E.J., Meydani, S.N., Elson, C.E., Woods, M., and Gorbach, S.L. (1990). Food uses and health effects of corn oil. *J. Am. Coll. Nutr.* 9, 438-470.

El-Ela, S.H.A., Prasse, K.W., Carroll, R., and Bunce, O.R. (1987). Effects of dietary primrose oil on mammary tumorigenesis induced by 7,12-dimethylbenz(a)anthracene. *Lipids* 22, 1041-1044.

Eustis, S.L., and Boorman, G.A. (1985). Proliferative lesions of the exocrine pancreas: Relationship to corn oil gavage in the National Toxicology Program. *JNCI* 75, 1067-1073.

Eustis, S.L., Boorman, G.A., and Hayashi, Y. (1990). Exocrine pancreas. In *Pathology of the Fischer Rat:* Reference and Atlas (G.A. Boorman, S.L. Eustis, M.R. Elwell, C.A. Montgomery, Jr., and W.F. MacKenzie, Eds.), pp. 95-108. Academic Press, Inc., San Diego, CA.

Galloway, S.M., Armstrong, M.J., Reuben, C., Colman, S., Brown, B., Cannon, C., Bloom, A.D., Nakamura, F., Ahmed, M., Duk, S., Rimpo, J., Margolin, B.H., Resnick, M.A., Anderson, B., and Zeiger, E. (1987). Chromosome aberrations and sister chromatid exchanges in Chinese hamster ovary cells: Evaluations of 108 chemicals. *Environ. Mol. Mutagen.* 10 (Suppl. 10), 1-175.

Gart, J.J., Chu, K.C., and Tarone, R.E. (1979). Statistical issues in interpretation of chronic bioassay tests for carcinogenicity. *J. Natl. Cancer Inst.* **62**, 957-974.

Geliebter, A., Torbay, N., Bracco, E.F., Hashim, S.A., and Van Itallie, T.B. (1983). Overfeeding with medium-chain triglyceride diet results in diminished deposition of fat. *Am. J. Clin. Nutr.* 37, 1-4.

Giovannucci, E., Stampfer, M.J., Colditz, G., Rimm, E.B., and Willett, W.C. (1992). Relationship of diet to risk of colorectal adenoma in men. *J. Natl. Cancer Inst.* **84**, 91-98.

Greenberger, N.J., and Skillman, T.G. (1969). Medium-chain triglycerides: Physiologic considerations and clinical implications. *N. Engl. J. Med.* **280**, 1045-1058.

Grünewald, K., Lyons, J., Fröhlich, A., Feichtinger, H., Weger, R.A., Schwab, G., Janssen, J.W.G., and Bartram, C.R. (1989). High frequency of Ki-ras codon 12 mutations in pancreatic adenocarcinomas. *Int. J. Cancer* 43, 1037-1041.

Harkins, R.W., and Sarett, H.P. (1968). Medium-chain triglycerides. *JAMA* 203, 110-112.

Haseman, J.K. (1984). Statistical issues in the design, analysis and interpretation of animal carcinogenicity studies. *Environ. Health Perspect.* 58, 385-392.

Haseman, J.K., and Rao, G.N. (1992). Effects of corn oil, time-related changes, and inter-laboratory variability on tumor occurrence in control Fischer 344 (F344/N) rats. *Toxicol. Pathol.* 20, 52-60.

Haseman, J.K., Huff, J., and Boorman, G.A. (1984). Use of historical control data in carcinogenicity studies in rodents. *Toxicol. Pathol.* 12, 126-135.

Haseman, J.K., Huff, J.E., Rao, G.N., Arnold, J.E., Boorman, G.A., and McConnell, E.E. (1985). Neoplasms observed in untreated and corn oil gavage control groups of F344/N rats and (C57BL/6N  $\times$  C3H/HeN)F<sub>1</sub> (B6C3F<sub>1</sub>) mice. *JNCI* 75, 975-984.

Hollander, M., and Wolfe, D.A. (1973). Nonparametric Statistical Methods, pp. 120-123. John Wiley and Sons, New York.

Ikeda, I., Tomari, Y., Sugano, M., Watanabe, S., and Nagata, J. (1991). Lymphatic absorption of structured glycerolipids containing medium-chain fatty acids and linoleic acid, and their effect on cholesterol absorption in rats. *Lipids* 26, 369-373.

Ingebretsen, W.R., Jr., and Wagle, S.R. (1974). Studies on the effects of tricaprylin on gluconeogenesis and ketogenesis in isolated perfused liver. *Proc. Soc. Exp. Biol. Med.* 147, 578-580.

Johnson, R.C., Young, S.K., Cotter, R., Lin, L., and Rowe, W.B. (1990). Medium-chain-triglyceride lipid emulsion: Metabolism and tissue distribution. *Am. J. Clin. Nutr.* 52, 502-508.

Jonckheere, A.R. (1954). A distribution-free k-sample test against ordered alternatives. Biometrika 41, 133-145.

Kaplan, E.L., and Meier, P. (1958). Nonparametric estimation from incomplete observations. *J. Am. Stat. Assoc.* 53, 457-481.

Katz, E.B., and Boylan, E.S. (1989). Effect of the quality of dietary fat on tumor growth and metastasis from a rat mammary adenocarcinoma. *Nutr. Cancer* 12, 343-350.

Keith, L.H., and Walters, D.B. (1992). The National Toxicology Program Chemical Data Compendium. II. Chemical and Physical Properties. Lewis Publishers, Ann Arbor, MI.

Kensese, S.M., Teng, J.I., and Smith, L.L. (1989). Mutagenic lipid peroxides from edible oils. *Teratogenesis Carcinog. Mutagen.* 9, 133-145.

Kushi, L.H., Sellers, T.A., Potter, J.D., Nelson, C.L., Munger, R.G., Kaye, S.A., and Folsom, A.R. (1992). Dietary fat and postmenopausal breast cancer. *J. Natl. Cancer Inst.* 84, 1092-1099.

Lands, W.E.M., Morris, A., and Libelt, B. (1990). Quantitative effects of dietary polyunsaturated fats on the composition of fatty acids in rat tissues. *Lipids* 25, 505-516.

Lasekan, J.B., Clayton, M.K., Gendron-Fitzpatrick, A., and Ney, D.M. (1990). Dietary olive and safflower oils in promotion of DMBA-induced mammary tumorigenesis in rats. *Nutr. Cancer* 13, 153-163.

Lhoste, E.F., Roebuck, B.D., Brinck-Johnsen, T., and Longnecker, D.S. (1987). Effect of castration and hormone replacement on azaserine-induced pancreatic carcinogenesis in male and female Fischer rats. *Carcinogenesis* 8, 699-703.

Locniskar, M., Belury, M.A., Cumberland, A.G., Patrick, K.E., and Fischer, S.M. (1991). The effect of the level of dietary corn oil on mouse skin carcinogenesis. *Nutr. Cancer* 16, 1-11.

Longnecker, D. (1990). Experimental pancreatic cancer: Role of species, sex and diet [in French, English summary]. *Bull. Cancer* 77, 27-37.

Longnecker, D.S., Roebuck, B.D., Curphey, T.J., Lhoste, E., Coon, C.I., and MacMillan, D. (1986). Effects of corn oil and benzyl acetate on number and size of azaserine-induced foci in the pancreas of LEW and F344 rats. *Environ. Health Perspect.* 68, 197-201.

Longnecker, D.S., Pettengill, O.S., Davis, B.H., Schaeffer, B.K., Zurlo, J., Hong, H.L., and Kuhlmann, E.T. (1991). Characterization of preneoplastic and neoplastic lesions in the rat pancreas. *Am. J. Pathol.* 138, 333-340.

McConnell, E.E., Solleveld, H.A., Swenberg, J.A., and Boorman, G.A. (1986). Guidelines for combining neoplasms for evaluation of rodent carcinogenesis studies. *JNCI* 76, 283-289.

McKnight, B., and Crowley, J. (1984). Tests for differences in tumor incidence based on animal carcinogenesis experiments. J. Am. Stat. Assoc. 79, 639-648.

Maronpot, R.R., and Boorman, G.A. (1982). Interpretation of rodent hepatocellular proliferative alterations and hepatocellular tumors in chemical safety assessment. *Toxicol. Pathol.* 10, 71-80.

Mead, J.F., Alfin-Slater, R.B., Howton, D.R., and Popják, G. (1986). *Lipids: Chemistry, Biochemistry, and Nutrition*. Plenum Press, New York.

The Merck Index (1983). 10th ed. (M. Windholz, Ed.), Merck and Company, Rahway, NJ.

Miller, J.A., and Miller, E.C. (1977). Ultimate chemical carcinogens as reactive mutagenic electrophiles. In *Origins of Human Cancer* (H.H. Hiatt, J.D. Watson, and J.A. Winsten, Eds.), pp. 605-627. Cold Spring Harbor Laboratory, Cold Spring Harbor, NY.

Montgomery, C.A., Jr., and Seely, J.C. (1990). Kidney. In *Pathology of the Fischer Rat: Reference and Atlas* (G.A. Boorman, S.L. Eustis, M.R. Elwell, C.A. Montgomery, Jr., and W.F. MacKenzie, Eds.), pp. 127-154. Academic Press, Inc., San Diego, CA.

Myhr, B., McGregor, D., Bowers, L., Riach, C., Brown, A.G., Edwards, I., McBride, D., Martin, R., and Caspary, W.J. (1990). L5178Y mouse lymphoma cell mutation assay results with 41 compounds. *Environ. Mol. Mutagen.* 16 (Suppl. 18), 138-167.

National Cancer Institute (NCI) (1976). Guidelines for Carcinogen Bioassay in Small Rodents. Technical Report Series No. 1. NIH Publication No. 76-801. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, Bethesda, MD.

National Institutes of Health (NIH) (1978). Open Formula Rat and Mouse Ration (NIH-07). Specification NIH-11-1335. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, Bethesda, MD.

National Research Council (NRC) (1966). Biological Energy Relationships and Glossary of Energy Terms. National Academy of Sciences, Washington, DC.

National Toxicology Program (NTP) (1986a). Toxicology and Carcinogenesis Studies of Dichloromethane (Methylene Chloride) (CAS No. 75-09-2) in F344/N Rats and B6C3F<sub>1</sub> Mice (Inhalation Studies). NTP TR No. 306. NIH Publication No. 86-2562. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC.

National Toxicology Program (NTP) (1986b). Toxicology and Carcinogenesis Studies of Benzyl Acetate (CAS No. 140-11-4) in F344/N Rats and B6C3F<sub>1</sub> Mice (Gavage Studies). Technical Report Series No. 250. NIH Publication No. 86-2506. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC.

National Toxicology Program (NTP) (1993). Toxicology and Carcinogenesis Studies of Benzyl Acetate (CAS No. 140-11-4) in F344/N Rats and B6C3F<sub>1</sub> Mice (Feed Studies). NTP TR No. 431. NIH Publication No. 93-3162. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC.

Nelson, R., and Holian, O. (1991). Effects of dietary fish oil and corn oil on protein kinase C distribution in the rat colon with and without 1,2-dimethylhydrazine treatment and in rat colonic adenocarcinoma. *Anticancer Res.* 11, 157-160.

O'Connor, T.P., Roebuck, B.D., Peterson, F.J., Lokesh, B., Kinsella, J.E., and Campbell, T.C. (1989). Effect of dietary omega-3 and omega-6 fatty acids on development of azaserine-induced preneoplastic lesions in rat pancreas. *J. Natl. Cancer Inst.* 81, 858-863.

Perino, G., Conti, B., Ciliberti, A., and Maltoni, C. (1988). Incidence of pancreatic tumors and tumor precursors in Sprague-Dawley rats after administration of olive oil. *Ann. N. Y. Acad. Sci.* **534**, 604-617.

Rao, G.N., Piegorsch, W.W., and Haseman, J.K. (1987). Influence of body weight on the incidence of spontaneous tumors in rats and mice of long-term studies. *Am. J. Clin. Nutr.* 45, 252-260.

Reddy, B.S., and Sugie, S. (1988). Effect of different levels of omega-3 and omega-6 fatty acids on azoxymethane-induced colon carcinogenesis in F344 rats. *Cancer Res.* 48, 6642-6647.

Reddy, B.S., Burill, C., and Rigotty, J. (1991). Effect of diets high in  $\omega$ -3 and  $\omega$ -6 fatty acids on initiation and postinitiation stages of colon carcinogenesis. *Cancer Res.* 51, 487-491.

Richardson, S., Gerber, M., and Cenée, S. (1991). The role of fat, animal protein and some vitamin consumption in breast cancer: A case control study in Southern France. *Int. J. Cancer* 48, 1-9.

Roebuck, B.D. (1986). Effects of high levels of dietary fats on the growth of azaserine-induced foci in the rat pancreas. *Lipids* 21, 281-284.

Roebuck, B.D., Yager, J.D., Jr., Longnecker, D.S., and Wilpone, S.A. (1981). Promotion by unsaturated fat of azaserine-induced pancreatic carcinogenesis in the rat. *Cancer Res.* 41, 3961-3966.

Roebuck, B.D., Kaplita, P.V., Edwards, B.R., and Praissman, M. (1987). Effects of dietary fats and soybean protein on azaserine-induced pancreatic carcinogenesis and plasma cholecystokinin in the rat. *Cancer Res.* 47, 1333-1338.

Sadtler Standard Spectra. IR No. 1011, NMR No. 6401M (dichloromethane); IR No. 42385, NMR No. 14226M (tricaprylin). Sadtler Research Laboratories, Philadelphia.

Schaeffer, B.K., Zurlo, J., and Longnecker, D.S. (1990). Activation of c-Ki-ras not detectable in adenomas or adenocarcinomas arising in rat pancreas. *Mol. Carcinog.* 3, 165-170.

Serota, D.G., Thakur, A.K., Ulland, B.M., Kirschman, J.C., Brown, N.M., Coots, R.H., and Morgareidge, K. (1986). A two-year drinking-water study of dichloromethane in rodents. I. Rats. *Food Chem. Toxicol.* 24, 951-958.

Shirley, E. (1977). A non-parametric equivalent of Williams' test for contrasting increasing dose levels of a treatment. *Biometrics* 33, 386-389.

Silverman, J.A., Kuhlmann, E.T., Zurlo, J., Yager, J.D., and Longnecker, D.S. (1990). Expression of c-myc, c-raf-1, and c-Ki-ras in azaserine-induced pancreatic carcinomas and growing pancreas in rats. *Mol. Carcinog.* 3, 379-386.

Solomon, T.E., Morisset, J., Wood, J.G., and Bussjaeger, L.J. (1987). Additive interaction of pentagastrin and secretin on pancreatic growth in rats. *Gastroenterology* 92, 429-435.

Stadler, J., Stern, H.S., Yeung, K.S., McGuire, V., Furrer, R., Marcon, N., and Bruce, W.R. (1988). Effect of high fat consumption on cell proliferation activity of colorectal mucosa and on soluble faecal bile acids. *Gut* 29, 1326-1331.

Straus, D.S. (1981). Somatic mutation, cellular differentiation, and cancer causation. *JNCI* 67, 233-241.

Sumi, C., Longnecker, D.S., Roebuck, B.D., and Brinck-Johnsen, T. (1989). Inhibitory effects of estrogen and castration on the early stage of pancreatic carcinogenesis in Fischer rats treated with azaserine. *Cancer Res.* 49, 2332-2336.

Swenson, E.S., Selleck, K.M., Babayan, V.K., Blackburn, G.L., and Bistrian, B.R. (1991). Persistence of metabolic effects after long-term oral feeding of a structured triglyceride derived from medium-chain triglyceride and fish oil in burned and normal rats. *Metabolism* 40, 484-490.

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

Tennant, R.W., Margolin, B.H., Shelby, M.D., Zeiger, E., Haseman, J.K., Spalding, J., Caspary, W., Resnick, M., Stasiewicz, S., Anderson, B., and Minor, R. (1987). Prediction of chemical carcinogenicity in rodents from *in vitro* genetic toxicity assays. *Science* 236, 933-941.

Vergroesen, A.J. (1989). Introduction. In *The Role of Fats in Human Nutrition* (A.J. Vergroesen and M. Crawford, Eds.), 2nd ed., pp. 1-44. Academic Press, London.

## APPENDIX A SUMMARY OF LESIONS IN MALE RATS IN THE 2-YEAR GAVAGE STUDY OF CORN OIL

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TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Gavage Study of Corn Oila

	Untreated Control	10 mL/kg Saline	2.5 mL/kg	5 mL/kg	10 mL/kg
Disposition Summary					
Animals initially in study	50	50	50	50	50
Early deaths					
Moribund	16	14	9 .	6	4
Natural deaths	8	4	8	. 6	6
Survivors	, ,	₹	J		,
Died last week of study	1		,		
Terminal sacrifice		22	22	20	40
Terminal sacrifice	25	32	33	38	40
Animals examined microscopically	50	50	50	50	50
		· · · · · · · · · · · · · · · · · · ·			
Alimentary System	(10)	440			
Intestine large, colon	(49)	(49)	(46)	(49)	(48)
Intestine large, cecum	(46)	(49)	(45)	(48)	(46)
Intestine small, duodenum	(48)	(49)	(47)	(50)	(48)
Intestine small, jejunum	(44)	(49)	(45)	(48)	(47)
Muscularis, leiomyosarcoma		` '			1 (2%)
Intestine small, ileum Adenocarcinoma	(46)	(49)	(45) 1 (2%)	(48)	(47)
Liver	(50)	(50)	(50)	(50)	(50)
Hepatocellular adenoma	4 (8%)	(50)	2 (4%)	(30)	(50)
Hepatocellular adenoma, multiple	4 (0/0)	à · .	1 (2%)		
Histiocytic sarcoma	4.45				1 (2%)
Mesentery	(6)	(7)	(8)	(4)	(8)
Pancreas	(50)	(50)	(47)	(50)	(50)
Mixed tumor benign	*	1 (2%)	*		•
Acinus, adenoma	1 (2%)	1 (2%)	6 (13%)	3 (6%)	11 (22%)
Acinus, adenoma, multiple Acinus, carcinoma			2 (4%)	7 (14%) 1 (2%)	12 (24%)
Pharynx	(1)		(1)	• • • •	
Palate, squamous cell papilloma	` '		ì (100%)		
Salivary glands	(50)	(50)	(50)	(50)	(49)
Stomach, forestomach	(50)	(49)	(50)	(50)	(50)
	(50)	(42)	(30)		(50)
Squamous cell papilloma	(50)	(EO)	(50)	1 (2%)	(40)
Stomach, glandular	(50)	(50)	(50)	(50)	(48)
Leiomyosarcoma		'	(0)	1 (2%)	(0)
Tongue Squamous cell papilloma		(3)	(2)	ta e e	(3) 2 (67%)
	· · · · · · · · · · · · · · · · · · ·		v 4	<del></del>	
Cardiovascular System		:			ا د د د د د د د د د د د د د د د د د د د
Heart	(50)	(50)	(50)	(50)	(50)
Carcinoma, metastatic, Zymbal's gland			ŧ .		1 (2%)
Endocrine System		·····			
Adrenal cortex	(E0)	(50)	(50)	(50)	(50)
AGREDAL CONTRY	(50)	(50)	(50)	(50)	(50)

TABLE A1 Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Gavage Study of Corn Oil (continued)

	Untreated Control	10 mL/kg Saline	2.5 mL/kg	5 mL/kg	10 mL/kg
Endocrine System (continued)					
Adrenal medulla	(49)	(49)	(50)	(50)	(50)
Ganglioneuroma			1 (2%)		
Pheochromocytoma malignant	2 (4%)	1 (2%)	1 (2%) 1 (2%)	1 (2%)	2 (4%)
Pheochromocytoma complex	19 (27%)	13 (27%)	15 (30%)	3 (6%)	7 (14%)
Pheochromocytoma benign Bilateral, pheochromocytoma malignant	18 (37%) 1 (2%)	13 (2170)	13 (30%)	3 (0%)	7 (1470)
Bilateral, pheochromocytoma benign	2 (4%)	2 (4%)	4 (8%)	1 (2%)	
Islets, pancreatic	(50)	(49)	(47)	(50)	(50)
Adenoma	9 (18%)	5 (10%)	3 (6%)	4 (8%)	7 (14%)
Parathyroid gland	(44)	(47)	(49)	(40)	(45)
Pituitary gland	(50)	(49)	(50)	(49)	(50)
Carcinoma, metastatic, Zymbal's gland	( <del>-</del> - /	()	<b>V-</b> - <b>/</b>	<b>V</b> /	1 (2%)
Pars distalis, adenoma	5 (10%)	6 (12%)	10 (20%)	6 (12%)	7 (14%)
Pars intermedia, adenoma	1 (2%)		• •	` '	` ,
Thyroid gland	(50)	(49)	(49)	(49)	(49)
Bilateral, C-cell, adenoma	, ,		, ,	1 (2%)	2 (4%)
C-cell, adenoma	4 (8%)	3 (6%)	5 (10%)	3 (6%)	8 (16%)
C-cell, carcinoma	1 (2%)		1 (2%)		1 (2%)
Follicular cell, adenoma		2 (4%)			
Follicular cell, carcinoma					1 (2%)
None		• •			
<del></del>				·	
None  Genital System  Ductus deferens		· · · · · · · · · · · · · · · · · · ·	(1)	·	
Genital System	(50)	(50)	(1)	(50)	(48)
Genital System Ductus deferens	(50) (50)	(50) (50)	(1) (50) (50)	(50) (50)	(48) (48)
Genital System Ductus deferens Epididymis	(50)	(50)	(50)		(48)
Genital System Ductus deferens Epididymis Preputial gland			(50) (50) 2 (4%)	(50)	
Genital System  Ductus deferens  Epididymis  Preputial gland  Adenoma	(50)	(50)	(50) (50)	(50) 3 (6%)	(48) 3 (6%) (48)
Genital System  Ductus deferens  Epididymis  Preputial gland  Adenoma  Bilateral, adenoma	(50) 6 (12%)	(50) 8 (16%)	(50) (50) 2 (4%) 1 (2%)	(50) 3 (6%) 1 (2%)	(48) 3 (6%) (48)
Genital System Ductus deferens Epididymis Preputial gland Adenoma Bilateral, adenoma Prostate	(50) 6 (12%)	(50) 8 (16%)	(50) (50) 2 (4%) 1 (2%)	(50) 3 (6%) 1 (2%) (50)	(48) 3 (6%) (48) 2 (4%) (48)
Genital System Ductus deferens Epididymis Preputial gland Adenoma Bilateral, adenoma Prostate Adenoma Seminal vesicle Testes	(50) 6 (12%) (50) (50) (50)	(50) 8 (16%) (49)	(50) (50) 2 (4%) 1 (2%) (50)	(50) 3 (6%) 1 (2%) (50)	(48) 3 (6%) (48) 2 (4%)
Genital System Ductus deferens Epididymis Preputial gland Adenoma Bilateral, adenoma Prostate Adenoma Seminal vesicle Testes Bilateral, interstitial cell, adenoma	(50) 6 (12%) (50) (50) (50) 40 (80%)	(50) 8 (16%) (49) (49) (50) 39 (78%)	(50) (50) 2 (4%) 1 (2%) (50) (49) (50) 43 (86%)	(50) 3 (6%) 1 (2%) (50) (50) (50) 41 (82%)	(48) 3 (6%) (48) 2 (4%) (48) (49) 39 (80%)
Genital System Ductus deferens Epididymis Preputial gland Adenoma Bilateral, adenoma Prostate Adenoma Seminal vesicle Testes	(50) 6 (12%) (50) (50) (50)	(50) 8 (16%) (49) (49) (50)	(50) (50) 2 (4%) 1 (2%) (50) (49) (50)	(50) 3 (6%) 1 (2%) (50) (50) (50)	(48) 3 (6%) (48) 2 (4%) (48) (49)
Genital System Ductus deferens Epididymis Preputial gland Adenoma Bilateral, adenoma Prostate Adenoma Seminal vesicle Testes Bilateral, interstitial cell, adenoma Interstitial cell, adenoma	(50) 6 (12%) (50) (50) (50) 40 (80%)	(50) 8 (16%) (49) (49) (50) 39 (78%)	(50) (50) 2 (4%) 1 (2%) (50) (49) (50) 43 (86%)	(50) 3 (6%) 1 (2%) (50) (50) (50) 41 (82%)	(48) 3 (6%) (48) 2 (4%) (48) (49) 39 (80%)
Genital System Ductus deferens Epididymis Preputial gland Adenoma Bilateral, adenoma Prostate Adenoma Seminal vesicle Testes Bilateral, interstitial cell, adenoma Interstitial cell, adenoma	(50) 6 (12%) (50) (50) (50) 40 (80%) 8 (16%)	(50) 8 (16%) (49) (49) (50) 39 (78%) 8 (16%)	(50) (50) 2 (4%) 1 (2%) (50) (49) (50) 43 (86%) 3 (6%)	(50) 3 (6%) 1 (2%) (50) (50) (50) 41 (82%) 6 (12%)	(48) 3 (6%) (48) 2 (4%) (48) (49) 39 (80%)
Genital System Ductus deferens Epididymis Preputial gland Adenoma Bilateral, adenoma Prostate Adenoma Seminal vesicle Testes Bilateral, interstitial cell, adenoma Interstitial cell, adenoma	(50) 6 (12%) (50) (50) (50) 40 (80%) 8 (16%)	(50) 8 (16%) (49) (49) (50) 39 (78%) 8 (16%)	(50) (50) 2 (4%) 1 (2%) (50) (49) (50) 43 (86%) 3 (6%)	(50) 3 (6%) 1 (2%) (50) (50) (50) 41 (82%) 6 (12%)	(48) 3 (6%) (48) 2 (4%) (48) (49) 39 (80%) 9 (18%)
Genital System  Ductus deferens Epididymis Preputial gland Adenoma Bilateral, adenoma Prostate Adenoma Seminal vesicle Testes Bilateral, interstitial cell, adenoma Interstitial cell, adenoma  Hematopoietic System Blood Bone marrow	(50) 6 (12%) (50) (50) (50) 40 (80%) 8 (16%)	(50) 8 (16%) (49) (49) (50) 39 (78%) 8 (16%) (9) (50)	(50) (50) 2 (4%) 1 (2%) (50) (49) (50) 43 (86%) 3 (6%)	(50) 3 (6%) 1 (2%) (50) (50) (50) 41 (82%) 6 (12%) (3) (50)	(48) 3 (6%) (48) 2 (4%) (48) (49) 39 (80%) 9 (18%)
Genital System Ductus deferens Epididymis Preputial gland Adenoma Bilateral, adenoma Prostate Adenoma Seminal vesicle Testes Bilateral, interstitial cell, adenoma Interstitial cell, adenoma Hematopoietic System Blood Bone marrow Lymph node	(50) 6 (12%) (50) (50) (50) 40 (80%) 8 (16%) (8) (50) (28)	(50) 8 (16%) (49) (50) 39 (78%) 8 (16%) (9) (50) (22)	(50) (50) 2 (4%) 1 (2%) (50) (49) (50) 43 (86%) 3 (6%)	(50) 3 (6%) 1 (2%) (50) (50) (50) 41 (82%) 6 (12%) (3) (50) (13)	(48) 3 (6%) (48) 2 (4%) (48) (49) 39 (80%) 9 (18%)
Genital System Ductus deferens Epididymis Preputial gland Adenoma Bilateral, adenoma Prostate Adenoma Seminal vesicle Testes Bilateral, interstitial cell, adenoma Interstitial cell, adenoma  Hematopoietic System Blood Bone marrow Lymph node Lymph node, mandibular	(50) 6 (12%) (50) (50) (50) 40 (80%) 8 (16%) (8) (50) (28) (50)	(50) 8 (16%) (49) (50) 39 (78%) 8 (16%) (9) (50) (22) (50)	(50) (50) 2 (4%) 1 (2%) (50) (49) (50) 43 (86%) 3 (6%) (4) (50) (15) (49)	(50) 3 (6%) 1 (2%) (50) (50) (50) 41 (82%) 6 (12%) (3) (50) (13) (50)	(48) 3 (6%) (48) 2 (4%) (48) (49) 39 (80%) 9 (18%) (50) (8) (48)
Genital System Ductus deferens Epididymis Preputial gland Adenoma Bilateral, adenoma Prostate Adenoma Seminal vesicle Testes Bilateral, interstitial cell, adenoma Interstitial cell, adenoma  Hematopoietic System Blood Bone marrow Lymph node Lymph node, mandibular Lymph node, mesenteric	(50) 6 (12%) (50) (50) (50) 40 (80%) 8 (16%) (8) (50) (28) (50) (50)	(50) 8 (16%) (49) (50) 39 (78%) 8 (16%) (9) (50) (22) (50) (50)	(50) (50) 2 (4%) 1 (2%) (50) (49) (50) 43 (86%) 3 (6%) (4) (50) (15) (49) (50)	(50) 3 (6%) 1 (2%) (50) (50) (50) 41 (82%) 6 (12%) (3) (50) (13) (50) (50)	(48) 3 (6%) (48) 2 (4%) (48) (49) 39 (80%) 9 (18%) (50) (8) (48) (49)
Genital System Ductus deferens Epididymis Preputial gland Adenoma Bilateral, adenoma Prostate Adenoma Seminal vesicle Testes Bilateral, interstitial cell, adenoma Interstitial cell, adenoma  Hematopoietic System Blood Bone marrow Lymph node Lymph node, mandibular Lymph node, mesenteric Spleen	(50) 6 (12%) (50) (50) (50) 40 (80%) 8 (16%) (8) (50) (28) (50)	(50) 8 (16%) (49) (50) 39 (78%) 8 (16%) (9) (50) (22) (50)	(50) (50) 2 (4%) 1 (2%) (50) (49) (50) 43 (86%) 3 (6%) (4) (50) (15) (49) (50) (49)	(50) 3 (6%) 1 (2%) (50) (50) (50) 41 (82%) 6 (12%) (3) (50) (13) (50)	(48) 3 (6%) (48) 2 (4%) (48) (49) 39 (80%) 9 (18%) (50) (8) (48)
Genital System Ductus deferens Epididymis Preputial gland Adenoma Bilateral, adenoma Prostate Adenoma Seminal vesicle Testes Bilateral, interstitial cell, adenoma Interstitial cell, adenoma  Hematopoietic System Blood Bone marrow Lymph node Lymph node, mandibular Lymph node, mesenteric Spleen Hemangioma	(50) 6 (12%) (50) (50) (50) 40 (80%) 8 (16%) (8) (50) (28) (50) (50)	(50) 8 (16%) (49) (50) 39 (78%) 8 (16%) (9) (50) (22) (50) (50)	(50) (50) 2 (4%) 1 (2%) (50) (49) (50) 43 (86%) 3 (6%) (4) (50) (15) (49) (50)	(50) 3 (6%) 1 (2%) (50) (50) (50) 41 (82%) 6 (12%) (3) (50) (13) (50) (50)	(48) 3 (6%) (48) 2 (4%) (48) (49) 39 (80%) 9 (18%) (50) (8) (48) (49) (49)
Genital System Ductus deferens Epididymis Preputial gland Adenoma Bilateral, adenoma Prostate Adenoma Seminal vesicle Testes Bilateral, interstitial cell, adenoma Interstitial cell, adenoma  Hematopoietic System Blood Bone marrow Lymph node Lymph node, mandibular Lymph node, mesenteric Spleen	(50) 6 (12%) (50) (50) (50) 40 (80%) 8 (16%) (8) (50) (28) (50) (50)	(50) 8 (16%) (49) (50) 39 (78%) 8 (16%) (9) (50) (22) (50) (50)	(50) (50) 2 (4%) 1 (2%) (50) (49) (50) 43 (86%) 3 (6%) (4) (50) (15) (49) (50) (49)	(50) 3 (6%) 1 (2%) (50) (50) (50) 41 (82%) 6 (12%) (3) (50) (13) (50) (50)	(48) 3 (6%) (48) 2 (4%) (48) (49) 39 (80%) 9 (18%) (50) (8) (48) (49)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Gavage Study of Corn Oil (continued)

	Untreated Control	10 mL/kg Saline	2.5 mL/kg	5 mL/kg	10 mL/kg
Integumentary System					
Mammary gland	(31)	(42)	(39)	(39)	(40)
Fibroadenóma	<b>4</b> (13%)	<b>2</b> (5%)	1 (3%)	ì (3%)	Ì (8%)
Skin	(50)	(50)	(50)	(50)	(50)
Basal cell adenoma					1 (2%)
Basal cell carcinoma	1 (2%)				
Keratoacanthoma	1 (2%)		1 (2%)		1 (2%)
Squamous cell carcinoma	2 (4%)	1 (2%)			
Squamous cell papilloma	1 (2%)		1 (2%)	5 (10%)	1 (2%)
Sebaceous gland, adenoma		1 (2%)			
Subcutaneous tissue, fibroma	1 (2%)	3 (6%)	1 (2%)	1 (2%)	5 (10%)
Subcutaneous tissue, hemangioma				1 (2%)	
Musculoskeletal System					
Bone	(50)	(50)	(50)	(50)	(50)
Osteosarcoma	()	()	1 (2%)	()	(-7)
Skeletal muscle	(50)	(50)	(50)	(50)	(50)
				· · · · · · · · · · · · · · · · · · ·	·
Nervous System			•		
Brain	(50)	(49)	(50)	(50)	(50)
Spinal cord			(1)	(1)	(1)
Astrocytoma malignant					1 (100%)
Respiratory System					
Lung	(49)	(49)	(50)	(49)	(49)
Alveolar/bronchiolar adenoma	1 (2%)	1 (2%)	(55)	1 (2%)	3 (6%)
Alveolar/bronchiolar carcinoma	1 (270)	1 (2%)	1 (2%)	1 (2%)	3 (0,0)
Carcinoma, metastatic, thyroid gland		1 (270)	1 (2%)	1 (270)	***
Carcinoma, metastatic, Zymbal's gland			- (=/-)		1 (2%)
Fibrosarcoma, metastatic, ear		1 (2%)			- (=,=,
Pheochromocytoma malignant,		- (~~)			
metastatic, adrenal medulla	1 (2%)				
Mediastinum, carcinoma, metastatic,	` '				
Zymbal's gland					1 (2%)
Nose	(50)	(50)	(50)	(49)	(49)
Caralal Carana Carata	<del>.</del>				
Special Senses System		(2)	(1)	: (2)	
Ear Fibrosarcoma		(2) 1 (50%)	(1)	(2)	
Fibrous histiocytoma Harderian gland		1 (50%)		(1)	
Carcinoma				1 (100%)	
Out Official		(2).		1 (10070)	(1)
Zvmhal's gland					
Zymbal's gland Adenoma		1 (50%)			(-)

TABLE A1 Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Gavage Study of Corn Oil (continued)

	Untreated Control	10 mL/kg Saline	2.5 mL/kg	5 mL/kg	10 mL/kg
Urinary System					
Kidney	(50)	(49)	(48)	(50)	(49)
Urinary bladder	(49)	(49)	(47)	(50)	(48)
Systemic Lesions					
Multiple organs <sup>b</sup> Histiocytic sarcoma Leukemia granulocytic	(50)	(50)	(50)	(50)	(50) 1 (2%)
Leukemia mononuclear	27 (54%)	20 (60%)	16 (22%)	11 (22%)	1 (2%)
Lymphoma malignant	1 (2%)	30 (60%)	16 (32%)	11 (22%)	7 (14%)
Mesothelioma malignant	2 (4%)	1 (2%)	1 (2%)	1 (2%)	3 (6%)
Neoplasm Summary	<del> </del>				
Total animals with primary neoplasms <sup>c</sup>	50	48	49	48	50
Total primary neoplasms	144	133	128	106	142
Total animals with benign neoplasms	50	48	49	48	50
Total benign neoplasms	107	96	105	89	123
Total animals with malignant neoplasms	33	31	21	16	16
Total malignant neoplasms	37	37	23	17	19
Total animals with metastatic neoplasms	3 8	2	3	1	3
Total metastatic neoplasms	ð	4	7	13	12
Total animals with malignant neoplasms of uncertain primary site			1		

Number of animals examined microscopically at site and number of animals with lesion Number of animals with any tissue examined microscopically Primary neoplasms: all neoplasms except metastatic neoplasms

Table A2	
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Corn Oil: United St	treated Control

			· ·	5	~	6	6	6	6	6	6	6	6	6 ·	6	5 . 6	6	6	6	6	7	7	7	7	Ź	7			-
umber of Days on Study			1			1							8		8				9		ó	ó		1		_			
umber of Days on Study			6	3	9	0	8								5				7	7	4	4	4	0	5				
		•	. 0	0	0	0	0	0	0	0	0	0	0	0	0	0 (	0	0	0	0	0	0	Ó	0	0	0	<del></del>		
arcass ID Number			· 1	. 3	3	2	2	4 :	0	2	1	3	5	1	0 :	2 3	3 4	0	3	4	0	1	3	0	4	1			
			0	9	1											3 4	1 4	3	3	3	8	8	7	5	5	7			
imentary System				-										-		_			-		-		-				_;		
Esophagus				_		_	_	_	_	M	_	_	_	_	_	<b>.</b> .			_	i	_	_	_	_	_		:		•
Intestine large, colon	•		+	· T	+		T .	<b>T</b>	T .	M A	<b>T</b>	T 1	T _	т·	T. _	T :	T 7	- T			<b>T</b>	<b>T</b>	<u> </u>		<b>T</b>	T	•		
Mesothelioma malignant, metastatic	,		_	т	_	т	Т	_	Τ.	^	_	Τ.	_	т :	т	Τ	7	· ·	7	+ }	Τ		_	т	_	T.,		,	
testes																										Х	,		
Intestine large, rectum			+	+	+	+	+	+	+	Α	+	+	+	+.	+ .	Α.	+ 4	+	+	Α	+	+	+	+	+	+.		21	
Intestine large, cecum			+	+	+	+	+	+	+	+	+	A	+	+:	+	A ·	+ 4	٠ +	+	Α	+	+	+	+	+	+			
Intestine small, duodenum			+	+	+	+	+	+	+	+	+:	Α	+	+	+	+ .	+ 4	٠ +	+	+	+	+	+	+	+	+			
Intestine small, jejunum			: +	+	+	+	+	+	+.	A.	+	Α	+.	+	+	A ·	+ 4	٠ +	+	Α	+	+	+,	+	Α	+			
Intestine small, ileum		;	+	+.	+	+	+	+	+,	A	+	A.	+	+	+ .	A ·	+ 4	+	+	+	+	+	+	+	; <b>+</b> .	+.			
Liver			+	+	+	+	+	+	+	+	+,	+	+	+.	+	+ -	+ -	+ +	+	+	+	+	+	+	+	+			٠,
Hepatocellular adenoma						X													X					Х		٠.			
Mesothelioma malignant, metastatic																					٠,							2:	
testes																				,						х			
Mesentery											+									+			+			+			
Mesothelioma malignant, metastatic																													
testes																					٠					X			
Pancreas			+	+	. +.	+	+.	+	+	+;	+	+	+	+	+.	+ .	+ -	· +	+	+	+	+	+	+	+	+			
Mesothelioma malignant, metastatic																													
testes																		•								X	٠.	•	
Acinus, adenoma																													;
Pharynx																											•		
Salivary glands			+	÷	. +	+	+	+	+	+	+	+	+	+	+	+ .	+ -	<b>+</b> +	+	+	+	+	+	+	+	+			
Stomach, forestomach			4	+	+	+	<u>.</u>	+	+	+	+	+	+	+	+	· ∔ ·	· + -	- +	+	+	+	+	<u>.</u>	+	+	+		٠.	
Stomach, glandular	ŧ		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+ -	+	+	+	+	+	.+	+	+	+			
ardiovascular System												_																	
Heart			+	+.	+	+	+	+	+	+	+	+	+	+	+	+ .	+ -	<b>-</b> +	+	+	+	+	+	+	+	+	.,		
														_		_													
ndocrine System																										•		• • • •	•
Adrenal cortex			+	+	+	+	+	+	+.	+	+	+	+	+	+	+	+ -	+ +	+	+	+	+	+	+	+	+		•	
Adrenal medulla			+	+	+	+	. +	+	+	+	+	+	+	+	+	+	+,-	+ +	+	+	+	+	+	+	+	#	٠.		
Pheochromocytoma malignant																		_							X				· .
Pheochromocytoma benign						Х	X			X						X	7	(		X		X	:			X			
Bilateral, pheochromocytoma maligr									X											•	•		٠.		L	-			
Bilateral, pheochromocytoma benigi	1											X										,		X			-		
Islets, pancreatic			+	+	+	+	+	+	+.	+	+	+	+	+	+	+	+ -	+ +	+		+	+	+	+	+	+.			; •
Adenoma										X									Х					_	X			. •	
Parathyroid gland			+	+	+	+	+	+	+,	+	+	+	+	+.	+	+ -	+ 1	<b>1</b> +	+	M	+	+	+	+	+:	+	1 3.		
Pituitary gland			+	٠+	. +	+	+	+	+	+	+	+	+	+	+.	+	+	+ +	+	+	+	+	+	+	+	+			. •
Pars distalis, adenoma								X												•				X				, .	
Pars intermedia, adenoma																							. ,						
Thyroid gland			+	+	+	+	+	+	+.	+	+	+	+	+	+ .	+	+ -	+ +	+	+	+	+	+	+	+	+.			
C-cell, adenoma								X													X								
									X																43	,			
C-cell, carcinoma																													

None

M: Missing tissue I: Insufficient tissue

X: Lesion present Blank: Not examined

<sup>+:</sup> Tissue examined microscopically

A: Autolysis precludes examination

TABLE A2

,	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
lumber of Days on Study	3	3	. 3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
amber of Buye on Stary	7	7	7	7	7	7	7	7	7	7	7			7				7	7	7	7	7	7	7	7	
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	Total
arcass ID Number	0	0	0	0	1	1	1	1	1	2	2	2	2	2	2	3	3	3	3	4	4	4	4	4	4	Tissues
· · · · · · · · · · · · · · · · · · ·	2	4			`1														8	1	2	6	7	8	9	Tumor
limentary System		-														<u> </u>	_						_			
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	٠+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Mesothelioma malignant, metastatic, testes																				٠,٠						1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	٠+	+	46
Intestine small, duodenum		i		i	. 🛓	i	i	·	Ţ	i	i	i	4	i	i	i	Ţ	i	i	_	į.	<u>.</u>	<u>.</u>	+	į.	48
	· · ·					_ T	.L	т "L				т Т	<u> </u>	Ι	<u> </u>	<b>T</b>	<u></u>	<u> </u>			_ T				Ţ	44
Intestine small, jejunum	· ·		•	7	•	Τ.	7	Τ.	Τ.	Τ.	Т.			T.	Τ.	T.	7			T.		T .			<b>.</b>	
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver Hepatocellular adenoma Mesothelioma malignant, metastatic,	+	+	+	+	• +	+	+	+ X	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50 4
testes																										1
Mesothelioma malignant, metastatic,											+														+	6
testes																										1
Pancreas Mesothelioma malignant, metastatic,	+	+	+	+	• +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
testes			٦,																							-1
Acinus, adenoma			X																							1
Pharynx																				+						1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	. +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	• +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System			-					_																		
Heart	+	+	+	+	• +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Indocrine System																										
Adrenal cortex	+	+	+	+	. +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulia	+	+	+	+	+	+	+	+		M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma malignant								X																		2
Pheochromocytoma benign						Х			X		Х	X				X		X	X		Х	X	X			18
Bilateral, pheochromocytoma malignant Bilateral, pheochromocytoma benign																						,				1 2
Islets, pancreatic	+	+	- +	+	- +	+	+	+	+	٠+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma	Х	X	X		X																		Х			9
Parathyroid gland	+						+	М	+	М	М	+	+	+	+	+	+	+	М	+	+	+			+	44
Pituitary gland	+								+		+			+	+	+	+	+	+						+	50
Pars distalis, adenoma	•	·	•	•	,	•		Х		•	•	•	•	٠	•	•	•	X		•	•	٠	•	•	•	5
Pars intermedia, adenoma							71																		х	1
Thyroid gland	+					<b>ا</b> ـــ	. д					ı		_ر		<u>ــــــــــــــــــــــــــــــــــــ</u>	ı	+	.1	ı,			,		+	50
		7	- 1	7	•						_	т	_	т	Ŧ	-	_	T	v	+	_	-	. +		+	
C-cell, adenoma																			X				X	•		4
C-cell, carcinoma																										. 1

Eye

TABLE A2 Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Corn Oil: Untreated Control (continued) 2 5 5 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 Number of Days on Study 1 2 6 1 1 2 3 3 5 7 8 8 8 8 8 8 9 990 0 0 1 1 3 6 3 9 0 8 0 5 8 1 8 1 3 5 7 8 8 1 7 7 4 Carcass ID Number 1 3 3 2 2 4 0 2 1 3 5 1 0 2 3 4 0 3 4 0 5 5 5 0 2 9 3 4 4 3 3 3 8 **Genital System Epididymis** Mesothelioma malignant, metastatic, testes Preputial gland Adenoma Prostate Seminal vesicle Testes + + + + Bilateral, interstitial cell, adenoma X X X XInterstitial cell, adenoma  $\mathbf{X} \mathbf{X}$  $\mathbf{X}$ Hematopoietic System Blood Bone marrow Lymph node Lymph node, mandibular Lymph node, mesenteric Spleen Thymus Epithelial cell, thymoma benign Integumentary System Mammary gland MM++ M + M M + M +Fibroadenoma Х Skin Basal cell carcinoma Keratoacanthoma Squamous cell carcinoma X Squamous cell papilloma Subcutaneous tissue, fibroma Х Musculoskeletal System Bone Skeletal muscle Mesothelioma malignant, metastatic,  $\mathbf{X}$ testes **Nervous System** Brain Respiratory System Lung Alveolar/bronchiolar adenoma Pheochromocytoma malignant, metastatic, adrenal medulla Nose Trachea **Special Senses System** 

Individual Animal Tumor Pathology of	1.2																										
	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	,	
Number of Days on Study	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	}	
	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		Total
Carcass ID Number	0	0	0				1		1	2	2	2	2	2		3	3	3	3	4	4	4	4	4			Tissues/
Carcass and isomoca	2														9					-		-		8	-		Tumors
_ <del></del>			_						_						_			_		_	_		_				
Genital System																											50
Epididymis  Mesothelioma malignant, metastatic,	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	- +		-	50
testes																											2
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	- +		+	50
Adenoma									X										X								6
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	. +		+	50
Seminal vesicle	· +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	- +	ـ ـ	+	50
Testes				+	+	+	+	÷	+	+	+	+	+	+	+	+	+	+	+		+	+	4		٠.	+	50
Bilateral, interstitial cell, adenoma	ż	Ý	v		x			Ÿ	Ÿ						x												40
Interstitial cell, adenoma	Λ.	Λ	^	Λ		_	^	^		_	X	^		^	^	_					^		21			` <b>`</b>	8
Hematopoietic System									.1																		8
Blood									+												+	+					
Bone marrow	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	- +	٠ -	+	50
Lymph node	+						+					+	+		+					+	+	+		4	-		28
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	- 4	٠ ٠	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	- 1	- 4	٠ ٠	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	- 4	- +		+	49
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	- 4	- 4	٠ ٠	+	48
Epithelial cell, thymoma benign																											1
Integumentary System												_	-			_			_				_				<del></del>
Mammary gland	_		. 4		м	[ +	4	4	+	+	м	4	_	м	M	+	+	+	4	+	M	ı av	<b>1</b> 4	_ 4	<b>⊢</b> 1	м	31
Fibroadenoma	'	•	•	•	141	٠.	•	•	•			•	,			•	'		x	•	14.		• '		, ,		4
Skin																		+			1.						50
	+		7			_	+	+	_	т	т	+	_		_	_	+	7	_	_	_			7	+ -	т	
Basal cell carcinoma	Х	•	_																								1
Keratoacanthoma			X																								1
Squamous cell carcinoma																Х											2
Squamous cell papilloma																	Х										1
Subcutaneous tissue, fibroma																											1
Musculoskeletal System					_			_	_								_	_		_	_		_				
Bone	+	+	. 4	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	. 4	<b>-</b> -	+ .	+	50
Skeletal muscle	+		. 4	. +	. +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	. 4		-	+ .	+	50
Mesothelioma malignant, metastatic,				•	'	•	,	•	'	•	•	•	•	•	•	•	•	•	•	•	•	•			•	•	50
testes																											1
Nervous System			_				_				-					_					_	_		-	-		
Brain	+	+	. 4	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		⊦ -	+	+	50
Respiratory System			-			Ť								_				_				_	_				·
Lung	+	. 4	- +		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		<b>-</b> -	+	+	49
Alveolar/bronchiolar adenoma	•																		•		,						1
Pheochromocytoma malignant,																											-
metastatic, adrenal medulla																											1
																							_	_	_	_	50
Nose	-+		1	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• •	•	r -	•	<b>T</b>	
Trachea	+		- 1	• +	+		+	+	+	+	+		+				+	+	+		+	- +		-	+	+	50
Special Senses System			_																								
Eye			4																								1

TABLE A2

Individual Animal Tumor Pathology  Number of Days on Study			Ra 5 :		in 1	6 2		6 3		6 7	6	6	6	6	6	6		6		_	7 0	7	7	7 1	7		(con	·
•	. (		3 9	9 (	) 8	0	5	8	1	8	1	3	5	7	8	8	1	7	7	4	4	4	0	5	5			
	(	) (	0 (	) (	) (	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			
Carcass ID Number	. 1		3 3	3 2	2 2	4	0	2	1	3	5	1	0	2	3	4	0	3	4	0	1	3	0	4	1			٠
• .	(	) 9	9 :	1 4	ŧ (	0	1	5	5	5	0	2	9	3	4	4	3	3	3	8	8	7	5	5	7			
Urinary System																									-			
Kidney	-	٠ ١	+ .	+ -	+ -	+ +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	,		2
Urinary bladder		٠ ١	+ -	+ -	+ -	+ +	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	<b>`.</b>		
Systemic Lesions									_													_		_			<i>ī</i> -,	
Multiple organs	-	٠.	+ -	+ -	+ -	+ +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Leukemia mononuclear		2	<b>X</b> :	X X	<b>X</b> >	(		X	X	X	$\mathbf{x}$	$\mathbf{x}$		٠,		Х	$\mathbf{x}$	$\mathbf{X}$	X		X	X	X			:	٠	
Lymphoma malignant											Х																	
Mesothelioma malignant							Х															,			X			

Table A2

Individual Animal Tumor Pathol	ogy of Mal	e I	Rat	s i	n tl	he .	2-}	/ea	ır. C	Ja7	\ <b>න</b> ්	e S	Stw	dу	lo	Co	duan	0	il:	U	mtı	rea	ite		on	trol (co	ntinued
<del></del>	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7		
Number of Days on Study	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3		
	. 7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7		
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	T	otal
Carcass ID Number	0	0	0	0	1	1	1	1	1	2	2	2	2	2	2	3	3	3	3	4	4	4	4	4	4	T	issues/
	2	4	6	7	1	3	4	6	9	1	2	6	7	8	9	0	2	6	8	1	2	6	7	8	9	T	umors
Urinary System					-													-									
Kidney	+	- 4	+ +	+ +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	5	60
Urinary bladder	+	٠ +	+ +	- +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	4	19
Systemic Lesions	<del></del>														•							_					·
Multiple organs	+	- 4	+ +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	. +	+	+	5	50
Leukemia mononuclear	х	. >	(			X	Х		X		Х		X						X	Х	X	X				2	27
Lymphoma malignant	•																										1
Mesothelioma malignant																											2

	2	3	4	5	5	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7			
Number of Days on Study	7	6	8	9	9	0	2	5	6	6	7	7	8	0	0	1	2	2	2	2	2	2	2	2	2			
	2	_	_	1									5			9		6		9	9	_	_	9	_			
		2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2			_
Carcass ID Number	0	4	1	0	1	0	4	4	4	5	0	2	4	2	1	1	4	2	0	1	1	2	2	2	2			
	4	5	3	7	2	5	3	9			8	9			1	7	8	5	6	4	5	1	2	3	4			
Alimentary System					_			_																				
Esophagus	_	4	_	+	_	+	_	_	+	_	+	+	+	_	+	_	+	+	+	+	+	4	4	+	+			
Intestine large, colon		+		+	+	+	+		+						+				+	<u>.</u>	+	+	+	4	·			
Intestine large, rectum		i	·	Ĺ	<u>.</u>	Ţ	<u>.</u>	Ţ	+		+				+				+	Ţ	+	i	÷	<u>.</u>	<u>.</u>			
Intestine large, recum	·	÷	·	<u>.</u>	÷	÷	+	+	Ţ		+				+				+	÷	+	÷	<u>.</u>	÷	÷			
Intestine small, duodenum			<u> </u>	- T		<u> </u>	<u>.</u>	<u> </u>	_	<u> </u>	+	+	+		+			+	+	<u> </u>	÷	T	i	<u> </u>	ì			
Intestine small, jejunum					<b>T</b>	+	+	+	+	<b>T</b>	+	•			+			-	+	<b>T</b>	+				+			
Intestine small, ileum	+				т Т	+			+		+				+				+		+							
Liver	T	+	+		T	+			+		+			+		+	+		+		+	т _		+	т Т			
Mesentery	+	7		т	т	т	т	т	r	т.	1	7	•	т	+	т.	+	т.	'	т	'		+	т	7			
Mesothelioma malignant, metastatic,	т														т		т					т	_					
<del></del>																						х			,			
testes Pongress								,			٠		J			1	٠											
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+.	+	+	+	+	+	+	+	+	+	+	+	+			
Mesothelioma malignant, metastatic,																						**						
testes																						X						
Mixed tumor benign																												
Acinus, adenoma																												
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+		+		+			+	+	+		+	+	+			
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		٠	
Tongue			_		_												+			+		_		_		_		
Cardiovascular System	•				_												_											
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Endocrine System	******																											
Adrenal cortex	+	+	+	+	+.	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+			
Pheochromocytoma malignant																												•
Pheochromocytoma benign						Х		Х						Х			х	x										
Bilateral, pheochromocytoma benign																				X								
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	Α	+	+	+			+	+	+	+			
Adenoma	•	•	•	X		•		·	•	•	X	·	X		·		·	•	•	•	·	٠		٠				
Parathyroid gland	+	+	+		+	+	+	+	+	+		+		+	+	+	+	+	+	+	+	+	+	+	+			
Pituitary gland	+		-												+						+	+	+	+	+			
Pars distalis, adenoma	•	'		•	.71	•	'	•	٠	•	٠	•	•	•	•	•	•	•	•	•	•	•		•				
Thyroid gland		_	_	_	_	_	_	+	_	+	1	+	4	+	4-	Д	+	+	+	+	4	_	4	_	+			
C-cell, adenoma	7	'	1	T	1	٠	,		'	٠	T	•	'	•	•		•	٠	•	x	٠	•		•	•			
Follicular cell, adenoma																				•								
	<del></del>																								-		-	
General Body System None																									•			
			_			-																						
Genital System																												
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Mesothelioma malignant, metastatic,																												
testes																						X						
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Adenoma				X						Х								X							X		: .	
Prostate	+	+	. +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			

Individual Animal Tumor Pathology (		e IK	aus	s om	n Cilt	e z	3-Y	(Ca)	r u	ÿ <b>8</b> 0₹	/ag	e S	Stud	ПУ	Oil	Co	n in	(U)	0.02	πq	<u>ייי</u> ע	II Jia	yR.	28	uume	(continued
	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
Sumber of Days on Study	2	2	2	2		2		3		3	3	3				3	3	3	3	3	3	3	3	3	3	
valued of Days on Stady	9	9	9	9	_									0						0	0	0	0	0		
		_	_			_	<del>_</del>	_		2	_	_		_	_	_			_	_	2	2	2	2	2	Total
Carcass ID Number	3	2	2	2		2		_					2							2	3	3	4	4	_	Total Tissues
Carcass III 140111621	0	1					4														7		-	-	-	Tumors
		_	_			_	<u> </u>	_	_	_	_	<u> </u>		_					_	_	<u>.</u>	_	_	_		
Alimentary System																										
Esophagus	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	48
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery				+			+																			7
Mesothelioma malignant, metastatic,																										
testes																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic,	·				•			•																		
testes																										1
Mixed tumor benign															X											1
Acinus, adenoma															*										х	1
Salivary glands	_	_	_	4	_	_	4	4	_	_	4	4	+	+	+	4	_	_	4	_	_	_	_	+	_	50
Stomach, forestomach	M.	·	<u>.</u>	<u>.</u>	<u>.</u>	i	i	<u>.</u>		Ţ	+	+	i	Ţ	+	÷	+	i	i	<u>.</u>	i	i	·	<u>.</u>	i	49
Stomach, glandular	141	· _	+	+		+	+	+	+	+	-	+	+	<u>.</u>	+			+	+	т Д.	<u>'</u>	+	<u>'</u>	+	1	50
Tongue		т	т.	т	т	Т		7	+	Т	т.	т		Т	-	т	т	T		_	Т.	Т		т	т	3
	·					_								_						_		_	_			
Cardiovascular System																										50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma malignant														X												1
Pheochromocytoma benign	Х				X						X			Х	X	X		$\mathbf{x}$					Х			13
Bilateral, pheochromocytoma benign									Х																	2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																			х				X		-	5
Parathyroid gland	+	+	+	М	+	+	+	+	+	+	+	+	M	+	+	+	+	+		+	м	+			+	47
Pituitary gland	+	+	+		+	+	+	+	+	+			+												·	49
Pars distalis, adenoma	T	-	X		'	•	,	'	'	•	•			X	'	•	•	'	,	X		,-	X		r	6
Thyroid gland	_					_	+			_	_				_	_		_	_			_	_		_	49
C-cell, adenoma		7	7	X		_	Т	Т	Т	т	т	т	т	т	т	т	_	+	_	т	т	Т	_	X		
Follicular cell, adenoma	Х			^																	х			А		3 2
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic,																										
testes																										1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma			•	•	•	•	•	•	•	x	•	•	•	x	•	•	x	•	•	•	•	•	•	X		8
				_	_	+	_	_	+	+		_	+		+	+	+	+	+	+	+		+		+	49
Prostate	-4-																									
Prostate Seminal vesicle	<del>+</del>	۰			<u>.</u>	·	<u>,</u>	<u>,</u>	<u>.</u>	·	Ţ	<u>.</u>	<u>.</u>	·	<u>.</u>	+	+		+		+		٠,		+	49

																		-				_								
			2	3	4	5	5	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7			
lumber of Days on Study			7	6	8	9	9	0	2	5	6	6	7	7	8	0	0	1	2	2	2	2	2	2	. 2	2	2	2.7	c., .	w. s;
			2	0	3	1	8	0	8	8	1	1	0	1	5	1	7	9	3	6	9	9	9	9	9	9	9			
			-	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	_			
Carcass ID Number			0	4	1	0	1	0	4	4	4	5	0	2	4			2 1	4	2	0	1	1	2	2		. 2			
Carcass ID Number			4	5	3	7	_	-	3	•	2	_	-		6				8			4	5	1		3				**,3
												_				_														
Genital System (continued)																						1		٠.		٠.			· · ·	i in i
Testes			+	*	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		٠.	• •
Bilateral, interstitial cell, adenoma	1	•			Х	X		X			X		X		Х	X	X	Х	Х		Х	X	Х			·X	X	.*1	•	
Interstitial cell, adenoma			:				X		X	Х		X		Х						Х			•	. •	1.5		,		٠,	•
Hematopoietic System																										.:			,	
Blood															+	+			+	+					+		+		, ,	
Bone marrow		, .	+	+	+	+	+	4	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	14.		
Lymph node			•	•	•	i	·	·	÷	<u>.</u>	<u>.</u>	÷	•	<u>.</u>	Ţ	÷	<u>.</u>	•	<u>.</u>	÷	•		÷	•	·	•	Ţ	•	. ,	į.
			_	_	_		<u>'</u>		<u>.</u>	1	<u>'</u>	1	_	·	· ·	i	i	_	i	i	_	<u>.</u>	<u>.</u>	_	i	٠	<u>.</u>			٠.
Lymph node, mandibular							Ţ	+		<b>T</b>	Ţ	Ţ.	T.	Τ.		Ţ	Τ.	Τ	Τ.	Τ	Τ.	Ţ.	T.,	~ <b>T</b>	Τ.	. T				
Lymph node, mesenteric			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	. +	+	+	:::		,	•
Spleen			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		•	
Thymus		•	+	+	-+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+		25	•
Integumentary System								_				_				_												"·		13.5
Mammary gland			4	+	+	+	+	м	м	+	+	+	+	+	+	+	+	м	4	+	+	+	+	+	+	4	+			
Fibroadenoma			•	•	•	•	•	•••		•		•	•	•		•	•	•••	•	•	•	٠.	•	•	x	·				*
Skin																								+	+					
			· T	· •		Т	•	т	т	т	т.	т	т	·T	т	т	т	Τ.	т	Τ.	.T	т	т	T	┰		T			t .
Squamous cell carcinoma																												*	•	
Sebaceous gland, adenoma																						,		•					14.	
Subcutaneous tissue, fibroma										X						X											,		٠	•
Musculoskeletal System	_																									•		•;		,
Bone			+		+	+	+	+	+	4	4	+	+	4	+	+	+	4	+	+	+	+	+	+	+	+	+			
Skeletal muscle			i		· .		i	÷	Ϊ.	÷	i	÷	<u>.</u>	i	i	+	i	÷	÷	i	i	i	÷		÷	i				2.50
- Skeletai musele								'									<u> </u>													
Nervous System																											÷	٠.٠	٠.	٠.,
Brain			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	Α	+	+	+	+	+	+	+	+	+			1 Y
Respiratory System																	•											. ,		
Lung			+	- 4	+	+	+	+	+	+	+	4	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+ +	. •
Alveolar/bronchiolar adenoma					•		•	•		•	·	Ċ		•	•		-	•		•	•			Ť						
Alveolar/bronchiolar carcinoma															x							•	•			•				
															^						•									5
Fibrosarcoma, metastatic, ear																		_							•				•	
Nose		•	+	+	+	+	+	+	+	<b>*+</b>	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		٠	•
Trachea	•		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		٠,٠٠	
Special Senses System																												:		4.47
Ear																														
Fibrosarcoma																										-	<b>.</b> .			
																														.,
Fibrous histiocytoma																									Ì.	4			1	
Eye																														**
Zymbal's gland													+		+												. *		•	
Adenoma													Х														,	`-		,-
Carcinoma															X													s, e file		
Urinary System				-													_		_			_	_						1:.	· ·
Kidney			_				+	+	.+	+	4	_	+	+	+	4	+	A	+	+	+	4	+	_	4	4	+			
- Autoricy			. 1						•			•	•	•	•	•			•		•		•		•					:11
Urinary bladder												_1			_1_			^					_1	•	- 4					

								_							_	_		_		_	_	Ξ	_	_		
_ ·_		7		7				-	7	-		7	7		7		7	7		7		7	7	7		
lumber of Days on Study	2	2	2 9	2 9	_	_	_	3 0	-	3 0	3 0	3 0	3 0	3	3 0	3	3 0	3	3 0	3	3 · 0	3	3 0	3	3 · 0	•
						_																_	_	_	_	T-4-1
The Division of the Control of the C		_		2	-				_	2			1			2	2	2	2	2	2	2	2 4	2	_	Total Tissues
Carcass ID Number	3 0	3 1								-					9						7	-		1	-	Tumon
Genital System (continued)						_										_		_			_					· , <del>- , , </del>
Testes	+	+	+	+	+	4	+.	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma Interstitial cell, adenoma	Х	. <b>X</b>	Х	Х		x	X	X	X	X	X	X	X	x	X	X	X		X	X	X	X	X	Х	Х	39 8
lematopoietic System				_																			-			
Blood		+					+							+												9
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node		+	٠.	+			+			+						+										. 22
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	. +	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	.+	+	+	+	+	+	+	+	+	+	+	+	+	+	.+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ntegumentary System																						"				
Mammary gland	+	M	M	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	42
Fibroadenoma						Х																			•	2
Skin	+	+	+	+	+	+	+	.+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma												X											٠			F 1
Sebaceous gland, adenoma																	X					•				1
Subcutaneous tissue, fibroma										Х											٠					3
Musculoskeletal System		,			_																	٠.				
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										•
Brain	+	. +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Respiratory System																										
Lung	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49.
Alveolar/bronchiolar adenoma																			Х						٠,	· 1
Alveolar/bronchiolar carcinoma																			•		٠.					1
Fibrosarcoma, metastatic, ear				X																	+ 1					1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	1	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear				+						+																2
Fibrosarcoma				X																						1
Fibrous histiocytoma										X														:		1
Eye						+		+							+											3
Zymbal's gland																										2
Adenoma																										. 1
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	·+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder																		- 1								49

TABLE A2

Individual Animal Tumor		logy	of	Mal	e F	lat	s i	n ti	he	2-Y	Yea	ır (	Ga	vag	ge S	Stu	ıdy	of	C	ort	Ç	il:	1	0 r	nL	/kg	S	alin	e (co	ntinued)
				2	.3	4	5	5	6	6	6	.6	6	6	-	6	7	7	7	7	7	7	7	7	7	7	7	7		
Number of Days on Study				7 2	6	3	9	8	, 0	8	5 8	6	6	7 0	7	8 5	1	0 7	9	3	2 6	9	9	9	9	9	9	9		
Carcass ID Number		<u></u>	2 3	Q	4	1	2 0 7	1	Ó	4	4	4	5	0	2	4	2	. 1	1	4	2	0	1	1	2	2	2	2		
Systemic Lesions Multiple organs	•		•;	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Leukemia mononuclear Mesothelioma malignant			• •			Х	X	Х	. <b>X</b>	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х		Х	x	Х		Х		

TABLE	A2

Individual Animal	Tumor	Pathology	of Male	Ratsim	the 2-Year	Gavage Study	of Corn Oil:	10 ml/k	g Saline (continue	d)

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Number of Days on Study		2	2	2	2	2	2	2	3	3	3	3	3	3	3	3	3	3	3	ż	3	3	3	3	3	3			
		9	9	9	. 9	9	ġ	9	0	0	Ó	0	0	0	0	0	0	Ö	0	0	0	0	0	0	0	0		•	
		2	. 2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		Total	_
Carcass ID Number		3	3	3	3	3	3	4	0	0	Ò	Ō	1	1	1	1	2	2	2	3	3	3	3	4	4	4		Tissues/	
		0	1	2	3	4	9	4	1	2	3	9	0	6	8	9	0	7	8	5	6	7	8	0	1	7		Tumors	
Systemic Lesions				-		_	٠,	-			_							•		-	-		•	_	*			***	-
Multiple organs		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50	
Leukemia mononuclear			X		X			X	X		Х	Х	X		X		X		X									30	
Mesothelioma malignant																												1	

Individual Animal Tumor Pathology						_		_															_			_				
		4	4	5	5	5											7	7		7	7	7	7	7	7	7				·
Number of Days on Study		0		2		7				5						0	0		3							3				
		9	0	0	2	5	6	9	9	3	6	9	0	8	5	5	7	0	6	6	6	6	6	6	6	6				
		0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0				_
Carcass ID Number		7		0		-	9			5						5				5				-	-	٠7,	¢.	٠.	<b></b> :	
·	,	6	9	0	7	0	4	3	7	5	2	1	1	2	4	1	2	5	7	8	0	1	2	3	5	4				
Alimentary System																									:					
Esophagus		+	+	+	+	+	+	+	:+	+	+	-+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Intestine large, colon		+	+	+	Α	+	+	+	+	+	+	Α	+	+	Α	+	Α.	+	+	+	+	+	+	+	. +	. +				
Intestine large, rectum		+	+	Α	Α	+	+	+	+	+	+	+	Α	+	Α	+	Α	+	+	+	+	+	+	+	+	+				
Intestine large, cecum		+	+	Α	Α	+	+	+	+	+	+	+	Α	+	Α	+	Α	+	+	+	+	+	+	. +	+	. +				
Intestine small, duodenum		+	+	Α	Α	+	+	+	+	+	+	+	+	+	+	+	Α	+	+	+	+	+	+	+	+	+				
Intestine small, jejunum		+	+	Α	Α	+	+	+	.+	+	+	+	Α	+	Α	+	Α	+	+	+	+	+	+	;+	. +	+				
Intestine small, ileum		+	+	Α	Α	+	+	+	+	+	+	+	Α	+	Α	+	Α	+	+	+	+	+	+	+	+	+			:	
Adenocarcinoma																														
Liver		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	. +	. +				
Hepatocellular adenoma				-		-		•		-			-				-									1				
Hepatocellular adenoma, multiple															х					,					7	. ,.		,	•	
Mesentery					+													+				•							•	
Mesothelioma malignant, metastatic,					•													•												
testes					х																									
Pancreas		_	_	_	_		4	_	_	_	_	_	Δ	_	_	_	_	+	_	_	_	_	N							
Acinus, adenoma		1	7	7	141	. T	•	т	•	т	т.	-	А	•	т	•	т	Ψ.	-	X		X			•	X				
																				^		Λ		Х	•	^	•			
Acinus, adenoma, multiple Pharynx																					•			^ +						
																								X						
Palate, squamous cell papilloma																								^	٠.			•		
Salivary glands		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	* *	• +	. +				
Stomach, forestomach		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			+		+		+	•	+	,	•		
Stomach, glandular		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		•		
Tongue																							+						-	
Cardiovascular System																														
Heart		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	•		٠.	
Endocrine System																														
Adrenal cortex		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		٠.		
Adrenal medulla		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	. +	+				
Ganglioneuroma																													_	
Pheochromocytoma malignant									Х																					
Pheochromocytoma complex				Х																										
Pheochromocytoma benign							Х							X	х	Х			X					Х	X					
Bilateral, pheochromocytoma benign							-					х					х			,				-	-					
Islets, pancreatic		+	+	+	М	+	+	+	+	+	+			+	+	+		+	+	+	+	+	N	<b>1</b> +	. 4	+				
Adenoma			•					X		·	•	•					·		•	•		•				•				
Parathyroid gland		+	+	м	+	+	+			+	+	+	+	+	+	+	+	+	+	+	+	+	+		. +	- 4				
Pituitary gland		<u>.</u>		+			·	<u>.</u>	·	Ţ	<u>.</u>	<u>.</u>	i		·	Ţ	<u>.</u>	<u>.</u>	i	<u>.</u>		_		' ــــــــــــــــــــــــــــــــــــ						,
Pars distalis, adenoma		x	•				•	X		X	•	•	•	X	•	,		x	•	X	1		,	•	r	-		•		
Thyroid gland			_	_	Α		+		_		_		+			+	+		+			+	_	۰.					•	
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C-cell, adenoma										Λ		x													^					
C-cell, carcinoma										_		_^											_					•		
General Body System																								-			,			
General body System																														

3 6			3 6	3 6				3	3		3										3 7	3 7			
0	-	0	0			-	_	-	-											0	0	0	_	-	Total
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				_								_							_		_				
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+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
·		·	+	+	+	+	<u>.</u>	+	+	+	+	+	+	+		<u>.</u>	÷	+	÷	+	+	+	+	+	45
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																									1
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		Х					Х																X		6
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+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	50
																		Х							1
																									1
																									1
			Х	X		X		X		X		Х							X					X	15
Х														Х											4
+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	47
			X							Х															3
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+	+			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
	•	•	x		•	•	•	•	•	•	•	•	×	•	•	•	•	•	•	•	×	•	•	×	10
4	4				+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+		4		49
7	-	4	•	7	1	1.	v	Y	•	•	т	Т		'		•	•	Y	т.	T	7,"	т	т.	-	5
							^	^										^							1
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N			. 4			2														_	,		_						
Number of Days on Study		0	2	2	6	7	8		. 1					7		-	0	2	3	3	3	3	3	3	_	3			
		9	0	0	2	5	6	9	9	3	6	9	0	8	5	5	7	0	6	6	6	6	6	6	6	6			
		_	0	1	0	0	n	0	n	_	n	0	0	0	0	0	n	0	<u></u>	0	0	0	0	0	0	^			
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Carcass ID Number																													
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Genital System									<u> </u>																				_
Ductus deferens					+																								
					т																								
Mesothelioma malignant, metastatic,					1/																								
testes					Х																								
Epididymis	~	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Mesothelioma malignant, metastatic					X															-									
Preputial gland		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Adenoma																	Х						X						
Bilateral, adenoma																													
Prostate		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Seminal vesicle	ŧ	+	+	Α	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Mesothelioma malignant, metastatic,																					•		·		·	•			
testes					х																								
Testes		.1.		_	+	٠.	_	_	_			_	_		_	+	_	ــــــــــــــــــــــــــــــــــــــ	ı		.1.	_		_	.1.	4			
	•	+	т		X			+	v	-	v	X	т	*		X													
Bilateral, interstitial cell, adenoma				Х	Х	Х	Х		X		Х	Х			Х	Х	А	Х	X	Х	X	Х	Х	X	Х				
Interstitial cell, adenoma										X			X													X			
Hematopoietic System																													_
Blood																+				+									
Bone marrow		_	_	_	i.	_	_	Δ.	_	_	_	_	_		_	i	_	_	_	Ė	_	_		_		_			
Lymph node		<u>.</u>	•	'	i	'	i	'	i	٠.	<u>.</u>	•	•	•	1	'	1		•		1	'	,	_	-	-			
		+			T		Ţ		<b>T</b>		Ţ.				Ţ		+	+		+									•
Lymph node, mandibular		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Lymph node, mesenteric		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Spleen		+	+	+	Α	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Hemangioma																													
Thymus		+	+	M	+	+	+	+	+	+	+	+	+	+'	+	+	M	+	+	+	+	+	+	+	+	+			
Epithelial cell, thymoma benign																													
Introduce State																			_		_	_						-	
Integumentary System  Mammary gland					M		M		į.		1.	14		14		M	1.											•	
		+	+	+	IVI	+	IVI	+	+	+	+	IVI	+	IVI	+	M	+	+	+	+	+			+	IVI	+			
Fibroadenoma																						X							
Skin		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Keratoacanthoma																													
Squamous cell papilloma																													
Subcutaneous tissue, fibroma									X																				
							-							<u> </u>			_	-	_	<u></u>									_
Musculoskeletal System			_																										
Bone	*.	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Osteosarcoma											X																		
Skeletal muscle		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Mesothelioma malignant, metastatic,																						,							
testes					Х																						-		
Mesothelioma malignant, metastatic,																													
uncertain primary site									X																				
						/ <u>*</u>						_																	_
Nervous System																											• -	•	
Brain		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Spinal cord			+																										

Number of Days on Study	3	3	3		3			3	7	3										, 3	3	3	3		7 3		
	6	6	6	6																	7		7	7	7		
	0	0	0	0																	0	0	0	-	0	_	Total
Carcass ID Number	7 5	8 1	8 4	_	9 3	9 5		9 7		-	5 3	-	5 6								7 9	8 6	8 8	8 9	-		Tissue: Tumoi
Genital System													_			_					_	_		_			·
Ductus deferens																											1
Mesothelioma malignant, metastatic, testes																		٠.									1
Epididymis Epididymis	_				4	_		_	_	_	_	_	_	_	_	_	_	_	_	_	_	_	4	_	_		50
Mesothelioma malignant, metastatic		•	•	•	•	•	•	•	•	,	•	•	•	•	•	•	•	•	•	٠.	٠.	•	•	•	•		1
Preputial gland	_				_	_	_	_	_	_	_	_	_	_	_	_	_	_	_	_		_	_	_	_		50
Adenoma	-	_	-	7	т	•	7	т	•	т.	т.	•	7	4	•	7	т.	•	т.	-		7	7	. T	_		2
Bilateral, adenoma					х																						1
Prostate	+		. +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	٠,	+	+	+	4	+	+		50
Seminal vesicle	+	. +	. +	+	+	+	+	+	+	+	+	+	+	+	<u>.</u>	+	+	+	+.	4	. +	+	+	+	+		49
Mesothelioma malignant, metastatic,	,	,	'	,	•	•	•	•	•	٠	•	•	•	•	•	•	•	•	•	•	•	,	•	•	•		
testes																											1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Bilateral, interstitial cell, adenoma Interstitial cell, adenoma	Х	. х	. х	X	Х	Х	Х	Х		Х	<b>X</b>		Х	Х	X	Х		X		Х	Х	X	X	Х	Х		43 3
Hematopoietic System					-				-								_		_	_							
Blood																			+					+			4
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	٠+	+	+	+	+		50
Lymph node					+						+				+	+			+		+						15
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	÷	+	+	+	+	+	+	+	+	+		49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Hemangioma																				X							1
Thymus	+	+	+			+	+	+	+	M	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+		45
Epithelial cell, thymoma benign				X																							1
integumentary System																											
Mammary gland	+	+	+	. +	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	M	M	M	+	+	+		39
Fibroadenoma																											1
Skin Keratoacanthoma	+	• +	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+		50
Squamous cell papilloma																X		v									1
Subcutaneous tissue, fibroma																		X									1 1
Musculoskeletal System		_										-					-		_	-			_				
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Osteosarcoma																											1
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Mesothelioma malignant, metastatic,																											-
testes																4			٠.			٠					1
Mesothelioma malignant, metastatic, uncertain primary site																	-	-									1
Nervous System			_						_			"	_														
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Spinal cord																									•		1

Individual Ammai Tumor Famology o	I TATSTI	СГ	var	3 11	1 11	ic .	&- I	ca		JAV	ag		) tu	uy	O1		<b>71 1</b>			. 4	J 1		, in E	, (0	Olli	IIUC	u). 	_
	4	4	5	5	5	5	5	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7			
Number of Days on Study	0	2	2	6	7	8	9	1	5	5	6	7	7	9	0	0	2	3	3	3	3	3	3	3	3 -			
•	9	0	0	2	5	6	9	9	3	6	9	0	8	5	5	7	0	6	6	6	6	6	6	6	6			
	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	-	0	0	0	0	0	0	0			
Carcass ID Number	7	5	0	6	8	9	8	8	5	7	9	7	5	6	5	8	8	5	5	6	6	6	6	6	7			
	6	9	0	7	0	4	3	7	5	2	1	1	2	4	1	2	5	7	8	0	1	2	3	5	4			
Respiratory System																												
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Alveolar/bronchiolar carcinoma																												
Carcinoma, metastatic, thyroid gland											X																	
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Special Senses System																												
Ear																		+										
Eye							+			+																		
Urinary System	<del></del>														•		•											
Kidney	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+			
Urinary bladder	+	+	Α	. <b>A</b>	+	+	+	+	+	+	+	Α	+	+	+	+	+	+	+	+	+	+	+	+	+		:	
Systemic Lesions			_																					_			·········	÷
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Leukemia mononuclear						X		X		Х				X	X	X	X		X				٠.		٠,			
Mesothelioma malignant				X																			1					,

																						_					
	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7		7	
Number of Days on Study	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	•	3	
	6	6	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7		7	
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		0	Total
Carcass ID Number	7	8	8	9	9	9	9	9	9	9	5	5	5	6	6	6	7	7	7	7	7	8	8	8		9	Tissues/
•	5	1	4	2	3	5	6	7	8	9	3	4	6	6	8	9	0	3	7	8	9	6	8	9		0	Tumors
Respiratory System																											· · · · · · · · · · · · · · · · · · ·
Lung	+	+	- +	- +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	. +	+	+	50
Alveolar/bronchiolar carcinoma																				X							1
Carcinoma, metastatic, thyroid gland																											1
Nose	+	+	- 4	- +	٠ +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	- +	- +	۲	+	50
Trachea	+	+	- 4	- +	- +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	. +	. +	۲	+	50
Special Senses System		_									-					_	_			_							
Ear																											1
Eye																											2
Urinary System		_							_						_					_		_	_	_		_	
Kidney	+	+	- 4	+ +	- +	- +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	- +	- +	۲	+	48
Urinary bladder	+	+			- +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	. +	. 4	۲	+	47
Systemic Lesions							_		_	_	_						_										
Multiple organs	+	. 4	+ +	+ 4	- +	- +	. +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	- +	- 4	+	+	50
Leukemia mononuclear		>	ζ	>	K	٠					X								X			X	X	( )	<		16
Mesothelioma malignant		-	-	•	_ •	-																-	•		_		1
																											•

Number of Days on Study									7 0		7				7 3											
Number of Days on Study									6					4			4						4	4		
	1	1	_	_											1						_	_		1	1	
Carcass ID Number	4	2 7	3 0	2 0	4 4	2	1 8	4 6	0 4	0 5	1 7	7	1 6	1 9	2 1	2	2 4	2 6	2 8	2 9	3 4	_	4 1	3	4 5	·
Mimentary System		_			_				_																	·
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	Α	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Mesothelioma malignant, metastatic,																										
testes						X																				
Intestine large, rectum	+	+	+	+					Α							+	+	+	+	+	+	+	+	+	+	
Intestine large, cecum	+	+	+	+	+	+	+	+	Α	+	Α	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Mesothelioma malignant, metastatic, testes						X																				
Intestine small, duodenum	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Intestine small, jejunum	+	+	+	+	+	+									+				+		+	+	+	+	+	
Intestine small, ileum	+	+	+	+	+	+									+		+	+	+	+	+	+			+	
Mesothelioma malignant, metastatic,	•	٠	•	•	•	•	•	•		•		•	•	٠			٠	•	•	•	٠	•	•		•	
testes						х																				
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Mesothelioma malignant, metastatic,		•			•		-	•				•					•		•				•			
testes						X														,						
Mesentery						+		+															+			
Mesothelioma malignant, metastatic,																										
testes						Х																				
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Mesothelioma malignant, metastatic,																										
testes						Х																				
Acinus, adenoma									Х																	
Acinus, adenoma, multiple						X									X						Х					
Acinus, carcinoma																										
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Squamous cell papilloma										•														X		
Stomach, glandular	. +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Leiomyosarcoma									X																	
Cardiovascular System		_			_	_					•		_													
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Endocrine System			_																							
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			+	+	+	
Pheochromocytoma malignant																					Х					
Pheochromocytoma benign														X						٠						
Bilateral, pheochromocytoma benign																										•
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			+	+	+	+	
Adenoma																				X						
Parathyroid gland															+											
Pituitary gland	+	+	+	+			+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	
Pars distalis, adenoma					X									X												
Thyroid gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Bilateral, C-cell, adenoma																										- '
C-cell, adenoma														Х							X					

	~	7	~	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
lumber of Days on Study					3	-	•	-									3		3	•	-		-	3	-	
umber of Days on Study	3	3	_	3 5	-	3 5	3	3		3	3 5	3	3	3	3	3		3		3	3	3	3			
	4	4	5	3	5	)	5	5	3	3	3	3	)	3	5	3	3	3	0.	0	0	0	0	0	0	
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	Total
Carcass ID Number	4	4	0	0	0	0	0	0	0	1	1	1	1	1	1	2	3	5	3	3	3	3	3	3	4	Tissues
	8	9	1	2	3		-	-			1	2											6	7	0	Tumor
			_							_		_						_	_							
Alimentary System																										
Esophagus	+	+	+ ٍ +	- ,+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	4	- +	- +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Mesothelioma malignant, metastatic,																										
testes																										1
Intestine large, rectum	+	٠ +	+ +	- +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	٠ ٦	+ +	- +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Mesothelioma malignant, metastatic, testes																										1
Intestine small, duodenum	+	-	+ +	- +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+ +	- +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	٠ -	⊦ +	- 4	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Mesothelioma malignant, metastatic, testes																										1
Liver	+	٠ 4	+ +	- 4	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, testes																										1
Mesentery																						+				4
Mesothelioma malignant, metastatic, testes																						•				1
Pancreas	+		٠ -	- 4	. +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, testes	,			ľ	·	ľ	•	•	•	Ċ	•	•	'	,	'		•	•	•	•	Ċ	•	Ċ	•	•	1
Acinus, adenoma													x					X								3
Acinus, adenoma, multiple								х			х		7.				х	1			х					7
Acinus, carcinoma								1.			11			x			<i>,</i> ,				1					1
Salivary glands	+		٠ -	- 4	. 4-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	4	+	4	+	4	+	50
Stomach, forestomach			, ,  -	- 4		·	· +	+	+	+	+	+	+	<u>.</u>	+	+	<u>.</u>		4	·	<u>.</u>	<u>.</u>	·	+	<u>.</u>	50
Squamous cell papilloma					•	•	•	•	•	•	•	٠	٠	•		•	•	•	'	'	1	'	•	•	7	1
Stomach, glandular	4		٠.	- 4	. 4	+	+	+	+	+	4	4	_	_	_	+	+	_	_	_	_	_	_	_	_	50
Leiomyosarcoma	•				٠		•	•	•	•		'	•	•	,	•		•	,	•	٠	•	•	•	'	1
Cardiovascular System		_		_			_															_				
Heart	+		۱ -	- 4	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System							_	_		_																
Adrenal cortex	+	-	۲ ۱	- 4	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+		+ 4	- 4	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																										1
Pheochromocytoma benign													X								X					3
Bilateral, pheochromocytoma benign									Х																	1
Islets, pancreatic	+	-	+ +	- 4	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma				>				_	Х										X							4
Parathyroid gland					+		+	M	+					+	+	+	+	+	+	+	M	M	+	+	+	40
Pituitary gland	+	. 1	A 4		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+		+	+	49
Pars distalis, adenoma									X												X	X			X	6
Thyroid gland	+		+ +			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Bilateral, C-cell, adenoma				Σ																						1
C-cell, adenoma					X																					3

Spinal cord

TABLE A2 Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Corn Oil: 5 mL/kg (continued) 3 5 5 5 5 6 Number of Days on Study 8 3 5 6 6 6 7 3 0 0 2 2 3 3 3 3 3 3 3 2 6 2 5 0 2 7 6 1 6 11111111 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 **Carcass ID Number** 2 3 2 4 2 1 4 0 0 1 4 1 1 2 2 2 2 2 2 3 3 4 4 4 7 0 0 4 3 8 6 4 5 7 7 6 9 1 2 4 8 3 5 **General Body System** None **Genital System Epididymis** Mesothelioma malignant, metastatic, testes Preputial gland Adenoma Bilateral, adenoma Prostate Mesothelioma malignant, metastatic, testes Seminal vesicle Mesothelioma malignant, metastatic, testes Testes Bilateral, interstitial cell, adenoma **X X X X X X X X X X X X X X X X X X X** Interstitial cell, adenoma X Х Hematopoietic System Blood Bone marrow Lymph node Lymph node, mandibular Lymph node, mesenteric Spleen Mesothelioma malignant, metastatic, testes Thymus **Integumentary System** Mammary gland Fibroadenoma Skin Squamous cell papilloma Subcutaneous tissue, fibroma Subcutaneous tissue, hemangioma Musculoskeletal System Bone Skeletal muscle Mesothelioma malignant, metastatic, testes **Nervous System** Brain

ndividual Animal Tumor Pathology	OH TATSHIR	- H								J 64	~ <del>~</del> ~					-,				-		-	J	•		٠,
<del></del>	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
Sumber of Days on Study	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	∙3	3	3	
-	4	4	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	6	6	6	6	6	6	6	
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	Total
Carcass ID Number	4		0	0		0			0										3	_	3	3	3	-	4	Tissues
one cause and inclinate	-	-	-				7																_	7		Tumor
General Body System													_								_		_	_		
None System																										
Genital System							-																			
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, testes																										1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																Х				X						3
Bilateral, adenoma																										1
Prostate	+	. +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, testes																										1
Seminal vesicle	. +	+	+	+	+	+	+	+	+	+	+	4	4	+	+	+	+	+	+	+	+	+	4	+	+	50
Mesothelioma malignant, metastatic, testes	·	·	•	·	•	•	·	•	•	,	•	•	•	•	•	•	•	•		•		•		,	,	1
Testes		_1		_	_	_	_	_	+		_			_	_	_	+	_	_	_	_	_	_		_	50
Bilateral, interstitial cell, adenoma					+ X		Y	_	+	v	+ X	_			+ X										X	41
Interstitial cell, adenoma	Λ	. ^	. ^	^	^	^	Λ	x	x		^	X		Λ	^	^	^	^	^	^	^	^	. ^	X		6
lematopoietic System																										
Blood						+								+												3
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node														+												13
Lymph node, mandibular	. +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic,																										
testes																										1
Thymus	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	M	M	( +	+	+	+	+	45
ntegumentary System																										
Mammary gland	+	+	+	+	+	M	M	+	M	+	+	M	+	+	+	+	+	+	M	+	+	+	N	1 +	+	39
Fibroadenoma															X											1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma	X											X							Х							5
Subcutaneous tissue, fibroma		Х																								1
Subcutaneous tissue, hemangioma											X															1
Ausculoskeletal System																								-		
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	- 4	+	+	50
Mesothelioma malignant, metastatic,																										
testes																										1
Vervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spinal cord																										1

