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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

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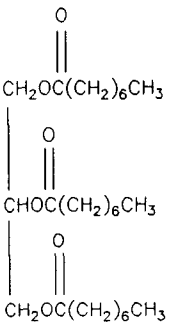
ABSTRACT



Corn Oil

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

Tricaprylin

CAS No. 538-23-8
Chemical Formula: $C_{27}H_{50}O_6$
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 dose-related 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 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 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:

- 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, safflower 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 cell hyperplasia, adenoma, and carcinoma. Dr. Boorman agreed. Dr. van Zwieten said brief comments on the possible mechanism for the dose-related 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.

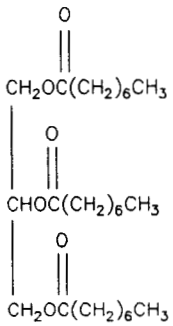
Dr. Ryan, the second principal reviewer, said that she had difficulty interpreting the comparisons between corn oil alone and the dichloromethane groups and the report should be modified to clarify the fact that the addition of corn oil seems to change the shape of the dose-response curve for effects 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 forestomach." Dr. Davidson agreed to the addition. 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



Corn Oil

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

Tricaprylin

CAS No. 538-23-8
Chemical Formula: $C_{27}H_{50}O_6$
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 carcinogen-induced mammary gland neoplasms in rats (El-Ela *et al.*, 1987) while diets supplemented with medium-chain 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 ^{14}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 medium-chain 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 medium-chain fatty acids which do not easily bind to the fatty-acid 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 ^{14}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 inhibition 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 azaserine-induced 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 chemical-induced 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 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.

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_2 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 yet 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 Began			
7 weeks	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_2 asphyxiation	70% CO_2 asphyxiation	"Biotol" (an ultra fast-acting barbiturate)	70% CO_2 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	5
Method of Animal Distribution			
Animals were assigned to cages and then to groups with tables of random numbers.	Same as corn oil study	Same as corn oil study	Same as corn oil study
Method of Animal Identification			
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 Room			
Safflower oil and tricaprylin	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: 21°-22° C Relative humidity: 47.1% ± 4.9% Fluorescent light: 12 hours/day Room air changes: At least 10/hour	Same as corn oil study	Same as corn oil study	Average temperature: 22°-23° C Relative humidity: 47.5% ± 3.7% Fluorescent light: 12 hours/day Room air changes: At least 10/hour
Type and Frequency of Observation			
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)

Corn Oil Study	Safflower Oil Study	Tricaprylin Study	Dichloromethane in Corn Oil Study
Histopathology Complete histopathology was performed on all rats. Tissues examined included: adrenal gland, bone and marrow, brain, esophagus, gross lesions, heart, kidney, large intestine (cecum, colon, rectum), liver, lung, mammary gland, lymph nodes (mandibular and mesenteric), pancreas, parathyroid gland, pituitary gland, preputial gland, salivary gland, skin, small intestine (duodenum, jejunum, ileum), spleen, stomach, testis with epididymis and seminal vesicle, thymus, thyroid gland, tissue masses, trachea, and urinary bladder.	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[a]	33	38	40
Percent probability of survival at end of study[b]	52	66	76	80
Mean survival (days)[c]	689	691	697	715
Survival analysis[d]	P=0.005N	P=0.305N	P=0.029N	P=0.007N

[a] Includes one rat that died during the last week of the study
[b] Kaplan-Meier determinations
[c] Mean of all deaths (uncensored, censored, terminal sacrifice)
[d] The result of the life table trend test (Tarone, 1975) is in the control column, and the results of the life table pairwise comparisons (Cox, 1972) with the controls are in the 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
15-Month interim evaluation[a]	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[b]	60	67	81	71
Mean survival (days)[c]	656	650	649	665
Survival analysis[d]	P=0.252N	P=0.756N	P=0.075N	P=0.341N

[a] Censored from survival analyses
[b] Kaplan-Meier determinations
[c] Mean of all deaths (uncensored, censored, terminal sacrifice)
[d] The result of the life table trend test (Tarone, 1975) is in the control column, and the results of the life table pairwise comparisons (Cox, 1972) with the controls are in the dosed columns. A negative trend or lower mortality in a dose group is indicated by N.

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[a]	10	10	10	7
Natural deaths	4	7	4	13
Moribund kills	15	13	15	17
Animals surviving until study termination	31[b]	30	31[b]	23[b]
Percent probability of survival at end of study[c]	62	61	63	46
Mean survival (days)[d]	651	639	642	553
Survival analysis[e]	P=0.004	P=0.944	P=0.969	P=0.014

[a] Censored from survival analyses
[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.
[c] Kaplan-Meier determinations
[d] Mean of all deaths (uncensored, censored, terminal sacrifice)
[e] 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.

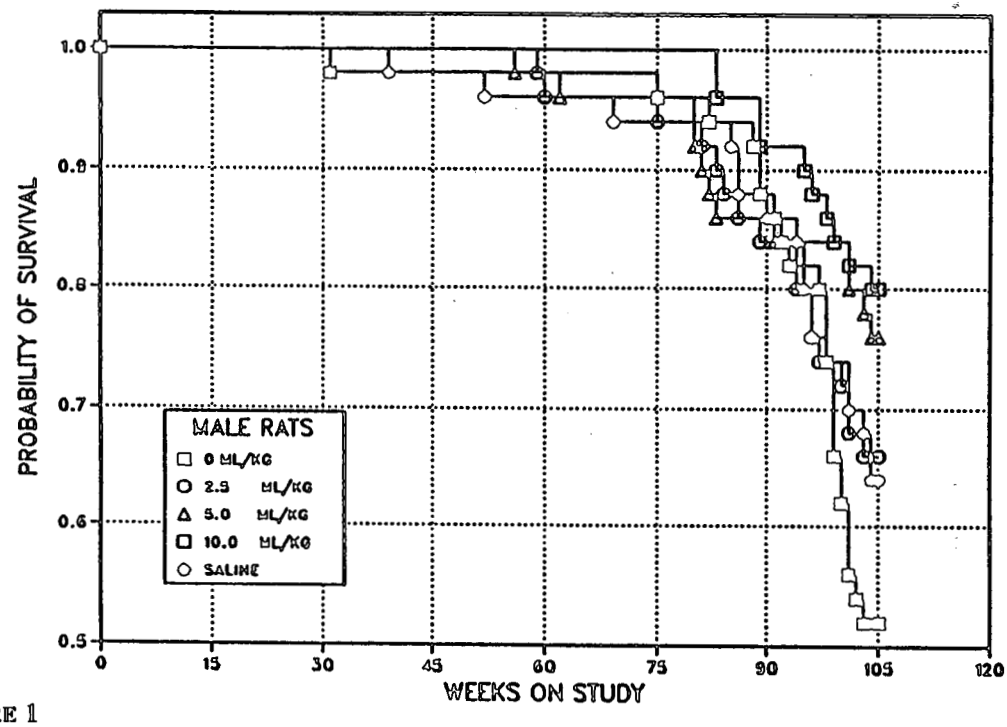


FIGURE 1
Kaplan-Meier Survival Curves for Male Rats Administered Corn Oil by Gavage for 2 Years

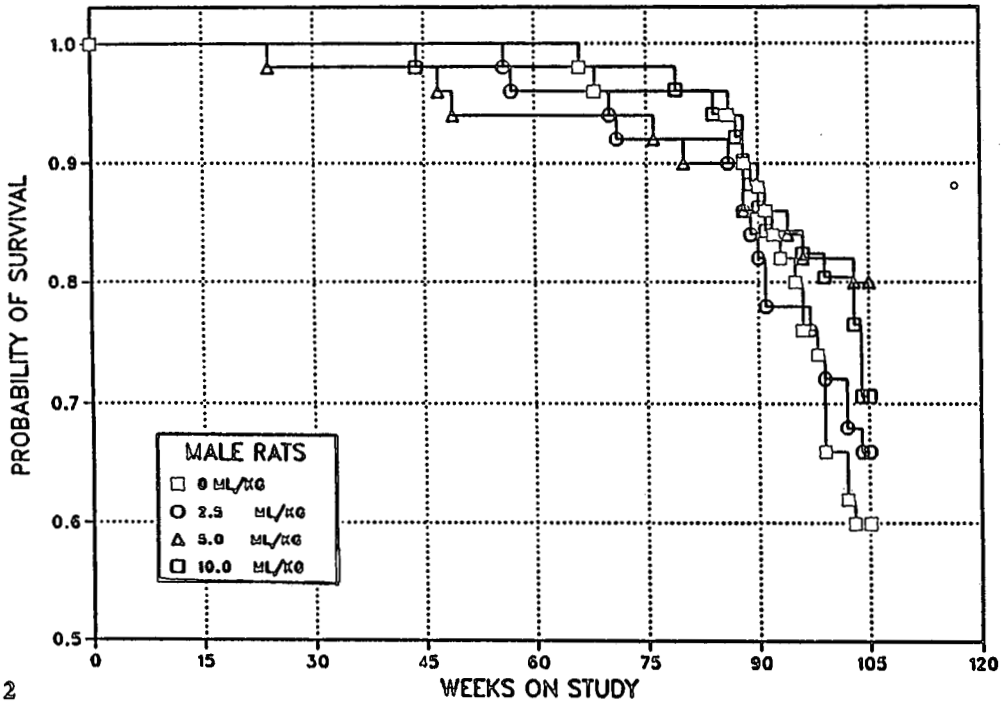


FIGURE 2
Kaplan-Meier Survival Curves for Male Rats Administered Safflower Oil by Gavage for 2 Years

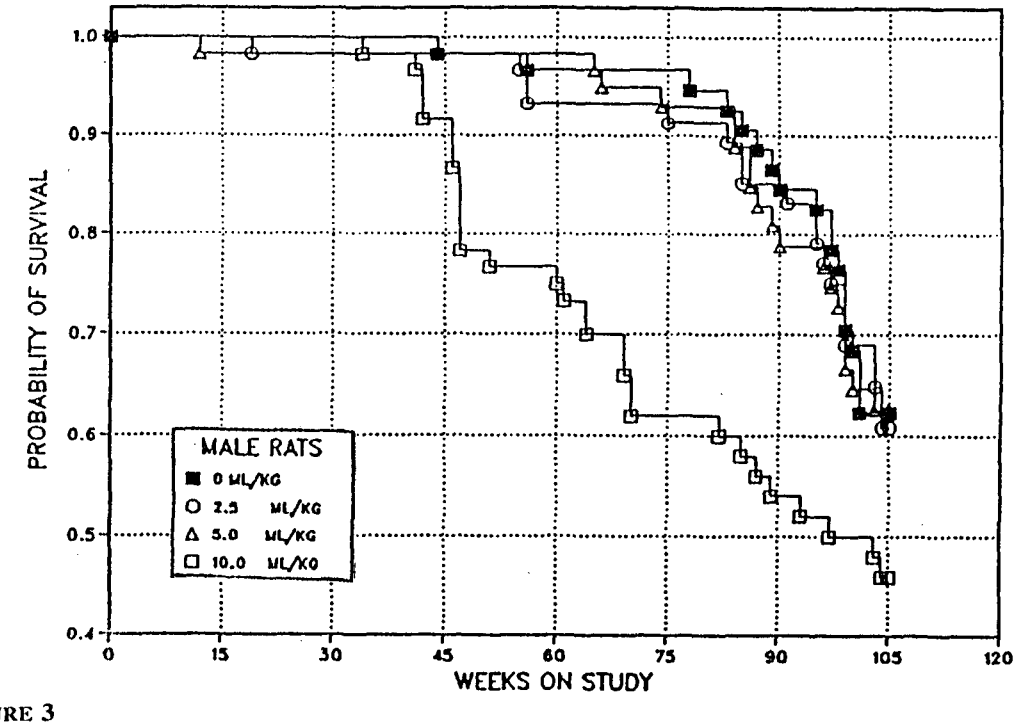


FIGURE 3
Kaplan-Meier Survival Curves for Male Rats Administered Tricaprylin by Gavage for 2 Years

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 on Study	Untreated Control		2.5 mL/kg			5 mL/kg			10 mL/kg		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of 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 weeks											
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	

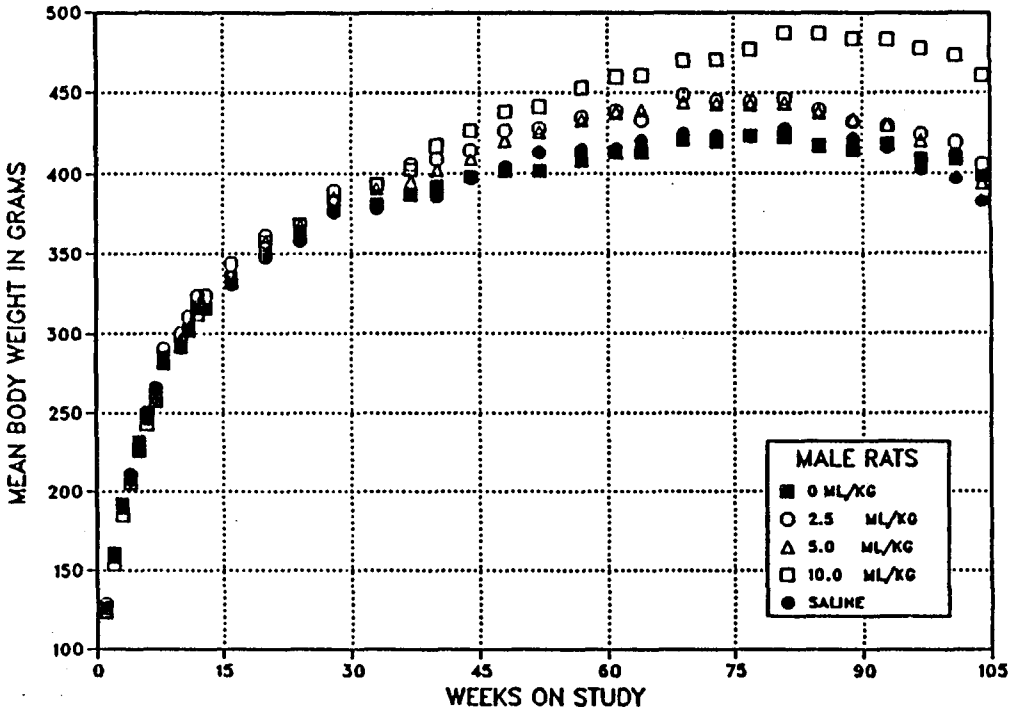


FIGURE 4
Growth Curves for Male Rats Administered Corn Oil by Gavage for 2 Years

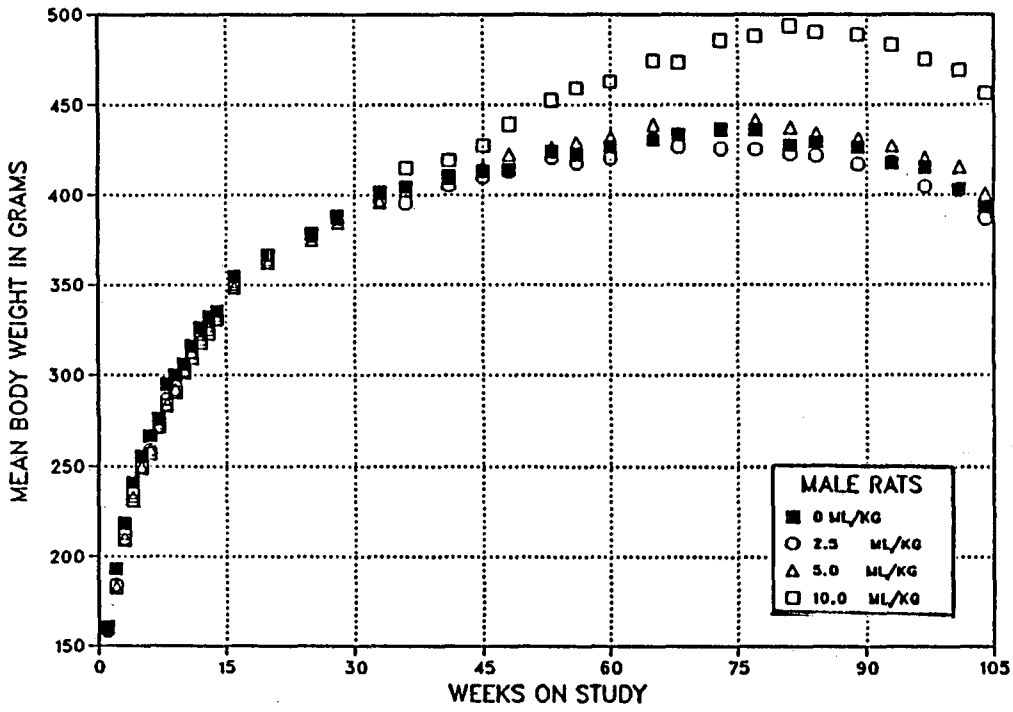


FIGURE 5
Growth Curves for Male Rats Administered Safflower Oil by Gavage for 2 Years

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

Weeks on Study	Untreated Control		2.5 mL/kg			5 mL/kg			10 mL/kg		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of 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[a]	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	438	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 sacrifice		30			33			40			36
Mean for weeks											
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	

[a] 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 on Study	Untreated Control		2.5 mL/kg			5 mL/kg			10 mL/kg		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of 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	46
57	404	58	411	102	56	394	98	59	380	94	46
61	403	58	416	103	56	400	99	59	390	97	45
65	408	58	419	103	56	399	98	59	392	96	42
69[a]	406	48	421	104	46	400	99	47	392	97	35
73	408	48	422	103	46	403	99	47	395	97	31
77	414	48	423	102	45	406	98	46	403	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	103	42	390	97	41	395	98	28
93	400	42	413	103	41	393	98	39	397	99	26
97	393	40	406	103	38	386	98	38	391	99	26
101	387	34	404	104	34	379	98	32	379	98	25
104	386	31	391	101	30	371	96	31	366	95	23
Terminal sacrifice		31			30			31			23
Mean for weeks											
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	

[a] Interim evaluation occurred during week 67.

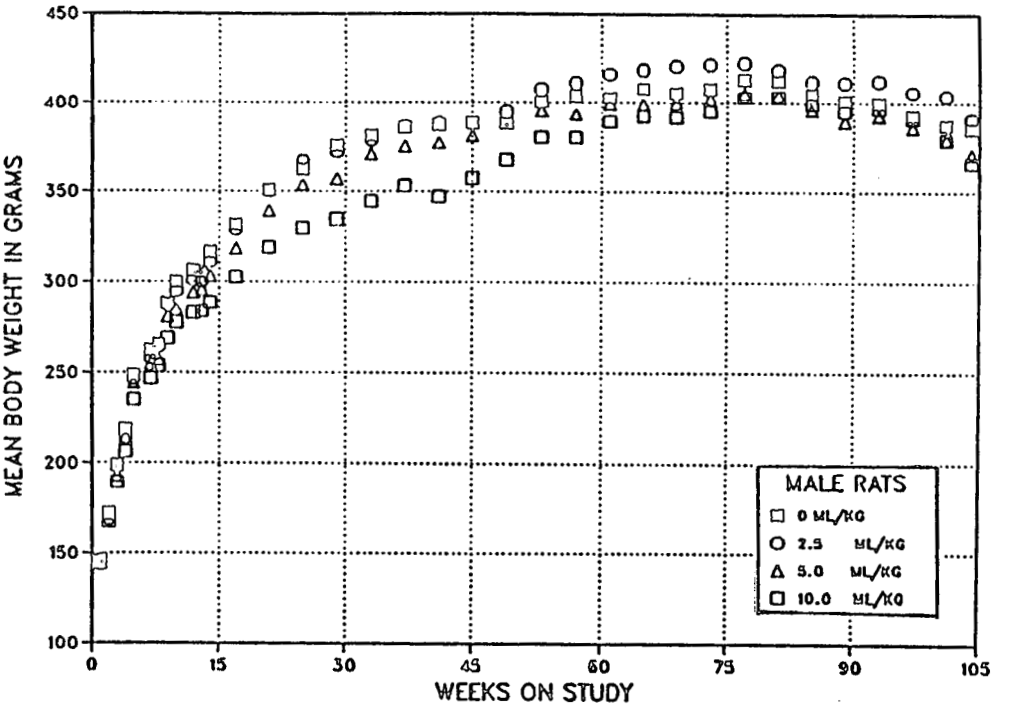


FIGURE 6
Growth Curves for Male Rats Administered Tricaprylin by Gavage for 2 Years

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 Rat[a]

Dose (mL/kg)	Source of energy (AEG[b])	Corn Oil (Kcal/day (%))	Safflower Oil (Kcal/day (%))	Tricaprylin (Kcal/day (%)) (PFV[c])	Dichloromethane in corn oil (Kcal/day (%))
0	Diet	58.1 (100)	57.5 (100)	58.1 (100)	NA[d]
	Oil gavage	0	0	0	0
	Total	58.1	57.5	58.1	NA
	Protein (g/rat/day)	3.88	3.84	3.88	NA
2.5	Diet	50.0 (87.4)	50.3 (87.8)	50.2 (89.6)	47.3 (87.8)
	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
	Protein (g/rat/day)	3.34	3.36	3.45	3.15
5.0	Diet	41.8 (74.4)	42.8 (74.8)	44.9 (80.2)	41.8 (74.1)
	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
10.0	Diet	34.0 (53.0)	34.0 (52.7)	39.3 (64.6)	34.3 (51.6)
	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

[a] 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).
[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).
[d] NA = Not available

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[a]

Study	Incidence in Controls		
	Benign Pheochromocytoma	Malignant Pheochromocytoma	Benign or Malignant Pheochromocytoma
Historical Incidence at EG&G Mason Research Institute (Feed and Drinking Water Studies)			
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, Drinking Water, and Inhalation Studies)			
Total	617/1,980 (31.2%)	73/1,980 (3.7%)	673/1,980[b] (34.0%)
Standard deviation	11.5%	4.1%	10.6%
Range	0%–63%	0%–20%	14%–63%

[a] Data as of 31 March 1993
[b] Includes data for complex and unspecified pheochromocytomas

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 high-dose 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.