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	•	3	4	5	5	5	5	5	6	7	7	7	7	7	7	7 '	7	7	7	7	7	7	7	7	7	7	
Number of Days on Study		8	3	5	6	6	6	7	3	0	0	2	2	3	3	3	3	3	3	3	3	3	3	3	3	3	
		6	2	5	0	2	9	6	2	6	7	1	6	4	4	4	4	4	4	4	4	4	4	4	4	4	
			<u>.</u>				,				<u> </u>							_			_						
		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
Carcass ID Number		4	2	3	2	4	2	1	4	0	0	1	4	1	1	2 :	2	2	2	2	2	3	3	4	4	4	
$(x_1, \dots, x_n) = (x_1, \dots, x_n) + (x_1, \dots, x_n)$		2	7	0	0	4	3	8	6	4	5	7	7	6	9	1 :	2	4	6	8	9	4	9	1	3	5	
Respiratory System						·-	-							`			_										_
Lung		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+ .	+	+	+	+	+	+	+	+	+	+	
Alveolar/bronchiolar adenoma			٠.							Х																	
Alveolar/bronchiolar carcinoma																											
Nose		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Trachea		+	+	+	+	+	<u>.</u>	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
71001100						•,									·				•			,				•	
Special Senses System									_			_											-		_		
Ear																							+				
Eye																						+				+	
Harderian gland			+																								
Carcinoma			X																								
		_				_	_			_															_		
Urinary System		٠,٠					٠,				•																
Kidney		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Mesothelioma malignant, metastatic,																											
testes							X.																				
Urinary bladder		+.	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Mesothelioma malignant, metastatic,	•																										
testes							x																				
Systemic Lesions																										• •	
Multiple organs		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Leukemia mononuclear				Х					Х		Х	X	X														
Mesothelioma malignant							X																				

	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	-	7	
Number of Days on Study	3 4	3 4	3 5	3 5	3 5	3 5	3 5	3 5	3 5	3 5	3 5	3 5	3 5	3 5	3 5	3 5	3 5	3 5	3 6							
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	 Total
Carcass ID Number	4 8	4 9	0 1	0. 2	0 3	0 6	0 7	0 8	0 9	1. 0	1 1	1 2	1 3	1 4	1 5	2 5	3 8	5 0	3 1	3 2	3	3 5	3 6	3 7	4 0	Tissues/ Tumors
Respiratory System	-										_	_	-					_				_		٠.		 
Lung Alveolar/bronchiolar adenoma	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	· +	+	+	49 1
Alveolar/bronchiolar carcinoma Nose	+	M	X + 1	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	1 49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	. +	+	+	50
Special Senses System		_									-									•		•				 
Ear																								,	+	2
Eye Harderian gland Carcinoma														+												3 1 1
Urinary System		_	_	_										_	_	-	<del>-</del>	_		_	_	_	_			 
Kidney  Mesothelioma malignant, metastatic,	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	- +	+	+	50
testes Urinary bladder	+	+	. +	. +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	- +	. +	+	 1 50
Mesothelioma malignant, metastatic, testes																		-			-					1
Systemic Lesions															·			_		-						
Multiple organs	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	- +	+	+	50
Leukemia mononuclear Mesothelioma malignant	Х				,	X						X		X	X								Х		٠	11 - 1

TABLE A2	
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Corn Oil:	10 mL/kg

mber of Days on Study	7 5	5 7 6	2 2	2	6	7	6 8 0	9		2		3	3	3		3	3	3	3	3	3	3	3	3	3				
rcass ID Number	1 8 4	1 5 9	1 8 0	6	7	1 6 6	7	6	6	7	5	5	5	5	1 5 4	5	5	5	6	6	6	6	6	6	7		۲.	:	
mentary System		_																										,	
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			•	
Intestine large, colon	+	+	Α	Α	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	•			
Intestine large, rectum	+	+		Α						Α		+	+	+	+	+	+	+	+	+	+	+	+	+	+		•		
Intestine large, cecum	+		-	Α			_				+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Intestine small, duodenum	+			A			+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	,			
Intestine small, jejunum	+	+	Α	Α	+	+	+	+	+	Α	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		٠		٠
Muscularis, leiomyosarcoma																								Х		٠.			
Intestine small, ileum	+	+	A	Α	+	+	+	+	+	Α	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			,	
Histiocytic sarcoma			Х																						•		• *		
Mesentery									+			+						+											
Mesothelioma malignant, metastatic, testes																											•		
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		,		
Mesothelioma malignant, metastatic, testes																													
Acinus, adenoma		Х	Х							X	Х							X				Х							
Acinus, adenoma, multiple												X		X		X			Х				Х						
Salivary glands	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		4.75		٠
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Stomach, glandular	+	+	Α	Α	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	•		•		
Tongue	+																							+					
Squamous cell papilloma	Х																					•		X					
rdiovascular System																									4.2				
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			. "	
Carcinoma, metastatic, Zymbal's gland								X										~ /											
Mesothelioma malignant, metastatic, testes			,																								, 		
docrine System				_	<u> </u>			_						_			_			-			_		٠.	_	·		-
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Pheochromocytoma malignant	•	X					·									X													
Pheochromocytoma benign					х																X							,	•
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Adenoma	•	•			·		x		•	X				X								X		•				,	
Parathyroid gland	+	+	+	+	+	+		+	+		+	+	+		+	+	+	+	+	+	M		+	+	+				
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Carcinoma, metastatic, Zymbal's gland								X																					
Pars distalis, adenoma	X								X					X										•				٠,	
Thyroid gland	. +	+	+	+	+	+	Α	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	٠.			
Bilateral, C-cell, adenoma																х										:			
C-cell, adenoma													Х					X								٠.,	٠.,		
C-cell, carcinoma																					$\mathbf{x}$				. '				
Follicular cell, carcinoma																													•

umber of Days on Study	7 3	3	3	3	3	3	3	3	3	3	7	3	3	3	3	3	3	3	7 3	3	3	7	3	3		
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	4	4	4	4	4	4	4	
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	2	1	1	1	1	1	1	1	Total
Carcass ID Number	7	7	7	-	8	8	8	9	9	9	9	9	9						7	7		8	8	8		Tissues
	2	3	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	0	6	9	1	2	3	5	Tumor
limentary System													_						-							
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Muscularis, leiomyosarcoma		*																								1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	÷	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Mesentery							+						+		+									+	+	8
Mesothelioma malignant, metastatic,																								<b>1</b> /		
testes																								X		1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic,																										_
testes																								X		1
Acinus, adenoma		X						X					X	X											X	11
Acinus, adenoma, multiple	Х									X		X					X				X			X		12
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Tongue																								+		3
Squamous cell papilloma																										2
ardiovascular System														_	_		_							_		
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, Zymbal's gland										-	-			·								•		•	•	1
Mesothelioma malignant, metastatic,								•																		•
testes																								X		1
- J : - C4											_	_			_	_								_		
ndocrine System Adrenal cortex		_	_	_	_	_	Д.	_		_		_		1												50
Adrenal medulla	T	T	<b>T</b>		I		T	T		I				T	T	Ţ	Ţ	Ţ	7	<b>T</b>	Ŧ	+	+	+		
	т	~	7	Τ	т		_	Ŧ	_	_	_	_	~	Τ.	_	_	_	_	т	+	+	+	+	+	+	50
Pheochromocytoma malignant			v	х		v			х				х													2
Pheochromocytoma benign			^	^		X			^																	7
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma													X								X		X			7
Parathyroid gland	+	+	+	M			+	+	+				+					+	+	+	+	+	+	+	+	45
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, Zymbal's gland																										1
Pars distalis, adenoma			X							X								X							X	7
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	49
Bilateral, C-cell, adenoma																	_		_					X		2
C-cell, adenoma				X										X	X		X		X				X			8
C-cell, carcinoma																		_								1
Follicular cell, carcinoma																		Х								1

		-	_	_	_	_	_	_	7	_	_	_	<del>-</del>	_	7	,	7 .	<del>,</del> –	7	_	7	<del>-</del>	7	7	~	 	
Number of Days on Study	3			6			6 8		7			7		7			7 ′ 3 ′			7		7	2	7			
Number of Days on Study	5						0		0 5	2	3	3			3 : 1 :								3	3			
	—	<u>.</u>		<u>.</u>	<del>,</del>		<u> </u>							*.	1	<u>.                                    </u>	1		1	_	1	_			1	 	
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1		
Carcass ID Number	8	5	8	6	7	6	7	6	6	7	5	5	5	5	5	5 .	5 :	5	6	6	6	6	6	6	7		
	4	9	0	4	8	6	7	5	2	4	5	1	2	3	4	6	7	3	0	1	3	7	8	9	1		
Genital System	7								_	_	_	_						_								 	
Epididymis	+	+	+	+	+	+	+	+	+	м	+		+	+	+	+	+	+	+	+	+	+	+	+	+		
Mesothelioma malignant, metastatic,	•	•	•	•	•		•	•	•		•		•	•	•	•	•	•	•	•		•	•	•	•		
testes								X													х						
Preputial gland	+	+	+	4	+	+			+	м	+	4	+	+	+	+	+	_	+	+			+	+	+		
Adenoma		,	•	•	•	•	•	•	•	141	•	•	x	'	'	•	•	•	•	•	•	•	•	•	'		
Prostate	+	+	+	+	_	+	+	+	+	м	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Adenoma	•	•	•	•	•	•	•	•	•	171	•	•	•	•	•	•	•	•	•	•	•	٠	•	•	•		
Seminal vesicle	_	1.	_	1	_	_	_	_		М	_	٠.	_	_	_	_	_				_	_		_			
Testes	T .	T .	T	Ţ	T .	Τ.	Ţ	Ţ	+			<b>T</b>	T	Τ.	T.	Τ.	Τ.	Τ.	Τ.	Ţ	_	T		Ţ	T		
	+	+	+	† V	Y	Y	*	*	+	M		v	v	*	-	+	+	+	† V	*	+	*	+	+	*		
Bilateral, interstitial cell, adenoma		.,	.,	А	А	А	X	А	٠.		Λ	А	X	Х			<b>X</b> :	X.	A	А	Х	A.			X		
Interstitial cell, adenoma		<b>X</b>	X						Х							X							X				
Hematopoietic System																											7,
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Lymph node			+			+		+	+								+								+		
Lymph node, mandibular	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Lymph node, mesenteric	+	+	+	Α	+	+	+	+	+	÷	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Spleen	•	+	+	+	+	+	+	+	+	Α	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Histiocytic sarcoma	•		X		·	•			·		٠	·		Ť				•	•			•		•	•		
Thymus	+	+		+	+	+	+	+	М	М	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
	<del>-</del> -															_							_	_		 	
Integumentary System																											
Mammary gland	+	+		M	M	+	M	M	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+		+		
Fibroadenoma			X																					X			
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Basal cell adenoma															-	X											
Keratoacanthoma																											
Squamous cell papilloma																											
Subcutaneous tissue, fibroma						X																					
Musculoskeletal System					,				÷	_						_										 	
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
<del> </del>																		_	_					_		 _	
Nervous System	*				-	- ·.																					
Brain	. +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Spinal cord	:										+		2														
Astrocytoma malignant	:										X																
Respiratory System		<del></del>	_				<u> </u>	_										_								 	
Lung	+	+	+	: +	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Alveolar/bronchiolar adenoma	•	•	•	•	•	•		•	•	•	x	•	•	•	•		•	•	-	•	x	•	٠	•	•		
Carcinoma, metastatic, Zymbal's gland								x																			
Mediastinum, carcinoma, metastatic,																											
								v																			
Zymbal's gland								X																			
Mediastinum, mesothelioma malignant,																											
metastatic, testes																											
Pleura, mesothelioma malignant,																											
metastatic, testes						-																					

																				_						
	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
Number of Days on Study	3	-	3	3	3	3	3	3	3	3	3	3	3	3		-		_		3	3	3	3		3	
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	l	4	4	4	4	4	4	4	
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	2	1	1	1	1	1	1	1	Total
Carcass ID Number	7	7	7	8	8	8	8	9	9	9	9	9	9	9	9	9	9	0	7	7	7	8	8	8	8	Tissues
	2	3	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	0	6	9	1	2	3	5	Tumors
Genital System		_	_									_			_	_		_		_				_		
Epididymis	+	٠ +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Mesothelioma malignant, metastatic, testes																								х		3
Preputial gland	+	. 4	. +	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma	X							X																		3
Prostate	+	- 4	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma			Х																					Х		2
Seminal vesicle	+	- 4	- +	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Testes	+	٠ 4	- +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Bilateral, interstitial cell, adenoma	Х	. >			Х	X	X	X	X	Х	X	X	X	X	X	X	X :	X	X	X	$\mathbf{X}$		X		X	39
Interstitial cell, adenoma			X	X																		X		X		9
Hematopoietic System			_	_		_	_					_	_									_		_		
Bone marrow	+	. 4	- +	- 4	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node					+															•	•	•	·	+		8
Lymph node, mandibular	+	- 4	- +	. +	+	+	+	+	+	+	+	+	+	+	+	+	+	+ '	+	+	+	+	+	+	+	48
Lymph node, mesenteric	+	- 4	- +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	- 4	- +	. +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Thymus	+	- N	1 +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	46
Integumentary System		_	_	_	-									_		_				-		_		_		
Mammary gland	+	- 4	- N	1 +	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	М	+	+	+	40
Fibroadenoma	X			• '	•	•	•	•	•	•	•	•	•	•••	•	•	• • •	•	•	•	•		•	•	•	3
Skin	4		- +	. +	. +	+	+	+	+	+	+	+	+	+	+	+	+	+	_	_	4	+	4	4	+	50
Basal cell adenoma	,		•	·	•	•	•		•	•	•	•	•	•	•	•	•	•	•		•	•	•	,	•	1
Keratoacanthoma													х													1
Squamous cell papilloma												X	**													1
Subcutaneous tissue, fibroma					X										X	X			х							5
Musculoskeletal System		_				_								_												
Bone	+	- +	- +	- +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle	+	- +	- +	- +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System														_				_		_	_	_				<del></del>
Brain	+		- +	- +	. +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spinal cord																									·	1
Astrocytoma malignant																										1
Respiratory System				<u> </u>						_	_		_				-	_		-						
Lung	+		+ +	- +	. +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma								-								x		•	•				·	·	•	3
Carcinoma, metastatic, Zymbal's gland																										1
Mediastinum, carcinoma, metastatic,																										•
Zymbal's gland																										1
Mediastinum, mesothelioma malignant,																										1
																								х		1
																								1		
metastatic, testes																										
																								х		1

Individual Animal Tumor Pa	thole	ogy	OI V	<b>1</b> al	е н	(at	S II	1 ti	ne	Z-1	ea	ir (	jav	vag	e :	Stu	dy	or	C	orn	U	11:	, 10	) n	nL,	kg	(00	ntir	ued)	)	100
				5	5	6	-	6	6		-	7		7	7	7	7	7	7	7	7	7	7	7	7	7	7	7			
Number of Days on Study			ī	7 5	7 6	.2 .2	.2	6 4	7 2	8 0	2	, 0 5	2	3 0	· 3	3 1	.3	3	3 1	3 <sub>.</sub>			1 2/ 1								
			· · ·	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	ï	1	1	1	1	1	1			
Carcass ID Number	•			8 4	5	8 0	6 4	7 8	6	7 7	6	6	7 4	5 5	5 1	5 2	5 3	5 4	5 6	.7	5 8	6 0	6 1	6 3	6 7	6 8	6 9	7 1			
Respiratory System (continued)	٠.			-				•	-	,				,				•						·	. 14		_				
Nose				+	+	+	M	+	+	+	+	+	+	+	. +	+	+	+	+	+	.+	+	+	+	+	+	+	+		• •	
Trachea				+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Special Senses System		<b>3</b> -		,.	11		-	-		_		· ·	•				•	_		* 1		-				7.1			•		
Eye															+	+															
Zymbal's gland											+																				
Carcinoma											X									٠								•			
Urinary System				7.	-					-						7			Ţ							- v 1	_				٠,
Kidney				+	+	+	Α	+	+	+	+	+	+	+	+	+	_ +	+	+	+	+	+	+	+	+	+	+	+			
Urinary bladder		,		+	+	+	+	+	+	+	M	+	M	.+	, +	+	+	+	+	+	+	+	+	+	+	+	÷	+,	47.		it , 1
Systemic Lesions															-			,				~,		. ,							
Multiple organs				+	, +	+	+	+	+	+	+	,+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Histiocytic sarcoma	•					X										•															
Leukemia granulocytic						Х																: '				,					
Leukemia mononuclear							X	X				X					·X								Х						
Mesothelioma malignant											X													X	; ,		. •				

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Corn Oil: 10 mL/kg (continued)

Number of Days on Study	:	7 3	7	7	7	7	7	7	7	7	7	7	7	7 3	7	7	7 3	7	7	7	7	7	7	7	7	7	
	*	1	1	1	1	1	1	1	-1	1	1	1	1	1	1	1	1	1	1	4	4	4	4	4	4	4	
		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	2	1	1	1	1	1	1	1	Total
Carcass ID Number		7	7	7	8	8	8	8	9.	9	9	9	9	9	9	9	9	9	0	7	7	7	8	8	_	8	Tissues,
•		2	3	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	0	6	9	1	2	3	5	Tumors
Respiratory System (continued)																											
Nose		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System	***************************************																										
Eye																											2
Zymbal's gland																											1
Carcinoma																											1
Urinary System			-		_												_							_	_		
Kidney		+	+:	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Systemic Lesions			_								_	_		_													
Multiple organs		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																											1
Leukemia granulocytic																								•			1
Leukemia mononuclear		Х				X																					7
Mesothelioma malignant																									Х		3

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Corn Oil

		Untreated Control	2.5 mL/kg	5 mL/kg	10 mL/kg	_
Adrenal Medulla: Benign Phe	ochromocytoma					
Overall rate <sup>a</sup>		20/49 (41%)	19/50 (38%)	4/50 (8%)	7/50 (14%)	
Adjusted rate <sup>b</sup>		56.3%	48.3%	10.5%	16.8%	
Terminal rate <sup>c</sup>		11/25 (44%)	13/33 (39%)	4/38 (11%)	6/40 (15%)	
First incidence (days)		610	586	730 (T)	664	
Life table test <sup>d</sup>		P<0.001N	P = 0.250N	P<0.001N	P<0.001N	
Logistic regression test <sup>d</sup>		P<0.001N	P = 0.460N	P<0.001N	P = 0.002N	
Cochran-Armitage test <sup>d</sup>		P<0.001N				
Fisher exact test <sup>d</sup>			P = 0.468N	P<0.001N	P = 0.003N	
Adrenal Medulla: Malignant l	Pheochromocytoma			-	•	
Overall rate		3/49 (6%)	1/50 (2%)	1/50 (2%)	2/50 (4%)	
Adjusted rate		9.7%	2.3%	2.6%	4.5%	
Terminal rate		1/25 (4%)	0/33 (0%)	1/38 (3%)	1/40 (3%)	
First incidence (days)		635	619	730 (T)	576	
Life table test		P = 0.375N	P = 0.272N	P = 0.210N	P = 0.373N	
Logistic regression test	* - *	P = 0.511N	P = 0.300N	P = 0.292N	P = 0.552N	
Cochran-Armitage test	0	P = 0.468N			•	
Fisher exact test			P = 0.301N	P = 0.301N	P = 0.490N	
Adrenal Medulla: Pheochrom	ocytoma (Benign, Co	omplex, or Malignant	)	•		
Overall rate		23/49 (47%)	21/50 (42%)	5/50 (10%)	9/50 (18%)	
Adjusted rate		61.8%	50.6%	13.2%	20.9%	
Terminal rate		12/25 (48%)	13/33 (39%)	5/38 (13%)	7/40 (18%)	
First incidence (days)		610	520	730 (T)	576	
Life table test	,	P<0.001N	P = 0.201N	P<0.001N	P<0.001N	
Logistic regression test		P<0.001N	P = 0.380N	P<0.001N	P = 0.002N	
Cochran-Armitage test		P<0.001N	•			
Fisher exact test	•	٠	P = 0.385N	P<0.001N	P = 0.002N	
Liver: Hepatocellular Adenon	18		•	•		
Overall rate		4/50 (8%)	3/50 (6%)	0/50 (0%)	0/50 (0%)	
Adjusted rate	•	12.0%	8.6%	0.0%	0.0%	
Terminal rate		1/26 (4%)	2/33 (6%)	0/38 (0%)	0/40 (0%)	
First incidence (days)		610	695	_e	-	
Life table test		P = 0.008N	P = 0.423N	P = 0.041N	P = 0.037N	
Logistic regression test		P = 0.015N	P = 0.499N	P = 0.064N	P = 0.068N	
Cochran-Armitage test		P = 0.016N				
Fisher exact test			P=0.500N	P = 0.059N	P=0.059N	
Lung: Alveolar/bronchiolar A	denoma					
Overall rate		1/49 (2%)	0/50 (0%)	1/49 (2%)	3/49 (6%)	
Adjusted rate		3.6%	0.0%	2.4%	7.5%	
Terminal rate		0/25 (0%)	0/33 (0%)	0/37 (0%)	3/40 (8%)	
First incidence (days)		710	_	706	730 (T)	
Life table test		P = 0.165	P = 0.461N	P = 0.673N	P = 0.475	
Logistic regression test		P = 0.122	P = 0.493N	P = 0.757N	P = 0.404	
O		P = 0.095				
Cochran-Armitage test Fisher exact test			P = 0.495N	P = 0.753N	P=0.309	

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Corn Oil (continued)

	Untreated Control	2.5 mL/kg	5 mL/kg	10 mL/kg	
Lung: Alveolar/bronchiolar Adenoma or Carcinoma		D	4.		
Overall rate	1/49 (2%)	1/50 (2%)	2/49 (4%)	3/49 (6%)	
Adjusted rate	3.6%	3.0%	5.0%	7.5%	
Terminal rate	0/25 (0%)	1/33 (3%)	1/37 (3%)	3/40 (8%)	
First incidence (days)	710	730 (T)	706	730 (T)	
Life table test	P = 0.281	P=0.707N	P = 0.631	P = 0.475	
Logistic regression test	P = 0.219	P = 0.746N	P = 0.523	P = 0.404	
Cochran-Armitage test	P = 0.162				
Fisher exact test		P = 0.747N	P = 0.500	P = 0.309	
Mammary Gland: Fibroadenoma					
Overall rate	4/50 (8%)	1/50 (2%)	1/50 (2%)	3/50 (6%)	
Adjusted rate	11.0%	3.0%	2.6%	7.0%	
Terminal rate	1/26 (4%)	1/33 (3%)	1/38 (3%)	2/40 (5%)	
First incidence (days)	216	730 (T)	730 (T)	622	
Life table test	P = 0.402N	P = 0.154N	P = 0.125N	P = 0.370N	
Logistic regression test	P = 0.565	P = 0.187N	P = 0.197N	P = 0.628	
Cochran-Armitage test	P = 0.523N				
Fisher exact test	-	P = 0.181N	P = 0.181N	P = 0.500N	
Pancreas: Adenoma					
Overall rate	1/50 (2%)	8/47 (17%)	10/50 (20%)	23/50 (46%)	
Adjusted rate	3.8%	25.0%	24.6%	53.2%	
Terminal rate	1/26 (4%)	8/32 (25%)	8/38 (21%)	20/40 (50%)	
First incidence (days)	730 (T)	730 (T)	569	576	
Life table test	P<0.001	P = 0.033	P = 0.023	P<0.001	
ogistic regression test	P<0.001	P = 0.033	P = 0.006	P<0.001	
Cochran-Armitage test	P<0.001				
Fisher exact test		P=0.012	P = 0.004	P<0.001	
Pancreas: Adenoma or Carcinoma					
Overall rate	1/50 (2%)	8/47 (17%)	11/50 (22%)	23/50 (46%)	
Adjusted rate	3.8%	25.0%	27.2%	53.2%	
Cerminal rate	1/26 (4%)	8/32 (25%)	9/38 (24%)	20/40 (50%)	
First incidence (days)	730 (T)	730 (T)	569	576	
Life table test	P<0.001	P=0.033	P=0.015	P<0.001	
ogistic regression test	P<0.001	P = 0.033	P = 0.003	P<0.001	
Cochran-Armitage test Fisher exact test	P<0.001	P=0.012	P = 0.002	P<0.001	
Pomamostic Halaton Adamana					
Pancreatic Islets: Adenoma Overall rate	0/50 (199/)	2147 1500	A160 /00/	750 /140/	
Overan rate Adjusted rate	9/50 (18%) 29.0%	3/47 (6%)	4/50 (8%)	7/50 (14%)	
Ferminal rate	5/26 (19%)	8.4% 2/32 (6%)	10.5%	16.6%	
First incidence (days)	638	2/32 (6%) 599	4/38 (11%) 730 (T)	5/40 (13%) 680	
Life table test	P=0.246N	P=0.038N	730 (T) P=0.034N		
Logistic regression test	P=0.400N	P = 0.038N P = 0.073N	P = 0.034N P = 0.086N	P=0.147N P=0.299N	
Cochran-Armitage test	P=0.470N	1 -0.07314	1 ~0.00014	1 -0.27719	
Fisher exact test	1 -0.4/014	P=0.075N	P=0.117N	P=0.393N	

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Corn Oil (continued)

· ;	£		Untreated Control	2.5 mL/kg	5 mL/kg	10 mL/kg
Pituitary Gland (Pars Dist	alis): Adenoma	8				
Overall rate	3 11 183		5/50 (10%)	10/50 (20%)	6/49 (12%)	7/50 (14%)
Adjusted rate	• •		16.6%	25.0%	15.4%	16.3%
erminal rate	4.5.2	2	3/26 (12%)	5/33 (15%)	5/37 (14%)	5/40 (13%)
irst incidence (days)		•	620	409	562	575
ife table test	t Katha a		P = 0.360N	P=0.218	P = 0.560N	P = 0.602N
ogistic regression test			P = 0.472	P = 0.130	P=0.495	P=0.386
Cochran-Armitage test			P = 0.498	•		**
isher exact test		* *		P=0.131	P=0.486	P=0.380
reputial Gland: Adenoma				•		
Overall rate			6/50 (12%)	3/50 (6%)	4/50 (8%)	3/48 (6%)
Adjusted rate			16.3%	8.7%	10.0%	7.7%
Terminal rate	1	. *	2/26 (8%)	2/33 (6%)	3/38 (8%)	3/39 (8%)
First incidence (days)			.610	707	576	730 (T)
ife table test			P=0.133N	P=0.198N	P=0.265N	P=0.139N
ogistic regression test			P = 0.251N	P = 0.242N	P = 0.375N	P=0.271N
Cochran-Armitage test		•	P = 0.259N		**	+ M
isher exact test	A	:	. 314	P = 0.243N	P=0.370N	P=0.264N
ikin: Squamous Cell Papil	loma .					
Overall rate			1/50 (2%)	1/50 (2%)	5/50 (10%)	1/50 (2%)
Adjusted rate		ς,	3.8%	3.0%	13.2%	2.5%
Cerminal rate	* * * * * * * * * * * * * * * * * * * *	,	1/26 (4%)	1/33 (3%)	5/38 (13%)	1/40 (3%)
irst incidence (days)			730 (T)	.730 (T)	730 (T)	730 (T)
ife table test	4.5		P=0.529N	P = 0.708N	P = 0.208	P=0.663N
ogistic regression test			P = 0.529N	P = 0.708N	P = 0.208	P=0.663N
Cochran-Armitage test			P = 0.500			18.0
isher exact test	٠.		-	P = 0.753N	P = 0.102	P=0.753N
Skin: Squamous Cell Papil	loma or Squamou	s Cell Car	cinoma	•	4 × 2 5	grand in the second
Overall rate			3/50 (6%)	1/50 (2%)	5/50 (10%)	1/50 (2%)
Adjusted rate			10.1%	3.0%	13.2%	2.5%
Terminal rate	,		2/26 (8%)	1/33 (3%)	5/38 (13%)	1/40 (3%)
First incidence (days)	: 1		685	730 (T)	730 (T)	730 (T)
Life table test			P = 0.220N .	P = 0.247N	P = 0.554	P=0.191N
ogistic regression test			P = 0.270N	P = 0.288N	P = 0.458	P=0.252N
Cochran-Armitage test			P = 0.371N	, •		e jara jarah sarah
isher exact test			•	P = 0.309N	P = 0.357	P=0.309N
ikin: Squamous Cell Papil	loma, Keratoacan	thoma, Bas	sal Cell Adenon	na, Squamous Cell	Carcinoma, or B	Basal Cell Carcinoma
Overall rate			5/50 (10%)	2/50 (4%)	5/50 (10%)	3/50 (6%)
Adjusted rate			17.6%	6.1%	13.2%	7.5%
Terminal rate			4/26 (15%)	2/33 (6%)	5/38 (13%)	3/40 (8%)
irst incidence (days)			685	730 (T)	730 (T)	730 (T)
ife table test			P = 0.214N	P=0.143N	P = 0.401N	P=0.169N
ogistic regression test	* *		P=0.262N	P = 0.177N	P = 0.492N	P=0.229N
Cochran-Armitage test	•	•	P=0.410N	.4	• .	العالمين والمرفع يعرب والعراجي
isher exact test						

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Corn Oil (continued)

	Untreated Control	2.5 mL/kg	5 mL/kg	10 mL/kg	2.7
kim (Subcutaneous Tissue): Fibroma			•		
Overall rate	1/50 (2%)	1/50 (2%)	1/50 (2%)	5/50 (10%)	
djusted rate	3.2%	2.3%	2.6%	12.0%	
erminal rate	0/26 (0%)	0/33 (0%)	1/38 (3%)	4/40 (10%)	
irst incidence (days)	704 ` ´	619 `	730 (T)	672	
ife table test	P=0.054	P = 0.749N	P=0.683N	P = 0.205	
ogistic regression test	P = 0.028	P = 0.760	P = 0.749N	P=0.125	
ochran-Armitage test	P = 0.025				
sher exact test		P = 0.753N	P=0.753N	P = 0.102	
estes: Adenoma					
verall rate	48/50 (96%)	46/50 (92%)	47/50 (94%)	48/49 (98%)	
djusted rate	100.0%	100.0%	100.0%	100.0%	
erminal rate	26/26 (100%)	33/33 (100%)	38/38 (100%)	40/40 (100%)	
rst incidence (days)	523	520	432	576	
fe table test	P = 0.002N	P = 0.074N	P = 0.006N	P = 0.003N	
ogistic regression test	P = 0.586N	P = 0.420N	P = 0.590N	P = 0.680N	
ochran-Armitage test	P = 0.300				
sher exact test	**	P = 0.339N	P = 0.500N	P=0.508	
nyroid Gland (C-cell): Adenoma					
verall rate	4/50 (8%)	5/49 (10%)	4/49 (8%)	10/49 (20%)	
djusted rate	12.7%	14.2%	10.5%	25.0%	
erminal rate	2/26 (8%)	4/33 (12%)	4/38 (11%)	10/40 (25%)	
irst incidence (days)	620	653	730 (T)	730 (T)	
ife table test	P=0.138	P = 0.604	P = 0.463N	P=0.251	
ogistic regression test	P=0.065	P = 0.495	P = 0.627N	P=0.118	
ochran-Armitage test	P=0.037				
isher exact test		P=0.487	P=0.631	P=0.068	
hyroid Gland (C-cell): Adenoma or Carcinoma		(110 (100)		4440 (000)	
verall rate	5/50 (10%)	6/49 (12%)	4/49 (8%)	11/49 (22%)	
djusted rate	14.6%	16.4%	10.5%	27.5%	
erminal rate	2/26 (8%)	4/33 (12%)	4/38 (11%)	11/40 (28%)	
rst incidence (days)	620	653	730 (T)	730 (T)	
fe table test	P=0.173	P=0.589	P=0.335N	P=0.287	
ogistic regression test	P=0.071	P≈0.488	P = 0.500N	P=0.113	
ochran-Armitage test	P=0.048				
sher exact test		P=0.486	P=0.513N	P=0.079	
ll Organs: Mononuclear Cell Leukemia	08/50 (516)	1750 (000)		### (1 AM)	
verall rate	27/50 (54%)	16/50 (32%)	11/50 (22%)	7/50 (14%)	
djusted rate	62.6%	39.6%	25.4%	15.9%	
erminal rate	11/26 (42%)	9/33 (27%)	6/38 (16%)	4/40 (10%)	
irst incidence (days)	523	586	555 D - 2 224 N	623	
ife table test	P<0.001N	P=0.016N	P<0.001N	P<0.001N	
ogistic regression test	P<0.001N	P = 0.022N	P = 0.001N	P<0.001N	
ochran-Armitage test	P<0.001N				
isher exact test	•	P = 0.021N	P<0.001N	P<0.001N	

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Corn Oil (continued)

	<u> </u>	<del></del>		<del> </del>	<del></del>
		Untreated Control	2.5 mL/kg	5 mL/kg	10 mL/kg
All Organs: Malignant Mes	sothelioma				
Overall rate	, on the same	2/50 (4%)	1/50 (2%)	1/50 (2%)	3/50 (6%)
Adjusted rate		6.0%	2.1%	2.2%	7.2%
Terminal rate		1/26 (4%)	0/33 (0%)	0/38 (0%)	2/40 (5%)
First incidence (days)		635	562	569	692
Life table test		P=0.411	P=0.480N	P=0.469N	P=0.641
Logistic regression test		P=0.259	P=0.511N	P=0.520N	P=0.504
Cochran-Armitage test		P=0.324			,
Fisher exact test	•		P = 0.500N	P=0.500N	P=0.500
All Organs: Benign Neopla	sms				• • • • • • • • • • • • • • • • • • •
Overall rate		50/50 (100%)	49/50 (98%)	48/50 (96%)	50/50 (100%)
Adjusted rate		100.0%	100.0%	100.0%	100.0%
Terminal rate		26/26 (100%)	33/33 (100%)	38/38 (100%)	40/40 (100%)
First incidence (days)		216	409	432	575
Life table test	·	P = 0.002N	P = 0.115N	P = 0.005N	P=0.003N
Logistic regression test		P=0.357N	P = 0.362N	P = 0.140N	_ <b>f</b>
Cochran-Armitage test		P=0.616		, <b>'</b>	•
Fisher exact test			P = 0.500N	P = 0.247N	P=1.000N
All Organs: Malignant Neo	plasms				
Overall rate		33/50 (66%)	21/50 (42%)	16/50 (32%)	16/50 (32%)
Adjusted rate		72.6%	48.2%	34.6%	34.3%
Terminal rate		14/26 (54%)	11/33 (33%)	8/38 (21%)	10/40 (25%)
First incidence (days)		523	520	432	576
Life table test		P<0.001N	P = 0.014N	P<0.001N	P<0.001N
Logistic regression test		P = 0.003N	P = 0.027N	P<0.001N	P=0.001N
Cochran-Armitage test		P<0.001N			
Fisher exact test			P = 0.013N	P<0.001N	P<0.001N
All Organs: Benign or Mal	ignant Neoplasms		•		<i>i</i> *
Overall rate		50/50 (100%)	49/50 (98%)	48/50 (96%)	50/50 (100%)
Adjusted rate		100.0%	100.0%	100.0%	100.0%
Terminal rate		26/26 (100%)	33/33 (100%)	38/38 (100%)	40/40 (100%)
First incidence (days)		216	409	432	575
Life table test		P = 0.002N	P = 0.115N	P=0.005N	P = 0.003N
Logistic regression test		P = 0.357N	P = 0.362N	P = 0.140N	<del>-</del> ·
Cochran-Armitage test	,	P = 0.616			
Fisher exact test	· a		P = 0.500N	P = 0.247N	P = 1.000N

(T)Terminal sacrifice

Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, bone marrow, brain, epididymis, heart, kidney, larynx, liver, lung, nose, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, spleen, testes, thyroid gland, and urinary bladder; for other tissues, denominator is number of animals necropsied.

b Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality

Observed incidence at terminal kill

Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table test regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.

Not applicable; no neoplasms in animal group Value of statistic cannot be computed.

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Corn Oil<sup>a</sup>

	Untreated Control	10 mL/kg Saline	2.5 mL/kg	5 mL/kg	10 mL/kg
Disposition Summary					
Animals initially in study Early deaths	50	50	50	50	50
Moribund	16	14	9	6	4
Natural deaths	8	4	8	6	6
Survivors	,	•	· ·	·	ū
Died last week of study	· 1				
Terminal sacrifice	25	32	33	38	40
Terminal Sacrifice	23	<i>3</i> <b>.</b>	33	50	40
Animals examined microscopically	50	50	50	50	50
Alimentary System					
Esophagus	(49)	(48)	(50)	(50)	(50)
Hyperkeratosis	(**)	(10)	1 (2%)	(54)	(50)
Intestine large, colon	(49)	(49)	(46)	(49)	(48)
Cyst	(17)	(17)	. (.~)	(17)	1 (2%)
Intestine large, cecum	(46)	(49)	(45)	(48)	(46)
Erosion	3 (7%)	1 (2%)	()	(10)	(.~)
Inflammation, granulomatous Ulcer	5 (1,70)	1 (270)	1 (2%) 1 (2%)		
Intestine small, ileum	(46)	(49)	(45)	(48)	(47)
Erosion	(40)	1 (2%)	. (43)	(40)	(47)
Fibrosis		1 (270)		1 (2%)	
Pigmentation		1 (2%)		1 (270)	
Liver	(50)	(50)	(50)	(50)	(50)
Angiectasis	(50)	2 (4%)	1 (2%)	(50)	(50)
Basophilic focus	33 (66%)	33 (66%)	38 (76%)	37 (74%)	46 (92%)
Clear cell focus	11 (22%)	16 (32%)	27 (54%)	24 (48%)	21 (42%)
Congestion	1 (2%)	10 (3270)	27 (3170)	21 (4070)	21 (4270)
Degeneration, cystic	1 (270)		2 (4%)		
Eosinophilic focus	9 (18%)	3 (6%)	4 (8%)	4 (8%)	6 (12%)
Fatty change, diffuse	3 (6%)	2 (4%)	19 (38%)	27 (54%)	33 (66%)
Fatty change, focal	3 (6%)	4 (8%)	19 (3070)	21 (3470)	
Hematocyst	1 (2%)	7 (0/0)			3 (6%)
Hematopoietic cell proliferation	1 (2%)				
Hepatodiaphragmatic nodule	4 (8%)	6 (12%)	4 (8%)	8 (16%)	5 (10%)
Infarct	1 (2%)	0 (12/0)	+ (070)	5 (1070)	3 (1070)
Mixed cell focus	5 (10%)	5 (10%)	1 (2%)	8 (16%)	8 (16%)
Necrosis	1 (2%)	3 (10/0)	1 (270)	1 (2%)	3 (10%)
Mesentery	(6)	(7)	(8)	(4)	(8)
Fat, hemorrhage	(4)	. (7)	1 (13%)	(7)	(0)
Fat, inflammation, chronic active Fat, mineralization	1 (17%)	1 (14%)	1 (15/0)		2 (250/
Fat, necrosis	2 (33%)	3 (43%)	5 (63%)	2 (50%)	2 (25%) 7 (88%)
Pancreas	(50)	(50)		` '	7 (88%) (50)
Metaplasia	(50)	(50)	(47)	(50)	(50)
Thrombosis			1 (2%)		1 (2%)
Acinus, atrophy	38 (76%)	40 (80%)	25 (53%)	32 (64%)	24 (480%)
Acinus, hyperplasia	8 (16%)	5 (10%)	28 (60%)	28 (56%)	24 (48%) 35 (70%)
Acinus, hyperplasia Acinus, hypertrophy, focal	J (10/0)	3 (1070)	20 (00/0)	23 (30%)	
Actions, hypertrophy, rocal Artery, hyperplasia			1 (2%)		1 (2%)
Artery, hyperplasia  Artery, inflammation, chronic active	2 (4%)	2 (4%)	5 (11%)	1 (2%)	1 (2%)

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Corn Oil (continued)

	Untreated Control	10 mL/kg Saline	2.5 mL/kg	5 mL/kg	10 mL/kg
Alimentary System (continued)		• • •		* "	
Pharynx	(1)		(1)		•
Hyperkeratosis	1 (100%)		, ,		
Inflammation, chronic active	1 (100%)		$(\mathbf{r}_{i}, \dots, \mathbf{r}_{i}) = (\mathbf{r}_{i}, \dots, \mathbf{r}_{i})$	•	A Company of the Comp
Salivary glands	(50)	(50)	(50)	(50)	(49)
Inflammation, chronic active	1 (2%)	, ,		` ,	
Duct, metaplasia, squamous	6 (12%)	6 (12%)	11 (22%)	8 (16%)	8 (16%)
Stomach, forestomach	(50)	(49)	<b>(50)</b>	(50)	(50)
Fibrosis	` '	` '	ì (2%)		
Hyperkeratosis	3 (6%)	1 (2%)	1 (2%)	2 (4%)	5 (10%)
Hyperplasia, basal cell	4 (8%)	4 (8%)	2 (4%)	1 (2%)	8 (16%)
Ulcer	2 (4%)	. (/	3 (6%)	1 (2%)	3 (6%)
Stomach, glandular	(50)	(50)	(50)	(50)	(48)
Erosion	10 (20%)	4 (8%)	2 (4%)	2 (4%)	2 (4%)
Hyperplasia	20 (2070)	3 (6%)	- ()	-()	_ (***)
Mineralization		5 (5.5)	1 (2%)		1 (2%)
Tongue		(3)	(2)		(3)
Hemorrhage	•	(9)	2 (100%)		(a)
Hyperplasia, squamous	, ,	, ·	2 (20070)		1 (33%)
Cardiovascular System					
Heart	(50)	(50)	(50)	(50)	(50)
Cardiomyopathy	47 (94%)	42 (84%)	46 (92%)	47 (94%)	45 (90%)
Pigmentation	(7 (7 (7)	12 (0170)	1 (2%)	., (> 1,0)	45 (50%)
Thrombosis	3 (6%)	1 (2%)	1 (2%)		1 (2%)
Artery, inflammation, chronic active	3 (070)	1 (2%)	1 (2%)		1 (270)
Attery, initialimation, enfonce active		1 (270)	1 (270)	·	
Endocrine System					
Adrenal cortex	(50)	(50)	(50)	(50)	<b>(50)</b>
Accessory adrenal cortical nodule		` '	` '	ì (2%)	
Hypertrophy	2 (4%)	3 (6%)	4 (8%)	` ,	in a second second second
Adrenal medulla	(49)	(49)	(50)	(50)	(50)
Cyst	` '	<b>、</b> /	` '	` '	1 (2%)
Hyperplasia	8 (16%)	7 (14%)	12 (24%)	11 (22%)	9 (18%)
Islets, pancreatic	(50)	(49)	(47)	(50)	(50)
Hyperplasia	1 (2%)	2 (4%)	4 (9%)	2 (4%)	3 (6%)
Parathyroid gland	(44)	(47)	(49)	(40)	(45)
Hyperplasia	1 (2%)	1 (2%)	(42)	1 (3%)	(43)
Pituitary gland	(50)	(49)	(50)	(49)	(50)
Pars distalis, angiectasis	5 (10%)	6 (12%)	5 (10%)	4 (8%)	6 (12%)
Pars distalis, cyst	5 (10/0)	1 (2%)	3 (6%)	1 (2%)	· (12/0)
Pars distalis, hyperplasia	9 (18%)	9 (18%)	13 (26%)	9 (18%)	9 (18%)
Pars intermedia, hyperplasia	9 (1070)		13 (2070)	) (10%)	1 (2%)
Rathke's cleft, cyst	(50)	1 (2%)	(40)	(40)	(40)
Thyroid gland	(50)	(49)	(49)	(49)	(49)
Bilateral, C-cell, hyperplasia	A //A	0./40~	1 (2%)	1 (2%)	44 (000)
C-cell, hyperplasia	3 (6%)	9 (18%)	8 (16%)	7 (14%)	11 (22%)
Follicle, cyst	1 (2%)				
Follicular cell, hyperplasia			3 (6%)		2 (4%)

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Corn Oil (continued)

* '	Untreated Control	10 mL/kg Saline	2.5 mL/kg	5 mL/kg	10 mL/kg
General Body System	· ·				
Genital System					
<b>Epididymis</b>	(50)	(50)	(50)	(50)	(48)
Spermatocele	• ;	ì (2%)		, ,	, ,
Preputial gland	(50)	(50)	(50)	(50)	(48)
Abscess	3 (6%)	4 (8%)	4 (8%)	5 (10%)	7 (15%)
Hyperplasia, squamous	2 (2,2)	. ()	1 (2%)	- (/	(*)
Inflammation, chronic active	2 (4%)	• •	1 (2%)		
Prostate	(50)	(49)	(50)	(50)	(48)
Hyperplasia	2 (4%)	4 (8%)	6 (12%)	7 (14%)	4 (8%)
Inflammation, acute	- ( , ~) ,	· (= /~)	- (/-)	(2)	1 (2%)
Inflammation, chronic active	2 (4%)	2 (4%)	3 (6%)		- (-,-)
Testes	(50)	(50)	(50)	(50)	(49)
Interstitial cell, hyperplasia	(5-7)	4 (8%)	3 (6%)	4 (8%)	4 (8%)
Seminiferous tubule, atrophy	7 (14%)	4 (8%)	2 (4%)	4 (8%)	6 (12%)
Seminiferous tubule, mineralization	, (1470)	1 (2%)	~ (.//)	. (0,0)	: (12/0)
Hematopoletic System Bone marrow Depletion cellular	(50) 1 (2%)	(50)	(50)	(50)	(50)
Fibrosis	1 (2%)				4,
Lymph node	(28)	(22)	(15)	(13)	(8)
Lumbar, pigmentation	()	1 (5%)	<b>\</b> )	, , ,	(-)
Mediastinal, angiectasis	4 (14%)	1 (5%)	3 (20%)	5 (38%)	1 (13%)
Mediastinal, ectasia	1 (4%)	1 (070)	0 (20/0)	0 (00%)	1 (10,0)
	- ( T/O )				
	. ,				
Mediastinal, infiltration cellular, mast					
Mediastinal, infiltration cellular, mast cell	1 (4%)		4 (27%)	1 (8%)	2 (25%)
Mediastinal, infiltration cellular, mast cell Mediastinal, pigmentation	1 (4%)		4 (27%)	1 (8%) 1 (8%)	2 (25%)
Mediastinal, infiltration cellular, mast cell Mediastinal, pigmentation Pancreatic, angiectasis	1 (4%) 1 (4%)			1 (8%) 1 (8%)	2 (25%)
Mediastinal, infiltration cellular, mast cell Mediastinal, pigmentation Pancreatic, angiectasis Pancreatic, ectasia	1 (4%)		4 (27%) 2 (13%)		2 (25%)
Mediastinal, infiltration cellular, mast cell Mediastinal, pigmentation Pancreatic, angiectasis Pancreatic, ectasia Pancreatic, infiltration cellular,	1 (4%) 1 (4%) 3 (11%)				
Mediastinal, infiltration cellular, mast cell Mediastinal, pigmentation Pancreatic, angiectasis Pancreatic, ectasia Pancreatic, infiltration cellular, histiocyte	1 (4%) 1 (4%)		2 (13%)		2 (25%)
Mediastinal, infiltration cellular, mast cell Mediastinal, pigmentation Pancreatic, angiectasis Pancreatic, ectasia Pancreatic, infiltration cellular, histiocyte Pancreatic, pigmentation	1 (4%) 1 (4%) 3 (11%)	1 (50%)			
Mediastinal, infiltration cellular, mast cell Mediastinal, pigmentation Pancreatic, angiectasis Pancreatic, ectasia Pancreatic, infiltration cellular, histiocyte Pancreatic, pigmentation Renal, pigmentation	1 (4%) 1 (4%) 3 (11%) 2 (7%)	1 (5%)	2 (13%)	1 (8%)	2 (25%) 1 (13%)
Mediastinal, infiltration cellular, mast cell Mediastinal, pigmentation Pancreatic, angiectasis Pancreatic, ectasia Pancreatic, infiltration cellular, histiocyte Pancreatic, pigmentation Renal, pigmentation Lymph node, mandibular	1 (4%) 1 (4%) 3 (11%)	1 (5%) (50)	2 (13%)		2 (25%) 1 (13%) (48)
Mediastinal, infiltration cellular, mast cell Mediastinal, pigmentation Pancreatic, angiectasis Pancreatic, ectasia Pancreatic, infiltration cellular, histiocyte Pancreatic, pigmentation Renal, pigmentation Lymph node, mandibular Angiectasis	1 (4%) 1 (4%) 3 (11%) 2 (7%)		2 (13%) 1 (7%) (49)	1 (8%)	2 (25%) 1 (13%)
Mediastinal, infiltration cellular, mast cell Mediastinal, pigmentation Pancreatic, angiectasis Pancreatic, ectasia Pancreatic, infiltration cellular, histiocyte Pancreatic, pigmentation Renal, pigmentation Lymph node, mandibular Angiectasis Necrosis	1 (4%) 1 (4%) 3 (11%) 2 (7%) (50)	(50)	2 (13%) 1 (7%) (49) 1 (2%)	1 (8%)	2 (25%) 1 (13%) (48) 1 (2%)
Mediastinal, infiltration cellular, mast cell Mediastinal, pigmentation Pancreatic, angiectasis Pancreatic, ectasia Pancreatic, infiltration cellular, histiocyte Pancreatic, pigmentation Renal, pigmentation Lymph node, mandibular Angiectasis Necrosis Lymph node, mesenteric	1 (4%) 1 (4%) 3 (11%) 2 (7%) (50)		2 (13%) 1 (7%) (49)	1 (8%) (50)	2 (25%) 1 (13%) (48)
Mediastinal, infiltration cellular, mast cell Mediastinal, pigmentation Pancreatic, angiectasis Pancreatic, ectasia Pancreatic, infiltration cellular, histiocyte Pancreatic, pigmentation Renal, pigmentation Lymph node, mandibular Angiectasis Necrosis Lymph node, mesenteric Angiectasis	1 (4%) 1 (4%) 3 (11%) 2 (7%) (50) (50) 1 (2%)	(50)	2 (13%)  1 (7%)  (49)  1 (2%) (50)	1 (8%) (50) (50) 1 (2%)	2 (25%) 1 (13%) (48) 1 (2%)
Mediastinal, infiltration cellular, mast cell Mediastinal, pigmentation Pancreatic, angiectasis Pancreatic, ectasia Pancreatic, infiltration cellular, histiocyte Pancreatic, pigmentation Renal, pigmentation Lymph node, mandibular Angiectasis Necrosis Lymph node, mesenteric Angiectasis Ectasia	1 (4%) 1 (4%) 3 (11%) 2 (7%) (50) (50) 1 (2%) 2 (4%)	(50)	2 (13%) 1 (7%) (49) 1 (2%)	1 (8%) (50)	2 (25%) 1 (13%) (48) 1 (2%)
Mediastinal, infiltration cellular, mast cell Mediastinal, pigmentation Pancreatic, angiectasis Pancreatic, ectasia Pancreatic, infiltration cellular, histiocyte Pancreatic, pigmentation Renal, pigmentation Lymph node, mandibular Angiectasis Necrosis Lymph node, mesenteric Angiectasis	1 (4%) 1 (4%) 3 (11%) 2 (7%) (50) (50) 1 (2%)	(50)	2 (13%)  1 (7%)  (49)  1 (2%) (50)	1 (8%) (50) (50) 1 (2%)	2 (25%) 1 (13%) (48) 1 (2%)

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Corn Oil (continued)

	Untreated Control	10 mL/kg Saline	2.5 mL/kg	5 mL/kg	10 mL/kg
Hematopoietic System (continued)					
Spleen	(49)	(50)	(49)	(50)	(49)
Angiectasis	2 (4%)				1 (2%)
Fibrosis	12 (24%)	8 (16%)	9 (18%)	3 (6%)	4 (8%)
Hematopoietic cell proliferation	8 (16%)	6 (12%)	3 (6%)	5 (10%)	5 (10%)
Infarct	2 (4%)	2 (4%)	1 (2%)	2 (4%)	*4
Infiltration cellular, lipocyte					1 (2%)
Metaplasia		•			1 (2%)
Pigmentation			2 (4%)	1 (2%)	1 (2%)
Capsule, fibrosis			1 (2%)	,	
Capsule, hemorrhage			` '	1 (2%)	
Thymus	(48)	(48)	(45)	(45)	(46)
Cyst		1 (2%)	` /	` /	` '
Epithelial cell, hyperplasia	10 (21%)	7 (15%)	5 (11%)	5 (11%)	9 (20%)
Integumentary System					
Mammary gland	(31)	(42)	(39)	(39)	(40)
Galactocele	(31)	(42)	(37)	(33)	2 (5%)
Skin	(50)	(50)	(50)	(50)	(50)
Cyst epithelial inclusion	(30)	(30)	4 (8%)	2 (4%)	2 (4%)
Developmental malformation			1 (2%)	,2 (470)	2 (470)
Erosion		1 (2%)	1 (2%)		
Fibrosis		1 (270)	1 (270)	1 (2%)	
	·			1 (270)	1 (20)
Hemorrhage			•		1 (2%) 2 (4%)
Hyperkeratosis					
Inflammation, acute			1 (201)		1 (2%)
Mineralization	•		1 (2%)	1 (201)	
Ulcer				1 (2%)	
Musculoskeletal System					
Bone	(50)	(50)	(50)	(50)	(50)
Hyperostosis		, ,	2 (4%)	, ,	
Skeletal muscle	(50)	(50)	(50)	(50)	(50)
Atrophy	5 (10%)	3 (6%)	8 (16%)	5 (10%)	2 (4%)
Inflammation, chronic active	1 (2%)	• •		, ,	
Mineralization	1 (2%)	,			•
Nervous System	· · · · · · · · · · · · · · · · · · ·	<u></u> .	<del></del>	· · · · · · · · · · · · · · · · · · ·	······································
Brain	(50)	(49)	(50)	(50)	(50)
Compression	1 (2%)	(**)	1 (2%)	(-9)	, , , , , , , , , , , , , , , , , , , ,
Spinal cord	1 (2/0)		(1)	(1)	(1)
Hemorrhage			(*)	1 (100%)	(*)

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Corn Oil (continued)

	Untreated Control	10 mL/kg Saline	2.5 mL/kg	5 mL/kg	10 mL/kg
Respiratory System					
Lung	(49)	(49)	(50)	(49)	(49)
Edema	1 (2%)		1 (2%)	2 (4%)	1 (2%)
Foreign body			1 (2%)		
Fungus	1 (2%)				
Hemorrhage			2 (4%)		1 (2%)
Infarct	1 (2%)			4 (00)	a
Infiltration cellular, histiocyte	2 (4%)	5 (10%)		1 (2%)	2 (4%)
Inflammation, acute			1 (2%)		
Inflammation, granulomatous		1 (2%)	1 (2%)		
Metaplasia, osseous	1 (00)	1 (2%)	1 (00)	1 (00%)	0 (40%
Alveolar epithelium, hyperplasia	1 (2%)	1 (2%)	1 (2%)	1 (2%)	2 (4%)
Nose	(50)	(50)	(50)	(49)	(49)
Fungus	13 (26%)	12 (24%)	12 (24%)	18 (37%)	15 (31%)
Hyperplasia	1 (2%)	14 (200%)	17 (24%)	21 (43%)	21 (42%)
Inflammation, acute	16 (32%)	14 (28%)	17 (34%)	1 (2%)	21 (43%)
Metaplasia, cartilaginous Respiratory epithelium, hyperkeratosis			3 (6%)	1 (2%)	
Respiratory epithelium, metaplasia,			3 (0%)	1 (270)	
squamous	7 (14%)	8 (16%)	2 (4%)	7 (14%)	8 (16%)
Special Senses System Eye	(1)	(3)	(2)	(3)	(2)
Synechia	, ,	1 (33%)	` `	1 (33%)	2 (100%)
Lens, cataract		2 (67%)		2 (67%)	
Retina, atrophy	1 (100%)	1 (33%)		1 (33%)	2 (100%)
Sclera, mineralization			1 (50%)		
Urinary System					
Kidney	(50)	(49)	(48)	(50)	(49)
Degeneration	1 (2%)	(17)	(10)	(00)	(12)
Hydronephrosis	~ (=,,,		1 (2%)		
Infarct	1 (2%)		- ()		
Nephropathy	47 (94%)	45 (92%)	43 (90%)	45 (90%)	40 (82%)
Cortex, mineralization	` /	1 (2%)	` /	` '	2 (4%)
Cortex, necrosis		1 (2%)			<b>()</b>
Papilla, mineralization					2 (4%)
Renal tubule, pigmentation			*		1 (2%)

A Number of animals examined microscopically at site and number of animals with lesion

ರ ಕಟ್ಟಿಕೆ ಮಾಡಲಾಗಿ ಬೆಂದು ಬರುವುದು ಬರುವುದು ಬರುವುದು ಬರುವುದು ಬರುವುದು ಬರುವುದು ಬರುವುದು ಬರುವುದು ಅವರಿ ಅವರಿ ಮಾಡಲಾಗುವುದು ಪ್ರಾಥಾಣಕ್ಕೆ ಬರುವುದು ಬರುವುದು ಪ್ರತಿಕಾರ ಮಾಡಲಾಗುವುದು ಬರುವುದು ಬರುವುದು ಬರುವುದು ಬರುವುದು ಬರುವುದು ಬರುವುದು ಬರುವುದು ಬರುವು ಪ್ರಾಥಾಣಕ್ಕೆ ಮುಂದು ಮಾಡಲಾಗುವುದು ಬರುವುದು ಪ

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## APPENDIX B SUMMARY OF LESIONS IN MALE RATS IN THE 2-YEAR GAVAGE STUDY OF SAFFLOWER OIL

Table B1	Summary of the Incidence of Neoplasms in Male Rats	
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TABLE B1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Gavage Study of Safflower Oila

	Untreated Control	2.5 mL/kg	5 mL/kg	10 mL/kg
Disposition Summary		,		
Animals initially in study	60	60	60	60
15-Month interim evaluation	10	10	10	9
Early deaths				-
Moribund	12	9	7	5
Natural deaths	8	8	3	10
Survivors	8	0	3	10
Terminal sacrifice	30	22	40	26
	30	33	40	36
Animals examined microscopically	60	60	60	60
15-Month Interim Evaluation				
Alimentary System				,
Liver	(10)	(10)	(10)	(9)
Pancreas	(10)	(10)	(10)	(9)
Acinus, adenoma	(**)	()	(**)	1 (11%)
				1 (1170)
Cardiovascular System				
Heart	(10)	(10)	(10)	(9)
Endocrine System				
Adrenal gland, medulla	(10)	(10)	(10)	(9)
Pheochromocytoma benign	4 (40%)	(10)	1 (10%)	
Pituitary gland		(10)		1 (11%)
Pars distalis, adenoma	(10)	(10)	(10)	(9)
	1 (10%)	(10)	(10)	(0)
Thyroid gland C-cell, adenoma	(10) 1 (10%)	(10)	(10) 1 (10%)	(9)
General Body System None		<del>, , , , , , , , , , , , , , , , , , , </del>		
Conital System				
Genital System	(10)	(10)	(10)	<b>10</b> 3
Preputial gland	(10)	(10)	(10)	(9)
Adenoma	1 (10%)	1 (10%)		1 (11%)
Testes	(10)	(10)	(10)	(9)
Bilateral, interstitial cell, adenoma	4 (40%)	4 (40%)	6 (60%)	4 (44%)
Interstitial cell, adenoma	3 (30%)	4 (40%)	4 (40%)	2 (22%)
Hematopoietic System	<u> </u>	·	· · · · · · · · · · · · · · · · · · ·	<del>-:</del>
	(10)	(10)	(10)	(0)
Spleen	(10)	(10)	(10)	(9)
Integumentary System				
Skin	(8)	(9)	(10)	(9)
Subcutaneous tissue, fibroma	(~)	(~)	1 (10%)	(7)
Dubbataneous tissue, Hotoma			1 (10/0)	

TABLE B1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Gavage Study of Safflower Oil (continued)

	Untreated Control	2.5 mL/kg	5 mL/kg	10 mL/kg
15-Month Interim Evaluation (continued Musculoskeletal System None	)			
Nervous System None				
Respiratory System  Lung  Alveolar/bronchiolar adenoma	(10)	(10)	(10)	(9) 1 (11%)
Special Senses System None				
Urinary System None	***************************************			
Systemic Lesions				
Multiple organs <sup>b</sup> Leukemia mononuclear	(10) 2 (20%)	(10)	(10)	(9)
2-Year Study		· · · · · · · · · · · · · · · · · · ·		
Alimentary System				
Esophagus	(49)	(48)	(48)	(49)
Carcinoma, metastatic, uncertain primary site	1 (2%)			
Intestine large, cecum	(45)	(48)	(47)	(48)
Intestine large, colon	(46)	(49)	(48)	(49)
Sarcoma Intestine large, rectum	(47)	(47)	1 (2%)	(47)
Fibrous histiocytoma, metastatic, skin	(47)	(47) 1 (2%)	(47)	(47)
Intestine small, duodenum	(48)	(50)	(48)	(49)
Intestine small, ileum	(45)	(49)	(48)	(47)
Intestine small, jejunum	(45)	(48)	(48)	(46)
Liver	(50)	(50)	(50)	(51)
Carcinoma, metastatic, pancreas	1 (20%)			1 (2%)
Carcinoma, metastatic, uncertain primary site	1 (2%)	1 (20%)		
Fibrous histiocytoma, metastatic, skin Hepatocellular carcinoma	1 (2%)	1 (2%)	1 (2%)	
Hepatocellular adenoma	2 (4%)	2 (4%)	1 (2%)	
Mesentery	(9)	(8)	(10)	(7)
Pancreas	(50)	(50)	(49)	(50)
Acinus, adenoma	1 (2%)	5 (10%)	9 (18%)	9 (18%)
Acinus, adenoma, multiple		2 (4%)	6 (12%)	19 (38%)
Acinus, carcinoma				1 (2%)
Acinus, carcinoma, multiple			1 (20%)	1 (2%)
Acinus, mixed tumor benign			1 (2%)	

TABLE B1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Gavage Study of Safflower Oil (continued)

	Untreated Control	2.5 mL/kg	5 mL/kg	10 mL/kg
2-Year Study (continued)				
Alimentary System (continued)				
Pharynx	•	(1)		
Palate, squamous cell carcinoma		1 (100%)		
Salivary glands	(50)	(49)	(50)	(51)
Adenoma	1 (2%)	(42)	(30)	(31)
Carcinoma	1 (270)	1 (2%)		
Stomach, forestomach	(50)	(50)	(50)	(51)
Squamous cell papilloma	1 (2%)	(30)	2 (4%)	1 (2%)
Stomach, glandular	(49)	(50)	(49)	(50)
Carcinoma	(42)	(30)	(42)	1 (2%)
Tongue	(1)			(1)
Squamous cell papilloma	1 (100%)			(1)
Tooth		,		•
Odontoma	(1) 1 (100%)	* **		e e e e e e e e e e e e e e e e e e e
Cardiovascular System			.=	·.
Heart	(50)	(50)	(50)	(51)
Endocrine System				
Adrenal gland, cortex	(50)	(49)	(50)	(49)
Adenoma				2 (4%)
Adrenal gland, medulla Ganglioneuroma	(49)	(48)	(49) 1 (2%)	(49)
Pheochromocytoma malignant	2 (4%)	•	` . '	1 (2%)
Pheochromocytoma benign	10 (20%)	10 (21%)	7 (14%)	6 (12%)
Bilateral, pheochromocytoma benign	1 (2%)	2 (4%)	3 (6%)	1 (2%)
Islets, pancreatic	(49)	(50)	(49)	(49)
Adenoma	6 (12%)	2 (4%)	5 (10%)	3 (6%)
Adenoma, multiple	1 (2%)	1 (2%)	` ,	
Pituitary gland	(50)	(48)	(49)	(50)
Pars distalis, adenoma	7 (14%)	<b>10 (21%)</b>	4 (8%)	8 (16%)
Thyroid gland	(48)	(49)	(48)	(49)
C-cell, adenoma	4 (8%)	4 (8%)	7 (15%)	4 (8%)
Follicular cell, adenoma	2 (4%)	2 (4%)	()	1 (2%)
General Body System		, <u></u>		· ·
Tissue NOS	(1)	(1)	(1)	
Genital System			***************************************	
Epididymis	(50)	(50)	(49)	(51)
Preputial gland	(50)	(50)	(49)	(49)
Adenoma	7 (14%)	5 (10%)	4 (8%)	1 (2%)
Bilateral, adenoma	<b>\</b>	1 (2%)	\ ·-/	1 (2%)
Prostate	(49)	(49)	(48)	(49)
Seminal vesicle	(50)	(49)	(50)	(50)
Testes	(50)	(50)	(49)	(51)
Bilateral, interstitial cell, adenoma	46 (92%)	42 (84%)	44 (90%)	43 (84%)

TABLE B1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Gavage Study of Safflower Oil (continued)

	Untreated Control	2.5 mL/kg	5 mL/kg	10 mL/kg
2-Year Study (continued)				
Hematopoietic System				
Blood	(15)	(11)	(7)	(2)
Bone marrow	(49)	(49)	(50)	(50)
Lymph node	(50)	(50)	(50)	(51)
Lymph node, mandibular	(50)	(47)	(48)	(50)
Fibrosarcoma, metastatic, skin	(30)	()	(13)	1 (2%)
Lymph node, mesenteric	(50)	(50)	(49)	(50)
Spleen	(50)	(50)	(48)	(51)
Thymus	(40)	(42)	(41)	(43)
Schwannoma malignant, metastatic, uncertair		(42)	(44)	(45)
primary site	1	1 (2%)		i
Thymoma benign	1 (3%)	1 (270)		1 (2%)
Thymoma ochign	1 (370)			
Integumentary System				
Mammary gland	(42)	(45)	(43)	(46)
Fibroadenoma	6 (14%)	2 (4%)	1 (2%)	2 (4%)
Fibroadenoma, multiple	1 (2%)			
Skin	. (50)	(50)	(50)	(51)
Basal cell adenoma				1 (2%)
Fibrous histiocytoma		1 (2%)		, ,
Keratoacanthoma		1 (2%)	3 (6%)	1 (2%)
Squamous cell carcinoma		1 (2%)	1 (2%)	1 (2%)
Squamous cell papilloma	2 (4%)	2 (4%)	4 (8%)	1 (2%)
Subcutaneous tissue, fibroma	1 (2%)	3 (6%)	1 (2%)	2 (4%)
Subcutaneous tissue, fibroma, multiple	1 (2%)	, , , ,	<b>(</b> **** <b>)</b>	- ()
Subcutaneous tissue, fibrosarcoma	- ()	2 (4%)		1 (2%)
Subcutaneous tissue, lipoma		1 (2%)		2 (=10)
Musculoskeletal System				
Bone	(50)	(50)	(50)	(51)
	(50)	(50)	(50)	(51)
Osteosarcoma Skaletal musele	(50)	(50)	1 (2%)	(51)
Skeletal muscle	(50)	(50)	(50)	(51)
Fibrous histiocytoma, metastatic, skin		1 (2%)		
Rhabdomyosarcoma		1 (2%)		
Nervous System				
Brain	(50)	(50)	(50)	(51)
Astrocytoma malignant	(- · /	1 (2%)	()	(-4)
Glioma malignant		- (-/-)	1 (2%)	
Oligodendroglioma malignant			1 (2%)	
Spinal cord	(1)		(1)	
	(+)		(-)	

TABLE B1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Gavage Study of Safflower Oil (continued)

	Untreated Control	2.5 mL/kg	5 mL/kg	10 mL/kg
2-Year Study (continued)	***			
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	1 (2%)			
Fibrosarcoma, metastatic, skin				1 (2%)
Fibrous histiocytoma, metastatic, skin		1 (2%)		
Mediastinum, sarcoma, metastatic, heart		4 /00/		1 (2%)
Mediastinum, schwannoma malignant	(50)	1 (2%)	(50)	7545
Nose	(50)	(50)	(50)	(51)
Carcinoma, metastatic, harderian gland		1 (201)		1 (2%)
Squamous cell papilloma	1 (201)	1 (2%)		
Nasopharyngeal duct, squamous cell carcinoma	1 (2%)		· ·	
Special Senses System				
Harderian gland				(1)
Carcinoma				ì (100%)
Zymbal's gland		(2)		• /
Carcinoma		2 (100%)		
Urinary System		<u> </u>		
Kidney	(50)	(50)	(50)	(49)
Sarcoma	1 (2%)	(50)	(50)	(42)
Renal tubule, adenoma	1 (2%)			
Urinary bladder	(48)	(49)	(49)	(48)
				(40)
Systemic Lesions				
Multiple organs	(50)	(50)	(50)	(51)
Leukemia mononuclear	33 (66%)	19 (38%)	18 (36%)	7 (14%)
Mesothelioma malignant		2 (4%)		2 (4%)
Neoplasm Summary	· · · · · · · · · · · · · · · · · · ·			
Total animals with primary neoplasms <sup>c</sup>				
15-Month interim evaluation	9 ·	. 8	10	8
2-Year study	50	50	48	51
Total primary neoplasms				
15-Month interim evaluation	16	9	13	10
2-Year study	147	135	129	129
Total animals with benign neoplasms				
15-Month interim evaluation	8	8	10	8
2-Year study	50	49	46	50
Total benign neoplasms				
15-Month interim evaluation	14	9	13	10
2-Year study	109	103	105	113
Total animals with malignant neoplasms				
15-Month interim evaluation	2			
2-Year study	36	29	23	15
Total malignant neoplasms				
	2			
15-Month interim evaluation	2			

TABLE B1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Gavage Study of Safflower Oil (continued)

Untreated Control	2.5 mL/kg	5 mL/kg	10 mL/kg
1	4		6
2	7		7
1	1		
	1	1 4	1 4

<sup>&</sup>lt;sup>a</sup> Number of animals examined microscopically at site and number of animals with lesion

b Number of animals with any tissue examined microscopically

c Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE B2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Safflower Oil: Untreated Control

	4	4					6				6	6					6	7			7	7	7	7	7				
Number of Days on Study	5 7	7 6	0 1	1 0			3 5		4 7		7 1	7 2		9. 1				0 8	1 0	1 5	3 6	3 6	3 6	3 6	6	, .			2
	0	0	0	0	0.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0				
Carcass ID Number	- 5						0			2			4								1	-		-	-				
	6	7	2	4	4	5	3	4			3	4	9	0															
Alimentary System		_		-										_			_							_			_		<del></del>
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Carcinoma, metastatic, uncertain primary site			·																,										
Intestine large	+	+	+	+	+	+	+	Α	+	+	+	+	+	A·	+	+	+	+	+	Α	+	+	+	٠+	+				
Intestine large, cecum	+	+	+	+	+	+	+			+	+	+			+			À	À	A	+	+	.+	+	+				
Intestine large, colon	+	+	+	+	+	+			÷	+	+		+									+	+	+	+				
Intestine large, rectum	+	+	+	+	+	+			+	+	÷				+				+			+	+	+	÷.				
Intestine small	+	+	+	+	+	+	+		+	+	+	+		A		+	+	+	+	+	+	+	+	+	+				
Intestine small, duodenum	+	+	+	+	+	+			+	+			+						+	+	+	+	+	+	+				
Intestine small, ileum	+	+	+	+	+	+			+				+									+	+	. +	+				
Intestine small, jejunum	·	+	+	+	+	+			+		+		+									+	· +	+	+				
Liver		·	+	+	÷	+							+						+			+	+	·	·				
Carcinoma, metastatic, uncertain primary site	,	•	•	•	·	•	·	·	•	·	·	•	•	•	•	·	·	•	·		•	•	÷	·	•	•	•	٠	
Hepatocellular carcinoma																						х							
Hepatocellular adenoma																											,		
Mesentery						+																							
Pancreas	+	+	4	+	+	÷	+	+	_	+	+	+	+	+	_	+	+	_	+	4	_	+	_	_	_				
Acinus, adenoma	'	•	•	'	'	•	'	•	•	'	,	•	•	•	'	•	•	'	•	•		'			•				
Salivary glands	_	_	+	_	_	+	4	+	+	_	+	_	_	_	_	_	_	_	_	_	+	_	+		_				
Adenoma	ŗ	•	•	٠	•	•	•		•	•	•	٠	•	•	•	•	ı	٠	T	•	١.	. '	'	-	4				
Stomach		_	_	_	_	_	_	_	_	_	_	_	_	_	_	_	_	_	_	_	_		_		_				
Stomach, forestomach					<b>T</b>	<b>T</b>	<b>T</b>	+	T-	<u> </u>	+	+	+	+	<b>T</b>	+	+	+	+		+				+				
Squamous cell papilloma		•	•	т	•	_	т	т	т	т	T	т	Ψ.	_	т	т	1	т	т	т.	т	т		т	т				
Stomach, glandular	_	_		_	_	_		Δ.	_		_	+		٠.	+		_	_	_	٠.	_				+				
Tongue		-		т	т	т	т	А	+	_			т	т	т	т	т	+	+		т	т	т	т	_				7
Squamous cell papilloma												+ X																	
Tooth												Λ																	
Odontoma																		+ X											
Cardiovascular System		_			_			_			_												·					_	
Heart	• +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+				
Endocrine System																_						·							
Adrenal gland	+	_	_	_	_	_	_	_	_	_	_	_	_	_	_	_	_	_	4	_	_	٠.	_		_				
Adrenal gland, cortex	T ,L	<b>→</b>					T	<u></u>		T	+	+	+		+	+			T	T.	T	<b>T</b>	т Т	T.	+				
Adrenal gland, cortex Adrenal gland, medulla	<del>+</del>	<b>→</b>	· T	_T	<b>T</b>	т Т	T.	_T	<b>T</b>	т Т		т Т			+	<u> </u>		<b>⊤</b>	<b>T</b>	т Т	т Т	T _			T				
Pheochromocytoma malignant		Τ.		т	7	т	Τ.	Т	Т	_	-	т	_	т	_	_	т	•	т	Τ.	т	_	• т	. 🕶	Τ.				
Pheochromocytoma benign						х											x							х					
Bilateral, pheochromocytoma benign						^											^							^	· .				,
Islets, pancreatic	_				_	٠.	_	Α	_		_	_	_	_	_	_	_		_	٠.			٠						
Adenoma	-	X	T	-	_	-	X	^	т	7	т	т	т	_	_	X	-	_	Τ'	т	X	_	т-						
		Λ			x		Λ									^					Λ								
Adenoma, multiple				J.			_1	_1		.1	_1	.1		د	J		_1	1/	.1				1		<b>1</b> .7				
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	IVI	+	+	+	+	+	+	M				

<sup>+:</sup> Tissue examined microscopically

M: Missing tissue I: Insufficient tissue X: Lesion present Blank: Not examined

A: Autolysis precludes examination

		_	_	_		_		_	_	_	_	_		_	_	_	_	_	_	_	_	_	~	_	_	
	7	7	7	7	7	7		7	7	7	7	7			_	7	7	7	7	7	7	7	7	7		
Number of Days on Study	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
•	6	6	6	6	6	6	6	6	6	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	Total
Carcass ID Number	3	3	3	3	3	4	4	5	5	0	0	1	1	1	1	2	2	3	4	4	4	5	5	5	5	Tissues/
	5	6	7	8	9	3	6	3	4	1	2	1	4	6	9	1	2	0	2	5	7	0		8	9	Tumors
Alimentary System		_					_				_	_		_	_					_	_	_		_		
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, metastatic, uncertain																										
primary site										Х																1
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum		+	+	+	+	<u>.</u>	+	÷	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum		·	÷	<u>.</u>	<u>.</u>	<u>.</u>	·	·	Ţ	į.	·		+	, +	+	<u>.</u>	, +	<u>.</u>	+	÷	·	<u>.</u>	÷	i	÷	45
Intestine small, jejunum		+	<u>.</u>	+	+	4	<u>,</u>	<u>.</u>	1	+	+	+	<u> </u>	<u>,</u>	+	<u>.</u>	4	<u> </u>	+	1	1	+	4	1	+	45
Liver		Ė		<u>.</u>	Ĺ	<u>.</u>	÷	÷	Ţ	<u>.</u>	·		<u>.</u>	<u>.</u>	<u>.</u>	<u>.</u>	i	<u>.</u>	<u>.</u>	Ţ	<u>.</u>	·		<u>.</u>	ì	50
Carcinoma, metastatic, uncertain		•	•	•	•	•	•	•	'	,	•	•	•	•	•	•	•	•	•	1	•	•	•	'	•	30
primary site										х																1
Hepatocellular carcinoma										^																1
Hepatocellular adenoma									Х											х						2
Mesentery	1	٠.				4.			+								_	_		Λ						9
Pancreas	T	+			i	+			T .				,			,	+					7				50
· · · · · · · · · · · · · · · · · · ·	т	_			7	+	_	т	_		т	_	+	_	т	+	+	_	т	+	_	_	_	+	+	
Acinus, adenoma																										1
Salivary glands		+	+	+	*	+	+	+ X	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																							X			1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tongue																										1
Squamous cell papilloma																										1
Tooth																										1
Odontoma																										1
Cardiovascular System				****																						
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																					_	_	_			
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+		+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma malignant	·		X		•	•	•	٠	X		•	•	•	•	•	•	•	•	٠	•	•	•	•	•	•	2
Pheochromocytoma benign								X				Х		X			Х		X			Х		X		10
Bilateral, pheochromocytoma benign								- ~									-					•	Х			1
Islets, pancreatic	4.	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	4	+	+		+	+	49
Adenoma			•	•	,	•	•	X		•	•	,		X		,		'	•	•	'		•	1	,	6
Adenoma, multiple								^						^												1
Parathyroid gland	_1	۰			A.f			.1.			.1.	_	M	4	_L	<b>R</b> /		.1	_	_	_	ı.	.1	1	_	45
i atatilytoid gialid	+	_	-	7	IVI	. —	-	*	+	_	_	+	IVI	+	+	IAI		+	+	+	+	+	+	+	+	43

(continues)																													
		4	4	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7			
Number of Days on Study		5	7	0	1	1	2	3	4	4	6	7	7	8	9	9	9	9	0	1	1	3	3	3	3	3			
· ·		7	6	1	0	3	7	5	1	7	1	1	2	4	1	2	2	2	8	0	5	6	6	6	6	6			
		_	_	_	_	_	_	_		_	_	_	_	_	_	_	_	_	_	_	_	_	_	_	_	_			 
o ton i		-	0	_				0														0				0			
Carcass ID Number		_	0 7	-	4	3				0																3 2			
		0			4	4	3	3	4	0	0	3	4	<u> </u>	···		<del>У</del>		′										
Endocrine System (continued)																													
Pituitary gland		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	. +	- +	-		
Pars distalis, adenoma							Х											X		Х						Х	2		
Thyroid gland		+	+	+	+	+		+	Α	+	+	+	+	+	+	+	+	+	+	+	+	+	+	. +	. +	- +	_		
C-cell, adenoma				-					•-			X			X														
Follicular cell, adenoma								X				-			••			X											
Conord Pody System																										—			 
General Body System Tissue NOS																													•
11SSUC NOS																													
Genital System																													
Epididymis		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	- +	- +	-		
Preputial gland		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	. +	- 4	- +	-		
Adenoma																													
Prostate		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	М	+	+	+	+	. +	- +	- +	-		
Seminal vesicle		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	. +	- +	r +	-		
Testes		+	+	+	+	+	+	+	+	+	+	+	+	+		+								. +	- +	· +	_		
Bilateral, interstitial cell, adenoma		x	•		x		,			X																X			
Interstitial cell, adenoma		-	х		71		X		7.	1	11	,,	1.	7.	11	X		1	71	11	-		- 11				•		
Hematopoietic System																													
Blood										+	+	+	+			+		+				+	+						
Bone marrow		+	+	+	+	+	+	+	Α	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	. +	٠ +	-		
Lymph node	•	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	. +	- +	- +	_		
Lymph node, mandibular		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	. +	- +	- +	Γ.		
Lymph node, mesenteric		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	. +	- 4	+ +	-		
Spleen		+	+	+	+	+	+	+	+	+	+	+	+	. +	+	+	+	+	+	+	+	+	+	. +	- +	+ +	-		
Thymus		+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	M	[ +	+	- N	<i>I</i> +	+ +	-		
Thymoma benign																									X	ζ			
Ind S		_	_																	_					—				 
Integumentary System Mammary gland		_	M			N/			4.	_										М	1.								
• •		+	IVI	_	+	IVI	I IVI	+	+	+	+	+	+	+		+	+	+	+	IVI	+	+	+			· N	4		
Fibroadenoma															X								•	. X					
Fibroadenoma, multiple																							Х						
Skin		+	+	+	+	+	+			+	+	+	+	+	+	+	+	+	+	+	+	+	+	. +	- +	+ +	-		
Squamous cell papilloma								X																					
Subcutaneous tissue, fibroma																													
Subcutaneous tissue, fibroma,																													
multiple																													
Musculoskeletal System																												-	 
Bone		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	. 4	- 4	- 4	+ +	۲		
Skeletal muscle		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	. +	- 4	+ +	-		
Nervous System				-							_					_		_			-		_	_		_	_	•	 
Brain		+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• +	. +	- +	•		
Spinal cord				+																									
											_		_			-				_									 

(continued)																											
	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7		
Number of Days on Study	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3		
	6	6	6	6	6	6	6	6	6	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9		
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		Total
Carcass ID Number	3	3	3	3	3	4	4	5	5	0	0	1	1	1	1	2	2	3	4	4	4	5	5	5	5		Tissues
			7												9									8	9		Tumor
Endocrine System (continued)								_																			
Pituitary gland	+	+	+	+	+	+	+	+	4	+	+	+	+	+	+	+	+	+	+	+	4	+	4		4		50
Pars distalis, adenoma		٠	•	•		x	•	•	•	•	•		x			•	•	•	•	•	•	,		•	•		7
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+			+	+	+	+	+	+	+	+	+	+	+	+		48
C-cell, adenoma	•	•		•	•	•	•	٠	•	•	•	•	•••	•	X	•		•	X	•		•		•	•		4
Follicular cell, adenoma															•												2
General Body System									_						_							_			_		
Tissue NOS																				+							1
Genital System		_						_				_						_			_	_			_		
Epididymis	4	+	+	4.	+	+	+	+	4	+	4	+	+	+	+	+	+	+	4	+	+	4	4	. ـ			50
Preputial gland		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	. 4	· +	•	50
Adenoma	•		x	•	X	•	x	•	x	•	•	•	•	•	•	x	•	•	x	•	•	•	1	•	•		7
Prostate	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	4	. 4	. +		49
Seminal vesicle		+	+		+	+	+	+	+	·	+	+	+	+	+	+	+	+		+	·	+			. +		50
Testes	+	+			+	+	+	+		+	+	+	+	+		+	+			+	+	+	+		. +		50
Bilateral, interstitial cell, adenoma	×														x												46
Interstitial cell, adenoma	71	7	1	Λ	1	^	^	1	^	^	1	71	^	7.	^	Λ.	^	71	Λ	^	^					•	4
Hematopoietic System	<del></del>								_	_						_	_			_	_	_					
Blood				+				+		+			+					+		+			+				15
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	. +	. 4	i.	49
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	. +	. +		50
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	. +			. ,	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	. +			50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	. +	. +		50
Thymus	+	+		M	+	+	+	+	+						+	+		-		-		4	N				40
Thymoma benign													2		•			·	·						•		1
Integumentary System		_	_	-		_		_	_	_						_								_	_		
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	М	+	+	+	+	+	+		· N	ſ	42
Fibroadenoma						X			X				•					•	•	·	·	•	•	X		•	6
Fibroadenoma, multiple									•																•		1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				. 4		50
Squamous cell papilloma	•	•		•	•	•	•	•	•	•	•	•		•	Ċ	X		•	·	•	•		•	,	'		2
Subcutaneous tissue, fibroma											Х																_
Subcutaneous tissue, fibroma,											^																1
multiple																		X									1
Musculoskeletal System							_	_								_		_		_			_				
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	. 4	. +		50
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	. +	į	50
Nervous System	<del></del>			_												_				_	_	_					
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	- +	- +	•	50
Spinal cord																											

(continued)									_	_		_																	
	4	4	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7				
Number of Days on Study	5	7	0	1	1	2	3	4	4	6	7	7	8	9	9	9	9	0	1	1	3	3	3	3	. 3				
•	7	6	1	0	3	7	5	1	7	1	1	2	4	1	2	2	2	8	0	5	6	6	6	6	6			,	
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0				
Carcass ID Number	. 5	0	5	4	3	0	0	0	0	2	3	2	4	4	2	2	6	1	5	1	1	2	2	3	3	, <i>'</i>			
	6	7	2	4	4	5	3	4	6	6	3	4	9	0	5	9	0	7	5	2	8	0	8	1	2	,			
Respiratory System																													_
Lung	+	+	- +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	- +	- +	-		•	
Alveolar/bronchiolar adenoma																								•					
Nose	+	+	- +	- +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	- +	- 4	+			
Nasopharyngeal duct, squamous cell																							."						
carcinoma																X													
Trachea	+	+	- +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	- +	۲		•	
Special Senses System						_																						*	
Ear													+																
Eye																+													
Urinary System						_							_				,	_	-					_					<del>.</del> .
Kidney	+	+	- +	- +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	- +	- 4	۲		•	
Sarcoma																													
Renal tubule, adenoma																													
Urinary bladder	+	+	- +	- +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	. +	+	+	+	- 4	۲			
Systemic Lesions												_															٠.		
Multiple organs	+	. +	- +	- +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	- +	- 4	۲			
Leukemia mononuclear	Х		Х	X	X	X		Х	Х	Х	X	X		X	X		Х	X				Х	X	X	ς ,	ζ.			