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				
Overall rate[a]	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[b]	3.8%	25.0%	24.6%	53.2%
Terminal rate[c]	1/26 (4%)	8/32 (25%)	8/38 (21%)	20/40 (50%)
First incidence (days)	730 (T)	730 (T)	569	576
Logistic regression test[d]	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	Untreated Control	2.5 mL/kg	5 mL/kg	10 mL/kg
Safflower Oil Study (continued)				
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%
Terminal rate	1/30 (3%)	7/33 (21%)	14/40 (35%)	24/36 (67%)
First incidence (days)	729 (T)	729 (T)	531	633
Logistic regression test	P<0.001	P=0.041	P<0.001	P<0.001
Tricaprylin Study				
Hyperplasia				
Overall rate	8/49 (16%)	9/49 (18%)	18/49 (37%)*	28/50 (56%)**
Adenoma				
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 (days)	729 (T)	729 (T)	518	485
Logistic regression test	P<0.001	P=0.129	P=0.002	P<0.001
Adenoma, Multiple				
Overall rate	0/49 (0%)	1/49 (2%)	2/49 (4%)	11/50 (22%)**

* Significantly different (P≤0.05) from the control group by the logistic regression test
** P≤0.01
(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
[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 logistic regression test regards neoplasms as nonfatal.

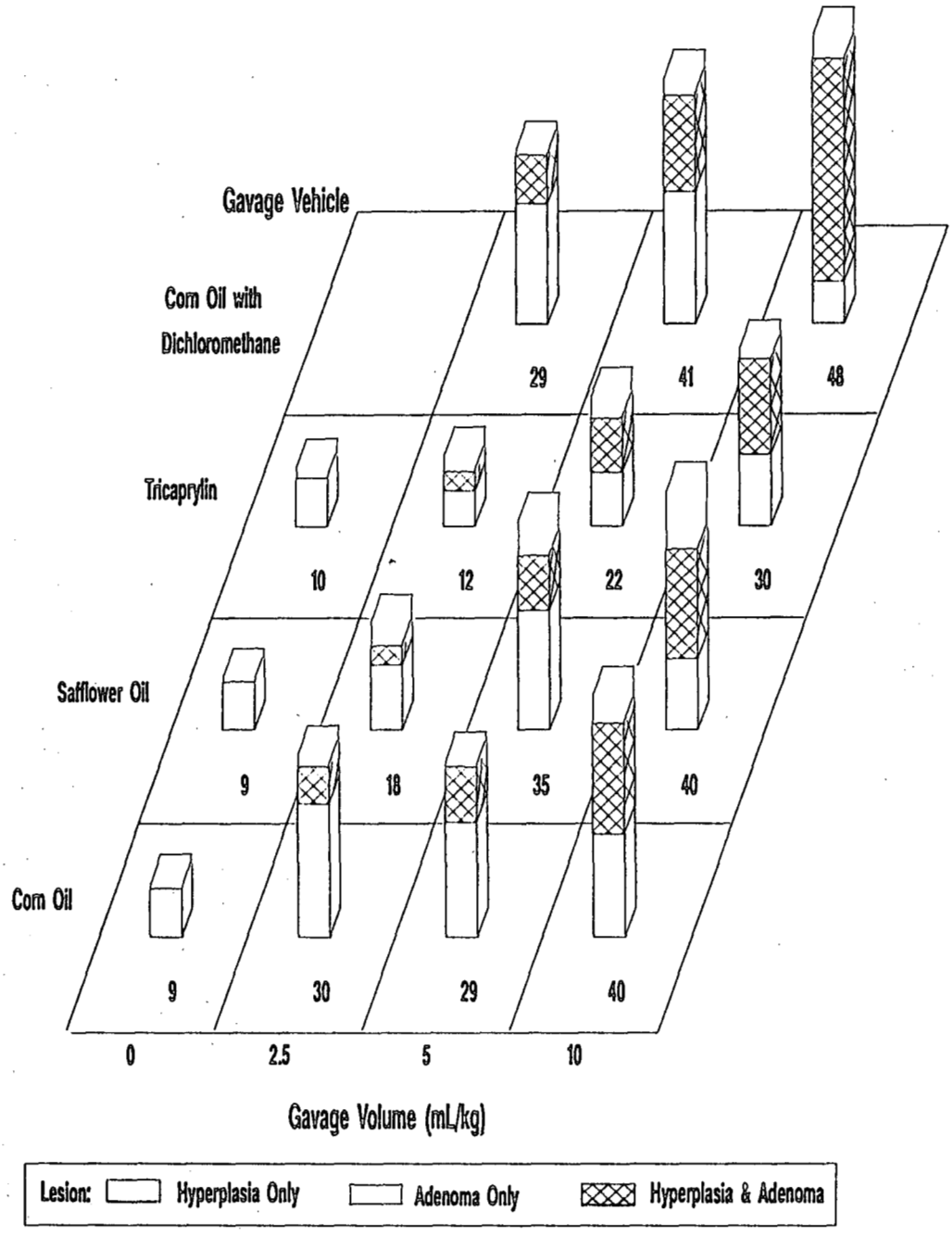


FIGURE 7
Pancreatic Acinar Cell Lesions in Male Rats Administered Corn Oil, Safflower Oil, Tricaprylin, or Dichloromethane in Corn Oil by Gavage for 2 Years and Total Number of Male Rats with Proliferative Lesions

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

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at EG&G Mason 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%

[a] 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[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at EG&G Mason 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%

[a] 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				
Squamous Cell Papilloma				
Overall rate[a]	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[b]	0.0%	0.0%	8.7%	41.3%
Terminal rate[c]	0/31 (0%)	0/30 (0%)	2/31 (6%)	9/23 (39%)
First incidence (days)	–[e]	–	623	623
Logistic regression test[d]	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
[c] 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[a]

Study	Incidence in Controls
Historical Incidence at EG&G Mason Research Institute	
1,2,3-Trichloropropane	0/50
2,4-Diaminophenol dihydrochloride	0/50
Tribromomethane	0/50
Hexachloroethane	0/50
Phenylbutazone	0/50
Probenecid	0/50
Titanocene dichloride	0/60
Overall Historical Incidence	
Total	5/1,020 (0.5%)
Standard deviation	1.1%
Range	0%–4%

[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[a]	47/50 (94%)	43/48 (90%)	45/50 (90%)	40/49 (82%)**
Average severity grade[b]	2.1 ± 0.13	1.8 ± 0.11*	1.4 ± 0.11**	1.2 ± 0.12**
Safflower Oil Study				
Overall rate	49/50 (98%)	50/50 (100%)	47/50 (94%)	49/49 (100%)
Average severity grade	2.0 ± 0.10	1.8 ± 0.10*	1.1 ± 0.07**	1.1 ± 0.04**
Tricaprylin Study				
Overall rate	46/50 (92%)	42/50 (84%)	45/50 (90%)	27/49 (55%)*
Average severity grade	2.0 ± 0.12	1.5 ± 0.13**	1.7 ± 0.11*	0.9 ± 0.13**

* Significantly different ($P \leq 0.05$) from the control group by the logistic regression test (overall rate) or the Mann-Whitney U test (severity)
** $P \leq 0.01$
[a] Number of lesion-bearing animals/number of animals examined microscopically
[b] Average severity grade is given as mean ± 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 mL/kg
Corn Oil Study				
Hyperplasia				
Overall rate[a]	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[b]	56.3%	48.3%	10.5%	16.8%
Terminal rate[c]	11/25 (44%)	13/33 (39%)	4/38 (11%)	6/40 (15%)
First incidence (days)	610	586	730 (T)	664
Logistic regression test[d]	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 Pheochromocytoma[e]				
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

(continued)

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 Pheochromocytoma[e]				
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

(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
[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 logistic regression test regards neoplasms as nonfatal. A negative trend or lower incidence in a dose group is indicated by N.
[e] 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[a]	27/50 (54%)	16/50 (32%)	11/50 (22%)	7/50 (14%)
Adjusted rate[b]	62.6%	39.6%	25.4%	15.9%
Terminal rate[c]	11/26 (42%)	9/33 (27%)	6/38 (16%)	4/40 (10%)
First incidence (days)	523	586	555	623
Life table test[d]	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

[a] 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[a]

Study	Incidence in Controls
Historical Incidence in Untreated Controls (Feed and Drinking Water Studies) at EG&G Mason Research Institute	
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 (Gavage Studies) at EG&G Mason Research Institute	
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%)
Standard deviation	9.5%
Range	4%–46%

[a] 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[a]	2.5 mL/kg	5 mL/kg	10 mL/kg
Animals initially in study	50	50	50	50
Accidental deaths[b]		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[d]	52	51	57	66
Mean survival (days)[e]	689	653	669	674
Survival analysis[f]		P=0.810	P=0.807N	P=0.402N

[a] Untreated control from corn oil study
[b] Censored from survival analyses
[c] Includes one rat that died during the last week of the study
[d] 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.

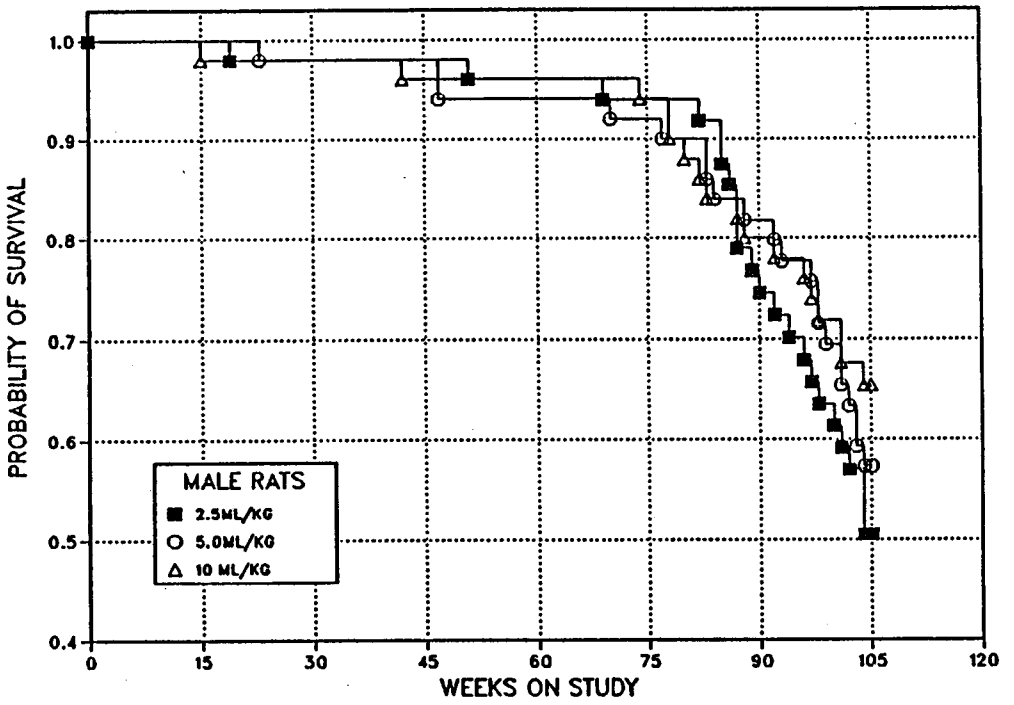


FIGURE 8
Kaplan-Meier Survival Curves for Male Rats Administered Dichloromethane in Corn Oil by Gavage for 2 Years

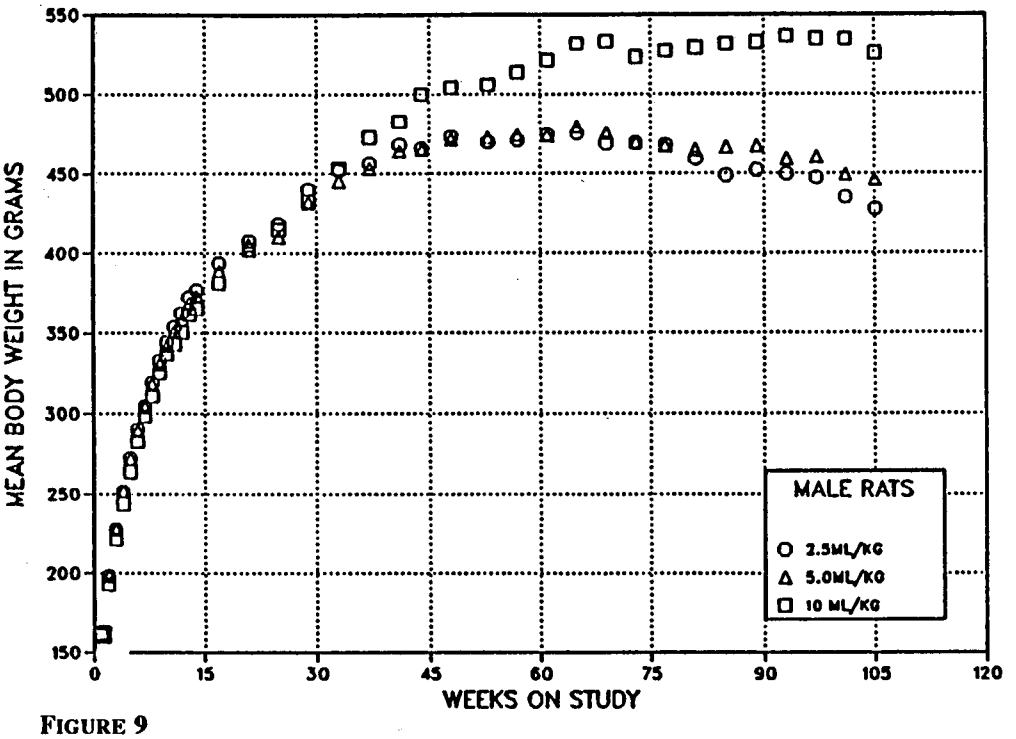


FIGURE 9
Growth Curves for Male Rats Administered Dichloromethane in Corn Oil by Gavage for 2 Years

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

Weeks on Study	2.5 mL/kg		5 mL/kg			10 mL/kg		
	Av. Wt. (g)	Number of Survivors	Av. Wt. (g)	Wt. (% of 2.5 mL/kg group)	Number of Survivors	Av. Wt. (g)	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 sacrifice		23			28			31
Mean for weeks								
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[a]	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[b]	3.8%	25.0%	24.6%	53.2%
Terminal rate[c]	1/26 (4%)	8/32 (25%)	8/38 (21%)	20/40 (50%)
First incidence (days)	730 (T)	730 (T)	569	576
Logistic regression test[d]	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

(continued)

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%)$^{\Delta}$	44/50 (88%)$^{\Delta\Delta}$
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[e]	P<0.001	P=0.047	P<0.001
Adenoma, Multiple			
Overall rate	2/50 (4%)	13/50 (26%)$^{\Delta}$	34/50 (68%)$^{\Delta\Delta}$
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
** P≤0.01
Δ Significantly different (P≤0.05) from the low-dose group by the logistic regression test
$\Delta\Delta$ P≤0.01
(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
[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 logistic regression test regards neoplasms as nonfatal.
[e] 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.
[f] 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	Corn Oil	Dichloromethane in Corn Oil
2.5 mL/kg		
Hyperplasia		
Overall rate[a]	28/47 (60%)	28/50 (56%)
Adjusted rate[b]	73.0%	81.5%
Terminal rate[c]	22/32 (69%)	17/23 (74%)
First incidence (days)	409	572
Logistic regression test[d]		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
[a] 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
[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.
[e] Not applicable; no lesions in animal group

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

Dose	Corn Oil	Dichloromethane in Corn Oil
2.5 mL/kg		
Islet Cell Hyperplasia		
Overall rate[a]	4/47 (9%)	7/50 (14%)
Adjusted rate[b]	10.0%	25.7%
Terminal rate[c]	1/32 (3%)	4/23 (17%)
First incidence (days)	653	626
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
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	4/38 (11%)	6/28 (21%)
First incidence (days)	730 (T)	643
Logistic regression test		P=0.078

(continued)

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 mL/kg		
Islet 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
[a] 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
[d] 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.
[e] Not applicable; no lesions in animal group

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 dose-related 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[a]	13/50 (26%)	9/50 (18%)
Adjusted rate[b]	37.9%	36.4%
Terminal rate[c]	12/33 (36%)	8/23 (35%)
First incidence (days)	656	605
Logistic regression test[d]		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

(continued)

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 (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

[a] 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
[d] 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[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence in Untreated Controls (Feed and Drinking Water Studies) at EG&G Mason Research Institute			
1-Amino-2,4-dibromoanthraquinone	21/48	0/48	21/48
Acetaminophen	16/48	1/48	17/48
HC Yellow 4	17/45	0/45	17/45
Methylphenidate hydrochloride	11/48	1/48	12/48
Pentaerythritol tetranitrate	13/49	0/49	13/49
Quercetin	14/46	0/46	14/46
Turmeric oleoresin	23/50	0/50	23/50
Barium 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%
Historical Incidence in Vehicle Controls (Gavage Studies) at EG&G Mason Research Institute			
1,2,3-Trichloropropane	9/48	0/48	9/48
2,4-Diaminophenol dihydrochloride	23/50	1/50	24/50
Tribromomethane	12/50	0/50	12/50
Hexachloroethane	24/49	0/49	24/49
Phenylbutazone	16/48	0/48	16/48
Probenecid	15/50	0/50	15/50
Titanocene dichloride	23/56	0/56	23/56
Overall Historical Incidence			
Total	328/996 (32.9%)	14/996 (1.4%)	342/996 (34.3%)
Standard deviation	9.1%	2.3%	9.4%
Range	18%–49%	0%–8%	19%–49%

[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[a]

Study	Incidence in Controls		
	Fibroadenoma	Adenoma	Fibroadenoma or Adenoma
Historical Incidence in Untreated Controls (Feed and Drinking Water Studies) at EG&G Mason Research Institute			
1-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
Turmeric 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 Controls (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
Tribromomethane	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			
Total	66/1,020 (6.5%)	2/1,020 (0.2%)	68/1,020 (6.7%)
Standard deviation	3.3%	0.6%	3.3%
Range	2%–14%	0%–2%	2%–14%

[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[a]	2.5 mL/kg	5 mL/kg	10 mL/kg
Corn Oil Study				
Overall rate[b]	27/50 (54%)	16/50 (32%)	11/50 (22%)	7/50 (14%)
Adjusted rate[c]	62.6%	39.6%	25.4%	15.9%
Terminal rate[d]	11/26 (42%)	9/33 (27%)	6/38 (16%)	4/40 (10%)
First incidence (days)	523	586	555	623
Life table test[e]	P<0.001N	P=0.016N	P<0.001N	P<0.001N
Dichloromethane in Corn Oil Study				
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[f]		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.
[b] 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
[e] 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.
[f] 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
Pancreatic 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)	
Pancreatic islet cell adenoma or carcinoma*Δ			
2.5	6% (3/47)	10% (5/50)	
5	8% (4/50)	18% (9/50)	Not significant
10	14% (7/50)	30% (15/50)	
Pituitary gland adenomaΔ			
2.5	20% (10/50)	40% (20/50)	
5	12% (6/49)	37% (18/49)	Not significant
10	14% (7/50)	33% (16/49)	
Mononuclear cell leukemia▽			
2.5	32% (16/50)	26% (13/50)	
5	22% (11/50)	28% (14/50)	Not significant
10	14% (7/50)	10% (5/50)	

* Significant ($P<0.01$) corn oil effect by the logistic regression test
Δ Significant ($P<0.01$) dichloromethane effect by the logistic regression test
▽ Significant ($P<0.01$) corn oil effect by the life table test

GENETIC TOXICOLOGY

Corn oil and safflower oil (100 to 10,000 μg/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 μg/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 μg/mL) in the presence or the absence of S9 (Anderson *et al.*, 1990).

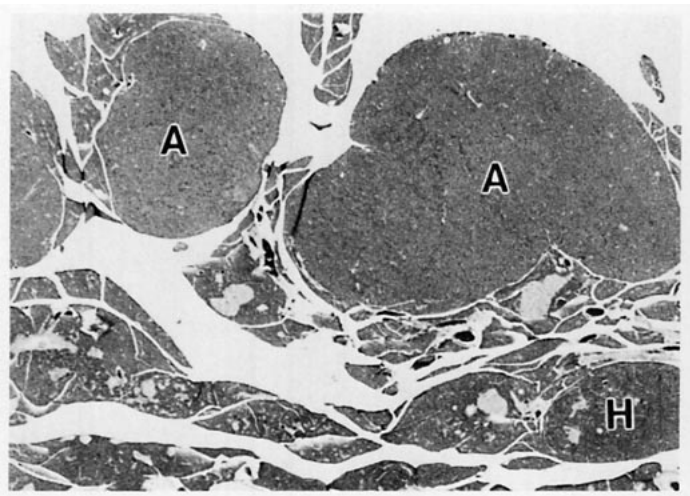


PLATE 1
Multiple pancreatic exocrine adenomas (A) and pancreatic exocrine hyperplasia (H) in a male F344/N rat exposed to 10 mL/kg corn oil in the 2-year gavage study. H&E, 10×.

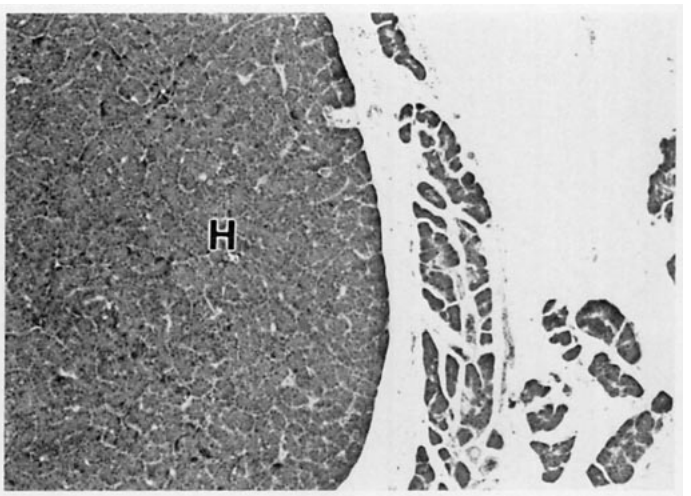


PLATE 2
Pancreatic exocrine adenoma (H) in a male F344/N rat exposed to 10 mL/kg tricaprylin in the 2-year gavage study. The loose lobular arrangement of the pancreas makes it difficult to judge compression at the margin of the lesions H&E, 45×.

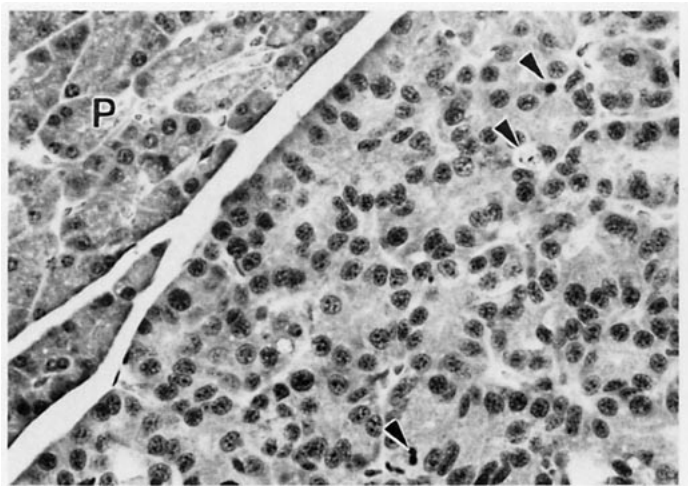


PLATE 3
Pancreatic exocrine adenoma in a male F344/N rat exposed to 10 mL/kg corn oil in the 2-year gavage study. The normal pancreas (P) shows an acinar arrangement while within the adenoma there is apoptosis (arrows), less organized acinar pattern, and more variation in size and shape of nuclei. H&E,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

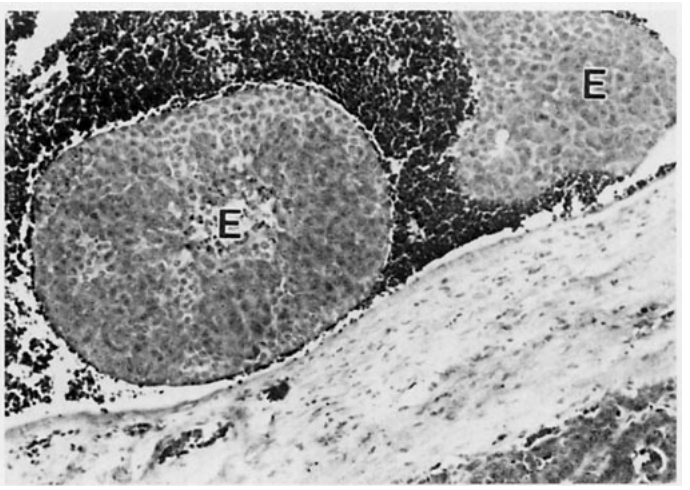


PLATE 4
Pancreatic exocrine carcinoma emboli (E) in the pancreas of a male F344/N rat exposed to 10 mL/kg safflower oil in the 2-year gavage study. H&E, 100×.

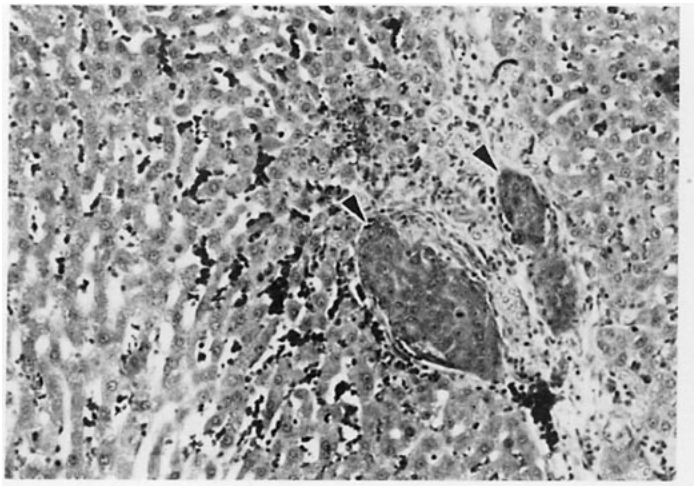


PLATE 5
Pancreatic exocrine carcinoma metastases (arrows) in the liver of a male F344/N rat exposed to 10 mL/kg safflower oil in the 2-year gavage study. H&E, 120×.

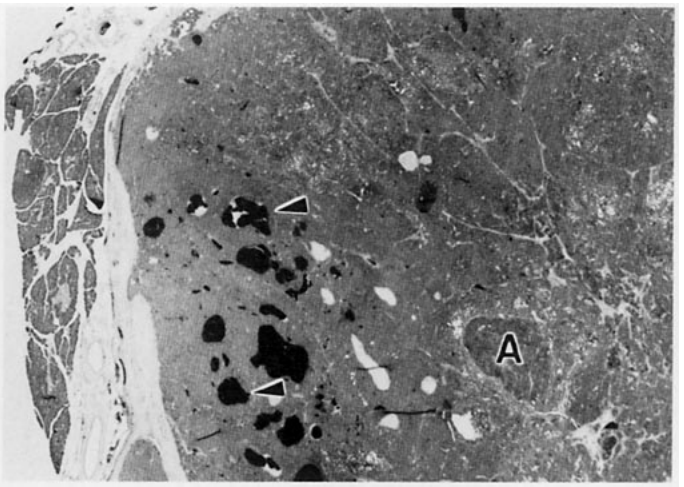


PLATE 6
Pancreatic exocrine carcinoma in a male F344/N rat exposed to 500 mg/kg dichloromethane in 10 mL/kg corn oil in the 2-year gavage study. There are numerous dilated blood filled vessels (arrows) within the carcinoma plus an area that shows increased atypia (A). H&E, 10×.

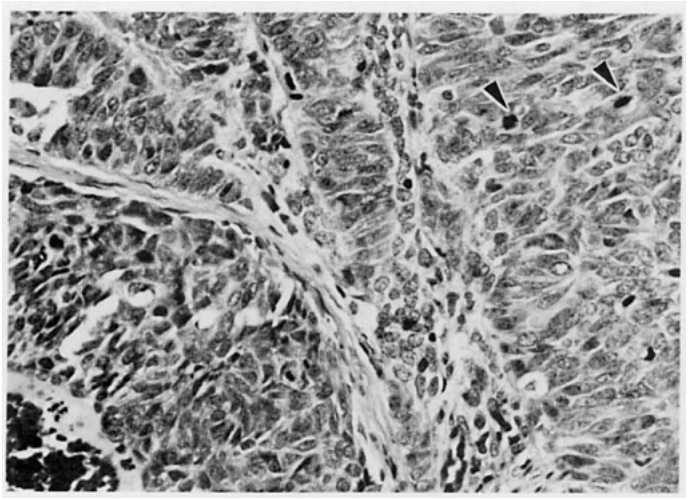


PLATE 7
Pancreatic exocrine carcinoma in a male F344/N rat exposed to 500 mg/kg dichloromethane in 10 mL/kg corn oil in the 2-year gavage study (detail of Plate 6). There are numerous mitotic figures (arrows). There tends to be solid growth with moderate cellular atypia. H&E, 200×.

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 for corn oil. 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. The 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 acids in each. Further, the magnitude of the 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 high-dose 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). Medium-chain 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). Further 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%. The 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. In the 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.

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

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Gavage Study of Corn Oil[a]

	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					
Died last week of study	1				
Terminal sacrifice	25	32	33	38	40
Animals examined microscopically	50	50	50	50	50
Alimentary System					
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	(46)	(49)	(45)	(48)	(47)
Adenocarcinoma			1 (2%)		
Liver	(50)	(50)	(50)	(50)	(50)
Hepatocellular adenoma	4 (8%)		2 (4%)		
Hepatocellular adenoma, multiple			1 (2%)		
Histiocytic sarcoma					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			2 (4%)	7 (14%)	12 (24%)
Acinus, carcinoma				1 (2%)	
Pharynx	(1)		(1)		
Palate, squamous cell papilloma			1 (100%)		
Salivary glands	(50)	(50)	(50)	(50)	(49)
Stomach, forestomach	(50)	(49)	(50)	(50)	(50)
Squamous cell papilloma				1 (2%)	
Stomach, glandular	(50)	(50)	(50)	(50)	(48)
Leiomyosarcoma				1 (2%)	
Tongue		(3)	(2)		(3)
Squamous cell papilloma					2 (67%)
Cardiovascular System					
Heart	(50)	(50)	(50)	(50)	(50)
Carcinoma, metastatic, Zymbal's gland					1 (2%)
Endocrine System					
Adrenal cortex	(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%)	2 (4%)
Pheochromocytoma complex			1 (2%)		
Pheochromocytoma benign	18 (37%)	13 (27%)	15 (30%)	3 (6%)	7 (14%)
Bilateral, pheochromocytoma malignant	1 (2%)				
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					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%)
General Body System					
None					
Genital System					
Ductus deferens			(1)		
Epididymis	(50)	(50)	(50)	(50)	(48)
Preputial gland	(50)	(50)	(50)	(50)	(48)
Adenoma	6 (12%)	8 (16%)	2 (4%)	3 (6%)	3 (6%)
Bilateral, adenoma			1 (2%)	1 (2%)	
Prostate	(50)	(49)	(50)	(50)	(48)
Adenoma					2 (4%)
Seminal vesicle	(50)	(49)	(49)	(50)	(48)
Testes	(50)	(50)	(50)	(50)	(49)
Bilateral, interstitial cell, adenoma	40 (80%)	39 (78%)	43 (86%)	41 (82%)	39 (80%)
Interstitial cell, adenoma	8 (16%)	8 (16%)	3 (6%)	6 (12%)	9 (18%)
Hematopoietic System					
Blood	(8)	(9)	(4)	(3)	
Bone marrow	(50)	(50)	(50)	(50)	(50)
Lymph node	(28)	(22)	(15)	(13)	(8)
Lymph node, mandibular	(50)	(50)	(49)	(50)	(48)
Lymph node, mesenteric	(50)	(50)	(50)	(50)	(49)
Spleen	(49)	(50)	(49)	(50)	(49)
Hemangioma			1 (2%)		
Histiocytic sarcoma					1 (2%)
Thymus	(48)	(48)	(45)	(45)	(46)
Epithelial cell, thymoma benign	1 (2%)		1 (2%)		

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)
Fibroadenoma	4 (13%)	2 (5%)	1 (3%)	1 (3%)	3 (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%)		
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%)		1 (2%)	3 (6%)
Alveolar/bronchiolar carcinoma		1 (2%)	1 (2%)	1 (2%)	
Carcinoma, metastatic, thyroid gland			1 (2%)		
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)
Special Senses System					
Ear		(2)	(1)	(2)	
Fibrosarcoma		1 (50%)			
Fibrous histiocytoma		1 (50%)			
Harderian gland				(1)	
Carcinoma				1 (100%)	
Zymbal's gland		(2)			(1)
Adenoma		1 (50%)			
Carcinoma		1 (50%)			1 (100%)

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[b]	(50)	(50)	(50)	(50)	(50)
Histiocytic sarcoma					1 (2%)
Leukemia granulocytic					1 (2%)
Leukemia mononuclear	27 (54%)	30 (60%)	16 (32%)	11 (22%)	7 (14%)
Lymphoma malignant	1 (2%)				
Mesothelioma malignant	2 (4%)	1 (2%)	1 (2%)	1 (2%)	3 (6%)
Neoplasm Summary					
Total animals with primary neoplasms[c]	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	2	3	1	3
Total metastatic neoplasms	8	4	7	13	12
Total animals with malignant neoplasms of uncertain primary site			1		

[a] 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 A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Corn Oil: Untreated Control

Number of Days on Study	2 1 6	5 2 3	5 6 9	6 1 0	6 1 8	6 2 0	6 3 5	6 3 8	6 5 1	6 7 8	6 8 1	6 8 3	6 8 5	6 8 7	6 8 8	6 8 8	6 9 1	6 9 7	6 9 7	7 0 4	7 0 4	7 0 4	7 1 0	7 1 5	7 3 5
Carcass ID Number	0 1 0	0 3 9	0 3 1	0 2 4	0 2 0	0 4 0	0 0 1	0 2 5	0 1 5	0 3 5	0 5 0	0 1 2	0 0 9	0 2 3	0 3 4	0 4 4	0 0 3	0 3 3	0 4 3	0 1 8	0 3 8	0 4 7	0 5 5	0 4 5	0 1 7
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes																									X
Intestine large, rectum	+	+	+	+	+	+	+	A	+	+	+	+	+	A	+	A	+	+	A	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	A	+	+	+	A	+	A	+	+	A	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	A	+	A	+	+	+	A	+	A	+	+	A	+	+	+	+	A	+
Intestine small, ileum	+	+	+	+	+	+	+	A	+	A	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma				X														X					X		
Mesothelioma malignant, metastatic, testes																									X
Mesentery									+										+			+			+
Mesothelioma malignant, metastatic, testes																									X
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes																									X
Acinus, adenoma																									
Pharynx																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																								X	
Pheochromocytoma benign				X	X			X						X		X			X		X				X
Bilateral, pheochromocytoma malignant							X																		
Bilateral, pheochromocytoma benign										X													X		
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma								X										X					X	X	
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma						X																	X		
Pars intermedia, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma						X														X					
C-cell, carcinoma							X																		
General Body System																									
None																									

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Corn Oil: Untreated Control (continued)

Number of Days on Study	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	0 0 2	0 0 4	0 0 6	0 0 7	0 1 1	0 1 3	0 1 4	0 1 6	0 1 9	0 2 1	0 2 2	0 2 6	0 2 7	0 2 8	0 2 9	0 3 0	0 3 2	0 3 6	0 3 8	0 4 1	0 4 2	0 4 6	0 4 7	0 4 8	0 4 9	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Mesothelioma malignant, metastatic, testes																										1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma								X																		4
Mesothelioma malignant, metastatic, testes																										1
Mesentery											+														+	6
Mesothelioma malignant, metastatic, testes																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, testes																										1
Acinus, adenoma			X																							1
Pharynx																				+						1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma malignant								X																		2
Pheochromocytoma benign						X			X		X	X				X		X	X		X	X	X			18
Bilateral, pheochromocytoma malignant																										1
Bilateral, pheochromocytoma benign																										2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma	X	X	X		X																		X			9
Parathyroid gland	+	+	+	+	+	+	+	M	+	M	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	44
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma							X	X										X								5
Pars intermedia, adenoma																									X	1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma																			X				X			4
C-cell, carcinoma																										1
General Body System																										
None																										

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Corn Oil: Untreated Control (continued)

Number of Days on Study	2 1 6	5 2 3	5 6 9	6 1 0	6 1 8	6 2 0	6 3 5	6 3 8	6 5 1	6 7 8	6 8 1	6 8 3	6 8 5	6 8 7	6 8 8	6 8 8	6 9 1	6 9 7	6 9 7	7 0 4	7 0 4	7 0 4	7 1 0	7 1 5	7 3 5
Carcass ID Number	0 1 0	0 3 9	0 3 1	0 2 4	0 2 0	0 4 0	0 0 1	0 2 5	0 1 5	0 3 5	0 5 0	0 1 2	0 0 9	0 2 3	0 3 4	0 4 4	0 0 3	0 3 3	0 4 3	0 0 8	0 1 8	0 3 7	0 0 5	0 4 5	0 1 7
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes							X																		X
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma				X					X	X				X											
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma		X	X	X	X			X	X		X		X		X	X	X	X	X	X		X		X	
Interstitial cell, adenoma						X	X			X		X		X							X				X
Hematopoietic System																									
Blood			+	+														+			+	+			
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node			+	+	+	+	+	+	+	+	+	+				+	+	+	+		+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Epithelial cell, thymoma benign																				X					
Integumentary System																									
Mammary gland	+	M	M	+	+	+	M	+	M	+	M	M	+	+	M	M	+	+	M	+	M	M	+	M	+
Fibroadenoma	X												X					X							
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma																									
Keratoacanthoma																									
Squamous cell carcinoma													X												
Squamous cell papilloma																									
Subcutaneous tissue, fibroma																				X					
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes																									X
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																						X			
Pheochromocytoma malignant, metastatic, adrenal medulla																							X		
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Corn Oil: Untreated Control (continued)

Number of Days on Study	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	0 0 2	0 0 4	0 0 6	0 0 7	0 1 1	0 1 3	0 1 4	0 1 6	0 1 9	0 2 1	0 2 2	0 2 6	0 2 7	0 2 8	0 2 9	0 3 0	0 3 2	0 3 6	0 3 8	0 4 1	0 4 2	0 4 6	0 4 7	0 4 8	0 4 9	Total Tissues/ Tumors
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, testes																										2
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma									X										X							6
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	40
Interstitial cell, adenoma											X															8
Hematopoietic System																										
Blood									+												+	+				8
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+						+					+	+		+					+	+	+		+		28
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Epithelial cell, thymoma benign																										1
Integumentary System																										
Mammary gland	+	+	+	+	M	+	+	+	+	+	M	+	+	M	M	+	+	+	+	+	M	M	+	+	M	31
Fibroadenoma																			X							4
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell carcinoma	X																									1
Keratoacanthoma			X																							1
Squamous cell carcinoma																X										2
Squamous cell papilloma																	X									1
Subcutaneous tissue, fibroma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, testes																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma																										1
Pheochromocytoma malignant, metastatic, adrenal medulla																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye			+																							1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Corn Oil: Untreated Control (continued)

Number of Days on Study	2	5	5	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	7	7	7	7	7	7		
	1	2	6	1	1	2	3	3	5	7	8	8	8	8	8	8	9	9	9	0	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	4	4	0	5	5	
Carcass ID Number	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	
	1	3	3	2	2	4	0	2	1	3	5	1	0	2	3	4	0	3	4	0	1	3	0	4	1	
	0	9	1	4	0	0	1	5	5	5	0	2	9	3	4	4	3	3	3	8	8	7	5	5	7	
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Leukemia mononuclear		X	X	X	X			X	X	X	X	X				X	X	X	X		X	X	X			
Lymphoma malignant											X															
Mesothelioma malignant							X																		X	

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Corn Oil: Untreated Control (continued)

Number of Days on Study	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	0 0 2	0 0 4	0 0 6	0 0 7	0 1 1	0 1 3	0 1 4	0 1 6	0 1 9	0 2 1	0 2 2	0 2 6	0 2 7	0 2 8	0 2 9	0 3 0	0 3 2	0 3 6	0 3 8	0 4 1	0 4 2	0 4 6	0 4 7	0 4 8	0 4 9	Total Tissues/ Tumors
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X	X				X	X		X		X		X						X	X	X	X				27
Lymphoma malignant																										1
Mesothelioma malignant																										2