																_										
·	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
Number of Days on Study	3	3	3	3	3	3.	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
•	6	6	6	6	6	6	6	6	6	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	
· · · · · · · · · · · · · · · · · · ·	0	0	0	0	0	0	0.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	Total
Carcass ID Number	, 3	3	3	3	3	4	4	5	5	0	0	1	1	1	1	2	2	3	4	4	4	5	5	5	5	Tissues/
	5	6	7	8	9	3	6	3	4	1	2	1	4	6	9	1	2	0	2	5	7	0	7	8	9	Tumors
Respiratory System			_		_																					
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma															X											1
Nose	+	+	+	. +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nasopharyngeal duct, squamous cell carcinoma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	
Special Senses System				_			_								_										_	
Ear																										1
Eye															+											2
Urinary System			_							_		_					_		_				_			
Kidney	+	+	+	- +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	. 4	+	+	+	+	50
Sarcoma																									Х	1
Renal tubule, adenoma																							Х			1
Urinary bladder	+	+	+	- +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	[ +			+	
Systemic Lesions			_	_														-	_							
Multiple organs	+	+	+	- +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	Х		X	X	X	X		X		X	X	X	X				X	X		X			X	X		33

TABLE B2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Safflower Oil: 2.5 mL/kg

Number of Days on Study	3 8	3 9	8		-	-		-	6 2		6			6		7	2	3		3	3	3	3		3		
tumber of Days on Staay	8		5	1			5							3		Ô	7	5		5	5	5	5	-	5		
																							0			 	
Carcass ID Number	6 6		0 2						6 9						7 7								7 6				٠.
Mimentary System				_										-													
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	Α	+	+	+	+	+	+	+	+	+		
Intestine large, cecum	+	+	+	+	+	+	Α	+	+	+	+	+	+	+	+	Α	+	+	. +	+	+	+	+	, +	+		
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	Α	+	+	+	+	+	+	+	+	+	6-	
Intestine large, rectum Fibrous histiocytoma, metastatic, skin	+	+	+	+	+	+	A	Α	+	+	+	+	+	+	+	Α	+	+	+	+	+	+	+ X		+		
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Intestine small, duodenum	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Intestine small, ileum	+	+	+	+	+	+									+		+	+	+	+	+	+	+	+	+		
Intestine small, jejunum	+	+	+	+	+	+					+			+		Α		+	+	+	+	+	+	+	+		
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+		
Fibrous histiocytoma, metastatic, skin																							X				
Hepatocellular adenoma									X													X					
Mesentery				+	+																+		+				
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+		+	+	+		
Acinus, adenoma																			X			X					
Acinus, adenoma, multiple																											
Pharynx																								+			•
Palate, squamous cell carcinoma																								X			
Salivary glands			+	+	+	М	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Carcinoma	X																										
Stomach	+	+	+	+	+	+	+	+	+	+	+	+			+		+	+	+	+	+	+	+	+	+		
Stomach, forestomach Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+		
	····																					<u> </u>	<u> </u>			 	
Cardiovascular System Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Endocrine System		_						-																		 	
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+		
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+		
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+		
Pheochromocytoma benign											X			$\mathbf{X}$			Х								X		
Bilateral, pheochromocytoma benign																					X	X					
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Adenoma																							X				
Adenoma, multiple																											
Parathyroid gland	+	+	+	+	+	+	M	+.	M	+	+	+	+	M	+	+	+	+	+	+	+	+	M	M	+		
Pituitary gland	+	+	+		+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+		
Pars distalis, adenoma			X										Х			X							X	X			
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	Α	+	+	+	+	+	+	+	+	+		
C-cell, adenoma																											
Follicular cell, adenoma																					X						

			_	_	_						7															
Sumber of Days on Study	3 5	3 5	3 5	3 5	3 6	3 6	3 6		3 6	3 6	3 6	3 6	3 6	-												
	0	0	0			1	1	1	1	1	1	1	1	1	1	0	0	<u> </u>	0	0	1	1	1	1	1	Total
Carcass ID Number							o										7				0			1		Tissues
							3													7	0	6	0	2	3	Tumor
Alimentary System																		•							<del>,-</del>	
Esophagus	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum Fibrous histiocytoma, metastatic, skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47 1
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	.+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma, metastatic, skin Hepatocellular adenoma																										1 2
Mesentery	+							+													+					8
Pancreas	+	+	+	+			+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	50
Acinus, adenoma					X	X														X						5
Acinus, adenoma, multiple												Х									X					2
Pharynx																										1
Palate, squamous cell carcinoma																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma																										1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+ . +	+	+	+	+	+	+	+	+	+	+	+	+	+	50 50
Cardiovascular System							_			_																<del></del>
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System						_									_					_	_	_	_	_		<del></del> -
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	М	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pheochromocytoma benign									X							X		Х		X		X			X	10
Bilateral, pheochromocytoma benign																										2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																								Х		2
Adenoma, multiple					X																					1
Parathyroid gland	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	M	+	+	+	M	[ +	+	+	+	40
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pars distalis, adenoma				X					X						X		X			X						10
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+			+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell, adenoma	X					X						X											X			4
Follicular cell, adenoma												,									X					2

Number of Days on Study	3 8 8	9	8	4 9 1	0	6 1 4		1		3		6 7 9		9	7 0 8	7 1 0	7 2 7	7 3 5				,							
Carcass ID Number	6	0	0	9	8	1	7	9	0 6 9	7	2	9	9	8	0 7 7	8		6	0 6 2	_	6		7	7					,
Genital System	-																							-					_
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	. +	+			•	
Mesothelioma malignant, metastatic, testes																											·		
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Adenoma																								Х	:		•		
Bilateral, adenoma													X											٠					
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			*	
Bilateral, interstitial cell, adenoma Interstitial cell, adenoma				X	Х	x	X	X	X	Х	x	х	Х	Х	Х	<b>X</b>	X	X	Х	Х	X	X	X	X	X				
Hematopoietic System					_									_		_		<u> </u>						•					_
Blood											+	+						+			+	+			+				
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	Α	+	+	+	+	+	+	+	- +	+				
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	- +	+				
Lymph node, mandibular	M	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	. 4	- +	+				
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	. 4	- +	+				
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	. +	- +	+				
Thymus Schwannoma malignant, metastatic, uncertain primary site	M	+	+	+	M	+	+	+	+	+	M	+	+	+	+	M	M	+	+	+	+		+	- +	+		•		
Integumentary System																													_
Mammary gland Fibroadenoma	M	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	- +	+				
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	. +	- +	+				
Fibrous histiocytoma																							X						
Keratoacanthoma																					•			- 1					
Squamous cell carcinoma																			X										
Squamous cell papilloma										X										Х									
Subcutaneous tissue, fibroma		Х					X			X																			
Subcutaneous tissue, fibrosarcoma																						Х							
Subcutaneous tissue, lipoma																													
Musculoskeletal System														_															
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	- 4	- 4	+				
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	. 4	- +	- +				
Fibrous histiocytoma, metastatic, skin																							X	<b>.</b>					
Rhabdomyosarcoma																X													
Nervous System												_		_					_	-						_			<del>.</del>
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	٠ +	- +	+				
Astrocytoma malignant									X																				
Respiratory System		_		_										_												7.			_
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	. 4	+	- 4	- 4	- +			e .	
Fibrous histiocytoma, metastatic, skin Mediastinum, schwannoma malignant		•		-	•	-	-		٠		-		•	-		•					Í		>	(			.**		

Table B2

	7	7	7	7	7	~	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
Manual and Danie and Consider		•	-			-			-	3	3	•		3				3	3	3	3	3	3	3		
Number of Days on Study	3 5	3 5	3 5	-	3 5	_	-	3 5	3 5		5	3 5	3 5		5					_			_	6		
	_	_	0	0		1		1	1	1	1		1	1	1	_	_	0	0	_	1	1	_	1		Total
Carcass ID Number	8	0 8	9	_	-	0		.0					1		1				7		0		1	1		Tissues
Saccase and learnest	3												6													Tumor
Genital System					_					-					_											
Epididymis	+	+	+	- 4	- +	<b>⊦</b> ⊣	+ +	- +	. +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, testes										Х			X													2
Preputial gland	+	+	+	- +	- +	+ +	+ +	- +	. +	. +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma						>	( X	[					X					Х								. 5
Bilateral, adenoma																										1
Prostate	+	+	. +	-	+	۲ -	+ +	- +	- +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Seminal vesicle	+	+	. +	-	4	٠ -	+ +	- +	- +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Testes	+	. 4	. +		1	- +	- +	- +	- +	+	. +		+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma	x	X	K					X					X												X	42
Interstitial cell, adenoma				>	_				X								X									5
Hematopoietic System	-		٠.	*		٠	.,					_		:							,	_		-		· · · · · · · · · · · · · · · · · · ·
Blood			4	۲				+	-		+	+												+		11
Bone marrow	+	. 4	. 4	+ +	٠ 4	+ +	+ +	+ +	- +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node	+	. +	. 4	<b>-</b> -	- 4	+ -	+ +		- +	. +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	·			- 4		-	 - 4	- 4			+	+	+	+	+	+	+	+	+	+	+	+	. +	+	·	47
Lymph node, mesenteric			. 4	- 4	, .	+ -	 + 4	- 4	· +	. +	. +	+	·	+	+	÷	+	+	+	+	+	+	<u>.</u>	+	+	50
Spleen	·			L 4		L -		, . ⊾ .4				·	·	<u>.</u>	÷	<u>.</u>	Ţ	<u>.</u>	<u>.</u>	i	÷	<u>.</u>	Ţ	Ţ	<u>.</u>	50
Thymus			. T			+ 1	г ¬	- T	, т	. +		RA	+	+	+	<b>T</b>	1	Ţ	<b>T</b>		_ T			+	+	42
Schwannoma malignant, metastatic,	. T	7	٠,			T 1	VI 7	- 1/	/1 T	· •	<b>T</b>	IAI	. T	т	т	_	т	т	_	7	7	Τ.	_	т	т	42
uncertain primary site																		X								1
Integumentary System								_							_											
Mammary gland	+	. 4	- 4	<b>⊦</b> -	<b>-</b> 4	+ -	+ +	<b>⊦</b> ,+	+ +	- +	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	45
Fibroadenoma								•					X											X		2
Skin	+	٠ ٦	- 4	+ -	٠ -	+ -	+ +	+ 4	+ +	- +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma																										1
Keratoacanthoma							>	ζ.																		1
Squamous cell carcinoma																										1
Squamous cell papilloma																										2
Subcutaneous tissue, fibroma																										3
Subcutaneous tissue, fibrosarcoma							,	ζ.																		2
Subcutaneous tissue, lipoma							•	`											X							1
Musculoskeletal System	-											_				•						_				
Bone	+	- 4	+ +	+ -	+ -	+ -	+ -	+ +	+ +	- +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle	+	- 4	+ +	+ -	+ -	+ -	+ -	+ +	+ +	- +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma, metastatic, skin																										1
Rhabdomyosarcoma																										1
Nervous System																										
Brain	+	- +		+ -	+ -	+ -	+ -	+ -	+ +	+ +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma malignant																										1
Respiratory System																										
Lung	+		- ۱	+ -	+ -	+ .	+ -	+ -	+ +	+ +	- +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma, metastatic, skin																										1
Mediastinum, schwannoma malignant																		X								1

												•		•								1			_	•		,
	3	3	4	4	6	6	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7			
	8	9	8	9	0	1	1	1	2	3	3	7	8	9	0	1	2	3	3	3	3	3	3	3	3			
	8	8	5	1	0	4	5	8	4	4	4	9	3	3	8	0	7	5	5	5	5	5	5	5	5			
	0	1	1	0	0	1	0	0	0	0	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0			
	6	0	0	9	8	1	7	9	6	7	2	9	9	8	7	8	0	6	6	6	6	6	7	7	8			
	6	8	2	2	5	8	5	1	9	0	0	4	3	4	7	7	7	1	2	3	4	7	6	9	0			
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																								Х				
	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
	+	+	+	+	+	+	Α	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	- 4	+	+			
				X		X	Х				X	X						X			X	X		Х	X			
		3 8 8 0 6 6	3 3 8 9 8 8 0 1 6 0 6 8 + + + +	3 3 4 8 9 8 8 8 5 0 1 1 6 0 0 6 8 2 + + + + + +	3 3 4 4 8 9 8 9 8 8 5 1 0 1 1 0 6 0 0 9 6 8 2 2 + + + + + + + + + + +	3 3 4 4 6 8 9 8 9 0 8 8 5 1 0 0 1 1 0 0 6 0 0 9 8 6 8 2 2 5 + + + + + + + + + +	3 3 4 4 6 6 8 9 8 9 0 1 8 8 5 1 0 4 0 1 1 0 0 1 6 0 0 9 8 1 6 8 2 2 5 8 + + + + + + + + + + + + + + + +	3 3 4 4 6 6 6 8 9 8 9 0 1 1 8 8 5 1 0 4 5 0 1 1 0 0 1 0 6 0 0 9 8 1 7 6 8 2 2 5 8 5 + + + + + + + + + + + + + + + + + + +	3 3 4 4 6 6 6 6 8 9 8 9 0 1 1 1 1 8 8 5 1 0 4 5 8 0 1 1 0 0 1 0 0 6 0 0 9 8 1 7 9 6 8 2 2 5 8 5 1 +	3 3 4 4 6 6 6 6 6 6 8 9 8 9 0 1 1 1 1 2 8 8 5 1 0 4 5 8 4  0 1 1 0 0 1 0 0 0 6 0 0 9 8 1 7 9 6 6 8 2 2 5 8 5 1 9  + + + + + + + + + + + + + + + + + +	3 3 4 4 6 6 6 6 6 6 6 8 9 8 9 0 1 1 1 1 2 3 8 8 5 1 0 4 5 8 4 4  0 1 1 0 0 1 0 0 0 0 6 0 0 9 8 1 7 9 6 7 6 8 2 2 5 8 5 1 9 0  + + + + + + + + + + + + + + + + + +	3 3 4 4 6 6 6 6 6 6 6 6 6 8 9 8 9 0 1 1 1 1 2 3 3 8 8 5 1 0 4 5 8 4 4 4 4  0 1 1 0 0 1 0 0 0 0 1 6 0 0 9 8 1 7 9 6 7 2 6 8 2 2 5 8 5 1 9 0 0  + + + + + + + + + + + + + + + + +	3 3 4 4 6 6 6 6 6 6 6 6 6 6 8 9 8 9 0 1 1 1 1 2 3 3 7 8 8 5 1 0 4 5 8 4 4 4 9 9 0 1 1 0 0 0 0 0 1 0 6 0 0 9 8 1 7 9 6 7 2 9 6 8 2 2 5 8 5 1 9 0 0 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4	3 3 4 4 6 6 6 6 6 6 6 6 6 6 6 6 8 9 8 9 0 1 1 1 1 2 3 3 3 7 8 8 8 5 1 0 4 5 8 4 4 4 4 9 3  0 1 1 0 0 1 0 0 0 0 1 0 0 6 0 0 9 8 1 7 9 6 7 2 9 9 6 8 2 2 5 8 5 1 9 0 0 4 3  + + + + + + + + + + + + + + + + + +	3 3 4 4 6 6 6 6 6 6 6 6 6 6 6 6 6 8 9 8 9 0 1 1 1 1 2 3 3 3 7 8 9 8 8 5 1 0 4 5 8 4 4 4 9 9 3 3  0 1 1 0 0 1 0 0 0 0 1 0 0 0 6 0 0 9 8 1 7 9 6 7 2 9 9 8 6 8 2 2 5 8 5 1 9 0 0 4 3 4  + + + + + + + + + + + + + + + + + +	3 3 4 4 6 6 6 6 6 6 6 6 6 6 6 7 8 9 8 9 0 1 1 1 1 2 3 3 7 8 9 0 8 8 5 1 0 4 5 8 4 4 4 9 3 3 8 0 1 1 0 0 1 0 0 0 0 1 0 0 0 0 6 0 0 9 8 1 7 9 6 7 2 9 9 8 7 6 8 2 2 5 8 5 1 9 0 0 4 3 4 7 + + + + + + + + + + + + + + + + + + +	3 3 4 4 6 6 6 6 6 6 6 6 6 6 7 7 8 9 8 9 0 1 1 1 1 2 3 3 7 8 9 0 1 8 8 5 1 0 4 5 8 4 4 4 9 3 3 8 0  0 1 1 0 0 1 0 0 0 0 1 0 0 0 0 0 6 0 0 9 8 1 7 9 6 7 2 9 9 8 7 8 6 8 2 2 5 8 5 1 9 0 0 4 3 4 7 7  + + + + + + + + + + + + + + + + +	3 3 4 4 6 6 6 6 6 6 6 6 6 6 7 7 7 8 9 8 9 0 1 1 1 1 2 3 3 7 8 9 0 1 2 8 8 5 1 0 4 5 8 4 4 4 4 9 3 3 3 8 0 7  0 1 1 0 0 1 0 0 0 0 1 0 0 0 0 0 1 0 0 0 0 0 1 6 0 0 9 8 1 7 9 6 7 2 9 9 8 7 8 0 6 8 2 2 5 8 5 1 9 0 0 4 3 4 7 7 7  + + + + + + + + + + + + + + + +	3 3 4 4 6 6 6 6 6 6 6 6 6 6 7 7 7 7 7 8 9 8 9 0 1 1 1 1 2 3 3 7 8 9 0 1 2 3 8 8 5 1 0 4 5 8 4 4 4 4 9 3 3 8 0 7 5  0 1 1 0 0 1 0 0 0 0 1 0 0 0 0 0 1 0 0 0 0 1 0 6 0 0 9 8 1 7 9 6 7 2 9 9 8 7 8 0 6 6 8 2 2 5 8 5 1 9 0 0 4 3 4 7 7 7 1  + + + + + + + + + + + + + + + + + +	3 3 4 4 6 6 6 6 6 6 6 6 6 6 7 7 7 7 7 7 8 9 8 9 0 1 1 1 1 2 3 3 7 8 9 0 1 2 3 3 8 8 5 1 0 4 5 8 4 4 4 9 3 3 8 0 7 5 5  0 1 1 0 0 1 0 0 0 0 1 0 0 0 0 0 1 0 0 0 0 1 0 0 6 0 0 9 8 1 7 9 6 7 2 9 9 8 7 8 0 6 6 6 8 2 2 5 8 5 1 9 0 0 4 3 4 7 7 7 1 2  + + + + + + + + + + + + + + + + + +	3 3 4 4 6 6 6 6 6 6 6 6 6 6 6 7 7 7 7 7 7 7	3 3 4 4 6 6 6 6 6 6 6 6 6 6 7 7 7 7 7 7 7 7	3 3 4 4 6 6 6 6 6 6 6 6 6 6 6 7 7 7 7 7 7 7	3 3 4 4 6 6 6 6 6 6 6 6 6 6 6 7 7 7 7 7 7 7	3 3 4 4 6 6 6 6 6 6 6 6 6 6 6 7 7 7 7 7 7 7	3 3 4 4 6 6 6 6 6 6 6 6 6 6 6 7 7 7 7 7 7 7	3 3 4 4 6 6 6 6 6 6 6 6 6 6 6 7 7 7 7 7 7 7	3 3 4 4 6 6 6 6 6 6 6 6 6 6 6 7 7 7 7 7 7 7

TABLE B2

Individual Animal Tumor	· Pathology of Ma	le Prote im the 2-Ve	ar Cavage Study of S	allower Oil :	2.5 mill /kg (continued)

Number of Days on Study	7 3 5	7 3 5	3	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	3		7 3 6												
	0	0		۰	0	1	1	1	1	1	1	1	1	1	1	0	0	0	0	0	1	1	1	1		1	Total
Carcass ID Number	8	6	_	-	9	1	3	4	5	1	4	5	6	7	9	1	2	3	4	9 7	0	6	0	2	2	3	Tissues/ Tumors
Respiratory System (continued)	<del></del>																								_		<del></del>
Nose Squamous cell papilloma	+	4	+ -	+ +	- +	- +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	- 4		+	+	50 1
Trachea	+	+	<b>⊦</b> ⊣	+ +	- 4	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	- 4		+	+	50
Special Senses System																											<del></del>
Ear																											2
Zymbal's gland										+																	2
Carcinoma										X																	2
Urinary System																											······································
Kidney	+	-	+ -	+ +	- 4	+ +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	4		٠ ٠	+	+	50
Urinary bladder	+	-	+ -	+ +	- 4	+ +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	4	- +	⊦ -	+	+	49
Systemic Lesions	·····																								_		
Multiple organs	+	-	+ -	+ +	٠ -	+ +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	4		<b>⊢</b> -	+	+	50
Leukemia mononuclear	х		7	ζ.	>	ζ.		Х			X	X							Х		Х			2	X		19
Mesothelioma malignant									X			X															2

TABLE B2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Safflower Oil: 5 mL/kg

•			1	1	3 :	3	5	5	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7				
Number of Days on Study			6				-	-			-		2	3	3	3	3	3	3	2	3	3	3	3	3	3		3				,
vumber of Days on Study			_	5	_			-	_				1	2	2	2		2	3	3	3	3		.3			3	_				
				,			_	<b>-</b>		<i>.</i>	<i>-</i>	-			_		-			<i></i>									_			
			1		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1				
Carcass ID Number			. 2	2 :	3	2 :	5	7	3	2	7	4	7	5	5	6	7	7	2 ·	2	2	3	3	3	3	3	4	4				
			3	3			5			4	9	6	2					7									0	2				
<u></u>					_																				_							
Alimentary System									_	_				_																	٠,	
Esophagus			•	+ .	M		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+				
Intestine large			-	+		A	+				+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Intestine large, cecum			•	+		-	+	A				+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	•			
Intestine large, colon			-	+	+ .	A	+	+	-	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	٠.	,	
Sarcoma									X																						**	
Intestine large, rectum	•	,	-	-	+ .		+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	M	+	+	+				
Intestine small			-	+	+ .	A	+	+	+	+	+		A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		. "		
Intestine small, duodenum			-	•	+ .	A.	+	+	+	+			A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		***		
Intestine small, ileum			-	+	+ .	A.	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Intestine small, jejunum			. •	+	+ .	A	+	+	+	+	+		Α	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Liver			-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	,.			
Hepatocellular carcinoma																		X									31	1			ŝ	
Hepatocellular adenoma																									•2	•	٠	X				
Mesentery							+			+					,		+											:	٠, '		* . *	
Pancreas			-	+	+ .			+ -	+	+	+	+	+	+	+	+	+	+	+			+	+	+	+	+	+	+		:		
Acinus, adenoma		٠.					X			•										X	X					X			:	٠.	. *	
Acinus, adenoma, multiple																					٠			٠.	(F.)			X	4	٠		
Acinus, mixed tumor benign																									,4					•		
Salivary glands		:	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	:			•
Stomach			-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		1		
Stomach, forestomach .	-		-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	1	٠	•	
Squamous cell papilloma							•						X													. •		•		7,		
Stomach, glandular	•		-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			•	•
Cardiovascular System																										٠.		٠				
Heart			•	+	+	+	+	÷	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Endocrine System											_									_		_			_					_		
Adrenal gland				_	_	_	4	_	+	+	_	4	+	+	+	+	+	+	+	+	+	+	+	į.	+	+	+	+	•			
Adrenal gland, cortex				<u>.</u>	Ţ	·	ì	<u>.</u>	ì	·	i	÷	<u>.</u>	÷	·	4	÷	÷	4	÷	<u>.</u>		ì	i	÷		<u>.</u>					
Adrenal gland, medulla				+	+	<u>+</u>	+	+	+	+	+	+	<u>.</u>	+	+	+	<u> </u>	<u> </u>	+	+	÷	+	+	+	+		+	+				
Ganglioneuroma				1	т	т		X	•	•		•	,	•	'	•	'	•	•	•	•	•	•	•	•		•					
Pheochromocytoma benign								^							x									Y			•	Х				
Bilateral, pheochromocytoma	enion														Λ										• •		.;; ·	<u>^</u>				
Islets, pancreatic	~ingii		_	_	_	Α	+	_	+	+	+	+	_	_	+	+	_	4	+	4	4	_	+	_		+		+				
Adenoma				r	т.	a	т	Τ.	т.	т′	т.	-	٠,٢	-	г	-	•	٢	-	-	г	.T		, T	7	7	. ~		٠,			
Adenoma Parathyroid gland				_	м	_	м	_	_	_	м	_	м	_	_	_	_	+	м	_	_	_	_	_	_	4	_	Λ +	•	•		
			•	r	T.	т Т				т М			+	+		+	+	+	+	+	T		т Т	T	T	T _L	T	-T -L				
Pituitary gland			•	Τ.	+	т	т	т	+	ivi	т	т	+	+	+	+		X	-	+	+	. —	+	7	Τ.	+	T	X	4			
Pars distalis, adenoma				1.			_					_	A	,	J	,			_		_1	1.1.						<b>.</b>	•	~ √ (		
Thyroid gland C-cell, adenoma			•	+	+	A	+	+	+		+ X	+	A	+	+	+	+ X	+	+	+	+	+	+ X		+	+	+					
																					_							_				
General Body System Tissue NOS																															÷.	•
Genital System								_	_												_			_								_
Epididymis -				+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Preputial gland				+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			•	
Adenoma								x				-				-			-			•		X	X			•			4.1.	
Prostate				+	+	+		+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+			+	+				٠.
							-															-								•		

	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
lumber of Days on Study	3	3	3	3	3	3			3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
·	3	3	3	3	3	3												4		4	4			5		
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	Total
Carcass ID Number	4	4	4	5	5	5		5		6		7				2		2	3	4	4		-	6		Tissues
•	4	8	9	0	1	2	3	7	8	0	4	5	6	8	0	6	7	8	0	1	5	5	1	4	7	Tumor
dimentary System						_																				-
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	. +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, colon Sarcoma	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48 1
Intestine large, rectum	+	. +	. +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small					+	<u>.</u>	<u>.</u>	<u>.</u>	<u>.</u>	<u>.</u>	+	<u>.</u>	<u>.</u>	+	+	<u>.</u>	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum						+	<u>.</u>	+	<u>.</u>	+	+	+	+	<u>.</u>	<u>.</u>	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum					·	+	·	<u>.</u>	<u>.</u>	<u>.</u>	÷	+	+	<u>.</u>	<u>.</u>	+	<u>.</u>	+	<u>.</u>	<u>.</u>	+	+	+	+	+	48
Intestine small, jejunum						+	÷	+	+	<u>.</u>	+	+	<u>.</u>	+	+	+	+	+	+	+	+	+	+		+	48
Liver						Ţ	÷	i	+	+	+	÷	<u>.</u>	+	÷	÷	<u>.</u>	+	Ţ	<u>.</u>	<u>.</u>	÷	<u>.</u>	· +	÷	50
Hepatocellular carcinoma	,	•	•	•		т	_	_	т.	۳.	т	т	1	•	т.	•	'	-	Ψ.		'		_	7	•	1
Hepatocellular adenoma																										1
Mesentery	+			_			_							_		_							_			10
Pancreas	+		1		+	_		_	_	_	_	_	_	т. Т		<u></u>	_	_	_	_	_	1.	<u> </u>	_	_	49
Acinus, adenoma	7	7	7	· •	т	~	т	X	т	т	X	т	X	т-	т	X	Τ.	Т	т	т	X	7	_	т	7	9
Acinus, adenoma, multiple					Х			^	х		Λ		Λ		х	^	X		v		^					
					Λ				Λ						А		А		X						v	6
Acinus, mixed tumor benign																									X	1
Salivary glands	+	. +	• +	• •	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	- +	- +	• •	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	- +	- +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma Stomach, glandular	+	- +	- +	. +	+	+	+	+	+	+	X +	+	+	+	+	+	+	+	+	+	+	+	+	+	•	2 49
Cardiovascular System										_								_								
Heart	+	- +	- +	- +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System					•						-															
Adrenal gland	+	- 4	- +	. +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	- 4	- +	. +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	- 4	- +	- +	. +	+	+	+	+	4	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	49
Ganglioneuroma																							•	•	•	1
Pheochromocytoma benign				Х					х	x											Х					7
Bilateral, pheochromocytoma benign				•	•	Х										X								Х		3
Islets, pancreatic	4		- 4				+	+	+	+	+	+	+	4			+	+	+	+	+	4	+			49
Adenoma			'		•	•	•		x	•	•	•	•	x	•	•	٠	•	•	•	X	•	•		x	5
Parathyroid gland						4	+	M		M		_	+		_	м	+	M	_	_		_	_	_	+	40
Pituitary gland			, L	اسا		η- _	, ,	+					+												+	49
Pars distalis, adenoma	7	٦	7	7	7		т	Т	Т	Т	т	Т	X		-	r		X		Τ'	Τ.	_	~	~	-	49
Thyroid gland	د.	د .	1	1		_		_	+		ı	ı	+		_					_		+		_	+	48 48
C-cell, adenoma	7	7	7	7	• т	т	т	т	т		X	т	т	_	т	т	Т	_	т		X		т	т	т	7
General Body System Tissue NOS		_																_								
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Genital System Epididymis			1	<u>.</u>	ر .	.1	М		.1.	_1	al.	,L		_1	ı	J.	_ــ	.1		.1	.1		. 1		و	49
Preputial gland	7		· •		· +	T-	.M. +		+	+ 	T _1_		T L	T	<b>∓</b>	T _L	T _L	<b>+</b>	<b>т</b>	+ _	+ 	+	+	+	T J.	49 49
Adenoma	٦	. 4	- 4	- 1	+	iVi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			+	+	
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LIOSING	- 1	- 4	- 1	- +	- +	+	+	+	+	+	+	+	+	IVI	+	+	+	+	-	-	+	-	-	-	-	48

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Number of Days on Study	3		-	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
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Carcass ID Number	4		1	4	5	5	5	5	5	5	_	7	7	7	_		2	2	2		4	4	6	6	6		Tissues
	4	8	3	9	-	1		3				4				0				0					_	-	Tumor
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Genital System (continued)																											
Seminal vesicle	+	•	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+		+	+	+	+	+	M		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Bilateral, interstitial cell, adenoma Interstitial cell, adenoma	Х		X.	Х	X	Х	X		A	А	X	Х	Х	X	Х	х	Х	Х	A	Х	A	Х	Х	Х	A	Х	44 2
interstitut cen, acenoma																_											
Hematopoietic System																											
Blood						+							+			+											7
Bone marrow	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+		+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mesenteric	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thymus	+	- ]	M	M	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	41
Integumentary System				_													-	-									
Mammary gland	4		+	+	+	+	+	+	+	+	М	+	+	+	+	М	М	+	+	+	+	+	+	М	М	+	43
Fibroadenoma			•	•	•	·	•	•	•	•		•	•	•	Ċ			•	•	•	•	•	·			•	1
Skin	4		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma					•	•	•	•	•	•	x	•	•	,	•	•	•	•	·	•	•	•	X		٠	-	3
Squamous cell carcinoma							X																				1
Squamous cell papilloma									X												X						4
Subcutaneous tissue, fibroma																											1
Musculoskeletal System		_																_									
Bone	4		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma	'		•	•	•	•	•	•	•	•	•	•	•	•	•	•	'	•			'	•	•	1		•	1
Skeletal muscle		_	+	+	+	_	_	_	_	_	+	+	+	+	+	+	+	+	_	+	_	_	_	1	+	+	50
	7		'	_	т'	Τ'	т	т		т	т	-					Г				т-		т.			т′	
Nervous System																											
Brain	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Glioma malignant																											1
Oligodendroglioma malignant																											1
Spinal cord																											1
Respiratory System																											
Lung	4	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nose	4	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																											
Ear																											1
The same of the same																					_						
Urinary System																											
Kidney	4	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	4	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																											
Multiple organs	4	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

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Number of Days on Study		0	4	8	0	1	1	2	3	7	9	1	1	2	2	2	2	2	2	2	2	2	2	2	2.	2	2		100
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Carcass ID Number		0	1	2	1	0	1	3	3	3	1	4	9	1	0	8	8	8	9	9	9	9	9	9	9	0	0		
		2	2	8	3	1	4	1	2	0	5	0	7	1	0	8	6	7	0	3	4	5	6	8	9	3	4		
Alimentary System		_											<u></u>													<u> </u>			
Esophagus		+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	5	
Intestine large		+	+	+	+	+	+	+	+	+	A	+	Α	+	+	+	+	+	+	+	+	+	+	+	+	+.	+		, P
Intestine large, cecum		+	+	+	+	+	+	+	+	+	Α	+	Α	+	+"	Α	+	+	+	+	+	+	+	+	+	+	+		
Intestine large, colon		+	+	+	+	+	+	+	+	+	Α	+	A.	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Intestine large, rectum		+	+	+	+	M	+	+	+	+		À				+	+	+	+	+	+	+	+	+	4	+	+		
Intestine small		+	<u>.</u>	+	+	+	<u>.</u>	+	+			+			+	+	<u>.</u>	+	<u>.</u>	+	+	+	+	+	+	+	+		,
Intestine small, duodenum		+	+	+	+	+	+	+	+			+			+	+	+	+	+	+	+	+	+	. 4	+	4	+		
Intestine small, ileum		<u>.</u>	+	+	·	+	·	+	+			À					+	+	+	+	·	+	+	÷	• +	÷	·		
Intestine small, jejunum		<u>.</u>	Ţ	1	1		1	, ,				A						<u>.</u>		Ţ			4	<u>.</u>	1	1	1		
Liver		<b>+</b>	<b>T</b>	<b>+</b>		<b>+</b>	<b>T</b>	+	+	+	+	+	+	+	+	+	_	<u>+</u>	<del>-</del>	+	т Т	<b>→</b>	<b>T</b>				<b>—</b>		
Carcinoma, metastatic, pancreas		-	T	-	т-	т	-	7	-	т	-	т	_	7	7	Т	т	Т	т.	-	т	. *	, T	Τ,	т.	т	. T		
Mesentery												_		+						_									
Pancreas						_				æ		T				_		_											
Acinus, adenoma	•	+	+	+	+	+	+	+	+	+		+	A	+	+	+	X	+	+	+	v	+	+	+	7	- <del>1</del>	. *		
•										×		X		х	•		^	x		х	X	,			:•	v	v .		
Acinus, adenoma, multiple									X					Λ	•			^		Λ					X	•			
Acinus, carcinoma									А													.,.							
Acinus, carcinoma, multiple																													
Salivary glands		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		.,
Stomach	*	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		• •
Stomach, forestomach		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	- 124	+	+		
Squamous cell papilloma																			X							, '	.,		
Stomach, glandular	•	+	+	+	+	+	+	· +	+	+.	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	· +	+	•	1
Carcinoma										X																			
Tongue												_								,								, .	
Cardiovascular System																								;					-
Heart		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		. 1
Endocrine System										<u> </u>														<u> </u>			•	-	· · ;
Adrenal gland		+	+	+	+	+	+	+	+	+	Α	+	Α	+	+	+	+	+	+	+	+	+	+	+	+	+	+	2"	
Adrenal gland, cortex		+	+	+	+	+	+	+	+			+						+	+	+	+	+	+	+	+	+	+	:	
Adenoma														X						X									٠,
Adrenal gland, medulla		+	+	+	+	+	+	+	+	+	Α	٠+	A		+	+	+	+	+		+	+	+	+	+	+	+	:	
Pheochromocytoma malignant			-			•		·		X		-			•		-							·	·	٠.	``	*	
Pheochromocytoma benign				X						**													×		x	:	1		
Bilateral, pheochromocytoma benign														X					• 2						1.		, ;		
Islets, pancreatic		_		4	_	_	4		4	_	Δ	Ψ.	Δ	+		_	_	4	_	4	_	_	4	_	4	Ή.	4		
Adenoma			•		•	•	•	'	•	'	•	•	41	٠	•	•		•	•	x	•	•	'	•	'	x	•	. ·	
Parathyroid gland		_	_	M	_	+	_		٠.	М	_	+	м	_	1	_	_	_	_	+	_	٠.	+	٠.	_	4	Έ.		
Pituitary gland				741		T		<b>T</b>	T-	T-			74.		T		_	4	<u>-</u>	1	<b>T</b>	T	<b>T</b>		T		M		
Pars distalis, adenoma		г		X	т	т	т	X	τ.	т	Т	. T	•	т	Т	٢	r	r	Т	r	X	т	т.	. · .	т	X			
Thyroid gland		_	_	7	_		_	+		_	_	Α	Δ	_	_	_	_	_	_		<u> </u>	.1.	_	_	_		+.		
C-cell, adenoma		Т	т	~	т	т	т	т	т	т		A	Λ	т	X	Т	-	-	т	-	т	т	т	-	т	. "	т,		
Follicular cell, adenoma										X					Λ												٠.		٠

None

	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7		
Number of Days on Study	2	2	2	2	2	2	2	2	2	2	2	3	3	3	3	3	3	3	3	3	3	3	3	_	3		
•	9	9	9	9	9	9	9	9	9	9	9	2	2	2	2	2	2	2	2	2	2	2	2	2	2		
	2	2	2	2	2	2	2	2	2	2	2	1	1	1	1	2	2	2	2	2	2	2	2	2	2		Total
Carcass ID Number	0	0	1	1	1	2	2	2	2	2	2	8	8	8	8	0	0	1	3	3	3	3	3	3	3		Tissues
	5	7	6	7	9	0	1	2	3	6	9	1	2	3	5	8	9	0	3	4	5	6	7	8	9		Tumors
Alimentary System														_			_						_				
Esophagus	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Intestine large	+	+	+	+.	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	. +	+		49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	. +	+		47
Intestine small		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	. +	+		49
Intestine small, duodenum		<u>.</u>	+	<u>.</u>	÷	+	+	+	<u>.</u>	÷	<u>.</u>	+	+	<u>.</u>	+	<u>.</u>	+	+	+	+	+	+	•		+		49
Intestine small, ileum			÷	ì	÷	<u>.</u>	4	÷	·	÷	<u>,</u>	÷	+	<u>.</u>	+	+	÷	<u>.</u>	÷	<u>.</u>	·	·	·		÷		47
Intestine small, jejunum	·		<u>.</u>	Ţ	·	·	i	Ţ	+	÷	+	+	+	÷	+	+	÷	·	+		<u>.</u>	<u>.</u>			·		46
Liver	4.	i	i	Ţ	i	i	i	i	÷	+	+	+		+	+	+	·	<u>.</u>	Ţ	·	i	÷	·		÷		51
Carcinoma, metastatic, pancreas	т	-	т	7	т.		1.	т	'	•	4	X		'	•	•	•	•	•	•	'	•	٠	•	•		1
, , , , , , , , , , , , , , , , , , ,												Λ															7
Mesentery				. :									+						+	+				+			
Pancreas	. +	+	+	+	. +	+	+	+	+.	+	+	+	+	+	+	+	+	+	+	+	+		+	• +	+		50
Acinus, adenoma	X			X										X									X			•	9
Acinus, adenoma, multiple		X	Х		X	X	X		X			Х	X				X			Х	X			Х	X		19
Acinus, carcinoma																											. 1
Acinus, carcinoma, multiple												X															1
Salivary glands	+	+	+	+	+	+	+	. +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	. +	+		51
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	. +	+		51
Stomach, forestomach	+	. +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	- , +	+		51
Squamous cell papilloma																											. 1
Stomach, glandular	+	+	+	+	+	. +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	- +	+		50
Carcinoma																											. 1
Tongue	+																										1
Cardiovascular System			_	•							-						٠.	; -		_		-					
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	- +	+		51
Endocrine System											-		-					-		_		_					
Adrenal gland	. +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	4	- 4	+		49
Adrenal gland, cortex	+	·	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	. 4	- 4			49
Adenoma	•	'	•	•	•	٠	'	•	٠	•		•					•		•	•	•	٠			•		2
Adrenal gland, medulla	_	_	_		_	_	_	_	_	_	_			_	_	_	_	_	_	_	_				+		49
	т		т	T	T	•	т	. T	Τ.			7	Т	т	т	т	т	т	т	т	т	•	7		. Т		
Pheochromocytoma malignant	37									v	w																1
Pheochromocytoma benign	Х									Х	X																6
Bilateral, pheochromocytoma benign																											1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	- +	+		49
Adenoma																							X				3
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	M	1 +	+	+	+	+	+	M	۱ +	+	+				1 +		43
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+			+	+	+	+	+	+	+			- +	+		50
Pars distalis, adenoma			X		X								X									X					8
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	٠ 4	+ +	+		49
C-cell, adenoma		Х					Х																X	ζ			4
Follicular cell, adenoma																											1

	3	5	5.	6	6	0	6	6	6	6	7	7	7	7 ′	7	7	7	7	7	7	7	7	7	7	7	7	
Number of Days on Study	0			o			2			_	_		_	2 :		2	2	2	2	2	2	2	2	2	2	2	
	2	-	2	7	3	-	7				5				6		9	9	9	9	9	9	9	9	9	_	
		_	_	_	_	_	<del>_</del> -		_	_	<u>~</u>	_	2			_	_	1		1	_	-	_	_	_		
Carcass ID Number	_	2	2	2	2	-	2		_				2 1	2			_	_	-	1	9	1 9	9	1		0	
Carcass ID Number													1		8 (	6						-		-	-		
		_			_		_	-	_	7.							_	:	_			-	_	_			
Genital System							•																				
Epididymis	+	+	+	+	+	+	<u>+</u>	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Mesothelioma malignant, metastatic, testes Preputial gland													+											X			
Adenoma	т	_	-	Ŧ	_	т	~	_	+	т	_	^	т	<b>T</b>	Τ .	Ŧ	т	Ŧ	1	~	_	+	_	~		_	
Bilateral, adenoma																							Х				
Prostate	+	_	+	_	+	+	_	+	+	+	+	+	+	+	+	_	+	м	4	+	+	+			4	+	
Seminal vesicle	+	<b>+</b>	+	<u> </u>	<u>,</u>	+							+														
Testes		+	<u>_</u>	4	+								+														
Bilateral, interstitial cell, adenoma	-1-	X		ŗ									Τ.														
Interstitial cell, adenoma		Л		X		1	^	1	Л	Л	Ą.		X	Λ.	/ <b>X</b> /	^	Ţ	^	Δ.	Л	Л	Λ	Ą	•	А	Л	
Hematopoietic System						_		_			÷	-	_			_			-	-							
Blood					+																						
Bone marrow	+	+	+	+		+	+	+	+	Α	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Fibrosarcoma, metastatic, skin	-																										
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	÷	+	+	+	+	+	+	+	+	+	+	
Thymus	+	+	M	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	
Thymoma benign		•																									
Integumentary System						-																					
Mammary gland	+	+	+	+	+	+	M	+	M	+	+	Α	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Fibroadenoma							•							•													
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Basal cell adenoma		•			-	٠.	X		•		-												•				
Keratoacanthoma																											
Squamous cell carcinoma		X																									
Squamous cell papilloma																						X					
Subcutaneous tissue, fibroma		X														X											
Subcutaneous tissue, fibrosarcoma																											
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	_+	
Nervous System								,																			
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Respiratory System									-												_						
Lung	+	+	+	+	+	+	+	+	+	#	+	Α	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Fibrosarcoma, metastatic, skin																											
Mediastinum, sarcoma, metastatic, heart											Х							٠									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Carcinoma, metastatic, harderian gland	X																										
Trachea	+	+	+	+	+	+	+	+	+	+	+	Α	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
																				_							

		~			<u> </u>	<u>~</u>	<del>-</del>	7	-	7	7	~	7	7	7	7 /	<del>-</del>	_	<del>-</del>	7	_	_	-	~	7	<del></del>
Name have an Danie are Charles		7	7		7	7	7	7	7	7	•	•		-						7	7	7	7	7		
Number of Days on Study	2 9	2 9	2 9	2 9	2 9	2 9	2 9	9	2 9	2 9	2 9	3 2								3 2	3 2	3 2	3 2		3	
	2	2	2	2	2	2	2	2	2	2	2	1	1	1	1 :	2 :	2	2	2	2	2	2	2	2	2	Total
Carcass ID Number	0	0	1	1	1	2	2	2	2	2	2	8							3	3	3	3	3	3	3	Tissue
	5	7	6	7	9	0	1	2				1	2			8 9			3	4	5	6	7	8	9	Tumo
Genital System															-		-			-						· · · · · ·
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Mesothelioma malignant, metastatic, testes																										2
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma									X																	1
Bilateral, adenoma																										1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+ :	M	+	+	+	+	+	+	+	+	+	49
Seminal vesicle	+	+	+	+	+	+	+	+	+	+.	+	+	+	+	+	+	÷	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Bilateral, interstitial cell, adenoma	Х	X	X	X	Х	X	X	X	X		X	X	X	X		X		Х	Х	X	X	X		X	X	43
Interstitial cell, adenoma										X	:				X		X				•		X			6
Hematopoietic System														•					-	•				-		
Blood											+															2
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	50
Fibrosarcoma, metastatic, skin																							X			1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Thymus	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	43
Thymoma benign										X																1
Integumentary System		-		-																						<del></del>
Mammary gland	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	46
Fibroadenoma									X												X					2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Basal cell adenoma											٠														•	1
Keratoacanthoma																				X						1
Squamous cell carcinoma																										1
Squamous cell papilloma																										1
Subcutaneous tissue, fibroma																										2
Subcutaneous tissue, fibrosarcoma																							X			1
Musculoskeletal System					_							_			<u> </u>									_		
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Nervous System				-	_																					<del></del>
Brain	+	+	+	+	+	+	+	+	+	+	+,	+	+	+	+	+	+	+	+	+	+	+	+	÷	+	51
Respiratory System			_									_				_		_	_		-	_	-	_		
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, skin																							X			1
Mediastinum, sarcoma, metastatic, heart																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Carcinoma, metastatic, harderian gland																			•			•	•	•		1

3																												
	5	5	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7			
0	4	8	0	1	1	2 -	3	7	9	1	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	•		
2	7	2	7	3	7	7	3	2	1.	5	8	2	4	6	9	9	9	9	9	9	9	9	9	9	9	•		
2	2	2	2	2	2	2	2	2	2	2	1	2	2	1	1`	1	1	1	1	1	1	1	1	2	2		~ .	
0	1	2	1	0	. 1	3	3	3	1	4	9	1	0	8	8	8	9	9	9	9	9	9	9	0	0			
2	2	8	3	1	4	1	2	0	5	0	7	1	0	8	6	7	0	3	4	5	6	8	9	3	4		•	
				-										-		-		Τ,			-	_					•	
			+																							-		
+																									+			
+																											,	:
X																									4.	··· .		
				•	,									•	- 1							•						_
+	+	+	+	+	+	+	+	+ ,	+	+	Α	+,	+,	Α	+	+	+	+	+	+	+	+	+	+	+	٠.		
+	+	+	+	+	+	+	+	+	+	<b>+</b> ,	A	+	+,	A	+	+	M	+	+	+	+	+	+	+	+			
				_						•		141			•		-			-								-
+	+	. +	. +	+	+	+	+	+.	+	+	+.	+	+	+	+	+	+	+	+	+	+	+	+	.+	`+			
•				Х	X			•	X		X										Х				٠.			
																									. u			
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Number of Days on Study		7 2	7 2	7 2	7 2	7 2	7 2	7 2	7 2	7 2	7 2	7 2	7	7	7	7	7	7	7	7	7	7	7	7	7	7 3	
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Carcass ID Number	· (	0	0	1	1	1	2	2	2	2	2	2	8	8	8	8	0	0	1	3	3	3	3	3	3	3	Tissues/
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Special Senses System									-							_									_		
Ear																											1
Eye																											2
Harderian gland																											. 1
Carcinoma																											1
Urinary System						_																-					
Kidney		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Systemic Lesions			-						-						_			•••	_					_			
Multiple organs		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Leukemia mononuclear												Х											Х				7
Mesothelioma malignant																									Х		2

TABLE B3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Safflower Oil

	Untreated Control	2.5 mL/kg	5 mL/kg	10 mL/kg	
Adrenal Medulla: Benign Pheochromocytoma					
Overall rate <sup>a</sup>	11/49 (22%)	12/48 (25%)	10/49 (20%)	7/49 (14%)	
Adjusted rate <sup>b</sup>	34.4%	33.8%	25.6%	17.8%	
Terminal rate <sup>c</sup>	9/29 (31%)	9/32 (28%)	10/39 (26%)	5/36 (14%)	
First incidence (days)	627	634	729 (T)	582	
Life table test <sup>d</sup>	P = 0.054N	P = 0.588	P = 0.236N	P = 0.112N	
Logistic regression test <sup>d</sup>	P = 0.096N	P = 0.480	P = 0.392N	P = 0.187N	
Cochran-Armitage test <sup>d</sup>	P = 0.137N				
Fisher exact test <sup>d</sup>		P = 0.477	P=0.500N	P = 0.217N	
Adrenal Medulla: Benign or Malignant Pheochron	nocytoma	•		٠.	
Overall rate	13/49 (27%)	12/48 (25%)	10/49 (20%)	8/49 (16%)	
Adjusted rate	41.0%	33.8%	25.6%	19.7%	
Terminal rate	11/29 (38%)	9/32 (28%)	10/39 (26%)	5/36 (14%)	
First incidence (days)	627	634	729 (T)	582	
Life table test	P = 0.041N	P = 0.405N	P = 0.103N	P = 0.074N	
Logistic regression test	P = 0.077N	P = 0.518N	P = 0.207N	P = 0.136N	
Cochran-Armitage test	P=0.112N				
Fisher exact test		$P = 0.524N^{2}$	P = 0.317N	P=0.162N	
Liver: Hepatocellular Adenoma or Carcinoma					
Overall rate	3/50 (6%)	2/50 (4%)	2/50 (4%)	0/51 (0%)	
Adjusted rate	10.0%	5.3%	5.0%	0.0%	
Terminal rate	3/30 (10%)	1/33 (3%)	2/40 (5%)	0/36 (0%)	
First incidence (days)	729 (T)	624	729 (T)	_e ` ´	
Life table test	P = 0.062N	P = 0.472N	P = 0.370N	P = 0.090N	
Logistic regression test	P = 0.077N	P = 0.506N	P = 0.370N	P = 0.090N	
Cochran-Armitage test	P = 0.084N				
Fisher exact test		P = 0.500N	P = 0.500N	P = 0.118N	
Mammary Gland: Fibroadenoma					
Overall rate	7/50 (14%)	2/50 (4%)	1/50 (2%)	2/51 (4%)	
Adjusted rate	22.2%	6.1%	2.5%	5.6%	
Terminal rate	6/30 (20%)	2/33 (6%)	1/40 (3%)	2/36 (6%)	
First incidence (days)	691	729 (T)	729 (T)	729 (T)	
Life table test	P = 0.030N	P = 0.062N	P = 0.012N	P=0.046N	
Logistic regression test	P = 0.032N	P = 0.067N	P = 0.018N	P = 0.047N	
Cochran-Armitage test	P = 0.051N				
Fisher exact test		P = 0.080N	P = 0.030N	P = 0.075N	
Pancreas: Adenoma					
Overall rate	1/50 (2%)	7/50 (14%)	15/49 (31%)	28/50 (56%)	
Adjusted rate	3.3%	21.2%	36.4%	69.8%	
Terminal rate	1/30 (3%)	7/33 (21%)	14/40 (35%)	24/36 (67%)	
First incidence (days)	729 (T)	729 (T)	531	672	
Life table test	P<0.001	P = 0.041	P = 0.001	P<0.001	
Logistic regression test	P<0.001	P = 0.041	P<0.001	P<0.001	
Cochran-Armitage test	P<0.001				
Fisher exact test		P = 0.030	P<0.001	P<0.001	

TABLE B3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Safflower Oil (continued)

	Untreated Control	2.5 mL/kg	5 mL/kg	10 mL/kg
Pancreas: Adenoma or Carcinoma				
Overall rate	1/50 (2%)	7/50 (14%)	15/49 (31%)	29/50 (58%)
Adjusted rate	3.3%	21.2%	36.4%	70.5%
Ferminal rate	1/30 (3%)	7/33 (21%)	14/40 (35%)	24/36 (67%)
First incidence (days)	729 (T)	729 (T)	531	633
Life table test	P<0.001	P = 0.041	P = 0.001	P<0.001
ogistic regression test	P<0.001	P = 0.041	P<0.001	P<0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		P = 0.030	P<0.001	P<0.001
Pancreatic Islets: Adenoma				
Overall rate	7/49 (14%)	3/50 (6%)	5/49 (10%)	3/49 (6%)
Adjusted rate	18.1%	9.1%	12.5%	8.3%
Terminal rate	3/30 (10%)	3/33 (9%)	5/40 (13%)	3/36 (8%).
First incidence (days)	476	729 (T)	729 (T)	729 (T)
Life table test	P = 0.121N	P = 0.148N	P = 0.258N	P = 0.120N
Logistic regression test	P = 0.178N	P = 0.139N	P = 0.375N	P = 0.159N
Cochran-Armitage test	P = 0.181N			
Fisher exact test		P = 0.151N	P = 0.380N	P = 0.159N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	7/50 (14%)	10/48 (21%)	4/49 (8%)	8/50 (16%)
Adjusted rate	20.2%	27.6%	10.0%	20.6%
Terminal rate	4/30 (13%)	7/32 (22%)	4/40 (10%)	6/35 (17%)
First incidence (days)	627	485	729 (T)	582
Life table test	P = 0.389N	P = 0.342	P = 0.148N	P = 0.604
Logistic regression test	P = 0.490N	P = 0.258	P = 0.252N	P = 0.505
Cochran-Armitage test	P = 0.504N			
Fisher exact test		P=0.266	P=0.274N	P = 0.500
Preputial Gland: Adenoma				
Overall rate	7/50 (14%)	6/50 (12%)	4/49 (8%)	2/49 (4%)
Adjusted rate	23.3%	17.4%	9.7%	5.7%
Ferminal rate	7/30 (23%)	5/33 (15%)	3/39 (8%)	2/35 (6%)
First incidence (days)	729 (T)	683	554	729 (T)
Life table test	P=0.026N	P=0.431N	P=0.144N	P=0.047N
Logistic regression test	P=0.040N	P = 0.457N	P = 0.261N	P = 0.047N
Cochran-Armitage test	P = 0.051N			
Fisher exact test		P=0.500N	P=0.274N	P=0.085N
Skin: Keratoacanthoma				
Overall rate	0/50 (0%)	1/50 (2%)	3/50 (6%)	1/51 (2%)
Adjusted rate	0.0%	3.0%	7.5%	2.8%
Terminal rate	0/30 (0%)	1/33 (3%)	3/40 (8%)	1/36 (3%)
First incidence (days)	-	729 (T)	729 (T)	729 (T)
Life table test	P=0.407	P=0.519	P=0.176	P=0.536
Logistic regression test	P=0.407	P=0.519	P = 0.176	P = 0.536
Cochran-Armitage test	P = 0.358	D-0.500	D0.101	D_0.505
Fisher exact test		P = 0.500	P = 0.121	P = 0.505

TABLE B3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Safflower Oil (continued)

	Untreated Control	2.5 mL/kg	5 mL/kg	10 mL/kg	
Skin: Squamous Cell Papilloma					
Overall rate	2/50 (4%)	2/50 (4%)	4/50 (8%)	1/51 (2%)	
Adjusted rate	5.5%	5.4%	10.0%	2.8%	
Terminal rate	1/30 (3%)	1/33 (3%)	4/40 (10%)	1/36 (3%)	*
First incidence (days)	635	634	729 (T)	729 (T)	
Life table test	P = 0.368N	P = 0.692	P = 0.450	P = 0.461N	•
Logistic regression test	P = 0.410N	P = 0.690N	P = 0.345	P = 0.493N	
Cochran-Armitage test	P = 0.422N				
Fisher exact test		P = 0.691N	P=0.339	P=0.492N	
Skin: Squamous Cell Papilloma or Squa	mous Cell Carcinoma				
Overall rate	2/50 (4%)	3/50 (6%)	5/50 (10%)	2/51 (4%)	
Adjusted rate	5.5%	8.4%	12.5%	4.7%	
Terminal rate	1/30 (3%)	2/33 (6%)	5/40 (13%)	1/36 (3%)	
First incidence (days)	635	634	729 (T)	547	1000
Life table test	P = 0.506N	P = 0.509	P = 0.325	P=0.658N	
Logistic regression test	P=0.565N	P = 0.500	P = 0.228	P = 0.686N	·
Cochran-Armitage test	P=0.569N				
Fisher exact test	<i>A</i>	P = 0.500	P=0.218	P=0.684N	
Skin: Squamous Cell Papilloma, Kerator	acanthoma, Basal Cell Adenon	na, or Squamous C	Cell Carcinoma		
Overall rate	2/50 (4%)	4/50 (8%)	8/50 (16%)	4/51 (8%)	
Adjusted rate	5.5%	11.3%	20.0%	9.5%	
Terminal rate	1/30 (3%)	3/33 (9%)	8/40 (20%)	2/36 (6%)	
First incidence (days)	635	634	729 (T)	547	
Life table test	P=0.365	P = 0.353	P = 0.104	P=0.384	
Logistic regression test	P=0.300	P = 0.333	P = 0.056	P = 0.345	* ,
Cochran-Armitage test	P = 0.291				
Fisher exact test		P = 0.339	P = 0.046	P = 0.348	
Skin (Subcutaneous Tissue): Fibroma					
Overall rate	2/50 (4%)	3/50 (6%)	1/50 (2%)	2/51 (4%)	
Adjusted rate	6.7%	6.6%	2.5%	4.7%	
Terminal rate	2/30 (7%)	0/33 (0%)	1/40 (3%)	1/36 (3%)	
First incidence (days)	729 (T)	398	729 (T)	547	•
Life table test	P = 0.458N	P = 0.507	P = 0.400N	P = 0.640N	
	P=0.493N	P=0.588	P = 0.400N	P=0.691N	•
Logistic regression test	=				
Cochran-Armitage test	P = 0.491N				
0 0	=	P=0.500	P=0.500N	P=0.684N	•
Cochran-Armitage test Fisher exact test  Skin (Subcutaneous Tissue): Fibroma or	P=0.491N			e e e e e e e e e e e e e e e e e e e	•
Cochran-Armitage test Fisher exact test  Skin (Subcutaneous Tissue): Fibroma or Overall rate	P=0.491N  • Fibrosarcoma 2/50 (4%)	5/50 (10%)	1/50 (2%)	3/51 (6%)	
Cochran-Armitage test Fisher exact test  Skin (Subcutaneous Tissue): Fibroma or Overall rate Adjusted rate	P=0.491N  • Fibrosarcoma  2/50 (4%) 6.7%	5/50 (10%) 12.3%	1/50 (2%) 2.5%	3/51 (6%) 7.4%	
Cochran-Armitage test Fisher exact test  Skin (Subcutaneous Tissue): Fibroma or Overall rate Adjusted rate Terminal rate	P=0.491N  Fibrosarcoma 2/50 (4%) 6.7% 2/30 (7%)	5/50 (10%) 12.3% 2/33 (6%)	1/50 (2%) 2.5% 1/40 (3%)	3/51 (6%) 7.4% 2/36 (6%)	
Cochran-Armitage test Fisher exact test  Skin (Subcutaneous Tissue): Fibroma or Overall rate Adjusted rate Terminal rate First incidence (days)	P=0.491N  Fibrosarcoma  2/50 (4%) 6.7% 2/30 (7%) 729 (T)	5/50 (10%) 12.3% 2/33 (6%) 398	1/50 (2%) 2.5% 1/40 (3%) 729 (T)	3/51 (6%) 7.4% 2/36 (6%) 547	
Cochran-Armitage test Fisher exact test  Skin (Subcutaneous Tissue): Fibroma or Overall rate Adjusted rate Terminal rate First incidence (days) Life table test	P=0.491N  Fibrosarcoma  2/50 (4%) 6.7% 2/30 (7%) 729 (T) P=0.501N	5/50 (10%) 12.3% 2/33 (6%) 398 P=0.237	1/50 (2%) 2.5% 1/40 (3%) 729 (T) P=0.400N	3/51 (6%) 7.4% 2/36 (6%) 547 P=0.570	
Cochran-Armitage test Fisher exact test  Skin (Subcutaneous Tissue): Fibroma or Overall rate Adjusted rate Terminal rate First incidence (days) Life table test Logistic regression test	P=0.491N  Fibrosarcoma  2/50 (4%) 6.7% 2/30 (7%) 729 (T) P=0.501N P=0.559N	5/50 (10%) 12.3% 2/33 (6%) 398	1/50 (2%) 2.5% 1/40 (3%) 729 (T)	3/51 (6%) 7.4% 2/36 (6%) 547	
Cochran-Armitage test Fisher exact test  Skin (Subcutaneous Tissue): Fibroma or Overall rate Adjusted rate Terminal rate First incidence (days) Life table test	P=0.491N  Fibrosarcoma  2/50 (4%) 6.7% 2/30 (7%) 729 (T) P=0.501N	5/50 (10%) 12.3% 2/33 (6%) 398 P=0.237	1/50 (2%) 2.5% 1/40 (3%) 729 (T) P=0.400N	3/51 (6%) 7.4% 2/36 (6%) 547 P=0.570	

TABLE B3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Safflower Oil (continued)

	Untreated Control	2.5 mL/kg	5 mL/kg	10 mL/kg
Testes: Adenoma				
Overall rate	50/50 (100%)	47/50 (94%)	46/49 (94%)	49/51 (96%)
Adjusted rate	100.0%	100.0%	100.0%	100.0%
Terminal rate	30/30 (100%)	33/33 (100%)	39/39 (100%)	36/36 (100%)
First incidence (days)	457	491	531	547
Life table test	P = 0.066N	P = 0.200N	P = 0.007N	P = 0.092N
ogistic regression test	P=0.077N	P = 0.296N	_f	P=0.277N
Cochran-Armitage test	P = 0.321N			
Fisher exact test		P = 0.121N	P=0.117N	P=0.252N
Thyroid Gland (C-cell): Adenoma				
Overall rate	4/48 (8%)	4/49 (8%)	7/48 (15%)	4/49 (8%)
Adjusted rate	11.7%	12.1%	17.0%	10.7%
Terminal rate	2/29 (7%)	4/33 (12%)	6/40 (15%)	3/36 (8%)
First incidence (days)	671	729 (T)	655 `	724
Life table test	P = 0.485N	P = 0.590N	P = 0.422	P = 0.535N
Logistic regression test	P = 0.554N	P = 0.637N	P = 0.276	P = 0.605N
Cochran-Armitage test	P = 0.526			
Fisher exact test		P = 0.631N	P = 0.262	P=0.631N
All Organs: Mononuclear Cell Leukemia				
Overall rate	33/50 (66%)	19/50 (38%)	18/50 (36%)	7/51 (14%)
Adjusted rate	74.1%	48.8%	42.8%	16.5%
Terminal rate	19/30 (63%)	14/33 (42%)	16/40 (40%)	3/36 (8%)
First incidence (days)	457	491	655	613
Life table test	P<0.001N	P = 0.008N	P<0.001N	P<0.001N
Logistic regression test	P<0.001N	P = 0.005N	P = 0.003N	P<0.001N
Cochran-Armitage test	P<0.001N			
Fisher exact test		P=0.004N	P = 0.002N	P<0.001N
All Organs: Benign Neoplasms				
Overall rate	50/50 (100%)	49/50 (98%)	46/50 (92%)	50/51 (98%)
Adjusted rate	100.0%	100.0%	97.9%	100.0%
Terminal rate	30/30 (100%)	33/33 (100%)	39/40 (98%)	36/36 (100%)
First incidence (days)	457	398	531	547
ife table test	P = 0.081N	P = 0.315N	P = 0.005N	P = 0.127N
Logistic regression test	P = 0.389N	P = 0.638N	P = 0.212N	<del>-</del>
Cochran-Armitage test	P = 0.344N			
Fisher exact test		P = 0.500N	P = 0.059N	P = 0.505N
All Organs: Malignant Neoplasms				
Overall rate	36/50 (72%)	29/50 (58%)	23/50 (46%)	16/51 (31%)
Adjusted rate	79.4%	68.4%	49.7%	34.3%
Terminal rate	21/30 (70%)	20/33 (61%)	17/40 (43%)	7/36 (19%)
First incidence (days)	457	388	329	302
ife table test	P<0.001N	P = 0.104N	P = 0.002N	P<0.001N
ogistic regression test	P<0.001N	P = 0.107N	P = 0.007N	P<0.001N
Cochran-Armitage test	P<0.001N			
Fisher exact test		P = 0.104N	P = 0.007N	P<0.001N

TABLE B3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Safflower Oil (continued)

	Untreated Control	2.5 mL/kg	5 mL/kg	10 mL/kg	
All Organs: Benign or Malignant Neoplasms					
Overall rate	50/50 (100%)	50/50 (100%)	48/50 (96%)	51/51 (100%)	
Adjusted rate	100.0%	100.0%	98.0%	100.0%	
Terminal rate	30/30 (100%)	33/33 (100%)	39/40 (98%)	36/36 (100%)	
First incidence (days)	457	388	329	302	
Life table test	P = 0.118N	P = 0.379N	P = 0.017N	P = 0.169N	
Logistic regression test	P = 0.683N	_	P = 0.435N	-	
Cochran-Armitage test	P = 0.599N		•		
Fisher exact test		P = 1.000N	P = 0.247N	P = 1.000N	

(T)Terminal sacrifice

b Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality

Observed incidence at terminal kill

Not applicable; no neoplasms in animal group

Value of statistic cannot be computed.

Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, bone marrow, brain, epididymis, heart, kidney, larynx, liver, lung, nose, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, spleen, testes, thyroid gland, and urinary bladder; for other tissues, denominator is number of animals necropsied.

Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table test regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Safflower Oil<sup>a</sup>

	Untreated Control	2.5 mL/kg	5 mL/kg	10 mL/kg
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	10	10	10	9
Early deaths				
Moribund sacrifice	12	9	7	5
Natural deaths	8	8	3	10
Survivors				
Terminal sacrifice	30	33	40	36
Animals examined microscopically	60	60	60	60
15-Month Interim Evaluation				
Alimentary System				
Intestine large, colon	(10)	(10)	(10)	(9)
Ulcer	1 (10%)			
Intestine small, ileum	(10)	(10)	(10)	(9)
Fibrosis		1 (10%)		
Liver	(10)	(10)	(10)	(9)
Basophilic focus		1 (10%)	3 (30%)	
Clear cell focus				2 (22%)
Fatty change, diffuse			1 (10%)	6 (67%)
Fatty change, focal			2 (20%)	2 (22%)
Hepatodiaphragmatic nodule	1 (10%)		2 (20%)	1 (11%)
Mixed cell focus	, ,		1 (10%)	, ,
Necrosis		1 (10%)	, ,	
Mesentery	(1)	` /	(1)	
Fat, inflammation, chronic active	ì (100%)		``	
Fat, necrosis	- (- ' '		1 (100%)	
Pancreas	(10)	(10)	(10)	(9)
Acinus, atrophy	9 (90%)	7 (70%)	6 (60%)	6 (67%)
Acinus, fibrosis	1 (10%)	, (10,0)	0 (0070)	0 (0770)
Acinus, hyperplasia	2 (20%)	1 (10%)	4 (40%)	7 (78%)
Salivary glands	(10)	(10)	(10)	(9)
Duct, metaplasia	1 (10%)			
Duct, metaplasia, squamous	2 (20%)	(10)	(10)	<b>(0</b> )
Stomach, glandular	(10)	(10)	(10)	(9)
Mineralization				1 (11%)
Cardiovascular System		40	40	461
Heart	(10)	(10)	(10)	(9)
Cardiomyopathy	9 (90%)	7 (70%)	6 (60%)	9 (100%)
Endocrine System				
Adrenal gland, medulia	(10)	(10)	(10)	(9)
Hyperplasia	, ,	• •	, <i>,</i>	Ì (11%)
Islets, pancreatic	(10)	(10)	(10)	(9) ` ´
Hyperplasia	1 (10%)	• •	• •	Ì (11%)
Parathyroid gland	(10)	(10)	(10)	(8)
Hyperplasia	` '	` '	` '	1 (13%)

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Safflower Oil (continued)

Para distalis, cyst			Untreated Control		2.5 mL/kg		5 mL/kg	10 mL/kg
Pars distalis, cyst	15-Month Interim Evaluation	n (continued	)				*	
Pars distalis, cyst 1 (10%) 2 (20%) 1 (11%) Pars distalis, hyperplasia 2 (20%) 3 (30%) Pars nervosa, cyst 1 (10%) C-cell, hyperplasia 6 (60%) 6 (60%) 3 (30%) 5 (56%) C-cell, hyperplasia 1 (10%) C-ce	Endocrine System (continued)							and the second second second
Pars distalis, hyperplasia 2 (20%) 3 (30%) Pars nervosa, cyst 1 (10%) Pars	Pituitary gland		(10)	•			(10)	<b>(9)</b>
Pars nervosa, cyst 1 (10%) Cocell, hyperplasia (10) (10) (10) (9) Cocell, hyperplasia 1 (10%) 1 (10%) 4 (44%)  Control Body System None  Cential System Treputial gland (10) (10) (10) (9) The system (10%) 1 (10%) 1 (10%) 1 (10%) The system (10%) 1 (10%) 1 (10%) 1 (10%)  Cential System (10%) 1 (10%) 1 (10%) 1 (10%) The system (10%) 1 (10%) 1 (10%) 1 (10%) The system (10%) 1 (10%) 1 (10%) 1 (10%) The system (10%) 1 (10%) 1 (10%) 1 (10%) 1 (10%) 1 (10%) The system (10%) 1 (10%) 1 (10%) 1 (10%) 1 (10%) 1 (10%) The system (10%) 1 (10%) 1 (10%) 1 (10%) 1 (10%) 1 (10%) The system (10%) 1 (10%) 1 (10%) 1 (10%) 1 (10%) The system (10%) 1 (10%) 1 (10%) 1 (10%) 1 (10%) The system (10%) 1 (10%) 1 (10%) The system (10%) 1 (10%) 1 (10%) The system (10%) 1 (10%) 1 (10%) 1 (10%) The system (10%		•						1 (11%)
C-cell, hyperplasia		•			3 (30%)			· · · · · · · · · · · · · · · · · · ·
C-cell, hyperplasia 1 (10%) 1 (10%) 4 (44%)  General Body System  None  Genital System  Treputia gland (10) (10) (10) (9)  Abscess 3 (30%) 1 (11%)  Inflammation, chronic active  Inflammation, chronic active  Inflammation, chronic active  Inflammation, chronic active  Inflammation (10) (10) (10) (10) (10)  Interstitial cell, hyperplasia 6 (60%) 6 (60%) 3 (30%) 5 (56%)  Hematopoietic System  Jumph node (10) (10) (10) (10) (9)  Mediastinal, pigmentation 1 (10%)  Renal, angiectasis 1 (10%)  Renal, infiltration cellular, histiocyte 1 (10%)  Epiecen (10) (10) (10) (10) (9)  Hematopoietic cell proliferation 1 (10%) (10) (9)  Hematopoietic cell proliferation 1 (10%) (10) (9)  Depletion lymphoid 1 (10%)  Epithelial cell, hyperplasia (10%)  Musculoskeletal System  None  None		V.		•		,		
Central Body System   None   System   Streputial gland   (10)						•	(10)	(9)
Central System   Cent	C-cell, hyperplasia	•	1 (10%)		1 (10%)			4 (44%)
Computed	General Body System				-·-			
Computed							<u> </u>	
Computed	Genital System							
Abscess 3 (30%)   1 (11%)   Hyperplasia	Preputial gland		(10)		(10)	Sap	(10)	(9)
Hyperplasia					• •			
Cestes   (10)   (10)   (10)   (9)     Interstitial cell, hyperplasia   6 (60%)   6 (60%)   3 (30%)   5 (56%)     Interstitial cell, hyperplasia   6 (60%)   6 (60%)   3 (30%)   5 (56%)     Itematopoietic System							•	
Interstitial cell, hyperplasia	Inflammation, chronic active				:	•		1 (11%)
Iematopoietic System		*.				*		(-)
Mediastinal, angiectasis	Interstitial cell, hyperplasia		6 (60%)	,	6 (60%)		3 (30%)	5 (56%)
Mediastinal, angiectasis	Jematopojetic System							
Mediastinal, angiectasis			(10)		(10)		(10)	(9)
Mediastinal, pigmentation 1 (10%) Renal, angiectasis 1 (10%) Renal, infiltration cellular, histiocyte 1 (10%) Geleen (10) (10) (10) (10) (9) Hematopoietic cell proliferation 1 (10%) 1 (10%) 3 (33%) Chymus (10) (9) (10) (9) Depletion lymphoid 1 (10%) Epithelial cell, hyperplasia 1 (10%)  Integumentary System None  Musculoskeletal System None		•			(20)		(20)	
Renal, angiectasis								
Renal, infiltration cellular, histiocyte 1 (10%) Spleen (10) (10) (10) (20) Hematopoietic cell proliferation 1 (10%) 1 (10%) 3 (33%) Thymus (10) (9) (10) (9) Depletion lymphoid 1 (10%) Epithelial cell, hyperplasia 1 (11%)  Integumentary System None  Musculoskeletal System None  Nervous System						,		
Spleen		te ·						
Hematopoietic cell proliferation  Thymus  (10)  Depletion lymphoid  Epithelial cell, hyperplasia  Integumentary System  None  Musculoskeletal System  None  Nervous System					(10)		(10)	(9)
Depletion lymphoid 1 (10%) Epithelial cell, hyperplasia 1 (11%) Integumentary System None  Musculoskeletal System None  Nervous System	Hematopoietic cell proliferation		, ,	•.			1 (10%)	3 (33%)
Epithelial cell, hyperplasia 1 (11%)  Integumentary System  None  Musculoskeletal System  None  Nervous System			(10)				(10)	
Integumentary System None  Musculoskeletal System None  Nervous System			1 (10%)					
Musculoskeletal System None	Epithelial cell, hyperplasia	•						1 (11%)
Musculoskeletal System None  Nervous System	ntegumentary System			3 +		1		
None Nervous System					•			
None Nervous System	Musculoskeletal System	<del>*************************************</del>		. 4				5 . 7
	None						The state of the s	A CARL CARLON
None	Nervous System							
	Vone				t y s			

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Safflower Oil (continued)

	Untreated Control	2.5 mL/kg	5 mL/kg	10 mL/kg
5-Month Interim Evaluation (continu	ıed)			
Respiratory System				
Lung	(10)	(10)	(10)	(9)
Hemorrhage	(=-/	` '	1 (10%)	` '
Infiltration cellular, histiocyte	10 m	1 (10%)	2 (20%)	
Nose	(10)	(10)	(10)	(9)
Fungus	2 (20%)	<b>5</b> (50%)	5 (50%)	<b>2</b> (22%)
Inflammation, acute	2 (20%)	9 (90%)	10 (100%)	8 (89%)
Respiratory epithelium, hyperplasia	_ (====,	6 (60%)	10 (100%)	2 (22%)
Respiratory epithelium, metaplasia, squamou	s	` '	1 (10%)	1 (11%)
Special Senses System None				
Urinary System				
Kidney	(10)	(10)	(10)	(9)
Nephropathy	10 (100%)	6 (60%)	3 (30%)	6 (67%)
Urinary bladder	(10)	(10)	(10)	(9)
Calculus gross observation	•	3 (30%)	2 (20%)	1 (11%)
Calculus microscopic observation only		3 (30%)	2 (20%)	1 (11%)
2-Year Study	:			
Alimentary System				
Intestine large, rectum	(47)	(47)	(47)	(47)
Submucosa, edema				1 (2%)
Intestine small, duodenum	(48)	(50)	(48)	(49)
Mucosa, hyperplasia, diffuse	<b>1</b> (2%)	, ,	• •	• •
Intestine small, ileum	(45)	(49)	(48)	(47)
Inflammation, chronic active	· ,	, ,	• •	ì (2%)
Ulcer			1 (2%)	
Intestine small, jejunum	(45)	(48)	(48)	(46)
Mucosa, hyperplasia, diffuse	ì (2%)	• ,	• •	, ,
Liver	(50)	(50)	(50)	(51)
Basophilic focus	36 (72%)	33 (66%)	`38́ (76%)	42 (82%)
Clear cell focus	23 (46%)	22 (44%)	25 (50%)	33 (65%)
Cyst	2 (4%)	• •	` ,	` ,
Eosinophilic focus	5 (10%)	2 (4%)	4 (8%)	2 (4%)
Fatty change, focal	7 (14%)	4 (8%)	5 (10%)	8 (16%)
,g-,	3 (6%)	3 (6%)	` '	1 (2%)
Hepatodiaphragmatic nodule	5 (070)			` '
	5 (0%)	1 (270)		1 (00)
Hepatodiaphragmatic nodule	4 (8%)	1 (2%) 1 (2%)	1 (2%)	1 (2%)
Hepatodiaphragmatic nodule Hepatodiaphragmatic nodule, multiple Hyperplasia	4 (8%)	1 (2%)	1 (2%)	1 (2%)
Hepatodiaphragmatic nodule Hepatodiaphragmatic nodule, multiple	4 (8%) 1 (2%)	1 (2%)	·	
Hepatodiaphragmatic nodule Hepatodiaphragmatic nodule, multiple Hyperplasia Hyperplasia, focal	4 (8%) 1 (2%) 1 (2%)	1 (2%) 2 (4%)	1 (2%)	6 (12%)
Hepatodiaphragmatic nodule Hepatodiaphragmatic nodule, multiple Hyperplasia Hyperplasia, focal Mixed cell focus Necrosis	4 (8%) 1 (2%)	1 (2%) 2 (4%) 3 (6%)	·	
Hepatodiaphragmatic nodule Hepatodiaphragmatic nodule, multiple Hyperplasia Hyperplasia, focal Mixed cell focus Necrosis Pigmentation	4 (8%) 1 (2%) 1 (2%)	1 (2%) 2 (4%) 3 (6%) 1 (2%)	1 (2%)	6 (12%)
Hepatodiaphragmatic nodule Hepatodiaphragmatic nodule, multiple Hyperplasia Hyperplasia, focal Mixed cell focus Necrosis	4 (8%) 1 (2%) 1 (2%)	1 (2%) 2 (4%) 3 (6%)	1 (2%)	6 (12%)

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Safflower Oil (continued)

(9)  1 (11%) 1 (11%) 8 (89%) 50) 39 (78%) 8 (16%) 1 (2%) 1 (2%) 50)  12 (24%) (50) 11 (22%) 21 (42%) 3 (6%) 49) 8 (16%)	(8)  1 (13%)  1 (13%)  1 (13%)  5 (63%) (50)  38 (76%)  14 (28%)  3 (6%)  (49)  2 (4%)  1 (2%) (50)  17 (34%)  17 (34%)  2 (4%) (50)  6 (12%)	(10) 1 (10%) 1 (10%) 8 (80%) (49) 35 (71%) 29 (59%) 1 (2%) (50) 10 (20%) (50) 20 (40%) 26 (52%) 1 (2%) 2 (4%) (49) 1 (2%)	(7)  1 (14%)  6 (86%) (50)  37 (74%) 30 (60%) 1 (2%)  (51)  1 (2%)  13 (25%) (51)  24 (47%) 29 (57%)  4 (8%) (50) 2 (4%)
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39 (78%) 8 (16%) 1 (2%) 1 (2%) (50) 12 (24%) (50) 11 (22%) 21 (42%) 3 (6%) (49)	38 (76%) 14 (28%) 3 (6%)  (49) 2 (4%)  1 (2%) 11 (22%) (50) 17 (34%) 17 (34%) 2 (4%) (50)	35 (71%) 29 (59%) 1 (2%) (50) (50) 10 (20%) (50) 20 (40%) 26 (52%) 1 (2%) 2 (4%) (49)	37 (74%) 30 (60%) 1 (2%) (51) 1 (2%) 13 (25%) (51) 24 (47%) 29 (57%) 4 (8%) (50)
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12 (24%) (50) 11 (22%) 21 (42%) 3 (6%)	2 (4%)  1 (2%) 11 (22%) (50) 17 (34%) 17 (34%) 2 (4%) (50)	10 (20%) (50) 20 (40%) 26 (52%) 1 (2%) 2 (4%) (49)	1 (2%) 13 (25%) (51) 24 (47%) 29 (57%) 4 (8%) (50)
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50) 11 (22%) 21 (42%) 3 (6%) 49)	11 (22%) (50) 17 (34%) 17 (34%) 2 (4%) (50)	(50) 20 (40%) 26 (52%) 1 (2%) 2 (4%) (49)	13 (25%) (51) 24 (47%) 29 (57%) 4 (8%) (50)
50) 11 (22%) 21 (42%) 3 (6%) 49)	11 (22%) (50) 17 (34%) 17 (34%) 2 (4%) (50)	(50) 20 (40%) 26 (52%) 1 (2%) 2 (4%) (49)	(51) 24 (47%) 29 (57%) 4 (8%) (50)
50) 11 (22%) 21 (42%) 3 (6%) 49)	(50) 17 (34%) 17 (34%) 2 (4%) (50)	(50) 20 (40%) 26 (52%) 1 (2%) 2 (4%) (49)	(51) 24 (47%) 29 (57%) 4 (8%) (50)
11 (22%) 21 (42%) 3 (6%) 49)	17 (34%) 17 (34%) 2 (4%) (50)	20 (40%) 26 (52%) 1 (2%) 2 (4%) (49)	24 (47%) 29 (57%) 4 (8%) (50)
21 (42%) 3 (6%) 49)	17 (34%) 2 (4%) (50)	26 (52%) 1 (2%) 2 (4%) (49)	29 (57%) 4 (8%) (50)
3 (6%) (49)	2 (4%) (50)	1 (2%) 2 (4%) (49)	4 (8%) (50)
49)	(50)	2 (4%) (49)	(50)
49)	(50)	(49)	(50)
8 (16%)			
0 (10/0)	0 (12/0)		
	, ,	1 (=/0)	1 (2%)
		1 (2%)	1 (270)
		1 (2%)	
		1 (2%)	
	1 (2%)	in the second	
(1)			(1)
		. '	1 (100%)
<del></del>			
50)	(50)	(50)	(51)
	` '		42 (82%)
47 (2470)	47 (7070)	43 (60%)	1 (2%)
*	1 (2%)	. •	1 (2%)
2 (4%)		· · · · · · · · · · · · · · · · · · ·	1 (2%)
	1 (2%)	1 (2%)	1(42)
	· · · · · · · · · · · · · · · · · · ·		
(50)	(49)	(50)	(49)
			(43)
	1 (270)	4 (6/0)	4
			•
	(50) 47 (94%) 2 (4%) (50) 1 (2%) 1 (2%) 1 (2%) 1 (2%)	(50) 1 (2%) 2 (4%) 3 (6%) 1 (2%) 1 (2%) (49) 1 (2%) 1 (2%) 1 (2%) 1 (2%) 1 (2%)	(50) 1 (2%) 2 (4%) 3 (6%) 1 (2%) 1 (2%) 1 (2%) 1 (2%) 1 (2%) 1 (2%) 1 (2%) 1 (2%) 1 (2%)

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Safflower Oil (continued)

	Untreated Control	2.5 mI/kg	5 mL/kg	10 mL/kg
2-Year Study (continued)				
Endocrine System (continued)				
Adrenal gland, medulla	(49)	(48)	(49)	(49)
Hyperplasia	23 (47%)	24 (50%)	16 (33%)	18 (37%)
Islets, pancreatic	(49)	(50)	(49)	(49)
Hyperplasia	<b>4</b> (8%)	4 (8%)	4 (8%)	4 (8%)
Parathyroid gland	(45)	(40)	(40)	(43)
Hyperplasia	2 (4%)	•	• •	` '
Pituitary gland	(50)	(48)	(49)	(50)
Congestion			•	1 (2%)
Pars distalis, angiectasis	4 (8%)	6 (13%)	3 (6%)	5 (10%)
Pars distalis, cyst	1 (2%)	6 (13%)	1 (2%)	1 (2%)
Pars distalis, hyperplasia	7 (14%)	13 (27%)	11 (22%)	10 (20%)
Pars intermedia, angiectasis	()	1 (2%)	()	(=-,-)
Thyroid gland	(48)	(49)	(48)	(49)
C-cell, hyperplasia	9 (19%)	5 (10%)	9 (19%)	15 (31%)
Follicle, cyst	1 (2%)	1 (2%)	,	1 (2%)
General Body System Tissue NOS Abdominal, ectopic tissue Oral, hyperplasia, squamous	(1)	(1) 1 (100%)	(1) 1 (100%)	
Genital System	<u> </u>		<u> </u>	<del></del>
Preputial gland	(50)	(50)	(49)	(49)
Abscess	2 (4%)	6 (12%)	¥ (8%)	4 (8%)
Cyst	3 (6%)	2 (4%)	1 (2%)	1 (2%)
Dilatation	8 (16%)	` '	2 (4%)	` /
Dilatation, multiple	1 (2%)		` /	
Hyperplasia	` '	1 (2%)		
Inflammation, acute	1 (2%)	1 (2%)		
Prostate	(49)	(49)	(48)	(49)
Hyperplasia	1 (2%)	5 (10%)	2 (4%)	3 (6%)
Inflammation, acute	1 (2%)	` '	` '	
Inflammation, chronic	` /	1 (2%)		•
Metaplasia, squamous	2 (4%)			
Interstitium, edema	1 (2%)			
Seminal vesicle	(50)	(49)	(50)	(50)
Depletion cellular	18 (36%)	<b>\''</b>	()	()
Testes	(50)	(50)	(49)	(51)
Interstitial cell, hyperplasia	2 (4%)	5 (10%)	3 (6%)	6 (12%)
	<b>■</b> \ T/U	J (10/0)	~ (V/U)	V (14/0)

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Safflower Oil (continued)

	Untreated Control	2.5 mL/kg	5 mL/kg	10 mI/kg
2-Year Study (continued)				
Hematopoietic System				
Lymph node	(50)	(50)	(50)	(51)
Inguinal, infiltration cellular, plasma cell	` '		1 (2%)	
Mediastinal, angiectasis	1 (2%)	1 (2%)	3 (6%)	3 (6%)
Mediastinal, ectasia	` ,	1 (2%)	` ,	and the second of the second
Mediastinal, hematopoietic cell proliferation	1 (2%)	` '		Same to
Mediastinal, hemorrhage	1 (2%)			
Mediastinal, hyperplasia, lymphoid	, ,		1 (2%)	and the second second
Mediastinal, infiltration cellular, plasma cell			1 (2%)	A Commence
Mediastinal, infiltration cellular,			, ,	
polymorphonuclear			1 (2%)	(-2.1, 9.1, 1.2) + 2.1 + 1.1
Mediastinal, inflammation, acute		1 (2%)	•	section of the section of
Mediastinal, pigmentation	1 (2%)	5 (10%)		• • •
Mediastinal, lymphatic, ectasia	1 (2%)			
Pancreatic, angiectasis		1 (2%)		1 (2%)
Pancreatic, hyperplasia, lymphoid	3 (6%)	1 (2%)	3 (6%)	
Pancreatic, infiltration cellular, histiocyte	1 (2%)	1 (2%)		
Pancreatic, pigmentation	1 (2%)			
ymph node, mandibular	(50)	(47)	(48)	(50)
Angiectasis		4 (9%)		
Congestion		1 - 1 - 1	the state of the state of	1 (2%)
Ectasia		2 (4%)	1 (2%)	1 (2%)
Hyperplasia, lymphoid	•	1 (2%)	,	1 (2%)
Infiltration cellular, plasma cell	3 (6%)			
Inflammation, acute		1 (2%)		
Pigmentation		2 (4%)		•
Lymphatic, ectasia	100 cm 1 100 cm 1 100 cm	1 (2%)		1 (2%)
Lymph node, mesenteric	(50)	(50)	(49)	(50)
Angiectasis	1 (2%)	3 (6%)	2 (4%)	
Congestion	•			1 (2%)
Ectasia	•		1 (2%)	
Hyperplasia, lymphoid	1 (2%)			1 (2%)
Inflammation, acute	1 (2%)	·		
Pigmentation		1 (2%)		
Spleen	(50)	(50)	(48)	(51)
Angiectasis		1 (2%)		at a second of
Atrophy	1 (2%)		•	
Depletion lymphoid	2 (4%)	1.0	1 (2%)	1 (2%)
Developmental malformation	•	į		1 (2%)
Fibrosis	14 (28%)	4 (8%)		1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
Hematocyst		* .		1 (2%)
Hematopoietic cell proliferation	2 (4%)	7 (14%)	5 (10%)	3 (6%)
Infarct	3 (6%)	40.00	3 (6%)	The second
Pigmentation	1 (2%)	13 (26%)		2 (4%)
Pigmentation, hemosiderin	·.;	1 (2%)	•	
Lymphoid follicle, atrophy				1 (2%)
hymus	(40)	(42)	(41)	(43)
Hemorrhage			1 (2%)	

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Safflower Oil (continued)

	Untreated Control	2.5 mL/kg	5 mL/kg	10 mL/kg
2-Year Study (continued)				ı
ntegumentary System				
Mammary gland	(42)	(45)	(43)	(46)
Galactocele	` '	<b>2</b> (4%)	` ,	1 (2%)
Skin	(50)	(50)	(50)	(51)
Cyst epithelial inclusion	2 (4%)	2 (4%)	` .	, -
Erosion	` '	, ,	1 (2%)	
Hyperkeratosis	1 (2%)	• .	` '	1 (2%)
Hyperplasia, basal cell	1 (2%)	•		` '
Inflammation, chronic active	1 (2%)		٠,	
Foot, acanthosis	` '			1 (2%)
Foot, inflammation, chronic active				1 (2%)
Subcutaneous tissue, granuloma			1 (2%)	,
Musculoskeletal System				(MA)
Skeletal muscle	(50)	(50)	(50)	(51)
Fibrosis	1 (2%)	1 (2%)		
Inflammation, acute		<i></i>		1 (2%)
Abdominal, fibrosis	1 (2%)			
Nervous System	· .			
Brain	(50)	(50)	(50)	(51)
Congestion	ì (2%)	` ,	• /	ì (2%)
Hemorrhage	1 (2%)			, , ,
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Congestion	2 (4%)	2 (4%)	2 (4%)	2 (4%)
Edema	= ( : - )	1 (2%)	- (·/·)	1 (2%)
Fibrosis	1 (2%)	- ()	1 (2%)	- (=/-)
Hemorrhage	2 (4%)	1 (2%)	1 (2%)	
Hemorrhage, focal	- ()	1 (2%)	- (=/-)	
Infiltration cellular, histiocyte	4 (8%)	10 (20%)	3 (6%)	
Inflammation, acute	1 (2%)	(/-)	1 (2%)	1 (2%)
Inflammation, chronic	- (-~)	1 (2%)	- (=/~)	1 (270)
Mineralization		1 (2%)		
Alveolar epithelium, hyperplasia	4 (8%)	2 (4%)	3 (6%)	3 (6%)
Alveolus, foreign body	. (5,0)	1 (2%)	- (0/0)	2 (0,0)
Alveolus, infiltration cellular, histiocyte	1 (2%)	1 (2%)		
Alveolus, inflammation, acute	1 (2%)	- (-10)		
Alveolus, pigmentation, focal	1 (2%)			
Bronchiole, metaplasia, squamous	- (-/-)		1 (2%)	
Interstitium, inflammation, chronic active		1 (2%)	- (2/0)	
		<u> </u>		1 (2%)