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

Number of Days on Study	2 7 2	3 6 0	4 8 3	5 9 1	5 9 8	6 0 0	6 2 8	6 5 8	6 6 1	6 6 1	6 7 0	6 7 1	6 8 5	6 0 1	7 0 7	7 1 9	7 2 3	7 2 6	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	2 0 4	2 4 5	2 1 3	2 0 7	2 1 2	2 0 5	2 4 3	2 4 9	2 4 2	2 5 0	2 0 8	2 2 9	2 4 6	2 2 6	2 1 1	2 1 7	2 4 8	2 2 5	2 0 6	2 1 4	2 1 5	2 2 1	2 2 2	2 2 3	2 2 4
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery	+														+		+					+	+		
Mesothelioma malignant, metastatic, testes																						X			
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes																						X			
Mixed tumor benign																									
Acinus, adenoma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																	+			+					
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Pheochromocytoma malignant																									
Pheochromocytoma benign						X		X						X			X	X							
Bilateral, pheochromocytoma benign																				X					
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Adenoma				X							X		X												
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
C-cell, adenoma																				X					
Follicular cell, adenoma																									
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes																						X			
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma				X						X								X							X
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

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

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	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 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	
Carcass ID Number	2 3 0	2 3 1	2 3 2	2 3 3	2 3 4	2 3 9	2 4 4	2 0 1	2 0 0 2	2 0 0 3	2 0 0 9	2 0 1 0	2 1 1 6	2 1 1 8	2 1 1 9	2 2 0	2 2 2 7	2 2 2 8	2 3 5	2 3 3 6	2 3 3 7	2 3 3 8	2 4 0	2 4 1	2 4 4 7	Total Tissues/ Tumors
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																									X	1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue									+																	3
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma malignant														X												1
Pheochromocytoma benign	X				X						X			X	X	X		X					X			13
Bilateral, pheochromocytoma benign									X																	2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																			X				X			5
Parathyroid gland	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	47
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma		X	X									X		X						X			X			6
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell, adenoma				X																				X		3
Follicular cell, adenoma	X																				X					2
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, testes																										1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma										X				X			X							X		8
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	49
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	49

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

Number of Days on Study	2 7 2	3 6 0	4 8 3	5 9 1	5 9 8	6 0 0	6 2 8	6 5 8	6 6 1	6 6 1	6 7 0	6 7 1	6 8 5	7 0 1	7 0 7	7 1 9	7 2 3	7 2 6	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	2 0 4	2 4 5	2 1 3	2 0 7	2 1 2	2 0 5	2 4 3	2 4 9	2 4 2	2 5 0	2 0 8	2 2 9	2 4 6	2 2 6	2 1 1	2 1 7	2 4 8	2 2 5	2 0 6	2 1 4	2 1 5	2 2 1	2 2 2	2 2 3	2 2 4
Genital System (continued)																									
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma			X	X		X			X		X		X	X	X	X	X		X	X	X	X	X	X	X
Interstitial cell, adenoma					X		X	X		X		X						X							
Hematopoietic System																									
Blood													+	+			+	+					+		+
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node				+	+	+	+	+	+	+		+	+	+	+		+	+		+	+		+		+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Fibroadenoma																							X		
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																									
Sebaceous gland, adenoma																									
Subcutaneous tissue, fibroma								X						X											
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma													X												
Fibrosarcoma, metastatic, ear																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																									
Fibrosarcoma																									
Fibrous histiocytoma																									
Eye																									
Zymbal's gland											+		+												
Adenoma											X														
Carcinoma													X												
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+

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

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	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 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	
Carcass ID Number	2 3 0	2 3 1	2 3 2	2 3 3	2 3 4	2 3 9	2 4 4	2 0 1	2 0 2	2 0 3	2 0 9	2 1 0	2 1 6	2 1 8	2 1 9	2 2 0	2 2 7	2 2 8	2 3 5	2 3 6	2 3 7	2 3 8	2 4 0	2 4 1	2 4 7	Total Tissues/ Tumors
Genital System (continued)																										
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma	X	X	X	X	X		X	X	X	X	X	X	X		X	X	X		X	X	X	X	X	X	X	39
Interstitial cell, adenoma						X								X												8
Hematopoietic System																										
Blood		+					+							+												9
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node		+		+			+			+						+									22
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Integumentary System																										
Mammary gland	+	M	M	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	42
Fibroadenoma						X																				2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma												X														1
Sebaceous gland, adenoma																	X									1
Subcutaneous tissue, fibroma										X																3
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Respiratory System																										
Lung	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma																			X							1
Alveolar/bronchiolar carcinoma																										1
Fibrosarcoma, metastatic, ear				X																						1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49

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

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

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

Number of Days on Study	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	23040	23101	23202	23303	23404	23509	24004	20101	20002	20003	20009	21006	21168	21199	21200	22307	22358	23035	23366	23377	23388	24040	24141	24247		Total Tissues/ Tumors
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X		X			X	X		X	X	X		X		X		X								30
Mesothelioma malignant																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Corn Oil: 2.5 mL/kg

Number of Days on Study	4 0 9	4 2 0	5 2 0	5 6 2	5 7 5	5 8 6	5 9 9	6 1 9	6 5 3	6 5 6	6 6 9	6 7 0	6 7 8	6 9 5	7 0 5	7 0 7	7 2 0	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6
Carcass ID Number	0 7 6	0 5 9	1 0 0	0 6 7	0 8 0	0 9 4	0 8 3	0 8 7	0 5 5	0 7 2	0 9 1	0 7 1	0 5 2	0 6 4	0 5 1	0 8 2	0 8 5	0 5 7	0 5 8	0 6 0	0 6 1	0 6 2	0 6 3	6 5	7 4
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	A	+	+	+	+	+	+	A	+	+	A	+	A	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	A	A	+	+	+	+	+	+	+	A	+	A	+	A	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	A	A	+	+	+	+	+	+	+	A	+	A	+	A	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	A	A	+	+	+	+	+	+	+	A	+	A	+	A	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	A	A	+	+	+	+	+	+	+	A	+	A	+	A	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Hepatocellular adenoma, multiple														X											
Mesentery				+													+								
Mesothelioma malignant, metastatic, testes				X																					
Pancreas	+	+	+	M	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	M	+	+	+
Acinus, adenoma																			X		X				X
Acinus, adenoma, multiple																						X			
Pharynx																						+			
Palate, squamous cell papilloma																						X			
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																						+			
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ganglioneuroma																									
Pheochromocytoma malignant								X																	
Pheochromocytoma complex			X																						
Pheochromocytoma benign						X								X	X	X			X				X	X	
Bilateral, pheochromocytoma benign											X						X								
Islets, pancreatic	+	+	+	M	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	M	+	+	+
Adenoma							X																		
Parathyroid gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma	X						X		X				X				X		X						
Thyroid gland	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma									X															X	
C-cell, carcinoma											X														
General Body System																									
None																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Corn Oil: 2.5 mL/kg (continued)

Number of Days on Study	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	0 7 5	0 8 1	0 8 4	0 9 2	0 9 3	0 9 5	0 9 6	0 9 7	0 9 8	0 9 9	0 5 3	0 5 4	0 5 6	0 6 6	0 6 8	0 6 9	0 7 0	0 7 3	0 7 7	0 7 8	0 7 9	0 8 6	0 8 8	0 8 9	0 9 0	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Adenocarcinoma													X													1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma								X											X							2
Hepatocellular adenoma, multiple																										1
Mesentery							+			+		+							+		+	+				8
Mesothelioma malignant, metastatic, testes																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Acinus, adenoma			X					X																X		6
Acinus, adenoma, multiple						X																				2
Pharynx																										1
Palate, squamous cell papilloma																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue				+																						2
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Ganglioneuroma																			X							1
Pheochromocytoma malignant																										1
Pheochromocytoma complex																										1
Pheochromocytoma benign				X	X		X		X		X		X							X					X	15
Bilateral, pheochromocytoma benign	X														X											4
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma				X							X															3
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma				X										X								X			X	10
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell, adenoma								X	X										X							5
C-cell, carcinoma																										1
General Body System																										
None																										

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Corn Oil: 2.5 mL/kg (continued)

Number of Days on Study	4 0 9	4 2 0	5 2 0	5 6 2	5 7 5	5 8 6	5 9 9	6 1 9	6 5 3	6 5 6	6 6 9	6 7 0	6 7 8	6 9 5	7 0 5	7 0 7	7 2 0	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6
Carcass ID Number	0 7 6	0 5 9	1 0 0	0 6 7	0 8 0	0 9 4	0 8 3	0 8 7	0 5 5	0 7 2	0 9 1	0 7 1	0 5 2	0 6 4	0 5 1	0 8 2	0 5 5	0 5 7	0 6 8	0 6 0	0 6 1	0 6 2	0 6 3	0 6 5	0 7 4
Genital System																									
Ductus deferens				+																					
Mesothelioma malignant, metastatic, testes				X																					
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic				X																					
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																X						X			
Bilateral, adenoma																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes				X																					
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma			X	X	X	X		X		X	X			X	X	X	X	X	X	X	X	X	X	X	
Interstitial cell, adenoma									X			X													X
Hematopoietic System																									
Blood																+			+						
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+			+		+		+		+				+		+	+		+						
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Thymus	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Epithelial cell, thymoma benign																									
Integumentary System																									
Mammary gland	+	+	+	M	+	M	+	+	+	+	M	+	M	+	M	+	+	+	+	+	+	+	+	M	+
Fibroadenoma																					X				
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																									
Squamous cell papilloma																									
Subcutaneous tissue, fibroma								X																	
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma										X															
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes				X																					
Mesothelioma malignant, metastatic, uncertain primary site								X																	
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord		+																							

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Corn Oil: 2.5 mL/kg (continued)

Number of Days on Study	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	0 0 7 5	0 0 8 1	0 0 8 4	0 0 9 2	0 0 9 3	0 0 9 5	0 0 9 6	0 0 9 7	0 0 9 8	0 0 9 9	0 0 5 3	0 0 5 4	0 0 5 6	0 0 6 6	0 0 6 8	0 0 6 9	0 0 7 0	0 0 7 3	0 0 7 7	0 0 7 8	0 0 7 9	0 0 8 6	0 0 8 8	0 0 8 9	0 0 9 0	Total Tissues/ Tumors
Genital System																										
Ductus deferens																										1
Mesothelioma malignant, metastatic, testes																										1
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic																										1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										2
Bilateral, adenoma					X																					1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Mesothelioma malignant, metastatic, testes																										1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	43
Interstitial cell, adenoma																										3
Hematopoietic System																										
Blood																			+					+		4
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma																X										1
Squamous cell papilloma																		X								1
Subcutaneous tissue, fibroma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma																										1
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, testes																										1
Mesothelioma malignant, metastatic, uncertain primary site																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spinal cord																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Corn Oil: 2.5 mL/kg (continued)

Number of Days on Study	4	4	5	5	5	5	5	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7
	0	2	2	6	7	8	9	1	5	5	6	7	7	9	0	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
Carcass ID Number	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	7	5	0	6	8	9	8	8	5	7	9	7	5	6	5	8	8	5	5	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	4
Respiratory System																								
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma																								
Carcinoma, metastatic, thyroid gland											X													
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																								
Ear																		+						
Eye							+			+														
Urinary System																								
Kidney	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Urinary bladder	+	+	A	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear						X		X		X				X	X	X	X		X					
Mesothelioma malignant				X																				

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Corn Oil: 2.5 mL/kg (continued)

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Corn Oil: 5 mL/kg

Number of Days on Study	3 8 3 6	4 3 2 5	5 5 5 0	5 6 0 0	5 6 2 4	5 6 9 3	5 7 6 8	6 3 2 6	7 0 6 4	7 0 7 5	7 2 1 7	7 2 6 7	7 3 4 6	7 3 4 9	7 3 4 4	7 3 4 4	7 3 4 4	7 3 4 4	7 3 4 6	7 3 4 8	7 3 4 9	7 3 4 4	7 3 4 1	7 3 4 3	7 3 4 5
Carcass ID Number	1 4 2 2	1 2 7 0	1 3 0 0	1 2 4 0	1 4 4 4	1 2 4 3	1 1 8 8	1 4 6 6	1 0 4 4	1 0 5 5	1 1 7 7	1 4 7 6	1 1 6 9	1 1 9 1	1 2 1 2	2 2 4 4	2 2 4 6	2 2 6 8	2 2 9 9	2 3 4 4	3 3 4 9	4 4 1 1	4 4 3 3	4 4 3 5	1 4 4 5
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes						X																			
Intestine large, rectum	+	+	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes						X																			
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes						X																			
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes						X																			
Mesentery						+		+														+			
Mesothelioma malignant, metastatic, testes						X																			
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes						X																			
Acinus, adenoma									X																
Acinus, adenoma, multiple						X								X						X					
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																				X					
Pheochromocytoma benign														X											
Bilateral, pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																			X						
Parathyroid gland	M	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	M	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma					X									X											
Thyroid gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, C-cell, adenoma																									
C-cell, adenoma														X						X					

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Corn Oil: 5 mL/kg (continued)

Number of Days on Study	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	1 4 8	1 4 9	1 0 1	1 0 2	1 0 3	1 0 6	1 0 7	1 0 8	1 0 9	1 1 0	1 1 1	1 1 2	1 1 3	1 1 4	1 1 5	1 2 5	1 3 8	1 5 0	1 3 1	1 3 2	1 3 3	1 3 5	1 3 6	1 3 7	1 4 0	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Mesothelioma malignant, metastatic, testes																										1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Mesothelioma malignant, metastatic, testes																										1
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Mesothelioma malignant, metastatic, testes																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, testes																										1
Mesentery																						+				4
Mesothelioma malignant, metastatic, testes																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, testes																										1
Acinus, adenoma													X					X								3
Acinus, adenoma, multiple								X			X						X				X					7
Acinus, carcinoma														X												1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma																										1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																										1
Pheochromocytoma benign													X								X					3
Bilateral, pheochromocytoma benign									X																	1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma				X					X											X						4
Parathyroid gland	M	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	M	M	+	+	+	40
Pituitary gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma									X												X	X			X	6
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Bilateral, C-cell, adenoma				X																						1
C-cell, adenoma					X																					3

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Corn Oil: 5 mL/kg (continued)

Number of Days on Study	3 8 6	4 3 2	5 5 5	5 6 0	5 6 2	5 6 9	5 7 6	6 3 2	7 0 6	7 0 7	7 2 1	7 2 6	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4
Carcass ID Number	1 4 2	1 2 7	1 3 0	1 2 0	1 4 4	1 2 3	1 1 8	1 4 6	1 0 4	1 0 5	1 1 7	1 4 7	1 1 6	1 1 9	1 2 1	2 2 2	2 2 4	2 2 6	2 2 8	2 3 9	3 4 4	3 3 9	4 4 1	4 4 3	4 4 5
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes						X																			
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma							X																		
Bilateral, adenoma																				X					
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes						X																			
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes						X																			
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma			X				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Interstitial cell, adenoma		X				X																			
Hematopoietic System																									
Blood												+													
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+		+		+	+		+	+	+	+	+							+				+		+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes						X																			
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	M	+	M	+	+	M	+	+	+	+	+	M	+	+	+	+	M	+	+
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																	X							X	
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, hemangioma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes						X																			
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord	+																								

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Corn Oil: 5 mL/kg (continued)

Number of Days on Study	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	1 4 8	1 4 9	1 0 1	1 0 2	1 0 3	1 0 6	1 0 7	1 0 8	1 0 9	1 1 0	1 1 1	1 1 2	1 1 3	1 1 4	1 1 5	1 2 5	1 3 8	1 5 0	1 3 1	1 3 2	1 3 3	1 3 5	1 3 6	1 3 7	1 4 0	Total Tissues/ Tumors
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, testes																										1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																X				X						3
Bilateral, adenoma																										1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, testes																										1
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, testes																										1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma	X	X	X	X	X	X	X			X	X		X	X	X	X	X	X	X	X	X	X	X		X	41
Interstitial cell, adenoma								X	X			X												X		6
Hematopoietic 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
Integumentary System																										
Mammary gland	+	+	+	+	+	M	M	+	M	+	+	M	+	+	+	+	+	+	M	+	+	+	M	+	+	39
Fibroadenoma															X											1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma	X											X							X							5
Subcutaneous tissue, fibroma		X																								1
Subcutaneous tissue, hemangioma											X															1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, testes																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spinal cord																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Corn Oil: 5 mL/kg (continued)

Number of Days on Study	3 8 6	4 3 2	5 5 5	5 6 0	5 6 2	5 6 9	5 7 6	6 3 2	7 0 6	7 0 7	7 2 1	7 2 6	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4
Carcass ID Number	1 4 2	1 2 7	1 3 0	1 2 0	1 4 4	1 2 3	1 1 8	1 4 6	1 0 4	1 0 5	1 1 7	1 4 7	1 1 6	1 1 9	1 2 1	1 2 2	1 2 4	1 2 6	1 2 8	1 2 9	1 3 4	1 3 9	1 4 1	1 4 3	1 4 5
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma									X																
Alveolar/bronchiolar carcinoma																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																						+			
Eye																					+				+
Harderian gland		+																							
Carcinoma		X																							
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes						X																			
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes						X																			
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X					X		X	X	X													
Mesothelioma malignant						X																			

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Corn Oil: 5 mL/kg (continued)

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

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

Number of Days on Study	5 7 5	5 7 6	6 2 2	6 2 3	6 6 4	6 7 2	6 8 0	6 9 2	7 0 5	7 2 2	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
Carcass ID Number	1 8 4	1 5 9	1 8 0	1 6 4	1 7 8	1 6 6	1 7 7	1 6 5	1 6 2	1 7 4	1 5 5	1 5 1	1 5 2	1 5 3	1 5 4	1 5 6	1 5 7	1 5 8	1 6 0	1 6 1	1 6 3	1 6 7	1 6 8	1 6 9	1 7 1
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	A	A	+	+	M	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	A	A	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	A	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Muscularis, leiomyosarcoma																								X	
Intestine small, ileum	+	+	A	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma			X																						
Mesentery									+			+						+							
Mesothelioma malignant, metastatic, testes																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes																									
Acinus, adenoma		X	X							X	X							X				X			
Acinus, adenoma, multiple												X		X		X			X				X		
Salivary glands	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue	+																							+	
Squamous cell papilloma	X																							X	
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, Zymbal's gland								X																	
Mesothelioma malignant, metastatic, testes																									
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant		X														X									
Pheochromocytoma benign					X																X				
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma							X			X				X									X		
Parathyroid gland	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, Zymbal's gland								X																	
Pars distalis, adenoma	X								X					X											
Thyroid gland	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, C-cell, adenoma																X									
C-cell, adenoma													X					X							
C-cell, carcinoma																					X				
Follicular cell, carcinoma																									
General Body System																									
None																									

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 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	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	
Carcass ID Number	1 7 2	1 7 3	1 7 5	1 8 6	1 8 7	1 8 8	1 8 9	1 9 0	1 9 1	1 9 2	1 9 3	1 9 4	1 9 5	1 9 6	1 9 7	1 9 8	1 9 9	2 0 0	1 7 0	1 7 6	1 7 9	1 8 1	1 8 2	1 8 3	1 8 5	Total Tissues/ Tumors
Alimentary 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, testes																								X		1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, testes																								X		1
Acinus, adenoma		X						X					X	X											X	11
Acinus, adenoma, multiple	X									X		X					X				X		X	X		12
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Tongue																								+		3
Squamous cell papilloma																										2
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, Zymbal's gland																										1
Mesothelioma malignant, metastatic, testes																								X		1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																										2
Pheochromocytoma benign			X	X		X			X				X													7
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma													X								X		X			7
Parathyroid gland	+	+	+	M	+	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																		X								1
General Body System																										
None																										

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	5 7 5	5 7 6	6 2 2	6 2 3	6 6 4	6 7 2	6 8 0	6 9 2	7 0 5	7 2 2	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
Carcass ID Number	1 8 4	1 5 9	1 8 0	1 6 4	1 7 8	1 6 6	1 7 7	1 6 5	1 6 2	1 7 4	1 5 5	1 5 1	1 5 2	1 5 3	1 5 4	1 5 6	1 5 7	1 5 8	1 6 0	1 6 1	1 6 3	1 6 7	1 6 8	1 6 9	1 7 1
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	M	+		+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes								X													X				
Preputial gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma													X												
Prostate	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Seminal vesicle	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma				X	X	X	X	X			X	X	X	X	X		X	X	X	X	X	X		X	X
Interstitial cell, adenoma		X	X						X							X							X		
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node			+			+		+	+								+								+
Lymph node, mandibular	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma			X																						
Thymus	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord											+														
Astrocytoma malignant											X														
Respiratory System																									
Lung	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma											X										X				
Carcinoma, metastatic, Zymbal's gland								X																	
Mediastinum, carcinoma, metastatic, Zymbal's gland								X																	
Mediastinum, mesothelioma malignant, metastatic, testes																									
Pleura, mesothelioma malignant, metastatic, testes																									

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 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	7 3 1	7 3 1	7 3 1	7 3 1	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	1 7 2	1 7 3	1 7 5	1 8 6	1 8 7	1 8 8	1 8 9	1 9 0	1 9 1	1 9 2	1 9 3	1 9 4	1 9 5	1 9 6	1 9 7	1 9 8	1 9 9	2 0 0	1 7 0	1 7 6	1 7 9	1 8 1	1 8 2	1 8 3	1 8 5	Total Tissues/ Tumors
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Mesothelioma malignant, metastatic, testes																								X		3
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma	X							X																		3
Prostate	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma			X																					X		2
Seminal vesicle	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Bilateral, interstitial cell, adenoma	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X	39
Interstitial cell, adenoma			X	X																		X		X		9
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node					+																			+		8
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Thymus	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	46
Integumentary System																										
Mammary gland	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	M	+	+	+	40
Fibroadenoma	X																									3
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell adenoma																										1
Keratoacanthoma													X													1
Squamous cell papilloma												X														1
Subcutaneous tissue, fibroma					X										X	X			X							5
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spinal cord																										1
Astrocytoma malignant																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma																X										3
Carcinoma, metastatic, Zymbal's gland																										1
Mediastinum, carcinoma, metastatic, Zymbal's gland																										1
Mediastinum, mesothelioma malignant, metastatic, testes																								X		1
Pleura, mesothelioma malignant, metastatic, testes																								X		1

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	5	5	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	7	7	2	2	6	7	8	9	0	2	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	5	6	2	3	4	2	0	2	5	2	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Carcass ID Number	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	8	5	8	6	7	6	7	6	6	7	5	5	5	5	5	5	5	5	6	6	6	6	6	6	6	7
	4	9	0	4	8	6	7	5	2	4	5	1	2	3	4	6	7	8	0	1	3	7	8	9	1	
Respiratory System (continued)																										
Nose	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																										
Eye												+	+													
Zymbal's gland								+																		
Carcinoma								X																		
Urinary System																										
Kidney	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma			X																							
Leukemia granulocytic			X																							
Leukemia mononuclear				X	X				X					X								X				
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 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	7 3 1	7 3 1	7 3 1	7 3 1	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	1 7 2	1 7 3	1 7 5	1 8 6	1 8 7	1 8 8	1 8 9	1 9 0	1 9 1	1 9 2	1 9 3	1 9 4	1 9 5	1 9 6	1 9 7	1 9 8	1 9 9	1 9 9	2 0 0	1 7 0	1 7 6	1 7 9	1 8 1	1 8 2	1 8 3	1 8 5	Total Tissues/ 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	X				X																						7
Mesothelioma malignant																									X		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 Pheochromocytoma				
Overall rate[a]	20/49 (41%)	19/50 (38%)	4/50 (8%)	7/50 (14%)
Adjusted rate[b]	56.3%	48.3%	10.5%	16.8%
Terminal rate[c]	11/25 (44%)	13/33 (39%)	4/38 (11%)	6/40 (15%)
First incidence (days)	610	586	730 (T)	664
Life table test[d]	P<0.001N	P=0.250N	P<0.001N	P<0.001N
Logistic regression test[d]	P<0.001N	P=0.460N	P<0.001N	P=0.002N
Cochran-Armitage test[d]	P<0.001N			
Fisher exact test[d]		P=0.468N	P<0.001N	P=0.003N
Adrenal Medulla: 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
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	P=0.468N			
Fisher exact test		P=0.301N	P=0.301N	P=0.490N
Adrenal Medulla: Pheochromocytoma (Benign, Complex, 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		P=0.385N	P<0.001N	P=0.002N
Liver: Hepatocellular Adenoma				
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 Adenoma				
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
Cochran-Armitage test	P=0.095			
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				
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
Logistic 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%
Terminal 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
Logistic regression test	P<0.001	P=0.033	P=0.003	P<0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		P=0.012	P=0.002	P<0.001
Pancreatic Islets: Adenoma				
Overall rate	9/50 (18%)	3/47 (6%)	4/50 (8%)	7/50 (14%)
Adjusted rate	29.0%	8.4%	10.5%	16.6%
Terminal rate	5/26 (19%)	2/32 (6%)	4/38 (11%)	5/40 (13%)
First incidence (days)	638	599	730 (T)	680
Life table test	P=0.246N	P=0.038N	P=0.034N	P=0.147N
Logistic regression test	P=0.400N	P=0.073N	P=0.086N	P=0.299N
Cochran-Armitage test	P=0.470N			
Fisher exact test		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 Distalis): Adenoma				
Overall rate	5/50 (10%)	10/50 (20%)	6/49 (12%)	7/50 (14%)
Adjusted rate	16.6%	25.0%	15.4%	16.3%
Terminal rate	3/26 (12%)	5/33 (15%)	5/37 (14%)	5/40 (13%)
First incidence (days)	620	409	562	575
Life table test	P=0.360N	P=0.218	P=0.560N	P=0.602N
Logistic regression test	P=0.472	P=0.130	P=0.495	P=0.386
Cochran-Armitage test	P=0.498			
Fisher exact test		P=0.131	P=0.486	P=0.380
Preputial 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	2/26 (8%)	2/33 (6%)	3/38 (8%)	3/39 (8%)
First incidence (days)	610	707	576	730 (T)
Life table test	P=0.133N	P=0.198N	P=0.265N	P=0.139N
Logistic regression test	P=0.251N	P=0.242N	P=0.375N	P=0.271N
Cochran-Armitage test	P=0.259N			
Fisher exact test		P=0.243N	P=0.370N	P=0.264N
Skin: Squamous Cell Papilloma				
Overall rate	1/50 (2%)	1/50 (2%)	5/50 (10%)	1/50 (2%)
Adjusted rate	3.8%	3.0%	13.2%	2.5%
Terminal rate	1/26 (4%)	1/33 (3%)	5/38 (13%)	1/40 (3%)
First incidence (days)	730 (T)	730 (T)	730 (T)	730 (T)
Life table test	P=0.529N	P=0.708N	P=0.208	P=0.663N
Logistic regression test	P=0.529N	P=0.708N	P=0.208	P=0.663N
Cochran-Armitage test	P=0.500			
Fisher exact test		P=0.753N	P=0.102	P=0.753N
Skin: Squamous Cell Papilloma or Squamous Cell Carcinoma				
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)	685	730 (T)	730 (T)	730 (T)
Life table test	P=0.220N	P=0.247N	P=0.554	P=0.191N
Logistic regression test	P=0.270N	P=0.288N	P=0.458	P=0.252N
Cochran-Armitage test	P=0.371N			
Fisher exact test		P=0.309N	P=0.357	P=0.309N
Skin: Squamous Cell Papilloma, Keratoacanthoma, Basal Cell Adenoma, Squamous Cell Carcinoma, or 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%)
First incidence (days)	685	730 (T)	730 (T)	730 (T)
Life table test	P=0.214N	P=0.143N	P=0.401N	P=0.169N
Logistic regression test	P=0.262N	P=0.177N	P=0.492N	P=0.229N
Cochran-Armitage test	P=0.410N			
Fisher exact test		P=0.218N	P=0.630N	P=0.357N

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
Skin (Subcutaneous Tissue): Fibroma				
Overall rate	1/50 (2%)	1/50 (2%)	1/50 (2%)	5/50 (10%)
Adjusted rate	3.2%	2.3%	2.6%	12.0%
Terminal rate	0/26 (0%)	0/33 (0%)	1/38 (3%)	4/40 (10%)
First incidence (days)	704	619	730 (T)	672
Life table test	P=0.054	P=0.749N	P=0.683N	P=0.205
Logistic regression test	P=0.028	P=0.760	P=0.749N	P=0.125
Cochran-Armitage test	P=0.025			
Fisher exact test		P=0.753N	P=0.753N	P=0.102
Testes: Adenoma				
Overall rate	48/50 (96%)	46/50 (92%)	47/50 (94%)	48/49 (98%)
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)	523	520	432	576
Life table test	P=0.002N	P=0.074N	P=0.006N	P=0.003N
Logistic regression test	P=0.586N	P=0.420N	P=0.590N	P=0.680N
Cochran-Armitage test	P=0.300			
Fisher exact test		P=0.339N	P=0.500N	P=0.508
Thyroid Gland (C-cell): Adenoma				
Overall rate	4/50 (8%)	5/49 (10%)	4/49 (8%)	10/49 (20%)
Adjusted rate	12.7%	14.2%	10.5%	25.0%
Terminal rate	2/26 (8%)	4/33 (12%)	4/38 (11%)	10/40 (25%)
First incidence (days)	620	653	730 (T)	730 (T)
Life table test	P=0.138	P=0.604	P=0.463N	P=0.251
Logistic regression test	P=0.065	P=0.495	P=0.627N	P=0.118
Cochran-Armitage test	P=0.037			
Fisher exact test		P=0.487	P=0.631	P=0.068
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rate	5/50 (10%)	6/49 (12%)	4/49 (8%)	11/49 (22%)
Adjusted rate	14.6%	16.4%	10.5%	27.5%
Terminal rate	2/26 (8%)	4/33 (12%)	4/38 (11%)	11/40 (28%)
First incidence (days)	620	653	730 (T)	730 (T)
Life table test	P=0.173	P=0.589	P=0.335N	P=0.287
Logistic regression test	P=0.071	P=0.488	P=0.500N	P=0.113
Cochran-Armitage test	P=0.048			
Fisher exact test		P=0.486	P=0.513N	P=0.079
All Organs: Mononuclear Cell Leukemia				
Overall rate	27/50 (54%)	16/50 (32%)	11/50 (22%)	7/50 (14%)
Adjusted rate	62.6%	39.6%	25.4%	15.9%
Terminal rate	11/26 (42%)	9/33 (27%)	6/38 (16%)	4/40 (10%)
First incidence (days)	523	586	555	623
Life table test	P<0.001N	P=0.016N	P<0.001N	P<0.001N
Logistic regression test	P<0.001N	P=0.022N	P=0.001N	P<0.001N
Cochran-Armitage test	P<0.001N			
Fisher 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)

	Untreated Control	2.5 mL/kg	5 mL/kg	10 mL/kg
All Organs: Malignant Mesothelioma				
Overall rate	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 Neoplasms				
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	–[f]
Cochran-Armitage test	P=0.616			
Fisher exact test		P=0.500N	P=0.247N	P=1.000N
All Organs: Malignant Neoplasms				
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 Malignant Neoplasms				
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	–
Cochran-Armitage test	P=0.616			
Fisher exact test		P=0.500N	P=0.247N	P=1.000N

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, 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
[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. 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.
[e] Not applicable; no neoplasms in animal group
[f] 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[a]

	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					
Died last week of study	1				
Terminal sacrifice	25	32	33	38	40
Animals examined microscopically	50	50	50	50	50
Alimentary System					
Esophagus	(49)	(48)	(50)	(50)	(50)
Hyperkeratosis			1 (2%)		
Intestine large, colon	(49)	(49)	(46)	(49)	(48)
Cyst					1 (2%)
Intestine large, cecum	(46)	(49)	(45)	(48)	(46)
Erosion	3 (7%)	1 (2%)			
Inflammation, granulomatous			1 (2%)		
Ulcer			1 (2%)		
Intestine small, ileum	(46)	(49)	(45)	(48)	(47)
Erosion		1 (2%)			
Fibrosis				1 (2%)	
Pigmentation		1 (2%)			
Liver	(50)	(50)	(50)	(50)	(50)
Angiectasis		2 (4%)	1 (2%)		
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%)				
Degeneration, cystic			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%)			3 (6%)
Hematocyst	1 (2%)				
Hematopoietic cell proliferation	1 (2%)				
Hepatodiaphragmatic nodule	4 (8%)	6 (12%)	4 (8%)	8 (16%)	5 (10%)
Infarct	1 (2%)				
Mixed cell focus	5 (10%)	5 (10%)	1 (2%)	8 (16%)	8 (16%)
Necrosis	1 (2%)			1 (2%)	
Mesentery	(6)	(7)	(8)	(4)	(8)
Fat, hemorrhage			1 (13%)		
Fat, inflammation, chronic active	1 (17%)	1 (14%)			
Fat, mineralization					2 (25%)
Fat, necrosis	2 (33%)	3 (43%)	5 (63%)	2 (50%)	7 (88%)
Pancreas	(50)	(50)	(47)	(50)	(50)
Metaplasia					1 (2%)
Thrombosis			1 (2%)		
Acinus, atrophy	38 (76%)	40 (80%)	25 (53%)	32 (64%)	24 (48%)
Acinus, hyperplasia	8 (16%)	5 (10%)	28 (60%)	28 (56%)	35 (70%)
Acinus, hypertrophy, focal					1 (2%)
Artery, hyperplasia			1 (2%)		
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%)				
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)	(50)	(50)	(50)
Fibrosis			1 (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		3 (6%)			
Mineralization			1 (2%)		1 (2%)
Tongue		(3)	(2)		(3)
Hemorrhage			2 (100%)		
Hyperplasia, squamous					1 (33%)
Cardiovascular System					
Heart	(50)	(50)	(50)	(50)	(50)
Cardiomyopathy	47 (94%)	42 (84%)	46 (92%)	47 (94%)	45 (90%)
Pigmentation			1 (2%)		
Thrombosis	3 (6%)	1 (2%)	1 (2%)		1 (2%)
Artery, inflammation, chronic active		1 (2%)	1 (2%)		
Endocrine System					
Adrenal cortex	(50)	(50)	(50)	(50)	(50)
Accessory adrenal cortical nodule				1 (2%)	
Hypertrophy	2 (4%)	3 (6%)	4 (8%)		
Adrenal medulla	(49)	(49)	(50)	(50)	(50)
Cyst					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%)		1 (3%)	
Pituitary gland	(50)	(49)	(50)	(49)	(50)
Pars distalis, angiectasis	5 (10%)	6 (12%)	5 (10%)	4 (8%)	6 (12%)
Pars distalis, cyst		1 (2%)	3 (6%)	1 (2%)	
Pars distalis, hyperplasia	9 (18%)	9 (18%)	13 (26%)	9 (18%)	9 (18%)
Pars intermedia, hyperplasia					1 (2%)
Rathke's cleft, cyst		1 (2%)			
Thyroid gland	(50)	(49)	(49)	(49)	(49)
Bilateral, C-cell, hyperplasia			1 (2%)	1 (2%)	
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					
None					
Genital System					
Epididymis	(50)	(50)	(50)	(50)	(48)
Spermatocele		1 (2%)			
Preputial gland	(50)	(50)	(50)	(50)	(48)
Abscess	3 (6%)	4 (8%)	4 (8%)	5 (10%)	7 (15%)
Hyperplasia, squamous			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					1 (2%)
Inflammation, chronic active	2 (4%)	2 (4%)	3 (6%)		
Testes	(50)	(50)	(50)	(50)	(49)
Interstitial cell, hyperplasia		4 (8%)	3 (6%)	4 (8%)	4 (8%)
Seminiferous tubule, atrophy	7 (14%)	4 (8%)	2 (4%)	4 (8%)	6 (12%)
Seminiferous tubule, mineralization		1 (2%)			
Hematopoietic System					
Bone marrow	(50)	(50)	(50)	(50)	(50)
Depletion cellular	1 (2%)				
Fibrosis	1 (2%)				
Lymph node	(28)	(22)	(15)	(13)	(8)
Lumbar, pigmentation		1 (5%)			
Mediastinal, angiectasis	4 (14%)	1 (5%)	3 (20%)	5 (38%)	1 (13%)
Mediastinal, ectasia	1 (4%)				
Mediastinal, infiltration cellular, mast cell	1 (4%)				
Mediastinal, pigmentation			4 (27%)	1 (8%)	2 (25%)
Pancreatic, angiectasis	1 (4%)			1 (8%)	
Pancreatic, ectasia	3 (11%)		2 (13%)		
Pancreatic, infiltration cellular, histiocyte	2 (7%)				2 (25%)
Pancreatic, pigmentation			1 (7%)		1 (13%)
Renal, pigmentation		1 (5%)			
Lymph node, mandibular	(50)	(50)	(49)	(50)	(48)
Angiectasis					1 (2%)
Necrosis			1 (2%)		
Lymph node, mesenteric	(50)	(50)	(50)	(50)	(49)
Angiectasis	1 (2%)			1 (2%)	
Ectasia	2 (4%)		1 (2%)	1 (2%)	
Infiltration cellular, mast cell	1 (2%)				
Necrosis				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%)	
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					2 (5%)
Skin	(50)	(50)	(50)	(50)	(50)
Cyst epithelial inclusion			4 (8%)	2 (4%)	2 (4%)
Developmental malformation			1 (2%)		
Erosion		1 (2%)	1 (2%)		
Fibrosis				1 (2%)	
Hemorrhage					1 (2%)
Hyperkeratosis					2 (4%)
Inflammation, acute					1 (2%)
Mineralization			1 (2%)		
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					
Brain	(50)	(49)	(50)	(50)	(50)
Compression	1 (2%)		1 (2%)		
Spinal cord			(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%)				
Infiltration cellular, histiocyte	2 (4%)	5 (10%)		1 (2%)	2 (4%)
Inflammation, acute			1 (2%)		
Inflammation, granulomatous		1 (2%)	1 (2%)		
Metaplasia, osseous		1 (2%)			
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%)				
Inflammation, acute	16 (32%)	14 (28%)	17 (34%)	21 (43%)	21 (43%)
Metaplasia, cartilaginous				1 (2%)	
Respiratory epithelium, hyperkeratosis			3 (6%)	1 (2%)	
Respiratory epithelium, metaplasia, 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%)				
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%)			
Papilla, mineralization					2 (4%)
Renal tubule, pigmentation					1 (2%)

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

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 in the 2-Year Gavage Study of Safflower Oil[a]

	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				
Terminal sacrifice	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%)
Cardiovascular System				
Heart	(10)	(10)	(10)	(9)
Endocrine System				
Adrenal gland, medulla	(10)	(10)	(10)	(9)
Pheochromocytoma benign	4 (40%)		1 (10%)	1 (11%)
Pituitary gland	(10)	(10)	(10)	(9)
Pars distalis, adenoma	1 (10%)			
Thyroid gland	(10)	(10)	(10)	(9)
C-cell, adenoma	1 (10%)		1 (10%)	
General Body System				
None				
Genital System				
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				
Spleen	(10)	(10)	(10)	(9)
Integumentary System				
Skin	(8)	(9)	(10)	(9)
Subcutaneous tissue, fibroma			1 (10%)	

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	(10)	(10)	(10)	(9)
Alveolar/bronchiolar adenoma				1 (11%)
Special Senses System				
None				
Urinary System				
None				
Systemic Lesions				
Multiple organs[b]	(10)	(10)	(10)	(9)
Leukemia mononuclear	2 (20%)			
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			1 (2%)	
Intestine large, rectum	(47)	(47)	(47)	(47)
Fibrous histiocytoma, metastatic, skin		1 (2%)		
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 (2%)
Carcinoma, metastatic, uncertain primary site	1 (2%)			
Fibrous histiocytoma, metastatic, skin		1 (2%)		
Hepatocellular carcinoma	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 (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%)			
Carcinoma		1 (2%)		
Stomach, forestomach	(50)	(50)	(50)	(51)
Squamous cell papilloma	1 (2%)		2 (4%)	1 (2%)
Stomach, glandular	(49)	(50)	(49)	(50)
Carcinoma				1 (2%)
Tongue	(1)			(1)
Squamous cell papilloma	1 (100%)			
Tooth	(1)			
Odontoma	1 (100%)			
Cardiovascular System				
Heart	(50)	(50)	(50)	(51)
Endocrine System				
Adrenal gland, cortex	(50)	(49)	(50)	(49)
Adenoma				2 (4%)
Adrenal gland, medulla	(49)	(48)	(49)	(49)
Ganglioneuroma			1 (2%)	
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%)	10 (21%)	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				
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		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%)
Interstitial cell, adenoma	4 (8%)	5 (10%)	2 (4%)	6 (12%)

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				1 (2%)
Lymph node, mesenteric	(50)	(50)	(49)	(50)
Spleen	(50)	(50)	(48)	(51)
Thymus	(40)	(42)	(41)	(43)
Schwannoma malignant, metastatic, uncertain primary site		1 (2%)		
Thymoma benign	1 (3%)			1 (2%)
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%)			
Subcutaneous tissue, fibrosarcoma		2 (4%)		1 (2%)
Subcutaneous tissue, lipoma		1 (2%)		
Musculoskeletal System				
Bone	(50)	(50)	(50)	(51)
Osteosarcoma			1 (2%)	
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%)		
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				1 (2%)
Mediastinum, schwannoma malignant		1 (2%)		
Nose	(50)	(50)	(50)	(51)
Carcinoma, metastatic, harderian gland				1 (2%)
Squamous cell papilloma		1 (2%)		
Nasopharyngeal duct, squamous cell carcinoma	1 (2%)			
Special Senses System				
Harderian gland				(1)
Carcinoma				1 (100%)
Zymbal's gland		(2)		
Carcinoma		2 (100%)		
Urinary System				
Kidney	(50)	(50)	(50)	(49)
Sarcoma	1 (2%)			
Renal tubule, adenoma	1 (2%)			
Urinary bladder	(48)	(49)	(49)	(48)
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[c]				
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				
15-Month interim evaluation	2			
2-Year study	38	32	24	16