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Safflower Oil (continued)

	Untreated Control	2.5 mL/kg	5 mL/kg	10 mL/kg
2-Year Study (continued)		*		
Respiratory System (continued)				
Nose	(50)	(50)	(50)	(51)
Foreign body	· 7 (14%)	`50 (100%)	48 (96%)	) 51 (100%)
Fungus	22 (44%)	41 (82%)	36 (72%)	39 (76%)
Hyperkeratosis	1 (2%)			,
Inflammation, acute	24 (48%)	50 (100%)	50 (100%)	, 51 (100%)
Metaplasia, squamous	1 (2%)	* * * * * * * * * * * * * * * * * * * *		
Nasolacrimal duct, inflammation, acute	1 (2%)			
Respiratory epithelium, hyperplasia	13 (26%)	42 (84%)	46 (92%)	51 (100%)
Respiratory epithelium, metaplasia, squamous	16 (32%)	39 (78%)	33 (66%)	28 (55%)
Vein, thrombosis	1 (2%)		and the second	
Trachea	(49)	(50)	(50)	(50)
Lumen, thrombosis	1 (2%)			
Special Senses System				
Ear	(1)	(2)	(1)	(1)
Inflammation, chronic active	(-)	(-)	1 (100%)	1 (100%)
Eye	(2)		- (55575)	(2)
Inflammation, chronic active	(-)			1 (50%)
Cornea, necrosis	1 (50%)		Programme and the second programme	2 (00/0)
Lens, cataract	1 (50%)			1 (50%)
Retina, atrophy	, = (==/5)			1 (50%)
		·		- (
Urinary System				
Kidney	(50)	(50)	(50)	(49)
Cyst	2 (4%)	1 - 1 - 1 - 1 - 1 - 1 - 1 - 1 - 1 - 1 -	3 (6%)	
Degeneration, hyaline		1 (2%)	$(x_1, x_2, \dots, x_n) = (x_1, x_2, \dots, x_n)$	
Glomerulosclerosis	1 (2%)			
Nephropathy	49 (98%)	50 (100%)	47 (94%)	49 (100%)
Pigmentation	5 (10%)			
Renal tubule, degeneration	1 (2%)			
Urinary bladder	(48)	(49)	(49)	(48)
Calculus gross observation		1 (2%)	1 (2%)	2 (4%)
Calculus microscopic observation only	**	1 (2%)		2 (4%)
Inflammation, chronic active			1 (2%)	
Transitional epithelium, hyperplasia		1 (2%)		

<sup>&</sup>lt;sup>a</sup> Number of animals examined microscopically at site and number of animals with lesion

## APPENDIX C SUMMARY OF LESIONS IN MALE RATS IN THE 2-YEAR GAVAGE STUDY OF TRICAPRYLIN

Table C1	Summary of the Incidence of Neoplasms in Male Rats	
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TABLE C1 Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Gavage Study of Tricaprylin<sup>a</sup>

	Untreated Control	2.5 mL/kg	5 mL/kg	10 mL/kg
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month Interim Evaluation	10	10	10	7
Early deaths				
Moribund	15	13 · · · · · · · · · · · · · · · · · · ·	15	17
Natural deaths	4	7	4	13
Survivors	•	•	•	-
Died last week of study	2	·	1	1
Terminal sacrifice	29	. 30	30	22
Terminal sacrifice	43	30	<b></b>	
Animals examined microscopically	60	60	60	60
15-Month Interim Evaluation	. 8 "			
Alimentary System				
Liver	(10)	(10)	(10)	(7)
Pancreas Acinus, adenoma	(10)	(10)	(10)	(7) 1 (14%)
Cardiovascular System None		<del></del>		
	inger and a second			and the second of the second o
Endocrine System				
Thyroid gland	(10)	(10)	(10)	(7)
C-cell, adenoma			1 (10%)	W <sub>i</sub> ,,
General Body System				
None				
Genital System				
Epididymis	(10)	(10)	(10)	(7)
Testes	(10)	(10)	(10)	(7) (7)
Bilateral, interstitial cell, adenoma Interstitial cell, adenoma	6 (60%) 3 (30%)	4 (40%) 5 (50%)	7 (70%) 3 (30%)	5 (71%) 1 (14%)
Hematopoietic System				
Lymph node, mesenteric	(10)	(10)	(10)	(7)
	(10)	(10)		(7)
Spleen	(10)	(10)	(10)	<b>(7)</b>
Integumentary System		<del></del>		
Skin	(10)	(10)	(9)	(7)
Subcutaneous tissue, fibroma	1 (10%)			
Musculoskeletal System				
None				

TABLE C1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Gavage Study of Tricaprylin (continued)

	Untreated Control	2.5 mL/kg	5 mL/kg	10 mL/kg
<i>15-Month Interim Evaluation</i> (contin Nervous System None	ued)			
Respiratory System Lung	(10)	(10)	(10)	(7)
Special Senses System None				
Urinary System None				
Systemic Lesions Multiple organs <sup>b</sup> Leukemia mononuclear Mesothelioma malignant	(10) 1 (10%)	(10) 1 (10%)	(10) 1 (10%)	(7)
2-Year Study				
Alimentary System				
Esophagus	(48)	(48)	(50)	(52)
Intestine large, colon	(47)	(46)	(48)	(44)
Adenocarcinoma				1 (2%)
Polyp adenomatous	(40)	440	1 (2%)	
Intestine large, rectum	(48)	(46)	(48)	(44)
Circumanal gland, adenoma Intestine large, cecum	1 (2%)	(45)	(40)	(40)
Intestine large, œcum  Intestine small, duodenum	(47) (49)	(45) (46)	(48)	(42)
Intestine small, jejunum	(46)	(46) (46)	(48) (47)	(42)
Adenocarcinoma	(**)	1 (2%)	(71)	(40)
Intestine small, ileum	(46)	(46)	(48)	(42)
Leiomyosarcoma	•		1 (2%)	()
Liver	(50)	(50)	(50)	(51)
Hepatocellular adenoma	1 (2%)	, ,	3 (6%)	4 (8%)
Osteosarcoma, metastatic, bone	*	1 (2%)		, `. /
Mesentery Leiomyosarcoma, metastatic, intestine small	, (8)	(14)	(4)	(5)
ileum	(40)	. (40)	1 (25%)	/#^:
Pancreas Acinus, adenoma	(49)	(49)	(49)	(50)
Acinus, adenoma Acinus, adenoma, multiple	2 (4%)	5 (10%)	11 (22%)	7 (14%)
Pharynx	(1)	1 (2%)	2 (4%)	11 (22%)
Palate, squamous cell carcinoma	(1)	(1) 1 (100%)		
Salivary glands	(50)	(49)	(48)	(51)

TABLE C1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Gayage Study of Tricaprylin (continued)

	Untreated Control	,	2.5 mL/kg	5 mL/kg	10 mL/kg
2-Year Study (continued)		•			en e
Alimentary System (continued)				• .	
Stomach, forestomach	(50)		(50)	(49)	(52)
Squamous cell papilloma	, .		•	3 (6%)	8 (15%)
Squamous cell papilloma, multiple		•			2 (4%)
Stomach, glandular	(50)		(48)	(49)	(50)
Tongue	(2)			(1)	
Squamous cell papilloma	2 (100%)	?		F A.S.	and the second s
Cardiovascular System		·		, , , , , , , , , , , , , , , , , , , ,	and the second s
Blood vessel	(1)			(1)	
Leiomyoma	(-)			1 (100%)	
Vena cava, chemodectoma benign	1 (100%)	, ,	•	- (//)	<i>:</i>
Heart	(50)		(50)	(49)	(51)
Adenocarcinoma, metastatic, uncertain	()		V-7	\	(/
primary site			1 (2%)		- ' '
Schwannoma malignant	٠.		- ()	1 (2%)	
Endocrine System			<del></del>		<del></del>
Adrenal cortex	(50)	.''	(49)	(49)	(51)
Adenoma	(00)		1 (2%)	(17)	(52)
Adrenal medulla	(50)		(49)	(49)	(51)
Pheochromocytoma malignant	2 (4%)		()	1 (2%)	()
Pheochromocytoma complex	1 (2%)	‡ '	*	- (-/-)	
Pheochromocytoma benign	10 (20%)		9 (18%)	13 (27%)	7 (14%)
Bilateral, pheochromocytoma benign	1 (2%)		2 (4%)	3 (6%)	7 (14%)
Islets, pancreatic	(49)		(48)	(49) (	(49)
Adenoma	3 (6%)		<b>2</b> (4%)	3 (6%)	1 (2%)
Carcinoma	2 (4%)		• •	` ,	
Pituitary gland	(50)		(47)	(49)	(51)
Pars distalis, adenoma	8 (16%)	*	8 (17%)	5 (10%)	4 (8%)
Pars intermedia, adenoma					1 (2%)
Thyroid gland	(47)		(46)	(49)	(47)
C-cell, adenoma	6 (13%)		7 (15%)	8 (16%)	2 (4%)
C-cell, carcinoma				1 (2%)	
Follicular cell, adenoma			1 (2%)	1 (2%)	1 (2%)
Follicular cell, carcinoma		•	, * ** *		1 (2%)
General Body System	· · · · · · · · · · · · · · · · · · ·			· · · · · · · · · · · · · · · · · · ·	
Peritoneum	4	•		, ; ;	(1) W. H. W. H.
Genital System			<del></del>	*	
Epididymis	(49)		(50)	(50)	(52)
Leiomyosarcoma, metastatic, intestine small ileum		•	(~~)	1 (2%)	
Preputial gland	(50)		(49)	(50)	(52)
Adenoma	6 (12%)		4 (8%)	6 (12%)	2 (4%)
Carcinoma	1 (2%)		1 (2%)	0 (12/0)	2 (7/0)
Bilateral, adenoma	1 (2%)		1 (2%)		
Dilateral, accircina	1 (270)		1 (4/0)		

TABLE C1 Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Gavage Study of Tricaprylin (continued)

÷	Untreated Control	2.5 mL/kg	5 mL/kg	10 mL/kg
2-Year Study (continued)				
Genital System (continued)				•
Prostate	(49)	(49)	(49)	(52)
Seminal vesicle	(49)	(50)	(50)	(52)
Leiomyosarcoma, metastatic, intestine small,	<b>(</b> **)	` '	` '	` ,
ileum			1 (2%)	
Testes Testes	(49)	(50)	(50)	(52)
Bilateral, interstitial cell, adenoma	41 (84%)	40 (80%)	42 (84%)	32 (62%)
Interstitial cell, adenoma	7 (14%)	4 (8%)	7 (14%)	11 (21%)
Hematopoietic System				
Blood	(11)	(11)	(7)	(2)
Bone marrow	(50)	(49)	(50)	(53)
Lymph node	(24)	(25)	(24)	(14)
Lumbar, leiomyosarcoma, metastatic,	, ,	• •	• •	•
intestine small, ileum			1 (4%)	
Mediastinal, osteosarcoma, metastatic, bone		1 (4%)		
Lymph node, mandibular	(49)	(46)	(49)	(50)
Fibrosarcoma, metastatic, ear	•	1 (2%)		
Lymph node, mesenteric	(48)	(49)	(50)	(48)
Carcinoma, metastatic, islets, pancreatic	1 (2%)			
Leiomyosarcoma, metastatic, intestine small,				
ileum		<b></b>	1 (2%)	,,,,
Spleen	(49)	(50)	(49)	(51)
Hemangiosarcoma		1 (2%)		
Osteosarcoma, metastatic, bone	(46)	1 (2%)	(46)	(46)
Thymus	(46)	(45)	(46)	(46)
Integumentary System				
Mammary gland	(44)	(40)	(43)	(44)
Adenoma	1 (2%)	e e e e e e e e e e e e e e e e e e e	1 (2%)	
Carcinoma	<b></b>	<b>.</b>	1 (2%)	
Fibroadenoma	5 (11%)	2 (5%).	3 (7%)	2 (5%)
Skin	(49)	(49)	(49)	(52)
Basal cell adenoma	1 (2%)	4 /554	A	
Keratoacanthoma	2 (4%)	1 (2%)	3 (6%)	
Schwannoma malignant	1 (2%)	A / 1645	0 /100	4 /86/
Squamous cell papilloma	4 (8%)	2 (4%)	2 (4%)	1 (2%)
Trichoepithelioma		1 (2%)	•	
Pinna, schwannoma malignant	2 (407)	1 (2%)	2 (60%)	1 (201)
Subcutaneous tissue, fibroma multiple	2 (4%)	2 (4%)	3 (6%)	1 (2%)
Subcutaneous tissue, fibroma, multiple Subcutaneous tissue, neurofibroma			1 (2%)	
			1 (2%)	1 (2%)
			•	1 (270)
Subcutaneous tissue, neurofibrosarcoma Subcutaneous tissue, sarcoma		2 (4%)		1 (2%)

TABLE C1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Gavage Study of Tricaprylin (continued)

	Untreated Control		2.5 mL/kg		5 mL/kg	10	mI./kg
2-Year Study (continued)						A Section	
Musculoskeletal System					•	A	
Bone	(50)	•	(50)		(50)	(53)	
Osteosarcoma	. ,	'	1 (2%)	*,	•	1	(2%)
Vertebra, chordoma	1 (2%)					3	
Skeletal muscle	(49)	,	(50)	•	(47)	(53)	
Leiomyosarcoma, metastatic, intestine small,				•		a	
ileum			4 (00)		1 (2%)	13.34	
Sarcoma		·	1 (2%)	:			
Nervous System		*		٠٠,			
Brain	(50)		(50)	2	<b>(49)</b>	(53)	
Respiratory System	,	•					
Lung	(50)		(50)	*	(50)	(51)	
Alveolar/bronchiolar adenoma			2 (4%)		2 (4%)		
Carcinoma, metastatic, thyroid gland Carcinosarcoma					1 (2%)	· 1	(2%)
Fibrosarcoma, metastatic, ear	1 (2%)		1 (2%)			, · . · . <del>-</del>	(=/0)
Osteosarcoma, metastatic, bone	- ( )		1 (2%)			1.0	
Mediastinum, leiomyosarcoma, metastatic, intestine small, ileum			- ( )		1 (2%)		
Nose	(50)	,	(49)		(50)	(52)	
Chondroma	` '		` '		1 (2%)	1.	
Squamous cell carcinoma					1 (2%)		
Special Senses System			12 12 E 1 E 1 E 1 E 1 E 1 E 1 E 1 E 1 E	4	· · · · · · · · · · · · · · · · · · ·		
Ear				in Sec.	(1)	and the stage	* * * * * * * * * * * * * * * * * * *
Fibrosarcoma			ينيه والمراجعة المراجعة	1.00	1 (100%)	*, * .*,	Hay you year "
Eye	(1)				(1)	(3)	•
Harderian gland	(1)		44.				
			(1)				
Zymbal's gland			1 (1000)				
Zymbai's gland Carcinoma			1 (100%)				
Carcinoma Urinary System			1 (100%)				
Carcinoma  Urinary System  Kidney	(50)		(50)		(50)	(49)	
Carcinoma  Urinary System  Kidney  Carcinoma		<u>.</u>	1 (100%)			1	(2%)
Carcinoma  Urinary System  Kidney  Carcinoma  Urinary bladder	(50) (48)	·	(50)		(50) (48)		(2%)
Carcinoma  Urinary System  Kidney  Carcinoma  Urinary bladder  Transitional epithelium, carcinoma			1 (100%)		(48)	1	(2%)
Carcinoma  Urinary System  Kidney  Carcinoma  Urinary bladder			(50)			1	(2%)
Carcinoma  Urinary System  Kidney  Carcinoma  Urinary bladder  Transitional epithelium, carcinoma			(50)		(48)	1	(2%)
Carcinoma  Urinary System  Kidney Carcinoma Urinary bladder Transitional epithelium, carcinoma Transitional epithelium, papilloma  Systemic Lesions  Multiple organs	(48)		(50) (47) 1 (2%)		(48)	1	(2%)
Carcinoma  Urinary System  Kidney Carcinoma Urinary bladder Transitional epithelium, carcinoma Transitional epithelium, papilloma  Systemic Lesions  Multiple organs Leukemia mononuclear	(48)		(50) (47) 1 (2%)		(48) 1 (2%) (50) 22 (44%)	(53) 9	(17%)
Carcinoma  Urinary System  Kidney Carcinoma Urinary bladder Transitional epithelium, carcinoma Transitional epithelium, papilloma  Systemic Lesions  Multiple organs	(48)		(50) (47) 1 (2%)		(48) 1 (2%) (50)	(53) 9 1	(2%)

TABLE C1 Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Gavage Study of Tricaprylin (continued)

	Untreated . Control	2.5 mL/kg	5 mL/kg	10 mL/kg
Neoplasm Summary				
Total animals with primary neoplasms <sup>c</sup>				
15-Month interim evaluation	9	9	10	6
2-Year study	49	48	49	43
Total primary neoplasms				
15-Month interim evaluation	11	10	12	7
2-Year study	140	136	160	124
Total animals with benign neoplasms			•	•
15-Month interim evaluation	9	9	10	6
2-Year study	48	45	49	43
Total benign neoplasms				
15-Month interim evaluation	10	9	11	7
2-Year study	105	95	127	104
Total animals with malignant neoplasms		`.		
15-Month interim evaluation	1.		1	
2-Year study	33	36	29	18
Total malignant neoplasms				
15-Month interim evaluation	1	1	1	
2-Year study	35	41	33	20
Total animals with metastatic neoplasms			,	*
15-Month interim evaluation	1			
2-Year study	5	5	. 4	3
Total metastatic neoplasms				• •
15-Month interim evaluation	· <b>2</b>		• •	• •
2-Year study	27	12	25	15
Total animals with malignant neoplasms		•	•	
of uncertain primary site		•		
2-Year study		1		

Number of animals examined microscopically at site and number of animals with lesion

Number of animals with any tissue examined microscopically Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE C2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Tricaprylin: Untreated Control

Now have at Danie and Charles		3	5					• •	6									7			7	_	_		7.	
lumber of Days on Study	0 6	9	1		9 3						7 8 8 3			7	9 9		0 ( 4 :	5		3 2	6	7	3 7	3 7		
	0	0	0	0.	0	0.	0	0	0	0	0.	<del>-</del>	0 (	0	0 (	)	0	0 .	0	0	0	0	0	0	0	
Carcass ID Number	5	4	1	4	2	Ô	4	1	3	4	0	1	0 :	1	0 5	5	2 :	5	4	3	2	0	0	0	0	
	6	4	9												6 8											
Alimentary System								,					•		,			_						-		_
Esophagus	+	+	+	+	+			+		+	+	+	+ -	+	+ -	+	+	÷	+	+	÷	+	+	+	+	
Intestine large, colon	+	÷	+	+	+	+	+	+	+	+	+	+	+ .	+	+ -	+	+ .	A	+	Ą	Ą	+	+	+	+	
Mesothelioma malignant, metastatic,																										
testes		X						X.																		
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+ .	+	+ .	A	+	Α	+	+,	+	+	+	
Circumanal gland, adenoma		,					•			•	٠			•												
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+ -	+	+ .	A	+	A	Α	+	+	+	+	
Intestine small, duodenum	+	÷	÷	+	+	+	+	+	+	+	+	+	+	+	+ -	+	+	+	+	Ą	+	+	+	+	+	
Mesothelioma malignant, metastatic, testes	•	•	•		•	•			•												•		X			
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+ 4	4	<u>+</u> .	A	+	Α	Α	+	+	+	+	
Intestine small, ileum	+	+	+	+	+	+	+	+	+	÷	+	+	+	+	+ 4	4	+ .	A	+	Α	Α	+	+	+	+	
Mesothelioma malignant, metastatic, testes		x						X.	-																	
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+ -	+	+	+	+	+	+	+	+	+	+	
Hepatocellular adenoma	•	•	•	•	•	•	•	•	7	•	•	•	•	•	•	•	•	•	•	•	•	•		•	•	
Mesentery		÷			+		+	+		+			+									-	+			
Mesothelioma malignant, metastatic,		Ţ			'			•		•			•													
testes		Х						x															X			
Pancreas		Λ 1	_	_	_	_	_	<b>+</b>	_	_	_	4	_	4	<b>.</b>		_	_	+	_				+	_	
Mesothelioma malignant, metastatic,	7	~		-	Ţ	7	7	Ψ.	7	₹	т′	Τ'	т .	•		•	Τ.	1	5	-	-	7"	141	т	r	
testes		v						Y																		
Acinus, adenoma		X						X																		
Pharynx																										
Salivary glands		_	_	4.	+	4	+	+	+	+	+	+	+	+	<b>.</b>	+	+	+	+	+	_	_	Ŧ	_	+	
Stomach, forestomach	- T - ⊥-	<b>T</b>	<b>+</b>	Ξ		+	+	+	+	7	T.	T.	+	! +	+	, +	+	1	÷	I	Ī	T.	ı.	I	- -	
Stomach, glandular	т "	<b>⊤</b>	<b>T</b>	<u> </u>	I	+	Ŧ	Ψ 4	Ĭ	+	т 4	т Т	<b>+</b>	ĭ	Ţ.	+	Ţ	+	4	i.	4	<b>T</b>	i	<b>T</b>	, 4	
Mesothelioma malignant, metastatic,		т	Τ.	т	+7-	Τ.	;			т	Ţ	T.		Т	т '	r		T	-	Τ,	Τ.	~		_	r	
testes		v																								
		X																								
Tongué Squamous cell papilloma																										
			_		_	_	_	_								_		_								_
Cardiovascular System	٠.	•		-				٠			•			٠				٠.			,			•		
Blood vessel																										
Vena cava, chemodectoma benign																										
Heart	+			+	+	+	†	+	+	+	<u>+</u>	+ —	+	+	+	+	_	+ -	+	+	+		+		+	
Endocrine System				•			• •	٠. ٠		-		, ·	4	٠.								•	•			
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+ .	+	+	+	+	+	+	+	+	+	+	
Adrenal medulla	+	+	+	÷	+	+	+	+	+	+	+	+	+	+	+ -	+	+	+	+	+	+	+	+	+	+	
Pheochromocytoma malignant				X																						
Pheochromocytoma complex				-																X						
Pheochromocytoma benign											Х				X				X			X			X	
Bilateral, pheochromocytoma benign																						,				

<sup>+:</sup> Tissue examined microscopically

A: Autolysis precludes examination

M: Missing tissue
I: Insufficient tissue

X: Lesion present Blank: Not examined

 $\begin{tabular}{ll} \textbf{Table C2} \\ \textbf{Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Tricaprylin: } \textbf{Untreated Control (continued)} \\ \end{tabular}$ 

	_	7													7			7	_			_	~	7		
Number of Days on Study	3 7	3 7	3 7		3 7	3 7	3 7	3 7	3 7	3 7	3 7	3 7	3 7	3 7												
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	Total
Carcass ID Number	1	1	1	2	2	2		3		3	3	3						4		-			-	5		Tissue
	1	4	5	0	6	7	8	1	2	3	4	5	6	7	8	0	1	6	9	0	2	5	7	9	0	Tumo
Alimentary System					_			-																		
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	48
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Mesothelioma malignant, metastatic, testes																										2
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Circumanal gland, adenoma											•											X				1
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+,	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Mesothelioma malignant, metastatic, testes														•												1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Mesothelioma malignant, metastatic, testes																										2
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma														X												1
Mesentery																+										8
Mesothelioma malignant, metastatic, testes																										3
Pancreas	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Mesothelioma malignant, metastatic, testes	·	·	•	·	•		·	·	·	·	•	•	•	•	·		•	•	•	·		•		•		2
Acinus, adenoma			x	X																						2
Pharynx																									+	1
Salivary glands	+	. +			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	_	4	_		i	50
Stomach, forestomach		. 4		. +	·	+	+	+	÷	+	·	<u>,</u>	+	÷	+	<u>.</u>	+	÷	+	·	·				÷	50
Stomach, glandular	+	. 4		. +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	•	4		+	50
Mesothelioma malignant, metastatic, testes	,	1		,	•	•	•	•	•	٠	٠	•	•	•	•	•	•	•	•	•		•	•	•		1
Tongue										+		+														2
Squamous cell papilloma										x		x														2
Cardiovascular System							_						_		_	_										
Blood vessel											+															1
Vena cava, chemodectoma benign											X															1
Heart	+	. +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System								_																		
Adrenal cortex	+	- +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	. +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																								X		2
Pheochromocytoma complex																										1
Pheochromocytoma benign	χ								X							X	X	X								10
Bilateral, pheochromocytoma benign										X																1

TABLE C2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Tricaprylin: Untreated Control (continued)

0 6 0 5 6 + + + + + + + + + + + + + + + + + +	9 0 4 4 + + + +	4 1 0 1 9 + + + +	7 6 0 4 2 +	9 3 0 2 3	0 4 0 0	3 5 6 4 1 8 6	2 6 5 3 0 0 1 3	5 7 3 3 0 0 3 4	7 8 0 0	1 .0	8 7 0 1	9 1 0 0	9 9 0 5	0 4 0 2	0 5 0 5	7 7 0 3 7 2 0 0 4 3 5 9	3 6 0 2	3 7 0 0	3 7 0	3 7 0 0	3 7 0 0		
+ + +	+ + +	1 9 + +	+ +	+	0	4 1 8 6	1 3	3 4	0	1 .0	1	0	5	2	5	4 3	2	0	0	0	0		
+ + + +				+ M	+	+ ·	+ -	+ +	+	+ +					-								<del></del>
+ +				М						•	r., +	» <b>+</b>	+	+	+	+ +	+ X	+	M	+	+ X		
		•	+	X	+	+ -	+ -	+ +	+	+ +	+ + X	,+ X	+	+ X	+	M + + + A	+	+	+	Х +	+ + +		: 
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+		+		+	+			+ +	+ -	+ -	+ +	+	+	+	+	+ N	. +	. +	x	+	+		
+	+ v	+	+	+	+	+ -	+ -	+ +	+	+ -			+	+	+	+ +					+		
	+ X +	+	+	+	+	+ -	X + - X	+ · + X	-+	+ · - X	+ : + 'X	+	+			 + N	1 +	+	+ X +	+	+		
, <del></del>		X	<u>x</u>	<u> </u>				<u> </u>			<u></u>		X	<u>x</u>			_						<del></del>
+++	+ + +	++++	+++	+ + + +	+ + + +	+ + + + + + + + + + + + + + + + + + + +	+ · - + ·	+ + + + + +	+ + + + +	+ - + - + -					+ + +				+++	+ + + +	+ + +		
+	+	+	+	+		+	+ -								2				X				
	+ + + + +	+ + + X + + + X X + + + + + + + + + + +	X + + + + X + + + + X X + + + + + + + + + + +	+ + + + + + + + + + + + + + + + + + +	+ + + + + + + + + + + + + + + + + + +	+ + + + + + + + + + + + + + + + + + +	+ + + + + + + + + + + + + + + + + + +	+ + + + + + + + + + + + + + + + + + +	+ + + + + + + + + + + + + + + + + + +	+ + + + + + + + + + + + + + + + + + +	+ + + + + + + + + + + + + + + + + + +	+ + + + + + + + + + + + + + + + + + +	+ + + + + + + + + + + + + + + + + + +	+ + + + + + + + + + + + + + + + + + +	+ + + + + + + + + + + + + + + + + + +	+ + + + + + + + + + + + + + + + + + +	X	+ + + + + + + + + + + + + + + + + + +	+ + + + + + + + + + + + + + + + + + +	+ + + + + + + + + + + + + + + + + + +	+ + + + + + + + + + + + + + + + + + +	+ + + + + + + + + + + + + + + + + + +	+ + + + + + + + + + + + + + + + + + +

TABLE C2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Tricaprylin: Untreated Control (continued)

(commuta)																										
Number of Days on Study	7	7	7	7	7	7	7 3	7		7 3	7	7	7		7			7	7	7	7	7	7	7	7 3	
. Table of Buys on Stady	7	7	7	7	7	7	7	7		7	7	7	7					7		7	7	7	7	7		
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	Total
Carcass ID Number	1	1	1	2	2	2	2	3	3	3	3	3	3	3	3	4	4	4	4	5	5	5	5	5	6	Tissues/
	1	4	5	0	6	7	8	1	2	3	4	5	6	7	8	0	1	6	9	0	2	5	7	9	0	Tumors
Endocrine System (continued)						_		_								_	_	_						_		
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma		Х																								3
Carcinoma																										2
Parathyroid gland	+	M	M	+	+	M	+	+	+	+	+	+	+	+	M	+	+	M	+	M	+	+	+	+	+	40
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma							Х			Х								х								8
Thyroid gland	+	+	+	+	+	+		+	+		+	+	+	+	+	+			+	+	+	+	+	+	+	47
C-cell, adenoma								X									X				X		X		·	6
General Body System Tissue NOS				_		_														_				_		
		_																						_		1
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Mesothelioma malignant, metastatic, testes																x										4
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+			+	+	+	+	+	+	+	+	+	50
Adenoma	•	X	•	•	•	•	•	x	•	•	'		'	'		x		•		•	•	'	'	x		6
Carcinoma		•						*								•								^	x	1
Bilateral, adenoma																									Λ	1
Prostate	_	_	_	_	_	_	_	_	_	_	_	_	_	_	_	_	_	_	_			_		_		49
Mesothelioma malignant, metastatic,	т.	-	т	-	т	т	т	т	т	Τ.	_	Τ.	т	т	_	т	т	Τ.	_	Ŧ	+	_	+	7	+	49
testes																										•
Seminal vesicle																										2
	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Mesothelioma malignant, metastatic, testes																										3
Testes															+											49
Bilateral, interstitial cell, adenoma	X	Х	X	X	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	X	X	X	X	X	41
Interstitial cell, adenoma																										7
Hematopoietic System																_						_				
Blood		+						+						+									+	+		11
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node		+			+	+					+		+	+		+		+					+	+	+	24
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma, metastatic, islets, pancreatic												-	-					,	-			•		•	-	1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	4	_	+	+	49
Mesothelioma malignant, metastatic, testes	·	•		•	•	·	Ċ	•	•	•	•	•	•	•	•	•	•	•	,	г	τ.	,	*	т	r	
Thymus	_		۰	4	_		_		_	_	_		_		_			n.e				,				1
Liijiius	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	IVI	+	+	+	+	+	+	+	46

TABLE C2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Tricaprylin: Untreated Control (continued)

(continued)		
Number of Days on Study	3 3 5 5 5 6 6 6 6 6 6 6 6 6 6 6 6 7 7 7 7 7	
Carcass ID Number	0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	
Integumentary System  Mammary gland  Adenoma  Fibroadenoma  Skin	+ + + + + + + + + + + + + + + + + + +	
Basal cell adenoma Keratoacanthoma Mesothelioma malignant, metastatic, testes Schwannoma malignant Squamous cell papilloma	x x x	
Subcutaneous tissue, fibroma	X	
Musculoskeletal System  Bone Vertebra, chordoma Skeletal muscle Mesothelioma malignant, metastatic, testes	+ + + + + + + + + + + + + + + + + + +	
Nervous System Brain Spinal cord	+ + + + + + + + + + + + + + + + + + + +	
Respiratory System  Lung  Fibrosarcoma, metastatic, ear  Nose  Trachea	+ + + + + + + + + + + + + + + + + + +	
Special Senses System Eye Harderian gland	+ +	
Urinary System  Kidney Urinary bladder  Mesothelioma malignant, metastatic, testes	+ + + + + + + + + + + + + + + + + + +	
Systemic Lesions  Multiple organs  Leukemia mononuclear  Mesothelioma malignant	+ + + + + + + + + + + + + + + + + + +	

TABLE C2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Tricaprylin: Untreated Control (continued)

· · ·																_	_	_		_					
	7	7	7	7	7	7	7	7	7	7	7 ′	7 7	7	7	7	7	7	7	7	7	7	7	7	7	
Number of Days on Study	3	3	3	3	3	3	3	3	3,	3	3 3	3 3	3	3	3	3	3	3	3	3	3	3	3	3	
	7	7	7	7	7	7	7	7	7	7	7 ′	7	7	7	7	7	7	7	7	7	7	7	7	7	
	0	0	0	0	0	0	0	0	0	0	0 (	0 (	0	0	0	0	0	0	0	0	0	0	0	0	Total
Carcass ID Number	1	1	1	2	2			3	3					3			4	4	5	5		5	5	6	Tissue
Out custo and it custom	-													8											Tumor
								_										_					—		·····
Integumentary System  Mammary gland	+	+	+		M	+	+	+	+	+	+	+	+ 4	٠ +	+	+	+	+	+	+	+	+	+	+	44
Adenoma	•	•	•	·	•••	•	•	•	•	•		•	•		•	•	•	•	٠	•	·	•	•	•	1
Fibroadenoma													X					X		Х			Х		5
Skin	_	+	4	+	4	+	+	+	+	+	+			+ +	+	+	+	+	+	+	+	+			49
Basal cell adenoma	i	1	•	•	•	,	'	•	•	•	•	•	•	' '	'	•	x	•	•	•	•	•	•		1
Keratoacanthoma															х		7.					х			2
															^							^			
Mesothelioma malignant, metastatic, testes																									2
	х																								1
Schwannoma malignant	А					х			х																4
Squamous cell papilloma			х			А			^																2
Subcutaneous tissue, fibroma																									- 4
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+ -	+ +	+	+	+	+	+	+	+	+	+	+	50
Vertebra, chordoma																									1
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+ -	+ +	+	+	+	+	+	+	+	+	+	+	49
Mesothelioma malignant, metastatic,																									
testes																									1
Nervous System							-					_			_					_			_		
Brain	+	+	4		+	+	+	+	+	+	4	_	<b>.</b>	٠.		+	+	4	. +	+	4	_		+	50
Spinal cord	•	•		•	,	•	•	•	•	•	•	•	•	' '		•	•	•	•	•	•		•	•	1
			_	_									-									_			<del></del>
Respiratory System																									<b>5</b> 0
Lung	+		+	+	+	+	+	+	+	+	+	+	+ -	+ +	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, ear	X																								1
Nose	+		+	+	+	+	+	+	+	+	+	+	+ -	+ +	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+ -	+ +	- +	+	+	+	+	+	+	+	+	+	50
Special Senses System	•			'																					
Eye																									1
Harderian gland																									1
Urinary System			_				-	_								_						_			
Kidney			ىد		1.	_		_	<b>.</b>	4	_	_		L .1		. ـ		ı.L		_		ر		4	50
Urinary bladder		· -	T L		<b>T</b>	<b>T</b>		+	<b>+</b>	+	<del>-</del>	+		ļ		. <del>.</del> ⊥		<b>∓</b>		T.		۲.	۳ د.	+	30 48
Mesothelioma malignant, metastatic,	+		+	4	_	т	т	т	₹.	~	Τ.	т	т .	τ- 1	+		Т	+	+	+	_	+	_	т	48
testes																									1
Systemic Lesions				-		_							_		_					_	_		—		<del></del> -
																									50
Multiple organs	+		+	. +	+	+	+	+	+	+		+		+ +	- +	+			+	+	+	+		+	50
Leukemia mononuclear		Х	X	•	X	X		Х	•	Х		X	X :	Χ.			X					Х	X		23
Mesothelioma malignant															X										4

TABLE C2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gayage Study of Tricaprylin: 2.5 mL/kg

										/ag			•				-											
1	3	3	3			5	5	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7				
2	7	8	9	2	7	9	9	3	5	6	6	7	8	9	9	1	2	2	2	3	3	. 3	3	3				
7	9	6	1	4	9	2	3	2	9	3	6	8	7	0	1	8	1	3	6	6	6	6	6	6				
1	0	0	1	0	1	0	1	0	0	1	0	1	0	0	0	1	0	0	0	0	1	1	1	1				
_		8	-	-																				-				
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+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	4	+	+	+	м	4	4	+	+	+				
	À	+	+	+	÷	+	+	<u>.</u>	À	+	+	+	+		-		-	-			+	+	. +	+				
+	+	. +	+	. +	+	+					+					-								+	•			
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+	+	+	+	+																								
. +	+		+	·	÷	+	+	+	A	+	÷	+									÷	+	+	+				•
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. +	+	+	+	+	+	+	+	+	Α	+	+	+	+	+	+	A	Α	+	Α	+	+	+	+					
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+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	,			
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+	+	+	+																		+			+				
				$\mathbf{X}$								Х												X		, .		
+	+	+	+	+	+	+	+	+	Α	+	+		+	+	+	Α	+	+	Α	+	+	+	+			,		
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TABLE C2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Tricaprylin: 2.5 mL/kg (continued)

Number of Days on Study	3	7 3	3	3	7 3	7 3	3	7	3	3	7	3	7	3	3	3	3	7 3	7	3	7 3	7 3 7	7 3 7	3		
	6	7	7	7	7	7	7	7	7	7	7	7	7	<u>′</u>	7	<u>′</u>		7	7	7	7	7 —		7		
•	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	Total
Carcass ID Number	1	6	6	6	6	6	7	7	7	7	8	8	8				9	9	9	9	1	1		1		Tissues
	0	3	4	5	7	8	0	2	4	8	0	1	2	6	9	0	5	6	7	9	4	5	6	7	0	Tumor
Alimentary System														_										************		
Esophagus	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, jejunum	+	+	+	+	- +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Adenocarcinoma																									X	1
Intestine small, ileum	+	+	+	. +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	. 4	. +	- +	- +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma, metastatic, bone													X													1
Mesentery			+															+			+	+		+	+	14
Mesothelioma malignant, metastatic,																										
testes																										1
Pancreas	+	- +	. +	- 4	- +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Mesothelioma malignant, metastatic,																										
testes																										1
Acinus, adenoma															Х						Х		Х		Х	5
Acinus, adenoma, multiple			X																							1
Pharynx																										i
Palate, squamous cell carcinoma																										ì
Salivary glands	4	. 4	- 4	- 4	- 4		. +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach			- 4		+ +		. +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	- 4	- 4		+ +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Cardiovascular System																			_							
Heart					1			_	+	+	+	+	_	+	+	+	+		+	+	_	_			+	50
Adenocarcinoma, metastatic,	1		,	,		Т.	•	,	'	_			'		_	7	'	•	-	-	.1	'	•	7	7	50
uncertain primary site																										1
uncertain primary site																								_		1
Endocrine System																										
Adrenal cortex	+	- +	- +	+ +	+ +	- +	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	49
Adenoma																										1
Adrenal medulla	4			+ +	+ +	- +	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma benign		>	(			X																				9
Bilateral, pheochromocytoma benign								X						X												2
Islets, pancreatic	4	- +	+ +	+ +	+ +	- +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma																										2
Parathyroid gland	4		+ +		+ +	- +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Pituitary gland	4	- +	+ +	<b>⊢</b> I\	ΛH	- +		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Pars distalis, adenoma							X						X									X		X		8
Thyroid gland			+ +	- ۱	+ +	- +	+	+	+	+	+	+	+	+	+	+	+	+	+	+			+	+	+	46
C-cell, adenoma	>	(																X			X					7
Follicular cell, adenoma																							X			1

Table C2 Individual Animal Tumor Pathology o	f Mal	e I	lat	s i	n tl	he	2-Y	ea	ır (	Ga	vag	e S	Stu	dy	of	Tı	ice	ıpr	yli	n:	2.	5 ı	nL	/kg	(∞	ntinu	ıed)	
<del></del>		3	3	3	5	5	5	5	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7			
Number of Days on Study							9																		3			
							2																	6	6			·
							0										1		0		_	1	_	1	_			
Carcass ID Number							8 5																	0 6				
Genital System																	_		-	_								
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		•	
Mesothelioma malignant, metastatic,	•	٠	•	•	•	•	r	•	•	•	•	•	•	•	•	•	•	•	•	·	•	•	•	•	•			
testes								x							х							. 1						
Preputial gland	_	4		+	+	_	+		+	+	+	+	+	+		+	+	+	+	+	м	1 +	4	+	+			
Adenoma	•	•	. '	•	•	•	•	•	٠.	٠	'	•	,	•	•	•	•	x		•	14.		•	•	•			
Carcinoma														х				^										
- "														^														
Bilateral, adenoma				٠,				,	. 1	. 1			.1.		"Ł		A		.1	_		. 1			.1.			
Prostate	+	+	+	+	+	+	+	+	+		+	+	+			+	A	+			+	+	+	+	+			
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	_ +			
Mesothelioma malignant, metastatic, testes															x													
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Bilateral, interstitial cell, adenoma Interstitial cell, adenoma					X	X		X	x		X	X	X	X	X	X	x		X	X	Х	X	X	X	X			
Hematopoietic System					_		_	_				_	,								-		-					
Blood						+					+	+									+							
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	Α	+	+	+	+	+	+	+	+			
Lymph node	,	+			+	+	+	+			+	+		+		+	+			+	+	+		+	+			
Mediastinal, osteosarcoma, metastatic, bone		•				·															·						,	
Lymph node, mandibular	+	+	М	1 +	+	+	+	+	М	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Fibrosarcoma, metastatic, ear	•	•		• •	•	•	•	•	***	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•			
Lymph node, mesenteric	_	4	. 4	4	+	+	+	4	+	+	+	+	+	+	+	_	+	4	+	4	4							
Spleen		·	. +		+	+	+	·	+		· _	·	+	<u>.</u>	+	+	+	+	<u>.</u>		+				+			•
Hemangiosarcoma	•	•	•	•		•			'	•	•	•	X		•	•		•	•	•	•	ľ		•	•			
Osteosarcoma, metastatic, bone													*															
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+		,	
Integumentary System																		_										
Mammary gland	+	N	1 +	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	M	M	[ +	+	M	( +	+	•		
Fibroadenoma											•																	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Keratoacanthoma																							Х					
Squamous cell papilloma														Х													٠.	
Trichoepithelioma																						٠.						
Pinna, schwannoma malignant																												
Subcutaneous tissue, fibroma																							Х					
Subcutaneous tissue, sarcoma			Х						X											•			Δ	•				
Musculoskeletal System				_															_									
Bone	+	+	. +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	. +	+	+	+			
Osteosarcoma		·	•						•	-			•		•						,	•	•		•			
Skeletal muscle	+	4		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	. 4		. +	+			
Sarcoma	. '	'	•	•	,		•	•	•	Ċ	•	•	•	•	•	•	•	•	•	•	•		•	,	•		.*	
Nervous System	.,	_									٠			<del>,</del>					_	-								
Brain	+	- 4	+	+	+	+	+	+	+	+	+	+	+	+	4	+	4	+	+	+	-	. 4		. 4	. 4			

TABLE C2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Tricaprylin: 2.5 mL/kg (continued)

3 6 1 1 0 + + +	7 3 7 0 6 3 + + + +	3 7 0 6	3	3 : 7 : 5	3 : 7 : 0 :	7 0 6	3 : 7 ·	3 : 7 : 0 :	3 : 7 : 0 :	3 3 7 7 0 (	3 3 7 7 0 0 8 8	3 3 7 7 0 0	7 7 3 3 7 7 0 0 8 8 2 6	3 3 7 7 7 7 9 8 8 8 8	3 3 7 7 0 0 3 9	3 3 7 7 7	3 3 7 7 9 9 9	7 7 0 0	7	3 : 7 ·	3 7 1 1	3 7 1 1	1	1	3 7 1 2	Total Tissues
6 1 1 0 + + + +	7 0 6	7 0 6		7 ·	0	7 0 6	7 · 0 · 7 ·	7 0 7	7 · 0 · 7 ·	7 ' 0 (	7 · 0 (	7 7	7 7 0 0 8 8	7 7	7 7	) (	7 7	7	0 0	) ·	7 1 1	1	1	1	1 2	
+ + + + +	6	6		5	6	6	7	7	7 '	7 :	8 8	3 8	8 8	3 8	3 9	9	9	9	9	)	1	1	1	1	2	
+ + + + +					+																					Tissues
	++++	· +	- -	+	+	+	+	· +														J	0	1	U	Tumor
	+++++	- <del>-</del> -	+ ·	+	+	+	+	+													_					
	++++	- 4	<b>.</b>	+	+	+			+	+	+	+ .	+ -	+ -	+ -	+ .	+ -	- ۱	+ +	+	+	+	+	+	+	50
	++++	- 4	<b>-</b>	+	+	+																				2
	++			т	т		_	_	_	_	_		<b>.</b>	<b>.</b> .	<b>.</b> .	<b>.</b> .	<u>.</u> .	<b>.</b> .	L _	L	_	_	_	_	_	49
	+	- 4				•	X	•	•	•	٠.	X	•	•	•	٠,	χ̈́	•	•	'	•	•	•	•	•	4
	+	- 4					7.									•										1
	+	- 4									X															1
	+		+	+	+	+	+	+	+			+	+ -	+ -	+ -	+	+ -	+ -	+ -	+	+	+	+	+	+	49
		- 4	+	+	+	+	+	+	+	+	+	+	+ -	+ -	+ -	+	+ -	<b>⊦</b> -	+ -	+	+	+	+	+	+	50
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X	+	- 4	٠	+	+	+							+ -								+	+	+	+	+	50
	X	( )	K :	X	X			X	X	X	X :	X :	X Z	X :	X Z	<b>X</b> :	X X	<b>X</b> 2	X X	X	X		Х		X	40
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	+	-				+	+			+		+										+		+		11
+			+	+	+	+	+	+	+	+	+	+	+ •	+ ·	+ •	+	+ -	+ -	+ -	+	+	+	+	+	+	49
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+	. 4		+	+	+											-	τ ·	τ ·	+ -	+	+	+	+	+	+	50
•			•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	1
													$\mathbf{x}$													1
+	- 1		+	+	+	+	+	+	+	+	M			+	+	+	+ -	+ -	+ -	+	M	+	+	+	+	45
M	1		+	M	+	M	+	+	+	+	+	+	+	+	+	+	+ .	+ .	+ -	+	+	+	+	+	M	40
											X							2	X							2
+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+ -	+ •	+ -	+	+	+	+	+	M	49
																										1
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															•	X										2 2
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																										1
+	٠ +		+	+	+	+ X	+	+	+	+	+	+	+	+	+	+	+	+	+ ·	+	+	+	+	+	+	50 1
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TABLE C2

Individual Animal Tumor Pathology	of Mal	e R	lat	s ir	n tl	he	2-1	Yea	ır (	Ga	vaş	ge :	Stu	ıdy	of	T	ric	apı	ryli	n:	2.	5 ı	nL	/kg	(00	ntir	iued)	
Number of Days on Study	1 2	3 7	8	3	5 2	5 7	5 9	5	3	6 5	6	6	7		9	9	1	7 2	2	7 2	3	3	3	_	3			
	7	9	6	1	4	9	2	3	2	9	3	6	8	7	0	1	8	1	3	6	6	6	6	6	6			
	1	0	0	1	0	1	0	1	0	0	1	0	1	0		0	1	0	0	0	0	1	1	1	1			
Carcass ID Number	1 3	7 9	8 8	0 1	9 1	0 4	8 5	0 9	7 3	6 6	0	8 7	1 2	6 1	8 3	9 3	0 8	9 4	6 9	7 5	7 7	0 3	0 5	0 6	0 7			** *
Respiratory System																					-				٠.			
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Alveolar/bronchiolar adenoma																	X				. X				•		. 1	
Fibrosarcoma, metastatic, ear																										٠.		
Osteosarcoma, metastatic, bone																			,									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			,
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	Α	. +	+	+	+	+	+	+			
Special Senses System																							,					4
Zymbal's gland					+																							
Carcinoma					X																						,	
Urinary System													-								•					,		·
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		100	
Urinary bladder	+	+	+	+	+	+	+	+	+	Α	+	+	+	+	+	+	A	A	. +	+	+	+	+	+	.+			
Transitional epithelium, carcinoma				X															2									
Systemic Lesions																												
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			*
Leukemia mononuclear					X	X	X				Х	X			X	X			Х	X	X			X	X	:		
Mesothelioma malignant								X							Х							4						

Table C2

Individual Animal Tumor Pathology	of Mal	e R	lat	s i	n t	he	2-1	/ea	or (	Gar	vag	ge i	Stu	ıdy	of	T	rica	ppr	yli	n:	2.	5 m	nL	/kg	(co	ntinued)
· · · · · · · · · · · · · · · · · · ·	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
Number of Days on Study	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
•	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	Total
Carcass ID Number	1	6	6	6	6	6	7	7	7	7	8	8	8	8	8	9	9	9	9		1	1	1	1	2	Tissues
	0	3	4	5	7	8	0	2	4	8	0	1	2	6	9	0	5	6	7	9	4	5	6	7	0	Tumors
Respiratory System							_																			
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										2
Fibrosarcoma, metastatic, ear								X																		1
Osteosarcoma, metastatic, bone													X													1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																										
Zymbal's gland																										1
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Transitional epithelium, carcinoma																										1
Systemic Lesions											-												<u> </u>			
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X	X		Х		X	X	Х	X	Х	X	X				X	X	х		Х		Х		Х		28
Mesothelioma malignant																										2

	- 0	- 4	4	- 5	- 5	5	•	6	6	6	6	6	h	6	6	6	6	6	7	7	7	7	7	- /	7			
lumber of Days on Study	_	-			8	8				2		7	7			8	8	9		2	3	2						.:
dumber of Days on Study	8		5	1 8	7		9 7	0		3					7				2	-	4	3	3 4	_	3 4			
		-	_ ′	٥.			′	1		3	•	٠.	•	•	′	<u>'</u> _	0	0	1	_	•	•	4	-	4			
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1			
Carcass ID Number	5	7	3	6	5	7	3	4	6	6	4	7	6	2	2	7	5	7	3	3	3	3	3	3	4			
	. 8						8																					
					_	_				_				_							_							
limentary System																										•		
Esophagus	4	- +	. +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		•	
Intestine large, colon	· +	- A	+	+	+	+	Α	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Mesothelioma malignant, metastatic,																												-
testes																	Х											
Polyp adenomatous								X									1.											
Intestine large, rectum	ل	- Δ			i	_	Α		_	_	_	_	_	_	_	_	_	_	_	_	_	_	_	_	_			
	, '							Τ.		T.	T.			T .	T.	7	T.	T.		T.	-							
Intestine large, cecum	٦	- A	. +	•	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Mesothelioma malignant, metastatic,																	.,											
testes																	X											
Intestine small, duodenum	4	- A	+	+	+	+	Α	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Mesothelioma malignant, metastatic,																											~	
testes																	X											
Intestine small, jejunum	4	- A	+	+	+	+	Α	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Mesothelioma malignant, metastatic,																												
testes																	Х											
Intestine small, ileum	4	- A	+	. 4	+	+	Α	+	+	+	_	4	+	+	+	+		+	+	+	+	+	+	+	+			
Leiomyosarcoma		•	• '	•	•	•	••	•	X	•	•	•	•	•	•	•	•	٠	•	٠	•	•		•	'	•		
Mesothelioma malignant, metastatic,									А													•						
<del></del>																	v											
testes																	X											
Liver	٦	- +	- +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Hepatocellular adenoma																												
Mesothelioma malignant, metastatic,																												
testes																	Х											
Mesentery									+								+										•	
Leiomyosarcoma, metastatic,																												
intestine small, ileum									X																			
Mesothelioma malignant, metastatic,																												
testes																	Х											
Pancreas	4	- +	. 4	. 4	+	+	+	+	м	+	+	_	+	+	+	4	+	+	+	+	+	4	+	+	4			
Mesothelioma malignant, metastatic,	•	,	•	•	•	•	•	•		•	•	•	•	•	•	•	•	•	•	•	•	•		•	•			
testes																	X											
				v		X											Λ				v	v						
Acinus, adenoma				X		А															Х	X						
Acinus, adenoma, multiple																							X					
Salivary glands	. 4	- +	- +	+	+	+	+	+	+	+	, <b>+</b>	+	+	M	M	+	+	+	+	+	+	+	+	+	+			-
Stomach, forestomach	4	+ +	- +	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Squamous cell papilloma										Х																		
Stomach, glandular	4	- A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		,	
Mesothelioma malignant, metastatic,																		•								-		
testes																	Х											
Tongue																									+			
Tooth				+																					•			
												`								_								
Cardiovascular System																											•	
Blood vessel																									+			
Leiomyoma																									X			
Heart	4	- +	- +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Schwannoma malignant																												

Number of Days on Study	7 3 4	7 3 4	7 3 4	3	3	3	3	3		3	7 3 5	3	3	3	7 3 5	3	3	3	7 3 6	3	3	3	3		7 3 6		
Carcass ID Number	5	6	6	1 2 5	2	2	3	4	4	4	4	5	6	6	6	6	7	2	4	4	5	7	7	7	1 8 0		tal sues/ mors
Alimentary System																											
Esophagus Intestine large, colon Mesothelioma malignant, metastatic, testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	. +	+	50 48 1	:
Polyp adenomatous																										1	
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	. 4	. +	48	
Intestine large, cecum  Mesothelioma malignant, metastatic, testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		3
Intestine small, duodenum  Mesothelioma malignant, metastatic, testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	· +	+	48	3
Intestine small, jejunum  Mesothelioma malignant, metastatic, testes	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	- +	. +		,
Intestine small, ileum Leiomyosarcoma Mesothelioma malignant, metastatic,	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	- +	- +	48	3
testes																										1	
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	- +	. +	50	
Hepatocellular adenoma  Mesothelioma malignant, metastatic, testes		Х				х													Х							3	
Mesentery		+						+																		4	
Leiomyosarcoma, metastatic, intestine small, ileum																										1	
Mesothelioma malignant, metastatic, testes																										1	
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	. 4	- 4	- 4	- 49	
Mesothelioma malignant, metastatic, testes	•	·	·	•	•	•	•		·	•	•	•	•	•	•	•	•	•	•	•		•	•	•		1	
Acinus, adenoma					Х				Х	Х			Х				X				Х		>	(		11	l
Acinus, adenoma, multiple							Х																			2	;
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	٠ +	- +	- +	. 48	3
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	٠ +	- 4	- +		
Squamous cell papilloma																			X						X		
Stomach, glandular  Mesothelioma malignant, metastatic, testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• +	. 4	1	- +	· 49	
Tongue																										1	
Tooth																										1	
Cardiovascular System	•															-											
Blood vessel																										1	
Leiomyoma																										1	
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	- +	+ +		- 49	
Schwannoma malignant									Х																	1	

		4	4	5	5	5	5 6	6	6	6	6	6 6	6	6	6	6	7	7	7	7	7	7	7				
Number of Days on Study	8		5	-	8		9 0					78			8			2	3	3		3	3	,			
	3		7			7	7 1	8	3			8 6							4	4	4	4	4				
	1	1	1	1	1	1	1 1	1	1	1	1	1 1	1	1	1	1	1	1	1	1	1	1	1				
Carcass ID Number	. 5 8	7 8	3 7	6 1	5 2		3 4 8 4		6 8	4 8		6 2 0 2		7 7	5 1	7 4		3 4	3 1	3	3 6	3 9	-		- `		•
Endocrine System						-						···,								_							
Adrenal cortex	+	. +	+	+	+	+	+ -	+ +	+	+	+	+ +	+ +	+	+	+	+	+	+	+	+	+	+				
Adrenal medulla	+	+	+	+	+	+	+ -	+ +	+	+	+	+ +	+	+	+	+	+	+	+	+	+	+	+				
Pheochromocytoma malignant																$\mathbf{x}$											
Pheochromocytoma benign							X					X					X	Х									
Bilateral, pheochromocytoma benign																					Х				:		
Islets, pancreatic	+	+	+	+	+	+	+ -	+ M	+	+	+	+ +	+ +	+	+	+	+	+	+	+	+	+	+				
Adenoma																											
Parathyroid gland	+	+	+	+	+	+	+ -	+ +	+	+	+	+ +	- +	+	+	+	+	+	+	+	+	. +	+				
Pituitary gland	+	+	+	+	+	+	+ -	+ +	+	+	+	+ +	+ +	+	+	+	+	+	+	+	+	+	+				
Pars distalis, adenoma				X								>	ζ.														
Thyroid gland	+	+	+	+	+	+	Α -	+ +	+	+	+	+ +	+ +	+	+	+	+	+	+	+	+	+	+.				
C-cell, adenoma								X												X	$\mathbf{x}$		X				
C-cell, carcinoma																											
Follicular cell, adenoma																X									•		
General Body System None																							*		•		
Genital System																										-	
Epididymis	+	+	+	+	+	+	+ -	+ +	+	+	+	+ +	+ +	+	+	+	+	+	+	+	+	+	+		ι .	,	
Leiomyosarcoma, metastatic,																											
intestine small, ileum								X																. •	-		
Mesothelioma malignant, metastatic,																				*							
testes															X												
Preputial gland	+	+	+	+	+	+	+ -	+ +	+	+	+	+ -	+ +	+	+	+	+	+	+	. +	+	+	+				
Adenoma										X		X			X												
Prostate	+	+	+	+	+	+	Α -	+ +	+	+	+	+ +	+ +	+	+	+	+	+	+	+	+	+	+				
Mesothelioma malignant, metastatic,																			٠,				•				
testes															X												
Seminal vesicle	+	+	+	+	+	+	+ -	+ +	+	+	+	+ +	+ +	+	+	+	+	+	+	+	+	+	+	,			
Leiomyosarcoma, metastatic,																											
intestine small, ileum								X																			
Mesothelioma malignant, metastatic,																											
testes															X												
Testes	+	+	+	+	+	+	+ -	+ +	+	+	+	+ +	+ +	+	+	+	+	+	+	+	+	+	+			,	
Bilateral, interstitial cell, adenoma					Х	X		X			X	X X	X	X		X	X	X	X	X	$\mathbf{X}_{i}$	X	X				
Interstitial cell, adenoma		_X	X					X	Х						х							_		,			
Hematopoietic System																	,									,	
Blood											+			+			+			+					•		
Bone marrow	+	+	+	+	+	+	+ -	+ +	+	+	+	+ -	+ +	+	+	+	+	+	+	+	+	+	+		•		
Lymph node		+	•	+	+	+	-	+ +	+		+	-	۲	+	+		+	+		+				, 1	,		
Lumbar, leiomyosarcoma, metastatic,								_																	•		
intestine small, ileum								X														, .					
Lymph node, mandibular	+	+	+	+	+	+	+ -	+ +	+	+	+	+ -	⊦ N	1 +	+	+	+	+	+	+	+	+	+	•			
Lymph node, mesenteric	+	+	+	+	+	+	+ -	+ +	+	+	+	+ -	+ +	+	+	+	+	+	+	+	+	.+	+	•			
Leiomyosarcoma, metastatic,																							r				
intestine small, ileum								X																			

Table C2			
Individual Animal Tumor Patholo	gy of Male Rats in the 2-Year	Gavage Study of Tricaprylin:	5 mL/kg (continued)

										_		_															
	· 7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
Sumber of Days on Study	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
•	4	4	4	5	5	5	5	5	5 5	5	5	5	5	5	5	5	5	5	6	6	6	6	6	6	6	6	
, , , , , , , , , , , , , , , , , , ,	1	1	1	1	1	1	1	1	1 1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	Total
Carcass IID Number	5	6	6	2	2	2	3	4	1 4	4	4	4	5	6	6	6	6	7	2	4	4	5	7	7	7	8	Tissues
															3	4				6			2	5	9	0	Tumor
Endocrine System		_		_				_						·								_	_				
Adrenal cortex	_							L .	٠.	_	_	_	М	_	4	_	+	_	+	+	+	+	+	+	+	+	49
Adrenal medulla		4	. 4		- 1	_			· + ·	+	+	+	M	-	+	<u>.</u>	<u>.</u>	<u>.</u>	<u>.</u>	+	+	+	+	+	+	<u>.</u>	49
Pheochromocytoma malignant	•		•		,		' '	•	•		•	•	•••	•	•	•	•	•	•	•	•	•	•	•	•	•	1
Pheochromocytoma benign	х				>	7	3	(	,	X							x	x				X			x	X	13
Bilateral, pheochromocytoma benign	1				•	_	Κĺ		χĺ	•								•							••	••	3
Islets, pancreatic	+	4			<b>⊢</b> 4		• + +		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma	,		X	,			,		•	•	•	•	•	•	•	•	•	•	•	x	'		•	•	•	•	3
Parathyroid gland	_				<b>⊢</b> N	<b>1</b> -			+	_	_	М	_	_	_	+	м	+	+	+	+	+	+	+	+	+	47
Pituitary gland		٦ .				vı -				+	-		-	+	<u>,</u>		+			+	+	+	+	+	+	+	49
Pitultary gland Pars distalis, adenoma	+	1	7	•	7			r -		T	X	-	141	-	7	7	7	-	-	•	т	Τ'	Τ'	7	7	7	5
	.1.	ا ۔		L - 4	L	L	+ +		_	_		+	_	+	_	_	+		_	_	_	+	_	_	_	+	49
Thyroid gland	+	٦	- 1	•	- 4	r	т -	r ' '	_	7	7	_	7	+	7	X	+	+	т			X		~	~	7	8
C-cell, adenoma C-cell, carcinoma											x					^				^	^	^					1
Follicular cell, adenoma											^																1
None Canidal Sustam		_									_																
Genital System	_									_			_	_	_	_	_	_	_	_	_	_	_	_	_	_	50
Epididymis	+	•					+ -	•	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	30
Leiomyosarcoma, metastatic, intestine small, ileum																											1
,																											1
Mesothelioma malignant, metastatic, testes																										x	2
Preputial gland	+		+ +		+ -	L .	+ -	_	_	_	_	_	_	_	_	_	_	_	_	+	_	_	_	_	_	<u>^</u>	50
Adenoma	X			_	-		X	т :	т	Τ	_	_	т	т	т	т	т	т	т	X		•	•	•	т	т	6
Prostate				١.	+ -		Λ. + ·		_	+	_	_	_	_	_	_	_	+	4	+		+	_	+	4	+	49
Mesothelioma malignant, metastatic,	. '				•	•	'		'	•	•	'	'	'	•	•	'	'	•	•	•	•	'	'	•		77
testes																											1
Seminal vesicle	+	• •	٠ -	٠ ٠	+ -	+ .	+ -	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	. +	+	+	+	50
Leiomyosarcoma, metastatic,																											
intestine small, ileum																											1
Mesothelioma malignant, metastatic,																											
testes	_																									,	1
Testes	+		٠ • •	+ :	+ :	+ :	+ :	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma	Х		( )	( )	<b>X</b> 2	Χ	X 2	Χ.	X	X	v		X	X	X	X			X	X	X	X	X	. X	. X	X	42
Interstitial cell, adenoma											X						X										7
Hematopoietic System																											_
Blood							+		+											+							7
Bone marrow	+		+ -	+ -	+ -	+	+ .	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node		•	+				+ -	+	+	+	+			+						+	+				+	•	24
Lumbar, leiomyosarcoma, metastatic, intestine small, ileum																											1
Lymph node, mandibular	+		+ -	+ -	+ -	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	4		+ -	+ -	+ .	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma, metastatic,																											

	0	4	- 4	١.	ο.	•	3	<b>5</b>	6	6	6	6	6	6	6	6 (	6	6	6	/	/	/	/	′	,	7	
Number of Days on Study	8 3	5 4		5	1	8	8	9	0	0	2	2	7	7 8	8	8	8	8	9	2	2	3	3	3	3		
	1	1	1	[	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
Carcass ID Number	5	7	3			5					6				2			_	7	3	3	3	3	3	3	4	
	8	8	7	7	1	2	3	8	4	7	8	8		0			7	1	4	5	4	1	3	6	9	0	
Hematopoietic System (continued)																						_					
Spleen	+	- 4	- +	+	+	+	+	Α	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Mesothelioma malignant, metastatic,																											
testes																		X									
Thymus	· M	[ -		+	M	+	M	+	+	+	+	+	+	+	+	+		+		+	+	+	+	+	+	+	
Integumentary System						_						_		_			_										<del></del>
Mammary gland	+	· N	и·	+	М	+	+	+	+	+	М	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	
Adenoma	•	•	•		• • •	•			•	•	•••	•	•	•		•											
Carcinoma						٠.			X																		
Fibroadenoma									-				x														
Skin	.1		L	_	_	_	_		_			_	^ +	_	_	_	_	_	_	_	_	.1	_		.1	+	
	+	7	г.	_	т	т	т	т	т	_	~	Τ-	т	т	т	X	Τ'	т	т	7	т	X	7	7	X		
Keratoacanthoma																Λ						Λ			Λ	•	
Mesothelioma malignant, metastatic,																		.,									
testes																		X								_	
Squamous cell papilloma					*							X													Х		
Subcutaneous tissue, fibroma					X															Х				X			
Subcutaneous tissue, fibroma,																											
multiple																											
Subcutaneous tissue, neurofibroma																											
Subcutaneous tissue, schwannoma																											
malignant																X											
						_			_			_								_							
Musculoskeletal System																											
Bone	+	٠ -	٠ -	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Skeletal muscle			•	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	•
Leiomyosarcoma, metastatic,										_																	
intestine small, ileum										X																	
Mesothelioma malignant, metastatic,																											
testes																		X									
Nervous System			_						_																		
Brain	+	. 4	⊦ -	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Respiratory System																											
Lung	+	. 4	٠ ٠	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	- +	
Alveolar/bronchiolar adenoma																											
Carcinoma, metastatic, thyroid gland																											
Mediastinum, leiomyosarcoma,																											
metastatic, intestine small,																											
ileum										х																	
Nose			_	1	_	_	_	_			,			+	_	_	4	_	_		.1	i		ر			
	+	-	г .	_	т	<b>T</b>	Τ.	т	Τ-	+	+	<b>T</b>	~	+	7	Τ'		т Х	т	+	+		_	_	-	+	-
Chondroma			,	,														Λ									
Squamous cell carcinoma				X										,			1.	.1		_		٠.		,			
Trachea	+	_	<u> </u>	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		• +	
Special Senses System																											
Ear																											
Fibrosarcoma																											
Tibiosaicoma																											

<b></b>											•							•									
Number of Days on Study	7 3 4	7 3 4	7 3 4	7 3 5	3	3	3	3	3	3	3	3	3	3		3	3	3	7 3 6	3	7 3 6	3	3		3		
Carcass ID Number	1 5 4	6	1 6 9	2	2	2		4	4	4	4	5	6	6		6	7	1 2 3	4	1 4 9	1 5 0	7	1 7 5	7	1 8 0		Total Tissues/ Tumors
Hematopoletic System (continued) Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Mesothelioma malignant, metastatic, testes																											1
Thymus	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	46
Integumentary System  Mammary gland  Adenoma  Carcinoma	+	+	+	М	+	+		+ X	+	+	+		+	M	+	+	+	+	+	+	+	+	+	M	[ +	-	43 1 1
Fibroadenoma  Skin  Keratoacanthoma  Mesothelioma malignant, metastatic, testes	+	+	+	+	+	+	+	+	+	+	+	<b>X</b> +	+	+	М	+	+	+	+	X +		+	+	+	+	-	3 49 3
Squamous cell papilloma Subcutaneous tissue, fibroma Subcutaneous tissue, fibroma, multiple			х																								2 3
Subcutaneous tissue, neurofibroma Subcutaneous tissue, schwannoma malignant				Х																							1
Musculoskeletal System																											
Bone Skeletal muscle Leiomyosarcoma, metastatic, intestine small, ileum	+	+	. +	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	. +	. +	- +	<b>+</b>	50 47 1
Mesothelioma malignant, metastatic, testes																											1
Nervous System Brain	+	+	. +	+	+	+	+	М	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	. +		<b>-</b>	49
Respiratory System														•							-					*****	
Lung Alveolar/bronchiolar adenoma Carcinoma, metastatic, thyroid gland Mediastinum, leiomyosarcoma, metastatic, intestine small,	+	+	• +	+	+	+ X	+	+	+	+ X	+	+	+	* X	+	+	+	+	+	+	+	+	+	· +	• +	+	50 2 1
ileum Nose	+	- +	. +	· +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	. 4	- +		+	1 50
Chondroma Squamous cell carcinoma Trachea	+	- 4	. 4	. +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	- 4	- +		+	1 1 50
Special Senses System													_							_				-			
Ear Fibrosarcoma Eye																					+					+ <b>X</b>	1 1 1

TA	BLE	C2

Individual Animal Tumor	Patholog	gy of	f M	ale	R	ats	i ir	ı tl	he	2-1	Yea	ir (	Ga	vag	je (	Stu	dу	of	Tı	rica	pr	yli	n:	5	m]	/k	<b>g</b> (0	ont	inued	):: -	. 1
				0	4	4	5	5	5	5	6	6	6	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7			_
Number of Days on Study				8	5	5	1	8	8	9	0	0	2	2	7	7	8	8	8	8	9	2	2	3	3	3	3	3		1.00	js
·	4. 12	٠.		3	4	7	8	7	7	7	1	8	3	8	0	8	6	7.	7	8	8	1	9	4	4	4	4	4			
	-			1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1			_
Carcass ID Number				5	7	3	6	5	7	3	4	6	6	4	7	6	2	2	7	5	7	3	3	3	3	3	3	4.	. * * .	-1-1-1-1-1-1-1-1-1-1-1-1-1-1-1-1-1-1-1	٠.
				8	8	7	1	2	3	. 8	4	7	8	8	1	0	2	7	7	1	4	<b>5</b> ,	4	1	3	6	9	0			
Urinary System																				-									5 , 4		
Kidney				+	+	+	+	+	+	+	+	+	+	+	٠+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Urinary bladder				+	Α	+	+	+	+	·A	+	+	+	+	+	+	+	+	+	+	, <b>+</b> .	+	+	+	+	+	+	+		10-16-63	
Mesothelioma malignant, n	netastatic,																							, 1		٠.	::		. ``.		
testes																				X		٠.,							٠.		
Transitional epithelium, pa	pilloma													,			,			X							٠,,,	·	٠.		
Systemic Lesions									,				i.			•					-	. ;	٠,	,					:.		
Multiple organs				+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	<u> </u>	.+	+	+	+		1, 18, 3	
Leukemia mononuclear					Х			X	X		X		X		X				Х			Х	X	X	X	"X	X		7	4 11	
Lymphoma malignant histi	ocytic													,	. :		X	:	٠.						٠.			٠.	13.	٠;	
Mesothelioma malignant	•																			X	٠,٠	٠,		,		٠	. 1		. ′	5,77	

Table C2

Individual Amimal Tumo	r Pathology of Ms	lle TRate im the 2	-Vear Cayage Stud	milwanwlime	5 ml /kg (continued)

			7	7	7	.7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
Number of Days on Study			3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
A STATE OF THE STA	٠.		4	4	.4	5	5	5	.5	5	5	5	5	5	5	5	5	5	5	6	6	6	6	6	6	6	6	
			1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	Total
Carcass ID Number	,		5	6	6	2	2	2	3	4	4	4	4	5	6	6	6	6	7	2	4	4	5	7	7	7	8	Tissues
			4	6	9	5	6	9	0	1	2	3	5	7	2	3	4	5	6	3	6	9	0	2	5	9	0	Tumors
Urinary System																								,				
Kidney			+	+	+	+	+	+	+	+	.+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Mesothelioma malignant, metastatic,	,																										-	
testes																												1
Transitional epithelium, papilloma	*																											1
Systemic Lesions		,													-													·
Multiple organs			+	+	. +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear						X		X	Х	Х	Х	·				Х					X	Х					X	22
Lymphoma malignant histiocytic																												1
Mesothelioma malignant																											Х	2

TABLE C2

TABLE C2 Individual Animal Tumor Pathology of	f Mal	e I	lat	s i	n tl	he	<b>2-</b> Y	Yes	ır (	Ga	vag	e i	Stu	dy	of	Tı	rica	pr	yli	n:	10	) n	ıL/	kg					.*
	2	2	2	2	2	3	3	3	3	3	3	3	3	3	4	4	4	4	4	4	4	4	5	5	6	6	6	6	_
Number of Days on Study	3	8	_	_	_	2	2	2	2	2	2	2	2	-	1	2	4	4	8	8	8	8	6	9	0	2	4	_	
•	3	2	8	2	2	2	2	2	4	4	4	8	8	6	5	6	6	7	3	3	5	5	9	0	8	3	5	4	
	1	2	2	1						1					1			2	2	2	2	2	1	2	2	2	2	2	٠,
Carcass ID Number	8 2	_	0 1	-			1 4			9 7					8 5				1 0			4 0		3 2		3 4			
Alimentary System								-		-																			
Esophagus	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Intestine large, colon	+	Α	+	Α	Α	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	Α	Α	+	+	+	Α	Α	
Adenocarcinoma  Mesothelioma malignant, metastatic, testes									х																				
Intestine large, rectum	+	A	+	A	Α	4	4	+	+	4	м	4	+	+	+	_	+	+	+	+	A	A	A	_	4		Δ	Α	
Intestine large, cecum  Mesothelioma malignant, metastatic,							+	+	+					+	+	+	+	+										A	
testes																													
Intestine small, duodenum																												·A	
Intestine small, jejunum	•																											Α	
Intestine small, ileum Mesothelioma malignant, metastatic,	+	Α	. +	Α	Α	+	+	+	+	+	M	+	+	+	+	+	A	+	+	+	A	Α	. <b>A</b>	. +	+	. +	A	<b>A</b>	
testes Liver								4.																					
Hepatocellular adenoma	т	7	•	Α	Λ	_	_	т	т		Т.	<b>T</b>	T	Τ	+	т	т	т	+	Т.	т	Т	т	•	Т.	_	· ·	_	
Mesentery																							+						
Mesothelioma malignant, metastatic, testes																											٠		,
Pancreas	+	+	+	M	Α	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	
Mesothelioma malignant, metastatic, testes																													
Acinus, adenoma Acinus, adenoma, multiple																					Х								
Salivary glands	+	+	+	+	М	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	М	( +	+	+	+	+	+	+	
Stomach, forestomach	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	• +	+	+	.+	+	+	+	+	+	•
Squamous cell papilloma																						٠				X			
Squamous cell papilloma, multiple Stomach, glandular	+	+	+	. <b>A</b>	Α	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	Α	+	+	+	+	+	~ +	
Cardiovascular System Heart	, <del>,</del> +	+	+	+	М	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Endocrine System			-											-							-								_
Adrenal cortex	+	+	+	+	Α	÷	+	. +	+	+	+	+	+	+	+	+	+	+	+	4	А	+	+	+	+	+	+	+	
Adrenal medulia															+														
Pheochromocytoma benign	•	•	•	•	••	•		·	•	•	·	·	•	·	•	·	•	•	·	·	••	•	•	•	·			x	
Bilateral, pheochromocytoma benign Islets, pancreatic	+	A	. +	M	<b>A</b>	+	+	+	+	+	+	+	+	+	+	+	. +	+	+	+	+	+	+	+	+	X +		[ ;+	
Adenoma									•	,												,							
Parathyroid gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	M	+	+	+	+	+	+	+
Pituitary gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	
Pars distalis, adenoma  Pars intermedia, adenoma																													
Thyroid gland	_	Δ	_	. 4	м	_	_	_	_	_	Δ	_	_	_	+	_	_	_	_	_	4	٨	Δ	_		٠.			
C-cell, adenoma	т	-	. 1	^	141	т.	т	т	~	Τ-	^	т	7	т	т	т	т.	т	~	т	~	Λ		. •	~	7		т	
Follicular cell, adenoma																													
Follicular cell, carcinoma																													

Individual Animal Tumor Pathology	of Mal	e F	ea i	s i	n tl	he	2-}	/ea	ır (	387	vag	e S	štu	dу	of	Tr	ica	pr	yli	m:	10	) m	nI./	kg	(coı	itinued)
	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
Number of Days on Study	1	2	2	2	2	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
	5	6	9	9	9	0	0	3	3	3	3	3	3	3	3	3	3	3	3	4	4	4	4	4	4	
	1	1	1	2	2	2	2	1	1	1	2	2	2	2	2	2	2	2	2	1	2	2	2	2	2	Total
Carcass ID Number	9	9	8	0	2	0	0	9	9	9	0	0	0	1	2	3	3	3	3	9	1	1	2	2	2	Tissue
	1	8	8	2	9	3	5	2	3	4	6	7	8	1	5	1	3	6	9	5	7	9	0	1	7	Tumo
Alimentary System										-					_											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Intestine large, colon	+	+	+	- +	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Adenocarcinoma																										1
Mesothelioma malignant, metastatic,																										
testes																		X								1
Intestine large, rectum	+	+	+	- +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine large, cecum	Α	. +	+	- +	· A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Mesothelioma malignant, metastatic,																										
testes																		X								1
Intestine small, duodenum	+	+	+	- +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Intestine small, jejunum	Α	. +	. +	- +	· A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Intestine small, ileum	+	+	. 4	- +	· A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Mesothelioma malignant, metastatic, testes																		х								1
Liver						_				1.	_	_	,				1.	+								51
Hepatocellular adenoma	X	. Т	٠ ٦	7		T	_	_	X	_	т	т	Τ	X	Т	_	+	т	T	_	_		7	+	+ X	
	^	•											_	^				ъ.							^	4 5
Mesentery  Mesothelioma malignant, metastatic,					+			+					+					+								3
testes																		x								1
Pancreas	+	+	٠ ٦	+ +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, testes																		х								1
Acinus, adenoma			>	C X	•			х							х			X				Х				7
Acinus, adenoma, multiple	х	•	-		•		х			x	x	x	х	x		x		"	х				X			11
Salivary glands	+		. 4	- +	. +	+	+	+				-	+			+	+	+	+	+	+	+			+	51
Stomach, forestomach			. 4	- +		·	+	+	+		+		+			+	+		+						+	52
Squamous cell papilloma	•		>		·	·	•	·	X	•	•		X	•	•	•	•	Ť	•	X		•	·		X	8
Squamous cell papilloma, multiple			•	•	x	X			•			-	71							7.				1	. /1	2
Stomach, glandular	+	- +	- 4	+ +			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
																		_							-	
Cardiovascular System Heart	+	. +	. 4	+ +	. +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	ı.	1 +	+	51
												_														
Endocrine System  Adrenal cortex		1			ر .	د .		Д.	_	.1	.1.	.1	_1	,L	JL.	_ا_	.1.	.1				,				£1
Adrenal medulla	-1	•	. '	•	٠.	•	•	_	-	-		7	+	-		, T	-	+	+	+	+	+	+	+	+	51 51
Pheochromocytoma benign	+	X			X		+	+	+	+	+	+	+	+	+	+	+	+	+	+					· +	51
Bilateral, pheochromocytoma benign		Λ	•	Λ			v		v		v		v					v			X		Х	•	X	7
Islets, pancreatic				- +	- +		X +		X						+			X								7
•	7						+	+			+	+	+	+	+	+	+	+	+	+	+	+	+	•	+	49
Adenoma Parathyroid gland				L 18	, a				X					D #								n.				1
, ,	+	. +					+												+	+					+	46 51
Pituitary gland Pars distalis, adenoma	7	- +		⊦ <del>1</del>	- +	+	+ X		+ X		+	+	+	+	+	+	+			+		+	+	• +	+	51
Pars intermedia, adenoma							А		Λ									X		X						4
Thyroid gland				1		د		.1	_	_1	٠,ـ	نے	_1	.1	_1	, i.	, L	.1		X		,				1
C-cell, adenoma	7	7	٠,	 (			Ŧ	_	T	т	т	+	+	+	+	+	X	+	+	+	+	+	+	+	+	47
Follicular cell, adenoma			,	•								х					А									2
Follicular cell, carcinoma										х		Λ														1
. Onicular will, carcillonia										Λ																1

Table C2 Individual Animal Tumor F	atholog	grý A	e N	[pl	e D	gfe	ir	r th	ıe	2.V	'eo	r ſ	ė	/ <b>A</b> O	e (	Stor	dv	of	T,	ics	nr	vli	n:	10	m	T.A	kσ	(00	nti	111 <i>0</i> 4	i)	٠٠
Thorvioual Ammai Tumoi T	athorog		, 1V.																			J						_		<u> </u>		٠,
Number of Days on Study	· · · ·			2	2 8	2 8	2 9.	2	3 2	3 2	3 2	3· · · · · · · · · · · · · · · · · · ·	3	3	2	2	3 5	4	4	4	4	4 Ω	8	4 8	-4 -8	5 6	5	6 0	6	.6	7	
Number of Days on Study				. 3			2	2	2	_	2	4	4	4	8	_	6	_	6	•	7	3	_	5	5	9	0	-	3	5	4	
te de la constant de				1	2.	2	1	2	2.	2	2	1	1	2	2	2	2	1	2	1	2	2	2	2	2	1	2	2	2	2	2	
Carcass ID Number				8	3 7	0 1	9 0	3 8	1 2	-	1 5	9 6	9 7	0 0	1. 6	3 5	1 8	8 5	1 3	8 6	9	1 0	_	2	4 0	8 1	3· 2	0	4	0 4		* '
General Body System				_						·····					_				-	<u></u>		-						,				
Peritoneum  Mesothelioma malignant, m	etastatic																								٠.,	•	• .			75 · ·	, e	٠,
testes	ciastatic,	•																						· ' '		*,			,	1		
Genital System											_										-									1335	,	
Epididymis Mesothelioma malignant, m	etastatic,	• •	• :	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	. +	+	+	. +	+	+	+	. <b>+</b> 2.70	+	+	+	
testes Preputial gland		,		+	+	+	+	. +	+	+	+	+	· +	M	+	+	+	+	+	+	+	+	+	+	+	+	+	. +	. +	ж., +	· +	٠.
Adenoma Prostate									_		_	_		. M	_	_		_	_	_	_	_				_		X				*
Mesothelioma malignant, m	etastatic,			_	т	_	Τ,	Τ	_	Т	т	<b>T</b>		. 141	т	Т	Т	т	_	т		Т.			т.			· 7	т.	• •	₹,	;.
testes Seminal vesicle				+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	· +	+	+	+	+	· * *;
Mesothelioma malignant, m testes	etastatic,																										•		•			
Testes			) r	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	٠+	+	+	+	+	+	
Bilateral, interstitial cell, ad Interstitial cell, adenoma	enoma				•.				x		x	X	·				X	x	x	x	X	×	X	X		Х	X	X	Х	X	x	
Hematopoietic System			_		-						<del></del>	_	-	· · · · · · · · · · · · · · · · · · ·				···						<del></del>		:	_	. 4			<u></u>	
Blood				٠																											. ,	- :
Bone marrow				+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Lymph node Lymph node, mandibular	-	,			_	_		M	_		ı	_	Ĺ	_	_	·	_	<b>+</b>	+	+	_	.1.	_	1.4		+	_		+		Ĺ	
Lymph node, mesenteric				+	A	+	м	M	+	+	+	+	+	м	+	+	+	+	+	+	+	+	+	141	. <del>.</del> +	. +	+	. +	+	•	- T	
Spleen				· +	+	+		A		+	+	÷	+	+	+	÷	+	+	+	+	+	+	+	+	+	+	÷	•	+	4	·+ ·	· ·,
Mesothelioma malignant, m testes	etastatic,		-										٠.										٠.	.: •		•	2 -			16.4 134		
Thymus				+	A	. +	A	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	
Integumentary System		٠,		_																					,			75"			4	
Mammary gland Fibroadenoma	•		. '	· M	+	. +	М	M	+	М	+	М	+	+	+	М	+	+	M	+	+	M	+	+	, +	+	М	+	. <del>†</del>	+	+	
Skin				+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	.+	+	+	
Squamous cell papilloma				•					•																		• ;				X	
Subcutaneous tissue, fibrom	ıa											٠.								X			7	•	:			-3.				
Subcutaneous tissue,																										•			:			
neurofibrosarcoma Subcutaneous tissue, sarcon	na												4	1				:			· .			•			X					
Musculoskeletal System				-										-	<u> </u>	-			<u>.</u>	.4.	`	_		<u>.</u>	<u> </u>		,		-	•		
Bone				+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	;
Osteosarcoma Skeletal muscle	51				+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	.+	+	4	4	+	. X	. +		4			
Mesothelioma malignant, m testes	etastatic,	1		r	•		•		•	•	•	•	•	•	•	•	•	•	•		•		. ;	•	•	4	•	. 1				
Nervous System				-222			-		_				-													٠			• 5			,
Brain	•			+	+	+	+	+-	+	+	+	+	+	+	+	+	+	+	+	+	.+	+	+	+	+	+	+	+	+	+	+	

TARRET	നാ	

		7	7	7	7	7	7.	7	7	7	7	7	<b>7</b> ·	7	7	7	7	7	7	7	7	7	7	7	7	7	
Landa and Change							-	•				•			-						3	3	3	2	3		
lumber of Days on Study	,	1		2	2 9	2	3 0		3	3	3 3		3				3	3	3		<i>3</i>	4	4	4	4	4	
		_	_	_			-										_					_	_	_	_		
Samesan III) Niverbar		1		_	2	_	2.	_	1	1 9	1	2 0	2	_	2.	_	2		2	_	1 9	2	2	2	2	2	Total Tissue
Carcass ID Number		-									-	-	7	8	_					_		_	9	0	_		Tumo
General Body System													-														
Peritoneum					•							,							+								1
Mesothelioma malignant, metastatic, testes																			Х								1
													_						_								
Genital System																						1.					52
Epididymis  Mesothelioma malignant, metastatic,		+	+	+	+	+	_	*	_	*	_	_	_	_	Т	т	<b>T</b>	Т			*	_	Т	<b>T</b>	_	т	
testes									X		X								X								3
Preputial gland	=	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Adenoma Prostate		ı	ı		ı	ı	ı	_		ı		_	ı	_	_		ı	+	+	X +	_					٠	2 52
Mesothelioma malignant, metastatic, testes		т	т	_	ਜਾ	_	_	т	T	_	_	т	т	т	Т	т	т	т	т	т	T	<b>T</b>	т	т	т	Τ.	1
Seminal vesicle		+	+	+	+	+	+	+	+	_	+	+	+	+	+	+	4	+	+	+	+	+	+	+	+	+	52
Mesothelioma malignant, metastatic, testes	•	•	•	,	,	•	•	•	×	•	•	•	•	•	•	•	•		×	•	•	•	·	Ċ	•	•	2
Testes		+	+	+	+	+	+	+			+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	52
Bilateral, interstitial cell, adenoma		X	X	X	X									X										X			32
Interstitial cell, adenoma																			X								11
lematopoietic System																							_			,	
Blood			+												+												2
Bone marrow		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Lymph node			+		+	+	+								+				+		+				+	+	14
Lymph node, mandibular		+	+.	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric		+,	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen Mesothelioma malignant, metastatic,		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
testes			» <i>«</i>																X								1
Thymus		<u>+</u>	M	+	+	M	+.	+	+	+	+	<u>+</u>	+	+	+	+	+	+	+	+	+	+	+	_ <del>+</del>	+	+	46
ntegumentary System	,																										
Mammary gland	•	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Fibroadenoma				X		X																					2
Skin		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	. +	+	+	+	52
Squamous cell papilloma Subcutaneous tissue, fibroma																											1
Subcutaneous tissue, fibroma Subcutaneous tissue,																•								•			1
neurofibrosarcoma			х																								1
Subcutaneous tissue, sarcoma			^																								1 1
Musculoskeletal System		•	_																					_	_		
Bone		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Osteosarcoma																											1
Skeletal muscle		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53.
Mesothelioma malignant, metastatic, testes																			x								1
Vervous System	•		٠						-			-					-			-							<del></del>
delaone parem																											