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
Neoplasm Summary (continued)				
Total animals with metastatic neoplasms				
2-Year study	1	4		6
Total metastatic neoplasms				
2-Year study	2	7		7
Total animals with malignant neoplasms of uncertain primary site				
2-Year study	1	1		

[a] 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

Number of Days on Study	4 5 7	4 7 6	6 0 1	6 1 0	6 1 3	6 2 7	6 3 5	6 4 1	6 4 7	6 6 1	6 7 1	6 7 2	6 8 4	6 9 1	6 9 2	6 9 2	6 9 2	7 0 8	7 1 0	7 1 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6
Carcass ID Number	0 0 5 6	0 0 5 7	0 0 5 2	0 0 4 4	0 0 3 4	0 0 5 5	0 0 0 3	0 0 0 4	0 0 0 6	0 0 2 6	0 0 3 3	0 0 2 4	0 0 4 9	0 0 4 0	0 0 2 5	0 0 2 9	0 0 6 0	0 0 1 7	0 0 5 5	0 0 1 2	0 0 1 8	0 0 2 0	0 0 2 8	0 0 3 1	0 0 3 2
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, uncertain primary site																									
Intestine large	+	+	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	A	A	A	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	A	+	A	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	A	A	A	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	A	A	A	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, uncertain primary site																									
Hepatocellular carcinoma																						X			
Hepatocellular adenoma																									
Mesentery						+																			
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinus, adenoma																							X		
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Stomach, glandular	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue												+													
Squamous cell papilloma												X													
Tooth																		+							
Odontoma																		X							
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																									
Pheochromocytoma benign						X											X							X	
Bilateral, pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma		X					X									X					X				
Adenoma, multiple					X																				
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M

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

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

Number of Days on Study	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	
Carcass ID Number	0 3 5	0 3 6	0 3 7	0 3 8	0 3 9	0 4 3	0 4 6	0 5 3	0 5 4	0 0 1	0 0 2	0 1 1	0 1 4	0 1 6	0 1 9	0 2 1	0 2 2	0 3 0	0 4 2	0 4 5	0 4 7	0 5 0	0 5 7	0 5 8	0 5 9	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, metastatic, uncertain primary site										X																1
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, uncertain primary site										X																1
Hepatocellular carcinoma																										1
Hepatocellular adenoma									X											X						2
Mesentery	+	+				+			+								+	+				+		+		9
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Acinus, adenoma																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma								X																		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						X																	2
Pheochromocytoma benign								X				X		X			X		X			X		X		10
Bilateral, pheochromocytoma benign																							X			1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma								X						X												6
Adenoma, multiple																										1
Parathyroid gland	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	45

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

Number of Days on Study	4 5 7	4 7 6	6 0 1	6 1 0	6 1 3	6 2 7	6 3 5	6 4 1	6 4 7	6 6 1	6 7 1	6 7 2	6 8 4	6 9 1	6 9 2	6 9 2	6 9 2	7 0 8	7 1 0	7 1 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6
Carcass ID Number	0 5 6	0 0 7	0 5 2	0 4 4	0 3 4	0 0 5	0 0 3	0 0 4	0 0 6	0 2 6	0 3 3	0 2 4	0 4 9	0 4 0	0 2 5	0 2 9	0 6 0	0 1 7	0 5 5	0 1 2	0 1 8	0 2 0	0 2 8	0 3 1	0 3 2
Endocrine System (continued)																									
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma						X											X		X						X
Thyroid gland	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma											X			X											
Follicular cell, adenoma							X										X								
General Body System																									
Tissue NOS																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma	X		X	X			X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X
Interstitial cell, adenoma		X			X	X									X										
Hematopoietic System																									
Blood									+	+	+	+			+		+				+	+			
Bone marrow	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	M	+	+	M	+	+
Thymoma benign																								X	
Integumentary System																									
Mammary gland	+	M	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M
Fibroadenoma														X									X		
Fibroadenoma, multiple																						X			
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma							X																		
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, fibroma, multiple																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord			+																						

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

Number of Days on Study	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	
Carcass ID Number	0 3 5	0 3 6	0 3 7	0 3 8	0 3 9	0 4 3	0 4 6	0 5 3	0 5 4	0 0 1	0 0 2	0 1 1	0 1 4	0 1 6	0 1 9	0 2 1	0 2 2	0 3 0	0 4 2	0 4 5	0 4 7	0 5 0	0 5 7	0 5 8	0 5 9	Total Tissues/ Tumors
Endocrine System (continued)																										
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma						X						X	X													7
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	48
C-cell, adenoma															X				X							4
Follicular cell, adenoma																										2
General Body System																										
Tissue NOS																				+						1
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma		X	X		X		X		X							X			X							7
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	46
Interstitial cell, adenoma																										4
Hematopoietic System																										
Blood				+				+		+			+						+		+			+		15
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	M	+	+	+	+	+	+	+	M	M	M	+	+	+	+	+	M	+	+	M	+	+	40
Thymoma benign																										1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	M	42
Fibroadenoma					X	X			X															X		6
Fibroadenoma, multiple																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																X										2
Subcutaneous tissue, fibroma											X															1
Subcutaneous tissue, fibroma, multiple																			X							1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spinal cord																										1

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

Number of Days on Study	4 5 7	4 7 6	6 0 1	6 1 0	6 1 3	6 2 7	6 3 5	6 4 1	6 4 7	6 6 1	6 7 1	6 7 2	6 8 4	6 9 1	6 9 2	6 9 2	6 9 2	7 0 8	7 1 0	7 1 5	7 3 6	7 3 6	7 3 6	7 3 6
Carcass ID Number	0 5 6	0 0 7	0 5 2	0 4 4	0 3 4	0 0 5	0 0 3	0 0 4	0 0 6	0 2 6	0 3 3	0 2 4	0 4 9	0 4 0	0 2 5	0 2 9	0 6 0	0 1 7	0 5 5	0 1 2	0 1 8	0 2 0	0 2 8	0 3 1	0 3 2
Respiratory System																								
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																								
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nasopharyngeal duct, squamous cell carcinoma																X								
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																								
Ear													+											
Eye																+								
Urinary System																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma																								
Renal tubule, adenoma																								
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X		X	X	X	X		X	X	X	X	X		X	X		X	X				X	X	X	X

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

Number of Days on Study	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	
Carcass ID Number	0 3 5	0 3 6	0 3 7	0 3 8	0 3 9	0 4 3	0 4 6	0 5 3	0 5 4	0 0 1	0 0 2	0 1 1	0 1 4	0 1 6	0 1 9	0 2 1	0 2 2	0 3 0	0 4 2	0 4 5	0 4 7	0 5 0	0 5 7	0 5 8	0 5 9	Total Tissues/ Tumors
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma															X											1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nasopharyngeal duct, squamous cell carcinoma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																										
Ear																										1
Eye															+											2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma																									X	1
Renal tubule, adenoma																							X			1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	48
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X		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 8	3 9 8	4 8 5	4 9 1	6 0 0	6 1 4	6 1 5	6 1 8	6 2 4	6 3 4	6 3 4	6 7 9	6 8 3	6 9 3	7 0 8	7 1 0	7 2 7	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5
Carcass ID Number	0 6 6	1 0 8	1 0 2	0 9 2	0 8 5	1 1 8	0 7 5	0 9 1	0 6 9	0 7 0	1 2 0	0 9 4	0 9 3	0 8 4	0 7 7	0 8 7	1 0 7	0 6 1	0 6 2	0 6 3	0 6 4	0 6 7	0 7 6	0 7 9	0 8 0
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, skin																							X		
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
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	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma	X																								
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign											X			X			X								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										X			X							X	X	
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
C-cell, adenoma																									
Follicular cell, adenoma																					X				
General Body System																									
Tissue NOS					+																				

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

Number of Days on Study	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	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	7 3 6	7 3 6	
Carcass ID Number	0 8 3	0 8 6	0 9 6	0 9 8	0 9 9	1 0 1	1 0 3	1 0 4	1 0 5	1 1 1	1 1 4	1 1 5	1 1 6	1 1 7	1 1 9	0 7 1	0 7 2	0 7 3	0 7 4	0 9 7	1 0 0	1 0 6	1 1 0	1 1 2	1 1 3	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Fibrous histiocytoma, metastatic, skin																										1
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma, metastatic, skin																										1
Hepatocellular adenoma																										2
Mesentery	+							+													+					8
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Acinus, adenoma					X	X														X						5
Acinus, adenoma, multiple												X									X					2
Pharynx																										1
Palate, squamous cell carcinoma																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma																										1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pheochromocytoma benign									X							X		X		X		X			X	10
Bilateral, pheochromocytoma benign																										2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																								X		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
General Body System																										
Tissue NOS																										1

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

Number of Days on Study	3 8 8	3 9 8	4 8 5	4 9 1	6 0 0	6 1 4	6 1 5	6 1 8	6 2 4	6 3 4	6 3 4	6 7 9	6 8 3	6 9 3	7 0 8	7 1 0	7 2 7	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5
Carcass ID Number	0 6 6	1 0 8	1 0 2	0 9 2	0 8 5	1 1 8	0 7 5	0 9 1	0 6 9	0 7 0	1 2 0	0 9 4	0 9 3	0 8 4	0 8 7	0 7 8	1 0 7	0 6 1	0 6 2	0 6 3	0 6 4	0 6 7	0 7 6	0 7 9	0 8 0
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes																									
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								X	
Bilateral, adenoma													X												
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma				X	X		X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Interstitial cell, adenoma						X					X														
Hematopoietic System																									
Blood											+	+						+			+	+			+
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	M	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	M	+	+	+	M	+	+	+	+	+	M	+	+	+	+	M	M	+	+	+	+	+	+	+	+
Schwannoma malignant, metastatic, uncertain primary site																									
Integumentary System																									
Mammary gland	M	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma																							X		
Keratoacanthoma																									
Squamous cell carcinoma																			X						
Squamous cell papilloma										X										X					
Subcutaneous tissue, fibroma		X					X			X															
Subcutaneous tissue, fibrosarcoma																						X			
Subcutaneous tissue, lipoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, skin																							X		
Rhabdomyosarcoma																X									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant									X																
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, skin																							X		
Mediastinum, schwannoma malignant																									

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

Number of Days on Study	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	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	7 3 6	
Carcass ID Number	0 8 3	0 8 6	0 9 6	0 9 8	0 9 9	1 0 1	1 0 3	1 0 4	1 0 5	1 0 1	1 1 1	1 1 4	1 1 5	1 1 6	1 1 7	1 1 9	0 7 1	0 7 2	0 7 3	0 7 4	0 9 7	1 0 0	1 0 6	1 1 0	1 1 2	1 1 3	Total Tissues/ Tumors
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, testes										X			X													2
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma						X	X						X						X							5
Bilateral, adenoma																										1
Prostate	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Seminal vesicle	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma	X	X	X		X	X	X	X		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	42
Interstitial cell, adenoma				X					X									X								5
Hematopoietic System																										
Blood			+					+			+	+													+	11
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	M	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Schwannoma malignant, metastatic, uncertain primary site																			X							1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	45
Fibroadenoma													X											X		2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma																										1
Keratoacanthoma							X																			1
Squamous cell carcinoma																										1
Squamous cell papilloma																										2
Subcutaneous tissue, fibroma																										3
Subcutaneous tissue, fibrosarcoma							X																			2
Subcutaneous tissue, lipoma																				X						1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma, metastatic, skin																										1
Rhabdomyosarcoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma malignant																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma, metastatic, skin																										1
Mediastinum, schwannoma malignant																			X							1

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

Number of Days on Study	3 8 8	3 9 8	4 8 5	4 9 1	6 0 0	6 1 4	6 1 5	6 1 8	6 2 4	6 3 4	6 3 4	6 7 9	6 8 3	6 9 3	7 0 8	7 1 0	7 2 7	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5
Carcass ID Number	0 6 6	1 0 8	1 0 2	0 9 2	0 8 5	1 1 8	0 7 5	0 9 1	0 6 9	0 7 0	1 2 0	0 9 4	0 9 3	0 8 4	0 7 7	0 8 7	1 0 7	0 6 1	0 6 2	0 6 3	0 6 4	0 6 7	0 7 6	0 7 9	0 8 0
Respiratory System (continued)																										
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																								X		
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																										
Ear							+								+											
Zymbal's gland															+											
Carcinoma															X											
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X		X	X				X	X						X			X	X		X	X
Mesothelioma malignant																										

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

Number of Days on Study	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	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	7 3 6	
Carcass ID Number	0 8 3	0 8 6	0 9 6	0 9 8	0 9 9	1 0 1	1 0 3	1 0 4	1 0 5	1 1 1	1 1 4	1 1 5	1 1 6	1 1 7	1 1 9	0 7 1	0 7 2	0 7 3	0 7 4	0 9 7	1 0 0	1 0 6	1 1 0	1 1 2	1 1 3	Total Tissues/ Tumors
Respiratory System (continued)																										
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear																										2
Zymbal's gland										+																2
Carcinoma										X																2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X		X		X			X			X	X							X		X			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

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

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

Number of Days on Study	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 5	7 5 5	7 3 5	
Carcass ID Number	1 4 4	1 4 8	1 4 9	1 5 0	1 5 1	1 5 2	1 5 3	1 5 7	1 5 8	1 6 0	1 7 4	1 7 5	1 7 6	1 7 8	1 8 0	1 2 6	1 2 7	1 2 8	1 3 0	1 4 1	1 4 5	1 6 5	1 6 1	1 6 4	1 6 7	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Sarcoma																										1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma																										1
Hepatocellular adenoma																										1
Mesentery	+			+			+							+		+							+			10
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Acinus, adenoma								X			X		X			X					X					9
Acinus, adenoma, multiple					X				X						X		X		X							6
Acinus, mixed tumor benign																									X	1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma											X															2
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	49
Ganglioneuroma																										1
Pheochromocytoma benign				X					X	X											X					7
Bilateral, pheochromocytoma benign						X										X								X		3
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma									X					X							X				X	5
Parathyroid gland	+	+	+	+	+	+	+	M	M	M	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	40
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma													X					X								4
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
C-cell, adenoma										X	X									X	X					7
General Body System																										
Tissue NOS																									+	1
Genital System																										
Epididymis	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Preputial gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																						X				4
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	48

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

Number of Days on Study	1 6 5	3 2 9	3 4 0	5 3 1	5 5 4	6 1 0	6 1 3	6 5 5	6 7 2	7 2 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3
Carcass ID Number	1 2 3	1 3 4	1 2 9	1 5 5	1 7 0	1 3 7	1 2 4	1 7 9	1 4 6	1 7 2	1 5 6	1 5 9	1 6 8	1 7 3	1 7 7	1 2 1	1 2 2	1 2 5	1 3 2	1 3 3	1 3 6	1 3 8	1 3 9	1 4 0	1 4 2
Genital System (continued)																									
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma				X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X
Interstitial cell, adenoma															X										
Hematopoietic System																									
Blood								+					+		+							+			
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	M	+	M	+	+	M	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Fibroadenoma													X												
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																				X					
Squamous cell carcinoma																									
Squamous cell papilloma																						X		X	
Subcutaneous tissue, fibroma																X									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma				X																					
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Glioma malignant		X																							
Oligodendroglioma malignant			X																						
Spinal cord				+																					
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear	+																								
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X	X				X	X	X					X	X	X			X

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

Number of Days on Study	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 5 5	7 5 5	7 3 5	
Carcass ID Number	1 4 4	1 4 8	1 4 9	1 5 0	1 5 1	1 5 2	1 5 3	1 5 7	1 5 8	1 6 0	1 7 4	1 7 5	1 7 6	1 7 8	1 8 0	1 2 6	1 2 7	1 2 8	1 3 0	1 4 1	1 4 5	1 6 5	1 6 1	1 6 4	1 6 7	Total Tissues/ Tumors
Genital System (continued)																										
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Bilateral, interstitial cell, adenoma	X	X	X	X	X	X		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	44
Interstitial cell, adenoma															X											2
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	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	M	+	+	+	+	+	+	M	M	+	43
Fibroadenoma																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma										X												X				3
Squamous cell carcinoma						X																				1
Squamous cell papilloma								X												X						4
Subcutaneous tissue, fibroma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma																										1
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Glioma malignant																										1
Oligodendroglioma malignant																										1
Spinal cord																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear			X	X	X			X		X		X			X			X				X				18

TABLE B2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Safflower Oil: 10 mL/kg

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

TABLE B2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Safflower Oil: 10 mL/kg (continued)

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	2 0 5	2 0 7	2 1 6	2 1 7	2 1 9	2 2 0	2 2 1	2 2 2	2 2 3	2 2 6	2 2 9	1 8 1	1 8 2	1 8 3	1 8 5	2 0 8	2 0 9	2 1 0	2 3 3	2 3 4	2 3 5	2 3 6	2 3 7	2 3 8	2 3 9	Total Tissues/ 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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Carcinoma, metastatic, pancreas												X														1
Mesentery													+						+	+				+		7
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Acinus, adenoma	X			X										X								X	X			9
Acinus, adenoma, multiple		X	X		X	X	X		X			X	X				X			X	X			X	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																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																										2
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma malignant																										1
Pheochromocytoma benign	X									X	X															6
Bilateral, pheochromocytoma benign																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																							X			3
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	M	M	M	+	43
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma			X		X								X									X				8
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell, adenoma		X					X																X			4
Follicular cell, adenoma																										1
General Body System																										
None																										

TABLE B2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Safflower Oil: 10 mL/kg (continued)

Number of Days on Study	3 0 2	5 4 7	5 8 2	6 0 7	6 1 3	6 1 7	6 2 7	6 3 3	6 7 2	6 9 1	7 1 5	7 1 8	7 2 2	7 2 4	7 2 6	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	2 0 2	2 1 2	2 2 8	2 1 3	2 0 1	2 1 4	2 3 1	2 3 2	2 3 0	2 1 5	2 4 0	2 9 7	1 1 1	2 0 0	2 8 8	1 8 6	1 8 7	1 9 0	1 9 3	1 9 4	1 9 5	1 9 6	1 9 8	1 9 9	1 0 3	1 0 4
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes																								X		
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	I	+	+	+	+	+	+	+
Adenoma																										
Bilateral, adenoma																							X			
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma		X			X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Interstitial cell, adenoma				X									X													
Hematopoietic System																										
Blood					+																					
Bone marrow	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma							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	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin																										
Mediastinum, sarcoma, metastatic, heart											X															
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, harderian gland	X																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE B2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Safflower Oil: 10 mL/kg (continued)

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	2 0 5	2 0 7	2 1 6	2 1 7	2 1 9	2 2 0	2 2 1	2 2 2	2 2 3	2 2 6	2 2 9	2 1 1	2 8 2	2 8 3	2 8 5	2 0 8	2 0 9	2 1 0	2 3 3	2 3 4	2 3 5	2 3 6	2 3 7	2 3 8	2 3 9	Total Tissues/ Tumors
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	X	X	X	X	X	X	X	X	X		X	X	X	X		X		X	X	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																										
Mammary gland	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	46
Fibroadenoma									X												X					2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Basal cell adenoma																										1
Keratoacanthoma																				X						1
Squamous cell carcinoma																										1
Squamous cell papilloma																										1
Subcutaneous tissue, fibroma																										2
Subcutaneous tissue, fibrosarcoma																							X			1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, skin																							X			1
Mediastinum, sarcoma, metastatic, heart																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Carcinoma, metastatic, harderian gland																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE B2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Safflower Oil: 10 mL/kg (continued)

Number of Days on Study	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	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
	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	9
Carcass ID Number	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	
Special Senses System																											
Ear				+																							
Eye	+																									+	
Harderian gland	+																										
Carcinoma	X																										
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	A	+	+	A	+	+	M	+	+	+	+	+	+	+	+	
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Leukemia mononuclear					X	X				X		X										X					
Mesothelioma malignant																							X				

TABLE B2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Safflower Oil: 10 mL/kg (continued)

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	2 0 5	2 0 7	2 1 6	2 1 7	2 1 9	2 2 0	2 2 1	2 2 2	2 2 3	2 2 6	2 2 9	1 8 1	1 8 2	1 8 3	1 8 5	2 0 8	2 0 9	2 1 0	2 3 3	2 3 4	2 3 5	2 3 6	2 3 7	2 3 8	2 3 9	Total Tissues/ Tumors
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											X											X			7
Mesothelioma malignant																							X		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[a]	11/49 (22%)	12/48 (25%)	10/49 (20%)	7/49 (14%)
Adjusted rate[b]	34.4%	33.8%	25.6%	17.8%
Terminal rate[c]	9/29 (31%)	9/32 (28%)	10/39 (26%)	5/36 (14%)
First incidence (days)	627	634	729 (T)	582
Life table test[d]	P=0.054N	P=0.588	P=0.236N	P=0.112N
Logistic regression test[d]	P=0.096N	P=0.480	P=0.392N	P=0.187N
Cochran-Armitage test[d]	P=0.137N			
Fisher exact test[d]		P=0.477	P=0.500N	P=0.217N
Adrenal Medulla: Benign or Malignant Pheochromocytoma				
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	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%
Terminal 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
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
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%
Terminal 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			
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 Squamous 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
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		P=0.500	P=0.218	P=0.684N
Skin: Squamous Cell Papilloma, Keratoacanthoma, Basal Cell Adenoma, or Squamous 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
Logistic regression test	P=0.493N	P=0.588	P=0.400N	P=0.691N
Cochran-Armitage test	P=0.491N			
Fisher exact test		P=0.500	P=0.500N	P=0.684N
Skin (Subcutaneous Tissue): Fibroma or Fibrosarcoma				
Overall rate	2/50 (4%)	5/50 (10%)	1/50 (2%)	3/51 (6%)
Adjusted rate	6.7%	12.3%	2.5%	7.4%
Terminal rate	2/30 (7%)	2/33 (6%)	1/40 (3%)	2/36 (6%)
First incidence (days)	729 (T)	398	729 (T)	547
Life table test	P=0.501N	P=0.237	P=0.400N	P=0.570
Logistic regression test	P=0.559N	P=0.250	P=0.400N	P=0.507
Cochran-Armitage test	P=0.552N			
Fisher exact test		P=0.218	P=0.500N	P=0.509

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
Logistic 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
Life 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	–
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
Life table test	P<0.001N	P=0.104N	P=0.002N	P<0.001N
Logistic 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
[a] 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
[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. 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.
[e] Not applicable; no neoplasms in animal group
[f] Value of statistic cannot be computed.

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Safflower Oil[a]

	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	1 (100%)			
Fat, necrosis			1 (100%)	
Pancreas	(10)	(10)	(10)	(9)
Acinus, atrophy	9 (90%)	7 (70%)	6 (60%)	6 (67%)
Acinus, fibrosis	1 (10%)			
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%)			
Stomach, glandular	(10)	(10)	(10)	(9)
Mineralization				1 (11%)
Cardiovascular System				
Heart	(10)	(10)	(10)	(9)
Cardiomyopathy	9 (90%)	7 (70%)	6 (60%)	9 (100%)
Endocrine System				
Adrenal gland, medulla	(10)	(10)	(10)	(9)
Hyperplasia				1 (11%)
Islets, pancreatic	(10)	(10)	(10)	(9)
Hyperplasia	1 (10%)			1 (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)

	Untreated Control	2.5 mL/kg	5 mL/kg	10 mL/kg
15-Month Interim Evaluation (continued)				
Endocrine System (continued)				
Pituitary gland	(10)	(10)	(10)	(9)
Pars distalis, cyst	1 (10%)	2 (20%)		1 (11%)
Pars distalis, hyperplasia	2 (20%)	3 (30%)		
Pars nervosa, cyst	1 (10%)			
Thyroid gland	(10)	(10)	(10)	(9)
C-cell, hyperplasia	1 (10%)	1 (10%)		4 (44%)
General Body System				
None				
Genital System				
Preputial gland	(10)	(10)	(10)	(9)
Abscess	3 (30%)			1 (11%)
Hyperplasia	1 (10%)			
Inflammation, chronic active				1 (11%)
Testes	(10)	(10)	(10)	(9)
Interstitial cell, hyperplasia	6 (60%)	6 (60%)	3 (30%)	5 (56%)
Hematopoietic System				
Lymph node	(10)	(10)	(10)	(9)
Mediastinal, angiectasis	1 (10%)			
Mediastinal, pigmentation	1 (10%)			
Renal, angiectasis	1 (10%)			
Renal, infiltration cellular, histiocyte	1 (10%)			
Spleen	(10)	(10)	(10)	(9)
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				
None				

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
15-Month Interim Evaluation (continued)				
Respiratory System				
Lung	(10)	(10)	(10)	(9)
Hemorrhage			1 (10%)	
Infiltration cellular, histiocyte		1 (10%)	2 (20%)	
Nose	(10)	(10)	(10)	(9)
Fungus	2 (20%)	5 (50%)	5 (50%)	2 (22%)
Inflammation, acute	2 (20%)	9 (90%)	10 (100%)	8 (89%)
Respiratory epithelium, hyperplasia		6 (60%)	10 (100%)	2 (22%)
Respiratory epithelium, metaplasia, squamous			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	1 (2%)			
Intestine small, ileum	(45)	(49)	(48)	(47)
Inflammation, chronic active				1 (2%)
Ulcer			1 (2%)	
Intestine small, jejunum	(45)	(48)	(48)	(46)
Mucosa, hyperplasia, diffuse	1 (2%)			
Liver	(50)	(50)	(50)	(51)
Basophilic focus	36 (72%)	33 (66%)	38 (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%)
Hepatodiaphragmatic nodule	3 (6%)	3 (6%)		1 (2%)
Hepatodiaphragmatic nodule, multiple		1 (2%)		
Hyperplasia	4 (8%)	1 (2%)	1 (2%)	1 (2%)
Hyperplasia, focal	1 (2%)			
Mixed cell focus	1 (2%)	2 (4%)	1 (2%)	6 (12%)
Necrosis	4 (8%)	3 (6%)	4 (8%)	4 (8%)
Pigmentation		1 (2%)		
Pigmentation, hemosiderin		1 (2%)		
Thrombosis	3 (6%)			
Centrilobular, degeneration		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)				
Alimentary System (continued)				
Mesentery	(9)	(8)	(10)	(7)
Abscess			1 (10%)	
Inflammation, chronic active		1 (13%)		
Artery, inflammation, chronic active			1 (10%)	
Fat, hemorrhage		1 (13%)		
Fat, inflammation, chronic active	1 (11%)			1 (14%)
Fat, mineralization	1 (11%)	1 (13%)		
Fat, necrosis	8 (89%)	5 (63%)	8 (80%)	6 (86%)
Pancreas	(50)	(50)	(49)	(50)
Acinus, atrophy	39 (78%)	38 (76%)	35 (71%)	37 (74%)
Acinus, hyperplasia	8 (16%)	14 (28%)	29 (59%)	30 (60%)
Artery, inflammation, chronic active	1 (2%)	3 (6%)	1 (2%)	1 (2%)
Vein, angiectasis	1 (2%)			
Salivary glands	(50)	(49)	(50)	(51)
Hyperplasia		2 (4%)		
Inflammation, acute				1 (2%)
Inflammation, chronic		1 (2%)		
Duct, metaplasia, squamous	12 (24%)	11 (22%)	10 (20%)	13 (25%)
Stomach, forestomach	(50)	(50)	(50)	(51)
Hyperkeratosis	11 (22%)	17 (34%)	20 (40%)	24 (47%)
Hyperplasia, basal cell	21 (42%)	17 (34%)	26 (52%)	29 (57%)
Inflammation, chronic			1 (2%)	
Ulcer	3 (6%)	2 (4%)	2 (4%)	4 (8%)
Stomach, glandular	(49)	(50)	(49)	(50)
Erosion	8 (16%)	6 (12%)	1 (2%)	2 (4%)
Hemorrhage				1 (2%)
Hyperplasia			1 (2%)	
Hyperplasia, lymphoid			1 (2%)	
Metaplasia, squamous			1 (2%)	
Mucosa, hyperplasia, diffuse		1 (2%)		
Tongue	(1)			(1)
Hyperkeratosis				1 (100%)
Cardiovascular System				
Heart	(50)	(50)	(50)	(51)
Cardiomyopathy	47 (94%)	49 (98%)	43 (86%)	42 (82%)
Inflammation, chronic				1 (2%)
Mineralization		1 (2%)		
Thrombosis	2 (4%)	3 (6%)		1 (2%)
Atrium, dilatation		1 (2%)	1 (2%)	
Endocrine System				
Adrenal gland, cortex	(50)	(49)	(50)	(49)
Hyperplasia	1 (2%)	1 (2%)	4 (8%)	
Inflammation, granulomatous	1 (2%)			
Metaplasia, osseous	1 (2%)			
Necrosis	1 (2%)			
Thrombosis	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)				
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	4 (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	(1)	(1)	(1)	
Abdominal, ectopic tissue		1 (100%)		
Oral, hyperplasia, squamous			1 (100%)	
Genital System				
Preputial gland	(50)	(50)	(49)	(49)
Abscess	2 (4%)	6 (12%)	4 (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%)			
Testes	(50)	(50)	(49)	(51)
Interstitial cell, hyperplasia	2 (4%)	5 (10%)	3 (6%)	6 (12%)
Seminiferous tubule, atrophy	3 (6%)	3 (6%)	1 (2%)	2 (4%)

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)				
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%)		
Mediastinal, hematopoietic cell proliferation	1 (2%)			
Mediastinal, hemorrhage	1 (2%)			
Mediastinal, hyperplasia, lymphoid			1 (2%)	
Mediastinal, infiltration cellular, plasma cell			1 (2%)	
Mediastinal, infiltration cellular, polymorphonuclear			1 (2%)	
Mediastinal, inflammation, acute		1 (2%)		
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%)			
Lymph node, mandibular	(50)	(47)	(48)	(50)
Angiectasis		4 (9%)		
Congestion				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		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%)		
Atrophy	1 (2%)			
Depletion lymphoid	2 (4%)		1 (2%)	1 (2%)
Developmental malformation				1 (2%)
Fibrosis	14 (28%)	4 (8%)		
Hematocyst				1 (2%)
Hematopoietic cell proliferation	2 (4%)	7 (14%)	5 (10%)	3 (6%)
Infarct	3 (6%)		3 (6%)	
Pigmentation	1 (2%)	13 (26%)		2 (4%)
Pigmentation, hemosiderin		1 (2%)		
Lymphoid follicle, atrophy				1 (2%)
Thymus	(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)				
Integumentary System				
Mammary gland	(42)	(45)	(43)	(46)
Galactocele		2 (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%)			
Foot, acanthosis				1 (2%)
Foot, inflammation, chronic active				1 (2%)
Subcutaneous tissue, granuloma			1 (2%)	
Musculoskeletal System				
Skeletal muscle	(50)	(50)	(50)	(51)
Fibrosis	1 (2%)	1 (2%)		
Inflammation, acute				1 (2%)
Abdominal, fibrosis	1 (2%)			
Nervous System				
Brain	(50)	(50)	(50)	(51)
Congestion	1 (2%)			1 (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%)		
Mineralization		1 (2%)		
Alveolar epithelium, hyperplasia	4 (8%)	2 (4%)	3 (6%)	3 (6%)
Alveolus, foreign body		1 (2%)		
Alveolus, infiltration cellular, histiocyte	1 (2%)	1 (2%)		
Alveolus, inflammation, acute	1 (2%)			
Alveolus, pigmentation, focal	1 (2%)			
Bronchiole, metaplasia, squamous			1 (2%)	
Interstitium, inflammation, chronic active		1 (2%)		
Mediastinum, abscess				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%)			
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)			(2)
Inflammation, chronic active				1 (50%)
Cornea, necrosis	1 (50%)			
Lens, cataract	1 (50%)			1 (50%)
Retina, atrophy				1 (50%)
Urinary System				
Kidney	(50)	(50)	(50)	(49)
Cyst	2 (4%)		3 (6%)	
Degeneration, hyaline		1 (2%)		
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%)		

[a] 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 in the 2-Year Gavage Study of Tricaprylin[a]

	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				
Alimentary System				
Liver	(10)	(10)	(10)	(7)
Pancreas	(10)	(10)	(10)	(7)
Acinus, adenoma				1 (14%)
Cardiovascular System				
None				
Endocrine System				
Thyroid gland	(10)	(10)	(10)	(7)
C-cell, adenoma			1 (10%)	
General Body System				
None				
Genital System				
Epididymis	(10)	(10)	(10)	(7)
Testes	(10)	(10)	(10)	(7)
Bilateral, interstitial cell, adenoma	6 (60%)	4 (40%)	7 (70%)	5 (71%)
Interstitial cell, adenoma	3 (30%)	5 (50%)	3 (30%)	1 (14%)
Hematopoietic System				
Lymph node, mesenteric	(10)	(10)	(10)	(7)
Spleen	(10)	(10)	(10)	(7)
Integumentary System				
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
15-Month Interim Evaluation (continued)				
Nervous System				
None				
Respiratory System				
Lung	(10)	(10)	(10)	(7)
Special Senses System				
None				
Urinary System				
None				
Systemic Lesions				
Multiple organs[b]	(10)	(10)	(10)	(7)
Leukemia mononuclear		1 (10%)	1 (10%)	
Mesothelioma malignant	1 (10%)			
2-Year Study				
Alimentary System				
Esophagus	(48)	(48)	(50)	(52)
Intestine large, colon	(47)	(46)	(48)	(44)
Adenocarcinoma				1 (2%)
Polyp adenomatous			1 (2%)	
Intestine large, rectum	(48)	(46)	(48)	(44)
Circumanal gland, adenoma	1 (2%)			
Intestine large, cecum	(47)	(45)	(48)	(42)
Intestine small, duodenum	(49)	(46)	(48)	(42)
Intestine small, jejunum	(46)	(46)	(47)	(40)
Adenocarcinoma		1 (2%)		
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	(8)	(14)	(4)	(5)
Leiomyosarcoma, metastatic, intestine small, ileum			1 (25%)	
Pancreas	(49)	(49)	(49)	(50)
Acinus, adenoma	2 (4%)	5 (10%)	11 (22%)	7 (14%)
Acinus, adenoma, multiple		1 (2%)	2 (4%)	11 (22%)
Pharynx	(1)	(1)		
Palate, squamous cell carcinoma		1 (100%)		
Salivary glands	(50)	(49)	(48)	(51)

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)				
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%)			
Cardiovascular System				
Blood vessel	(1)		(1)	
Leiomyoma			1 (100%)	
Vena cava, chemodectoma benign	1 (100%)			
Heart	(50)	(50)	(49)	(51)
Adenocarcinoma, metastatic, uncertain primary site		1 (2%)		
Schwannoma malignant			1 (2%)	
Endocrine System				
Adrenal cortex	(50)	(49)	(49)	(51)
Adenoma		1 (2%)		
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%)	2 (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				(1)
Genital System				
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%)		
Bilateral, adenoma	1 (2%)	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
2-Year Study (continued)				
Genital System (continued)				
Prostate	(49)	(49)	(49)	(52)
Seminal vesicle	(49)	(50)	(50)	(52)
Leiomyosarcoma, metastatic, intestine small, ileum			1 (2%)	
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			1 (2%)	
Spleen	(49)	(50)	(49)	(51)
Hemangiosarcoma		1 (2%)		
Osteosarcoma, metastatic, bone		1 (2%)		
Thymus	(46)	(45)	(46)	(46)
Integumentary System				
Mammary gland	(44)	(40)	(43)	(44)
Adenoma	1 (2%)		1 (2%)	
Carcinoma			1 (2%)	
Fibroadenoma	5 (11%)	2 (5%)	3 (7%)	2 (5%)
Skin	(49)	(49)	(49)	(52)
Basal cell adenoma	1 (2%)			
Keratoacanthoma	2 (4%)	1 (2%)	3 (6%)	
Schwannoma malignant	1 (2%)			
Squamous cell papilloma	4 (8%)	2 (4%)	2 (4%)	1 (2%)
Trichoepithelioma		1 (2%)		
Pinna, schwannoma malignant		1 (2%)		
Subcutaneous tissue, fibroma	2 (4%)	2 (4%)	3 (6%)	1 (2%)
Subcutaneous tissue, fibroma, multiple			1 (2%)	
Subcutaneous tissue, neurofibroma			1 (2%)	
Subcutaneous tissue, neurofibrosarcoma				1 (2%)
Subcutaneous tissue, sarcoma		2 (4%)		1 (2%)
Subcutaneous tissue, schwannoma malignant			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
2-Year Study (continued)				
Musculoskeletal System				
Bone	(50)	(50)	(50)	(53)
Osteosarcoma		1 (2%)		1 (2%)
Vertebra, chordoma	1 (2%)			
Skeletal muscle	(49)	(50)	(47)	(53)
Leiomyosarcoma, metastatic, intestine small, ileum			1 (2%)	
Sarcoma		1 (2%)		
Nervous System				
Brain	(50)	(50)	(49)	(53)
Respiratory System				
Lung	(50)	(50)	(50)	(51)
Alveolar/bronchiolar adenoma		2 (4%)	2 (4%)	
Carcinoma, metastatic, thyroid gland			1 (2%)	
Carcinosarcoma				1 (2%)
Fibrosarcoma, metastatic, ear	1 (2%)	1 (2%)		
Osteosarcoma, metastatic, bone		1 (2%)		
Mediastinum, leiomyosarcoma, metastatic, intestine small, ileum			1 (2%)	
Nose	(50)	(49)	(50)	(52)
Chondroma			1 (2%)	
Squamous cell carcinoma			1 (2%)	
Special Senses System				
Ear			(1)	
Fibrosarcoma			1 (100%)	
Eye	(1)		(1)	(3)
Harderian gland	(1)			
Zymbal's gland		(1)		
Carcinoma		1 (100%)		
Urinary System				
Kidney	(50)	(50)	(50)	(49)
Carcinoma				1 (2%)
Urinary bladder	(48)	(47)	(48)	(48)
Transitional epithelium, carcinoma		1 (2%)		
Transitional epithelium, papilloma			1 (2%)	
Systemic Lesions				
Multiple organs	(50)	(50)	(50)	(53)
Leukemia mononuclear	23 (46%)	28 (56%)	22 (44%)	9 (17%)
Lymphoma malignant histiocytic			1 (2%)	1 (2%)
Mesothelioma malignant	4 (8%)	2 (4%)	2 (4%)	3 (6%)

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[c]				
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	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	2			
2-Year study	27	12	25	15
Total animals with malignant neoplasms of uncertain primary site				
2-Year study		1		

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

Number of Days on Study	3 3 5 5 5 6 6 6 6 6 6 6 6 6 6 6 7 7 7 7 7 7 7 7 7 0 9 4 7 9 0 2 2 6 7 7 8 8 8 9 9 0 0 0 3 3 3 3 3 3 6 0 1 6 3 4 3 5 3 3 8 2 7 7 1 9 4 5 7 2 6 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 0 0 0 0 0 0 5 4 1 4 2 0 4 1 3 4 0 1 0 1 0 5 2 5 4 3 2 0 0 0 0 6 4 9 2 3 7 8 6 0 7 3 7 1 3 6 8 1 1 5 9 5 2 4 5 8
Alimentary System	
Esophagus	+ + + + + + M + + + + + + + + + + + + + + + + + +
Intestine large, colon	+ + + + + + + + + + + + + + + + + + A + A A + + + +
Mesothelioma malignant, metastatic, testes	X X
Intestine large, rectum	+ + + + + + + + + + + + + + + + + + A + A + + + + +
Circumanal gland, adenoma	
Intestine large, cecum	+ + + + + + + + + + + + + + + + + + A + A A + + + +
Intestine small, duodenum	+ A + + + + +
Mesothelioma malignant, metastatic, testes	X
Intestine small, jejunum	+ + + + + + + + + + + + + + + + A + A + A A + + + +
Intestine small, ileum	+ + + + + + + + + + + + + + + + A + A + A A + + + +
Mesothelioma malignant, metastatic, testes	X X
Liver	+ +
Hepatocellular adenoma	
Mesentery	+ + + + + + + + + + +
Mesothelioma malignant, metastatic, testes	X X X
Pancreas	+ M + +
Mesothelioma malignant, metastatic, testes	X X
Acinus, adenoma	
Pharynx	
Salivary glands	+ +
Stomach, forestomach	+ +
Stomach, glandular	+ +
Mesothelioma malignant, metastatic, testes	X
Tongue	
Squamous cell papilloma	
Cardiovascular System	
Blood vessel	
Vena cava, chemodectoma benign	
Heart	+ +
Endocrine System	
Adrenal cortex	+ +
Adrenal medulla	+ +
Pheochromocytoma malignant	X
Pheochromocytoma complex	X
Pheochromocytoma benign	X X X X
Bilateral, pheochromocytoma benign	

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

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

Number of Days on Study	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	0 1 1	0 1 4	0 1 5	0 2 0	0 2 6	0 2 7	0 2 8	0 3 1	0 3 2	0 3 3	0 3 4	0 3 5	0 3 6	0 3 7	0 3 8	0 4 0	0 4 1	0 4 6	0 4 9	0 5 0	0 5 2	0 5 5	0 5 7	0 5 9	0 6 0	Total Tissues/ Tumors
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, testes																									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	X								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)