TABLE C2 Individual Animal Tumor Pathology of	Mal	e R	at	s ir	ı tl	he	2-ነ	ea/	ır (	Gav	vag	ge S	Stu	ıdy	of	Tı	ica	ıpr	yli	n:	10	m	L/	kg:	( <b>c</b> o	nti	nue	d) :	
Number of Days on Study	2 3 3	2 8 2	2 8 8	2 9 2	2 9 2	3 2 2	3 2 2	3 2 2	3 2 4	3 2 4	3 2 4	3 2 8	3 2 8	3 5 6	4 1 5	4 2 6	4 4 6	4 4 7	4 8 3	4 8 3	8	4 8 5	6	9	0	-	4	6 7 4	
Carcass ID Number	1 8 2	2 3 7	2 0 1	1 9 0	2 3 8	2 1 2	2 1 4	2 1 5	1 9 6	1 9 7	2 0 0	2 1 6	2 3 5	2 1 8	1 8 5	2 1 3	1 8 6	2 0 9	2 1 0	2 2 8	2 2 4	2 4 0	1 8 1	2 3 2	2 3 0	2 3 4	2 0 4	2 2 2	
Respiratory System  Lung Carcinosarcoma Mediastinum, mesothelioma malignant, metastatic, testes Nose Trachea	+++	+ + +	+ + +	A A A	+	+	+ + +	+ + +	+ + +	+ + +	+ + +	+ + +	+ + +	+++	+ + +	+ X + +	+ + +	+ + +	+++	+ + +	+ + +	+ + +	+ + +	+ + +	+ + + +	+ + +	+	+ + +	
Special Senses System Eye																							+	1.7	,				<del></del>
Urinary System Kidney Carcinoma Urinary bladder				A A						+	+	+	+	+				X	+					1	+	+	+	+	
Systemic Lesions  Multiple organs  Leukemia mononuclear  Lymphoma malignant histiocytic  Mesothelioma malignant	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+ X	+	+	+	+	+	+	+	+ X	+ X	+ X	+	

Table C2

Individual Animal Torran Dath	alam of Mala Pata in (	the 2 Veer Corres Strade	. of Tricommilian	10 ma T /lear (+:
Individual Animal Tumor Path	Concorda our variable varies him s	THE 9- LEWIL CHANANGE DIMINI	a con unaccallon annu:	The minute (continued)

																									_		
	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
Number of Days on Study	1	2	2	2	2	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
	5	6	9	9	9	0	0	3	3	3	3	3	3	3	3	3	3	3	3	4	4	4	4	1 4	1	4	
	1	1	1	2	2	2	2	1	1	1	2	2	2	2	2	2	2	2	2	1	2	2	2	2 3	<del>-</del>	2	Total
Carcass ID Number	9	9	8	0	2	0	0	9	9	9	0	0	0	1	2	3	3	3	3	9	1	1	2	2 :	2	2	Tissues
	1	8	8	2	9	3	5	2	3	4	6	7	8	1	5	1	3	6	9	5	7	9	0	) 1	l	7	Tumors
Respiratory System																							_	_			
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	. +	. 4	۱ -	+ -	+	+	51
Carcinosarcoma																											1
Mediastinum, mesothelioma malignant,																											_
metastatic, testes																		Х									1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	. 4	. 4	ی ہ	+ .	+	+	52
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	. 4	٠ +	r -	+	+	+	51
Special Senses System			_			_														_			_		-		
Eye	+				+																						3
Urinary System									_			_			_									_			
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	. 4	. 4	ل ا	+	+	+	49
Carcinoma																					•						1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	- 4	- 4	<u> </u>	+	+	+	48
Systemic Lesions														-									_	_			
Multiple organs	+		. 4		+	+	_	+	4	_	+	4	+	_	+	+	+	+		_	. 4		L .	+ -		_	53
Leukemia mononuclear	•	X	. '	,	•	X	•	•	x	ſ	•	,	-	X	-		•	-	r	,	7	7	٦	•	_	X	9
Lymphoma malignant histiocytic		71	•			1			^					Λ						Х						Λ	1
Mesothelioma malignant								х		Х								х		Λ	•						1
Mesothenonia manghant								^		٨								٨									3

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Tricaprylin

	•		Untreated Control	2.5 mL/kg	5 mL/kg	10 mL/kg
Admin I Madulla, Barian Dhana	· h		<u> </u>			
Adrenal Medulla: Benign Pheod Overall rate <sup>a</sup>	inromocytoma		11/50 (22%)	11/49 (22%)	16/49 (33%)	14/51 (27%)
Adjusted rate <sup>b</sup>			31.9%	30.1%	47.8%	53.6%
Terminal rate <sup>c</sup>		•	8/31 (26%)	5/29 (17%)	13/30 (43%)	11/23 (48%)
First incidence (days)	;	1	678	659	597	623
Life table test <sup>d</sup>	.•	٠.,	P=0.042	P=0.550	P=0.161	P=0.082
Logistic regression test <sup>d</sup>			P=0.019	P=0.543	P=0.127	P=0.044
Cochran-Armitage test <sup>d</sup>			P=0.248	1 -0.545	1-0.127	
Fisher exact test <sup>d</sup>	•	r.	1 -0.2-10	P = 0.574	P = 0.168	P=0.343
Adrenal Medulla: Pheochromoc	vtoma (Renion.	Comple	ex. or Malionant)	•		Charles and the second
Overall rate	A-2 (recinight)	~~mpi	14/50 (28%)	11/49 (22%)	17/49 (35%)	14/51 (27%)
Adjusted rate	• .		39.1%	30.1%	49.3%	53.6%
Terminal rate	4. 7.		10/31 (32%)	5/29 (17%)	13/30 (43%)	11/23 (48%)
First incidence (days)			576	659	597	623
Life table test			P=0.114	P=0.376N	P=0.299	P=0.219
Logistic regression test			P=0.065	P=0.375N	P=0.257	P=0.148
Cochran-Armitage test	•		P=0.448			
Fisher exact test			•	P = 0.343N	P = 0.308	P=0.564N
Liver: Hepatocellular Adenoma						t v <sup>at</sup> v v v v
Overall rate	\$ *	<b>'</b> 、	1/50 (2%)	0/50 (0%)	3/50 (6%)	4/51 (8%)
Adjusted rate	• • •		3.2%	0.0%	9.7%	16.5%
Terminal rate		· t.	1/31 (3%)	0/30 (0%)	3/31 (10%)	3/23 (13%)
First incidence (days)	*		729 (T)	_e	729 (T)	715
Life table test		s · .	P=0.018	P = 0.507N	P = 0.304	P=0.106
Logistic regression test	·	7.6	P=0.015	P = 0.507N	P=0.304	P=0.091
Cochran-Armitage test			P=0.046			
Fisher exact test	**			P = 0.500N	P = 0.309	P=0.187
Mammary Gland: Fibroadenom	ıa				1	etti organization of the
Overall rate			5/50 (10%)	2/50 (4%)	3/50 (6%)	2/53 (4%)
Adjusted rate	**		16.1%	6.7%	8.9%	8.7%
Terminal rate			5/31 (16%)	2/30 (7%)	2/31 (6%)	2/23 (9%)
First incidence (days)			729 (T)	729 (T)	670	729 (T)
Life table test			P=0.324N	P=0.226N	P = 0.359N	P=0.348N
Logistic regression test	•		P=0.349N	P=0.226N	P=0.374N	P=0.348N
Cochran-Armitage test			P = 0.190N		. •	
Fisher exact test	4 4	•		P = 0.218N	P = 0.357N	P=0.195N
Mammary Gland: Fibroadenom	a or Adenoma				TE 18 14 14	James Committee
Overall rate			6/50 (12%)	2/50 (4%)	4/50 (8%)	2/53 (4%)
Adjusted rate			18.6%	6.7%	12.0%	8.7%
Terminal rate			5/31 (16%)	2/30 (7%)	3/31 (10%)	2/23 (9%)
First incidence (days)	•		704	729 (T)	670	729 (T)
Life table test			P=0.255N	P=0.143N	P=0.377N	P=0.248N
Logistic regression test	•		P=0.281N	P=0.128N	P=0.391N	P=0.258N
Cochran-Armitage test			P=0.134N		<del></del> -	
Fisher exact test		·	***	P = 0.134N	P = 0.370N	P=0.117N

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Tricaprylin (continued)

	Untreated Control	2.5 mL/kg	5 mL/kg	10 mL/kg	
√lammary Gland: Fibroadenoma, Adenoma, or Ca	cinoma	— .			
Overall rate	6/50 (12%)	2/50 (4%)	5/50 (10%)	2/53 (4%)	
Adjusted rate	18.6%	6.7%	14.0%	8.7%	
Terminal rate	5/31 (16%)	2/30 (7%)	3/31 (10%)	2/23 (9%)	
First incidence (days)	704	729 (T)	601	729 (T)	
ife table test	P = 0.293N	P = 0.143N	P = 0.510N	P = 0.248N	
ogistic regression test	P=0.319N	P = 0.128N	P = 0.521N	P=0.258N	
Cochran-Armitage test	P = 0.151N				
isher exact test		P=0.134N	P = 0.500N	P=0.117N	
ancreas: Adenoma		4			
overall rate	2/49 (4%)	6/49 (12%)	13/49 (27%)	18/50 (36%)	
djusted rate	6.7%	20.0%	38.2%	71.7%	
erminal rate	2/30 (7%)	6/30 (20%)	11/31 (35%)	16/23 (70%)	
irst incidence (days)	729 (T)	729 (T)	518	485	
ife table test	P<0.001	P=0.129	P=0.003	P<0.001	
ogistic regression test	P<0.001	P = 0.129	P = 0.002	P<0.001	
Cochran-Armitage test	P<0.001	D-0424	D-0.000	D +0.001	
isher exact test	•	P=0.134	P = 0.002	P<0.001	
ancreatic Islets: Adenoma					
verall rate	3/49 (6%)	2/48 (4%)	3/49 (6%)	1/49 (2%)	
djusted rate	10.0%	5.4%	9.7%	4.3%	
erminal rate	3/30 (10%)	0/30 (0%)	3/31 (10%)	1/23 (4%)	
rst incidence (days)	729 (T)	632 D. 0 407N	729 (T)	729 (T)	
ife table test ogistic regression test	P=0.364N P=0.392N	P=0.497N	P=0.650N	P=0.403N	·
ochran-Armitage test	P=0.261N	P = 0.520N	P = 0.650N	P = 0.403N	
isher exact test	1 -0.20114	P=0.510N	P=0.661N	P=0.309N	
ancreatic Islets: Adenoma or Carcinoma		•			
verall rate	5/40 (100%)	2/40 /40%	2/40 (60%)	1/40 /00/	
djusted rate	5/49 (10%) 14.6%	2/48 (4%) 5.4%	3/49 (6%) 9.7%	1/49 (2%) 4.3%	
erminal rate	3/30 (10%)	0/30 (0%)	9.7% 3/31 (10%)		
irst incidence (days)	625	632	729 (T)	1/23 (4%) 729 (T)	
ife table test	P=0.161N	P=0.224N	P=0.355N	P=0.191N	
ogistic regression test	P=0.161N	P=0.231N	P=0.365N	P=0.195N	
ochran-Armitage test	P=0.094N			1 0.17511	4
isher exact test		P=0.226N	P=0.357N	P = 0.102N	
ituitary Gland (Pars Distalis or Pars Intermedia	): Adenoma			,	
verall rate	8/50 (16%)	8/47 (17%)	5/49 (10%)	4/51 (8%)	
djusted rate	21.7%	24.5%	14.3%	17.4%	•
erminal rate	4/31 (13%)	6/29 (21%)	3/30 (10%)	4/23 (17%)	
irst incidence (days)	593	524	518	729 (T)	
ife table test	P=0.247N	P = 0.558	P = 0.310N	P=0.374N	
ogistic regression test	P = 0.213N	P = 0.538	P = 0.296N	P = 0.392N	•
Cochran-Armitage test	P = 0.092N				
Fisher exact test		P=0.554	P=0.290N	P=0.169N	

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Tricaprylin (continued)

	Untreated Control	2.5 mL/kg	5 mL/kg	10 mL/kg
Preputial Gland: Adenoma	. ,			
Overall rate	7/50 (14%)	5/49 (10%)	6/50 (12%)	2/52 (4%)
Adjusted rate	20.0%	16.4%	16.8%	7.6%
Terminal rate	5/31 (16%)	4/29 (14%)	3/31 (10%)	1/23 (4%)
irst incidence (days)	541	721	628	608
ife table test	P=0.173N	P = 0.417N	P = 0.515N	P=0.193N
ogistic regression test	P=0.155N	P = 0.415N	P = 0.512N	P=0.156N
ochran-Armitage test	P = 0.066N			the second second
isher exact test		P = 0.394N	P = 0.500N	P=0.071N
reputial Gland: Adenoma or Carcinoma				v v
Overall rate	8/50 (16%)	6/49 (12%)	6/50 (12%)	2/52 (4%)
djusted rate	23.1%	18.7%	16.8%	7.6%
'erminal rate	6/31 (19%)	4/29 (14%)	3/31 (10%)	1/23 (4%)
irst incidence (days)	541	687	628	608
ife table test	P = 0.108N	P = 0.428N	P = 0.404N	P=0.132N
ogistic regression test	P = 0.092N	P = 0.426N	P = 0.400N	P = 0.109N
ochran-Armitage test	P = 0.034N			-
isher exact test	•	P = 0.403N	P = 0.387N	P = 0.040N
kin: Keratoacanthoma	<b>*</b>			e e e e e e e e e e e e e e e e e e e
overall rate	2/50 (4%)	1/50 (2%)	3/50 (6%)	0/53 (0%)
djusted rate	6.5%	3.3%	9.1%	0.0%
erminal rate	2/31 (6%)	1/30 (3%)	2/31 (6%)	0/23 (0%)
irst incidence (days)	729 (T)	729 (T)	687	
ife table test	P = 0.325N	P = 0.512N	P=0.495	P = 0.306N
ogistic regression test	P=0.341N	P=0.512N	P = 0.484	P = 0.306N
Cochran-Armitage test	P = 0.227N			
isher exact test	•	P = 0.500N	P = 0.500	P=0.233N
kin: Squamous Cell Papilloma	4/50 (00%)	,		
Overall rate	4/50 (8%)	2/50 (4%)	2/50 (4%)	1/53 (2%)
djusted rate	12.2%	5.9%	5.6%	3.8%
erminal rate	3/31 (10%)	1/30 (3%)	1/31 (3%)	0/23 (0%)
irst incidence (days)	691	687	628	674
ife table test	P=0.224N	P=0.353N	P=0.349N	P=0.297N
ogistic regression test	P=0.206N	P = 0.347N	P=0.348N	P = 0.300N
ochran-Armitage test isher exact test	P=0.124N	P=0.339N	P=0.339N	P=0.164N
,	andhama Thillia (dh. 1)			· · · · · · · · · · · · · · · · · · ·
kin: Squamous Cell Papilloma, Keratoac verall rate	anthoma, Trichoepithelioma 7/50 (14%)	, or Basal Cell Ade 4/50 (8%)	enoma 4/50 (8%)	1/53 (2%)
adjusted rate	21.6%	12.4%	11.3%	3.8%
erminal rate	6/31 (19%)	3/30 (10%)	2/31 (6%)	0/23 (0%)
irst incidence (days)	691	687	628	674
ife table test	P=0.063N	P=0.280N	P=0.274N	P = 0.083N
ogistic regression test	P = 0.063N	P=0.265N	P = 0.279N	P = 0.090N
ochran-Armitage test	P = 0.022N			•
isher exact test		P = 0.262N	P = 0.262N	P = 0.025N

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Tricaprylin (continued)

	Untreated Control	2.5 mL/kg	5 mL/kg	10 mL/kg
Skin (Subcutaneous Tissue): Fibroma				
Overall rate	2/50 (4%)	2/50 (4%)	4/50 (8%)	1/53 (2%)
Adjusted rate	6.5%	6.7%	11.3%	2.7%
Terminal rate	2/31 (6%)	2/30 (7%)	2/31 (6%)	0/23 (0%)
First incidence (days)	729 (T)	729 (T)	518	446
Life table test	P=0.561N	P=0.684	P=0.340	P=0.599N
Logistic regression test	P=0.473N	P=0.684	P=0.331	P=0.497N
Cochran-Armitage test	P=0.405N	•		
Fisher exact test		P=0.691N	P=0.339	P = 0.478N
Skin (Subcutaneous Tissue): Fibroma or f	Neurofibroma			
Overall rate	2/50 (4%)	2/50 (4%)	5/50 (10%)	1/53 (2%)
Adjusted rate	6.5%	6.7%	14,4%	2.7%
Terminal rate	2/31 (6%)	2/30 (7%)	3/31 (10%)	0/23 (0%)
First incidence (days)	729 (T)	729 (T)	518	446
Life table test	P=0.588	P=0.684	P=0.220	P=0.599N
Logistic regression test	P=0.521N	P=0.684	P=0.210	P=0.497N
Cochran-Armitage test	P=0.428N			- *******
Fisher exact test	, <del>, , , , , , , , , , , , , , , , , , </del>	P=0.691N	P = 0.218	P = 0.478N
Skin (Subcutaneous Tissue): Fibroma, Ne	urofibroma, Neurofibrosarco	ma, or Sarcoma		
Overall rate	2/50 (4%)	4/50 (8%)	5/50 (10%)	3/53 (6%)
Adjusted rate	6.5%	10.8%	14.4%	9.9%
Terminal rate	2/31 (6%)	2/30 (7%)	3/31 (10%)	0/23 (0%)
First incidence (days)	729 (T)	386	518	446
Life table test	P=0.299	P=0.328	P=0.220	P=0.364
Logistic regression test	P=0.490	P=0.355	P=0.210	P=0.480
Cochran-Armitage test	P=0.497		3 3.2.0	
Fisher exact test		P=0.339	P = 0.218	P=0.528
Stomach (Forestomach): Squamous Cell P	Papilloma			
Overall rate	0/50 (0%)	0/50 (0%)	3/50 (6%)	10/53 (19%)
Adjusted rate	0.0%	0.0%	8.7%	41.3%
Terminal rate	0/31 (0%)	0/30 (0%)	2/31 (6%)	9/23 (39%)
First incidence (days)	_	_ ` ′	623	623
Life table test	P<0.001	<del></del>	P=0.119	P<0.001
Logistic regression test	P<0.001	_	P=0.118	P<0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		-	P = 0.121	P<0.001
Testes: Adenoma				
Overall rate	48/49 (98%)	44/50 (88%)	49/50 (98%)	43/52 (83%)
Adjusted rate	100.0%	97.8%	100.0%	100.0%
Terminal rate	30/30 (100%)	29/30 (97%)	31/31 (100%)	23/23 (100%)
First incidence (days)	390	524	454	322
Life table test	P=0.049	P = 0.327N	P=0.517	P=0.111
	P=0.071	P=0.071N	_t	P=0.934
Logistic regression test				
Logistic regression test Cochran-Armitage test	P=0.015N			

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Tricaprylin (continued)

· · · · · · · · · · · · · · · · · · ·			Untreated Control	2.5 mL/kg	5 mĽ/kg	10 mL/kg
Thyroid Gland (C-cell): Ad	denoma				the first	e i deni e i i
Overall rate	1	17.1	6/47 (13%)	7/46 (15%)	8/49 (16%)	2/47 (4%)
Adjusted rate		•	19.8%	20.7%	24.4%	8.7%
erminal rate			5/29 (17%)	4/29 (14%)	7/31 (23%)	2/23 (9%)
irst incidence (days)			· 707	678	608	729 (T)
ife table test	, ; q .	3 1	P=0.206N	P=0.497	P = 0.428	P=0.218N
ogistic regression test	1000	41.4	P=0.229N	P=0.457	P = 0.397	P=0.227N
Cochran-Armitage test			P = 0.102N	• •		
isher exact test	1	, , , ,		P = 0.483	P = 0.420	P=0.134N
hyroid Gland (C-cell): Ad	denoma or Carci:	noma		a <sup>n</sup> '	and the	and the specific
Overall rate		s de la la	6/47 (13%)	7/46 (15%)	9/49 (18%)	2/47 (4%)
djusted rate			19.8%	20.7%	27.6%	8.7%
erminal rate	*	1.5	5/29 (17%)	4/29 (14%)	8/31 (26%)	2/23 (9%)
irst incidence (days)		è	707	678	608	729 (T)
ife table test	1. 14	40.00	P=0.227N	P=0.497	P=0.325	P=0.218N
ogistic regression test			P=0.253N	P=0.457	P=0.295	P=0.227N
ochran-Armitage test			P=0.113N	* •		
isher exact test		· · ; · ·		P = 0.483	P = 0.319	P=0.134N
ll Organs: Mononuclear	Cell Leukemia		w , in bett			
verall rate			23/50 (46%)	28/50 (56%)	22/50 (44%)	9/53 (17%)
djusted rate	*	F. C	54.9%	71.2%	55.1%	30.9%
erminal rate	e commente de la commencia	wiger at the	13/31 (42%)	19/30 (63%)	14/31 (45%)	4/23 (17%)
irst incidence (days)		of the contract	593	524	454	446
ife table test	1.0	49 147 80 147	P=0.029N	P = 0.205	P = 0.525N	P=0.071N
ogistic regression test			P=0.014N	P=0.171	P=0.522N	P=0.059N
ochran-Armitage test		4.4	P<0.001N	1.4.		
isher exact test		3 1 L J	Same of the same	P=0.212	P=0.500N	P=0.001N
	Section 10 miles	and the same	Burgar Bar	3	F	
ll Organs: Malignant Me	sothelioma	State of the State	en la	A CONTRACTOR	r diskus ritus. Richardan	and the state of the second state of the second
verall rate			4/50 (8%)	2/50 (4%)	2/50 (4%)	3/53 (6%)
djusted rate	* .		10.5%	5.0%	6.1%	13.0%
erminal rate			2/31 (6%)	0/30 (0%)	1/31 (3%)	3/23 (13%)
irst incidence (days)			390	593	688	729 (T)
ife table test		•	P=0.533	P=0.356N	P=0.350N	P=0.641
ogistic regression test			P=0.514N	P = 0.290N	P = 0.314N	P = 0.587N
ochran-Armitage test	•		P=0.449N	D 0 000N	D 0.000M	D. O. ACTIV
isher exact test		•	•	P=0.339N	P = 0.339N	P=0.467N
ll Organs: Benign Neopla	asms					
verall rate			48/50 (96%)	45/50 (90%)	49/50 (98%)	43/53 (81%)
djusted rate			98.0%	100.0%	100.0%	100.0%
erminal rate			30/31 (97%)	30/30 (100%)	31/31 (100%)	23/23 (100%)
irst incidence (days)			390	524	454	322
ife table test			P = 0.041	P = 0.457N	P = 0.451	P = 0.090
• .• •		No. of the second	P = 0.048	P = 0.396N	P = 0.354	P=0.405
ogistic regression test Cochran-Armitage test Fisher exact test			P = 0.011N	P=0.218N	P=0.500	P=0.018N

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Tricaprylin (continued)

· .		Untreated Control	2.5 mL/kg	5 mL/kg	10 mL/kg
All Organs: Malignant Neoplasms					***
Overall rate		33/50 (66%)	36/50 (72%)	29/50 (58%)	18/53 (34%)
Adjusted rate		71.3%	79.6%	64.0%	52.8%
Terminal rate		18/31 (58%)	21/30 (70%)	15/31 (48%)	8/23 (35%)
First incidence (days)		390	386	454	324
Life table test		P=0.099N	P = 0.321	P = 0.359N	P = 0.182N
ogistic regression test		P = 0.002N	P = 0.269	P = 0.237N	P = 0.019N
Cochran-Armitage test		P<0.001N			4
Fisher exact test			P = 0.333	P = 0.268N	P=0.001N
All Organs: Benign or Malignant Neoplasms				gert en verget	4
Overall rate	4 -	49/50 (98%)	48/50 (96%)	49/50 (98%)	43/53 (81%)
Adjusted rate		100.0%	100.0%	100.0%	100.0%
Terminal rate		31/31 (100%)	30/30 (100%)	31/31 (100%)	23/23 (100%)
First incidence (days)		390	386	454	322
Life table test		P=0.076	P = 0.538	P = 0.517	P=0.112
Logistic regression test		P = 0.280	P = 0.638N		P=0.950
Cochran-Armitage test		P<0.001N			
Fisher exact test			P = 0.500N	P = 0.753N	P = 0.005N

(T)Terminal sacrifice

b Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality

C Observed incidence at terminal kill

Not applicable; no neoplasms in animal group

Value of statistic cannot be computed.

Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, bone marrow, brain, epididymis, heart, kidney, larynx, liver, lung, nose, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, spleen, testes, thyroid gland, and urinary bladder; for other tissues, denominator is number of animals necropsied.

Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table test regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.

TABLE C4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Tricaprylin<sup>a</sup>

	Untreated Control	2.5 mL/kg	5 mL/kg	10 mL/kg
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	10	10	10	7
Early deaths				
Moribund	15	13	15	17
Natural deaths	4	7	4 .	13
Survivors				
Died last week of study	2		1	1
Terminal sacrifice	29	30	30	22
Animals examined microscopically	60	60	60	60
15-Month Interim Evaluation		<del></del>		
Alimentary System				
Intestine small, duodenum	(10)	(10)	(10)	(7)
Hyperplasia, adenomatous	1 (10%)			
Intestine small, ileum	(10)	(10)	(10)	(7)
Inflammation, acute	1 (10%)			
Ulcer	1 (10%)			
Liver	(10)	(10)	(10)	(7)
Clear cell focus	A /AAA	1 (10%)		
Hepatodiaphragmatic nodule Necrosis	2 (20%)		1 (100/)	1 (14%)
	(1)		1 (10%)	(1)
Mesentery Fat, inflammation, chronic active	(1) 1 (100%)			(1)
Pancreas	(10)	(10)	(10)	1 (100%)
Atrophy	1 (10%)	(10)	(10)	(7)
Inflammation, chronic active	1 (10,0)	1 (10%)		
Acinus, atrophy	5 (50%)	6 (60%)	7 (70%)	2 (29%)
Acinus, hyperplasia	3 (30%)	2 (20%)	6 (60%)	7 (100%)
Salivary glands	(10)	(10)	(10)	(7)
Duct, metaplasia, squamous	` "	2 (20%)	` '	` '
Stomach, forestomach	(10)	(10)	(10)	(7)
Hyperplasia, basal cell, diffuse	` ',		` /	1 (14%)
Hyperplasia, basal cell, focal		•		1 (14%)
Hyperplasia, diffuse, squamous				1 (14%)
Cardiovascular System	<del></del>	and the second s		
Heart	(10)	(10)	(10)	(7)
Cardiomyopathy	7 (70%)	8 (80%)	10 (100%)	6 (86%)
Endocrine System				
Adrenal cortéx	(10)	(10)	(10)	(7)
Vacuolization cytoplasmic	(10)	1 (10%)	(10)	(1)
Adrenal medulla	(10)	(10)	(10)	(7)
Hyperplasia	(/	2 (20%)	(/	(1)
Islets, pancreatic	(10)	(10)	(10)	(7)
Hyperplasia	1 (10%)	<b>√` ∨</b>	<b>\-</b> ->	<b>(·)</b>

TABLE C4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Tricaprylin (continued)

	Untreated Control	2.5 mL/kg	5 mL/kg	10 mL/kg
15-Month Interim Evaluation (conti	inued)			
Endocrine System (continued)				
Pituitary gland	(10)	(10)	(10)	(7)
Pars distalis, cyst		2 (20%)		
Pars distalis, hyperplasia	2 (20%)	3 (30%)		
Pars intermedia, cyst		1 (10%)		
Thyroid gland	(10)	(10)	(10)	(7)
C-cell, hyperplasia		2 (20%)		1 (14%)
General Body System				
Genital System	(0)	(0)	(10)	(6)
Preputial gland	(9)	(9)	(10)	(6)
Necrosis	(10)	1 (11%)	(10)	(7)
Prostate	(10)	(10)	(10)	(7)
Hyperplasia Testas	(10)	2 (20%)	(10)	' (7)
Testes	(10)	(10)	(10)	(7) 2 (29%)
Interstitial cell, hyperplasia	2 (20%)	3 (30%)	2 (20%)	2 (29%)
Seminiferous tubule, atrophy	1 (10%)	2 (20%)		
Hematopoietic System				
Lymph node	(1)		(1)	(2)
Mediastinal, angiectasis	1 (100%)		` ,	2 (100%)
Mediastinal, pigmentation	` /		1 (100%)	` /
Lymph node, mandibular	(10)	(10)	(10)	(7)
Angiectasis	()	1 (10%)	()	(-)
Lymph node, mesenteric	(10)	(10)	(10)	(7)
Angiectasis	1 (10%)	(33)	(23)	(/)
Spleen	(10)	(10)	(10)	(7)
Hematopoietic cell proliferation	5 (50%)	6 (60%)	7 (70%)	4 (57%)
Integumentary System None				
Musculoskeletal System				
Skeletal muscle	(1)			
Infiltration cellular, histiocyte	1 (100%)			
Thrombosis	1 (100%)			
Nervous System	Maria Seria			
	(10)	(10)	(10)	(7)
Brain	(10)	(10)	(10)	('')

TABLE C4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Tricaprylin (continued)

	Untreated Control	2.5 mL/kg	5 mL/kg	10 mL/kg
15-Month Interim Evaluation (continued)			E- PA 7 . V	and the second second
Respiratory System				en grande en
Lung	(10)	(10)	(10)	(7)
Hemorrhage	1 (10%)			Line Service
Infiltration cellular, histiocyte		2 (20%)		2 (29%)
Vose	(10)	(10)	(10)	(7)
Fungus	3 (30%)	1 (10%)	3 (30%)	Programme Technology
Inflammation, acute	3 (30%)	2 (20%)	3 (30%) 3 (30%)	
Respiratory epithelium, hyperplasia	·	1 (10%)	3 (30%)	,
Special Senses System				
None	4 - 1			
		<u> </u>		
Urinary System				
Kidney	(10)	(10)	(10)	(7)
Hydronephrosis	` '	` ,	ì (10%)	
Nephropathy	10 (100%)	9 (90%)	5 (50%)	4 (57%)
Urinary bladder	(10)	(10)	(10)	(7)
Calculus gross observation		2 (20%)		
Calculus microscopic observation only		2 (20%)		
2-Year Study		· .		
Alimentary System	(47)	(46)	(40)	(44)
Intestine large, colon	(47)	(46)	(48) 1 (2%)	(44)
Ulcer Intestine small, duodenum	(49)	(46)	(48)	(42)
Ulcer	(47)	(40)	(40)	1 (2%)
Intestine small, ileum	(46)	(46)	(48)	(42)
Ulcer	(10)	1 (2%)	1 (2%)	
Liver	(50)	(50)	(50)	(51)
Basophilic focus	`35 (70%)	`39 (78%)	34 (68%)	31 (61%)
Clear cell focus	10 (20%)	19 (38%)	22 (44%)	13 (25%)
Congestion		1 (2%)	2 (4%)	
Cyst		₹ <sup>3</sup>		1 (2%)
Cyst multilocular			1 (2%)	
Eosinophilic focus	7 (14%)	4 (8%)	6 (12%)	3 (6%)
Fatty change, diffuse	1 (2%)		2 (4%)	
Fatty change, focal	4 (8%)	2 (4%)	· James	3 (6%)
Fibrosis		E (400T)	1 (2%)	1 (2%)
Hepatodiaphragmatic nodule	1 (2%)	5 (10%)	7 (14%)	5 (10%)
Hyperplasia	1 (2%)	5 (10%)	2 (4%)	1 (2%)
Hypertrophy Infarct	• • •			1 (2%)
Mixed cell focus	7 (14%)	7 (14%)	7 (14%)	4 (8%)
Necrosis	3 (6%)	2 (4%)	2 (4%)	1 (2%)
Necrosis, focal	- ()	1 (2%)	· · · · /	
Thrombosis	1 (2%)	<b>\ '</b> /'	1 (2%)	
Bile duct, hyperplasia	1 (2%)		1224 144	$(\mathbf{x}_{i}, \mathbf{y}_{i}, \mathbf{x}_{i}) = (\mathbf{x}_{i}, \mathbf{y}_{i}, \mathbf{y}_{i}, \mathbf{y}_{i}, \mathbf{y}_{i}, \mathbf{y}_{i}, \mathbf{y}_{i})$
Centrilobular, degeneration	` '	1 (2%)		

TABLE C4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Tricaprylin (continued)

	Untreated Control	2.5 mL/kg	5 mL/kg	10 mL/kg
2-Year Study (continued)			•	
Alimentary System (continued)				
Mesentery	(8)	(14)	(4)	(5)
Thrombosis	(-)	<b>1</b> (7%)	• •	• •
Artery, inflammation, chronic active	re .	1 (7%)		
Fat, hemorrhage		1 (7%)		
Fat, mineralization	1 (13%)	2 (14%)		
Fat, necrosis	3 (38%)	8 (57%)	1 (25%)	4 (80%)
Pancreas	(49)	(49)	(49)	(50)
Congestion	•			1 (2%)
Thrombosis			2 (4%)	
Acinus, atrophy	32 (65%)	35 (71%)	31 (63%)	27 (54%)
Acinus, basophilic focus	1 (2%)		1 (2%)	
Acinus, hyperplasia	8 (16%)	9 (18%)	18 (37%)	28 (56%)
Artery, hyperplasia	2 (4%)	1 (2%)	1 (2%)	3 (6%)
Artery, inflammation, chronic active	2 (4%)	4 (8%)	4 (8%)	2 (4%)
Artery, mineralization				1 (2%)
Pharynx	(1)	(1)		
Thrombosis	1 (100%)	•		
Salivary glands	(50)	(49)	(48)	(51)
Cyst				1 (2%)
Duct, metaplasia, squamous	10 (20%)	12 (24%)	4 (8%)	8 (16%)
Stomach, forestomach	(50)	(50)	(49)	(52)
Erosion			1 (2%)	
Hyperkeratosis	1 (2%)		1 (2%)	5 (10%)
Hyperplasia, basal cell	2 (4%)	5 (10%)	10 (20%)	20 (38%)
Hyperplasia, basal cell, diffuse		1 (2%)		
Hyperplasia, basal cell, focal	2 (4%)	1 (2%)	2 (4%)	1 (2%)
Inflammation, acute		•		3 (6%)
Mineralization, focal				1 (2%)
Ulcer	4 (8%)	1 (2%)	440	2 (4%)
Stomach, glandular	(50)	(48)	(49)	(50)
Erosion	6 (12%)	3 (6%)	7 (14%)	5 (10%)
Hyperplasia, lymphoid		4 (00)	5 (10%)	
Inflammation, chronic active	2 (4%)	1 (2%)	( (100)	0 (100)
Mineralization	1 (2%)	•	6 (12%)	2 (4%)
Tongue	(2)		(1)	
Hemorrhage, focal			1 (100%)	
Tooth			(1)	
Inflammation, chronic active			1 (100%)	
Cardiovascular System				
Heart	(50)	(50)	(49)	(51)
Cardiomyopathy	46 (92%)	45 (90%)	44 (90%)	43 (84%)
Infiltration cellular, histiocyte	(>=/0)	- (,,,,,	1 (2%)	.5 (5.70)
Inflammation, chronic active		1 (2%)	- (-/-/	
Thrombosis	5 (10%)	7 (14%)	4 (8%)	2 (4%)
Atrium, dilatation	1 (2%)		()	- ()

TABLE C4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Tricaprylin (continued)

Control	2.5 mL/kg	5 mL/kg	10 mL/kg
(50)	(49)	(49)	(51)
	()		()
- (=///		1 (2%)	1 (2%)
1 (2%)		- (=/0)	- (-/-)
1 (2%)			1 (2%)
(50)	(49)	(49)	(51)
			18 (35%)
			(49)
			1 (2%)
(40)	(47)	(47)	(46)
	1 (20%)		1 (2%)
(50)		(40)	1 (2%)
			(51)
3 (6%)		3 (6%)	2 (4%)
	1 (2%)	<u> </u>	
			4 (8%)
9 (18%)	8 (17%)		6 (12%)
		1 (2%)	
(47)	(46)	(49)	(47)
	1 (2%)		
7 (15%)	4 (9%)	9 (18%)	2 (4%)
` ,	2 (4%)		
			,
(50)	(49)		(52)
3 (6%)	4 (8%)	6 (12%)	3 (6%)
			1 (2%)
	2 (4%)	1 (2%)	2 (4%)
	1 (2%)		
	1 (2%)		
2 (4%)		1 (2%)	
	(49)	(49)	(52)
	` 7 (14%)	6 (12%)	7 (13%)
	` '	• •	, ,
		,	
		(50)	(52)
(**)		V: =/	\ ~/
1 (2%)	- (m/o)		•
	(50)	(50)	(52)
			8 (15%)
	` ,		3 (6%)
3 (10%)	4 (0%)	1 (270)	1 (2%)
	(50) 1 (2%) 1 (2%) (50) 22 (44%) (49) 6 (12%) (40) (50) 3 (6%) 2 (4%) 9 (18%) (47) 7 (15%) 1 (2%)	(50) (49) 1 (2%)  1 (2%)  (50) (49) 22 (44%) 18 (37%) (49) (48) 6 (12%) 5 (10%) (40) (47)  1 (2%) (50) (47) 3 (6%) 1 (2%) 2 (4%) 9 (18%) 8 (17%)  (47) (46) 1 (2%) 7 (15%) 4 (9%) 1 (2%) 2 (4%) 9 (18%) 2 (4%)  (50) (49) 3 (6%) 4 (8%)  (49) (49) 3 (6%) 7 (14%) 1 (2%) 1 (	(50) (49) (49) (49) 1 (2%) 1 (2%) 1 (2%)  (50) (49) (49) (22 (44%) 18 (37%) 22 (45%) (49) (48) (49) 6 (12%) 5 (10%) 3 (6%) (40) (47) (47)  (50) (47) (49) 3 (6%) 1 (2%) 3 (6%) 1 (2%) 2 (4%) 9 (18%) 8 (17%) 10 (20%) 1 (2%

TABLE C4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Tricaprylin (continued)

	Untreated Control	2.5 mL/kg	5 mL/kg	10 mL/kg
2-Year Study (continued)				
Hematopoietic System			(24)	(14)
Lymph node	(24)	(25)	(24)	(14)
Lymphatic, ectasia		1 (4%)	2 (12%)	7 (50%)
Mediastinal, angiectasis	2 (8%)	2 (8%)	3 (13%)	7 (3070)
Mediastinal, congestion		1 (4%)	5 (21%)	
Mediastinal, ectasia		4 (40%)	5 (21%)	
Mediastinal, hyperplasia		1 (4%)		
Mediastinal, hyperplasia, lymphoid		1 (4%)	2 (901)	
Mediastinal, infiltration cellular, mast cell	1 (4%)		2 (8%)	
Mediastinal, infiltration cellular,		A (64)		
histiocyte		2 (8%)	2 (00%)	1 (70%)
Mediastinal, pigmentation	3 (13%)	2 (8%)	2 (8%)	1 (7%)
Mediastinal, lymphatic, ectasia		1 (4%)	1 (40%)	1 (70%)
Pancreatic, angiectasis			1 (4%)	1 (7%)
Pancreatic, ectasia		1 (4%)	1 (4%)	1 (7%)
Pancreatic, hyperplasia, lymphoid	2 (8%)	2 (8%)		1 (7%)
Pancreatic, infiltration cellular, histiocyte	1 (4%)		1 (101)	
Pancreatic, pigmentation			1 (4%)	
Pancreatic, lymphatic, ectasia	1 (4%)	2 (8%)	1 (10%)	
Renal, pigmentation		44.0	1 (4%)	(50)
Lymph node, mandibular	(49)	(46)	(49)	(50)
Angiectasis	1 (2%)		a (184)	
Ectasia	1 (2%)		2 (4%)	
Hyperplasia, lymphoid			2 (4%)	
Infiltration cellular, plasma cell		2 (4%)		
Infiltration cellular, histiocyte		1 (2%)	.=	(40)
Lymph node, mesenteric	(48)	(49)	(50)	(48)
Angiectasis	1 (2%)		1 (2%)	2 (4%)
Ectasia	4 (8%)	2 (4%)	2 (4%)	1 (2%)
Hyperplasia, lymphoid			2 (4%)	
Infiltration cellular, histiocyte		3 (6%)		
Lymphatic, ectasia		1 (2%)		1 (2%)
Spleen	(49)	(50)	(49)	(51)
Angiectasis		1 (2%)		
Depletion lymphoid		1 (2%)	1 (2%)	3 (6%)
Developmental malformation	1 (2%)	1 (2%)		1 (2%)
Fibrosis	8 (16%)	13 (26%)	16 (33%)	9 (18%)
Hematopoietic cell proliferation	6 (12%)	3 (6%)	4 (8%)	3 (6%)
Hemorrhage	•		1 (2%)	
Infarct	2 (4%)		1 (2%)	1 (2%)
Mineralization	• •		1 (2%)	
Pigmentation				3 (6%)
Capsule, fibrosis				1 (2%)
Lymphoid follicle, atrophy	2 (4%)			-
Thymus	(46)	(45)	(46)	(46)
Congestion	1 (2%)			
Cyst	1 (2%)			
Epithelial cell, hyperplasia	, ,			1 (2%)

TABLE C4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Tricaprylin (continued)

	Untreated Control	2.5 mL/kg	5 mL/kg	10 mL/kg
2-Year Study (continued)				
Integumentary System  Mammary gland  Galactocele	(44)	(40)	(43)	(44) 2 (5%)
Hemorrhage, focal Skin Cyst	1 (2%) (49)	(49)	(49)	(52)
Cyst epithelial inclusion Developmental malformation Hyperkeratosis	1 (2%) 2 (4%)	1 (2%) 1 (2%)	1 (2%)	1 (2%) 2 (4%)
Inflammation, chronic active Ulcer	1	1 (2%) 1 (2%)	1 (2%)	
Musculoskeletal System				,
Bone	(50)	(50)	(50)	(53)
Hyperostosis	1 (2%)	( )	1 (2%)	. ()
Skeletal muscle	(49)	(50)	(47)	(53)
Atrophy	3 (6%)	1 (2%)	2 (4%)	
Mineralization				1 (2%)
Nervous System				
None				
None Respiratory System	(50)	(50)	(50)	(51)
None  Respiratory System  Lung	(50)	(50)	(50)	(51)
None  Respiratory System  Lung  Congestion	(50) 1 (2%)	(50)	1 (2%)	
None  Respiratory System  Lung  Congestion  Edema	1 (2%)	(50)		(51) 2 (4%)
None  Respiratory System  Lung  Congestion  Edema  Fungus	1 (2%) 1 (2%)		1 (2%) 2 (4%)	2 (4%)
Respiratory System Lung Congestion Edema Fungus Hemorrhage	1 (2%) 1 (2%) 1 (2%)	2 (4%)	1 (2%) 2 (4%) 1 (2%)	2 (4%) 1 (2%)
None  Respiratory System  Lung  Congestion  Edema  Fungus	1 (2%) 1 (2%) 1 (2%) 1 (2%)	2 (4%) 4 (8%)	1 (2%) 2 (4%) 1 (2%) 4 (8%)	2 (4%) 1 (2%) 2 (4%)
Respiratory System Lung Congestion Edema Fungus Hemorrhage Infiltration cellular, histiocyte	1 (2%) 1 (2%) 1 (2%)	2 (4%)	1 (2%) 2 (4%) 1 (2%)	2 (4%) 1 (2%)
Respiratory System Lung Congestion Edema Fungus Hemorrhage Infiltration cellular, histiocyte Inflammation, acute Inflammation, chronic active Alveolar epithelium, hyperplasia	1 (2%) 1 (2%) 1 (2%) 1 (2%)	2 (4%) 4 (8%) 1 (2%)	1 (2%) 2 (4%) 1 (2%) 4 (8%) 1 (2%)	2 (4%) 1 (2%) 2 (4%)
Respiratory System Lung Congestion Edema Fungus Hemorrhage Infiltration cellular, histiocyte Inflammation, acute Inflammation, chronic active Alveolar epithelium, hyperplasia Mediastinum, inflammation	1 (2%) 1 (2%) 1 (2%) 1 (2%)	2 (4%) 4 (8%) 1 (2%)	1 (2%) 2 (4%) 1 (2%) 4 (8%) 1 (2%) 1 (2%)	2 (4%) 1 (2%) 2 (4%) 1 (2%)
Respiratory System Lung Congestion Edema Fungus Hemorrhage Infiltration cellular, histiocyte Inflammation, acute Inflammation, chronic active Alveolar epithelium, hyperplasia Mediastínum, inflammation Pleura, inflammation, chronic active	1 (2%) 1 (2%) 1 (2%) 1 (2%) 1 (2%)	2 (4%) 4 (8%) 1 (2%) 1 (2%) 1 (2%)	1 (2%) 2 (4%) 1 (2%) 4 (8%) 1 (2%) 1 (2%) 3 (6%)	2 (4%) 1 (2%) 2 (4%) 1 (2%) 1 (2%)
Respiratory System Lung Congestion Edema Fungus Hemorrhage Infiltration cellular, histiocyte Inflammation, acute Inflammation, chronic active Alveolar epithelium, hyperplasia Mediastinum, inflammation Pleura, inflammation, chronic active Nose	1 (2%) 1 (2%) 1 (2%) 1 (2%) 1 (2%) 1 (2%)	2 (4%) 4 (8%) 1 (2%)  1 (2%) 1 (2%) (49)	1 (2%) 2 (4%) 1 (2%) 4 (8%) 1 (2%) 1 (2%) 3 (6%)	2 (4%) 1 (2%) 2 (4%) 1 (2%) 1 (2%) (52)
Respiratory System Lung Congestion Edema Fungus Hemorrhage Infiltration cellular, histiocyte Inflammation, acute Inflammation, chronic active Alveolar epithelium, hyperplasia Mediastinum, inflammation Pleura, inflammation, chronic active Nose Fungus	1 (2%) 1 (2%) 1 (2%) 1 (2%) 1 (2%)	2 (4%) 4 (8%) 1 (2%) 1 (2%) 1 (2%)	1 (2%) 2 (4%)  1 (2%) 4 (8%) 1 (2%) 3 (6%)  (50) 9 (18%)	2 (4%) 1 (2%) 2 (4%) 1 (2%) 1 (2%) (52) 5 (10%)
Respiratory System Lung Congestion Edema Fungus Hemorrhage Infiltration cellular, histiocyte Inflammation, acute Inflammation, chronic active Alveolar epithelium, hyperplasia Mediastinum, inflammation Pleura, inflammation, chronic active Nose Fungus Hyperkeratosis	1 (2%) 1 (2%) 1 (2%) 1 (2%) 1 (2%) 1 (2%) 1 (2%) 1 (2%)	2 (4%) 4 (8%) 1 (2%)  1 (2%) 1 (2%) (49) 6 (12%)	1 (2%) 2 (4%)  1 (2%) 4 (8%) 1 (2%) 3 (6%)  (50) 9 (18%) 1 (2%)	2 (4%)  1 (2%) 2 (4%) 1 (2%)  1 (2%)  (52) 5 (10%) 2 (4%)
Respiratory System Lung Congestion Edema Fungus Hemorrhage Infiltration cellular, histiocyte Inflammation, acute Inflammation, chronic active Alveolar epithelium, hyperplasia Mediastinum, inflammation Pleura, inflammation, chronic active Nose Fungus	1 (2%) 1 (2%) 1 (2%) 1 (2%) 1 (2%) 1 (2%)	2 (4%) 4 (8%) 1 (2%)  1 (2%) 1 (2%) (49)	1 (2%) 2 (4%)  1 (2%) 4 (8%) 1 (2%) 3 (6%)  (50) 9 (18%)	2 (4%) 1 (2%) 2 (4%) 1 (2%) 1 (2%) (52) 5 (10%)
Respiratory System Lung Congestion Edema Fungus Hemorrhage Infiltration cellular, histiocyte Inflammation, acute Inflammation, chronic active Alveolar epithelium, hyperplasia Mediastinum, inflammation Pleura, inflammation, chronic active Nose Fungus Hyperkeratosis Inflammation, acute Respiratory epithelium, metaplasia, squamous	1 (2%) 1 (2%) 1 (2%) 1 (2%) 1 (2%) 1 (2%) 1 (2%) (50) 18 (36%) 21 (42%)	2 (4%) 4 (8%) 1 (2%)  1 (2%) 1 (2%) (49) 6 (12%)	(50) 9 (18%) 1 (2%) 4 (8%) 1 (2%) 3 (6%)	2 (4%)  1 (2%) 2 (4%) 1 (2%)  1 (2%)  (52) 5 (10%) 2 (4%)
Respiratory System Lung Congestion Edema Fungus Hemorrhage Infiltration cellular, histiocyte Inflammation, acute Inflammation, chronic active Alveolar epithelium, hyperplasia Mediastinum, inflammation Pleura, inflammation, chronic active Nose Fungus Hyperkeratosis Inflammation, acute Respiratory epithelium, metaplasia, squamous  Special Senses System	1 (2%) 1 (2%) 1 (2%) 1 (2%) 1 (2%) 1 (2%) 1 (2%) 21 (42%) 9 (18%)	2 (4%) 4 (8%) 1 (2%)  1 (2%) 1 (2%) (49) 6 (12%)	(50) 9 (18%) 1 (2%) 4 (8%) 1 (2%) 3 (6%) (50) 9 (18%) 1 (2%) 12 (24%) 3 (6%)	2 (4%)  1 (2%) 2 (4%) 1 (2%)  1 (2%)  (52) 5 (10%) 2 (4%) 5 (10%)
Respiratory System Lung Congestion Edema Fungus Hemorrhage Infiltration cellular, histiocyte Inflammation, acute Inflammation, chronic active Alveolar epithelium, hyperplasia Mediastinum, inflammation Pleura, inflammation, chronic active Nose Fungus Hyperkeratosis Inflammation, acute Respiratory epithelium, metaplasia, squamous  Special Senses System Eye	1 (2%) 1 (2%) 1 (2%) 1 (2%) 1 (2%) 1 (2%) 1 (2%) (50) 18 (36%) 21 (42%)	2 (4%) 4 (8%) 1 (2%)  1 (2%) 1 (2%) (49) 6 (12%)	(50) 9 (18%) 1 (2%) 4 (8%) 1 (2%) 3 (6%)	2 (4%)  1 (2%) 2 (4%) 1 (2%)  1 (2%)  (52) 5 (10%) 2 (4%) 5 (10%)
Respiratory System Lung Congestion Edema Fungus Hemorrhage Infiltration cellular, histiocyte Inflammation, acute Inflammation, chronic active Alveolar epithelium, hyperplasia Mediastinum, inflammation Pleura, inflammation, chronic active Nose Fungus Hyperkeratosis Inflammation, acute Respiratory epithelium, metaplasia, squamous  Special Senses System	1 (2%) 1 (2%) 1 (2%) 1 (2%) 1 (2%) 1 (2%) 1 (2%) 21 (42%) 9 (18%)	2 (4%) 4 (8%) 1 (2%)  1 (2%) 1 (2%) (49) 6 (12%)	(50) 9 (18%) 1 (2%) 4 (8%) 1 (2%) 3 (6%) (50) 9 (18%) 1 (2%) 12 (24%) 3 (6%)	2 (4%)  1 (2%) 2 (4%) 1 (2%)  1 (2%)  (52) 5 (10%) 2 (4%) 5 (10%)

,这是一个时间,我们就是一个时间,我们就是一个时间,我们就是一个时间,我们就是一个时间,我们就是一个时间,我们也会看到一个时间,我们也会看到一个时间,我们就是一

TABLE C4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Tricaprylin (continued)

	Untreated Control	2.5 mL/kg	5 mL/kg	10 mL/kg
2-Year Study (continued)				
Urinary System				
Kidney	(50)	(50)	(50)	(49)
Cyst	2 (4%)	1 (2%)	2 (4%)	1 (2%)
Infarct	. ,		1 (2%)	
Nephropathy	46 (92%)	42 (84%)	45 (90%)	27 (55%)
Cortex, mineralization	2 (4%)	• •	, ,	, ,
Renal tubule, hyperplasia			1 (2%)	
Transitional epithelium, hyperplasia	2 (4%)		- *	
Urinary bladder	(48)	(47)	(48)	(48)
Calculus gross observation	• •	1 (2%)	. ,	. ,
Calculus microscopic observation only		1 (2%)		1 (2%)
Hemorrhage	1 (2%)	• •		` ,

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

## APPENDIX D SUMMARY OF LESIONS IN MALE RATS IN THE 2-YEAR GAVAGE STUDY OF DICHLOROMETHANE IN CORN OIL

Table D1	Summary of the Incidence of Neoplasms in Male Rats	
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,是是一个时间,这个时间,这个时间,这个时间,这个时间,这个时间,我们就是一个时间,我们就是一个时间,我们就是一个时间,我们也没有一个时间,我们就是一个时间,也 一个时间,这个时间,我们就是一个时间,我们就是一个时间,我们就是一个时间,我们就是一个时间,我们就是一个时间,我们就是一个时间,我们就是一个时间,我们就是一个时

TABLE D1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Gavage Study of Dichloromethane in Corn Oil<sup>a</sup>

	2.5 mL/kg	5 mL/kg	10 mL/kg
Disposition Summary			
Animals initially in study	50	50	50
Early deaths	50	30	30
Accidental deaths	4	1	2
Moribund	19	13	12
Natural deaths	4	8	5
Survivors	•		
Terminal sacrifice	23	28	31
Animals examined microscopically	50	50	50
<del></del>			<del></del>
Alimentary System			
Intestine large, cecum	(47)	(48)	(48)
Intestine large, colon	(47)	(49)	(50)
Intestine large, rectum	(47)	(46)	(49)
Intestine small, duodenum	(48)	(49)	(49)
Liver	(50)	(50)	(50)
Hepatocellular carcinoma	1 (2%)		2 (4%)
Hepatocellular adenoma	3 (6%)	4 (8%)	4 (8%)
Hepatocellular adenoma, multiple	3 (6%)		
Histiocytic sarcoma	1 (2%)		1 (2%)
Schwannoma malignant, metastatic, heart	1 (2%)		1 (270)
Mesentery	(12)	(10)	(7)
Hemangiosarcoma	1 (8%)	(10)	(7)
Sarcoma	1 (8%)		1 (14%)
Pancreas	(50)	(50)	(50)
		(30)	(30)
Histiocytic sarcoma	1 (2%)	1 (20%)	2 (40%)
Acinus, adenocarcinoma	7 (140)	1 (2%)	3 (6%)
Acinus, adenoma	7 (14%)	6 (12%)	7 (14%)
Acinus, adenoma, multiple	2 (4%)	13 (26%)	34 (68%)
Pharynx	(1)	(1)	(2)
Palate, squamous cell carcinoma		:	1 (50%)
Palate, squamous cell papilloma	1 (100%)	1 (100%)	1 (50%)
Salivary glands	(50)	(50)	(49)
Fibroma	1 (2%)		
Stomach, forestomach	(49)	(50)	(50)
Squamous cell papilloma	2 (4%)	2 (4%)	1 (2%)
Stomach, glandular	(50)	(48)	(48)
Condinuescular System			·
Cardiovascular System	(50)	(50)	(50)
Heart About a factor and the second	(50)	(50)	(50)
Alveolar/bronchiolar carcinoma, metastatic, lung		1 (2%)	1 (2%)
Schwannoma malignant	1 (2%)	1 (2/0)	1 (270)
Endossino System			
Endocrine System	(49)	(45)	(50)
Adrenal gland, cortex			

TABLE D1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Gavage Study of Dichloromethane in Corn Oil (continued)

	2.5 mL/kg	5 mL/kg	10 mL/kg
Endocrine System (continued)			
Adrenal gland, medulla	(49)	(45)	(50)
Pheochromocytoma malignant	,	2 (4%)	1 (2%)
Pheochromocytoma benign	10 (20%)	5 (11%)	6 (12%)
Bilateral, pheochromocytoma malignant	` ,	1 (2%)	·
Bilateral, pheochromocytoma benign	3 (6%)	3 (7%)	1 (2%)
slets, pancreatic	(50)	(50)	(50)
Adenoma	) 5 (10%)	7 (14%)	11 (22%)
Adenoma, multiple	` ,	1 (2%)	1 (2%)
Carcinoma		1 (2%)	3 (6%)
Pituitary gland	(50)	(49)	(49)
Pars distalis, adenoma	20 (40%)	16 (33%)	16 (33%)
Pars distalis, adenoma, multiple	` '	2 (4%)	•
Pars intermedia, adenoma		1 (2%)	
Thyroid gland	(48)	(49)	(48)
C-cell, adenoma	6 (13%)	7 (14%)	9 (19%)
C-cell, carcinoma	` ,	2 (4%)	,
Follicular cell, adenoma	3 (6%)	• •	2 (4%)
Follicular cell, carcinoma	2 (4%)		` '
General Body System None			•
None Genital System			
None	(49)	(50)	(50)
None Genital System	(49) (48)	(50) (44)	(50) (50)
None Genital System Epididymis			
None  Genital System  Epididymis  Preputial gland	(48) 6 (13%) 1 (2%)		(50)
None  Genital System  Epididymis  Preputial gland  Adenoma  Bilateral, adenoma  Testes	(48) 6 (13%) 1 (2%) (50)	(44)	(50)
None  Genital System  Epididymis  Preputial gland  Adenoma  Bilateral, adenoma  Testes  Histiocytic sarcoma	(48) 6 (13%) 1 (2%) (50) 1 (2%)	(44) 1 (2%) (49)	(50) 3 (6%)
Genital System  Epididymis Preputial gland Adenoma Bilateral, adenoma  Testes Histiocytic sarcoma Bilateral, interstitial cell, adenoma	(48) 6 (13%) 1 (2%) (50) 1 (2%) 36 (72%)	(44) 1 (2%) (49) 35 (71%)	(50) 3 (6%) (50) 36 (72%)
None  Genital System  Epididymis  Preputial gland  Adenoma  Bilateral, adenoma  Testes  Histiocytic sarcoma	(48) 6 (13%) 1 (2%) (50) 1 (2%)	(44) 1 (2%) (49)	(50) 3 (6%) (50)
Genital System  Epididymis Preputial gland Adenoma Bilateral, adenoma  Testes Histiocytic sarcoma Bilateral, interstitial cell, adenoma Interstitial cell, adenoma	(48) 6 (13%) 1 (2%) (50) 1 (2%) 36 (72%)	(44) 1 (2%) (49) 35 (71%)	(50) 3 (6%) (50) 36 (72%)
Genital System  Epididymis Preputial gland Adenoma Bilateral, adenoma  Testes Histiocytic sarcoma Bilateral, interstitial cell, adenoma	(48) 6 (13%) 1 (2%) (50) 1 (2%) 36 (72%) 7 (14%)	(44) 1 (2%) (49) 35 (71%) 7 (14%)	(50) 3 (6%) (50) 36 (72%)
Genital System  Epididymis Preputial gland Adenoma Bilateral, adenoma  Testes Histiocytic sarcoma Bilateral, interstitial cell, adenoma Interstitial cell, adenoma  Hematopoietic System  Blood	(48) 6 (13%) 1 (2%) (50) 1 (2%) 36 (72%) 7 (14%)	(44) 1 (2%) (49) 35 (71%) 7 (14%)	(50) 3 (6%) (50) 36 (72%) 8 (16%)
Genital System  Epididymis Preputial gland Adenoma Bilateral, adenoma  Testes Histiocytic sarcoma Bilateral, interstitial cell, adenoma Interstitial cell, adenoma  Hematopoietic System Blood Bone marrow	(48) 6 (13%) 1 (2%) (50) 1 (2%) 36 (72%) 7 (14%)	(44) 1 (2%) (49) 35 (71%) 7 (14%)	(50) 3 (6%) (50) 36 (72%)
Genital System  Epididymis Preputial gland Adenoma Bilateral, adenoma  Testes Histiocytic sarcoma Bilateral, interstitial cell, adenoma Interstitial cell, adenoma  Hematopoietic System Blood Bone marrow Histiocytic sarcoma	(48) 6 (13%) 1 (2%) (50) 1 (2%) 36 (72%) 7 (14%) (3) (50) 1 (2%)	(44) 1 (2%) (49) 35 (71%) 7 (14%) (3) (50)	(50) 3 (6%) (50) 36 (72%) 8 (16%)
Genital System  Epididymis Preputial gland Adenoma Bilateral, adenoma  Testes Histiocytic sarcoma Bilateral, interstitial cell, adenoma Interstitial cell, adenoma  Hematopoietic System Blood Bone marrow Histiocytic sarcoma Lymph node	(48) 6 (13%) 1 (2%) (50) 1 (2%) 36 (72%) 7 (14%) (3) (50) 1 (2%) (50)	(44) 1 (2%) (49) 35 (71%) 7 (14%) (3) (50)	(50) 3 (6%) (50) 36 (72%) 8 (16%) (50)
Genital System  Epididymis Preputial gland Adenoma Bilateral, adenoma  Testes Histiocytic sarcoma Bilateral, interstitial cell, adenoma Interstitial cell, adenoma  Hematopoietic System Blood Bone marrow Histiocytic sarcoma Lymph node Lymph node, mandibular	(48) 6 (13%) 1 (2%) (50) 1 (2%) 36 (72%) 7 (14%) (3) (50) 1 (2%) (50) (50)	(44) 1 (2%) (49) 35 (71%) 7 (14%) (3) (50) (50) (50)	(50) 3 (6%) (50) 36 (72%) 8 (16%) (50) (50) (47)
Genital System  Epididymis Preputial gland Adenoma Bilateral, adenoma  Testes Histiocytic sarcoma Bilateral, interstitial cell, adenoma Interstitial cell, adenoma  Hematopoietic System Blood Bone marrow Histiocytic sarcoma Lymph node Lymph node, mandibular Lymph node, mesenteric	(48) 6 (13%) 1 (2%) (50) 1 (2%) 36 (72%) 7 (14%)  (3) (50) 1 (2%) (50) (50) (49)	(44) 1 (2%) (49) 35 (71%) 7 (14%) (3) (50)	(50) 3 (6%) (50) 36 (72%) 8 (16%) (50)
Genital System  Epididymis Preputial gland Adenoma Bilateral, adenoma  Testes Histiocytic sarcoma Bilateral, interstitial cell, adenoma Interstitial cell, adenoma  Hematopoietic System Blood Bone marrow Histiocytic sarcoma Lymph node Lymph node, mandibular Lymph node, mesenteric Histiocytic sarcoma	(48) 6 (13%) 1 (2%) (50) 1 (2%) 36 (72%) 7 (14%)  (3) (50) 1 (2%) (50) (50) (49) 1 (2%)	(44) 1 (2%) (49) 35 (71%) 7 (14%) (3) (50) (50) (50) (49)	(50) 3 (6%) (50) 36 (72%) 8 (16%) (50) (50) (47) (48)
Genital System  Epididymis Preputial gland Adenoma Bilateral, adenoma  Testes Histiocytic sarcoma Bilateral, interstitial cell, adenoma Interstitial cell, adenoma  Hematopoietic System Blood Bone marrow Histiocytic sarcoma Lymph node Lymph node, mandibular Lymph node, mesenteric Histiocytic sarcoma Spleen	(48) 6 (13%) 1 (2%) (50) 1 (2%) 36 (72%) 7 (14%)  (3) (50) 1 (2%) (50) (50) (49) 1 (2%) (49)	(44) 1 (2%) (49) 35 (71%) 7 (14%) (3) (50) (50) (50)	(50) 3 (6%) (50) 36 (72%) 8 (16%) (50) (50) (47)
Genital System  Epididymis Preputial gland Adenoma Bilateral, adenoma  Testes Histiocytic sarcoma Bilateral, interstitial cell, adenoma Interstitial cell, adenoma  Hematopoietic System Blood Bone marrow Histiocytic sarcoma Lymph node Lymph node, mandibular Lymph node, mesenteric Histiocytic sarcoma Spleen Hemangiosarcoma	(48) 6 (13%) 1 (2%) (50) 1 (2%) 36 (72%) 7 (14%)  (3) (50) 1 (2%) (50) (50) (49) 1 (2%) (49) 1 (2%) (49) 1 (2%)	(44) 1 (2%) (49) 35 (71%) 7 (14%) (3) (50) (50) (50) (49)	(50) 3 (6%) (50) 36 (72%) 8 (16%) (50) (50) (47) (48)
Genital System  Epididymis Preputial gland Adenoma Bilateral, adenoma  Testes Histiocytic sarcoma Bilateral, interstitial cell, adenoma Interstitial cell, adenoma  Hematopoietic System Blood Bone marrow Histiocytic sarcoma Lymph node Lymph node, mandibular Lymph node, mesenteric Histiocytic sarcoma Spleen	(48) 6 (13%) 1 (2%) (50) 1 (2%) 36 (72%) 7 (14%)  (3) (50) 1 (2%) (50) (50) (49) 1 (2%) (49)	(44) 1 (2%) (49) 35 (71%) 7 (14%) (3) (50) (50) (50) (49)	(50) 3 (6%) (50) 36 (72%) 8 (16%) (50) (50) (47) (48)

TABLE D1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Gavage Study of Dichloromethane in Corn Oil (continued)

	2.5 mL/kg	5 mL/kg	10 mL/kg
Integumentary System			2.1
Mammary gland	(42)	(36)	(37)
Adenoma			1 (3%)
Fibroadenoma	1 (2%)	2 (6%)	6 (16%)
Skin	(50)	(50)	(50)
Basal cell carcinoma	2 (4%)		
Keratoacanthoma		1 (2%)	
Squamous cell carcinoma	1 (2%)		
Squamous cell papilloma	2 (4%)	1 (2%)	- / ·
Subcutaneous tissue, fibroma	3 (6%)	7 (14%)	5 (10%)
Subcutaneous tissue, sarcoma			1 (2%)
Musculoskeletal System			
Skeletal muscle	(3)	(2)	(2)
Alveolar/bronchiolar carcinoma, metastatic,	` /	` '	
lung			1 (50%)
Nervous System	<del></del>		
Brain	(50)	(50)	(50)
Astrocytoma malignant	` ,	2 (4%)	•
Respiratory System		· · · · · · · · · · · · · · · · · · ·	
Lung	(50)	(50)	(49)
Alveolar/bronchiolar adenoma	3 (6%)	1 (2%)	4 (8%)
Alveolar/bronchiolar carcinoma	3 (0%)	1 (2%)	1 (2%)
Carcinoma, metastatic, kidney		1 (2%)	1 (270)
Carcinoma, metastatic, thyroid gland		1 (2%)	
Histiocytic sarcoma	1 (2%)	1 (2/0)	
Histocytic sarcoma, metastatic, liver	1 (270)		1 (2%)
Osteosarcoma, metastatic, uncertain primary			1 (270)
site	1 (2%)		
Sarcoma, metastatic, mesentery	1 (2%)		1 (2%)
Sarcoma, metastatic, incertain primary site	1 (2%)		1 (270)
Nose	(50)	(50)	(50)
0 110 0 4			
Special Senses System	(4)	(3)	
Ear Sarcoma	(4)	(3)	
	1 (25%)	(1)	(2)
Zymbal's gland Carcinoma		(1) 1 (100%)	(2) 2 (100%)
·			
Urinary System	(50)	(50)	(50)
Kidney	(50)	(50)	(50)
Lipoma		1 (2%)	
Liposarcoma	·	1 (2%)	
Renal tubule, carcinoma		1 (2%)	(40)
Urinary bladder	(49)	(49)	(49)

TABLE D1 Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Gavage Study of Dichloromethane in Corn Oil (continued)

	2.5 mL/kg	5 mL/kg	10 mL/kg
Systemic Lesions			
Multiple organs <sup>b</sup>	(50)	(50)	(50)
Histiocytic sarcoma	1 (2%)		1 (2%)
Leukemia mononuclear	13 (26%)	14 (28%)	5 (10%)
Mesothelioma malignant	2 (4%)	3 (6%)	2 (4%)
Total animals with primary neoplasms <sup>c</sup> Total primary neoplasms Total animals with benign neoplasms Total benign neoplasms Total animals with malignant neoplasms Total malignant neoplasms	48 152 48 125 23 27	47 155 47 124 21 31	48 179 48 156 20 23
Total animals with metastatic neoplasms Total metastatic neoplasm Total animals with malignant neoplasms	19	16	12

Doses are given as 500 mg dichloromethane/kg body weight in mL corn oil/kg body weight. Number of animals examined microscopically at site and number of animals with lesion.

Number of animals with any tissue examined microscopically

c Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE D2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Dichloromethane in Corn Oil: 2.5 mL/kg<sup>a</sup>

			_			_							-						_	_					_				<del>, , ,</del>
Number of Days on Study	1 3 2	3 0 9	3 5 2		4 8 3	5 7 2	5 7 8	5 9 5	5 9 5	5 9 8	0	0	0	6 1 0	2	2	3	5	7	7	8	9	0.	1	2		٠.		:
										_				_			-	_		ر.		_		_					
•	1	2	1	1	1	1	2	1	1	1	1	1	2	1	1	1	2	1	1	1	1	1	1	1	1				
Carcass ID Number	7 5	0 5	8 1	6 1	4 5	4	0 3	3 5	7 4			1 5	0 1	8 5		8 <sub>.</sub>			8 2						5				
Alimentary System		_	_										-	•									_				<del></del>		
Esophagus	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Intestine large	+	+	+	+	+	Α	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	Α	+	+	Α			`.	
Intestine large, cecum	+	+	+	+	+	Α	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	Α	+	+	Α	-			
Mesothelioma malignant, metastatic, testes																										,			
Intestine large, colon	+	+	+	+	+	Α	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	Α	+	+	Α				
Mesothelioma malignant, metastatic, testes						•																				•			
Intestine large, rectum	+	+	+	+	+	Α	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	Α	+	+	Α				
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	A		a es		
Intestine small, duodenum  Mesothelioma malignant, metastatic, testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	. +	A				٠
Intestine small, ileum	+	+	. +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	Α	+	+	Α				
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	Α	+	+	A				
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Hepatocellular carcinoma Hepatocellular adenoma	v.														,						x	X			-	٠,			
Hepatocellular adenoma, multiple																					71	7.		٠ :				•	
Histiocytic sarcoma	i											X																	
Schwannoma malignant, metastatic, heart																									X				
Mesentery			+		+	+											+	+		+				+					
Hemangiosarcoma Mesothelioma malignant, metastatic,			•		•	X											•	•		·				•					
testes																													
Sarcoma																	X												
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		>		
Histiocytic sarcoma						,						X																Ç#	
Mesothelioma malignant, metastatic, testes																												٠.	
Acinus, adenoma															X														
Acinus, adenoma, multiple																													
Pharynx													+																
Palate, squamous cell papilloma													Х																
Salivary glands Fibroma	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	•			
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Stomach, forestomach Mesothelioma malignant, metastatic,	+	+	. +	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
testes Squamous cell papilloma		x																											
Stomach, glandular		^ +	_	_				_	_	_	_	_	_	_	_	_	_	_	_	_	_		_				•		
Mesothelioma malignant, metastatic,		+	_	_	_	_	Τ-	+	т	<b>T</b>	_	т	_	_		т	_	_	:	т			+	. —	Τ,			,	:
testes Tongue				.1																									
Tongue				+																									

<sup>+:</sup> Tissue examined microscopically

M: Missing tissue I: Insufficient tissue X: Lesion present Blank: Not examined

A: Autolysis precludes examination

・ 1 年 1 日本の 1 日本

Table D2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Dichloromethane in Corn Oil: 2.5 mL/kg (continued)

•	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
umber of Days on Study	2	2	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
	3	6	1	1	1	1	1	1	1	1	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	2	Total
arcass IID Number	4	-	1	2	3	3	_	7	7	7	4	4	5	5		_		-	6	9	9	9	9	9	0	Tissue
arcass and indirect	4				1		,	1	2	3	2				3											Tumoi
		_					_	_															_			
limentary System						۶.																				40
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Mesothelioma malignant, metastatic,																										
testes	X																									1
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Mesothelioma malignant, metastatic,																										
testes	X																									1
Intestine large, rectum	+		+	+	+	4	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small	- 4	4	·	+	+	<u>,</u>	+	4	+	+	+	<u>.</u>	+	<u>.</u>	+	+	+	<u>.</u>	+	+	+	+	+	+	+	48
Intestine small, duodenum	.t.	1	T-	_T		,L	-T	т "L	<u>_</u>	,L	ı.	T.	T.	T	-L	<u>-</u>	<u>-</u>			.1.	.1.	T'	т Т	+	-T-	48
Mesothelioma malignant, metastatic,		+	+	_	т	+	+	+	_	+	т	+	+	+	_	+	+	+	+	+	+	_	+	+	+	
testes	X																									1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma					X																					1
Hepatocellular adenoma																		Х								3
Hepatocellular adenoma, multiple				Х											Х					X						3
Histiocytic sarcoma																										1
Schwannoma malignant, metastatic,						•																				•
heart																										1
Mesentery	+								+	+																
Hemangiosarcoma	т								т	т			+								+					12
																										1
Mesothelioma malignant, metastatic,																										
testes	X												Х													2
Sarcoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Mesothelioma malignant, metastatic,																										
testes	Х												X													2
Acinus, adenoma		Х						Х	Х			Х						Х					Х			7
Acinus, adenoma, multiple					X													•					•		X	2
Pharynx																									^	1
Palate, squamous cell papilloma																										_
Salivary glands		_4	_1		.1		٠,								,	,										1
Fibroma	+	т	т	Т	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach																	,	X								1
	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Mesothelioma malignant, metastatic,																										
testes	X																									1
Squamous cell papilloma									Х																	2
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic,																		•	•	٠		•	•	٠	•	-
testes	x																									1
Tongue	^																									1
																										1

<sup>&</sup>lt;sup>a</sup> Volumes are given as 500 mg dichloromethane/kg body weight in mL corn oil/kg body weight.

TABLE D2		
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Dichloromethane in Co	rn (	Oil:
2.5 mL/kg (continued)		

2.5 mL/kg (continued)																												
	1	_	3	3	3	4	5	5	5	5	5	6	6	6	6	6	6	6	6	6	6	6	6	7	7	$\overline{}$	7	
Number of Days on Study	3			_			7	7		9		0								7								
Number of Days on Study	2					3	2		5	5										1								
			_	_	,		_	•		<i>-</i>	•		_		_		_	-			3	_	_					
	1		2	1	1	1	1	2	1	1	1	1	1	2	1	1	1	2	1	1	1	1	1	1	. 1		1	
Carcass ID Number	7	(	0	8	6	4	4	0	3	7	2	1	1	0	8	1	8	0	1	8	3	6	2	2	2	2 :	5	
	5	:	5	1	1	5	1	3	5	4	5	4	5	1	5	3	4	4	2	2	4	5	1	4	2	: :	5	
				_			_	_			_	_	_		_	_	_		_	_	_			_	_	_		
Cardiovascular System			_	_	_		1	_			_	_	_	_	_	_	_	_	_	_	_	_	_			L	_	
Heart	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	_	•	_		+	
Schwannoma malignant																											X	
Endocrine System		_																										
Adrenal gland	+	-	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	
Adrenal gland, cortex	+	-	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+ -	+	
Adrenal gland, medulla	+	-	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+ .	+	
Pheochromocytoma benign													X				X					Х		X		K		
Bilateral, pheochromocytoma benign																			X									
Islets, pancreatic	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+		+	+	
Adenoma										X			X			X					X							
Parathyroid gland	+	+	+	+	M	M	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	M	1 +		+	+	
Pituitary gland	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		- +				
Pars distalis, adenoma				X				X			X			X		X		X			X			X		K		
Thyroid gland	+	-			+	M	+		+	+	+	+	+	+	+	+	+	+		+		+	+	. +			A	
C-cell, adenoma				•	-		-		-														X					
Follicular cell, adenoma																												
Follicular cell, carcinoma											X												Х					
None																												
None			_	_	_	_		_	_		_		_	_		_		_	_		_	_			_			
Genital System		_	_	_	_	_		_	_		_		_	_		_		_	_		_			_	_			
Genital System Epididymis	+	<u> </u>	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	- +	-	+	+	
Genital System  Epididymis  Mesothelioma malignant, metastatic,	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	- +		+	+	
Genital System  Epididymis  Mesothelioma malignant, metastatic, testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	- +	-	+	+	
Genital System  Epididymis  Mesothelioma malignant, metastatic, testes  Preputial gland	+	- +	+	+	+	+	+	+ M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	- +		+	+	
Genital System  Epididymis  Mesothelioma malignant, metastatic, testes  Preputial gland  Adenoma	+	+ +	+	+	+	+	+	+ M	+	+	+	+	+ +	+	+	+	+ *	+	+	+	+	+	+	- +		+ + X	+	
Genital System  Epididymis  Mesothelioma malignant, metastatic, testes  Preputial gland  Adenoma  Bilateral, adenoma	+	 + -	+	+	+	+	+	+ M	+	+	+	+	+ + x	+	+	+	+ *	+	+	+	+	+	+	- +			+	
Genital System  Epididymis  Mesothelioma malignant, metastatic, testes  Preputial gland  Adenoma  Bilateral, adenoma  Prostate	+	+	+ +	+ +	+ +	+ +	+ +	+ M +	+ +	+ +	+ +	+ +	+ + X +	+ +	+ +	+ +	+ *	+ +	+	+ +	+	+ +	+ +	- + - +			+ + + + + + + + + + + + + + + + + + + +	
Genital System  Epididymis  Mesothelioma malignant, metastatic, testes  Preputial gland  Adenoma  Bilateral, adenoma  Prostate Seminal vesicle	+ + + + +	+	+ + ++	+ + +	+ + + +	+ + +	+ + +	+ M + +	+ + + +	+	++	+ + +	+	+ + +	+ + +	+ + +	+	+	+ + +	+ + + +	+ + +	+ + + +	+	- + - +	; + •	x + +	+ +	
Genital System  Epididymis Mesothelioma malignant, metastatic, testes Preputial gland Adenoma Bilateral, adenoma Prostate Seminal vesicle Testes	+ + + + + + + + + + + + + + + + + + + +	+	+ + +++	+ + + + +	+ + + + +	+ + + + +	+ + + + +	+ M + +	+ + + + +	+ + + + +	+ + + + +	+ + + + + +	+++	+++	+ + + + +	+ + + + +	+ * X + + +	+	+ + + + + + + + + + + + + + + + + + + +	+ + + + + + + + + + + + + + + + + + + +	+ + + +	+ + + + + +	+	- + - + - +	; + •		+ +	
Genital System  Epididymis Mesothelioma malignant, metastatic, testes Preputial gland Adenoma Bilateral, adenoma Prostate Seminal vesicle Testes Histiocytic sarcoma	+ + + + + + + + + + + + + + + + + + + +	+	+ + ++	+ + + + +	+ + + + +	+++	+++	+++	+++	+++	++++		+	+++			+++	++++		+ + + + + + + + + + + + + + + + + + + +	+ + +	+ + + + + + + + + + + + + + + + + + + +	+ + + + + + + + + + + + + + + + + + + +	- + - + - +	; ;	+ + +	+ + +	
Genital System  Epididymis Mesothelioma malignant, metastatic, testes Preputial gland Adenoma Bilateral, adenoma Prostate Seminal vesicle Testes Histiocytic sarcoma Bilateral, interstitial cell, adenoma	+ + + + + + +	+++++	+ + +++	+ + + + +	+ + + + +	+++	+ + + + X	+++	+++	+	++++		+ + X	+++	+ + + + X		+	++++	х	+ + + + X			+++++++++++++++++++++++++++++++++++++++		; ; ;	x + +	+ + +	
Genital System  Epididymis Mesothelioma malignant, metastatic, testes Preputial gland Adenoma Bilateral, adenoma Prostate Seminal vesicle Testes Histiocytic sarcoma	+ + + + + + + + + + + + + + + + + + + +	+ + +	+ + +++	+ + + + +	+ + + + +	+++	+++	+++	+++	+++	++++		+++	+++			+++	++++	х	+ + + X	+ + + + X		+ + + + + + + + + + + + + + + + + + + +	- + - + - + + +	; ; ;	+ + +	+ + +	
Genital System  Epididymis Mesothelioma malignant, metastatic, testes Preputial gland Adenoma Bilateral, adenoma Prostate Seminal vesicle Testes Histiocytic sarcoma Bilateral, interstitial cell, adenoma Interstitial cell, adenoma	+ + + + + +	+ + + +	+ + +++	+ + + + +	+ + + + +	+++	+++	+++	+++	+++	++++		+ + X	+++			+++	++++	х	+ + + + X			+ + + + + + + + + + + + + + + + + + + +		; ; ;	+ + +	+ + +	
Genital System  Epididymis Mesothelioma malignant, metastatic, testes Preputial gland Adenoma Bilateral, adenoma Prostate Seminal vesicle Testes Histiocytic sarcoma Bilateral, interstitial cell, adenoma Interstitial cell, adenoma	+ + + + +	++++	+ + +++	+ + + + +	+ + + + +	+++	+++	+++	+++	+++	++++		+ + X	+++			+++	++++	х	+ + + + X			+ + + + + + + + + + + + + + + + + + + +		; ; ;	+ + +	+ + +	
Genital System  Epididymis  Mesothelioma malignant, metastatic, testes  Preputial gland  Adenoma  Bilateral, adenoma  Prostate  Seminal vesicle  Testes  Histiocytic sarcoma  Bilateral, interstitial cell, adenoma  Interstitial cell, adenoma	+ + + + + + + + + + + + + + + + + + + +	- + + +	+ + +++	+ + + + + +	+ + + + + +	+++	+++	+++	+++	+++	++++		+ + X X	+ + +	x		+++	++++	х	+ + + + X			+ + + + + + + + + + + + + + + + + + +		; ; ;	+ + +	+ + +	
Genital System  Epididymis  Mesothelioma malignant, metastatic, testes  Preputial gland  Adenoma  Bilateral, adenoma  Prostate  Seminal vesicle  Testes  Histiocytic sarcoma  Bilateral, interstitial cell, adenoma  Interstitial cell, adenoma  Hematopoietic System  Blood	+ + + + + + + + + + + + + + + + + + + +	+ + + +	+ + +++	+ + +++	+ + + + + +	+++	+++	+++	+++	+++	++++		+ + X X	+ + +	x		++++	++++	х	+ + + + + X			+ + + + + + + + + + + + + + + + + + +		; ; ;	+ + +	+ + +	
Genital System  Epididymis Mesothelioma malignant, metastatic, testes Preputial gland Adenoma Bilateral, adenoma Prostate Seminal vesicle Testes Histiocytic sarcoma Bilateral, interstitial cell, adenoma Interstitial cell, adenoma  Hematopoietic System Blood Bone marrow Histiocytic sarcoma	+ + + + + + + + + + + + + + + + + + + +	- + + + +	+ + +++	+ + +++	+ + +++	+++	+++	+++	+++	+++	++++	*	+ + + X X X + X	+ + +	+	+	+ + X	+ + + X	×	+ + + + X	+		· + · + · · + · · · + · · · · · · · · ·		; ; ;	+ + +	+ + +	
Genital System  Epididymis  Mesothelioma malignant, metastatic, testes  Preputial gland  Adenoma  Bilateral, adenoma  Prostate  Seminal vesicle  Testes  Histiocytic sarcoma  Bilateral, interstitial cell, adenoma  Interstitial cell, adenoma  Hematopoietic System  Blood  Bone marrow  Histiocytic sarcoma  Lymph node	+ + + + + + + + + + + + + + + + + + + +	+ + + +	+ + +++	+ + + + + + + + + + + + + + + + + + + +	+ + + + + + +	+++	+++	+++	+++	+++	++++	*	+ + + X X X + X	+ + +	+	+	+ + X	+ + + X	×	+	+		+ + + + + + + + + + + + + + + + + + +		; ; ;	+ + +	+ + +	
Genital System  Epididymis Mesothelioma malignant, metastatic, testes Preputial gland Adenoma Bilateral, adenoma Prostate Seminal vesicle Testes Histiocytic sarcoma Bilateral, interstitial cell, adenoma Interstitial cell, adenoma  Hematopoietic System Blood Bone marrow Histiocytic sarcoma Lymph node Mediastinal, mesothelioma malignant,	+ + + + + + + + + + + + + + + + + + + +	+ + + +	+ + +++	+ + +++	+ + + + + +	+++	+++	+++	+++	+++	++++	*	+ + + X X X + X	+ + +	+	+	+ + X	+ + + X	×	+	+		· + · + · · + · · · · · · · · · · · · ·		; ; ;	+ + +	+ + +	
Genital System  Epididymis Mesothelioma malignant, metastatic, testes Preputial gland Adenoma Bilateral, adenoma Prostate Seminal vesicle Testes Histiocytic sarcoma Bilateral, interstitial cell, adenoma Interstitial cell, adenoma  Hematopoietic System Blood Bone marrow Histiocytic sarcoma Lymph node Mediastinal, mesothelioma malignant, metastatic, testes	+ + + + + + + + + + + + + + + + + + + +	- + + + +	+ + +++	+ + +++	+ + + + + + + + +	+++	+++	+++	+++	+++	++++	*	+ + + X X X + X	+ + +	+	+	+ + X	+ + + X	×	+	+		· + · + · · + · · · · · · · · · · · · ·		; ; ;	+ + +	+ + +	
Genital System  Epididymis  Mesothelioma malignant, metastatic, testes  Preputial gland  Adenoma  Bilateral, adenoma  Prostate  Seminal vesicle  Testes  Histiocytic sarcoma  Bilateral, interstitial cell, adenoma  Interstitial cell, adenoma  Hematopoietic System  Blood  Bone marrow  Histiocytic sarcoma  Lymph node  Mediastinal, mesothelioma malignant, metastatic, testes  Lymph node, mandibular	+ + + + + + + + + + + + + + + + + + + +	- + + + + +	+ + +++	+ + +++	+ + +++	+++	+++	+++++	+++	+++	++++	*	+ + + X X X + X	+ + +	+	+	+ + X	+ + + X	×	+	+		· + · + · · + · · · · · · · · · · · · ·		; ; ;	+ + +	+ + +	
Genital System  Epididymis Mesothelioma malignant, metastatic, testes Preputial gland Adenoma Bilateral, adenoma Prostate Seminal vesicle Testes Histiocytic sarcoma Bilateral, interstitial cell, adenoma Interstitial cell, adenoma  Hematopoietic System Blood Bone marrow Histiocytic sarcoma Lymph node Mediastinal, mesothelioma malignant, metastatic, testes	+ + + + + + + + + + + + + + + + + + + +	- + + + + +	+ + +++	+ + +++	+ + +++	+++	+ + + + X + + + +	+++++	+++	+++	++++	*	+ + + X X X + X	+ + + + + + + + + + + + + + + + + + + +	+	+	+ + X	+ + + X	×	+	+		· + · · + · · · · · · · · · · · · · · ·		; ; ;	+ + +	+ + +	

のでは、「「「「「」」というでは、「「」」というでは、「「」」というでは、「」」というでは、「」」というでは、「」」というでは、「」」というでは、「」」というでは、「」」というでは、「」」というでは、「」」というでは、「」 「「」」というでは、「」

TABLE D2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Dichloromethane in Corn Oil: 2.5 mL/kg (continued)

	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
Jumber of Deug on Study	2		3		3	-		3	3	3	3		3	3	3	3	3	3	3	3	3	3	3	3	3	
lumber of Days on Study	_	6	1		1				1	1	4	4	4	4		4		4	4	4	4	4	4		4	
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	2	Tota
Carcass ID Number	4	8	1	2	3	3	3	7	7	7	4	4	5	5		5			6		9	9	9		0	Tiss
	4	3	1					1	2	3	2	3	1	2	3				4	1	2	3	4	5	2	Tum
Cardiovascular System	-					-										_				_						
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma malignant																										1
Endocrine System									_							_				_					_	
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Pheochromocytoma benign											X	Х							Х		Х			Х		10
Bilateral, pheochromocytoma benign																X						Х				3
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Adenoma	,	,	•	-	-		-	•		•	X	-	-	•	-		-	٠,	•	•	-	-		•	•	5
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	44
Pituitary gland	<u>.</u>	+		+	+	+	+	+	+	+	+	+	+	+	+	+	÷	+	+	+	+	+	+		+	
Pars distalis, adenoma		Ý	×	•	Ÿ	x	'	'	x	•	Ÿ	x	Ÿ	•		x	'	'		•	•	•	Ý	X		20
Thyroid gland	+						+	_	+	+	+	+		+	+	+	_	_	_		_	+			· +	
C-cell, adenoma		т	•		т	т	т	+ X	т	т	_	_	+	т	_		т	_	+	Ŧ	т	т	т	_		
Follicular cell, adenoma			X					^					X		v	X			X							6
															X				А					Х		3
Follicular cell, carcinoma						-																		-		2
Follicular cell, carcinoma  General Body System  None																_										2
Follicular cell, carcinoma  General Body System  None  Genital System	м														_		<del>-</del>		_	_		_				
Follicular cell, carcinoma  General Body System None  Genital System Epididymis Mesothelioma malignant, metastatic,	М	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			- +	. 49
Follicular cell, carcinoma  General Body System None  Genital System Epididymis Mesothelioma malignant, metastatic, testes				+	+	+	+	+	+	+	+	+	+ x	+	+	+	+	+	+	+	+	+	+	. +		49
Follicular cell, carcinoma  General Body System None  Genital System Epididymis Mesothelioma malignant, metastatic, testes Preputial gland	M +	+	+	+	+	+ +	+	+	+ +	+	+	+ M	+ X +	+	+	+ +	+	+	+	+	+	+	+	. +	. +	. 49 1 48
Follicular cell, carcinoma  General Body System None  Genital System Epididymis Mesothelioma malignant, metastatic, testes Preputial gland Adenoma			+	+	+ +	+	+ +	+ +	+ +	+ + x	+ +	+ M		+	+ + X	+ +	+ +	+	+ +	+	+	+ + X	<del></del> +	. +	. +	. 49 1 48 6
Follicular cell, carcinoma  General Body System None  Genital System Epididymis Mesothelioma malignant, metastatic, testes Preputial gland Adenoma Bilateral, adenoma		+	+	+	+ +	+ +	+ +	+ +	+ +	+ *	+ +	+ M		+	+	+ +	+ +	+	+ +	+ +	+	+ + X	+	. +	· +	. 49 1 48
Follicular cell, carcinoma  General Body System None  Genital System Epididymis Mesothelioma malignant, metastatic, testes Preputial gland Adenoma Bilateral, adenoma Prostate		+	+	+ +	+ + +	+ +	+ + +	+ + +	+ +	+ + x +	+ + +	+ M +		+ +	+	+ + +	+ + +	+ + +	+ + +	+ +	+ +	+ + X	+ + +	. +	. +	. 49 1 48 6 1
Follicular cell, carcinoma  General Body System None  Genital System Epididymis Mesothelioma malignant, metastatic, testes Preputial gland Adenoma Bilateral, adenoma Prostate Seminal vesicle		+	+	+ + +	+ + +	+ + +	+ + +	+ + +	+ + +	+ * X + +	+ + +	+ M + +		+ + +	+	+ + +	+ + +	+ + +	+ + + +	+ + +	+ + +	+ * *	+ + + +	. +	. +	. 49 1 48 6
Follicular cell, carcinoma  General Body System None  Genital System Epididymis Mesothelioma malignant, metastatic, testes Preputial gland Adenoma Bilateral, adenoma Prostate Seminal vesicle Testes		+	+	+ + + + + + + + + + + + + + + + + + + +	+ + + + + + + + + + + + + + + + + + + +	+ + + + + + + + + + + + + + + + + + + +	+ + + + + + + + + + + + + + + + + + + +	+ + + + + + + + + + + + + + + + + + + +	+ + ++	+ + x + + + + + + + + + + + + + + + + +	+ + + + + + + + + + + + + + + + + + + +	+ M + + +		+ + + + + + + + + + + + + + + + + + + +	+	+ + +++	+ + ++	+ + + + + + + + + + + + + + + + + + + +	+ + + + + + + + + + + + + + + + + + + +	+ + +++	+ + + + + + + + + + + + + + + + + + + +	+ + X + + + + + + + + + + + + + + + + +	+ + + + + + + + + + + + + + + + + + + +	. +	· +	. 49 1 48 6 1
Follicular cell, carcinoma  General Body System None  Genital System Epididymis Mesothelioma malignant, metastatic, testes Preputial gland Adenoma Bilateral, adenoma Prostate Seminal vesicle Testes Histiocytic sarcoma		+	+	+ + + + + + + + + + + + + + + + + + + +	+ + + + + +	+ + + + +	+ + + + + +	+ + + + + + + + + + + + + + + + + + + +	+ + + + + + + + + + + + + + + + + + + +	+++	+++	+++	++++	+++	+ + X + + +	+ + ++	+ + ++	+ + ++	+ + + + +	+ + +++	+ + + + +	+++	+			1 48 6 1 50 50 50 1
Follicular cell, carcinoma  General Body System None  Genital System Epididymis Mesothelioma malignant, metastatic, testes Preputial gland Adenoma Bilateral, adenoma Prostate Seminal vesicle Testes		+ X + +	+ + + X	+ + + X	+ + + + X	+ + + + x		+ + + X	+ + + + x	+++	+++	+++	++++	+++	+ + X + +	+ + + x	+ + + X	+ + + x	+ + + x	+ + + + X	+ + + X	+++	+		· + · + · · + · · · · · · · · · · · · ·	1 48 6 1 50 50 50 1
Follicular cell, carcinoma  General Body System None  Genital System Epididymis Mesothelioma malignant, metastatic, testes Preputial gland Adenoma Bilateral, adenoma Prostate Seminal vesicle Testes Histiocytic sarcoma Bilateral, interstitial cell, adenoma Interstitial cell, adenoma	+ + + +	+ X + +	+ + + X	+ + + X	+ + + + X			+ + + X		+++	+++	+++	++++	+++	+ + X + +	+ + + + X	+ + + X	+ + + x	+ + + X	+ + + + X	+ + + X	+++	+			1 48 6 1 50 50 50 1 36
Follicular cell, carcinoma  General Body System None  Genital System Epididymis Mesothelioma malignant, metastatic, testes Preputial gland Adenoma Bilateral, adenoma Prostate Seminal vesicle Testes Histiocytic sarcoma Bilateral, interstitial cell, adenoma Interstitial cell, adenoma	+ + + +	+ X + +	+ + + X	+ + + X	+ + + X			+ + + X		+++	+++	+++	++++	+ + X	+ + X + +	+ + + + X	+ + + X	+ + + + X	+ + + x	+ + + + x	+ + + + + X	+++	+			1 48 6 1 50 50 50 1 36 7
Follicular cell, carcinoma  General Body System None  Genital System Epididymis Mesothelioma malignant, metastatic, testes Preputial gland Adenoma Bilateral, adenoma Prostate Seminal vesicle Testes Histiocytic sarcoma Bilateral, interstitial cell, adenoma Interstitial cell, adenoma	+ + + +	+ X + +	+ + + X	+ + + + X	+ + + + + X			+ + + + + X		+++	+++	+++	++++	+++	+ + X + +	+ + + + X	+ + + X	+ + + + x + + x	+ + + + x	+ + + + X ++	+ + + + X	+++	+			49 1 48 6 1 50 50 50 1 36 7
Follicular cell, carcinoma  General Body System None  Genital System Epididymis Mesothelioma malignant, metastatic, testes Preputial gland Adenoma Bilateral, adenoma Prostate Seminal vesicle Testes Histiocytic sarcoma Bilateral, interstitial cell, adenoma Interstitial cell, adenoma  Hematopoietic System Blood Bone marrow	+ + + +	+ X + +	+ + + X	+ + + + + X	+ + + + X			+ + + + X		+++	+++	+++	++++	+ + X	+ + X + +	+ + + + x +	+ + + X	+ + + + x +	+ + + + + x + + x	+ + + + X + +	+ + + + + X + + +	+++	+			49 1 48 6 1 50 50 1 36 7
Follicular cell, carcinoma  General Body System None  Genital System Epididymis Mesothelioma malignant, metastatic, testes Preputial gland Adenoma Bilateral, adenoma Prostate Seminal vesicle Testes Histiocytic sarcoma Bilateral, interstitial cell, adenoma Interstitial cell, adenoma  Hematopoietic System Blood Bone marrow Histiocytic sarcoma	+ + + + X	+ X + +	+ + + X	+ + + + + X	+ + + + + X + +			+ + + + X + +		+++	+++	+++	++++	+ + X	+ + X + +	+ + + + x - + ±	+ + + + x	+ + + + X + ±	+ + + + x + ±	+ + + + X + +	+ + + + + X + + +	+++	+			49 1 48 6 1 50 50 50 1 36 7
General Body System None  Genital System Epididymis Mesothelioma malignant, metastatic, testes Preputial gland Adenoma Bilateral, adenoma Prostate Seminal vesicle Testes Histiocytic sarcoma Bilateral, interstitial cell, adenoma Interstitial cell, adenoma  Hematopoietic System Blood Bone marrow Histiocytic sarcoma Lymph node Mediastinal, mesothelioma malignant,	+ + + X	+ X + + + + + + + + + + + + + + + + + +	+ + + X	+ + + + + X	+ + + + + + X + +			+ + + + + X + +		+++	+++	+++	++++	+ + X	+ + X + +	+ + +++ x + +	+ + + + x + +	+ + + + + X + +	+ + + + + x x + +	+ + + + x + +	+ + + + + X + + +	+++	+			1 48 6 1 50 50 1 36 7 3 50 1 50
General Body System None  Genital System Epididymis Mesothelioma malignant, metastatic, testes Preputial gland Adenoma Bilateral, adenoma Prostate Seminal vesicle Testes Histiocytic sarcoma Bilateral, interstitial cell, adenoma Interstitial cell, adenoma  Hematopoietic System Blood Bone marrow Histiocytic sarcoma Lymph node Mediastinal, mesothelioma malignant, metastatic, testes	+ + + X	+ X + + + + + + + + + + + + + + + + + +	+ + + X	+ + + + X	+ + + + + X + +			+ + + + X + +		+++	+++	+++	++++	+ + X	+ + X + +	+ + +++ x + +	+ + + + x + +	+ + + + X + +	+ + + + + x + +	+ + + + + + + + + + + + + + + + + + +	+ + + + + X + + +	+++	+			49 1 48 6 1 50 50 50 1 36 7
Follicular cell, carcinoma  General Body System None  Genital System Epididymis Mesothelioma malignant, metastatic, testes Preputial gland Adenoma Bilateral, adenoma Prostate Seminal vesicle Testes Histiocytic sarcoma Bilateral, interstitial cell, adenoma Interstitial cell, adenoma  Hematopoietic System Blood Bone marrow Histiocytic sarcoma Lymph node Mediastinal, mesothelioma malignant, metastatic, testes Lymph node, mandibular	+ + + X + + X	+ X + + + + + + + + + + + + + + + + + +	+ + + X	+ + + + + X + + + + + + + + + + + + + +	+ + + + + + + + + +			+ + + + + + + + + + +		+++	+++	+++	++++	+ + X	+ + X + +	+ + +++ x + + +	+ + + + + + + + + + + +	+ + + + + + + + +	+ + + + + + + + + + +	+ + +++ x ++++++++++++++++++++++++++++	+ + + + + + + + + + +	+++	+		· +	49 1 48 6 1 50 50 50 1 36 7
General Body System None  Genital System Epididymis Mesothelioma malignant, metastatic, testes Preputial gland Adenoma Bilateral, adenoma Prostate Seminal vesicle Testes Histiocytic sarcoma Bilateral, interstitial cell, adenoma Interstitial cell, adenoma  Hematopoietic System Blood Bone marrow Histiocytic sarcoma Lymph node Mediastinal, mesothelioma malignant, metastatic, testes	+ + + X	+ X + + + + + + + + + + + + + + + + + +	+ + + X	+ + + + + + + + + + + + + + + + + + +	+ + + + + + + + + + + + + + + + + + +			+ + + + + + + + + + + + + + + + + + +		+++	+++	+++	++++	+ + X	+ + X + +	+ + +++ x + + ++	+ + + + + + + + + + + + + + + + + + +	+ + + + + + + + + + + + + + + + + + +	+ + + + + + + + + + + + + + + + + + +	+ + +++ x ++ ++	+ + + + + + + + + + + + + + + + + + +	+++	+			49 1 48 6 1 50 50 50 1 36 7

TABLE D2				. •				100	٠.
<b>Individual Animal Tumor Patholog</b>	y of Male Rats in	the 2-Year Ga	ivage	Study of	Dichlor	omethane	in	Corn	Oil:
2.5 mL/kg (continued)		•				*		. •	

2.5 mL/kg (continued)										-																•			
Number of Days on Study		1 3 2	3 0 9	3 5 2	3 8 5		5 7 2	5 : 7 : 8 :	5 5 9 9 5 5	_	6 0 5	6 0 5	6 0 5	6 1 0	2	6 2 6	6 3 8	6 5 7	6 7 1	6 7 3	6 8 0	6 9 9	7 0 1	7 1 4	7 2 2				·:
Carcass ID Number	-	1 7 5	2 0 5	1 8 1	1 6 1	4	4	2 : 0 : 3 :	1 1 3 7 5 4	1 1 7 2 1 5	1 1 4	1 1 5	2 0 1		1	1 8 4	2 0 4	1 1 2	1 8 2	1 3 4	1 6 5	1 2 1	1 2 4	1 2 2	1 5 5		. :		
Hematopoietic System (continued) Spleen Hemangiosarcoma Histiocytic sarcoma Mesothelioma malignant, metastatic, testes Thymus Histiocytic sarcoma		+	+	+	+	+ + +	+ X +	+	+ -	+ +	+	+ x + x	М	+	+ : M	+	+ +	+ +	+	+ +	+	+	+	+ M	<b>A</b>			34.1.	
Integumentary System  Mammary gland Fibroadenoma Skin Basal cell carcinoma Squamous cell carcinoma Squamous cell papilloma Subcutaneous tissue, fibroma		+	M +	+	+ + + 3 3 3	M +	+	+	+ -	+ M + +	1 M	+ +	+	+ +	+	+	+ +	+ +	+ +	+ + X	+	+ X +	+	+ + X	M +				
Musculoskeletal System  Bone Skeletal muscle Mesothelioma malignant, metastatic, testes	,	+	+	+	+	+	+	+	+ -	+ +	+	+	+	+	+	+	+	+	†	+	+	+	+	+	+				•
Nervous System Brain		+	+	+	+	+	÷	+	+ •	+ +	. +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	13	1 ,		
Respiratory System  Lung Alveolar/bronchiolar adenoma Histiocytic sarcoma Mesothelioma malignant, metastatic, testes Osteosarcoma, metastatic, uncertain primary site Sarcoma, metastatic, uncertain primary site		+	+	+	+	+ x	+	+ X	+ X	+ +	- +	+ X	+	+	+	+	+	+	+	+	**************************************	+	+ X	+ * * * * * * * * * * * * * * * * * * *	<b>+</b> .				5.
Nose Trachea		+	+	+	+	+	+	+	+ -	+ +	- +	· +	+	+	+	+	+	+	+	+	+	+	+	+	+		٠.		
Special Senses System  Ear  Sarcoma  Eye	•	-		+			+ x									•			,									,	
Urinary System Kidney Urinary bladder Mesothelioma malignant, metastatic, testes		+	++	+	+	+ +	+ +	+ +	+ -	+ +	+ +	- +	++	+ +	+	+ +	+ +	+ +	++	++	+	+	+	+	+				

TABLE D2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Dichloromethane in Corn Oil:
2.5 mL/kg (continued)

2 3 1 4	2 6 1 8 3 +	3 1 1 1	1 2	1 1 3	1 1 3 3	3 3	3 : 1 1 7	3 : 1 7	3 1 1 7	3 : 4 : 1 : 4 :	3 4 1 4	7 7 7 3 3 4 4 4 4 5 5 5 5 1 2	1 1 1 5 5	3 3 4 4 1 1	1 2	7 7 7 3 3 4 4 4 4 4 6 6 6 6 6 6 6 6 6 6 6 6 6	1 1 5	1 6	7 3 4 1 9 1	7 3 4 1 9 2		4	3 4 1 9	3 4 1	2 0	Total Tissues Tumor
3 1 4 4 + X +	6 1 8 3 +	1 1 1	1 2	1 1 3	1 1 3 3	l 1 l 1 3 7	1 7	1 7	1 1 7	1 4	1	1 1 5 5	1 1	1 1 5 5		1 1 6 6	l 5	1 6	1 9	1 9		1	4 1 9	4 1 9	2 0	Tissue: Tumor
1 4 4 + X +	1 8 3 +	1 1	1 2	1 3	1 3 3	1 1	1	1 7	1 7	1 4	1	1 1 5 5	1 1	1 1		1 1	l 5	1	1 9	1 9		1	1	1 9	2 0	Tissue: Tumor
4 4 + X +	+ +	1	2	3	3 3	3 7	7	7	7	4	4	5 5	5 5	5 5	•	6 6	5	6	9	9		9	9	9	0	Tissue: Tumor
4 4 + X +	+ +	1	2	3	3 3	3 7	7	7	7	4	4	5 5	5 5	5 5	•	6 6	5	6	9	9		9	9	9	0	Tissue: Tumor
+ X +	+	+	+ +	+	+	+ -	+	+	+	+		-						+	+						-	Tumor
+	+ +	+	+	+	+	+ -	+	+	+	+	+	+	+ -	+ -	+	+	+	+	+	+	+	+	+	+	+	40
+	+	+	+	+	+	+ -	+	+	+	+	+	+ -	<del>t.</del> •	+ -	+	+ ·	+	+	+	+	۲	+	+	+	+	40
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+	+	+	+	+	+	+ -	+	+	+	+	+	+	+	+ -	+	+	+	+	+	<b>T</b>	+	+	+	<b>+</b>	+	30 49
	•	'	•	•	•	•		•	•	•		•	•	'	•	•	•	Τ'	_	т	•	T	т.	т		. 49
x																		•								1
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TABLE D2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Dichloromethane in Corn Oil: 2.5 mL/kg (continued)

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

### Lesions in Male Rats

Table D2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Dichloromethane in Corn Oil: 2.5 mL/kg (continued)

Number of Days on Study	2		3	7 3 1		-				3	3	3		3	3	3	3	3	3				7 3 4		•	
Carcass ID Number	•	1 8 3	-	1 2 3	_	1 3 2	-				-		1 5 1	_	-				-	1 9 1	-	-	-	1 9 5	2 0 2	Total Tissues/ Tumors
Systemic Lesions  Multiple organs  Histiocytic sarcoma	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	- +	+	+	50 1
Leukemia mononuclear Mesothelioma malignant	x	X	X						X				x	X						X	X			X	X	13 2

Table D2				,
<b>Individual Animal Tumor Pat</b>	hology of Male Rats in	the 2-Year Gavage	Study of Dichlorometh	nane in Corn Oil:
5.0 mL/kg				And the second

5.0 mL/kg									•																		
	-	1	3	3	4	5	5	5 5	5	6	6	6	6	6 6	6	7	7	7	7	7	7	. 7	7	7			
Number of Days on Study	•	5	2	2	8	3	7 - 8	8 8	8	1	4	4	7 8	8 8	3 9	0	0	1	1	2	2	3	3	3			
		5	3	7	4	6	0 - (	0 0	5	5	3	7	3	2 2	2	1	4	0	7	1	8	0	0	0	٠.		
		2	, <u>2</u>	2	3	2	2	2 2	2	2	2	2	2	2 2	2 2	2	2	3	2	2	2	2	2	2			
Carcass ID Number		. 4	1 -	4	0	2	8 . '	7 7	. 9	3	·9	6	8 :	5 9	2	2	6	0	8	1	Ś	1	1	1		100	
our cass 15 (vamoer			2	5			_	4 5		5	5	5	_	5 2				-	3	1	4	3	4	5			
Alimentary System		_																					_				
Esophagus			+	+	4	+	4	+ +		_	+	4.	4.	4		- 4			+	· +	·	+	_	<b>+</b> '	·	* 1	
Intestine large			1	i	<u>.</u>	<u>.</u>	<u>.</u>	 	. <u>.</u>	i	i	i	<u>.</u>					. 🛦	·			·	· i	Ĺ			
		- 1	1		1	1	1.			- 1	. 1	1.	1				Ā		· · · ·		-1	- 1	er Oto	Ţ			
Intestine large, cecum			+	+	+	+	+	+ +	- +	+	+	+	+	+ -	• 1	7	· A	A	+	+	+	+	+	+	31		
Intestine large, colon	•	•	+	+	+	+	+	+ +	- +	•+	+	+.	+	+ •	+ 1	+	- +	· A	+	+	+	+	+	+ .	7		
Mesothelioma malignant, metastatic, testes								X											si		. 1						
Intestine large, rectum			- 1	_		٠ ـــ	<u>.</u>		- M	1	_	_	_	<u>.</u>		_ 4	. Δ	A	٠.	_	4	-1	_	4			
Intestine small		1	1		т.	Ι.	i.	<u>.</u> .			i	į.	i.	<u>.</u> .	 L .				Ĺ	i	i		ı	i.	<i>"</i>	· .	
			•	_	Τ.	Τ.	Ŧ '	T T	- <del>-</del>	T.	<b>T</b>	T.	T:	•			7	^	т.	T.	T .		7	. •		1	
Intestine small, duodenum		+	+	+	+	+	+	+ +	- +	+	+	+	+	+ -	•	+	•	A	+	.+	+	+	. 🕇	+	1. 1.		
Intestine small, ileum	`	+	+	+	+	+	+	+ +	+	+	+	+	+	+ .	+ +	+	- A	-		+	+	+	+	+		\$ 12.00	
Intestine small, jejunum	`	+	+	+	+	+	+	+ +	- +	+	+	+	+	+ -	+ ,+	+ +	· A	A	. +	+	+	+	+	.+.	. :	. ,	
Liver		+	+	٠+	+	+	+.	+ +	- +	+	+	+	+	+ -	+ +	+ +	- +	+	+	+	, <b>+</b>	+	+	+		٠.	
Hepatocellular adenoma							•			X									X				, ×.	. :		40.00	
Mesentery							+	+			+		•	+						, ' '			+		,		
Mesothelioma malignant, metastatic,																			1		:	٠,٠	, ·	٠.			
testes								χ .												. •			٠.		. 7.		
Pancreas								^	٠,												٠.		٠.				,
		+	+	+	+	+	+	+ +	- +	7	17.	*		T : .	r 7	r 7	٠ ٦	•		. •				Τ,	· ,		
Mesothelioma malignant, metastatic, testes								x												•	٠.		. •			,	
Acinus, adenocarcinoma																Χ	ζ.				:	, .	٠				
Acinus, adenoma														X X	ĸ					X		٠.	•			,	
Acinus, adenoma, multiple															_		٠.			- :		,		3.5		, i, t,	
									•					٠.					٠		. *					•	
Pharynx												v													٠.		
Palate, squamous cell papilloma		٠.										X					٠.	٠	٠٠,	٠.							
Salivary glands		+	+	+	+	+	+	+ +	+	+	+	+	+	+ .	+ +	+ +	- +	+	+	. +	+	+	+	+			
Stomach		. +	+	+	· +	+	+	+ +	+ +	• +	+	+	+	+ .	+ -	+ +	- +	. +	+	+	+	+	+	+			:
Stomach, forestomach		+	+	•+	+	+	+ •	+ +	+ +	+	+	+	+	+ .	+ -	+ +	- 4	- +	· +	+	+	+	+	+ '	÷.		,
Mesothelioma malignant, metastatic,																			-:	10	787	100	.:		2		
testes								X										•		-		•			`		
Squamous cell papilloma														X							٠.				;		
Stomach, glandular		_	_	_	_	· 🚣 ·			٠.	. 4	_	į.	4.	<u>.                                    </u>	<b>.</b> .	L 4	- A	. 4	4		_	_	1	1	٠,		
Mesothelioma malignant, metastatic,		•	•	٠	•	•	•		•	٠.		•	•	•	•		•	•		•	٠	•	, .	•	٠.,		
								v					•						•	٠.,						i.,	
testes		_						X													<u>.</u> .		<u> </u>				
Cardiovascular System																					_		•				
Heart	,	·· +	+	+	+	. +	+	+ 4	F4 <b>+</b>	+	+	+	+	+ .	+ -	+ +	- 4	. +	+	+	+	,+	+	+			
Alveolar/bronchiolar carcinoma,	*.																					:	٠	. "		.* *	
metastatic, lung						X											٠.										
Fudanina Suntan				_	-	<del></del>	<del></del>		-		<u> </u>	_					<u>.</u>			<u> </u>					<del>.</del>		
Endocrine System						,																				•	
Adrenal gland				+	+	+	+	+ +	+	+	+	M	+	+	+ -	<b>-</b> −						+	+	+			-
Adrenal gland, cortex			+	+	+	+	+	+ +	+ +	+	+	M	+	+	+ -	+ +	- 4			+	+	+	+	+		•	
Adrenal gland, medulla		M	+	+	. +	+	+	+ +	+ +	+	+	M	+	+	+ -	+ +	- +	- M	1 +	+	· +	+	+	+		- :	
																				X	. *			1 -		., .	
Pheochromocytoma malignant						Х				X														٠.,	. :	v	
Pheochromocytoma benign						1				71							٠.	11.	4						1		
						•	*			1							٠.			· ·		 			,		

Table D2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Dichloromethane in Corn Oil: 5.0 mL/kg (continued)

	7	7	7	7	7	7	7	7 '	7	7	7 7	7	7	7	7	7	7	7	7	7	7	7	7	7	
Sumber of Days on Study	3	3	3	3	3.	3.			, 3 :		33	-	3	.3	3			3	3	3	3	3		3	
diffice of Days on Study	. 0	0	0	0	0	-	_		0	1		_	1	_	_						1		1	1	
	2		2	2	2	2	2	2 : :	2	2	2 2	2	2	2	2	2	2	2	2	2	2	3	3	3	Total
Carcass ID Number	2	2	3	-3	3	3 .	4	4	4 . :		5 5		6		7			8	8	9	9	0	0	0	Tissue
	.1	3	1	2	3	4	2	3	4	1 :	2 3	1	2	4	1	2	3	1	2	1	3	1	2	3	Tumo
limentary System		_								_	_		_												
Esophagus	+	+	+	+	+	+	+	+	+	+ -	+ - +	+	+	M	+	+	+	+	+	+	+	+	+	+	49
Intestine large	+	+	+	+	+	+	+.	+	+	+	+ +	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+ +	+	+	+	+	+	+	+	+	+	+	+	+	. +	. 48
Intestine large, colon	+	+	+	· +	+	+	+	+	+-	+	+ +	+	+	+	+	+	+	+	+	+	+	+	:+	+	49
Mesothelioma malignant, metastatic, testes																									1
Intestine large, rectum	. +	+	+	+	+	+	+	+	+.	+	+ +	- +	M	+	+	+	+	+	+	+	+	+	+	+	. 46
Intestine small		. +	+	+	+	+	<u>.</u>	+	<u>.</u>	<u>.</u>	+ +	· ·	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+.	+	+	+	+	+ +	+ +	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+.	+	+	+	+ +	· - '+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+ +	- M	1 +	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+ +	+ +	+	. +	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma									X														X		4
Mesentery	+					+					+	+	+		+										10
Mesothelioma malignant, metastatic, testes															x								٠		2
Pancreas	+	. +	+	+.	+	+	+	+ .	+	+	+ +	<b>+</b> +	+	+	+	+	+	+	+	+	+	+	+	+	- 50
Mesothelioma malignant, metastatic,	·		·	·	•		•	•	•	•	•		·	·		·	·	٠.	•	•	·		·	Ċ	,
testes															X										2
Acinus, adenocarcinoma			٠.												•				٠,						1.
Acinus, adenoma			X		v	х	v	v		x			х		X	v		v	X		v	v	37	v	6
Acinus, adenoma, multiple Pharynx				А	Λ	^	А	^		^			^			X		X			А		X	X	
Palate, squamous cell papilloma																									1 1
Salivary glands	+	. +	+	4	+	+	_	+	+	+	+ -	<b>-</b> 4		+	+	_	_	_	_	_	_	_		1	50
Stomach	+		+	+	+	+	+	+	+	+	+ +	' '	. +	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	. +	. +	. +	+	+	+	+	+	<u>.</u>	+ -	· ·		.+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic,			·		·					•			·			·		•	•	•	•	·	•	•	
testes Squamous cell papilloma				х																					1
Stomach, glandular				^								٠.											·	Ċ	2
Mesothelioma malignant, metastatic,	•	•	. 🛨	+	• 🛨	+	+	+	+	+	+ -	+	•	+	+	+	+	+	+	+	+	+	+	+	48
testes																									1
ardiovascular System			·						_						_					·-			_	_	
Heart	+	+	+	+	+	+	+ -	+	+	+	+ +	+ +	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma,				٠.																			. •		
metastatic, lung										_		:											_		1
ndocrine System																									
Advent land corter	+	+	+	+	+	+	+	+	+	+	+ 1	4 h	+	+	+	+			+	+	+	+	+	+	45
Adrenal gland, cortex Adrenal gland, medulia	+	+	+	+	+	+	+	+	+	+	+ 1	n +	+	+	+		M		+	+	+	+	+	+	45
Pheochromocytoma malignant	+	. +	+	+	+	+	+	+	+	4.	+ 1	A +	+	+	+	+	M	+	+	+	+	+		+	45
Pheochromocytoma benign	х						X											x			1	Х			2
Bilateral, pheochromocytoma malignant	^	•					^											Λ						v	5 1
Bilateral, pheochromocytoma manghant				Х																			x	X	3
bilateral, pilecentomocytoma benign				^													•						А		3

TABLE D2 Individual Animal Tumor Patholog 5.0 mL/kg (continued)	gy of Mal	e F	<b>Rat</b>	s i	n t	he	2-	Yea	ar (	Ga	vag	ge S	Stu	ıdy	of	D	ich	lor	on	net	ha	ne	in	Co	rn	Oil:	
					•																					·	
	1	3	3	4	5	5	5	5	5	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7		
	_	_	_	_									_	_													

5.0 mL/kg (continued)																											٠,		
		1	3	3	4	5	5	5	5	5	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7		 	
Number of Days on Study		5	2	2	8	3	7	8	8	8	1	4	4	7	8	8	9	0	0	1	1	2	2	3	3	3			
· · · · · · · · · · · · · · · · · · ·		5		7	4		0		0	5		3	7	3	2		2	1	4	0	7	1	8	0		0			
<del></del>		2	2	2	3	2	2	2	2	2	2	2	2	2	2	2	2	2	2	3	2	2	2	2		2		 	
Carcass ID Number		4		4	0		8	7	7	9	3	9	6	8	5.	9			6	0	8	1		1	1	1			
6								4		4						2									4	-			•
Endocrine System (continued)	<del>.</del>								_																			 	
Islets, pancreatic		_		_	_	_	_	_	_	_	_	_	_	_	_	_	_	_	_	_	_	-	_	_	_	_			•
Adenoma		'	•	'	•	'	•	'	•	•	٠	x	•	x	٠	,	•	'	•	•	'	'	'	•	'	т.			
Adenoma, multiple												1		7.							X								
Carcinoma																					Λ								
Parathyroid gland		٠.	_	_	_			1.	_	1.6	+	_	_	_	_	_		_	_	_	М			_	_				
			_ <u>_</u>	T		T	Ţ			141	· T	<i>T</i>		T	<b>+</b>	т _	т М	<b>T</b>	<b>T</b>	+	+					+			
Pituitary gland			_	+	T		т	Τ,	7	X	7	v	v	X	7	X	IAI	т	~	7	7	X	7	7	X				
Pars distalis, adenoma									х		х		Λ	Λ		Λ						Λ	,		Λ				
Pars distalis, adenoma, multiple									^		^		х																
Pars intermedia, adenoma											1.	+		+	_1_	_1.	ı		_1_	A		_	.1	_		.1.			
Thyroid gland		. +	+	+	+	+	+	+	+	v	+	+	+	4	+	+	+	+	+	A	+	+	+	+	Ť	+			
C-cell, adenoma									v	X												x			X				
C-cell, carcinoma									X													Λ			•				
Genital System																		_	_										
Epididymis		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Mesothelioma malignant, metastatic,																													
testes		_	_	_				X																		٠.			
Preputial gland		M	1 +	M	+	+	+	+	+	+	+	+	М	+	+	+	+	+	+	M	۱ +	+	+	+	+	+	•		
Bilateral, adenoma																										٠.			
Prostate		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+			
Seminal vesicle		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Testes		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			+							
Bilateral, interstitial cell, adenoma			•				Х	X							X		Х	Х	Х	X	Х	. X	X	X	X			,	
Interstitial cell, adenoma				_	X				X			X		X		X										Х			
Hematopoietic System								,																_		-			
Blood											+																		
Bone marrow		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Lymph node		. +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			•
Lymph node, mandibular		+	- +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	· +	+	+	:		
Lymph node, mesenteric		+	+	+	+	+	+	+	+	+	· +	+	+	+	+	+	+	+	+	+	+	+	+	+	. +	+			
Spleen		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Thymus		+	+	+	+	M	[ +	+	+	+	M	[ +	+	+	+	+	+	+	+	+	+	+	+	+	. +	+			
Integumentary System																									·				
Mammary gland		N	1 N	1 +	M	[ +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	I M	I M	ſ +	+		**	
Fibroadenoma																	X												
Skin		+	. +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	· +	+			
Keratoacanthoma																													
Squamous cell papilloma																													
Subcutaneous tissue, fibroma											X			Х			X					Х			<sup>*</sup> X				

Table D2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Dichloromethane in Corn Oil: 5.0 mL/kg (continued)

S. W IIII II Mg (COILLINGCE)					_							_			_					_						
	7	7	7 7	7	7	7	7	7	7	7	7	7	7	7	7	7	7 7	7	7	7	7	7	7	7	7	
Number of Days on Study	. 3	3	3 3	3	3	3	3	3	3	3	3	3	3	3	3 3	3 3	3 3	3	3	3	3	3	3	3	3	
•	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1 :	i :	1 1	1	1	1	1	1	1	1	1	
	2	2	2 2	2 2	2 2	2	2	2	2	2	2	2	2	2	2 :	2 :	2 2	2	2	2	2	2	3	3	3	Total
Carcass ID Number	2	2 2	2 3	3 3	3 3	3	4	4	4	5	5	5	6	6	6 '	7 '	7 1	7	8	8	9	9	0	0	0	Tissues
<b></b>	1	_		_	-			3	4	1	2						2 :				1	3	1	2	3	Tumor
Endocrine System (continued)				_				_		_	_	_				_	_	_		_				_		
Islets, pancreatic	4	+ -	+ .	+ -	+ +	+ +	- +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma		2	X		>	(		Х							X				Х							7
Adenoma, multiple																										1
Carcinoma																							Х			1
Parathyroid gland	4	+ -	+ .	+ -	+ +	+ +	- +	+	+	+	+	+	+	+	+	+ :	M I	M	+	+	+	M	+	+	+	45
Pituitary gland	+	٠ -	+ -	+ -	+ +	+ +	- +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma			7	X X	K		Х		Х										X			X	X	Х	X	16
Pars distalis, adenoma, multiple																										2
Pars intermedia, adenoma																										1
Thyroid gland	+	٠ -	+ .	+ -	+ +	+ +	- +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell, adenoma	3	K			2	<			X				X								X					7
C-cell, carcinoma																										2
General Body System None																_										
Genital System			_	_						_						_				_				_		
Epididymis	-	+ -	+ .	+ •	+ -	+ +	- +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, testes																v			v							2
Preputial gland		L .	1						_		M		<b>N</b> .		+	X			X							3
Bilateral, adenoma		Γ.	Τ.	т :	Τ -	7	, T	•	•	+	IVI	+	IVI	+	+	+	+	+	+	+	+	+	+	+	+	44
Prostate		<b>.</b> .	<b>.</b>	Ι.			` - +		_	+	+	_		_			1.	_	4.							1
Seminal vesicle		Г . L .	т ·	Τ.							+	+	+	7.4	+	+	+	+	+	+	+	+	+	+	+	49
Testes	-		+ -	•	• •	•	T T	+	+		+	+		M		+	+	+	+	+	+	+	+	+	+	49
					+ -				+						+				+	+	+	+	+		+	49
Bilateral, interstitial cell, adenoma Interstitial cell, adenoma	,	•	^ 4	^ -	^ /	. ,				А	Λ.	Х	A	Х	X	Λ.	А.	А	Х	X	X	X	X		v	35
			_							_															<u> </u>	7
Hematopoietic System																										_
Blood											+				+											3
Bone marrow	-	٠.	+ -	+ •	+ -	+ +	+ +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	-	+ -	+ •	+ •	+ -	+ +	+ +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	-	<b>.</b>	+ -	+ .	+ -	+ +	+ +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	-	+ •	+ •	+ ·	+ -	+ 4	+ +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	49
Spleen	-		+ -				+ +	+					+	+	+	+	+	+	+	+	+	+	+	+		50
Thymus	-	٠ ٠	+ ·	+ ·	+ -	+ +	+ +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Integumentary System							_																			
Mammary gland	-	٠ -	+ -	+ .	+ -	+ +	- N	1 +	M	M	M	M	+	+	+	M	+ :	M	+	+	+	M	+	+	+	36
Fibroadenoma																										2
Skin	-	٠ ٠	+ -	+ -	+ -	+ +	+ +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma																								X		1
Squamous cell papilloma																							X			1
Subcutaneous tissue, fibroma											X		X													7

Individual Animal Tumor Patholog 5.0 mL/kg (continued)	gy of	f M	ale	R	ats	in	th	ie :	2-Y	'ea	r (	Gav	vag	e s	Stu	dy	of	Di	ich	lor	on	net	ha	ne	in	Co	rn	Oil:	: '	1:
			1	3	3	4	5	5	5	-	5	6	_	6	6	6	6	6	7	7	7	7	7	7	7	7	<del>-</del>	`		
Number of Days on Study			5	2	2	8	3	7	_	8	8	1	4	4	-	8	-	9	ó	ó	1	1	2	2	ં 3	3:	3	e s	٠,	
	,		5	3	7	4	6	Ó	-	0	5	-	- 7	7		2		2	1	4	-		1	_	_	0	-			
			_	2	_	3	_	2	_	2	2	2	2	2		2	2	2	2	2	3	2	2	2	2	2	2			
Carcass ID Number			4	1 2	4 5	0 4	_	8 5.		7 Š	9 4		9 5		8 4				2 4	6 3	0 5	8 3	1 1	5 4	1	1	- 1 - 5	,		j.
Musculoskeletal System	<del></del>	<del></del>	<u> </u>							· · ·	-			_						·		- N		÷	<u> </u>		<del></del>	1		-
Bone Skeletal muscle	•		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Mesothelioma malignant, metastatic, testes						,			x																. • .					
Nervous System	<u> </u>		<u> </u>	<u> </u>		Ė					·		<u> </u>	_			-	•				<u> </u>				<u> </u>	•		-	•
Brain Astrocytoma malignant			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	- <del>  1</del> -	+	+	+	٠	. ;	
Respiratory System								· ·													,						7., e	· · ·	3.1	
Lung Alveolar/bronchiolar adenoma			+	+,	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+ X	+	+	+	+	*		
Aiveolar/bronchiolar carcinoma Carcinoma, metastatic, kidney Carcinoma, metastatic, thyroid gland							X,			X															4		•			
Mesothelioma malignant, metastatic, testes									x														•					1 4. 1 4.4	. r	
Nose			+	.+	+	+	+	+	^ +	÷	+	+	+	+	+	4	+	+	+	+	+	+	+	+	+	+	+		100	
Trachea			+	+	+	+	+	+	+	+	+	+	+	+	+	4	+	+	+	+	+	+	+	+	+	+	+			
Special Senses System				<u>, , , , , , , , , , , , , , , , , , , </u>						·											-							• :-	,	
Ear Eye								_	**				-				+								+				٠.	
Zymbal's gland								•							+		,										•			•
Carcinoma	<u> </u>							<u> </u>							X			_	·			. 11		-41		**				
Urinary System																														٠.
Kidney Lipoma			+	+	+	7	+	+	+	+	+	+	+	+	+	+	7	+	+	Τ.	+	7	7	1	_	. *	т.	, i		
Liposarcoma																•											·	٠,	; - i'	
Renal tubule, carcinoma Urinary bladder			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	Α	+	+	+	+	+	+	**.	٠.,	
Systemic Lesions				<del></del> -		<u>-</u> -							<u> </u>											_		<u>:-</u>	; •		<del></del>	-4
Multiple organs			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Leukemia mononuclear						,				Х		Х			Х	X			X	X	Х	X	:	•		,		,		

,并以外,这种是一种,我们也是

TABLE D2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Dichloromethane in Corn Oil: 5.0 mL/kg (continued)

2.4 mary reg (continued)																												
Number of Days on Study		7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	3		
Carcass ID Number	· · · ·	2 2 1	2 2 3	2 3 1	2 3 2	2 3 3	2 3 4	2 4 2	2 4 3	2 4 4	2 5 1	2 5 2	2 5 3	2 6 1	2 6 2	2 6 4	2 7 1	2 7 2	2 7 3	2 8 1	-	2 9 1	2 9 3	-	3 0 2	0		Total Tissues Tumors
Musculoskeletal System  Bone Skeletal muscle Mesothelioma malignant, metastatic,		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
testes																	X											2
Nervous System Brain Astrocytoma malignant	·	+	+	+	+	+	+	+	+	+	+	+	+	+	+ X	+	+	+	+ X	+	+	+	+	+	+	+		50 2
Respiratory System  Lung  Alveolar/bronchiolar adenoma  Alveolar/bronchiolar carcinoma	- :	+	+	+.	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50 1 1
Carcinoma, metastatic, kidney Carcinoma, metastatic, thyroid gland Mesothelioma malignant, metastatic, testes			х																			·					,	1 1
Nose Trachea		+	+	+ +	+	+	+	+	++	+	; <del>†</del> +	.+ +	+	+	; <del>+</del>	+	+	+	+	+	+	+	+	+	+	+		50 50
Special Senses System  Ear  Eye  Zymbal's gland  Carcinoma									+			_					++			-								3 3 1
Urinary System Kidney Lipoma Liposarcoma		+	+	+	+	+	+	+	+	+	+	+ X	+	+	+	+	+	+	+	+	+	+	+	+	+	+ X		50 1 1
Renal tubule, carcinoma Urinary bladder		+	<b>X</b> +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		1 49
Systemic Lesions Multiple organs Leukemia mononuclear Mesothelioma malignant	•	+	+	+	+	+	+	+	+	+	+	+ X	+	+	+ X	+ X	+ x	+	+	+ X	+	+ X	+	+ X		+ X		50 14 3

TABLE D2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Dichloromethane in Corn Oil: 10 mL/kg

	,	1	2	5	5	5	5	5	5	6	6			6				7	7	7	7	7	7	7	7	7		
umber of Days on Study				1 2		4· 6	5 5	7 4	7 9	0 5	1 5		7 0	7 8		7 9			0 5	2 4	2 9	2 9	2 9	2 9	2 9	2 9		
		3	3	3	4	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3		 
arcass ID Number		3 5	7 5	1 2	0 5	5 5	8 5	_	4 4	3 4	2 5	5 4	3 1		_			6 1				1 4			2 2			
imentary System					-				_									_		_		_						 
Esophagus		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Intestine large		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Intestine large, cecum		. +	+	+	+	+	Α	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Intestine large, colon		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	,	
Intestine large, rectum  Mesothelioma malignant, metastatic, testes		+	+	+	+	+	Α	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Intestine small		+	+	+	+	+	Α	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Intestine small, duodenum		+	+	+	+	+	Α	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Intestine small, ileum		+	+	+	+	+	Α	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Intestine small, jejunum		+	+	+	+	+	Α	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Liver		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Hepatocellular carcinoma Hepatocellular adenoma																				X	x	X	x					
Histiocytic sarcoma										X																		
Mesentery  Mesothelioma malignant, metastatic, testes																				+								
Sarcoma																				х								
Pancreas		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Mesothelioma malignant, metastatic, testes																									•			. *
Acinus, adenocarcinoma											.,	.,								.,								
Acinus, adenoma					.,	**				37	X		37			37	3.0	37	37	X	37	37	**		٦,	.,		
Acinus, adenoma, multiple					А	X				X			X			А	Х	X	А			Х	А	Х	Х	X		
Pharynx						+ X															+							
Palate, squamous cell carcinoma						Λ															X							
Palate, squamous cell papilloma Salivary glands		_	_	_		_		_	_	_	_	_	_	+	+	+	м	+	_	_	7	, -	4		_	1		
Stomach		<b>∓</b>	_	<b>+</b>	- <b>T</b>	<b>∓</b>	<b>∓</b>	τ ±	+	+	+	<u>_</u>	+	+	+	<u>_</u>	+	+	+	-	+	4	+	+	+	т -		
Stomach Stomach		- -	+	4	4	+	+	+	+	+	+	+	+	+	·	+	+	<u>,</u>	+	+	+	4	4	4	+	+		
Mesothelioma malignant, metastatic, testes		•	•	•	•	•	·	•	•	•	•		•	•	•	•	•	•	•	·	•	•	•		•	•		
Squamous cell papilloma										,														٠.				
Stomach, glandular .  Mesothelioma malignant, metastatic,		+	+	+	+	+	Α	+	+	+	+	+	+	+	+	+	+	+	+	<b>A</b>		+	+	+	+	+		
testes Tongue							+																					
ardiovascular System			_	_	_	-										_	_	_	_	_			-					 
Heart		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Alveolar/bronchiolar carcinoma,																												
metastatic, lung																	X											

TABLE D2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Dichloromethane in Corn Oil:
10 mL/kg (continued)

	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
umber of Days on Study	2	2	2	2	2	2		2	2	2 9	2	2		3 0			3 0	3 0	3 0	3 0	3 0	3	3	3	3 0	
		3	3	3	3	3	3	3		3	3			3	3	3	3	3	3	3	3	4	4	4	4	Total
Carcass ID Number	2	3	3	4	4	5	_	6	6	6	6	7				8	9	9	9	9	9	0	0		o	Tissues
THE PROPERTY OF THE PROPERTY O	4	2	3	1	2	1		2		4	5						1	2		4	5	1	2	3	4	Tumor
Alimentary System		_										_														
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum  Mesothelioma malignant, metastatic,	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
testes														X												1
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	#	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	• •	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma			х										v													2
Hepatocellular adenoma Histiocytic sarcoma			Λ										X													4
Mesentery						+								_		_					_					1 7
Mesothelioma malignant, metastatic,						+			+					+		+	+				+					,
testes														X		X										2
Sarcoma																-										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	. +	+	50
Mesothelioma malignant, metastatic, testes								·	•				·	x		•	·		·	·	·	·	•		·	1
Acinus, adenocarcinoma										X										Х				Х		3
Acinus, adenoma						x		х		-				х						X				- 11		7
Acinus, adenoma, multiple	х	x	Х	Х	Х		х			х	х	х	х		х	$\mathbf{x}$	x	x	x			Х		x	х	34
Pharynx															•-								'	•	•	2
Palate, squamous cell carcinoma																										1
Palate, squamous cell papilloma																										î
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	. +	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	. +	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	. +	+	50
Mesothelioma malignant, metastatic,																										
testes														X												1
Squamous cell papilloma															Х											1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	- +	+	48
Mesothelioma malignant, metastatic,																										
testes														X												1
Tongue																								+		2
Cardiovascular System										_	_			_	_			_			_	_		_		
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	- +	+	50
Alveolar/bronchiolar carcinoma,																										_
metastatic, lung																										1

																							~	-				
, , , , , , , , , , , , , , , , , , , ,	1		_	5 .	5 5	5 5	5	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	.7				
lumber of Days on Study	0	9	_	5	4 5			0 5	5	4	7 -				8	0	0 5	2	2	2 · 9	2. 9	2	· 2	9	ř.	. · ·		٠.
			_						_		_	_		_	_						_	_	_	_			-1 <u>-</u>	
Carcass ID Number	3	7		4 0	3 3	3 3 8 4	3	3	3		3	٠.		3 7	3 7	3 6	3 8	3 1	3 1	3	3	3	_	3 2				. >
arcas in Number	- 5				5 :			4	5		_					1			3	4	5	1	_	3				
ndocrine System							_		_				<u> </u>		_	-	<u> </u>		•			4 1	7.	. , ,	٠,.	,1		-
Adrenal gland	+	+	+	+ .	+	<b>4</b> } -	+ +	٠+	+	+.	+	+	+	+	+	+	+	+	+	+	+	+	+	+		٠.	.*	
Adrenal gland, cortex	. +	·· +	+	+	+ -	+ •	+ +	٠+،	+	+ .	+	+	+	+	+	+	+	+	+	+	+	+	+	+			'	
Adrenal gland, medulla	+	· +	+	+	+ .	+ ' -	+ +	+	+	+ -	+	+ .	+	+	+	+	+	+	+	+	+	+	9 <del>-</del>	+	. •	٠, .		
Pheochromocytoma malignant													,					4	Z.	24	٠.		j.	·, ´		`	3	
Pheochromocytoma benign					,	X														٠.	. ,	". ·.	•				,	
Bilateral, pheochromocytoma benign					-	,														70		· • • •	;					
Islets, pancreatic	+	٠.	+	+	+ .	+ -	+ +	+	+	+	+	+.	+	+	+	+	+	+	+	+	+	+	+	+	٠.			
Adenoma	•	•	•	•	•			•	•	•	x		•	x	×	•	•	•	•	x	x	•	·	į.	. : :	:. "		
Adenoma, multiple														-						•	1,	.,-	X					
Carcinoma					х																				٠.,		,	
Parathyroid gland	M	· +	_	_	<u> </u>	<b>.</b>		_	_		<u>.</u> .		м	_	_	_	_	_	· _	ı.	_	_	1			: :		
Pituitary gland	→ ⊥				Ι.	T''	, ,	· 🛨	1	<b>+</b>	_	<b>T</b>	. 1	<b>+</b>	<u>_</u>	1	_	<b>+</b>	<u> </u>	<u>+</u>	_	<u> </u>	4	<u> </u>			:	
		•	т	X	~	▼.'	·	·v	Τ	X	т	т	X	т	т	т	X	Τ,	_	т	v		v	. T				
Pars distalis, adenoma Thyroid gland		_	4.					X			_		^	_		+	+	_		_	^	_	7	· - 1				
	+	-	+	Τ,	+ 4	Α.		+	Ŧ	Ŧ	+	Τ.	т.	т	A	_	_	v	Τ	v	_	v	. T			١.		
C-cell, adenoma																	v	X		X		X				4.5		
Follicular cell, adenoma																	X	X										
None																												٠.
	+	: +	+	+	+	+	٠. +	+	+		<del>-</del> -	+	+	+	+	+	+	+	+	+	<u> </u>	+	+	·				
Genital System  Epididymis  Mesothelioma malignant, metastatic,	+	· +	+	+	+	+	+ +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Mesothelioma malignant, metastatic, testes	+	+	+	+	+	+	+ +	+	+	·+	+	+	+	+	+	+	+:	+	+	+	+	+	+	+				
Epididymis  Mesothelioma malignant, metastatic, testes  Preputial gland	,; +	+	+	+	+	+ ·	+ +	+	+	·+	+	+	+ +	+	+	+	+:	+	++	+	+	+	+	+			-4.	
Epididymis  Mesothelioma malignant, metastatic, testes  Preputial gland  Adenoma	+ ;; ;+	+	+ +	+ + +	+ + +	+ ·	+ +	+	+ +	+	+ +	+ + +	+ + +	+ +	+ +	+ +	+ + + +	+ + +	+ + +	+ + +	+ + +	+ + +	+	+		DO AN		
Epididymis  Mesothelioma malignant, metastatic, testes  Preputial gland  Adenoma  Prostate	+ + + + +	+ + +	+ + +	+ + +	+ + + +	+ - + +	+ + +	+ + + +	+ + +	·+ ·+ ·+	+ + +	+ + + +	+ + +	+ + +	+ + ++	+ + +	+ + + +	+ + +	+ + + +	+ + + +	+ + +	+ + +	+ + +	+ +				
Epididymis Mesothelioma malignant, metastatic, testes Preputial gland Adenoma Prostate Seminal vesicle	+ /+++	+ + + + +	+ + + +	+ + + +	+ + + + +	+ + + + + + + + + + + + + + + + + + + +	+ + + + + + + + + + + + + + + + + + + +	+ + + + +	+ + ++	+ + + + + + + + + + + + + + + + + + + +	+ + ++	+ + + +	+ + ++	+ + + +	+ + ++	+ + +++	+ + + + +	+ + +++	+. + +++	+ + + + +	+ + ++	+ + + + +	+ + + + +	+ + + +				
Epididymis Mesothelioma malignant, metastatic, testes Preputial gland Adenoma Prostate Seminal vesicle Testes	+ + + + +	+ + + ++	+ + + + X	+ + + + + + +	+ + + + + X	+ · · · · · · · · · · · · · · · · · · ·	+ + + + + + + +	+ + + + + +	+ + + + X	+ + + + + + + + + + + + + + + + + + + +	+ + + + X	+ + + + X	+ + + +	+ + + +	+ + + + X	+ + + X	+ + +++	+ + + + X	+ + + + X	+ + + + X	+ + +++	+ + + + X	+ + + + X	+ + + + X				
Epididymis Mesothelioma malignant, metastatic, testes Preputial gland Adenoma Prostate Seminal vesicle Testes Bilateral, interstitial cell, adenoma	+ + + +	+ + + + +	+ + + X	+ + + + + + + *	+ + + X	+ + + + + + + + + X	+ + + + + + + +	+ + + + X	+ + + X	+ + + + + + + + + + + + + + + + + + + +	+ + + X	+ + + X	+ + + X	+ + + X	+ + + X	+ + + X	+ + + + X	+ + + X	+ + + X		+ + ++ X		+ + + + X	+ + + + X				
Epididymis Mesothelioma malignant, metastatic, testes Preputial gland Adenoma Prostate Seminal vesicle Testes	+ + + +	+ + + +	+ + + X	+ + + + + + + + + + + + + + + + + + + +	+ + + + X	+ + + + + + X	+ + + + + + + +		+ + + X	+ + + + + + + + + + + + + + + + + + + +	+ + + X	+ + + X	+ + + + X	+ + + X	+ + + + X	+ + + X		+ + + X	+ + + X				+ + + + X	+ + + + X				
Epididymis Mesothelioma malignant, metastatic, testes Preputial gland Adenoma Prostate Seminal vesicle Testes Bilateral, interstitial cell, adenoma Interstitial cell, adenoma	+ + + +	+ + + + +	+ + + + X	+ + + + + + + + + + + + + + + + + + + +	+ + + + X	+ + + + + + X	+ + + + + + + + X		+ + + X	+ + + + + + + + + + + + + + + + + + + +	+ + + X	+ + + X	+ + + + X	+ + + + X	+ + + + X	+ + + X		+ + + X	+ + + + X				+ + + + X	;		prise (1) (2) (3) (4) (4) (4) (4) (4) (4) (4) (4) (4) (4		-
Epididymis Mesothelioma malignant, metastatic, testes Preputial gland Adenoma Prostate Seminal vesicle Testes Bilateral, interstitial cell, adenoma Interstitial cell, adenoma	+ + + +	+ + + + + + + + + + + + + + + + + + + +	+ + + X	+ + + + + + + + + + + + + + + + + + + +	+ + + X	+ + + + + + + + + + + + + + + + + + +	+ + + + + + + X		+ + + + X	+ + + + + + + +	+ + + + X +	+ + + X	+ + + + X	+ + + + X +	+ + ++X -+	+ + + + X +		+ + + + X +	+ + + + X +				+ + + + + X	;				
Epididymis Mesothelioma malignant, metastatic, testes Preputial gland Adenoma Prostate Seminal vesicle Testes Bilateral, interstitial cell, adenoma Interstitial cell, adenoma	+	+ + + + + + + + + + + + + + + + + + + +	+ + + X	+ + + + + + + + + + + + + + + + + + + +	+ + + + X	+ + + + + + + + + + + + + + + + + + +	+ + + + + + + + + + + + + + + + + + +		+ + + + X + +	+ + + + + + + + + + + + + + + + + + + +	+ + + + X + +	+ + + X	+ + + + X + +	+ + + + X + +	+ + +++X ++	+ + + + X + +		+ + + + X + +	+ + +++X ++				+ + + + + X	;				
Epididymis Mesothelioma malignant, metastatic, testes Preputial gland Adenoma Prostate Seminal vesicle Testes Bilateral, interstitial cell, adenoma Interstitial cell, adenoma  Iematopoietic System Bone marrow Lymph node	+ + + + + +	+ + + + + + + + + + + + + + + + + + + +	+ + + X + + +	+ + + + + + + + + + + + + + + + + + + +	+ + + + X + + + + + + + + + + + + + + +	+ + + + + + + + + + + + + + + + + + +	+ + + + + + + + + + + + + + + + + + +		+ + + + X + + +	+ + +++	+ + + + + X + + + +	+ + + + X + + +	+ + +++ X +++	+ + + + X + + +	+ + +++X ++M	+ + + + X + + +		+ + + + X + + +	+ + + + + X + + +				+ + + + X X + + + + + + + + + + + + + +	;				
Epididymis Mesothelioma malignant, metastatic, testes Preputial gland Adenoma Prostate Seminal vesicle Testes Bilateral, interstitial cell, adenoma Interstitial cell, adenoma  Iematopoietic System Bone marrow Lymph node Lymph node, mandibular	+ + + + + M	+ + + + + + + + + + + + + + + + + + + +	+ + + X + + +	+ + + + + + + + + + + + + + + + + + + +	+ + + + + + + + + + + + + + + + + + +	+ + + + + + + + + + + + + + + + + + +	+ + + + + + + + + + + + + + + + + + +		+ + + + X + + + +	+ + +++	+ + + + + X - + + + + +	+ + + + X + + + + +	+ + + + X + + + +	+ + + + X + + + +	+ + +++X ++MM	+ + + + X + + + +		+ + + + X + + + +	+ + + + + X + + + + +				+ + + + + X X + + + 4	;		property of the second		
Epididymis Mesothelioma malignant, metastatic, testes Preputial gland Adenoma Prostate Seminal vesicle Testes Bilateral, interstitial cell, adenoma Interstitial cell, adenoma  Iematopoietic System Bone marrow Lymph node Lymph node, mandibular Lymph node, mesenteric	+ + + + + + +	+ + + + + + + + + + + + + + + + + + + +	+ + + + X + + + + + + + + + + + + + + +	+ + + + + + + + + + + + + + + + + + + +	+ + + + + + + + + + + + + + + + + + +	+ + + + + + + + + + + + + + + + + + +	+ + + + + + + + + + + + + + + + + + +		+ + + + X + + + + + + + + + + + + + + +	+ + ++++	+ + + + + X + + + + + + + + + + + + + +	+ + +++X +++++	+ + + + X + + + + + + + + + + + + + + +	+ + +++ X ++++	+ + + + + X + + M M +	+ + + + + X + + + + + + + + + + + + + +		+ + + + X + + + + +	+ + +++X ++++				+ + + + X X + + + + + + + + + + + + + +	;				
Epididymis Mesothelioma malignant, metastatic, testes Preputial gland Adenoma Prostate Seminal vesicle Testes Bilateral, interstitial cell, adenoma Interstitial cell, adenoma  Iematopoietic System Bone marrow Lymph node Lymph node, mandibular Lymph node, mesenteric Spleen	+ + + + + + + + +	+ + + + + + + + + + + + + + + + + + + +	+ + + X + + + + + + + + + + + + + + + +	+ + + + + + + + + + + + + + + + + + + +	+ + + + + + + + + + + + + + + + + + +	+ + + + + + + + + + + + + + + + + + +	+ + + + + + + + + + + + + + + + + + +		+ + + + + + + + + + + + + + + + + + +	+ + + + + + + + + + + + + + + + + + + +	+ + +++X +++++	+ + +++X +++++	+ + + + X + + + + + + + + + + + + + + +	+ + + + X + + + + + + + + + + + + + + +	+ + + + X + + M M + M	+ + +++X +++++	+ + + + + + + + + + + + + + + + + + +	+ + + + +	+ + + + +				+ + + + + + + + + + + + + + + + + + +	;				
Epididymis Mesothelioma malignant, metastatic, testes Preputial gland Adenoma Prostate Seminal vesicle Testes Bilateral, interstitial cell, adenoma Interstitial cell, adenoma  lematopoietic System Bone marrow Lymph node Lymph node, mandibular Lymph node, mesenteric	+ + + + + M + +	+ + + + + + + + + + + + + + + + + + + +	+ + + + + + + + + + + + + + + + + + +	+ + +++	+ + + + + + + + + + + + + + + + + + +	+ + +++X ++++++	+ + + + + + + + + + + + + + + + + + + +		+ + + + + + + + + + + + + + + + + + +	+ + ++++	+ + +++X +++++	+ + + + + + + + + + + + + + + + + + +	+ + +++ X +++++	+ + + + X + + + + + + + + + + + + + + +	+ + + + X + + M M + M	+ + + + X + + + + + + + + + + + + + + +	+ + + + + + + + + + + + + + + + + + +	+ + + + X + + + H	+ + + + +				+ + + + + + + + + + + + + + + + + + +	;				
Epididymis Mesothelioma malignant, metastatic, testes Preputial gland Adenoma Prostate Seminal vesicle Testes Bilateral, interstitial cell, adenoma Interstitial cell, adenoma  Iematopoietic System Bone marrow Lymph node Lymph node, mandibular Lymph node, mesenteric Spleen Thymus	+ + + + + M + +	+ + + + + + + + + + + + + + + + + + + +	+ + + + X + + + + + + + + + + + + + + +	+ + + + + + + + + + + + + + + + + + + +	+ + + + + + + + + + + + + + + + + + +	+ + + + + + + + + + + + + + + + + + +	+ + + + + + + + + + + + + + + + + + + +		+ + + + + + + + + + + + + + + + + + +	+ + ++++	+ + +++X ++++++	+ + + + + + + + + + + + + + + + + + +	+ + + + X + + + + + + + + + + + + + + +	+ + + + X + + + + + + + + + + + + + + +	+ + + + X + + M M + M	+ + + + + X + + + + + + + + + + + + + +	+ + + + + + + + + + + + + + + + + + +	+ + + + +	+ + + + +		X + + + + + + + + + + + + + + + + + + +		+ + + + +	+ + + + •				-
Epididymis Mesothelioma malignant, metastatic, testes Preputial gland Adenoma Prostate Seminal vesicle Testes Bilateral, interstitial cell, adenoma Interstitial cell, adenoma  Hematopoietic System Bone marrow Lymph node Lymph node, mandibular Lymph node, mesenteric Spleen Thymus	+++++++++++++++++++++++++++++++++++++++	+ + + + +	+ + + + + +	+++++	+ + + + + + + + + + + + + + + + + + +	+ + + + + + + + + + + + + + + + + + + +	+ + + + + + +	X + + + + + + + + + + + + + + + + + + +	+++++	+ + + + + +	+++++	+ + + + + +	+ + + + +	+ + + + + +	+ + M M +	+ + + + + +	+ + + + M	+ + + + M	+ + + + +	+++++	X + + + + + + + + + + + + + + + + + + +	* + + + + + + + + *	+++++	· + · + · + · · · · · · · · · · · · · ·	1			
Epididymis Mesothelioma malignant, metastatic, testes Preputial gland Adenoma Prostate Seminal vesicle Testes Bilateral, interstitial cell, adenoma Interstitial cell, adenoma  Hematopoietic System Bone marrow Lymph node Lymph node, mandibular Lymph node, mesenteric Spleen Thymus  ntegumentary System Mammary gland	+ + + + + + + + + + + + + + + + + + + +	+ + + + +	+ + + + + + + + + + + + + + + + + + +	+++++	+ + + + + + + + + + + + + + + + + + +	+ + + + + + + + + + + + + + + + + + + +	+ + + + + + + + + + + + + + + + + + +	X + + + + + + + + + + + + + + + + + + +	+++++	+ + + + + +	+++++	+ + + + + +	+ + + + +	+ + + + + +	+ + M M +	+ + + + + +	+ + + + M	+ + + + M	+ + + + +	+++++	X + + + + + + + + + + + + + + + + + + +	* + + + + + + + + *	+++++	· + · + · + · · · · · · · · · · · · · ·	1			
Epididymis Mesothelioma malignant, metastatic, testes Preputial gland Adenoma Prostate Seminal vesicle Testes Bilateral, interstitial cell, adenoma Interstitial cell, adenoma  Ilematopoietic System Bone marrow Lymph node Lymph node, mandibular Lymph node, mesenteric Spleen Thymus  Integumentary System Mammary gland Adenoma	+ + + + + M + + +	+ + + + + + M	+ + + + + +	+++++	+ + + + + + + +	+ + + + + + + + + + + + + + + + + + + +	+ + + + + + +	X + + + + + + + + + + + + + + + + + + +	+++++	+ + + + + +	+++++	+ + + + + +	+ + + + +	+ + + + + +	+ + M M +	+ + + + + +	X + + + + + + M +	+ + + + M	+ + + + +	+++++	X + + + + + + + + + + + + + + + + + + +	* + + + + + + + + *	+++++	+ + + + + M	1			
Epididymis Mesothelioma malignant, metastatic, testes Preputial gland Adenoma Prostate Seminal vesicle Testes Bilateral, interstitial cell, adenoma Interstitial cell, adenoma  Hematopoietic System Bone marrow Lymph node Lymph node, mandibular Lymph node, mesenteric Spleen Thymus  ntegumentary System Mammary gland Adenoma Fibroadenoma	+ + + + + M + + +	+ + + + + + M	+ + + + +	+++++	+ + + + + + + +	+ + + + + + + + + + + + + + + + + + + +	+ + + + + + +	X + + + + + + + + + + + + + + + + + + +	+++++	+ + + + + +	+++++	+ + + + + +	+ + + + +	+ + + + + +	+ + M M +	+ + + + + +	X + + + + + + M +	+ + + + M	+ + + + +	+++++	X + + + + + + + + + + + + + + + + + + +	* + + + + + + + + *	+++++	+ + + + + M	1			<del>-</del> -
Epididymis Mesothelioma malignant, metastatic, testes Preputial gland Adenoma Prostate Seminal vesicle Testes Bilateral, interstitial cell, adenoma Interstitial cell, adenoma  Hematopoietic System Bone marrow Lymph node Lymph node, mandibular Lymph node, mesenteric Spleen Thymus  ntegumentary System Mammary gland Adenoma	+ + + + + M + + +	+ + + + + + M	+ + + + +	+++++	+ + + + + + + +	+ + + + + + + + + + + + + + + + + + + +	+ + + + + + +	X + + + + + + + + + + + + + + + + + + +	+++++	+++++++++++++++++++++++++++++++++++++++	+++++	+ + + + + +	+ + + + +	+ + + + + +	+ + M M +	+ + + + + +	X + + + + + + M +	+ + + + M	+ + + + +	+++++	X + + + + + + + + + + + + + + + + + + +	* + + + + + + + + + + + + + + + + + + +	+++++	+ + + + + M	1			

,一个时间,这个时间,这个时间,我们就是一个时间,我们就是一个时间,我们就是一个时间,我们就是一个时间,我们也会一个时间,我们也会一个时间,我们也会一个时间,也 一个时间,我们就是一个时间,我们就是一个时间,我们就是一个时间,我们就是一个时间,我们就是一个时间,我们就是一个时间,我们就是一个时间,我们就是一个时间,我们就

TABLE D2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Dichloromethane in Corn Oil:
10 mL/kg (continued)

OmL/kg (continued)																										
<del></del>	7	7	7	7	7	7	7	7	7	7	7 7	, ,	7 .7	7	7	7	7	7	7	7	7	7	7	7		
lumber of Days on Study	2		2	. 2				2	2	2	2 2	2 4	2 3	3	3	3	3	3	3	3	3	3	3	3		
dimber of mays on Study	9	9							9		9 9		9 0	0	0	0	0	0	0	0	0	0	0	0		
		_	_		<u> </u>		_			_				_	_		_		_	_		_		_		
	3	3	3	3	.3	3	3	3	3	3	3		3 :3	_	3	3	3		3	3	4	4	4	-		Total
Carcass ID Number	2	3	3	4	4.	5	5	<b>6</b> ,	6	6	6	7 '	78	8	8	9	9		9	9	0	0	0	-		Tissues
	. 4	2	3	1	·2	1	2	2	3	4	5 2	2 :	3 2	3	4	1	2	3	4	5	1	2	3	4		Tumors
Endocrine System		-	_								_		,				_					_				
Adrenal gland	.+	. +	. +	+	+	+	+.	+	+	+	+	+	+ +	+	+	+	+	+	+	+	+	+	+	.+		50
Adrenal gland, cortex	+	+	+	+	+	+	+.	+	+	+ .	+	+	+ +	+	+	+	+	+	+	+	+	+	+	+	٠.	50
Adrenal gland, medulia	. +	+	+	, +	+	+,	+	+	+	+	+	+	+.+	+	+	+	+	+	+	+	+	+	+	+,		50
Pheochromocytoma malignant									X																	1
Pheochromocytoma benign		X									X							Х		X			,	X		. 6
Bilateral, pheochromocytoma benign								X	,							,					٠,	٠.				1
Islets, pancreatic	+	. +	+	. +	+	+	+.	+	+	+	+	+	+ +	+	+	+	+	+	+	+	+	+	+	+		50
Adenoma		X									X					X	X			$\mathbf{x}$	X					. 11
Adenoma, multiple		-:																		_						1
Carcinoma						x																		X		3
Parathyroid gland				M	+	+	+	+	.+	+	+	+	+ 4	- +	+	+	+	+	+	+	+	+	+	+		47
Pituitary gland	A.	4 +		. +	+	+	+	+	+	+	+	+	+ +		+	+	+	+	+	+	+	+	+	+		49
Pars distalis, adenoma	. 14		-	•	•	•	Ý	X		•	X			٠.	X	•	•	x	•	•	•	×	•	x	-	16
Thyroid gland	+	_			ì	_	1	7	+	+	+	_	+. +	- +	+	+	+		+	+	+	+	+			48
	X		•		. т	X	т	X		x	•	'	1.	'	•	x	•	x	•	•		•	•	•		9
C-cell, adenoma Follicular cell, adenoma	^					^		^		^						^		Λ								2
										_					_		_			,.	_					
General Body System	,																						,			
None																										
Genital System			_		_	_	_	,	_	_			_		_	_					_	_				
Epididymis	+	- +	. +	+	+	+	+	+	+	+	+	+	+ +	- +	+	+	+	+	+	+	+	+	+	+		50
Mesothelioma malignant, metastatic,																										
testes													>	(	X											2
Preputial gland	4	- +	. +	. +	+	+	+	+	.+	+	+.	+.	+ . +			+	+	+	+	+	+	+	+	+		50
Adenoma	'	•	٠	٠,	•	•	'	'	. ,	x	•	•	'	'				•	Ÿ	x	•			'		3
Prostate				. A		_	_	_			M	_			_	_	_	_	Λ. 	7	_	_	_	4-		48
Seminal vesicle	7			. 14	. +	T	T	<b>T</b>		T.	· 141	T	T 7		_ T	T		T			<b>T</b>	_ T				50
Testes		7	. +		<b>T</b>		· T	+	<b>T</b>	T .	T	Τ.	+ -	r +	+	+				+	<b>+</b>	<b>T</b>		+		50
	7	7 T			·······································	v	Τ.	Τ	v	v	v	Τ.	XX				v	v	v	v	v	т	-	-		-
Bilateral, interstitial cell, adenoma			. ^	. ^	X	А			· <b>X</b> -	А		x	A /		^	^	^	•	^	^	٠,	X		Х		36 8
Interstitial cell, adenoma								X				^	_		_	_						_				•
Hematopoietic System	,																									
Bone marrow	4	<b>+.</b> +	- +	+	+	+	+	+	+	+	+	+	+ -	+ +	+	+	+	+	+	+	+	+	+	+		- 50
Lymph node	4	+ +	- +	. +	+	. +	+	+	+-	+	+	+	+ -	+ +	+	+	+	+	+	+	+	+	+	+		50
Lymph node, mandibular	4	+ +	- +	- , +	+	+	+	+	+	+	+	+	+ -	+ +	+	+	+	+	+	+	+	M	( +	+		47
Lymph node, mesenteric	4	· • •	- +	- +	+	+	+	+	+.	+	M	+	+ -	+ +	+	+	+	+	+	+	.+	+	+	+		48
Spleen	4	+ 4	- +	. +	+	+	. +	+	+	+	+	+	+ -	· ·	+	+	+	+	+	+	+	+	+	+		50
Thymus	4	+ +	- +	+	+								+ -			+	+	+	+	+	+	+				44
			-					_						<u> </u>				_	_	-			_			
Integumentary System	٠.																						,		:	,
Mammary gland	-	- 1	- IV	1 +	+	+	+	+	+ -	+	+	+	+ -	+ +	+	+	+	+	+	+	+	+	M	( +		. 37
																										· 1
Adenoma												Х	$\mathbf{x}$	<b>(</b>	Х			X								6
Fibroadenoma																										
Fibroadenoma Skin	+	+ +	+ +	- +	+	+	+	+	+	+			+ -	+ +	+	+	+	+	+	+	+	+	+	+		50
Fibroadenoma	4	+ + X		- +	+	+	+	+	+	+				+ +	+	+	+	+	+	+	+	+ X	+	+		50

TABLE D2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Dichloromethane in Corn Oil: 10 mL/kg (continued)

10 mil/kg (commuted)	,																								
Number of Days on Study				5					6 0				5 6	6		7	7	7 2	7 2	7 2	7	7	7 2		
rumber of Days on Study	-		-	5				ģ					8		-	-	-				9	9	_	_	
	3	_	3	•	3	-	3	_	-	- '	3 3			3								3	3	3	
Carcass ID Number	3 5		_	0 5		8 5	-						4 5 3 3									2 1	-	2	
Musculoskeletal System			_	<u>:-</u>	<u>·</u>	<u> </u>			• ,			<del></del>	•	<u>:</u>			<u>.</u>				<u>-</u> -	·			<del></del>
Bone	4	- +	+	+	+	+	+	÷	+	+	+ -	+ -	+ +	- +	+	+	+	+	+	+	+	+	+	+	
Skeletal muscle															+					+					
Alveolar/bronchiolar carcinoma, metastatic, lung															x										
Nervous System		,	<u> </u>																_						
Brain	٠. ٠	- , <b>+</b>	+	+	+	+	+	+	+	+	+	+ .	+ +	+ +	+	+	+	+	+	+	+	+	+	+	
Respiratory System						-																			
Lung	4	- +	+	+	+	+	+		+	+	+	+ .	+ +	+ +	+	+	+	+	+	+	+	+	+	+	
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma															X										
Histiocytic sarcoma, metastatic,																									
liver									X									v							
Sarcoma, metastatic, mesentery																		X							
Nose	+	- 4	- +	• +	+	+	+	+	+	+	+	+ .	+ +	+ +	+	+	+	+	+	+	+	+	+	+	
Trachea		- +	• +	+	+	+	+	+	+	+	+	+	+ 1	- +	- +	+	+	+	+		+	+	+		
Special Senses System					_																				
Zymbal's gland											+														
Carcinoma											X												_		
Urinary System																									
Kidney	4	- +	- +	+	+	÷	+	+	+	+	+	+	+ +	+ +	+	+	+	+	+	+	+	+	+	+	
Urinary bladder	-		- +	+	+	Α	+	+	+	+	+	+	+ +	+ +	- +	+	+	+	+	+	+	+	+	+	
Systemic Lesions	<del></del>						-									_			_						
Multiple organs	-	+ +	- 4	- +	+	+	+	+	+	+	+	+	+ +	+ +	- +	+	+	+	+	+	+	+	+	+	
Histiocytic sarcoma									X										,						
Leukemia mononuclear							X		X			$\mathbf{x}$ :	X						X						
Mesothelioma malignant												-													

是某些人,就是是一个人,不是一个人,不是一个人,不是一个人,不是一个人,不是一个人,不是一个人,不是一个人,不是一个人,不是一个人,不是一个人,不是一个人,不是 一个人,不是一个人,不是一个人,不是一个人,不是一个人,不是一个人,不是一个人,不是一个人,不是一个人,不是一个人,不是一个人,不是一个人,不是一个人,不是一个人

Table D2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Dichloromethane in Corn Oil:
10 mL/kg (continued)

_ · · · · · · · · · · · · · · · · · · ·																											
	7		7			•	7	•	7		•		7	7		7			7			7					
Number of Days on Study	2	1	2	2	2	2	2	2	2	2	2	2	2	2	3		3		3			3		3	3	-	
	9	9	9	9	9	9	9	9	9	9	9	9	9	9	0	0	0	0	0	0	0	0	0	0	0	0	
	3	:	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3				3	3	4	4	4	4	Total
Carcass ID Number	2		3	3	4	4	5	5	6	6	6	6	7	7	8	8	8	9	9	9	9	9	0	0	0	0	Tissues
	4	:	2	3	1	2	1	2	2	3	4	5	2	3	2	3	4	1	2	3	4	5	1	2	3	4	Tumors
Musculoskeletal System		_	-	-	_	_			_						_	_											
Bone	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																											2
Alveolar/bronchiolar carcinoma,																											
metastatic, lung																											1
Nervous System		_	_	_	_			_			_							_		_							
Brain	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System	<del></del>	-	_	_	_																_				-		
Lung	+	_	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma							X								X			·	x			x	Ť	•	•		4
Alveolar/bronchiolar carcinoma																											1
Histiocytic sarcoma, metastatic,																											_
liver																											1
Sarcoma, metastatic, mesentery																											1
Nose	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System			_		_	_			_			*											_	_	_		
Zymbal's gland	+	-																									2
Carcinoma	X																										2
Urinary System	<del></del>		_					_	_			_					-		_								
Kidney	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions		_					_		•																	_	<del></del>
Multiple organs	4		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	_	4	_	50
Histiocytic sarcoma	•		•	•	•	•	,	٠	•	•	,	•	•		,	1	'	'	τ.	г	-	•	т	Τ'	т	7	1
Leukemia mononuclear																											5
Mesothelioma malignant															х		x										2
															^		^										4

TABLE D3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Dichloromethane in Corn Oila

	2.5 mL/kg	5 mL/kg	10 mL/kg	
drenal Medulla: Benign Pheochromocyt	oma			
verall rate <sup>b</sup>	13/49 (27%)	8/45 (18%)	7/50 (14%)	
djusted rate <sup>c</sup>	42.6%	25.4%	21.1%	
erminal rate <sup>d</sup>	7/23 (30%)	5/26 (19%)	6/31 (19%)	
rst incidence (days)	605	536	555	
ife table test <sup>e</sup>	P=0.024N	P=0.106N	P=0.036N	
ogistic regression test <sup>e</sup>	P = 0.055N	P=0.180N	P = 0.069N	
ochran-Armitage test <sup>e</sup>	P = 0.074N	,		
sher exact test <sup>e</sup>		P = 0.221N	P = 0.096N	
irenal Medulla: Malignant Pheochromo	ocytoma			
verall rate	0/49 (0%)	3/45 (7%)	1/50 (2%)	
djusted rate	0.0%	10.8%	3.2%	
erminal rate	0/23 (0%)	2/26 (8%)	1/31 (3%)	,
rst incidence (days)	_f	721	729 (T)	
fe table test	P=0.378	P=0.146	P=0.560	
ogistic regression test	P=0.355	P=0.134	P=0.560	* .
ochran-Armitage test	P=0.301	,	<del></del>	
sher exact test	1 0.501	P = 0.106	P=0.505	
lrenal Medulla: Benign or Malignant F	Pheochromocytoma			
verall rate	13/49 (27%)	11/45 (24%)	8/50 (16%)	
djusted rate	42.6%	34.8%	24.3%	
erminal rate	7/23 (30%)	7/26 (27%)	7/31 (23%)	
rst incidence (days)	605	536	555	
fe table test	P = 0.053N	P=0.288N	P = 0.059N	
ogistic regression test	P=0.114N	P = 0.433N	P = 0.110N	
ochran-Armitage test	P=0.155N			
sher exact test	. 0,,,,,,	P = 0.503N	P = 0.150N	·
iver: Hepatocellular Adenoma				
verall rate	6/50 (12%)	4/50 (8%)	4/50 (8%)	
djusted rate	22.9%	12.3%	12.9%	
erminal rate	4/23 (17%)	2/28 (7%)	4/31 (13%)	
rst incidence (days)	680	615	729 (T)	
fe table test	P=0.168N	P=0.264N	P=0.215N	
ogistic regression test	P=0.225N	P=0.311N	P=0.266N	1 -
ochran-Armitage test	P=0.300N		· <del>···</del> ····	
isher exact test		P=0.370N	P=0.370N	
ver: Hepatocellular Adenoma or Carci	noma	•	e de la companya de La companya de la companya de l	
verall rate	7/50 (14%)	4/50 (8%)	6/50 (12%)	
djusted rate	27.0%	12.3%	18.8%	* 1
erminal rate	5/23 (22%)	2/28 (7%)	5/31 (16%)	
irst incidence (days)	680	615	724	
ife table test	P=0.224N	P=0.170N	P = 0.296N	
ogistic regression test	P=0.294N	P=0.204N	P=0.365N	
ochran-Armitage test	P=0.394N			
isher exact test	- 0.02 111	P = 0.262N	P = 0.500N	

多年,更是是一个人,我们就是一个人,我们就是一个人,我们就是一个人,我们就是一个人,我们就是一个人,我们就是一个人,我们就是一个人,我们就是一个人,我们就是一个人, 第二十二章 "我们是一个人,我们就是一个人,我们就是一个人,我们就是一个人,我们就是一个人,我们就是一个人,我们就是一个人,我们就是一个人,我们就是一个人,我们就

TABLE D3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Dichloromethane in Corn Oil (continued)

Adjusted rate 7.8% 3.3% 721 Terminal rate 0/23 (0%) 0/28 First incidence (days) 483 721 Life table test P=0.602N P=0. Logistic regression test P=0.530 P=0. Cochran-Armitage test P=0.523 Fisher exact test P=0.523 Fisher exact test P=0.523 Fisher exact test P=0.523 Fisher exact test P=0.523  Lung: Alveolar/bronchiolar Adenoma or Carcinoma Overall rate 3/50 (6%) 2/50 Adjusted rate 7.8% 5.4% Terminal rate 0/23 (0%) 0/28 First incidence (days) 483 536 Life table test P=0.452 P=0. Logistic regression test P=0.345 P=0. Cochran-Armitage test P=0.348 Fisher exact test P=0.348  Overall rate 1/50 (2%) 2/50 Adjusted rate 3.4% 5.5% Ferminal rate 0/23 (0%) 0/28 First incidence (days) 699 682 Life table test P=0.054 P=0. Cochran-Armitage test P=0.054 P=0. Cochran-Armitage test P=0.054 P=0. Mammary Gland: Adenoma or Fibroadenoma Overall rate 1/50 (2%) 2/50 Cochran-Armitage test P=0.047 Fisher exact test P=0.047 Fisher exact test P=0.054 P=0. Cochran-Armitage test P=0.047 Fisher exact test P=0.047 Fisher exact test P=0.049 P=0. Cochran-Armitage test P=0.030 P=0. Coch	nIJ/kg 10 mIJ/kg
Description   1/50	
Adjusted rate	(2%) 4/49 (8%)
Cerminal rate   0/23 (0%)   0/28	
Assembly	
ife table test P=0.602N P=0. ogistic regression test P=0.530 P=0. ogistic regression test P=0.530 P=0. ogistic regression test P=0.523 P=0.523 P=0. ochran-Armitage test P=0.523 P=0. ochran-Armitage test P=0.523 P=0. ochran-Armitage test P=0.523 P=0. ochran-Armitage test P=0.486 S.4% P=0.486 S.4% P=0.485 P=0. ochran-Armitage test P=0.485 P=0. ochran-Armitage test P=0.345 P=0. ochran-Armitage test P=0.348 Sisher exact test P=0.348 P=0. ochran-Armitage test P=0.348 Sisher exact test P=0.348 Sisher exact test P=0.049 P=0. ochran-Armitage test P=0.054 P=0. ochran-Armitage test P=0.047 Sisher exact test P=0.047 Sisher exact test P=0.047 Sisher exact test P=0.047 Sisher exact test P=0.049 P=0. ochran-Armitage test P=0	
Decisitic regression test	0.277N P=0.607
Cochran-Armitage test   P=0.523	0.318N P=0.493
Page	
Deverall rate   3/50 (6%)   2/50	0.309N P=0.489
Deverall rate   3/50 (6%)   2/50	
Adjusted rate	5/49 (10%)
Cerminal rate	• • •
Align   Alig	
Description   Period   Perio	
P=0.345	
P=0.348	
Page	7.5 22.1
Description	0.500N P=0.346
Description	
Adjusted rate 3.4% 5.5% Cerminal rate 0/23 (0%) 0/28 Cirst incidence (days) 699 682 Cife table test P=0.081 P=0. Cochran-Armitage test P=0.047 Cisher exact test P=0.049 Cirst incidence (days) 699 682 Cife table test P=0.049 P=0. Cochran-Armitage test P=0.030 P=0. Cochran-Armitage test P=0.026 Cisher exact test P=0.030 Cisher exa	(4%) (120%)
Cerminal rate	
First incidence (days)  Cife table test  Fisher exact test  Alammary Gland: Adenoma or Fibroadenoma  Example 1	
Page 20	
Page	
Cochran-Armitage test P=0.047  Fisher exact test P=0.047  Fisher exact test P=0.047  Fisher exact test P=0.047  Fisher exact test P=0.049 P=0.049 P=0.026  First incidence (days) Fisher exact test P=0.030 P=0.026  Fisher exact test P=0.026  Fisher exact test P=0.026  Fisher exact test P=0.026  Fisher exact test P=0.030 P=0.026  Fisher exact test P=0.030 P=0.026  Fisher exact test P=0.030 P=0.	
Pack	0.516 P=0.070
Overall rate       1/50 (2%)       2/50         Adjusted rate       3.4%       5.5%         Germinal rate       0/23 (0%)       0/28         First incidence (days)       699       682         Life table test       P=0.049       P=0.         Logistic regression test       P=0.030       P=0.         Cochran-Armitage test       P=0.026       P=0.         Fisher exact test       P=0.       P=0.         Pancreas: Adenoma       P=0.       P=0.         Overall rate       9/50 (18%)       19/50         Adjusted rate       35.2%       60.89         First incidence (days)       622       682	0.500 P=0.056
Overall rate       1/50 (2%)       2/50         Adjusted rate       3.4%       5.5%         Ferminal rate       0/23 (0%)       0/28         First incidence (days)       699       682         Life table test       P=0.049       P=0.         Logistic regression test       P=0.030       P=0.         Cochran-Armitage test       P=0.026       P=0.         Fisher exact test       P=0.026       P=0.         Pancreas: Adenoma       P=0.       P=0.         Overall rate       9/50 (18%)       19/50         Adjusted rate       35.2%       60.89         First incidence (days)       622       682	
Adjusted rate 3.4% 5.5% Exerminal rate 0/23 (0%) 0/28 First incidence (days) 699 682 Life table test P=0.049 P=0. Logistic regression test P=0.030 P=0. Cochran-Armitage test P=0.026 Fisher exact test	7/40/\
Cerminal rate   0/23 (0%)   0/28     Cirst incidence (days)   699   682     Cirst incidence (days)   699   682     Cirst incidence (days)   699   P=0.     Cogistic regression test   P=0.030   P=0.     Cochran-Armitage test   P=0.026     Cirst incidence (days)   7/20 (18%)   19/50     Cochran-Armitage test   P=0.026     Cirst incidence (days)   622   682     Circt i	
First incidence (days)  699  682  Life table test  P=0.049  P=0.  Cochran-Armitage test  P=0.026  Fisher exact test  P=0.026  Pancreas: Adenoma  Overall rate  49/50 (18%)  19/50  Adjusted rate  35.2%  60.89  Cerminal rate  7/23 (30%)  16/28  First incidence (days)  682	
Page	
Page	
Cochran-Armitage test       P=0.026         Fisher exact test       P=0.         Pancreas: Adenoma       P=0.         Overall rate       9/50 (18%)       19/50         Adjusted rate       35.2%       60.89         Ferminal rate       7/23 (30%)       16/28         First incidence (days)       622       682	
Pancreas: Adenoma  Overall rate 9/50 (18%) 19/50  Adjusted rate 35.2% 60.89  Ferminal rate 7/23 (30%) 16/28  First incidence (days) 622 682	0.516 P=0.040
Overall rate     9/50 (18%)     19/50       Adjusted rate     35.2%     60.89       Cerminal rate     7/23 (30%)     16/28       First incidence (days)     622     682	0.500 P=0.030
Overall rate     9/50 (18%)     19/50       Adjusted rate     35.2%     60.89       Cerminal rate     7/23 (30%)     16/28       First incidence (days)     622     682	
Adjusted rate 35.2% 60.89 Ferminal rate 7/23 (30%) 16/28 First incidence (days) 622 682	(n /29%) 41 (50 /02%)
Perminal rate     7/23 (30%)     16/28       Perminal rate     622     682	(0 (38%) 41/50 (82%)
irst incidence (days) 622 682	
16-4-11-4-1	• • • • • • • • • • • • • • • • • • • •
	0.068 P<0.001
	0.047 P<0.001
Cochran-Armitage test P<0.001 Fisher exact test P=0.	0.022 P<0.001

TABLE D3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Dichloromethane in Corn Oil (continued)

	2.5 mL/kg	5 mL/kg	10 mL/kg
Pancreas: Carcinoma			
Overall rate	0/50 (0%)	1/50 (2%)	3/50 (6%)
Adjusted rate	0.0%	2.9%	9.7%
Cerminal rate	0/23 (0%)	0/28 (0%)	3/31 (10%)
First incidence (days)	_	701	729 (T)
ife table test	P = 0.121	P=0.539	P=0.177
ogistic regression test	P = 0.104	P = 0.514	P=0.177
ochran-Armitage test	P = 0.086		
isher exact test		P = 0.500	P=0.121
ancreas: Adenoma or Carcinoma			
verall rate	9/50 (18%)	20/50 (40%)	41/50 (82%)
djusted rate	35.2%	62.0%	97.6%
erminal rate	7/23 (30%)	16/28 (57%)	30/31 (97%)
irst incidence (days)	622	682	545
ife table test	P<0.001	P = 0.048	P<0.001
ogistic regression test	P<0.001	P = 0.029	P<0.001
ochran-Armitage test	P<0.001		
isher exact test		P = 0.013	P<0.001
ancreatic Islets: Adenoma			
verall rate	5/50 (10%)	8/50 (16%)	12/50 (24%)
djusted rate	14.3%	24.5%	34.7%
erminal rate	1/23 (4%)	5/28 (18%)	9/31 (29%)
irst incidence (days)	595	643	670
ife table test	P = 0.135	P = 0.389	P = 0.146
ogistic regression test	P = 0.065	P = 0.296	P = 0.070
ochran-Armitage test	P = 0.050		
isher exact test		P = 0.277	P = 0.054
ancreatic Islets: Carcinoma			
verall rate	0/50 (0%)	1/50 (2%)	3/50 (6%)
djusted rate	0.0%	3.6%	8.5%
erminal rate	0/23 (0%)	1/28 (4%)	2/31 (6%)
irst incidence (days)	- D 011#	729 (T)	546
ife table test	P=0.115	P=0.539	P=0.161
ogistic regression test	P=0.088	P = 0.539	P = 0.121
ochran-Armitage test isher exact test	P = 0.086	P=0.500	P=0.121
ancreatic Islets: Adenoma or Carcinoma			
verall rate	5/50 (10%)	9/50 (18%)	15/50 (30%)
djusted rate	14.3%	27.8%	41.9%
erminal rate	1/23 (4%)	6/28 (21%)	11/31 (35%)
irst incidence (days)	595	643	546
ife table test	P=0.047	P=0.301	P=0.051
ogistic regression test	P=0.016	P = 0.213	P=0.016
Cochran-Armitage test	P=0.011	1-0.213	1 -0.010
isher exact test	. 0.011	P = 0.194	P = 0.011

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TABLE D3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Dichloromethane in Corn Oil (continued)

	2.5 mL/kg	5 mL/kg	10 mL/kg
Pituitary Gland (Pars Distalis): Aden	oma		
Overall rate	20/50 (40%)	18/49 (37%)	16/49 (33%)
Adjusted rate	58.2%	47.9%	41.2%
Terminal rate	10/23 (43%)	10/28 (36%)	9/30 (30%)
First incidence (days)	352	580	545 `
Life table test	P = 0.097N	P = 0.233N	P = 0.116N
Logistic regression test	P = 0.239N	P = 0.408N	P = 0.264N
Cochran-Armitage test	P = 0.273N		
Fisher exact test		P = 0.449N	P = 0.291N
Preputial Gland: Adenoma			
Overall rate	7/48 (15%)	1/44 (2%)	3/50 (6%)
Adjusted rate	24.5%	3.8%	9.7%
Terminal rate	3/22 (14%)	1/26 (4%)	3/31 (10%)
First incidence (days)	605	729 (T)	729 (T)
Life table test	P = 0.024N	P = 0.022N	P = 0.078N
Logistic regression test	P = 0.039N	P = 0.031N	P=0.110N
Cochran-Armitage test	P = 0.056N		
Fisher exact test		P=0.039N	P = 0.142N
Skin: Squamous Cell Papilloma, Ker			
Overall rate	4/50 (8%)	2/50 (4%)	0/50 (0%)
Adjusted rate	17.4%	7.1%	0.0%
Terminal rate	4/23 (17%)	2/28 (7%)	0/31 (0%)
First incidence (days)	729 (T)	729 (T)	-
Life table test	P=0.020N	P = 0.246N	P = 0.031N
Logistic regression test	P = 0.020N	P = 0.246N	P = 0.031N
Cochran-Armitage test	P=0.047N		
Fisher exact test		P = 0.339N	P=0.059N
Skin (Subcutaneous Tissue): Fibrom			
Overall rate	3/50 (6%)	7/50 (14%)	5/50 (10%)
Adjusted rate	10.9%	20.4%	13.9%
Terminal rate	1/23 (4%)	3/28 (11%)	3/31 (10%)
First incidence (days)	673 P. 0.202	615	579 D. 0.477
Life table test	P=0.392	P=0.249	P=0.477
Logistic regression test	P=0.286	P = 0.184	P = 0.379
Cochran-Armitage test	P=0.259	n 0.550	D 0.257
Fisher exact test	·	P=0.159	P=0.357
Skin (Subcutaneous Tissue): Fibrom		#IFO (2.19%)	(150 (400))
Overall rate	3/50 (6%)	7/50 (14%)	6/50 (12%)
Adjusted rate	10.9%	20.4%	16.5%
Terminal rate	1/23 (4%)	3/28 (11%)	3/31 (10%)
First incidence (days)	673 P. 0 200	615 D. 0.240	579 B-0.250
Life table test	P=0.300	P=0.249	P=0.359
Logistic regression test	P=0.203	P = 0.184	P = 0.264
Cochran-Armitage test	P = 0.181	D-0.150	P=0.242
Fisher exact test		P = 0.159	P=0.243

TABLE D3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Dichloromethane in Corn Oil (continued)

	2.5 mL/kg	5 mL/kg	10 mL/kg	
Testes: Adenoma				
Overall rate	43/50 (86%)	42/49 (86%)	44/50 (88%)	
Adjusted rate	100.0%	100.0%	97.8%	
Cerminal rate	23/23 (100%)	27/27 (100%)	30/31 (97%)	
irst incidence (days)	483	484	512	
ife table test	P = 0.062N	P=0.148N	P=0.086N	
ogistic regression test	P = 0.415N	P=0.448N	P=0.504N	
Cochran-Armitage test	P=0.476	2 0111021	. 0.00 1.1	
isher exact test		P = 0.597N	P=0.500	
hyroid Gland (C-cell): Adenoma				
overall rate	6/48 (13%)	7/49 (14%)	9/48 (19%)	
Adjusted rate	24.4%	23.3%	28.1%	-
erminal rate	5/23 (22%)	6/28 (21%)	8/31 (26%)	
irst incidence (days)	699	585	724	
ife table test	P=0.477	P = 0.603N	P=0.517	
ogistic regression test	P=0.395	P = 0.601	P=0.460	
Cochran-Armitage test	P=0.268	1 -0.001	1 0.400	
isher exact test	1 -0.200	P = 0.516	P=0.288	
hyroid Gland (C-cell): Adenoma or C	'arcinoma			
verall rate	6/48 (13%)	9/49 (18%)	9/48 (19%)	
Adjusted rate	24.4%	27.5%	28.1%	•
'erminal rate				
	5/23 (22%)	6/28 (21%)	8/31 (26%)	
irst incidence (days)	699 P=0.440	580 P=0.414	724 P-0 517	
ife table test		P=0.414	P=0.517	
ogistic regression test	P=0.335	P = 0.355	P=0.460	
Cochran-Armitage test Fisher exact test	P=0.239	P = 0.303	P=0.288	
Changid Cloud (Falliowless Call), Adams				
Thyroid Gland (Follicular Cell): Adeno Overall rate		0/40 (0%)	2/49 (40%)	
	3/48 (6%)	0/49 (0%)	2/48 (4%)	•
Adjusted rate	13.0%	0.0%	6.1%	
erminal rate	3/23 (13%)	0/28 (0%)	0/31 (0%)	
first incidence (days)	729 (T)	- A 00221	705	
ife table test	P=0.229N	P=0.087N	P=0.377N	
ogistic regression test	P=0.248N	P = 0.087N	P=0.410N	
Cochran-Armitage test Fisher exact test	P = 0.316N	P=0.117N	P=0.500N	٠
Thyroid Gland (Follicular Cell): Adend		0/40 (0%)	2/49 (40%)	٠.
Overall rate	5/48 (10%)	0/49 (0%)	2/48 (4%)	
Adjusted rate	18.1%	0.0%	6.1%	
Terminal rate	3/23 (13%)	0/28 (0%)	0/31 (0%)	
irst incidence (days)	598	- D 0.032N	705	
ife table test	P=0.046N	P=0.023N	P=0.143N	
ogistic regression test	P=0.061N	P = 0.027N	P=0.183N	
Cochran-Armitage test	P=0.074N		D 0000	
isher exact test		P = 0.027N	P = 0.218N	

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TABLE D3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Dichloromethane in Corn Oil (continued)

	2.5 mL/kg	5 mL/kg	10 mL/kg
All Organs: Mononuclear Cell Leukemia			
Overall rate	13/50 (26%)	14/50 (28%)	5/50 (10%)
Adjusted rate	43.0%	37.4%	12.4%
Terminal rate	7/23 (30%)	6/28 (21%)	1/31 (3%)
First incidence (days)	605	580	574
Life table test	P = 0.025N	P = 0.468N	P = 0.015N
Logistic regression test	P = 0.047N	P = 0.577	P = 0.026N
Cochran-Armitage test	P = 0.065N		
Fisher exact test		P = 0.500	P = 0.033N
All Organs: Malignant Mesothelioma			
Overall rate	2/50 (4%)	3/50 (6%)	2/50 (4%)
Adjusted rate	8.2%	9.3%	6.5%
Ferminal rate	1/23 (4%)	2/28 (7%)	2/31 (6%)
First incidence (days)	723	580	729 (T)
Life table test	P = 0.554N	P = 0.568	P = 0.588N
Logistic regression test	P = 0.618N	P = 0.528	P = 0.619N
Cochran-Armitage test	P = 0.583		
Fisher exact test		P = 0.500	P = 0.691N
All Organs: Benign Neoplasms			
Overall rate	48/50 (96%)	47/50 (94%)	48/50 (96%)
Adjusted rate	100.0%	100.0%	100.0%
Terminal rate	23/23 (100%)	28/28 (100%)	31/31 (100%)
First incidence (days)	309	484	512
Life table test	P = 0.053N	P = 0.133N	P = 0.073N
Logistic regression test	P = 0.373N	P = 0.414N	P = 0.711N
Cochran-Armitage test	P=0.583N		•
Fisher exact test		P = 0.500N	P = 0.691N
All Organs: Malignant Neoplasms			
Overall rate	25/50 (50%)	21/50 (42%)	20/50 (40%)
Adjusted rate	68.1%	52.7%	49.1%
Terminal rate	12/23 (52%)	10/28 (36%)	11/31 (35%)
First incidence (days)	572	536	546
Life table test	P = 0.054N	P = 0.139N	P=0.067N
Logistic regression test	P = 0.125N	P = 0.212N	P=0.148N
Cochran-Armitage test	P = 0.178N		
Fisher exact test		P=0.274N	P = 0.211N
All Organs: Benign or Malignant Neoplasms			
Overall rate	48/50 (96%)	47/50 (94%)	48/50 (96%)
Adjusted rate	100.0%	100.0%	100.0%
Terminal rate	23/23 (100%)	28/28 (100%)	31/31 (100%)
First incidence (days)	309	484	512
Life table test	P = 0.053N	P = 0.133N	P = 0.073N
Logistic regression test	P = 0.373N	P=0.414N	P = 0.711N
Cochran-Armitage test	P = 0.583N		
Fisher exact test		P = 0.500N	P = 0.691N

#### TABLE D3

# Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Dichloromethane in Corn Oil (continued)

# (T)Terminal sacrifice

a Volumes are given as 500 mg dichloromethane/kg body weight in mL corn oil/kg body weight.

Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, bone marrow, brain, epididymis, heart, kidney, larynx, liver, lung, nose, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, spleen, testes, thyroid gland, and urinary bladder; for other tissues, denominator is number of animals necropsied.

Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality

d Observed incidence at terminal kill

e Beneath the low-dose incidence are the P values associated with the trend test. Beneath the mid- and high-dose group incidence are the P values corresponding to pairwise comparisons between the low-dose group and that dosed group. The life table test regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.

Not applicable; no neoplasms in animal group

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Table D4 Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Dichloromethane in Corn  $\mathrm{Oil}^2$ 

	2.5 mL/kg	5 mL/kg	10 mL/kg
Disposition Summary			
Animals initially in study	50	50	50
	30	30	50
Early deaths Accidental deaths	4	1	2
	19	13	12
Moribund	4	8	5
Natural deaths	4	8	3
Survivors	23	28	31
Terminal sacrifice	is .	28	31
Animals examined microscopically	50	50	50
Alimentary System			
Esophagus	(49)	(49)	(50)
Hemorrhage	1 (2%)	` /	` /
Inflammation, chronic active	(=)		1 (2%)
Necrosis	1 (2%)		` '
Liver	(50)	(50)	(50)
Angiectasis	1 (2%)	` '	` '
Basophilic focus	32 (64%)	38 (76%)	44 (88%)
Clear cell focus	11 (22%)	12 (24%)	10 (20%)
Eosinophilic focus	11 (2270)	9 (18%)	3 (6%)
Fatty change, diffuse	13 (26%)	26 (52%)	45 (90%)
Fatty change, focal	1 (2%)	1 (2%)	4 (8%)
Fibrosis	1 (2%)	1 (2/0)	. (675)
Hepatodiaphragmatic nodule	6 (12%)	4 (8%)	5 (10%)
Infarct	0 (12/0)	. (670)	1 (2%)
Inflammation, chronic active		1 (2%)	1 (270)
Mixed cell focus	20 (40%)	14 (28%)	19 (38%)
Necrosis	2 (4%)	14 (20%)	1 (2%)
Pigmentation	1 (2%)		1 (270)
Thrombosis	1 (2%)		
Mesentery		(10)	(7)
Thrombosis	(12)	(10)	(7)
	1 (8%)	1 (100/)	
Fat, inflammation, chronic active		1 (10%)	
Fat, mineralization	O (TEM)	2 (20%)	2 (20%)
Fat, necrosis	9 (75%)	7 (70%)	2 (29%)
Fat, pigmentation	1 (8%)	(50)	450
Pancreas	(50)	(50)	(50)
Hyperplasia	A0 (#/~)	1 (2%)	
Acinus, atrophy	28 (56%)	26 (52%)	21 (42%)
Acinus, hyperplasia	28 (56%)	38 (76%)	44 (88%)
Artery, fibrosis		<b>_</b>	1 (2%)
Artery, inflammation, chronic active	3 (6%)	2 (4%)	2 (4%)
Artery, mineralization	1 (2%)	1 (2%)	2 (4%)
Artery, thrombosis			3 (6%)
Salivary glands	(50)	(50)	(49)
Hemorrhage	1 (2%)		
Duct, metaplasia, squamous	1 (2%)	3 (6%)	1 (2%)

Doses are given as 500 mg dichloromethane/kg body weight in mL corn oil/kg body weight. Number of animals examined microscopically at site and number of animals with lesion.

TABLE D4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Dichloromethane in Corn Oil (continued)

	2.5 mL/kg	5 mL/kg	10 mL/kg	
Alimentary System (continued)				
Stomach, forestomach	(49)	(50)	(50)	٠.
Hyperkeratosis	1 (2%)	(30)	1 (2%)	
Hyperplasia, basal cell	7 (14%)	3 (6%)	7 (14%)	
Hyperplasia, focal, squamous	7 (1470)	1 (2%)	1 (2%)	
Inflammation, acute		1 (270)	2 (4%)	
Ulcer			6 (12%)	
Stomach, glandular	(50)	(40)		•
	(30)	(48)	(48)	
Inflammation, chronic active	1 (201)	•	1 (2%)	
Mineralization	1 (2%)	1 (00)	•	
Necrosis	1 (2%)	1 (2%)		100
Ulcer	1 (2%)			
Tongue	(1)		(2)	
Hyperkeratosis	1 (100%)		•	
	<del> </del>	<del></del>		1 1
Cardiovascular System				•
Heart	(50)	(50)	(50)	
Cardiomyopathy	38 (76%)	39 (78%)	34 (68%)	
Thrombosis	` ,	, ,	1 (2%)	
Endocrine System			<del></del>	
	(40)	(45)	(50)	•
Adrenal gland, cortex	(49)	(45)	(50)	
Accessory adrenal cortical nodule	1 (2%)	(45)	(50)	
Adrenal gland, medulla	(49)	(45)	(50)	1
Hyperplasia	10 (20%)	11 (24%)	9 (18%)	
Islets, pancreatic	(50)	(50)	(50)	
Hyperplasia	7 (14%)	5 (10%)	7 (14%)	*,
Metaplasia	2 (4%)	2 (4%)	1 (2%)	•
Parathyroid gland	(44)	(45)	(47)	
Hyperplasia	1 (2%)		•	
Pituitary gland	(50)	(49)	(49)	
Angiectasis	1 (2%)			
Necrosis	1 (2%)			5
Pars distalis, angiectasis	8 (16%)	14 (29%)	9 (18%)	
Pars distalis, cyst	1 (2%)		1 (2%)	• •
Pars distalis, hyperplasia	9 (18%)	10 (20%)	7 (14%)	
Thyroid gland	(48)	(49)	(48)	
C-cell, hyperplasia	5 (10%)	3 (6%)	15 (31%)	
Follicle, cyst	1 (2%)	` '	1 (2%)	
Policie, cysi				

**General Body System** 

None

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TABLE D4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Dichloromethane in Corn Oil (continued)

	2.5 mL/kg	5 mL/kg	10 mL/kg
Genital System			
Prostate	(50)	(49)	(48)
Hyperplasia	7 (14%)	4 (8%)	12 (25%)
Testes .	(50)	(49)	(50)
Thrombosis	()	` '	1 (2%)
Interstitial cell, hyperplasia	2 (4%)	5 (10%)	5 (10%)
Seminiferous tubule, atrophy	2 (4%)	3 (6%)	3 (6%)
Hematopoletic System			
Lymph node	(50)	(50)	(50)
Bronchial, pigmentation	(50)	(50)	1 (2%)
Mediastinal, angiectasis	1 (2%)		- (=)
Mediastinal, hematopoietic cell proliferation	1 (2%)		
Mediastinal, pigmentation	2 (4%)	1 (2%)	1 (2%)
Lymph node, mandibular	(50)	(50)	(47)
Angiectasis	1 (2%)	(30)	(37)
Hematopoietic cell proliferation	1 (2%)		
Spleen	(49)	(50)	(50)
Fibrosis	3 (6%)	2 (4%)	3 (6%)
Hematopoietic cell proliferation	21 (43%)	18 (36%)	19 (38%)
Hemorrhage	1 (2%)	18 (30%)	15 (50%)
Infarct	1 (270)	2 (4%)	2 (4%)
Thymus	(47)	(48)	(44)
Necrosis	(.,)	()	1 (2%)
Integumentary System			
Mammary gland	(42)	(36)	(37)
Galactocele	2 (5%)	2 (6%)	()
Skin	(50)	(50)	(50)
Cyst epithelial inclusion	()	1 (2%)	()
Hyperkeratosis		1 (2%)	1 (2%)
Inflammation, acute		- (=/=/	1 (2%)
Necrosis		1 (2%)	- (-/-)
	-		
Musculoskeletai System			
Skeletal muscle	(3)	(2)	(2)
Necrosis	1 (33%)		

TABLE D4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Dichloromethane in Corn Oil (continued)

	2.5 mL/kg	5 mL/kg	10 mL/kg
Respiratory System	· ·		
Lung	(50)	(50)	(49)
Edema		1 (2%)	2 (4%)
Hemorrhage	3 (6%)	1 (2%)	4 (8%)
Infiltration cellular, histiocyte	3 (6%)	2 (4%)	3 (6%)
Inflammation, acute	2 (4%)	_ (.,.,	2 (3,0)
Inflammation, chronic active	- ()	3 (6%)	
Metaplasia, squamous			1 (2%)
Alveolar epithelium, hyperplasia		4 (8%)	2 (4%)
Mediastinum, hemorrhage	1 (2%)	(675).	- ( * ~ )
Mediastinum, inflammation, acute	1 (1/0)		1 (2%)
Mediastinum, pigmentation		1 (2%)	- (=/0)
Nose	(50)	(50)	(50)
Fungus	6 (12%)	4 (8%)	3 (6%)
Inflammation, acute	11 (22%)	6 (12%)	9 (18%)
Respiratory epithelium, hyperkeratosis	1 (2%)	- ()	(22,73)
Respiratory epithelium, hyperplasia	4 (8%)	2 (4%)	4 (8%)
Respiratory epithelium, metaplasia, squamous	3 (6%)	2 (***)	
Prachea	(50)	(50)	(50)
Erosion	()	1 (2%)	1 (2%)
Special Senses System			
Eye	(1)	(3)	
Hemorrhage		1 (33%)	
Inflammation, chronic active		1 (33%)	
Lens, cataract	1 (100%)	1 (33%)	
Retina, atrophy		1 (33%)	
Urinary System			
Kidney	(50)	(50)	(50)
Cyst	• •		1 (2%)
Developmental malformation	1 (2%)		
Nephropathy	42 (84%)	38 (76%)	29 (58%)
Cortex, mineralization	1 (2%)	1 (2%)	` '
Renal tubule, hyperplasia	1 (2%)	` '	
Urinary bladder	(49)	(49)	(49)
Calculus microscopic observation only	1 (2%)	` /	• •

## APPENDIX E GENETIC TOXICOLOGY

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## **GENETIC TOXICOLOGY**

## SALMONELLA TYPHIMURIUM MUTAGENICITY TEST PROTOCOL

Testing was performed with dichloromethane as reported by Zeiger (1990). For corn oil, safflower oil, and tricaprylin, testing was performed as reported by Zeiger et al. (1988). All chemicals were sent to the laboratory as coded aliquots from Radian Corporation (Austin, TX). Dichloromethane was tested three times, twice with a preincubation protocol and once in a sealed desiccator to control for volatility. In the preincubation experiments, dichloromethane was incubated with the Salmonella typhimurium tester strains TA97, TA98, TA100, TA1535, and TA1537 either in buffer or S9 mix (metabolic activation enzymes and cofactors from Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver) for 20 minutes at 37° C. Top agar supplemented with *l*-histidine and *d*-biotin was added, and the contents of the tubes were mixed and poured onto the surfaces of minimal glucose agar plates. Histidine-independent mutant colonies arising on these plates were counted following incubation for 2 days at 37° C. Corn oil, safflower oil, and tricaprylin were tested with a preincubation protocol, as described above, using strains TA97, TA98, TA100, and TA1535.

Dichloromethane was tested as a vapor using a desiccator procedure (Zeiger, 1990). The S. typhimurium strains TA98 and TA100 and S9 mix or buffer were each incorporated into the top agar and poured onto a minimal medium plate. The lids of the plates were removed and the plates were stacked on a perforated porcelain plate in a 9-liter desiccator jar containing a magnetic stirring bar. A measured volume of dichloromethane, in liquid form, was introduced into a glass petri dish suspended below the porcelain plate. The desiccator was sealed and placed on a magnetic stirrer in a 37° C incubator. After 24 hours, the plates were removed from the desiccator and incubated at 37° C, in air, for an additional 24 hours. The dose was expressed as mL dichloromethane per desiccator.

Each trial consisted of triplicate plates of concurrent positive and negative controls and at least five doses of dichloromethane. In the absence of toxicity,  $10,000 \mu g/\text{plate}$ , or 5.0 mL in the desiccator, was selected as the high dose (a high dose of  $16,666 \mu g/\text{plate}$  was used for tricaprylin). All positive trials were repeated under the conditions that elicited the positive response.

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

## MOUSE LYMPHOMA MUTAGENICITY TEST PROTOCOL

The experimental protocol is presented in detail by Myhr et al. (1990). Dichloromethane was supplied as a coded aliquot by Radian Corporation. The high dose of dichloromethane was determined by solubility and toxicity and did not exceed 3.0  $\mu$ L/mL in the absence of toxicity. L5178Y mouse lymphoma cells were maintained at 37° C as suspension cultures in Fischer's medium supplemented with *l*-glutamine, sodium pyruvate, pluronic F68, antibiotics, and heat-inactivated horse serum; normal cycling time was approximately 10 hours. To reduce the number of spontaneously occurring trifluorothymidine-resistant cells, subcultures were exposed to medium containing THMG (thymidine, hypoxanthine, methotrexate, and glycine) for 1 day, to medium containing THG for 1 day, and to normal medium for 3 to 5 days. For cloning, the horse serum content was increased and Noble agar was added.

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All treatment levels within an experiment, including concurrent positive and solvent controls, were replicated. Treated cultures contained  $6 \times 10^6$  cells in 10 mL medium. This volume included the S9 fraction in those experiments performed with metabolic activation. Cells were incubated with dichloromethane for 4 hours, after which time the medium with dichloromethane was removed and the cells were resuspended in fresh medium and incubated for an additional 2 days to express the mutant phenotype. Cell density was monitored so that log phase growth was maintained. After the 48-hour expression period,  $3 \times 10^6$  cells were plated in medium and soft agar supplemented with trifluorothymidine (TFT) for selection of TFT-resistant (TK<sup>-/-</sup>) cells; 600 cells were plated in nonselective medium and soft agar to determine cloning efficiency. Plates were incubated at 37° C in 5% CO<sub>2</sub> for 10 to 12 days. The test was initially performed without S9. If a clearly positive response was not obtained, the test was repeated using freshly prepared S9 from the livers of Aroclor 1254-induced male Fischer 344 rats.

Minimum criteria for accepting an experiment as valid and a detailed description of the statistical analysis and data evaluation are presented in Caspary et al. (1988). All data were evaluated statistically for trend and peak responses. Both responses had to be significant ( $P \le 0.05$ ) for dichloromethane to be considered positive, i.e., capable of inducing TFT resistance. A single significant response led to a "questionable" conclusion, and the absence of both a trend and peak response resulted in a "negative" call.

### CHINESE HAMSTER OVARY CELL CYTOGENETICS PROTOCOLS

Testing was performed as reported by Anderson et al. (1990). Dichloromethane was sent to the laboratory as a coded aliquot by Radian Corporation. It was tested in cultured Chinese hamster ovary (CHO) cells for induction of sister chromatid exchanges (SCEs) and chromosomal aberrations (Abs), both in the presence and absence of Aroclor 1254-induced male Sprague-Dawley rat liver S9 and cofactor mix. Cultures were handled under gold lights to prevent photolysis of bromodeoxyuridine-substituted DNA. Each test consisted of concurrent solvent and positive controls and of at least three doses of dichloromethane. In the absence of toxicity,  $5,000 \mu g/mL$  was selected as the high dose. A single flask per dose was used, and tests yielding equivocal or positive results were repeated.

Sister Chromatid Exchange Test: In the SCE test without S9, CHO cells were incubated for 26 hours with dichloromethane in McCoy's 5A medium supplemented with fetal bovine serum, *l*-glutamine, and antibiotics. Bromodeoxyuridine (BrdU) was added 2 hours after culture initiation. After 26 hours, the medium containing dichloromethane was removed and replaced with fresh medium plus BrdU and Colcemid, and incubation was continued for 2 hours. Cells were then harvested by mitotic shake-off, fixed, and stained with Hoechst 33258 and Giemsa. In the SCE test with S9, cells were incubated with dichloromethane, serum-free medium, and S9 for 2 hours. The medium was then removed and replaced with medium containing serum and BrdU and no dichloromethane and incubation proceeded for an additional 26 hours, with Colcemid present for the final 2 hours. Harvesting and staining were the same as for cells treated without S9. All slides were scored blind and those from a single test were read by the same person. Fifty second-division metaphase cells were scored for frequency of SCEs/cell from each dose level.

Statistical analyses were conducted on the slopes of the dose-response curves and the individual dose points (Galloway et al., 1987). An SCE frequency 20% above the concurrent solvent control value was chosen as a statistically conservative positive response. The probability of this level of difference occurring by chance at one dose point is less than 0.01; the probability for such a chance occurrence at two dose points is less than 0.001. An increase of 20% or greater at any single dose was considered weak evidence of activity; increases at two or more doses resulted in a determination that the trial was positive. A statistically significant trend (P<0.05) in the absence of any responses reaching 20% above background led to a call of equivocal.

Chromosomal Aberrations Test: In the Abs test without S9, cells were incubated in McCoy's 5A medium with dichloromethane for 10 hours; Colcemid was added and incubation continued for 2 hours. The cells were then harvested by mitotic shake-off, fixed, and stained with Giemsa. For the Abs test with S9, cells were treated with dichloromethane and S9 for 2 hours, after which the treatment medium was removed and the cells were incubated for 11 hours in fresh medium, with Colcemid present for the final 2 hours. Cells were harvested in the same manner as for the treatment without S9.

Cells were selected for scoring on the basis of good morphology and completeness of karyotype  $(21 \pm 2 \text{ chromosomes})$ . All slides were scored blind and those from a single test were read by the same person. Two hundred first-division metaphase cells were scored at each dose level. Classes of aberrations included simple (breaks and terminal deletions), complex (rearrangements and translocations), and other (pulverized cells, despiralized chromosomes, and cells containing 10 or more aberrations).

Chromosomal aberration data are presented as percentage of cells with aberrations. To arrive at a statistical call for a trial, analyses were conducted on both the dose response curve and individual dose points. For a single trial, a statistically significant ( $P \le 0.05$ ) difference for one dose point and a significant trend ( $P \le 0.015$ ) were considered weak evidence for a positive response; significant differences for two or more doses indicated the trial was positive. A positive trend test in the absence of a statistically significant increase at any one dose resulted in an equivocal call (Galloway et al., 1987). Ultimately, the trial calls were based on a consideration of the statistical analyses as well as the biological information available to the reviewers.

### RESULTS

Corn oil and safflower oil (100 to 10,000  $\mu$ g/plate) were tested for mutagenicity in Salmonella typhimurium strains TA97, TA98, TA100, and TA1535, using a preincubation protocol with and without hamster or rat S9 liver activation enzymes (Tables E1a,b). Neither oil produced an increase in revertants. Corn oil is used routinely as a solvent for *in vivo* bone marrow chromosome studies with mice. A comparison of saline- and corn oil-treated control groups shows no differences between these groups in frequencies of sister chromatid exchanges, chromosomal aberrations, or micronuclei (NTP, unpublished data).

Tricaprylin (Table E1c), however, was mutagenic in *S. typhimurium* strain TA1535 in the presence of hamster or rat S9, but only at very high concentrations (6,666 to 16,666  $\mu$ g/plate). No mutagenic activity was detected in strains TA97, TA98, or TA100 when treated with tricaprylin, with or without S9.

Dichloromethane was tested in two separate studies for induction of mutations in S. typhimurium (Table E1d; Zeiger, 1990). Using a preincubation protocol that did not control for volatility, dichloromethane (100 to 10,000  $\mu$ g/plate) did not induce mutations in strains TA97, TA98, TA100, TA1535, or TA1537, with or without S9 activation enzymes. However, when exposure occurred within the closed environment of a desiccator, dichloromethane (up to 1.0 mL/chamber) produced a positive response in strain TA100, with and without S9, and in TA98, but only in the presence of hamster liver S9.

Dichloromethane was tested for mutagenicity in L5178Y mouse lymphoma cells with and without S9 (Table E2; Myhr et al., 1990). Both with and without S9, the first of the three trials was positive, the second was judged equivocal, and the third trial in each case was negative. Therefore, the overall results for the test were considered equivocal. Although a significant increase in mutant colonies was observed at the highest dose tested in the third trial without S9, the presence of a precipitate at this concentration invalidated the data and the trial was judged negative.

No increase in sister chromatid exchanges (Table E3) or chromosomal aberrations (Table E4) was observed in Chinese hamster ovary cells treated with dichloromethane (up to 5,000  $\mu$ g/mL) in the presence or the absence of S9 (Anderson *et al.*, 1990).

TABLE E1a
Mutagenicity of Corn Oil in Salmonella typhimurium<sup>a</sup>

Strain	Mose		Revertants/plate <sup>b</sup>					
	Dose	S9		+hams		<u>+rat</u>	S9	
	(μg/plate)	Trial 1	Trial 2	10%	30%	10%	30%	
TA100	0	88 ± 5.2	129 ± 0.6	120 ± 16.5	89 ± 1.9	143 ± 5.5	117 ± 5.6	
	100	$80 \pm 2.7$	99 ± 0.9	$124 \pm 17.7$	$95 \pm 6.4$	$136 \pm 6.7$	131 ± 8.4	
	333	$94 \pm 4.9$	$103 \pm 2.9$	$117 \pm 11.9$	$107 \pm 10.2$	$138 \pm 7.6$	126 ± 10.5	
	1,000	$79 \pm 1.2$	$107 \pm 3.5$	$108 \pm 15.1$	$103 \pm 10.8$	$135 \pm 3.1$	$115 \pm 16.0$	
	3,333	$88 \pm 2.3$	$116 \pm 4.1$	$112 \pm 8.5$	$94 \pm 9.5$	$134 \pm 2.3$	$113 \pm 14.1$	
	10,000	$81 \pm 3.2$	$103 \pm 6.4$	$103 \pm 0.3$	$96 \pm 5.0$	$131 \pm 9.2$	$110 \pm 18.2$	
Trial sum	• -	Negative	Negative	Negative	Negative	Negative	Negative	
Positive co	ontrol <sup>c</sup>	872 ± 14.7	$795 \pm 8.2$	831 ± 88.5	691 ± 38.6	$344 \pm 4.9$	408 ± 9.3	
TA1535	0	5 ± 1.2	9 ± 1.8	10 ± 0.3	6 ± 0.6	10 ± 0.6	8 ± 1.5	
	100	$6 \pm 1.5$	12 ± 1.9	$10 \pm 2.0$	7 ± 1.2	$12 \pm 0.3$	9 ± 0.0	
	333	$5 \pm 0.6$	13 ± 1.5	9 ± 1.0	$3 \pm 0.9$	$10 \pm 2.3$	7 ± 0.7	
	1,000	$6 \pm 0.6$	$11 \pm 0.6$	$9 \pm 2.6$	$7 \pm 1.5$	11 ± 1.5	8 ± 0.7	
	3,333	$4 \pm 1.3$	$11 \pm 1.5$	$8 \pm 0.0$	$4 \pm 1.2$	$11 \pm 1.8$	7 ± 0.9	
	10,000	$3 \pm 0.3$	$11 \pm 2.0$	$10 \pm 0.9$	$8 \pm 0.9$	12 ± 1.2	9 ± 0.9	
Trial sum	•	Negative	Negative	Negative	Negative	Negative	Negative	
Positive co	ontroi	449 ± 32.5	836 ± 54.9	$107 \pm 5.8$	$176 \pm 17.0$	54 ± 1.0	73 ± 3.3	
TA97	0	128 ± 4.6	163 ± 10.9	174 ± 6.9	145 ± 5.0	169 ± 7.1	179 ± 8.5	
	100	$126 \pm 5.5$	$154 \pm 8.3$	$174 \pm 2.3$	$145 \pm 6.5$	$168 \pm 8.7$	159 ± 2.9	
	333	$127 \pm 6.5$	$158 \pm 8.0$	$163 \pm 5.5$	$133 \pm 14.8$	$151 \pm 14.0$	$173 \pm 2.6$	
	1,000	$126 \pm 7.3$	$185 \pm 0.9$	$166 \pm 7.0$	$143 \pm 7.1$	$176 \pm 11.5$	$185 \pm 8.1$	
	3,333	$115 \pm 4.3$	$164 \pm 8.6$	$159 \pm 8.0$	$162 \pm 11.5$	$167 \pm 7.9$	$199 \pm 3.2$	
	10,000	$134 \pm 2.3$	$193 \pm 3.5$	$187 \pm 9.4$	$139 \pm 7.6$	$165 \pm 18.4$	$205 \pm 4.7$	
Trial sumi	mary	Negative	Negative	Negative	Negative	Negative	Negative	
Positive co	ontrol	$553 \pm 26.8$	$426 \pm 29.4$	$446 \pm 20.9$	$367 \pm 9.7$	310 ± 1.0	386 ± 10.6	
TA98	0	18 ± 1.9	17 ± 0.9	29 ± 5.9	20 ± 4.2	31 ± 5.3	39 ± 3.5	
	100	$18 \pm 2.0$	23 ± 1.5	$22 \pm 2.8$	20 ± 4.2 22 ± 1.3	$23 \pm 5.0$	39 ± 3.3 22 ± 4.7	
	333	$20 \pm 3.2$	$19 \pm 2.7$	$20 \pm 3.7$	$21 \pm 4.2$	$23 \pm 4.3$	22 ± 4.7 22 ± 3.7	
	1,000	$18 \pm 3.5$	16 ± 3.2	23 ± 3.5	$26 \pm 3.3$	$27 \pm 4.3$ $27 \pm 2.0$	18 ± 1.7	
	3,333	19 ± 4.2	16 ± 1.9	23 ± 1.5	22 ± 1.8	$19 \pm 4.0$	17 ± 3.9	
	10,000	$18 \pm 3.5$	$17 \pm 2.3$	$21 \pm 2.8$	$20 \pm 0.9$	$24 \pm 5.5$	24 ± 6.7	
Trial sum	•	Negative	Negative	Negative	Negative	Negative	Negative	
Positive co	ontrol	528 ± 41.1	$777 \pm 9.2$	$954 \pm 30.9$	$503 \pm 36.3$	$262 \pm 11.5$	141 ± 5.8	

<sup>&</sup>lt;sup>a</sup> Study performed at SRI, International. The detailed protocol is presented in Zeiger et al. (1988).

Revertants are presented as mean ± standard error from three plates.

The positive controls in the absence of metabolic activation were sodium azide (TA100 and TA1535), 9-aminoacridine (TA97), and 4-nitro-o-phenylenediamine (TA98). The positive control for metabolic activation with all strains was 2-aminoanthracene.

TABLE E1b
Mutagenicity of Safflower Oil in Salmonella typhimurium<sup>a</sup>

	19.8	Revertants/plate <sup>b</sup>						
Strain	Dose				+hamster S9		9 :	
7	(μg/plate)	Trial 1	Trial 2	10%	30%	10%	30%	
TA100	0	108 ± 5.0	116 ± 6.4	118 ± 3.8	99 ± 9.8	140 ± 11.7	140 ± 9.2	
	100	$93 \pm 4.9$	$110 \pm 6.4$	$124 \pm 4.0$	$93 \pm 3.5$	$128 \pm 8.5$	126 ± 1.9	
	333	$81 \pm 3.2$	$119 \pm 5.5$	$143 \pm 6.9$	$109 \pm 2.0$	$121 \pm 15.5$	$116 \pm 11.0$	
	1,000	$83 \pm 5.2$	$115 \pm 9.3$	$142 \pm 6.6$	$113 \pm 3.8$	116 ± 4.8	$117 \pm 6.4$	
	3,333	$85 \pm 4.2$	$130 \pm 4.6$	$136 \pm 3.8$	$102 \pm 3.8$	$117 \pm 6.6$	$128 \pm 3.6$	
	10,000	$91 \pm 13.0$	$118 \pm 3.2$	$143 \pm 4.3$	$117 \pm 6.5$	$142 \pm 11.6$	$139 \pm 6.1$	
Trial sum		Negative	Negative	Negative	Negative	Negative	Negative	
Positive co	ontrol	872 ± 14.7	795 ± 8.2	831 ± 88.5	691 ± 38.6	344 ± 4.9	408 ± 9.3	
TA1535	0	4 ± 1.2	12 ± 0.9	10 ± 1.5	7 ± 0.9	16 ± 2.9	9 ± 0.7	
	100	$4 \pm 0.0$	$7 \pm 0.6$	$10 \pm 2.0$	7 ± 1.8	$14 \pm 0.9$	14 ± 0.3	
	333	$6 \pm 1.5$	$8 \pm 0.7$	$8 \pm 1.5$	9 ± 2.3	$10 \pm 1.5$	11 ± 1.8	
3	1,000	$3 \pm 0.0$	$12 \pm 2.0$	$9 \pm 1.2$	5 ± 1.5	9 ± 1.5	9 ± 0.9	
*	3,333	$5 \pm 0.6$	$10 \pm 1.8$	$8 \pm 0.6$	$8 \pm 1.2$	$12 \pm 3.4$	$12 \pm 0.7$	
	10,000	5 ± 1.2	6 ± 1.0	8 ± 1.5	$6 \pm 0.6$	11 ± 0.6	$10 \pm 2.2$	
Trial sum	•	Negative	Negative	Negative	Negative	Negative	Negative	
Positive co	ontrol	$449 \pm 32.5$	$836 \pm 54.9$	$107 \pm 5.8$	176 ± 17.0	54 ± 1.0	$73 \pm 3.3$	
. /:								
TA97	0	$149 \pm 6.6$	$165 \pm 5.8$	$168 \pm 5.6$	$148 \pm 6.1$	$189 \pm 5.7$	$196 \pm 8.4$	
	100	$137 \pm 5.8$	$174 \pm 4.7$	$149 \pm 18.0$	$132 \pm 3.6$	$213 \pm 3.2$	$213 \pm 6.4$	
	333	$135 \pm 9.4$	$168 \pm 4.5$	$167 \pm 2.6$	$134 \pm 5.9$	$206 \pm 4.7$	$206 \pm 14.8$	
	1,000	$139 \pm 22.5$	$169 \pm 6.7$	$155 \pm 2.6$	$155 \pm 16.3$	$193 \pm 7.2$	$230 \pm 3.7$	
	3,333	$140 \pm 7.6$	$173 \pm 4.2$	$165 \pm 6.6$	$154 \pm 0.7$	$192 \pm 3.8$	$224 \pm 3.5$	
	10,000	143 ± 17.6	$162 \pm 8.1$	166 ± 3.1	161 ± 4.6	$181 \pm 14.7$	$216 \pm 10.9$	
Trial sum	mary	Negative	Negative	Negative	Negative	Negative	Negative	
Positive co	ontrol	$553 \pm 26.8$	$426 \pm 29.4$	$446 \pm 20.9$	$367 \pm 9.7$	$310 \pm 1.0$	$386 \pm 10.6$	
,			•	1				
TA98	0	$32 \pm 4.6$	$18 \pm 0.6$	$36 \pm 5.9$	$24 \pm 3.2$	$47 \pm 4.1$	46 ± 1.5	
	100	$22 \pm 3.7$	$18 \pm 0.9$	$25 \pm 9.3$	$17 \pm 0.9$	$38 \pm 7.0$	$36 \pm 2.9$	
	333	$24 \pm 3.1$	$16 \pm 0.0$	$29 \pm 6.2$	$30 \pm 1.9$	46 ± 3.4	38 ± 3.6	
	1,000	$22 \pm 2.7$	$22 \pm 3.4$	$35 \pm 3.3$	$21 \pm 3.1$	$35 \pm 4.4$	$26 \pm 6.2$	
	3,333	$20 \pm 2.6$	$17 \pm 0.9$	$31 \pm 7.8$	$17 \pm 1.5$	$42 \pm 7.7$	$25 \pm 4.3$	
	10,000	24 ± 6.1	$19 \pm 2.1$	$31 \pm 8.4$	22 ± 3.2	$34 \pm 5.6$	$31 \pm 5.9$	
Trial sum	•	Negative	Negative	Negative	Negative	Negative	Negative	
Positive co	ontrol	$528 \pm 41.1$	$777 \pm 9.2$	$954 \pm 30.9$	$503 \pm 36.3$	$262 \pm 11.5$	$141 \pm 5.8$	

Study performed at SRI, International. The detailed protocol is presented in Zeiger et al. (1988).

b Revertants are presented as mean ± standard error from three plates.

The positive controls in the absence of metabolic activation were sodium azide (TA100 and TA1535), 9-aminoacridine (TA97), and 4-nitro-o-phenylenediamine (TA98). The positive control for metabolic activation with all strains was 2-aminoanthracene.

TABLE E1c Mutagenicity of Tricaprylin in Salmonella typhimurium<sup>a</sup>

			Revertants/plate <sup>b</sup>					
Strain	Dose	S9	-S9 +30% hamster S9				-30% rat S9	
· G	ug/plate)		Trial 1	Trial 2	Trial 3	Trial 1	Trial 2	Trial 3
TA100	0 .	144 ± 17.7	137 ± 7.0			193 ± 8.5		
	100	169 ± 5.2	$135 \pm 4.9$	•		$197 \pm 4.8$		
	333	$134 \pm 17.0$	$142 \pm 6.2$			$189 \pm 6.5$		
4	1,000	$108 \pm 1.9$	$147 \pm 5.7$			$190 \pm 3.8$	-	
	3,333	$112 \pm 1.0$	$137 \pm 5.0$			$176 \pm 4.5$		
.*	10,000	$131 \pm 5.2$	$176 \pm 2.2$			$188 \pm 9.5$	•	
Trial summary		Negative	Negative			Negative		
Positive contro	ol <sup>c</sup>	$955 \pm 37.8$	$837 \pm 39.5$		•	$440 \pm 26.1$		:
TA1535	0	12 ± 0.9	15 ± 0.9	11 ± 0.0	13 ± 2.6	18 ± 3.8	15 ± 1.2	20 ± 3.8
	100	14 ± 0.9	11 ± 2.3			16 ± 3.8		
	333	$13 \pm 3.4$	$14 \pm 2.0$			$17 \pm 1.2$		
	1,000	$15 \pm 2.6$	$12 \pm 0.9$	12 ± 2.9	$24 \pm 1.2$	$17 \pm 2.3$	$15 \pm 1.5$	28 ± 5.1
•	3,333	$14 \pm 1.3$	$15 \pm 0.3$	$18 \pm 1.5$	$45 \pm 4.5$	$20 \pm 2.6$	$19 \pm 1.7$	$37 \pm 1.5$
	6,666			$50 \pm 6.0$	$42 \pm 1.9$		$37 \pm 2.2$	39 ± 3.4
	10,000	$17 \pm 1.8$	$44 \pm 9.1$	$52 \pm 2.8$	55 ± 1.9	$42 \pm 1.5$	$49 \pm 5.5$	54 ± 3.8
	16,666			$85 \pm 2.8$	$107 \pm 10.7$		$76 \pm 2.4$	95 ± 3.
Trial summary		Negative	Equivocal	Positive	Positive	Equivocal	Positive	Positive
Positive contro	ol	$958 \pm 34.3$	$607 \pm 16.8$	$408 \pm 39.8$	$351 \pm 8.9$	$105 \pm 3.6$	$91 \pm 9.1$	90 ± 10.5
TA97	. 0	$222 \pm 6.9$	$185 \pm 6.9$			$216 \pm 5.3$		
	100	$228 \pm 3.8$	$198 \pm 7.3$			$205 \pm 20.4$		
•	333	$223 \pm 6.3$	$210 \pm 7.6$			$224 \pm 11.9$		
	1,000	$210 \pm 2.6$	$216 \pm 1.8$			$184 \pm 6.5$		•
	3,333	$212 \pm 7.6$	$203 \pm 21.5$			$168 \pm 3.7$		
	10,000	$225 \pm 4.0$	$197 \pm 19.4$		•	$152 \pm 10.4$		
Trial summary	,	Negative	Negative		-	Negative		
Positive contro		$742 \pm 42.2$	$436 \pm 2.2$			442 ± 3.5		
m s nei	•					,		
TA98	100	30 ± 4.7	$35 \pm 4.0$			38 ± 1.9		
	100	27 ± 1.5	$34 \pm 2.4$			$41 \pm 0.6$		
,	333	27 ± 0.9 28 ± 4.6	$33 \pm 6.7$	•		$36 \pm 3.8$		
	1,000 3,333	28 ± 4.6 28 ± 1.5	29 ± 1.7			$31 \pm 3.7$		
. *	3,333 10,000	$28 \pm 1.5$ $28 \pm 2.0$	$28 \pm 3.4$ $31 \pm 4.3$			$34 \pm 1.7$ $28 \pm 1.5$		
Trial summary	,	Negative	Negative			Negative		
Positive contro		$677 \pm 20.6$	$770 \pm 11.3$			168 ± 3.5		

Study performed at SRI, International. The detailed protocol is presented in Zeiger et al. (1988).

Revertants are presented as mean ± the standard error from three plates.

The positive controls in the absence of metabolic activation were sodium azide (TA100 and TA1535), 9-aminoacridine (TA97), and 4-nitro-o-phenylenediamine (TA98). The positive control for metabolic activation with all strains was 2-aminoanthracene.

TABLE E1d
Mutagenicity of Dichloromethane in Salmonella typhimurium<sup>a</sup>

Test 1 - Study performed using desiccator protocol  TA100		
Test 1 - Study performed using desiccator protocol  TA100		
TA100 0.00 115 $\pm$ 4.0 119 $\pm$ 11.0 144 0.005 1111 $\pm$ 1.2 178 $\pm$ 23.0 144 0.10 187 $\pm$ 6.1 291 $\pm$ 12.7 265 0.25 155 $\pm$ 27.4 325 $\pm$ 9.5 23 0.50 384 $\pm$ 39.3 668 $\pm$ 57.7 492 1.00 321 $\pm$ 46.3 571 $\pm$ 71.0 341 Trial summary Positive control 682 $\pm$ 18.2 630 $\pm$ 56.0 505 19 $\pm$ 2.2 32 $\pm$ 6.1 22 0.05 43 $\pm$ 3.3 46 $\pm$ 0.01 0.10 40 $\pm$ 4.2 45 $\pm$ 0.7 25 0.50 43 $\pm$ 3.3 75 $\pm$ 3.7 1.00 27 $\pm$ 4.2 54 $\pm$ 5.1 Trial summary Positive control 638 $\pm$ 50.7 264 $\pm$ 5.1 Trial summary Positive control 638 $\pm$ 50.7 264 $\pm$ 5.1 Trial summary Positive control 75.1 $\pm$ 68 100 173 $\pm$ 68 100 174 $\pm$ 68 100 175 $\pm$ 196 175 $\pm$ 196 175 $\pm$ 197 176 $\pm$ 197 177 177 178 $\pm$ 197 177 178 $\pm$ 197 179 179 179 179 179 179 179 179 179	90% rat	
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$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	7 ± 7.1	
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	8 ± 8.4	
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	9 ± 15.8	
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	$3 \pm 18.1$	
Trial summary Positive $\begin{array}{cccccccccccccccccccccccccccccccccccc$	5 ± 18.3	
Positive control 682 ± 18.2 630 ± 56.0 505  TA98 0.00 17 ± 0.3 28 ± 0.0 22 0.01 22 0.05 19 ± 2.2 32 ± 6.1 24 0.10 40 ± 4.2 45 ± 0.7 25 0.25 20 ± 3.3 46 ± 0.3 34 0.50 43 ± 3.3 75 ± 3.7 1.00 27 ± 4.2 54 ± 5.1  Trial summary Equivocal Positive Positive control 638 ± 50.7 263 ± 1.5 196  Test 1 - Study performed using preincubation protocol  TA100 0 109 ± 3.8 127 ± 7.5 134 333 104 ± 3.5 121 ± 6.1 117 1,000 103 ± 12.3 129 ± 11.0 114 3,333 104 ± 3.5 121 ± 6.1 117 1,000 103 ± 12.3 129 ± 11.0 114 3,333 109 ± 14.5 139 ± 2.3 120 10,000 100 ± 10.0° 138 ± 12.5 125  Trial summary Negative Negative Positive control 422 ± 14.1 590 ± 15.9 490  TA98 0.00 19 ± 1.2 25 ± 3.2 36 0.05 333.00 15 ± 0.9 29 ± 0.7 333.00 15 ± 2.4 25 ± 2.6 1,000.00 20 ± 2.2 25 ± 0.7 3,333.00 18 ± 2.0 28 ± 4.4	$1 \pm 39.0$	
TA98 0.00 17 ± 0.3 28 ± 0.0 22 0.01 25 0.01 25 0.01 22 0.05 19 ± 2.2 32 ± 6.1 26 0.10 40 ± 4.2 45 ± 0.7 25 0.25 20 ± 3.3 46 ± 0.3 3 0.50 43 ± 3.3 75 ± 3.7 1.00 27 ± 4.2 54 ± 5.1  Trial summary Equivocal Positive Positive control 638 ± 50.7 263 ± 1.5 196  Test 1 - Study performed using preincubation protocol  TA100 0 109 ± 3.8 127 ± 7.5 134 133 128 ± 3.2 141 333 104 ± 3.5 121 ± 6.1 117 1,000 103 ± 12.3 129 ± 11.0 114 3,333 109 ± 14.5 139 ± 2.3 120 ± 11.0 114 3,333 10.00 100 ± 10.0° 138 ± 12.5 125  Trial summary Negative Negative Negative Positive control 422 ± 14.1 590 ± 15.9 490  TA98 0.00 19 ± 1.2 25 ± 3.2 30 0.05 0.10 0.25 0.25 0.50 1.00 0.25 0.33 0.05 0.10 0.25 0.33 0.05 0.10 0.25 0.33 0.00 15 ± 0.9 29 ± 0.7 333.00 15 ± 2.4 25 ± 2.6 1,000.00 20 ± 2.2 25 ± 0.7 3,333.00 18 ± 2.0 28 ± 4.4	Positive	
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	$5 \pm 6.1$	
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	5 ± 4.2	
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	9 ± 1.2	
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	$4 \pm 1.2$	•
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	9 ± 2.4	
Trial summary Equivocal Positive Positive control $638 \pm 50.7$ $263 \pm 1.5$ 196  Test 1 - Study performed using preincubation protocol  TA100 0 109 ± 3.8 127 ± 7.5 134 100 113 ± 9.3 128 ± 3.2 141 333 104 ± 3.5 121 ± 6.1 117 1,000 103 ± 12.3 129 ± 11.0 114 3,333 109 ± 14.5 139 ± 2.3 120 10,000 100 ± 10.0° 138 ± 12.5 129  Trial summary Negative Negative Positive control 422 ± 14.1 590 ± 15.9 490  TA98 0.00 19 ± 1.2 25 ± 3.2 30 0.05 0.10 50 0.10 50 0.25 0.50 60 1.00 10 29 ± 0.7 333.00 15 ± 2.4 25 ± 2.6 1,000.00 20 ± 2.2 25 ± 0.7 3,333.00 18 ± 2.0 28 ± 4.4	$4 \pm 2.1$	
Trial summary Positive control $638 \pm 50.7$ $263 \pm 1.5$ $190$ $263 \pm 1.5$ $26$		
Positive control $638 \pm 50.7$ $263 \pm 1.5$ 196  Test 1 - Study performed using preincubation protocol  TA100 0 109 ± 3.8 127 ± 7.5 134 100 113 ± 9.3 128 ± 3.2 141 333 104 ± 3.5 121 ± 6.1 117 1,000 103 ± 12.3 129 ± 11.0 114 3,333 109 ± 14.5 139 ± 2.3 120 10,000 100 ± 10.0e 138 ± 12.5 129  Trial summary Negative Negative Negative Positive control 422 ± 14.1 590 ± 15.9 496  TA98 0.00 19 ± 1.2 25 ± 3.2 36 0.05 36 0.10 56 0.25 49 0.50 1.00 56 1.00 15 ± 0.9 29 ± 0.7 333.00 15 ± 2.4 25 ± 2.6 1,000.00 20 ± 2.2 25 ± 0.7 3,333.00 18 ± 2.0 28 ± 4.4		
TA100 0 109 ± 3.8 127 ± 7.5 134 100 113 ± 9.3 128 ± 3.2 141 333 104 ± 3.5 121 ± 6.1 111 1,000 103 ± 12.3 129 ± 11.0 114 3,333 109 ± 14.5 139 ± 2.3 120 10,000 100 ± 10.0e 138 ± 12.5 129  Trial summary Negative Negative Negative Negative Positive control 422 ± 14.1 590 ± 15.9 490  TA98 0.00 19 ± 1.2 25 ± 3.2 36 0.05 33 0.10 56 0.10 56 1.00 57 0.50 66 1.00 27 333.00 15 ± 0.9 29 ± 0.7 333.00 15 ± 2.4 25 ± 2.6 1,000.00 20 ± 2.2 25 ± 0.7 3,333.00 18 ± 2.0 28 ± 4.4	Negative	
TA100 0 109 $\pm$ 3.8 127 $\pm$ 7.5 134 100 113 $\pm$ 9.3 128 $\pm$ 3.2 141 333 104 $\pm$ 3.5 121 $\pm$ 6.1 117 1,000 103 $\pm$ 12.3 129 $\pm$ 11.0 114 3,333 109 $\pm$ 14.5 139 $\pm$ 2.3 120 10,000 100 $\pm$ 10.0e 138 $\pm$ 12.5 125 125 125 126 139 $\pm$ 3.2 3 126 10,000 100 $\pm$ 10.0e 138 $\pm$ 12.5 129 $\pm$ 17 129 $\pm$ 17 129 $\pm$ 18 129 $\pm$ 18 12 12 12 13 13 $\pm$ 12.5 129 $\pm$ 18 12 13 $\pm$ 18 12 15 12 15 12 15 12 15 15 15 15 15 15 15 15 15 15 15 15 15	$0 \pm 5.0$	
$\begin{array}{cccccccccccccccccccccccccccccccccccc$		,
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	4 ± 4.7	
333	1 ± 6.8	
1,000 $103 \pm 12.3$ $129 \pm 11.0$ $114$ $3,333$ $109 \pm 14.5$ $139 \pm 2.3$ $120$ $10,000$ $100 \pm 10.0^{\circ}$ $138 \pm 12.5$ $129$ Trial summary Negative Negative Negative ontrol $422 \pm 14.1$ $590 \pm 15.9$ $490$ TA98 $0.00$ $19 \pm 1.2$ $25 \pm 3.2$ $30$ $0.05$ $33$ $0.10$ $50$ $0.25$ $0.50$ $0$	$7 \pm 12.7$	•
3,333	4 ± 5.9	
10,000 $100 \pm 10.0^{\circ}$ $138 \pm 12.5$ $129$ Trial summary Negative Negative Normal System 15.9 Negative control $422 \pm 14.1$ $590 \pm 15.9$ $490$ TA98 $0.00$ $19 \pm 1.2$ $25 \pm 3.2$ $30$ $0.05$ $33$ $0.10$ $50$ $0.25$ $49$ $0.50$ $60$ $1.00$ $20$ $100.00$ $15 \pm 0.9$ $29 \pm 0.7$ $333.00$ $15 \pm 2.4$ $25 \pm 2.6$ $1,000.00$ $20 \pm 2.2$ $25 \pm 0.7$ $3,333.00$ $18 \pm 2.0$ $28 \pm 4.4$	$0 \pm 4.4$	
Trial summary Negative Negative 590 $\pm$ 15.9 490 201 25 $\pm$ 3.2 30 0.05 33 0.10 50 25 490 29 $\pm$ 0.50 1.00 201 201 201 201 201 201 201 201 201 2		
Positive control $422 \pm 14.1$ $590 \pm 15.9$ $490$	9 ± 12.1	
TA98 $0.00$ $19 \pm 1.2$ $25 \pm 3.2$ $36$ $0.05$ $35$ $0.10$ $55$ $0.25$ $45$ $0.50$ $65$ $1.00$ $29 \pm 0.7$ $100.00$ $15 \pm 0.9$ $29 \pm 0.7$ $333.00$ $15 \pm 2.4$ $25 \pm 2.6$ $1,000.00$ $20 \pm 2.2$ $25 \pm 0.7$ $3,333.00$ $18 \pm 2.0$ $28 \pm 4.4$	Negative	
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	0 ± 16.5	
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	$0 \pm 3.7$	
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	5 ± 1.8	΄.
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	6 ± 4.8	
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	9 ± 5.5	
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	9 ± 4.8	,
$100.00$ $15 \pm 0.9$ $29 \pm 0.7$ $333.00$ $15 \pm 2.4$ $25 \pm 2.6$ $1,000.00$ $20 \pm 2.2$ $25 \pm 0.7$ $3,333.00$ $18 \pm 2.0$ $28 \pm 4.4$	$7 \pm 5.1$	•
333.00 15 $\pm$ 2.4 25 $\pm$ 2.6 1,000.00 20 $\pm$ 2.2 25 $\pm$ 0.7 3,333.00 18 $\pm$ 2.0 28 $\pm$ 4.4		
1,000.00 $20 \pm 2.2$ $25 \pm 0.7$ 3,333.00 $18 \pm 2.0$ $28 \pm 4.4$		
$3,333.00$ $18 \pm 2.0$ $28 \pm 4.4$		
3,333.40 10 ± 2.0 20 ± 4.4		
10,000.00 $15 \pm 2.6^{e}$ $24 \pm 3.8$		
Trial summary Negative Negative N	Negative	•
	$3 \pm 8.1$	

TABLE E1d
Mutagenicity of Dichloromethane in Salmonella typhimurium (continued)

			<u> </u>	Revertants/plate						
Strain	Dose	S	9		ster S9	+rat				
		Trial 1	Trial 2	10%	30%	10%	30%			
Γest 2 - St	udy perfor	med using prein	cubation proto	col						
TA100	0	$137 \pm 4.4$	167 ± 10.2	179 ± 7.9	108 ± 8.2	126 ± 6.9	134 ± 10.4			
	100	$134 \pm 3.2$	$188 \pm 1.2$	$190 \pm 1.3$	$125 \pm 5.5$	$129 \pm 14.3$	$118 \pm 16.1$			
	333	$139 \pm 4.0$	$190 \pm 4.5$	$179 \pm 2.6$	$132 \pm 6.8$	$145 \pm 5.7$	$132 \pm 13.3$			
	1,000	$101 \pm 1.5$	$193 \pm 3.1$	$186 \pm 7.1$	$123 \pm 3.8$	$131 \pm 9.0$	$105 \pm 12.4$			
	3,333	$118 \pm 10.7$	$188 \pm 4.3$	$169 \pm 5.0$	$113 \pm 4.4$	$105 \pm 2.3$	$116 \pm 5.3$			
	6,666		$175 \pm 10.8$	$159 \pm 3.6$						
	10,000	$93 \pm 8.4$			95 ± 7.5 <sup>e</sup>	$108 \pm 10.1$	92 ± 4.6			
Trial summa	arv	Negative	Negative	Negative	Negative	Negative	Negative			
Positive con	•	$360 \pm 14.7$	470 ± 11.0	$1,180 \pm 35.5$	579 ± 21.7	$594 \pm 44.0$	404 ± 32.9			
TD 4 1 8 2 5		01	20	10 . 10	10	0 . 00	44 . 40			
TA1535	0	$21 \pm 1.2$	$28 \pm 2.8$	$13 \pm 1.5$	$10 \pm 2.9$	$8 \pm 0.0$	11 ± 1.2			
	100	18 ± 3.8	$31 \pm 2.0$	8 ± 1.3	8 ± 1.9	12 ± 1.5	11 ± 1.5			
	333	19 ± 2.9	$25 \pm 2.6$	$13 \pm 0.6$	$10 \pm 2.8$	$15 \pm 2.3$	9 ± 0.3			
	1,000	16 ± 1.8	28 ± 4.4	9 ± 3.4	13 ± 1.5	10 ± 2.6	10 ± 0.7			
	3,333	$13 \pm 2.4$	$25 \pm 0.0$	$10 \pm 0.9$	$10 \pm 0.7$	$12 \pm 1.2$	$12 \pm 0.9$			
	6,666 10,000	11 ± 1.2	$20 \pm 4.9$	9 ± 1.5	$8 \pm 0.3$	8 ± 2.3	9 ± 1.2			
Trial summ	ary	Negative	Negative	Negative	Negative	Negative	Negative			
Positive cor	trol	$331 \pm 16.4$	$354 \pm 19.0$	$219 \pm 9.0$	$431 \pm 35.8$	118 ± 8.0	143 ± 4.5			
TA1537	0	13 ± 1.9			10 ± 1.5		13 ± 0.3			
grance.	100	$12 \pm 2.5$			9 ± 1.5		13 ± 0.3			
	333	$11 \pm 2.0$			$9 \pm 0.3$		13 ± 2.8			
	1,000	9 ± 1.0			$13 \pm 0.9$		$13 \pm 0.7$ $14 \pm 0.7$			
	3,333 6,666	$10 \pm 2.7$			8 ± 2.3		8 ± 0.9			
	10,000	$10 \pm 1.9$			$12 \pm 0.6$		9 ± 0.6			
Trial summ	arv	Negative			Negative		Negative			
Positive cor	•	$653 \pm 32.8$			$80 \pm 11.6$		48 ± 8.0			
TA97	0	168 ± 2.9	196 ± 10.1	192 + 40	170 + 170	100 + 150	100 : 110			
IN	100	169 ± 4.6	$196 \pm 10.1$ $205 \pm 3.4$	$182 \pm 4.8$ $197 \pm 4.5$	$170 \pm 17.0$	199 ± 15.8	198 ± 11.0			
	333	169 ± 4.6 169 ± 4.1	$203 \pm 3.4$ $213 \pm 1.5$	197 ± 4.5 214 ± 3.2	194 ± 8.6 207 ± 2.6	187 ± 2.6 178 ± 9.9	$215 \pm 4.2$			
	1,000	$169 \pm 4.1$ $169 \pm 7.5$	$213 \pm 1.3$ $216 \pm 2.4$	$214 \pm 3.2$ $212 \pm 3.5$	$207 \pm 2.6$ $187 \pm 9.7$	$1/8 \pm 9.9$ $227 \pm 2.9$	$211 \pm 6.9$			
	3,333	$169 \pm 7.3$ $161 \pm 6.4$	$210 \pm 2.4$ $211 \pm 5.2$	$192 \pm 2.5$	187 ± 9.7 184 ± 9.6	$196 \pm 5.0$	203 ± 4.0 170 ± 9.8			
	6,666	101 = 0.7	2.1 - 7.2	170 = 4.0	104 2 7.0	150 ± 3.0	1/0 = 9.8			
	10,000	149 ± 1.9	$189 \pm 9.2$	$176 \pm 3.4$	$179 \pm 7.9$	$165 \pm 25.2$	159 ± 8.2			
Trial summ	ary	Negative	Negative	Negative	Negative	Negative	Negative			
Positive cor	itrol	$818 \pm 40.9$	661 ± 35.0	694 ± 55.9	$530 \pm 23.0$	$519 \pm 25.6$	$473 \pm 27.8$			

TABLE E1d

Mutagenicity of Dichloromethane in Salmonella typhimurium (continued)

	,		Rever	tants/plate		
Strain Dose	-S	39	+ham	ster S9	+rat	S9
* * * * * * * * * * * * * * * * * * *	Trial 1	Trial 2	10%	30%	10%	30%
TA98 0	17 ± 1.2	21 ± 1.5	27 ± 3.3	27 ± 0.6	31 ± 2.2	36 ± 5.0
100	$18 \pm 2.2$	$20 \pm 2.6$	$31 \pm 3.9$	$20 \pm 1.8$	$32 \pm 6.4$	$40 \pm 1.5$
333	$15 \pm 3.8$	$17 \pm 2.1$	$31 \pm 3.0$	$27 \pm 2.2$	$32 \pm 2.9$	$28 \pm 0.7$
1,000	$15 \pm 4.2$	$18 \pm 3.1$	$35 \pm 3.8$	$33 \pm 2.6$	$29 \pm 0.9$	$35 \pm 4.2$
3,333	$14 \pm 0.3$	$19 \pm 1.5$	$32 \pm 2.0$	$22 \pm 1.5$	$32 \pm 3.8$	$31 \pm 4.2$
6,666	4.5	$18 \pm 0.9$	$32 \pm 2.7$		$32 \pm 3.2$	
10,000	$14 \pm 2.1$			$16 \pm 2.2^{e}$	•	$17 \pm 2.3^{e}$
Trial summary	Negative	Negative	Negative	Negative	Negative	Negative
Positive control	$558 \pm 20.6$	$609 \pm 23.7$	$1,029 \pm 45.5$	$454 \pm 62.7$	$385 \pm 8.4$	170 ± 11.3

The detailed protocol and these data are presented in Zeiger (1990).

Revertants are presented as mean ± the standard error from three plates.

Doses are given as mL/desiccator for the desiccator protocol test and μg/plate for the preincubation protocol tests.

The positive controls in the absence of metabolic activation were sodium azide (TA100 and TA1535), 9-aminoacridine (TA97 and TA1537), and 4-nitro-ο-phenylenediamine (TA98). The positive control for metabolic activation with all strains was 2-aminoanthracene.

e Slight toxicity

 $\begin{array}{l} \textbf{TABLE E2} \\ \textbf{Induction of Trifluorothymidine Resistance in L5178Y Mouse Lymphoma Cells by Dichloromethane} \end{array}$ 

Compound	Concentration	Cloning Efficiency (%)	Relative Total Growth (%)	Mutant Count	Mutant Fraction <sup>b</sup>	Average Mutant Fraction <sup>c</sup>
S9	:					
rial 1						
Ethanol						
Luanoi		80	110	97	40	•
		103	104	92	30	
		98	99	74	25	
		81	87	73	30	31
Methylmethanesu	ılfonate (µg/mL)					i
		67	53	521	259	
**	5	66	52	564	286	
		54	49	558	342	296≎
Dichloromethane	/ut /ml )					
Dichioromethane	0.5	102	93	128	42	
	0.5	81	107	114	47	
		105	122	97	31	40
		• • • • • • • • • • • • • • • • • • • •	122			
	1.0	86	91	102	39	
		81	103	100	· 41	
		80	104	98	41	40
	••		40			
	2.0	65	58	119	61	
		83	61	143	58 51	57≎
		91	71	140	51	313
	3.0 <sup>d</sup>	Lethal				
	5.0	Lethal				
		Lethal				

Significant (P≤0.05) positive response

ΞĖ.

Mean  $\pm$  standard error from three replicate plates of approximately  $10^6$  cells each.

d Precipitation of dichloromethane occurred at this dose level.

a Study performed at Litton Bionetics, Inc. The experimental protocol and these data are presented in detail by Myhr et al. (1990).

Mutant fraction (frequency) is a ratio of the mutant count to the cloning efficiency, divided by 3 (to arrive at MF/10<sup>6</sup> cells treated); MF = mutant fraction.

TABLE E2
Induction of Trifluorothymidine Resistance in L5178Y Mouse Lymphoma Cells by Dichloromethane (continued)

Compound	Concentration	Cloning Efficiency (%)	Relative Total Growth (%)	Mutant Count	Mutant Fraction	Average Mutant Fraction
 59			<del></del>			
rial 2						
Ethanol						
		83	94	74	30	
		80	98	80	33	
		82	96	84	34	
		99	112	92	31	32
Methylmethanesu	lfonate (ug/ml.)					
, inicinancsu	, and the same of	65	56	487	250	
	5	62	44	605	328	-
*		64	57	525	274	284*
				•		
Dichloromethane	(μL/mL)					
	0.25	101	98	98	32	
		80	88	91 22	38	22
		100	115	77	26	32
	0.50	88	· <b>84</b>	95	36	
	0.50	69	. 105	73	35	
•		74	110	70	32	34
·	0.75	84	83	97	38	
		75	88	117	52	
		87	95	88	34	41
	1.00	86	88	115	45	
	1.00	72	102	93	43 43	
		83	80	102	41	43
						10
	1.50	. 97	84	128	44	
		- 96	93	111	39	
		. 91	44	144	53	45
	200		•			
	2.00	76	79	95 122	41	
		81 73	66 55	132 96	55 44	47
•		13	<b>33</b> ,	<del>70</del>	44	41
	3.00 <sup>d</sup>	Lethal				
	- · - <del>-</del>	Lethal				

TABLE E2
Induction of Trifluorothymidine Resistance in L5178Y Mouse Lymphoma Cells by Dichloromethane (continued)

Compound	Concentration	Cloning Efficiency (%)	Relative Total Growth (%)	Mutant Count	Mutant Fraction	Average Mutant Fraction
S9·						
Crial 3						
Ethanol						
		97	112	67	23	
		88	109	89	34	
		85	78	80	31	
		90	100	97	36	31
Methylmethanesu	ılfonate (μg/mL)					
•	,	94	79	192	68	
	5	76	80	217	95	82≎
Dichloromethane	: (μL/mL)					
	1.00	54	59	71	44	
	1	75	86	80	36	
		75	75	44	20	33
	1.50	71	56	85	40	
		83	37	89	36	
		70	63	78	37	38
	2.00	87	43	86	33	
		84	45	88	35	
		72	51	86	40	36
	2.25 <sup>d</sup>	87	34	77	30	
		69	24	104	50	40
		Lethal	2,	AV-T	50	70
	2.50 <sup>d</sup>	85	23	140	55	
	2.30	83 74	23 35	140	55 51	
		74 77	33	112 129	51	540
		"	33	129	56	54*

TABLE E2
Induction of Trifluorothymidine Resistance in L5178Y Mouse Lymphoma Cells by Dichloromethane (continued)

Compound	Concentration	Cloning Efficiency (%)	Relative Total Growth (%)	Mutant Count	Mutant Fraction	Average Mutant Fraction
+89	<del></del>	<del></del>	<del></del>	<del></del>		- 12, 3, 40, 10
Frial 1					'	* 4
Ethanol						**: : : : : : :
		69	90	154	75	
		83	93	112	45	
	÷	90	101	82	30	
a"		95	117	108	38	47
Methylcholanthre	ne (μg/mL)					to a to a minimum of the
	( <b>1.8</b> )	63	28	643	338	
	2.5	76	43	721	318	
• •		60	21	697	389	348*
Dichloromethane	(ul /ml)					
Dictionomethatic	0.25	- 89	82	190	71	
	0.20	82	63	114	46	
		83	84	123	49	56
	0.50	81	55	154	64	
•	0.50	80	70	150	63	
		88	82	138	52	60
		00	02	150	<b>52</b>	00
	1.00	117	52	157	45	
		106	58	137	43	
		78	63	145	62	50
	1.50	86	67	153	59	
		88	58	134	51	
		98	56	158	54	55
	2.00	95	52	242	85	•
	2.00	107	58	257	80	82*
	3.00 <sup>d</sup>	90	15	206	05	
	3.00	80	15 25	206	85 94	*
	•	· 77 99	25 27	216 185	62	81*
		77	21	163	04	01.

TABLE E2
Induction of Trifluorothymidine Resistance in L5178Y Mouse Lymphoma Cells by Dichloromethane (continued)

Compound	Concentration	Cloning Efficiency (%)	Relative Total Growth (%)	Mutant Count	Mutant Fraction	Average Mutant Fraction	
-S9	<del>- 1 - 1 - 1 - 1 - 1 - 1 - 1 - 1 - 1 - 1</del>						
rial 2							
Ethanol							
		88	92	124	47		
		79	117	111	47		
		86	127	89	35		
		68	63	121	59	47	
Methylcholanthre	ne (ug/mL)						
	···· (mg/iii)	50	18	780	517	and the state of	
	2.5	44	23	721	552		
		71	29	822	385	485≎	
	•						
Dichloromethane							
	0.25	77	91	140	60		
		. 68	62	126	62		
		70	70	129	62	61	
	0.50	73	72	138	63		
		80	102	124	52		
•	:	66	84	139	70	62	
					, •	<b>~2</b>	
	1.00	76	83	145	64		
		100	77	181	61		
		79	62	156	66	63	
	1.50	76	71	185	01		
	1.50	76 94	71 72	185 147	81 52		
•		69	52	147	32 72	68	
		<b>0</b> /	32	17/	12	08	
	2.00	93	68	202	73		
N. A.		78	59	159	68	70	
		Lethal					
*	3.00 <sup>d</sup>	(2	4.4	200	40-		
	<i>3.</i> 00"	63 78	14	239	127		
		78 <b>6</b> 7	19 11	187	80		
•		07	11	335	166	124*	

TABLE E2
Induction of Trifluorothymidine Resistance in L5178Y Mouse Lymphoma Cells by Dichloromethane (continued)

Compound	Concentration	Cloning Efficiency (%)	Relative Total Growth (%)	Mutant Count	Mutant Fraction	Average Mutant Fraction	
+S9							
rial 3							
Ethanol							
		111	94	211	64		
		82	83	165	67		
		104	111	194	62		
. *	$\epsilon_{\rm v}$	117	113	192	54	62	
Methylcholanthre	na (ua/mT )		e e		•		
Methylcholantine	ile (µg/iliL)	65	33	822	425		
	2.5	79	57	624	264		
	, 2.3	84	52	910	360	350*	
		04		,10	500	250	
Dichloromethane	(μL/mL)				· *		
	1.00	84	82	154	61		
		91	<b>7</b> 7	186	68		
		62	66	155	84	71	
	1.50	93	82	152	54		
	1.50	87	70	191	73		
		87	67	190	73	67	
	2.00	79	52	208	88		
		102	81	205	67		
		95	56	235	82	79	
	2.25 <sup>d</sup>	101	51	228	75		
		103	66	196	63		
		87	44	167	64	67	
•				100	02		
	2.50	81	27	199	82		
		97	37	187	65	(2	
		93	29	150	54	67	

TABLE E3
Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by Dichloromethane<sup>a</sup>

Compound	Dose (μg/mL)	Total Cells	No. of Chromo- somes	No. of SCEs	SCEs/ Chromo- some	SCEs/ Cell	Hrs in Br <b>d</b> U	Relative SCEs/ Chromosome <sup>b</sup> (%)
<b>-</b> \$9								
Trial 1 Summary: Negative								
Negative		50	1,045	381	0.36	7.6	26.0	
Mitomycin-C	0.0005 0.0050	50 10	1,030 208	556 296	0.53 1.42	11.1 29.6	26.0 26.0	48.06 290.32
Dichloromethane	160 500 1,600 5,000	50 50 50 50	1,038 1,043 1,033 1,040	432 411 419 425	0.41 0.39 0.40 0.40	8.6 8.2 8.4 8.5	26.0 26.0 26.0 26.0	14.15 8.08 11.25 12.08
								$P=0.104^{c}$
+S9								
Trial 1 Summary: Negative								
Negative		50	1,046	361	0.34	7.2	26.0	
Cyclophosphamide	0.1 0.6	50 10	1,048 210	500 196	0.47 0.93	10.0 19.6	26.0 26.0	38.24 170.44
Dichloromethane								
	160 500 1,600 5,000	50 50 50 50	1,049 1,050 1,045 1,048	353 368 387 376	0.33 0.35 0.37 0.35	7.1 7.4 7.7 7.5	26.0 26.0 26.0 26.0	-2.50 1.55 7.30 3.96
								P=0.146

Study performed at Environmental Health Research & Testing. SCE = sister chromatid exchange; BrdU = bromodeoxyuridine. A detailed description of the SCE protocol and these data are presented by Anderson et al. (1990).

SCEs/chromosome of culture exposed to dichloromethane relative to those of culture exposed to solvent
 Significance of relative SCEs/chromosomes tested by the linear regression trend test vs. log of the dose.

TABLE E4 Induction of Chromosomal Aberrations in Chinese Hamster Ovary Cells by Dichloromethane<sup>a</sup>

		-S9		* *					+89		
Dose (μg/mL)	Total ) Cells	No. of Abs	Abs/ Cell	Percent Cells w/Abs	•		Dose (μg/mL)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells w/Abs
Trial 1 - Harve Summary: Negat		hours					1 - Harvest ary: Negative	3	e alle	1,5 ×	\$ 20 to 12 1
Negative	<b>200</b>	0	0.00	0.0	·.	Negat		.54, a-4 <b>2</b>	0.01		
Mitomycin-C	200		0.00	, j. A . 3		Cyclo	phosphamid	<u>.</u>	a : ,	4-62-12	, , , , , , , , ,
0.0625	200	23	0.12	11.0			2.5	200	24	0.12	10.5
0.2500	50	14	0.28	26.0			7.5	50	17	0.34	30.0
Dichlorometha	ne					Dichl	oromethane				
1,600	200	1	0.01	0.5			1,600	200	0	0.00	0.0
3,000	200	0	0.00	0.0			3,000	200	1	0.01	0.5
5,000	200	1	0.01	0.5			5,000	200	1	0.01	0.5
				$P = 0.276^{b}$							P=0.671

Study performed at Environmental Health Research & Testing. Abs = aberrations. A detailed presentation of the technique for detecting chromosomal aberrations and these data are found in Anderson et al. (1990).

Significance of relative SCEs/chromosomes tested by the linear regression trend test vs. log of the dose.

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

Organ Weights and Organ-Weight-to-Body-Weight Ratios for Male Rats at the 15-Month Interim Evaluation in the 2-Year Gavage Study	
of Safflower Oil Organ Weights and Organ-Weight-to-Body-Weight Ratios for Male Rats	ZWK
at the 15-Month Interim Evaluation in the 2-Year Gavage Study	264

TABLE F1
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Male Rats at the 15-Month Interim Evaluation in the 2-Year Gavage Study of Safflower Oil<sup>a</sup>

	0 mL/kg	2.5 mL/kg	5 mL/kg	10 mL/kg
	10	9	10	9
Necropsy body wt	412 ± 16	403 ± 11	441 ± 13	496 ± 24**
Brain		•		
Absolute	$2.069 \pm 0.026$	$2.046 \pm 0.029$	$2.037 \pm 0.014$	$2.047 \pm 0.036$
Relative	$5.09 \pm 0.21$	$5.10 \pm 0.12$	$4.64 \pm 0.12$	4.19 ± 0.17**
R. Kidney				,
Absolute	$1.604 \pm 0.073$	$1.487 \pm 0.045$	$1.459 \pm 0.039$	$1.349 \pm 0.049*$
Relative	$3.93 \pm 0.20$	$3.71 \pm 0.16$	$3.31 \pm 0.08**$	$2.74 \pm 0.10**$
Liver				
Absolute	$15.261 \pm 0.822$	$14.912 \pm 0.378$	$15.501 \pm 0.479$	$15.549 \pm 0.858$
Relative	$37.41 \pm 2.26$	$37.12 \pm 0.82$	$35.25 \pm 1.19$	$31.37 \pm 0.74**$

<sup>\*\*</sup> Significantly different (P≤0.01) from the control group by Williams' or Dunnett's test

TABLE F2
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Male Rats at the 15-Month Interim Evaluation in the 2-Year Gavage Study of Tricaprylin<sup>a</sup>

	0 mL/kg	2.5 mL/kg	5 mL/kg	10 mL/kg		
n	10	10	10	7		
Necropsy body wt	$430 \pm 15$	419 ± 11	$402 \pm 15$	406 ± 12		
, Brain						
Absolute	$2.057 \pm 0.023$	$2.011 \pm 0.034$	$1.965 \pm 0.037$	$1.985 \pm 0.020$		
Relative	$4.83 \pm 0.16$	$4.83 \pm 0.15$	$4.93 \pm 0.14$	$4.91 \pm 0.13$		
R. Kidney						
Absolute	$1.349 \pm 0.040$	$1.233 \pm 0.036$	$1.194 \pm 0.041*$	$1.328 \pm 0.053$		
Relative	$3.15 \pm 0.07$	$2.95 \pm 0.07$	$2.98 \pm 0.07$	$3.27 \pm 0.08$		
Liver						
Absolute	$14.307 \pm 0.424$	$13.901 \pm 0.317$	$13.209 \pm 0.486$	$13.977 \pm 0.352$		
Relative	$33.38 \pm 0.74$	$33.35 \pm 0.91$	$33.06 \pm 1.13$	$34.42 \pm 0.20$		

<sup>\*</sup> Significantly different (P≤0.05) from the control group by Williams' or Dunnett's test

Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error)

a Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error)

# APPENDIX G HEMATOLOGY AND CLINICAL CHEMISTRY RESULTS

	Hematology and Clinical Chemistry Data for Male Rats at the 15-Month Interim Evaluation in the 2-Year Gavage Study	264
	of Safflower Oil 15 Bronth Interim Evaluation	
Table G2	Hematology Data for Male Rats at the 15-Month Interim Evaluation	26

TABLE G1
Hematology and Clinical Chemistry Data for Male Rats at the 15-Month Interim Evaluation in the 2-Year Gavage Study of Safflower Oil<sup>a</sup>

	0 mL/kg	2.5 mL/kg	5 mL/kg	10 mL/kg	
n .	. 10	9	10	9	.,
Hematology					
Hematocrit (%)	$44.3 \pm 0.7$	$45.0 \pm 0.8$	46.1 ± 1.6	$44.3 \pm 1.2$	
Hemoglobin (g/dL)	$16.6 \pm 0.3$	$16.8 \pm 0.3$	$17.3 \pm 0.7$	$16.7 \pm 0.3$	
Erythrocytes (10 <sup>6</sup> /μL)	$8.49 \pm 0.15$	$8.59 \pm 0.17$	$8.71 \pm 0.36$	$8.56 \pm 0.21$	
Mean cell volume (fL)	$52.3 \pm 0.3$	$52.6 \pm 0.6$	$53.1 \pm 0.6$	$51.9 \pm 0.5$	
Mean cell hemoglobin (pg)	$19.5 \pm 0.2$	$19.6 \pm 0.3$	$19.8\pm0.2$	$19.6 \pm 0.4$	
Mean cell hemoglobin			•		
concentration (g/dL)	$37.4 \pm 0.5$	$37.4 \pm 0.5$	$37.4 \pm 0.4$	$37.9 \pm 0.9$	
Reticulocytes (10 <sup>6</sup> /µL)	$0.31 \pm 0.01$	$0.27 \pm 0.02$	$0.26 \pm 0.02^{6}$	$0.31 \pm 0.01$	
Leukocytes (10 <sup>3</sup> /μL)	$7.62 \pm 0.41$	$7.74 \pm 0.36$	$7.96 \pm 0.64$	$7.87 \pm 0.70$	
Segmented neutrophils (10 <sup>3</sup> /µL)	$2.28 \pm 0.23$	$2.14 \pm 0.17$	$2.19 \pm 0.17$	$1.66 \pm 0.20$	
Lymphocytes (10 <sup>3</sup> /μL)	$4.72 \pm 0.25$	$4.92 \pm 0.29$	$5.15 \pm 0.52$	$5.69 \pm 0.67$	
Monocytes (10 <sup>3</sup> /μL)	$0.49 \pm 0.07$	$0.53 \pm 0.07$	$0.51 \pm 0.11$	$0.39 \pm 0.09$	
Eosinophils (10 <sup>3</sup> /μL)	$0.09 \pm 0.01$	$0.14 \pm 0.05$	$0.07 \pm 0.02$	$0.07 \pm 0.02$	•
Nucleated erythrocytes (10 <sup>3</sup> /µL)	$0.01 \pm 0.01$	$0.01 \pm 0.01$	$0.03 \pm 0.01$	$0.04 \pm 0.03$	
Clinical Chemistry		. '			.*
Potassium (mEq/L)	$6.1\pm0.1^{\mathbf{b}}$	$5.8 \pm 0.3^{c}$	$6.0 \pm 0.1^{d}$	$5.8 \pm 0.1^{e}$	·
Total protein (g/dL)	$8.7 \pm 0.2$	$9.1 \pm 0.1$	$8.7 \pm 0.1$	$8.5 \pm 0.1$	
Albumin (g/dL)	$5.9 \pm 0.2$	$6.5 \pm 0.2$	$6.6 \pm 0.1^*$	$6.2 \pm 0.2$	
Cholesterol (mg/dL)	102 ± 8	97 ± 6	67 ± 4**	48 ± 2**	
Alanine aminotransferase (IU/L)	$81 \pm 6^{\text{b}}$	115 ± 6**	85 ± 4	$86 \pm 3$	
Creatine kinase (IU/L)	$205 \pm 27^{b}$	$398 \pm 72^{\mathbf{d}}$	$184 \pm 20$	$267 \pm 66^{d}$	
Sorbitol dehydrogenase (IU/L)	15 ± 1	35 ± 4**	29 ± 3**	26 ± 2**	
Bile acids (µmol/L)	$19.50 \pm 7.58^{\mathrm{f}}$	$19.14 \pm 2.68^{e}$	$13.71 \pm 2.02^{e}$	$13.67 \pm 1.95$	

<sup>\*</sup> Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test

<sup>\*\*</sup> P≤0.01

a Mean ± standard error

b n=9

 $<sup>^{</sup>c}$  n=6

d n=8

e n=7

 $f_{n=4}$ 

Table G2 Hematology Data for Male Rats at the 15-Month Interim Evaluation in the 2-Year Gavage Study of Tricaprylina

	0 mL/kg	2.5 mL/kg	5 mL/kg	10 mL/kg
n	9	10	8	7
Hematocrit (%)	45.6 ± 1.1	$50.7 \pm 2.7$	49.2 ± 2.3	51.7 ± 2.0*
Hemoglobin (g/dL)	$15.6 \pm 0.4$	$17.3 \pm 0.8$	$16.7 \pm 0.6$	$17.5 \pm 0.6^{\circ}$
Erythrocytes (10 <sup>6</sup> /μL)	$8.77 \pm 0.31$	$9.72 \pm 0.41$	$9.30 \pm 0.34$	9.91 ± 0.32*
Mean cell volume (fL)	$52.3 \pm 1.0$	$51.8 \pm 0.7$	$52.9 \pm 0.8$	$52.3 \pm 0.8$
Mean cell hemoglobin (pg)	$17.8 \pm 0.3$	$17.8 \pm 0.3$	$18.0 \pm 0.2$	$17.7 \pm 0.2$
Mean cell hemoglobin	•			* *
concentration (g/dL)	$34.2 \pm 0.3$	$34.2 \pm 0.4$	$34.1 \pm 0.3$	$33.8 \pm 0.3$
Reticulocytes (10 <sup>6</sup> /μL)	$0.22 \pm 0.03^{b}$	$0.25 \pm 0.03$	$0.18 \pm 0.03^{c}$	$0.24 \pm 0.02$
Leukocytes (10 <sup>3</sup> /μL)	$2.91 \pm 0.40$	$2.82 \pm 0.21$	$2.90 \pm 0.37$	$3.50 \pm 0.40$
Segmented neutrophils (10 <sup>3</sup> /µL)	$1.26 \pm 0.25$	$1.17 \pm 0.15$	$0.96 \pm 0.10$	$1.79 \pm 0.31$
Lymphocytes (10 <sup>3</sup> /µL)	$1.46 \pm 0.20$	$1.40 \pm 0.13$	$1.72 \pm 0.29$	$1.52 \pm 0.17$
Monocytes (10 <sup>3</sup> /μL)	$0.17 \pm 0.02$	$0.21 \pm 0.02$	$0.18 \pm 0.05$	$0.15 \pm 0.03$
Eosinophils (10 <sup>3</sup> /µL)	$0.02 \pm 0.01$	$0.05 \pm 0.01$	$0.04 \pm 0.01$	$0.04 \pm 0.02$
Nucleated erythrocytes (10 <sup>3</sup> /µL)	$0.03 \pm 0.02$	$0.06 \pm 0.02$	$0.03 \pm 0.02^{c}$	$0.01 \pm 0.01$

<sup>°</sup> Significantly different (P $\leq$ 0.05) from the control group by Dunn's or Shirley's test Mean  $\pm$  standard error

n=8

n=7

## APPENDIX H CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

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	of Dichloromethane in Corn Oil	282

### CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

#### PROCUREMENT AND CHARACTERIZATION

#### Corn Oil

Corn oil was obtained as a gift from Best Foods (Union, NJ) in two lots (2325 and SFS-L050189) courtesy of Mark Bieber, Ph.D. Characteristics and composition analyses were conducted by Best Foods (Table H1). The supplied corn oil met all specifications for processed corn oil. During the study, corn oil was stored in amber glass bottles at 4° C under an argon headspace. As a means to evaluate stability of the corn oil, the study laboratory monitored the peroxide concentration (The Official Method Cd 8-53 of the American Oil Chemist Society) in each bottle prior to use. The acceptable peroxide concentration was set at 2 mEq/L. A bottle was discarded if the peroxide concentration exceeded this specification.

#### Safflower Oil

A gift of safflower oil was arranged by R.G. Krishnamurthy, Ph.D., of Kraft, Incorporated (Glenview, IL). Two suppliers provided the safflower oil: Oilseeds International, Ltd. (lot OISO) and Producers Cotton Oil Company (lot KISO). Both suppliers provided safflower oil that met all specifications for high linoleic acid safflower oil. Specific lot analyses were not provided. During the study, safflower oil was stored in amber glass bottles at 4° C under an argon headspace. Again, as a means to evaluate stability of the safflower oil, the study laboratory determined the peroxide concentration (The Official Method Cd 8-53 of the American Oil Chemist Society) in each bottle prior to use. The acceptable peroxide concentration was set at 2 mEq/L. A bottle was discarded if the peroxide concentration exceeded this specification.

#### Tricaprylin

Tricaprylin was obtained from Eastman Kodak (Rochester, NY) in three lots (A15, A11, and 8812-806876). Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute. The reports on analyses performed in support of the tricaprylin study are on file at the National Institute of Environmental Health Sciences.

The chemical, a clear, colorless to amber liquid, was identified as tricaprylin by infrared, ultraviolet/visible, and NMR spectroscopy. All spectra were consistent with those expected for the structure and with the literature spectra (Sadtler Standard Spectra) of tricaprylin (Figures H1 and H2).

The purity of all lots of tricaprylin was determined by elemental analyses; Karl Fischer water analysis; United States Pharmacopeia (USP) XX methods of titration for acid, saponification, and ester values; thin-layer chromatography (TLC); and gas chromatography. TLC was performed on silica gel plates with two solvent systems: A) cyclohexane:1,4-dioxane (90:10 for lot A15 and 95:5 for lots A11 and 8812-806876), and B) carbon tetrachloride:chloroform:methanol:glacial acetic acid (48:48:3:2 for lot A15 and 60:40:1:1 for lots A11 and 8812-806876). Visualization was accomplished with visible light and ultraviolet light (366 nm) following a spray of 1% vanillin in concentrated sulfuric acid and heating at 120° C for lot A15. For lots A11 and 8812-806876, visualization was accomplished with shortwave (254 nm) ultraviolet light and a spray of 5 g potassium dichromate in 40% sulfuric acid (100 mL), before and after heating at 120° C. For lots A15 and A11, gas chromatography was performed with a flame ionization detector (FID) using two systems:

A) a nitrogen carrier gas at 70 mL/minute, with a 1% SP-1000 on 100/120 Supelcoport column and two oven temperature programs: 1) 185° to 250° C at 10° C/minute, and
 2) 50° C for 5 minutes, then 50° to 250° C at 10° C/minute, and

B) a helium carrier gas at 20 mL/minute (lot A15) or 22 mL/minute (lot A11), with a DB-1 megabore capillary column and two oven temperature programs: 1) 260° C, isothermal, and 2) 50° C for 5 minutes, then 50° to 275° C at 10° C/minute.

For lot 8812-806876, System A with the second temperature program was used; System B for this lot included a nitrogen carrier gas with flow rate of 7 mL/minute, a nitrogen make-up gas with a make-up flow rate of 23 mL/minute, a DB-5 megabore column, and an oven temperature program of 50° C for 5 minutes, then 50° to 300° C at 10° C/minute.

For lot A15, elemental analyses for carbon and hydrogen were in agreement with the theoretical values for tricaprylin. Karl Fischer analysis indicated  $0.002 \pm 0.001\%$  water. USP methods of titration indicated an acid value of  $1.82 \pm 0.03$  mg KOH/g sample, equivalent to  $0.467 \pm 0.007\%$  octanoic acid, a saponification value of  $345 \pm 1$  mg KOH/g sample, and an ester value of 344 mg KOH/g of sample, equivalent to 96% of the theoretical ester value. TLC indicated a major spot and a slight trace impurity by System A and a major spot and a trace impurity by System B. Gas chromatography indicated a major peak and six impurities with a combined area of 5.7% relative to the major peak area by System A and a major peak and eight impurities with a combined area of 6.4% relative to the major peak area by System B. Each gas chromatographic system indicated one impurity with an area of approximately 5% relative to the major peak area. The overall purity was determined to be approximately 94%.

The largest impurity in lot A15 was identified as dicaprylin, using packed column gas chromatography/ mass spectrometry/full mass scan using System A described for the purity analyses, but with a helium carrier gas at 30 mL/minute; the second oven temperature program was used, with a 5-minute hold. Gas chromatographic System A, with an FID, a nitrogen carrier gas, and n-tetracosane added as an internal standard, indicated a concentration of approximately 5% dicaprylin.

For lot A11, elemental analyses for carbon and hydrogen were in agreement with the theoretical values for tricaprylin. Karl Fischer analysis indicated  $0.08 \pm 0.02\%$  water. USP methods of titration indicated an acid value of  $2.27 \pm 0.09$  mg KOH/g sample, equivalent to  $0.58 \pm 0.02\%$  octanoic acid, a saponification value of  $358 \pm 0$  mg KOH/g sample, and an ester value of 356 mg KOH/g sample, equivalent to 99.5% of the theoretical ester value. TLC indicated a major spot, a minor impurity, and a trace impurity by System A and a major spot, a minor impurity, and a slight trace impurity by System B. Concomitant TLC with lot A15 indicated a major spot and a minor, a trace, and a slight trace impurity by System B. Gas chromatography indicated a major peak and four impurities with a combined area of 2.4% relative to the major peak area by System A and a major peak and five impurities with a combined area of 3.6% relative to the major peak area by System B. Concomitant gas chromatography with lot A15 indicated a major peak and five impurities with a combined relative area of 4.1% by System A and a major peak and seven impurities with a combined relative area of 4.1% by System A and a major peak and seven impurities with a combined relative area of 4.1% by System B. Major peak comparison using System A with the first temperature program indicated that lot A11 had a purity of 107% relative to lot A15. The overall purity was determined to be approximately 97%.

For lot 8812-806876, elemental analyses for carbon and hydrogen were in agreement with the theoretical values for tricaprylin. Karl Fischer analysis indicated the presence of no more than 0.01% water. USP methods of titration indicated an acid value of  $0.60 \pm 0.03$  mg KOH/g sample, equivalent to  $0.155 \pm 0.007\%$  octanoic acid, a saponification value of  $354 \pm 4$  mg KOH/g sample, and an ester value of 353 mg KOH/g sample, equivalent to 99% of the theoretical ester value. TLC indicated a major spot and a minor impurity by System A and a major spot, a minor impurity, three trace impurities, and a slight trace impurity by System B. Concomitant TLC with lot A15 indicated a major spot and a minor impurity by System A and a major spot, a minor impurity, two trace impurities, and a slight trace impurity by System B. Gas chromatography indicated a major peak and four impurities with a combined area of 6.8% relative to the major peak area by System A and a major peak and five impurities with a combined area of

8.4% relative to the major peak area by System B. Concomitant gas chromatography with lot A15 indicated a major peak and four impurities with a combined relative area of 4.1% by System A and a major peak and five impurities with a combined relative area of 3.9% by System B. Major peak comparison by System A with the first oven temperature program indicated that lot 8812-806876 had a purity of 95% relative to lot A15. The overall purity was determined to be approximately 91%.

Accelerated stability studies were performed on lot A15 using gas chromatography with System A described for the purity analyses, with the first oven temperature program and with 0.2% octacosane added as an internal standard. The stability studies indicated that tricaprylin is stable as a bulk chemical for 2 weeks when stored protected from light at temperatures up to  $60^{\circ}$  C. The bulk chemical was stored in amber glass containers at  $4^{\circ} \pm 3^{\circ}$  C under an argon headspace. During the 2-year study, the stability of tricaprylin was monitored by the study laboratory with an ultraviolet spectroscopy extinction coefficient comparison method and with gas chromatography System A, but with an oven temperature program of  $185^{\circ}$  to  $250^{\circ}$  C at  $10^{\circ}$  C/minute, with a 4-minute hold. No significant degradation of the bulk chemical was observed throughout the study. In addition, the peroxide concentration in each bottle was determined prior to use. The acceptable peroxide concentration was set at 2 mEq/L. A bottle was discarded if the peroxide concentration exceeded the specification.

#### Dichloromethane

Dichloromethane was obtained from Dow Chemical Company (Midland, MI) in one lot (D112480), which was used throughout the study. Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO). The reports on analyses performed in support of the dichloromethane study are on file at the National Institute of Environmental Health Sciences.

The chemical, a clear, colorless liquid, was identified as dichloromethane by infrared spectroscopy. The spectrum was consistent with that expected for the structure and with the literature spectra of dichloromethane (Sadtler Standard Spectra) (Figure H3).

The purity of dichloromethane was further evaluated by Karl Fischer water analysis, free acid titration, and gas chromatography. Free acid titration was performed by dissolving a sample in 2-propanol and titrating with 0.01 N aqueous sodium hydroxide, using phenolphthalein as the indicator. Gas chromatography was performed with an FID and a nitrogen carrier gas at 70 mL/minute, and an oven temperature program of 60° C for six minutes, then 60° to 200° C at 10° C/minute (System A).

Karl Fischer analysis indicated  $0.0091 \pm 0.0001\%$  water. Free acid titration indicated less than 0.96 ppm acidic components expressed as hydrochloric acid. Gas chromatography using System A indicated a major peak and one impurity with a relative area greater than 0.1% of the major peak. An additional impurity, eluting before the major peak, with an area less than 0.1% relative to the major peak was also observed. The overall purity was determined to be approximately 99%.

Dichloromethane was analyzed for the presence of vinylidene chloride and *trans*-1,2-dichloroethylene with gas chromatography/mass spectroscopy/full mass scan using gas chromatography with a 10% Carbowax 20M-TPA on an 80/100 Chromosorb W(AW) column, a helium carrier gas at a flow rate of 30 mL/minute, and an oven temperature program of 60° C for 6 minutes, then 60° to 200° C at 10° C/minute (System B). Vinylidene chloride and *trans*-1,2-dichloroethylene were identified, as well as cyclohexane. Packed column gas chromatographic analysis using System B, but with a nitrogen carrier gas at a flow rate of 70 mL/minute, indicated 100 ppm *trans*-1,2-dichloroethylene. Capillary gas chromatography with an FID and a DB-5 fused silica capillary column with a nitrogen carrier gas at 19 mL/second and an oven temperature program of 30° C for 8 minutes, then 30° to 300° C at 40° C/minute, indicated less than 100 ppm vinylidene chloride (System C).

Gas chromatographic analysis of dichloromethane for 1,3-butadiene was performed using System C, but with a nitrogen carrier gas at 12 mL/second and an oven temperature program of 30° C for 10 minutes, then 30° to 210° C at 15° C/minute; this system indicated the presence of 1,3-butadiene at a concentration of less than 1 ppm.

Dichloromethane was analyzed for the presence of chloroform, carbon tetrachloride, and 1,2-dichloroethane by high resolution gas chromatography/mass spectroscopy/full mass scan. The gas chromatography system included a helium carrier gas at 30 mL/second, a fused silica capillary column, and an oven temperature program of 30° C for 10 minutes, then 30° to 200° C at 10° C/minute. Chloroform and carbon tetrachloride were identified. This analysis also identified bromochloromethane, which coeluted with chloroform; cyclohexane, which coeluted with carbon tetrachloride; and an unidentified impurity which coeluted with the major component. Quantitation of chloroform and carbon tetrachloride with high resolution gas chromatography using System C, with a nitrogen carrier gas at 30 mL/minute, electron capture detection, and an oven temperature program of 30° C for 10 minutes, then 30° to 300° C at 20° C/minute indicated a combined concentration of 18 ± 1 ppm for chloroform and bromochloromethane and less than 0.3 ppb carbon tetrachloride. No response was observed for cyclohexane. Gas chromatography using System C, but with a nitrogen carrier gas at 30 mL/minute and an oven temperature program of 30° C for 10 minutes, then 30° to 210° C at 15° C/minute, indicated a minimum detectable level of 19 ppm 1,2-dichloroethane. Further gas chromatographic/mass spectrometric and direct inlet mass spectrometric analyses indicated that the unidentified component was an experimental artifact produced by ion-molecule reactions occurring within the ion source of the quadrupole mass spectrometer.

Stability studies were performed on dichloromethane using gas chromatography with an FID and a Chromosorb 102 on 100/120 mesh column, with an oven temperature of 150° C. The stability studies indicated that dichloromethane is stable as a bulk chemical for at least 2 weeks at temperatures up to 35° C. Lot 766062 of dichloromethane was stored in amber glass containers in the dark at 20° C. Periodic reanalyses of dichloromethane were performed by the study laboratory using free acid titration with 0.005 N sodium hydroxide and using gas chromatography with an FID, a 10% Carbowax 20M-TPA on 80/100 Chromosorb W(AW) column, a nitrogen carrier gas at 70 mL/minute, and an oven temperature program of 50° C for 6 minutes, then 50° to 200° C at 25° C/minute, with a 1 minute hold. Decane (0.25% in o-dichlorobenzene) was added as an internal standard. No degradation of the bulk chemical was observed throughout the study.

#### Preparation and Analysis of Dose Formulations

The dose formulations (dichloromethane in corn oil) were prepared weekly by mixing dichloromethane with corn oil (Table H2). The dose formulations were stored at 4° C until use. Aliquots of corn oil, safflower oil, and tricaprylin were placed in gavage dosing vials weekly and stored at 4° C for no more than 3 weeks (oils). Saline solutions were prepared weekly by mixing sodium chloride with deionized water and stored at 4° C for no more than 4 weeks.

Stability studies of the dichloromethane dose formulations were performed by the analytical chemistry laboratory, using gas chromatography with an FID with a nitrogen carrier gas at a flow rate of 30 mL/minute, with a 20% SP-2100/0.1% Carbowax 1500 on 100/120 Supelcoport column and an oven temperature program of 40° C for 2 minutes, then 40° to 75° C at 10° C/minute. Chloroform was added as an internal standard. These studies indicated that the dose formulations were stable for 3 weeks when stored in the dark at room temperature.

Dose formulations of dichloromethane in corn oil were analyzed by the study laboratory approximately every 8 weeks using gas chromatographic System A as described for the stability studies; 41 of the 42 dose formulations analyzed were within 10% of the target concentrations. Results of the dose formulation

analyses are presented in Table H3. All animal room samples were within 10% of the target concentrations (Table H3). Results of periodic referee analyses performed by the analytical chemistry laboratory indicated good agreement with the results obtained by the study laboratory, with the exception of one dose formulation mixed on 18 November 1987 (Table H4). Animal room samples from this dose formulation were analyzed and were within 10% of the target concentrations.

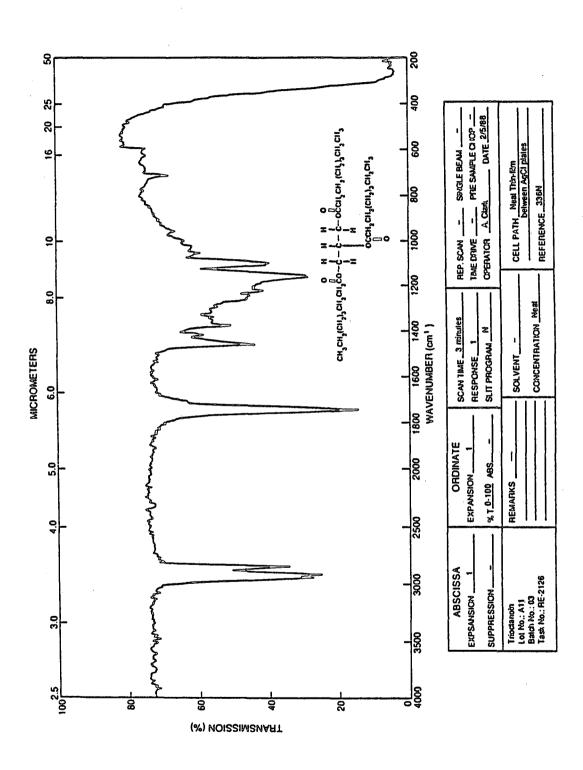


FIGURE II1 Infrared Absorption Spectrum of Tricaprylin

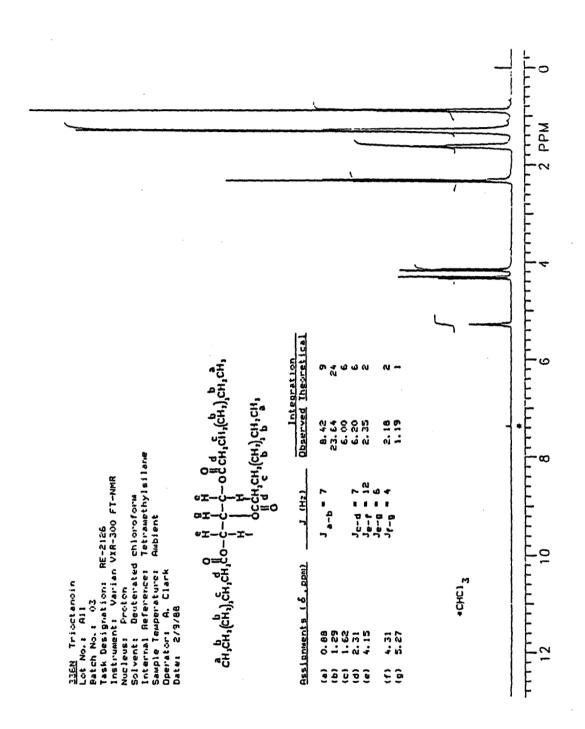


FIGURE II2
Nuclear Magnetic Resonance Spectrum of Tricaprylin

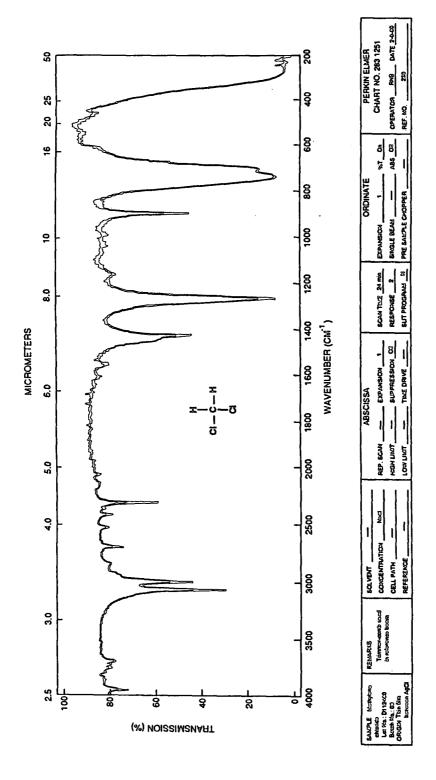


FIGURE II3
Infrared Absorption Spectrum of Dichloromethane

TABLE H1 Characteristics and Approximate Composition of Corn Oil

2 * 2 × 3 × 2 × 1	Lot 2325	Lot SFS-L050189
Calories per gram	8.9	8.9
Iodine value	127	127
Peroxide number	0.4	1.6
Anisidine value	4.6	2.3
Saponification equivalent <sup>a</sup>	191	191
Color	1.7 R/12 Y	2.3 R/14 Y
Components		
Glycerides <sup>a</sup>	>98.7%	>98.7%
Unsaponifiable matter <sup>a</sup>	1.25%	1.25%
Free fatty acids	0.04%	0.04%
Phosphorus	0.9 ppm	0.5 ppm
Sodium	0.2 ppm	0.1 ppm
Calcium	0.1 ppm	0.1 ppm
Magnesium	0.1 ppm	<0.1 ppm
Organo-chloride pesticides residues	<10 ppb <sup>b</sup>	<10 ppb <sup>b</sup>
Aflatoxin	<0.5 ppb <sup>b</sup>	<0.5 ppb <sup>b</sup>
Heavy metals (Pb, Cu, Ni, Fe)	<0.1 ppm <sup>b</sup>	<0.1 ppm <sup>b</sup>
Estrogenic activity <sup>a</sup>	None detectable (<5 ppb <sup>b</sup> )	None detectable (<5 ppb <sup>b</sup> )
Fatty Asid (anama/100 aroung of soun	ail)	
Fatty Acid (grams/100 grams of corn	94.3	94.3
Total fatty acids		
C12:0	Trace	Trace
C14:0	Trace	Trace
C16:0	10.0	9.5
C16:1	0.2	0.2
C18:0	1.7	2.3
C18:1	25.8	25.4
C18:2	54.2	55.1
C18:3	1.4	1.0
All others	1.0	0.8
Essential fatty acid (lipoxidase)	57.5	<b>56.8</b>
Unsaponifiables <sup>a</sup> (% of oil)	1.25	1.25
Phytosterols	>1.0	>1.0
Stigmasterol <sup>a</sup>	0.07	0.07
β-Sitosterol <sup>a</sup>	0.8	0.8
γ-Sitosterol or Campesterol <sup>2</sup>	0.2	0.2
Tocopherols - total	0.126	0.098
a-Tocopherol	0.032	0.014
γ-Tocopherol	0.091	0.084
δ-Tocopherol	0.003	<0.001
Ubiquinone (coenzyme Q-9) <sup>a</sup>	0.02	<0.02
Squalene <sup>a</sup>	0.02 Trace	Trace
Squarene Carotenoids <sup>a</sup>	Trace	Trace
Carotelloids	Trace	11906

From historical experience; not analyzed Limits of detection

TABLE H2
Preparation and Storage of Dose Formulations in the 2-Year Gavage Studies of Corm Oil, Safflower Oil, Tricaprylin, and Dichloromethane in Corn Oil

Corn Oil Study	Safflower Oil Study	Tricaprylin Study	Dichloromethane in Corn Oil Study				
Preparation Corn oil aliquots were placed in clear glass vials. Sodium chloride was weighed into a graduated cylinder and deionized water was added to obtain the correct value. Doses were prepared weekly.	Safflower oil aliquots were placed in clear glass vials with an argon headspace.  Doses were prepared weekly.	Tricaprylin aliquots were placed in clear glass vials with an argon headspace.  Doses were prepared weekly.	Dichloromethane was weighed into a graduated cylinder and corn oil was added to obtain the correct volume. Dose formulations were prepared weekly.				
Chemical Lot Number 2325 and SFS-L050189 (Manufacturer: Best Foods, Union, NJ)	OISO, KISO (Manufacturer: Oilseeds International, Ltd.; Producers Cotton Oil Company, arranged by Kraft Incorporated, Glenview, IL)	A15, A11, and 8812-806876	Dichloromethane: D112480 Corn oil: 2325 and SFS-L050189				
Maximum Storage Time 3 weeks (corn oil) 4 weeks (saline)	3 weeks	3 weeks	3 weeks				
Storage Conditions In the dark at 4° C	In the dark at 4° C	In the dark at 4° C	In the dark at 4° C				
Study Laboratory TSI Mason Research Institute, Worcester, MA	TSI Mason Research Institute, Worcester, MA	TSI Mason Research Institute, Worcester, MA	TSI Mason Research Institute, Worcester, MA				
Referee Laboratory None	None	None	Midwest Research Institute, Kansas City, MO				

TABLE H3
Results of Analysis of Dose Formulations Administered to Male Rats in the 2-Year Gavage Study of Dichloromethane in Corn Oil

Date Prepared	Date Analyzed	Target Concentration <sup>a</sup> (mg/g)	Determined Concentration <sup>b</sup> (mg/g)	Difference from Target (%)		
15 January 1986	17 January 1986	53.7	49.9	<b>-7</b>		
•	•	105.6 204.5	97.8 186.6	-7 -9		
		204.5	180.0	-9		
	31 January 1986 <sup>c</sup>	53.7	48.8	-9		
		105.6	96.3	-9		
		204.5	188.1	-8		
March 1986	7 March 1986	53.7	52.4	-2		
		105.6	102.2	-3		
		204.5	198.4	-3		
' May 1986	8 May 1986	53.7	51.6	-4		
<b>y</b>	y	105.6	103.0	-3		
		204.5	196.2	-4		
July 1986	3 July 1986	53.7	52.1	-3		
		105.6	101.1	-4		
		204.5	194.2	<b>-5</b>		
	28 August 1986 <sup>c</sup>	53.7	51.6	-4		
		105.6	98.4	<b>-7</b>		
		204.5	193.1	-6		
7 August 1986	28 August 1986	53.7	51.4	-4		
		105.6	98.4	<b>-7</b>		
		204.5	199.0	-3		
2 October 1986	23 October 1986	53.7	49.5	8		
		105.6	96.9	-8		
		204.5	187.9	-8		
7 December 1986	18 December 1986	53.7	53.8	0		
		105.6	104.9	-1		
	,	204.5	199.0	-3		
	6 January 1987 <sup>c</sup>	53.7	54.9	+2		
	-	105.6	103.3	-2		
		204.5	197.5	-3		
February 1987	4 February 1987	53.7	52.5	-2		
	•	105.6	102.0	-3		
		204.5	200.7	-2		
April 1987	9 April 1987	53.7	53.8	0		
-	· -	105.6	104.1	-1		
		204.5	199.5	-2		

TABLE H3
Results of Analysis of Dose Formulations Administered to Male Rats in the 2-Year Gavage Study of Dichloromethane in Corn Oil (continued)

Date Prepared	Date Analyzed	Target Concentration (mg/g)	Determined Concentration (mg/g)	Difference from Target (%)	
			50.4		
3 June 1987	3 June 1987	53.7	53.4 106.6	-1 +1	
		105.6 204.5	201.7	+1 -1	
		204.5	201.7	-1	
	24 June 1987 <sup>c</sup>	53.7	51.0	<b>-5</b>	
	2. June 150.	105.6	102.7	-3	
		204.5	199.3	-3	
00 T 1 100F	20 7 1 1007	52.7	53.1	-1	
29 July 1987	30 July 1987	53.7 105.6	104.1	-1 -1	
		204.5	196.7	-1 -4	
		204.3	190.7		
23 September 1987	24 September 1987	53.7	54.5	+2	
•	•	105.6	92.9	-12 <sup>d</sup>	
•		204.5	198.2	-3	
28 September 1987 <sup>e</sup>	28 September 1987	105.6	105.8	0	
18 November 1987	19 November 1987	53.7	53.4	-1	
		105.6	105.7	0	
		204.5	205.8	+1	
	14 December 1987 <sup>c</sup>	53.7	48.5	-10	
		53.7	52.5	-2	
		105.6	103.7	-2	
		204.5	206.2	+1	
		204.5	206.0	+1	
14 January 1988	14 January 1988	53.7	54.2	+1	
- · · · · · · · · · · · · · · · · · · ·	<b></b>	105.6	106.3	+1	
		204.5	205.8	+1	

Target concentrations for 500 mg dichloromethane/kg in corn oil: 204.5 mg/g = 2.5 mL corn oil/kg; 105.6 mg/g = 5 mL corn oil/kg; 53.7 mg/g = 10 mL corn oil/kg

b Results of duplicate analyses

c Animal-room samples

d Sample remixed

e Analysis results of remix

TABLE H4 Results of Referee Analysis of Dose Formulations in the 2-Year Gavage Study of Dichloromethane in Corn Oil

		Determined Concentration (mg/g)	
Date Prepared	Target Concentration (mg/g)	Study Referee Laboratory <sup>a</sup> Laboratory <sup>b</sup>	
15 January 1986	53.7	49.9 50.0 ± 0.7	
2 July 1986	204.5	$194.2$ $194 \pm 2$	• .
17 December 1986	105.6	104.9 $98.6 \pm 0.5$	
3 June 1987	53.7	$53.4$ $51.2 \pm 0.4$	
18 November 1987	105.6	105.7 52.2 $\pm$ 0.5	
18 November 1987	53.7	$53.4   57.7 \pm 12.3$	

Results of duplicate analyses
 Results of triplicate analyses

### APPENDIX I FEED CONSUMPTION IN THE 2-YEAR GAVAGE STUDIES

TABLE I	ia P	reed	Consumption	bу	Male	Rats	im	the	2-Year	Gavage	Study	of	Corn Oil .		 	• •	284
Table I	12 F	'eed	Consumption	bу	Male	Rats	im	the	2-Year	Gavage	Study	Оľ	Safflower	Oil	 	• •	285
TABLE I	13 F	i eed	Consumption	bу	Male	Rats	im	the	2-Year	Gavage	Study	Ol	Tricaprylin	n	 		286
Table I	[4] F	i ced	Consumption	bу	Male	Rats	im	the	2-Year	Gavage	Study						
	Œ	f Di	chloromethan	e in	a Corn	oil o							. <b></b> .		 		287

TABLE I1
Feed Consumption by Male Rats in the 2-Year Gavage Study of Corn Oil

Week	<u>Untreated Control</u> Mean <sup>a</sup>	10 mL/kg (Saline) Mean	2.5 mL/kg Mean	5 mL/kg Mean	10 mL/kg Mean
2	13.9	13.8	13.2	12.9	11.5
5	17.1	16.3	16.0	15.1	13.4
8	16.4	16.0	14.8	13.2	12.0
12	15.6	16.1	14.1	13.1	10.0
16	19.5	19.1	18.3	14.9	14.5
20	18.3	16.8	14.7	13.5	11.9
24	17.9	17.5	14.3	13.0	10.4
28	18.8	18.8	17.9	14.6	13.8
33	17.3	16.2	14.8	11.6	11.2
37	17.6	17.7	17.2	13.9	11.2
40	15.0	13.2	14.2	11.1	8.8
44	16.6	15.7	14.5	11.7	9.0
48	18.6	16.0	15.0	12.3	8.8
52	18.9	19.0	16.2	14.0	9.5
57	17.6	17.0	15.6	12.5	9.7
61	18.6	16.9	15.0	12.5	9.3
64	21.7	20.1	16.2	13.5	9.6
69	19.9	18.0	16.5	13.2	9.5
73	14.9	14.4	13.0	10.8	8.4
77	18.8	17.2	15.0	12.1	9.5
81	15.3	16.2	13.0	11.2	9.3
85	16.5	15.4	13.5	11.1	8.4
89	16.9	16.6	13.8	11.7	8.3
93	12.6	12.1	10.6	8.5	6.4
97	14.2	13.2	11.8	9.5	7.4
101	14.0	13.4	11.5	9.2	7.1
104	14.3	11.9	10.0	8.9	4.5
Aean	17.0	16.2	14.6	12.3	9.9

<sup>&</sup>lt;sup>a</sup> Mean = Average consumption in grams per animal per day

TABLE I2
Feed Consumption by Male Rats in the 2-Year Gavage Study of Safflower Oil

Week	<u>Untreated Control</u> Mean <sup>a</sup>	2.5 mL/kg Mean	5 mL/kg Mean	10 mL/kg Mean
2	15.8	14.0	13.4	12.1
5	15.7	14.6	13.7	12.2
9	14.9	14.5	13.6	12.2
13	15.1	13.3	12.0	9.6
16	21.2	18.9	16.6	14.4
20	18.1	15.3	12.9	11.8
25	16.5	15.0	13.5	12.3
28	16.9	15.0	12.2	9.7
33	15.7	13.7	11.5	10.9
36	19.7	17.5	14.7	11.6
41	16.0	13.7	10.9	8.4
45	16.9	14.6	12.9	10.7
48	16.0	13.9	12.3	9.0
53	20.1	17.3	14.4	9.9
56	18.9	16.8	13.1	9.4
60	16.9	16.3	12.8	8.8
65	15.3	15.7	12.6	9.3
68	19.4	16.1	13.1	10.3
73 .	17.9	14.6	12.4	9.2
77	17.3	14.9	13.0	10.0
81	15.0	13.2	12.0	8.9
84	19.0	16.1	12.7	9.7
89	16.4	14.9	12.4	9.6
93	14.3	12.3	9.6	5.2
97	15.0	11.9	10.7	7.7
101	13.0	10.8	8.5	5.4
104	13.5	9.8	8.1	5.2
Mean	16.8	14.8	12.6	10.0

<sup>&</sup>lt;sup>a</sup> Mean = Average consumption in grams per animal per day

TABLE I3
Feed Consumption by Male Rats in the 2-Year Gavage Study of Tricaprylin

Week	<u>Untreated Control</u> Mean <sup>a</sup>	2.5 mL/kg Mean	<u>5 mL/kg</u> Mean		10 mL/kg Mean	\$ + <b>5</b>
<del></del>	<del></del>					
2	14.2	13.7	12.5	:	11.4	
2 5 9 13	16.9	15.9	16.0		14.4	
9	17.1	16.5	16.4		13.6	,
13	13.0	12.1	9.9		8.9	
17	20.2	16.9	16.0		13.5	٠.
21	. 1 <b>5.8</b>	14.9	12.5		10.0	
25	18.3	18.3	16.5	•	13.5	
29	17.8	16.2	<b>14.0</b> ,		12.2	
33	17.8	16.3	16.0		13.7	** '
37	18.3	15.6	14.2		12.1	
41	15.2	12.8	11.5		8.8	
45	16.7	14.9	12.5	•	10.8	•
49	20.3	17.7,	15.8	•	13.3	
53	18.2	16.2	14.2		12.1	
57	20.4	17.5	14.1		12.7	
61	17.9	16.5	14.2		12.5	
65	16.8	13.7	11.9		10.6	
69	18.6	17.3	16.5		15.6	
73	16.8	14.1	12.9		10.2	
77	17.7	. 14.3	12.9		11.2	
81	17.7	14.5	13.2		10.7	
85	15.9	14.3	12.2		10.3	
89	13.9	12.6	10.6		9.5	
93	16.6	14.4	15.9		15.1	
97	16.5	12.3	12.3		12.9	
101	13.7	12.3	9.4		8.7	
101	13.5	10.6	9.2		7.6	
104	, 13.3	10.0	7, <b>L</b>		7.0	
Mean	17.0	15.1	13.6		11.8	

<sup>&</sup>lt;sup>a</sup> Mean = Average consumption in grams per animal per day

TABLE I4
Feed Consumption by Male Rats in the 2-Year Gavage Study of Dichloromethane in Corn Oil

Week	2.5 mL/kg Mean <sup>a</sup>	5 mL/kg Mean	10 mL/kg Mean
	<u> </u>		·
2	15.3	14.9	13.4
5	16.2	15.9	14.5
9	14.8	14.1	11.6
13	14.9	13.6	11.2
17	13.7	12.4	9.6
21	13.6	12.0	10.2
25	15.0	13.1	11.5
29	15.3	14.0	11.1
33	14.7	13.0	10.3
37	14.1	12.8	10.5
41	14.8	13.1	10.8
44	12.9	10.7	9.2
48	14.1	12.4	10.0
53	13.4	11.9	9.3
57	14.4	12.0	9.6
61	13.9	11.8	10.5
65	13.2	11.5	9.4
69	12.8	11.5	9.0
73	14.2	11.9	10.0
77	13.9	12.2	9.0
81	11.5	10.3	8.4
85	12.1	11.0	8.8
89	15.1	. 11.3	10.6
93	12.8	10.0	7.9
97	11.5	10.2	7.3
101	13.0	10.0	8.1
105	11.4	10.2	8.6
Iean	13.9	12.3	10.1

<sup>&</sup>lt;sup>a</sup> Mean = Average consumption in grams per animal per day

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

Table J1	Ingredients of NIH-07 Rat and Mouse Ration	ኃው
Table J2	Vitamins and Minerals in NIH-07 Rat and Mouse Ration	22V
Table J3	Nutrient Composition of NIH-07 Rat and Mouse Ration	201 201
Table J4	Contaminant Levels in NIH-07 Rat and Mouse Ration	اللاك
		292

TABLE J1 Ingredients of NIH-07 Rat and Mouse Ration<sup>a</sup>

Ingredients <sup>b</sup>	Percent by Weight	
Ground #2 yellow shelled corn	24.50	
Ground hard winter wheat	23.00	es e
Soybean meal (49% protein)	12.00	
Fish meal (60% protein)	10.00	
Wheat middlings	10.00	
Dried skim milk	5.00	1
Alfalfa meal (dehydrated, 17% protein)	4.00	
Corn gluten meal (60% protein)	3.00	
Soy oil	2.50	
Dried brewer's yeast	2.00	
Dry molasses	1.50	• •
Dicalcium phosphate	1.25	
Ground limestone	0.50	
Salt	0.50	
Premixes (vitamin and mineral)	0.25	

TABLE J2 Vitamins and Minerals in NIH-07 Rat and Mouse Ration<sup>a</sup>

	Amount	Source	•
Vitamins			
A	5,500,000 IU	Stabilized vitamin A palmitate of	r acetate
$D_3$	4,600,000 IU	D-activated animal sterol	· ·
K <sub>3</sub>	2.8 g	Menadione	1.1.
d-α-Tocopheryl acetate	20,000 IU	5	1 . 5.
Choline	560.0 g	Choline chloride	* * * * * * * * * * * * * * * * * * *
Folic acid	2.2 g		
Niacin	30.0 g		
d-Pantothenic acid	18.0 g	d-Calcium pantothenate	•
Riboflavin	3.4 g	•	41,141,141
Thiamine	10.0 g	Thiamine mononitrate	
B <sub>12</sub>	4,000 μg		
Pyridoxine	1.7 g	Pyridoxine hydrochloride	
Biotin	140.0 mg	d-Biotin	
			, # · ·
Minerals	,		* * * * * * * * * * * * * * * * * * *
Iron	120.0 g	Iron sulfate	Sign of the second
Manganese	60.0 g	Manganous oxide	
Zinc	16.0 g	Zinc oxide	
Copper	4.0 g	Copper sulfate	*. 9
Iodine	1.4 g	Calcium iodate	
Cobalt	0.4 g	Cobalt carbonate	1 - 1 - 2 + 1 - 1 -
			4.5

<sup>&</sup>lt;sup>a</sup> Per ton (2,000 lb) of finished product

a NCI, 1976; NIH, 1978
 b Ingredients ground to pass through a U.S. Standard Screen No. 16 before being mixed

TABLE J3
Nutrient Composition of NIH-07 Rat and Mouse Ration

	Mean 🛨 Standard		·	
Nutrient	Deviation	Range	Number of Samples	
Protein (% by weight)	22.54 ± 0.70	21.6 – 24.0	32	
Crude Fat (% by weight)	$5.53 \pm 0.28$	4.9 - 6.0	32	
Crude Fiber (% by weight)	$3.45 \pm 0.27$	2.7 - 4.0	32	
Ash (% by weight)	$6.64 \pm 0.33$	6.1 - 7.1	32	
Amino Acids (% of total diet)				
Arginine	$1.308 \pm 0.606$	1.210 - 1.390	8	
Cystine	$0.306 \pm 0.084$	0.181 - 0.400	8	
Glycine	$1.150 \pm 0.047$	1.060 - 1.210	8	
Histidine	$0.576 \pm 0.024$	0.531 - 0.607	8	
Isoleucine	$0.917 \pm 0.029$	0.881 - 0.944	8	
Leucine	$1.946 \pm 0.055$	1.850 - 2.040	8 '	
Lysine	$1.270 \pm 0.058$	1.200 - 1.370	8	
Methionine	$0.448 \pm 0.128$	0.306 ~ 0.699	8	
Phenylalanine	$0.987 \pm 0.128$	0.665 ~ 1.110	8	
Threonine				
	$0.877 \pm 0.042$	0.824 - 0.940	8	
Tryptophan	$0.236 \pm 0.176$	0.107 - 0.671	8	
Tyrosine	$0.676 \pm 0.105$	0.564 - 0.794	8	
Valine	$1.103 \pm 0.040$	1.050 - 1.170	8	
Essential Fatty Acids (% of total	•		_	
Linoleic	$2.393 \pm 0.258$	1.830 - 2.570	7	
Linolenic	$0.280 \pm 0.040$	0.210 - 0.320	7	
7itamins				
Vitamin A (IU/kg)	$6,997 \pm 2,045$	4,430 13,000	32	
Vitamin D (IU/kg)	$4,450 \pm 1,382$	3,000 - 6,300	4	
α-Tocopherol (ppm)	$37.95 \pm 9.406$	22.5 – 48.9	8	
Thiamine (ppm)	$19.75 \pm 2.59$	14.0 - 26.0	32	
Riboflavin (ppm)	$7.92 \pm 0.87$	6.10 - 9.00	8	
Niacin (ppm)	$103.4 \pm 26.59$	65.0 - 150.0	8	
Pantothenic acid (ppm)	$29.54 \pm 3.60$	23.0 - 34.0	8	
Pyridoxine (ppm)	$9.55 \pm 3.48$	5.60 - 14.0	8	
Folic acid (ppm)	$2.25 \pm 0.73$	1.80 - 3.70	8	
Biotin (ppm)	$0.254 \pm 0.042$	0.19 - 0.32	8	
Vitamin B <sub>12</sub> (ppb)	$38.45 \pm 22.01$	10.6 - 65.0	8	
Choline (ppm)	3,089 ± 328.69	2,400 - 3,430	8	
Minerals				
Calcium (%)	$1.21 \pm 0.12$	1.00 - 1.40	32	
Phosphorus (%)	$0.92 \pm 0.06$	0.73 - 1.00	32 32	
Potassium (%)	$0.883 \pm 0.078$			
Chloride (%)	$0.883 \pm 0.078$ $0.526 \pm 0.092$	0.772 - 0.971	6	
Sodium (%)		0.380 - 0.635	8	
` /	$0.313 \pm 0.390$	0.258 - 0.371	8	
Magnesium (%)	$0.168 \pm 0.010$	0.151 - 0.181	8	
Sulfur (%)	$0.280 \pm 0.064$	0.208 - 0.420	8	
Iron (ppm)	$360.5 \pm 100$	255.0 - 523.0	8	
Manganese (ppm)	$92.0 \pm 6.01$	81.70 - 99.40	8	
Zinc (ppm)	$54.72 \pm 5.67$	46.10 - 64.50	8	
Copper (ppm)	$11.06 \pm 2.50$	8.090 - 15.39	8 .	
Iodine (ppm)	$3.37 \pm 0.92$	1.52 - 4.13	6	
Chromium (ppm)	$1.79 \pm 0.36$	1.04 - 2.09	. 8	
Cobalt (ppm)	$0.681 \pm 0.14$	0.490 - 0.780	4	

TABLE J4
Contaminant Levels in NIH-07 Rat and Mouse Ration

	Mean ± Standard		**	· · · · · · · · · · · · · · · · · · ·
	Deviation <sup>a</sup>	Range	Number of	Samples
Contaminants				
	$0.46 \pm 0.32$	0.05 - 1.07	32	
Arsenic (ppm) Cadmium (ppm) <sup>b</sup>	$0.46 \pm 0.32 \\ 0.10 \pm 0.01$	0.03 - 1.07 $0.10 - 0.20$	32	
Lead (ppm)	$0.34 \pm 0.25$	$0.10 \pm 0.20$ $0.05 - 1.00$	32	
Mercury (ppm)	<0.05	0.05 - 1.00	. 32	
Selenium (ppm)	$0.37 \pm 0.10$	0.16 - 0.63	32	
Aflatoxins (ppb)	<5.0	0.10 - 0.03	32	
Nitrate nitrogen (ppm) <sup>c</sup>	$21.03 \pm 9.03$	11.0 - 41.0	32	10% 1 74 TO 12 ST
Nitrite nitrogen (ppm) <sup>c</sup>	$0.37 \pm 0.64$	<0.10 - 2.60	32	
BHA (ppm) <sup>d</sup>	$2.41 \pm 1.03$	<0.10 - 5.00	32	
BHT (ppm) <sup>d</sup>	$1.13 \pm 0.65$	<0.10 - 4.00	32	
Aerobic plate count (CFU/g) <sup>e</sup>	$63,174 \pm 83,703$	3,100 - 320,000	31	
Aerobic plate count (CFU/g) <sup>f</sup>	90,575 ± 175,516	3,100 - 940,000	32	
Coliform (MPN/g) <sup>g</sup>	$9.26 \pm 26.42$	<3.00 - 150	31	
Coliform (MPN/g) <sup>h</sup>	$43.34 \pm 195$	< 3.00 - 1,100	32	
E. coli (MPN/g) <sup>i</sup>	$3.03 \pm 0.18$	<3.00 - 4.00	32	
Total nitrosoamines (ppb)	9.75 ± 4.24	3.80 - 19.50	32	
N-Nitrosodimethylamine (ppb)	$7.91 \pm 3.46$	2.80 - 16.00	32	
N-Nitropyrrolidine (ppb)	$1.84 \pm 1.35$	0.90 - 5.40	32	
Pesticides (ppm)				
α-BHC <sup>k</sup>	< 0.01		32	
β-BHC	<0.01		32	
γ-BHC	< 0.02		32	
δ-BHC	<0.01		32	
Heptachlor	<0.01		32	
Aldrin	<0.01		32	
Heptachlor epoxide	<0.01		32	
DDE	<0.01		32	
DDD	<0.01		32	
DDT	<0.01		32	
НСВ	<0.01		32	
Mirex	<0.01		32	
Methoxychlor	<0.05		32	
Dieldrin	<0.01		32	
Endrin	<0.01		32	
Telodrin	< 0.01		32	
Chlordane	< 0.05		32	
Toxaphene	<0.1		32	
Estimated PCBs	<0.2		32	
Ronnel	< 0.01		32	
Ethion	<0.02		32	
Trithion	<0.05		32	
Diazinon	<0.1		32	
Methyl parathion	<0.02		32	
Ethyl parathion	<0.02		32	
Malathion l	$0.15 \pm 0.16$	0.05 - 0.60	32	
Endosulfan I	<0.01		32	
Endosulfan 2	< 0.01		32	
			J <b>.</b>	

Table J4 Contaminant Levels in NIH-07 Rat and Mouse Ration (continued)

- For values less than the limit of detection, the detection limit is given for the mean.
- One lot milled 4 June 1986 contained 0.20 ppm; all others measured 0.10 ppm or less.

Sources of contamination: alfalfa, grains, and fish meal

- Sources of contamination: soy oil and fish meal
- CFU = colony forming unit; excludes one high value of 940,000 CFU/g obtained in the lot milled 5 November 1987

Includes one high value of 940,000 CFU/g obtained in the lot milled 5 November 1987

MPN = most probable number; excludes one high value of 1,100 MPN/g obtained in the lot milled 5 July 1988

Includes one high value of 1,100 MPN/g obtained in the lot milled 5 July 1988

Includes one value of 4 MPN/g from the lot milled 4 April 1988

All values were correct for % recovery.

- BHC = hexachlorocyclohexane or benzene hexachloride
- Seventeen lots contained more than 0.05 ppm.

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# APPENDIX K SENTINEL ANIMAL PROGRAM

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# SENTINEL ANIMAL PROGRAM

### METHODS

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

# Corn Oil, Safflower Oil, and Tricaprylin Studies

Prior to the beginning of the 2-year studies, samples for viral screening were collected from five rats. During the studies, 15 male rats were maintained with the study animals to serve as sentinel animals. Five animals were to be killed at 6, 12, and 18 months on study; however, to better evaluate the virological burden of the study, some rats were live-bled so that sera could be collected at additional time points. For the 24-month viral screening, samples were collected from five animals each in the 5 mL/kg groups in the corn oil and tricaprylin studies. Blood collected from each animal was allowed to clot and the serum was separated. The serum was cooled on ice and shipped to Microbiological Associates, Inc. (Bethesda, MD), for determination of virus antibody titers. The following tests were performed:

Method of Analysis	Time of Analysis		
ELISA			
Mycoplasma arthritidis	24 months		
Mycoplasma pulmonis	24 months		
PVM (pneumonia virus of mice)	Preinitiation, 5½, 6, 7, 12, 18, and 24 months		
RCV/SDA			
(rat coronavirus/sialodacryoadenitis virus)	Preinitiation, 5½, 6, 7, 12, 18, and 24 months		
Sendai	Preinitiation, 5½, 6, 7, 12, 18, and 24 months		
Hemagglutination Inhibition			
H-1 (Toolan's H-1 virus)	Preinitiation, 5½, 6, 7, 12, 18, and 24 months		
KRV (Kilham rat virus)	Preinitiation, 5½, 6, 7, 12, 18, and 24 months		

# Dichloromethane in Corn Oil Study

During the 2-year study, 15 male rats were maintained with the study animals to serve as sentinel animals. Five animals were to be killed at 6, 12, and 18 months on study; however, to better evaluate the virological burden of the study, some rats were live-bled so that sera could be collected at additional time points. For the 24-month viral screening, samples were collected from two animals in each of the 2.5 and 5 mL/kg groups, one animal from the 10 mL/kg group, and one sentinel animal. Blood collected from each animal was allowed to clot and the serum was separated. The serum was cooled on ice and shipped to Microbiological Associates, Inc., for determination of virus antibody titers. The following tests were performed:

Method of Analysis	Time of Analysis
ELISA	
CARB (cilia-associated respiratory bacillus)	6 and 19 months
M. arthritidis	6 and 24 months
M. pulmonis	6 and 24 months
PVM	6, 12, 14, 14½, 19, 20, and 24 months
RCV/SDA	6, 12, 14, 14½, 19, 20, and 24 months
Sendai	6, 12, 14, 14½, 19, 20, and 24 months
Hemagglutination Inhibition	
H-1	6, 12, 14, 14½, 19, 20, and 24 months
KRV	6, 12, 14, 14½, 19, 20, and 24 months

Test results are presented in Table K1.

TABLE K1
Murine Virus Antibody Determinations for Male Rats in the 2-Year Gavage Studies of Corn Oil, Safflower Oil, Tricaprylin, and Dichloromethane in Corn Oil

Interval	Incidence of Antibody in Sentinel Animals	Positive Serologic Reaction for
Corn Oil, Safflower Oil, and Tricapi	ylin Studies	
Preinitiation	0/5	None positive
5½ months	0/2	None positive
6 months	1/5	RCV/SDA <sup>a</sup>
7 months	0/5	None positive
12 months	0/5	None positive
18 months	0/5	None positive
24 months	0/10	None positive
oichloromethane in Corn Oil Study		
6 months	0/5	None positive
12 months	0/5	None positive
14 months	0/2	None positive
14½ months	0/2	None positive
19 months	1/5	CARB
20 months	0/1	None positive
24 months	0/6	None positive

a Results of later testing of serum from this animal were negative; therefore, this response was determined to be false positive.

# APPENDIX L COOPERATIVE AGREEMENTS

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# FINAL PROGRESS REPORT DHHS #5 U01 ES 03687-05 Effect of fat on growth of pancreatic nodules.

Dates: 9-28-84 to 6-30-90.

The goals of this project can be stated briefly as follows. They were (1) to define the significance of pancreatic acinar cell hyperplastic nodules and adenomas in F-344 rats, and (2) to determine the mechanism of stimulation of the growth of such nodules by high corn oil diets.

This five year grant (extended to five years and 9 months without additional funds) supported work in several laboratories at Dartmouth, and provided the initial impetus for several lines of work that are still ongoing under other support. Most of the work has been summarized in publications by this time, but reports for a few projects are still in preparation for publication. In this narrative section, we will provide a brief summary of the published work, integrating related segments, rather than summarizing manuscripts independently. Slightly greater detail will be provided for some of the unpublished work.

Since the NTP studies utilize F344 rats and the NTP maintains a special interest in this strain, we initially focussed on adapting protocols for 4-month quantitative stereologic morphometric studies in F344 rats. Most of our prior work was done in Lewis rats and we had demonstrated that Lewis rats were more sensitive to initiation of pancreatic foci by azaserine than were F344 rats. This was documented again [1], but use of the 4-month protocols were quite feasible in the F344 strain by using two doses of azaserine to treat rats at 14 and 21 days of age.

In general, experiments were done by giving rats the carcinogen and autopsying them 4 months later to measure the size and number of preneoplastic lesions in the pancreas. Azaserine induces microscopically detectable foci of hyperplasia and dysplasia of acinar cells in the exocrine pancreas. Some of these lesions grow to become grossly visible nodules 1 mm or larger in diameter. These foci and nodules have collectively been termed atypical acinar cell nodules (AACN). Some observers prefer other designations such as focal cellular change and focal hyperplasia. The latter term has been preferred by the NTP. Phenotypic subtypes of AACN have been described, i.e. acidophilic foci which are ATPase positive and basophilic foci which are ATPase negative. AACN exclude iron in iron-loaded rats and show a variable reduction in histochemical staining for  $\gamma$ -glutamyl transferase. Counts and measurements of size in hematoxylin and eosin stained paraffin-embedded sections

are usually used for assessment of AACN size and number. The raw data is expressed per cm<sup>2</sup> of tissue and then formulae for quantitative stereology are applied to calculate the focus number per cm<sup>3</sup>, the true focus size (diameter or volume), and the fraction of the pancreatic tissue that is replaced by foci and nodules (volume per cent). In most such experiments, the rats are autopsied 4 months after treatment of rats with a single intraperitoneal injection of 30 mg azaserine/kg body weight. The whole pancreas is fixed and embedded in paraffin. In experiments designed to study post-initiation modulation (promotion or inhibition) of nodule growth, the azaserine is given when the rats are 2 weeks old. It has been shown that acinar cells are dividing actively at this age and that many foci are induced. Lewis strain rats are usually used because they are sensitive to focus induction by azaserine.

The 4-month protocol was used to study the effect of estrogen and testosterone on nodule development [2,4], the effect of two peptide hormones on nodule growth [5], and the effect of adding a synthetic trypsin inhibitor that stimulates CCK secretion from the intestine to the diet [7].

Another important aspect of the overall project was to establish a colony of "nodule donor" rats that were used in numerous studies during subsequent years of the project. This was done by treating male Lewis rats with a single dose of azaserine or N-nitroso(2-hydroxypropyl)(2-oxopropyl)amine when they were 2 weeks old, and then maintaining them on AIN76A or a derivative diet that contained 20% corn oil. From the age of 6 months on, but especially during the 1-2 year interval, these rats provided a source of acinar cell nodules that could be studied in situ by immunohistochemical stains, or be dissected out for molecular, and cell biology studies. These nodules were provided to a variety of investigators at other institutions for collaborative studies and were the basis of several papers and abstracts. Drs. Grossman and Beaudoin used these nodules to demonstrate an abnormality of estrogen receptor protein location in the nodules [16], and Dr. Richard Bell, working during a sabbatical leave at Dartmouth, used them to demonstrated the overexpression of CCK receptors in nodules and a transplantable pancreatic carcinoma that was established as part of the project. In addition to the carcinogen-induced nodules from our colony, we were supplied nodules and pancreases from rats maintained for two years on high corn oil diets at E. G. and G. Mason Research Institute, Worcester, MA (H. S. Lilja, Project Director). Certain characteristics of these nodules were compared with the spontaneous carcinogen-induced nodules and are reported in a recent publication [15] and summarized below.

Phenotypic and genotypic characteristics of azaserine-induced and spontaneous nodules and adenomas were compared with normal pancreas and azaserine-induced transplantable acinar cell carcinomas by several methods including flow cytometric determination of nuclear DNA content, ability to grow in soft agar, tumorigenicity after transplantation, histopathology, and transfection of DNA into NIH 3T3 cells. None of the parameters other than histologic appearance of nodules and adenomas was different from normal pancreas whereas several parameters differed for carcinomas. In particular, repeated subcutaneous and renal subcapsular transplantation of nodules and adenomas failed to yield growth. These studies indicated that cells from nodules and adenomas have low growth potential and lack critical phenotypic and genotypic characteristics of transformed malignant cells that were present in transplanted and some primary carcinomas. Some of the carcinomas were aneuploid, and only carcinomas had the ability to grow in soft agar or to survive transplantation. On new transplantable tumor line (DSL-6), originally a well differentiated acinar cell carcinoma, was established as part of this project.

Preneoplastic nodules and neoplasms induced in rats by azaserine and nafenopin, or occuring spontaneously were evaluated for mutations in the c-K-ras protooncogene using the polymerase chain reaction. Wild type but not mutated c-K-ras was demonstrated in all lesions. Thus, activation of c-K-ras by codon 12 mutation which is found in about 75% of human ductal pancreatic carcinomas [13] is not involved in the genesis of rat acinar cell carcinomas, raising the question of whether the critical difference is the species, the carcinogen, or the histologic type of the carcinoma.

Several azaserine-induced acinar cell carcinomas from Lewis rats have been serially transplanted and cryopreserved. Continuous cell lines have been established from two of these. As part of this project, the DSL-6 transplantable acinar cell carcinoma was placed in culture at the 9th transplantation and a cell line was obtained. Production of exocrine enzymes by the primary cultures ceased after 1-2 weeks. The cultured cells were tumorigenic in Lewis rats producing firm, solid tumors with a high content of fibrous tissue surrounding ductlike structures, histologically. The original tumor had a high content of CCK receptors (radioligand binding assay) but the cell line lacked the receptors [38,39]. A second cell line was established from the DSL-6 tumor. Electron microscopy showed ductlike cells without zymogen granules and with little rough endoplasmic reticulum. These cells were regrafted at the fourth passage producing partially solid and partially cystic tumors. Histologically, there was a mixed phenotype with squamous, mucinous, and poorly differentiated glandular areas (i.e., an adenosquamous pattern). Immunohistochemical studies of the regrafted tumor cells

were strongly positive using a pancytokeratin antibody, and showed variable expression of other ductal markers. This appears to reflect loss of acinar cell differentiation and acquistion of ductal markers in the tumor cells.

Pancreatic growth is regulated by several peptide hormones including cholecystokinin, bombesin, epidermal growth factor (EGF), and secretin--all of which stimulate growth, while somatostatin inhibits the growth of normal pancreas [18]. These agents act by binding to specific receptors. The role of such hormones in modulating the development of carcinoma of the pancreas was investigated in studies done by Dr. Evelyne Lhoste [5,7]. Sustained stimulation of normal pancreatic acinar cells by CCK results in cell division. She demonstrated that injection of CCK or bombesin following initiation with azaserine stimulated the growth of carcinogeninduced foci and nodules in a 4-month morphometric study [5]. Small, localized carcinomas were found in the caerulein-treated rats four months after azaserine treatment. She then added camostate, a trypsin inhibitor to the diet of azaserineinduced and control rats, and showed pancreatic hyperplasia and stimulation of the growth of foci and nodules. Dietary trypsin inhibitors are known to stimulate the secretion of endogenous CCK, a trophic hormone for pancreatic acinar cells. Administration of camostate (FOY-305), has been shown to induce pancreatic enlargement in rats by the same mechanism. In this study we investigated the effects of dietary camostate on the early stages of pancreatic carcinogenesis induced by azaserine. In one experiment, F344 and Lewis adult rats were fed a camostatecontaining diet at different levels for 3 or 5 days a week in order to investigate the effect on pancreatic growth. These rats were autopsied after 3 weeks. Protein, RNA, DNA and amylase content of the pancreas were measured. From this experiment, we concluded that camostate administered in the diet induced pancreatic hypertrophy and hyperplasia. In a second experiment, F344 rats received injections of azaserine at 16 and 23 days of age, and thereafter camostate was administered by gavage 5 days a week for 18 weeks until sacrifice. In a third experiment, Lewis rats received a single injection of azaserine at 14 days of age and after weaning camostate was administered in the diet 3 days a week for 8 or 16 weeks. Rats were autopsied 4 months after the azaserine injection. In both experiments 2 and 3, the number and size of atypical acinar cell foci and nodules (AACN) were measured in pancreas sections. Growth of acidophilic AACN was stimulated in camostate-fed groups. The number of acidophilic AACN was greater in camostate than in control diet groups. The size of acidophilic AACN was dramatically increased in camostate-fed rats. This increase was time dependent. The number of basophilic AACN was decreased in camostate-fed Lewis rats. The latter

result suggests that the camostate diet affected the phenotype of the carcinogen-induced AACN.

Dr. Richard Bell subsequently demonstrated that such nodules bind more CCK than normal pancreas suggesting that cells in the foci have more receptors [38, submitted]. Excessive CCK stimulation is regarded as the basis for enhanced carcinogenesis in carcinogen-treated rats that are fed raw soya flour or diets containing soy bean trypsin inhibitor (SBTI), and for the development of acinar cell tumors in rats with pancreaticobiliary diversion. The effect of high fat diets and of the peptide hormones (or dietary trypsin inhibitor) are different in several ways providing indirect evidence that the high fat effect is not mediated through GI peptide hormones.

The model has been used to show that males develop more foci than females and that several hormonal treatments can modulate focus growth [2,4,8]. Administration of testosterone to castrated males stimulated the growth of nodules, althought not to the level observed in intact males [2]. Castration and treatment with exogenous estradiol had additive effects inhibiting the growth of a transplanted azaserine-induced acinar cell carcinoma in syngeneic rats [9]. Such hormonal effects might reflect either a direct action of the steroid on the cancer cell, or alternately reflect an indirect action by altering the production of a polypeptide hormone that in turn affects cancer cell proliferation.

Our studies during this project supported earlier reports that diets with a high content of fat promote the development of preneoplastic and neoplastic acinar cell lesions in the rat pancreas [22]. We believe that high fat diets can speed the growth and progression of carcinogen-induced, or of spontaneously occurring initiated foci [22,17].

We conducted one study to compare the effect of several fats with varying degrees of unsaturation/saturation on the development of azaserine-induced foci. The effect of six different oils on the growth of pancreatic foci and nodules was compared by histologic evaluation of the size and number of acinar cell nodules. Each oil comprised 20% of a purified diet. These oils ranked as follows in regard to the volume fraction of pancreas that was composed of foci and nodules: corn (highest), high-oleic safflower oil, lard, safflower oil, beef tallow, and coconut oil (lowest and significantly less than corn oil). There was no significant difference between corn oil, lard, safflower oil, beef tallow, and high oleic safflower oil. These results were somewhat at odds with reports in the rat model that associated increased risk with high intake of unsaturated but not saturated fats [Roebuck BD et al., Cancer Res. 1981, 41:3961-3966]. Our results suggested that diets high in either saturated fats such as lard or beef tallow as well as unsaturated fats such as corn and safflower oils

promoted the development and growth of the foci. This report is consistent with independent reports in the BOP-induced hamster model of pancreatic carcinogenesis that have shown promotion by both lard and beef tallow supplemented diets. These results remove some of the stigmata that has accrued to unsaturated oils and corn oil in particular in relation to pancreatic carcinogenesis, but support the view that high fat diets promote carcinogenesis in the pancreas of rats.

An analytical method for determination of fatty acid composition by GC analysis of the corresponding methyl esters was set up and calibrated with known fatty acids. The method was then applied to analysis of body fat of rats from two experiments. In the first experiment, rats were maintained on AIN diets containing three levels of corn oil: 5%, 9-12%, and 20%. Fat samples of four animals from each diet group were taken after 2 weeks, 4 weeks, 2 months, and 4 months on the diet. An additional group of animals received 15% corn oil in AIN diet, but were sampled only after four months on diet. A final group, also sampled only at four months, received 5% corn oil by gavage. Approximately 80% of the body fat of these animals was found to consist of three fatty acids, 16:0, 18:1, and 18:2. The major change in fatty acid composition occurred rapidly, with an estimated half-life of about one week on diet. As the amount of corn oil in the diet increased, the percent of 18:2 in the body fat increased, principally at the expense of 16:0. After four months the fat of animals on the 5% corn oil diet consisted of 30.8% of 16:0, 29.8% of 18:1, and 21.6% of 18:2. At the other extreme, the corresponding figures for animals on the 20% corn oil diet were 18.6, 28.7, and 44.3%, respectively. Fat composition of animals receiving intermediate amounts of corn oil fell between these two extremes. Animals receiving 5 ml/kg 5 days per week corn oil by gavage had, at four months, less 16:0 (25.3%) and more 18:2 (32.9%) than the 5% diet animals. The amount of 18:1 was similar (29.9%).

Table. Acidophilic focus size and number in the pancreases of rats fed six different oils as 20% of the diet. The rats were pretreated with a single dose of azaserine, 30 mg/kg, and killed 4 months later (±SE).

Oil	n	#/cm <sup>3</sup>	diameter	/ vol %
coconut	9	325 ±30	427 ±19	1.6 ±0.2
beef	10	519 ±50	466 ±21	3.2 ±0.4
lard	10	624 ±69*	488 ±29	4.1 ±0.5
high oleic	10	531 ±48	469 ±31	4.4 ±0.7
corn	10	739 ±50*	438 ±19	5.4 ±1.1*
safflower	10	600 ±93*	445 ±20	$4.0 \pm 0.8$

<sup>\*</sup> p < 0.05, all comparisons are to coconut oil (ANOVAR).

Groups of animals (10 per group) were maintained for 4 months on diets containing one of six oils. Percents of fatty acids in the body fat at the end of this experiment were as follows:

Diet	16:0	18:0	18:1	18:2	<u>Other</u>
Làrd	26.6	5.0	51.4	7.2	·
Beef tallow	25.6	5.5	51.2	2.7	
Safflower oil	16.8	2.5	14.3	60.0	
High oleic safflower oil	15.1	2.0	68.2	9.1	·
Corn oil	18.9	2.2	26.1	46.1	
Coconut oil	26.8	4.1	23.5	3.5	12:0 (18.1%)
; .					14:0 (12.2%)

Nodule growth (reported above) did not correlate with the level of any single fatty acid, but there was a general correlation with the overall degree of unsaturation of the fat. This is reasonably represented by the combined level of 18:1 and 18:2 in the diet. Thus, the ability of fats to enhance the growth of acinar cell lesions does not correlate solely with their content of linoleic acid (18:2). The presence of oleic acid (18:1) may be equally important.

### Conclusions

High fat diets promote the growth of carcinogen-induced or spontaneously initiated foci in the rat pancreas. Unsaturated fats such as corn oil are particularly effective, but several more saturated fats such as lard and beef tallow also seem to enhance the growth of foci to a lesser degree. The critical level of corn oil for maximal effect appeared to be in the range of 12-15% of the diet by weight. Levels of intake achieved by gavage administration at doses of 5 or 10 ml corn oil/kg to chow fed rats fall into a range that enhances nodule growth.

The incidence and number of spontaneously occurring foci is lower in F344 rats than in Lewis strain rats.

Steroid hormones can promote, and also inhibit, carcinogenesis in the rat pancreas. Testosterone appears to promote the growth of carcinogen-induced foci, and estrogen to inhibit their growth in rats. This provides an explanation for the higher incidence of spontaneous neoplasms and carcinogen-induced neoplasms in male compared with female rats. Estrogen inhibits and testosterone enhances the growth of transplantable rat acinar cell carcinomas in vivo, although the mechanism is not known and could be indirect.

CCK and biologically active analogs clearly have the ability to promote carcinogenesis in rats. Bombesin has a similar effect. In rats, the ability of oral trypsin inhibitors to stimulate the release of endogenous CCK promotes carcinogenesis by the same mechanism.

Azaserine-induced nodules, adenomas and carcinomas have an increased number of CCK receptors compared with normal pancreas. This provides a mechanism for promotion of nodule growth by CCK, and may be a key change in providing a growth advantage for the focus/nodule.

Acinar cell lesions classed as nodules and adenomas did not grow in soft agar or when transplanted into syngeneic rats. Thus, they lack autonomy of growth that can be demonstrated for carcinomas by these procedures.

Nodules, adenomas and carcinomas of the rat pancreas lacked c-K-ras mutations that have been demonstrated in a high percentage of human carcinomas.

Metaplasia of cells of an acinar cell carcinoma to cells with a ductal phenotype was observed after the cells had been cultured for a period of weeks.

# LIST OF PUBLICATIONS

# **Journal Articles**

- 1. Longnecker, D.S., Roebuck, B.D., Curphey, T.J., Lhoste, E., Coon, C.I., and MacMillan, D. (1986). Effects of corn oil and benzyl acetate on number and size of azaserine-induced foci in the pancreas of LEW and F344 rats. *Environ. Health Perspect.* 68, 197-201.
- 2. Lhoste, E.F., Roebuck, B.D., Stern, J.E., and Longnecker, D.S. (1987). Effect of orchiectomy and testosterone on the early stages of azaserine-induced pancreatic carcinogenesis in the rat. *Pancreas* 2, 38-43.
- 3. Longnecker, D.S. (1987). Interface between adaptive and neoplastic growth in the pancreas. *Gut* 28 (Suppl. 1), 253-258.
- 4. Lhoste, E.F., Roebuck, B.D., Brinck-Johnsen, T., and Longnecker, D.S. (1987). Effect of castration and hormone replacement on azaserine-induced pancreatic carcinogenesis in male and female Fischer rats. *Carcinogenesis* 8, 699-703.
- 5. Lhoste, E.F., and Longnecker, D.S. (1987). Effect of bombesin and caerulein on early stages of carcinogenesis induced by azaserine in the rat pancreas. *Cancer Res.* 47, 3273-3277.
- 6. Roebuck, B.D., Baumgartner, K.J., and Longnecker, D.S. (1987). Growth of pancreatic foci and development of pancreatic cancer with a single dose of azaserine in the rat. *Carcinogenesis* 8, 1831-1835.
- 7. Lhoste, E.F., Roebuck, B.D., and Longnecker, D.S. (1988). Stimulation of the growth of azaserine-induced nodules in the rat pancreas by dietary camostate (FOY-305). *Carcinogenesis* 9, 901-906.
- 8. Sumi, C., Longnecker, D.S., Roebuck, B.D., and Brinck-Johnsen, T. (1989). Inhibitory effects of estrogen and castration on the early stage of pancreatic carcinogenesis in Fischer rats treated with azaserine. *Cancer Res.* 49, 2332-2336.
- 9. Sumi, C., Brinck-Johnsen, T., and Longnecker, D.S. (1989). Inhibition of a transplantable pancreatic carcinoma by castration and estradiol in rats. *Cancer Res.* 49, 6687-6692.
- 10. Longnecker, D. (1990). Experimental pancreatic cancer: Role of species, sex and diet [in French, English summary]. *Bull. Cancer* 77, 27-37.
- 11. Longnecker, D.S., and Sumi, C. (1990). Effects of sex steroid hormones on pancreatic cancer in the rat. *Int. J. Pancreatol.* 7, 159-165.
- 12. Longnecker, D.S. (1990). Hormones and receptors in gastrointestinal malignancies. *Digestion* 46 (Suppl. 2), 92-98.
- 13. Schaeffer, B.K., Zurlo, J., and Longnecker, D.S. (1990). Activation of c-K-ras not detectable in adenomas or adenocarcinomas arising in rat pancreas. *Mol. Carcinog.* 3, 165-170.

- Silverman, J.A., Kuhlmann, E.T., Zurlo, J., Yager, J.D., and Longnecker, D.S. (1990). Expression of c-myc, c-raf-1 and c-Ki-ras in azaserine-induced pancreatic carcinomas and growing pancreas in rats. Mol. Carcinog. 3, 379-386.
- Longnecker, D.S., Pettengill, O.S., Davis, B.H., Schaeffer, B.K., Zurlo, J., Hong, H.L., and Kuhlmann, E.T. (1991). Characterization of preneoplastic and neoplastic lesions in the rat pancreas. Am. J. Pathol. 138, 333-340.
- Beaudoin, A.R., Gronin, G., St. Jean, P., Pettengill, O., Longnecker, D.S., and Grossman, A. (1991).
   Marked differences in immunocytological localization of [3H]estradiol-binding protein in rat pancreatic acinar tumor cells as compared to normal acinar cells. *Endocrinology* 128, 1617-1622.
- 17. Longnecker, D.S., Chandar, N., Sheahan, D.G., Janosky, J.E., and Lombardi, B. (1991). Preneoplastic and neoplastic lesions in the pancreas of rats fed choline-devoid or choline-supplemented diets. *Toxicol. Pathol.* 19, 59-65.
- 18. Longnecker, D.S. (1991). Hormones and pancreatic cancer. Int. J. Pancreatol. 9, 81-86.

#### Chapters and Reviews

- 19. Longnecker, D.S. (1988). Experimental pancreatic carcinogenesis. *Curr. Opin. Gastroenterol.* 4, 843-848.
- 20. Longnecker, D.S., Jamieson, J.D., and Asch, H.L. (1989). Conference report: Regulation of growth and differention in pancreatic cancer. *Pancreas* 4, 256-275.
- 21. Longnecker, D.S. (1989). Experimental pancreatic carcinogenesis. *Curr. Opin. Gastroenterol.* 5, 723-727.
- 22. Roebuck, B.D., Longnecker, D.S., and Birt, D.F. (1989). Role of dietary fat in experimental pancreatic carcinogenesis. In *Carcinogenesis and Dietary Fat* (S. Abraham, Ed.), pp. 135-150. Kluwer Academic Publishers, Boston, MA.
- 23. Longnecker, D.S., and Millar, P.M. (1990). Tumours of the pancreas. In *Pathology of Tumours in Laboratory Animals* (V.S. Turusov, Ed.), 2nd ed., pp. 241-257. International Agency for Research on Cancer, Lyon, France.

## Abstracts

- 24. Lhoste, E.F., Roebuck, B.D., and Longnecker, D.S. (1985). Effect of testosterone and castration on azaserine-induced atypical acinar cell nodules (AACN) in the rat pancreas. *Dig. Dis. Sci.* 30, 981.
- 25. Lhoste, E.F., and Longnecker, D.S. (1986). Effect of bombesin and caerulein on azaserine-induced pancreatic carcinogenesis in the rat. *Dig. Dis. Sci.* 31, 1139.
- 26. Lhoste, E.F., Roebuck, B.D., and Longnecker, D.S. (1986). Effects of steroids on the early stages of azaserine-induced pancreatic carcinogenesis in the rat. *Dig. Dis. Sci.* 31, 1139.

- Faris, R.A., Monfils, B.A., Longnecker, D.S., and Roebuck, B.D. (1987). Characterization of
  azaserine-induced preneoplastic pancreatic lesions and transplantable tumor cell line using a panel of
  monoclonal antibodies (MAbs). Proc. Am. Assoc. Cancer Res. 28, 104.
- 28. Longnecker, D., Lhoste, E., and Roebuck, B. (1987). Enhancement of growth and conversion of phenotype in azaserine-induced acinar cell foci of rats fed FOY-305. Fed. Proc. 46, 586.
- 29. Lhoste, E.F., and Longnecker, D.S. (1987). Effect of trophic peptides on early stages of experimental carcinogenesis in the rat pancreas. *Digestion* 38, 36.
- 30. Lhoste, E.F., Roebuck, B.D., Longnecker, D.S. (1987). Stimulation of the growth of azaserine-induced nodules in the rat pancreas by dietary camostate (FOY-305). *Digestion* 38, 37.
- 31. Longnecker, D.S., Zurlo, J., Kuhlmann, E., Schaeffer, B., Davis, B., Pettengill, O. (1988). Phenotypic and genotypic characterization of acinar cell nodules in the rat pancreas. *Pancreas* 3, 605.
- 32. Longnecker, D.S. (1989). Steroid hormone effects in pancreatic carcinogenesis and transplanted tumor growth. *Pancreas* 4, 264-265.
- 33. Sumi, C., and Longnecker, D.S. (1989). Inhibitory effects of estrogen and castration on early stage of azaserine-induced pancreatic tumorigenesis in rats. *Pancreas* 4, 275.
- 34. Sumi, C., and Longnecker, D.S. (1989). Inhibition of transplantable rat pancreatic carcinoma by castration and estrogen treatment. *Proc. Am. Assoc. Cancer Res.* 30, 302.
- 35. Schaeffer, B., Zurlo, J., and Longnecker, D.S. (1990). Activation of c-K-ras not detectable in adenomas or adenocarcinomas arising in the rat pancreas. *Proc. Am. Assoc. Cancer Res.* 31, 133.
- 36. Silverman, J., Kuhlmann, E., Yager, J., Zurlo, J., and Longnecker, D. (1990). Oncogene expression in azaserine induced pancreatic carcinomas in rats. *Proc. Am. Assoc. Cancer Res.* 31, 311.
- 37. Sumi, C., and Longnecker, D. (1990). Influences of estrogen and antiestrogen on the growth and function of transplantable rat pancreatic carcinoma. *Proc. Am. Assoc. Cancer Res.* 31, 224.
- 38. Bell, R.H., Jr., Kuhlmann, E.T., Jensen, R.T., and Longnecker, D.S. (1991). Overexpression of cholecystokinin (CCK) receptors in azaserine-induced nodules and carcinoma in the rat pancreas. *Gastroenterology* 100, A266.
- 39. Longnecker, D.S., Faris, R.A., Bell, R.H., Jr., Kuhlmann, E.T., and Pettengill, O.S. (1991). Ductal metaplasia in cell lines derived from an acinar cell carcinoma of the rat pancreas. *Pancreas* 6, 710.
- 40. Bell, R.H., Zhou, W., Rosen, N., Longnecker, D.S. (1991). Novel expression of CCK-B (gastrin) receptors in azaserine-induced pancreatic carcinoma. *Pancreas* 6, 696.
- 41. Bell, R.H., Jr., Kuhlmann, E.T., Jensen, R.T., and Longnecker, D.S. (1992). Overexpression of cholecystokinin receptors in azaserine-induced neoplasms of the rat pancreas. *Cancer Res.* **52**, 3295-3299.

# Submitted/In Preparation

42. Pettengill, O.S., Faris, R.A., Bell, R.H., Jr., Kuhlmann, E.T., and Longnecker, D.S. Ductal metaplasia in cell lines derived from an acinar cell carcinoma of the rat pancreas (in preparation).

# NATIONAL TOXICOLOGY PROGRAM TECHNICAL REPORTS **PRINTED AS OF MARCH 1994**

TR No.	CHEMICAL	TR No.	CHEMICAL
201	2,3,7,8-Tetrachlorodibenzo-p-dioxin (Dermal)	273	Trichloroethylene (Four Rat Strains)
	1,2-Dibromo-3-chloropropane	274	Tris(2-ethylhexyl)phosphate
	Cytembena		2-Chloroethanol
208	FD & C Yellow No. 6		8-Hydroxyquinoline
209	2,3,7,8-Tetrachlorodibenzo-p-dioxin (Gavage)		Tremolite
210	1,2-Dibromoethane		2,6-Xylidine
211	C.I. Acid Orange 10	279	Amosite Asbestos
212	Di(2-ethylhexyl)adipate	280	Crocidolite Asbestos
213	Butyl Benzyl Phthalate		HC Red No. 3
214	Caprolactam		Chlorodibromomethane
	Bisphenol A		Diallylphthalate (Rats)
	11-Aminoundecanoic Acid		C.I. Basic Red 9 Monohydrochloride
	Di(2-Ethylhexyl)phthalate		Dimethyl Hydrogen Phosphite
	2,6-Dichloro-p-phenylenediamine		1,3-Butadiene
	C.I. Acid Red 14		Benzene
	Locust Bean Gum		Isophorone
	C.I. Disperse Yellow 3		HC Blue No. 2
	Eugenol		Chlorinated Trisodium Phosphate
	Tara Gum		Chrysotile Asbestos (Rats)
	D & C Red No. 9	296	Tetrakis(hydroxymethyl) phosphonium Sulfate &
	C.I. Solvent Yellow 14		Tetrakis(hydroxymethyl) phosphonium Chloride
	Gum Arabic		Dimethyl Morpholinophosphoramidate
	Vinylidene Chloride		C.I. Disperse Blue 1
	Guar Gum		3-Chloro-2-methylpropene
	Agar		o-Phenylphenol
	Stannous Chloride		4-Vinylcyclohexene
	Pentachloroethane		Chlorendic Acid
	2-Biphenylamine Hydrochloride		Chlorinated Paraffins (C <sub>23</sub> , 43% chlorine)
	Allyl Isothiocyanate		Dichloromethane (Methylene Chloride)
	Zearalenone		Ephedrine Sulfate
	D-Mannitol		Chlorinated Pariffins (C <sub>12</sub> , 60% chlorine)
	1,1,1,2-Tetrachloroethane		Decabromodiphenyl Oxide
	Ziram		Marine Diesel Fuel and JP-5 Navy Fuel
	Bis(2-chloro-1-Methylethyl)ether		
	Propyl Gallate		n-Butyl Chloride Mirex
	Diallyl Phthalate (Mice)		
	Trichlorethylene (Rats and Mice)		Methyl Methacrylate
	Polybrominated Biphenyl Mixture Melamine		Oxytetracycline Hydrochloride 1-Chloro-2-methylpropene
			Chlorpheniramine Maleate
	Chrysotile Asbestos (Hamsters) L-Ascorbic Acid		Ampicillin Trihydrate
	4,4'-Methylenedianiline Dihydrochloride		1,4-Dichlorobenzene
	Amosite Asbestos (Hamsters)		Rotenone
	Benzyl Acetate		Bromodichloromethane
	2,4- & 2,6-Toluene Diisocyanate		Phenylephrine Hydrochloride
	Geranyl Acetate		Dimethyl Methylphosphonate
	Allyl Isovalerate		Boric Acid
	Dichloromethane (Methylene Chloride)		Pentachloronitrobenzene
	1,2-Dichlorobenzene		Ethylene Oxide
	Diglycidyl Resorcinol Ether		Xylenes (Mixed)
	Ethyl Acrylate		Methyl Carbamate
	Chlorobenzene		1,2-Epoxybutane
	1,2-Dichloropropane		4-Hexylresorcinol
	Monuron		Malonaldehyde, Sodium Salt
	1,2-Propylene Oxide		2-Mercaptobenzothiazole
	Telone II® (1.3-Dichloropropene)		N-Phenyl-2-naphthylamine

333 N-Phenyl-2-naphthylamine

334 2-Amino-5-nitrophenol

335 C.I. Acid Orange 3

267 1,2-Propylene Oxide
269 Telone II® (1,3-Dichloropropene)

272 Propylene

271 HC Blue No. 1

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TR No.	CHEMICAL	TR	No.	CHEMICAL
336	Penicillin VK		386	Tetranitromethane
337	Nitrofurazone		387	Amphetamine Sulfate
	Erythromycin Stearate		388	Ethylene Thiourea
339	2-Amino-4-nitrophenol		389	Sodium Azide
	Iodinated Glycerol		390	3,3'-Dimethylbenzidine Dihydrochloride
341	Nitrofurantoin		391	Tris(2-chloroethyl) Phosphate
	Dichlorvos		392	Chlorinated Water and Chloraminated Water
343	Benzyl Alcohol		393	
344	Tetracycline Hydrochloride		394	Acetaminophen
	Roxarsone		395	Probenecid
346	Chloroethane		396	Monochloroacetic Acid
	D-Limonene			C.I. Direct Blue 15
	a-Methyldopa Sesquihydrate			Polybrominated Biphenyls
	Pentachlorophenol	•	399	Titanocene Dichloride
	Tribromomethane		400	2,3-Dibromo-1-propanol
			401	2,4-Diaminophenol Dihydrochloride
351	p-Chloroaniline Hydrochloride	***.		Furan
	N-Methylolacrylamide		403	Resorcinol
	2,4-Dichlorophenol		404	5,5-Diphenylhydantoin
	Dimethoxane  Dish a hadroning Hadrophlavida		405	C.I. Acid Red 114
	Diphenhydramine Hydrochloride		406	y-Butyrolactone
	Furosemide		407	C.I. Pigment Red 3
357	Hydrochlorothiazide	•	√407 √408	_
358			409	
	8-Methoxypsoralen		410	-
	N,N-Dimethylaniline		411	• •
	Hexachloroethane			4,4-Diamino-2,2-stilbenedisulfonic Acid
	4-Vinyl-1-Cyclohexene Diepoxide			
	/ Bromoethane (Ethyl Bromide)			Ethylene Glycol
	Rhodamine 6G (C.I. Basic Red 1)			Pentachloroanisole
	Pentaerythritol Tetranitrate		415	•
	Hydroquinone			o-Nitroanisole
	Phenylbutazone			p-Nitrophenol
•	Nalidixic Acid			p-Nitroaniline
369	Alpha-Methylbenzyl Alcohol			HC Yellow 4
370	Benzofuran		420	
371	Toluene		421	
372				Coumarin
373	•		423	3
374	Glycidol		424	1
375	•		425	•
	Allyl Glycidyl Ether		427	
377			428	8 ()
	Benzaldehyde		430	
	2-Chloroacetophenone		431	•
380			432	-
	d-Carvone		434	,
	Furfural		437	, ·
384			443	Oxazepam
385	Methyl Bromide			

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