Number of Days on Study	3 0 6	3 0 9	5 4 1	5 7 6	5 9 3	6 0 4	6 0 2	6 2 5	6 2 6	6 6 7	6 7 3	6 7 8	6 8 2	6 8 7	6 8 7	6 9 1	6 9 9	7 0 4	7 0 5	7 0 7	7 3 2	7 3 6	7 3 7	7 3 7	7 3 7
Carcass ID Number	0 5 6	0 4 4	0 1 9	0 4 2	0 2 3	0 0 7	0 4 8	0 1 6	0 3 0	0 4 7	0 0 3	0 1 7	0 1 0	0 1 1	0 1 3	0 5 6	0 5 8	0 2 1	0 5 1	0 4 5	0 3 9	0 2 5	0 0 2	0 0 4	0 0 5	0 0 8
Endocrine System (continued)																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Adenoma																					X				X
Carcinoma								X								X									
Parathyroid gland	+	+	+	+	M	+	+	+	+	+	M	+	+	+	M	+	+	+	M	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma					X										X	X		X						X	
Thyroid gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	A	+	+	+	+
C-cell, adenoma																			X					X	
General Body System																									
Tissue NOS																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Mesothelioma malignant, metastatic, testes		X						X															X		
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma			X																		X				
Carcinoma																									
Bilateral, adenoma															X										
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Mesothelioma malignant, metastatic, testes		X																					X		
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+
Mesothelioma malignant, metastatic, testes		X						X															X		
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Bilateral, interstitial cell, adenoma		X				X	X	X		X	X	X		X	X			X	X		X	X	X	X	X
Interstitial cell, adenoma			X	X	X				X				X			X	X								
Hematopoietic System																									
Blood											+	+	+	+					+					+	
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node		+			+	+	+		+	+	+	+	+	+					+			+		+	
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	M	+	+	+	+
Carcinoma, metastatic, islets, pancreatic								X																	
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+
Mesothelioma malignant, metastatic, testes																							X		
Thymus	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+

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

Number of Days on Study	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	0 1 1	0 1 4	0 1 5	0 2 0	0 2 6	0 2 7	0 2 8	0 3 1	0 3 2	0 3 3	0 3 4	0 3 5	0 3 6	0 3 7	0 3 8	0 4 0	0 4 1	0 4 6	0 4 9	0 5 0	0 5 2	0 5 5	0 5 7	0 5 9	0 6 0	Total Tissues/ Tumors
Endocrine System (continued)																										
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma		X																								3
Carcinoma																										2
Parathyroid gland	+	M	M	+	+	M	+	+	+	+	+	+	+	+	M	+	+	M	+	M	+	+	+	+	+	40
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma							X			X								X								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																										1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Mesothelioma malignant, metastatic, testes																										2
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Mesothelioma malignant, metastatic, testes																										3
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Bilateral, interstitial cell, adenoma	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Mesothelioma malignant, metastatic, testes																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	46

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

Number of Days on Study	3	3	5	5	5	6	6	6	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7
	0	9	4	7	9	0	2	2	6	7	7	8	8	8	9	9	0	0	0	3	3	3	3	3
	6	0	1	6	3	4	3	5	3	3	8	2	7	7	1	9	4	5	7	2	6	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	0	0	0	0	0
	5	4	1	4	2	0	4	1	3	4	0	1	0	1	0	5	2	5	4	3	2	0	0	0
	6	4	9	2	3	7	8	6	0	7	3	7	1	3	6	8	1	1	5	9	5	2	4	5
Integumentary System																								
Mammary gland	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	M	+	M	+	+	M	+
Adenoma																	X							
Fibroadenoma																								X
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma																								
Keratoacanthoma																								
Mesothelioma malignant, metastatic, testes		X																				X		
Schwannoma malignant																								
Squamous cell papilloma															X						X			
Subcutaneous tissue, fibroma																						X		
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Vertebra, chordoma																		X						
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Mesothelioma malignant, metastatic, testes		X																						
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord	+																							
Respiratory System																								
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, ear																								
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																								
Eye					+																			
Harderian gland					+																			
Urinary System																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Mesothelioma malignant, metastatic, testes		X																						
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X	X	X		X	X	X	X	X	X					X				X	
Mesothelioma malignant		X						X														X		

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

Number of Days on Study	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	0 1 1	0 1 4	0 1 5	0 2 0	0 2 6	0 2 7	0 2 8	0 3 1	0 3 2	0 3 3	0 3 4	0 3 5	0 3 6	0 3 7	0 3 8	0 4 0	0 4 1	0 4 6	0 4 9	0 5 0	0 5 2	0 5 5	0 5 7	0 5 9	0 6 0	Total Tissues/ Tumors
Integumentary System																										
Mammary gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Adenoma																										1
Fibroadenoma													X						X		X			X		5
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Basal cell adenoma																		X								1
Keratoacanthoma																X							X			2
Mesothelioma malignant, metastatic, testes																										2
Schwannoma malignant	X																									1
Squamous cell papilloma						X			X																	4
Subcutaneous tissue, fibroma			X																							2
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Vertebra, chordoma																										1
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Mesothelioma malignant, metastatic, testes																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spinal cord																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, ear	X																									1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																										1
Harderian gland																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Mesothelioma malignant, metastatic, testes																										1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X	X		X	X		X		X		X	X	X				X					X	X		23
Mesothelioma malignant																X										4

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

Number of Days on Study	1 2 7	3 7 9	3 8 6	3 9 1	5 2 4	5 7 9	5 9 2	5 9 3	6 3 2	6 5 9	6 6 3	6 6 6	6 7 8	6 8 7	6 9 0	6 9 1	7 1 8	7 2 1	7 2 3	7 2 6	7 3 6	7 3 6	7 3 6	7 3 6
Carcass ID Number	1 1 3	0 7 9	0 8 8	1 0 1	0 9 1	1 0 4	0 8 5	1 0 9	0 7 3	0 6 6	1 0 0	0 8 7	1 1 2	0 6 1	0 8 3	0 9 3	0 0 8	1 9 4	0 6 9	1 7 5	1 7 7	1 0 3	1 0 5	1 0 6	1 0 7
Alimentary System																								
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Intestine large, colon	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	A	A	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	A	A	+	A	+	+	+	+
Intestine large, cecum	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	A	A	+	A	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	A	A	+	A	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	A	A	+	A	+	+	+	+
Adenocarcinoma																								
Intestine small, ileum	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	A	A	+	A	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, bone																								
Mesentery				+				+		+	+				+						+		+	+
Mesothelioma malignant, metastatic, testes															X									
Pancreas	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes															X									
Acinus, adenoma																					X			
Acinus, adenoma, multiple																								
Pharynx																								+
Palate, squamous cell carcinoma																								X
Salivary glands	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Cardiovascular System																								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, uncertain primary site														X										
Endocrine System																								
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																						X		
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign										X			X	X		X	X		X		X			
Bilateral, pheochromocytoma benign																								
Islets, pancreatic	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Adenoma									X										X					
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	A	+	+	+	M
Pituitary gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Pars distalis, adenoma					X								X											X
Thyroid gland	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	A	+	+	A	+	+	+	M
C-cell, adenoma													X	X		X							X	
Follicular cell, adenoma																								
General Body System																								
None																								

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	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	1 1 0	0 6 3	0 6 4	0 6 5	0 6 7	0 6 8	0 7 0	0 7 2	0 7 4	0 7 8	0 8 0	0 8 1	0 8 2	0 8 6	0 8 9	0 9 0	0 9 5	0 9 6	0 9 7	0 9 9	1 1 4	1 1 5	1 1 6	1 1 7	1 2 0	Total Tissues/ Tumors
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma, metastatic, bone													X													1
Mesentery			+															+			+	+		+	+	14
Mesothelioma malignant, metastatic, testes																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Mesothelioma malignant, metastatic, testes																										1
Acinus, adenoma															X						X		X		X	5
Acinus, adenoma, multiple			X																							1
Pharynx																										1
Palate, squamous cell carcinoma																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, metastatic, uncertain primary site																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	49
Adenoma																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma benign		X				X																				9
Bilateral, pheochromocytoma benign								X						X												2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma																										2
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Pituitary gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Pars distalis, adenoma							X						X								X	X		X		8
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
C-cell, adenoma	X																	X			X					7
Follicular cell, adenoma																							X			1
General Body System																										
None																										

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	1 2 7	3 7 9	3 8 6	3 9 1	5 2 4	5 7 9	5 9 2	5 9 3	6 3 2	6 5 9	6 6 3	6 6 6	6 7 8	6 8 7	6 9 0	6 9 1	7 1 8	7 2 1	7 2 3	7 2 6	7 3 6	7 3 6	7 3 6	7 3 6
Carcass ID Number	1 1 3	0 7 9	0 8 8	1 0 1	0 9 1	1 0 4	0 8 5	1 0 9	0 7 3	0 6 6	1 0 0	0 8 7	1 1 2	0 6 1	0 8 3	0 9 3	1 0 8	0 9 4	0 6 9	0 7 5	0 7 7	1 0 3	1 0 5	1 0 6	1 0 7
Genital System																								
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes								X							X									
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Adenoma																		X						
Carcinoma														X										
Bilateral, adenoma																								
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes															X									
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma					X	X		X		X	X	X	X	X	X		X	X	X	X	X	X	X	X
Interstitial cell, adenoma									X								X							
Hematopoietic System																								
Blood						+					+	+									+			
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Lymph node		+			+	+	+	+			+	+		+		+	+			+	+	+		+	+
Mediastinal, osteosarcoma, metastatic, bone																								
Lymph node, mandibular	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, ear																								
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma													X											
Osteosarcoma, metastatic, bone																								
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+
Integumentary System																								
Mammary gland	+	M	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	M	M	+	+	M	+	+
Fibroadenoma																								
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																							X	
Squamous cell papilloma														X										
Trichoepithelioma																								
Pinna, schwannoma malignant																								
Subcutaneous tissue, fibroma																							X	
Subcutaneous tissue, sarcoma			X						X															
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma																								
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma																								
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

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	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	1 1 0	0 1 6	0 1 3	0 1 4	0 1 5	0 1 7	0 1 8	0 2 0	0 2 2	0 2 4	0 2 8	0 3 0	0 3 1	0 3 2	0 3 6	0 3 9	0 4 0	0 4 5	0 4 6	0 4 7	0 4 9	0 5 4	1 5 5	1 5 6	1 5 7	1 6 0	Total Tissues/ Tumors
Genital System																											
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, testes																											2
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma							X					X					X										4
Carcinoma																											1
Bilateral, adenoma											X																1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, testes																											1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X			X	40
Interstitial cell, adenoma							X																		X		4
Hematopoietic System																											
Blood		+				+	+				+		+										+		+		11
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node		+				+	+	+					+	+	+	+								+	+		25
Mediastinal, osteosarcoma, metastatic, bone														X													1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	46
Fibrosarcoma, metastatic, ear								X																			1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																											1
Osteosarcoma, metastatic, bone														X													1
Thymus	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	M	+	+	+	+		45
Integumentary System																											
Mammary gland	M	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	40
Fibroadenoma											X									X							2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	49
Keratoacanthoma																											1
Squamous cell papilloma																		X									2
Trichoepithelioma													X														1
Pinna, schwannoma malignant									X																		1
Subcutaneous tissue, fibroma																	X										2
Subcutaneous tissue, sarcoma																											2
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma														X													1
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma							X																				1
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

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	1 2 7	3 7 9	3 8 6	3 9 1	5 2 4	5 7 9	5 9 2	5 9 3	6 3 2	6 5 9	6 6 3	6 6 6	6 7 8	6 8 7	6 9 0	6 9 1	7 1 8	7 2 1	7 2 3	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6
Carcass ID Number	1 1 3	0 7 9	0 8 8	1 0 1	0 9 1	1 0 4	0 8 5	1 0 9	0 7 3	0 6 6	1 0 0	0 8 7	1 1 2	0 6 1	0 8 3	0 9 3	0 9 8	1 0 4	0 6 9	0 7 5	0 7 7	1 0 3	1 0 5	1 0 6	1 0 7
Respiratory System																								
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																	X				X			
Fibrosarcoma, metastatic, ear																								
Osteosarcoma, metastatic, bone																								
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Special Senses System																								
Zymbal's gland					+																			
Carcinoma					X																			
Urinary System																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	A	A	+	+	+	+	+	+
Transitional epithelium, carcinoma				X																				
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X	X	X				X	X			X	X			X	X	X		X	X
Mesothelioma malignant								X							X									

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	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	1 1 0	0 6 3	0 6 4	0 6 5	0 6 7	0 6 8	0 7 0	0 7 2	0 7 4	0 7 8	0 8 0	0 8 1	0 8 2	0 8 6	0 8 9	0 9 0	0 9 5	0 9 6	0 9 7	0 9 9	1 1 4	1 1 5	1 1 6	1 1 7	1 2 0	Total Tissues/ 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																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X	X		X		X	X	X	X	X	X	X				X	X	X		X		X		X		28
Mesothelioma malignant																										2

TABLE C2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Tricaprylin: 5 mL/kg

Number of Days on Study	0 8 3	4 5 4	4 5 7	5 1 8	5 8 7	5 8 7	5 9 7	6 0 1	6 0 8	6 2 3	6 2 8	6 7 0	6 7 8	6 8 6	6 8 7	6 8 7	6 8 8	6 9 1	7 2 9	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4
Carcass ID Number	1 5 8	1 7 8	1 3 7	1 6 1	1 5 2	1 7 3	1 3 8	1 4 4	1 6 7	1 6 8	1 4 8	1 7 1	1 6 0	1 2 2	1 2 7	1 7 7	1 5 1	1 7 4	1 3 5	1 3 4	1 3 1	1 3 3	1 3 6	1 3 9	1 4 0
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes																	X								
Polyp adenomatous								X																	
Intestine large, rectum	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes																	X								
Intestine small, duodenum	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes																	X								
Intestine small, jejunum	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes																	X								
Intestine small, ileum	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma									X																
Mesothelioma malignant, metastatic, testes																	X								
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Mesothelioma malignant, metastatic, testes																	X								
Mesentery									+								+								
Leiomyosarcoma, metastatic, intestine small, ileum									X																
Mesothelioma malignant, metastatic, testes																	X								
Pancreas	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes																	X								
Acinus, adenoma				X		X															X	X			
Acinus, adenoma, multiple																							X		
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma										X															
Stomach, glandular	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes																	X								
Tongue																									+
Tooth				+																					
Cardiovascular System																									
Blood vessel																									+
Leiomyoma																									X
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant																									

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

Number of Days on Study	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	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	
Carcass ID Number	1 5 4	1 6 6	1 6 9	1 2 5	1 2 6	1 2 9	1 3 0	1 4 1	1 4 2	1 4 3	1 4 5	1 5 7	1 6 2	1 6 3	1 6 4	1 6 5	1 7 6	1 2 3	1 4 6	1 4 9	1 5 0	1 7 2	1 7 5	1 7 9	1 8 0	Total Tissues/ Tumors
Alimentary System																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Mesothelioma malignant, metastatic, testes																										1
Polyp adenomatous																										1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Mesothelioma malignant, metastatic, testes																										1
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Mesothelioma malignant, metastatic, testes																										1
Intestine small, jejunum	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Mesothelioma malignant, metastatic, testes																										1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leiomyosarcoma																										1
Mesothelioma malignant, metastatic, testes																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma		X				X													X							3
Mesothelioma malignant, metastatic, testes																										1
Mesentery		+						+																		4
Leiomyosarcoma, metastatic, intestine small, ileum																										1
Mesothelioma malignant, metastatic, testes																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Mesothelioma malignant, metastatic, testes																										1
Acinus, adenoma					X				X	X			X				X					X		X		11
Acinus, adenoma, multiple							X																			2
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell papilloma																			X						X	3
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Mesothelioma malignant, metastatic, testes																										1
Tongue																										1
Tooth																										1
Cardiovascular System																											
Blood vessel																										1
Leiomyoma																										1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	49
Schwannoma malignant									X																	1

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

Number of Days on Study	0 8 3	4 5 4	4 5 7	5 1 8	5 8 7	5 8 7	5 9 7	6 0 1	6 0 8	6 2 3	6 2 8	6 7 0	6 7 8	6 8 6	6 8 7	6 8 7	6 8 8	6 9 8	7 2 1	7 2 9	7 3 4	7 3 4	7 3 4	7 3 4
Carcass ID Number	1 5 8	1 7 8	1 3 7	1 6 1	1 5 2	1 7 3	1 3 8	1 4 4	1 6 7	1 6 8	1 4 8	1 7 1	1 6 0	1 2 2	1 2 7	1 7 7	1 5 1	1 7 4	1 3 5	1 3 4	1 3 1	1 3 3	1 3 6	1 4 9	1 4 0
Endocrine System																								
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																		X						
Pheochromocytoma benign							X						X						X	X				
Bilateral, pheochromocytoma benign																						X		
Islets, pancreatic	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma				X										X										
Thyroid gland	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma									X													X	X	X
C-cell, carcinoma																								
Follicular cell, adenoma																		X						
General Body System																								
None																								
Genital System																								
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma, metastatic, intestine small, ileum									X															
Mesothelioma malignant, metastatic, testes																	X							
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma											X		X				X							
Prostate	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes																	X							
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma, metastatic, intestine small, ileum									X															
Mesothelioma malignant, metastatic, testes																	X							
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma				X	X	X	X		X		X	X	X	X	X	X		X	X	X	X	X	X	X
Interstitial cell, adenoma		X	X					X		X							X							
Hematopoietic System																								
Blood												+				+			+			+		
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node		+		+	+	+		+	+	+		+		+		+	+		+	+		+		
Lumbar, leiomyosarcoma, metastatic, intestine small, ileum									X															
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma, metastatic, intestine small, ileum									X															

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

Number of Days on Study	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	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	
Carcass ID Number	1 5 4	1 6 6	1 6 9	1 2 5	1 2 6	1 2 9	1 3 0	1 4 1	1 4 2	1 4 3	1 4 5	1 5 7	1 6 2	1 6 3	1 6 4	1 6 5	1 7 6	1 2 3	1 4 6	1 4 9	1 5 0	1 7 2	1 7 5	1 7 9	1 8 0	Total Tissues/ Tumors
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma malignant																										1
Pheochromocytoma benign	X				X		X		X							X	X				X			X	X	13
Bilateral, pheochromocytoma benign						X		X																		3
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma			X				X												X							3
Parathyroid gland	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	47
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma							X	X		X																5
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell, adenoma															X				X	X	X					8
C-cell, carcinoma										X																1
Follicular cell, adenoma																										1
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma, metastatic, intestine small, ileum																										1
Mesothelioma malignant, metastatic, testes																									X	2
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma	X					X													X							6
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Mesothelioma malignant, metastatic, testes																										1
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma, metastatic, intestine small, ileum																										1
Mesothelioma malignant, metastatic, testes																										1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma	X	X	X	X	X	X	X	X	X		X	X	X	X	X		X	X	X	X	X	X	X	X	X	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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma, metastatic, intestine small, ileum																										1

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

Number of Days on Study	0 8 3	4 5 4	4 5 7	5 1 8	5 8 7	5 8 7	5 9 7	6 0 1	6 0 8	6 2 3	6 2 8	6 7 0	6 7 8	6 8 6	6 8 7	6 8 7	6 8 8	6 9 1	7 2 9	7 2 4	7 3 4	7 3 4	7 3 4	7 3 4
Carcass ID Number	1 5 8	1 7 8	1 3 7	1 6 1	1 5 2	1 7 3	1 3 8	1 4 4	1 6 7	1 6 8	1 4 8	1 7 1	1 6 0	1 2 2	1 2 7	1 7 7	1 5 1	1 7 4	1 3 5	1 3 4	1 3 1	1 3 3	1 3 6	1 3 9	1 4 0
Hematopoietic System (continued)																									
Spleen	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes																	X								
Thymus	M	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	M	+	M	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma								X																	
Fibroadenoma												X													
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma															X					X			X		
Mesothelioma malignant, metastatic, testes																	X								
Squamous cell papilloma												X											X		
Subcutaneous tissue, fibroma				X														X				X			
Subcutaneous tissue, fibroma, multiple																									
Subcutaneous tissue, neurofibroma																									
Subcutaneous tissue, schwannoma malignant															X										
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma, metastatic, intestine small, ileum									X																
Mesothelioma malignant, metastatic, testes																	X								
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Carcinoma, metastatic, thyroid gland																									
Mediastinum, leiomyosarcoma, metastatic, intestine small, ileum									X																
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Chondroma																	X								
Squamous cell carcinoma			X																						
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																									
Fibrosarcoma																									
Eye																									

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

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

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

Number of Days on Study	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	
	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	
	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	
Carcass ID Number	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	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	7	1	2	3	8	4	7	8	8	1	0	2	7	7	1	4	5	4	1	3	6	9	0	
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Urinary bladder	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Mesothelioma malignant, metastatic, testes																	X									
Transitional epithelium, papilloma																	X									
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Leukemia mononuclear		X			X	X		X		X		X				X			X	X	X	X	X	X		
Lymphoma malignant histiocytic														X												
Mesothelioma malignant																	X									

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

Number of Days on Study	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	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	
Carcass ID Number	1 5 4	1 6 6	1 6 9	1 2 5	1 2 6	1 2 9	1 3 0	1 4 1	1 4 2	1 4 3	1 4 5	1 5 7	1 6 2	1 6 3	1 6 4	1 6 5	1 7 6	1 2 3	1 4 6	1 4 9	1 5 0	1 7 2	1 7 5	1 7 9	1 8 0	Total Tissues/ 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	X	X	X				X						X	X					X	22
Lymphoma malignant histiocytic																											1
Mesothelioma malignant																									X		2

TABLE C2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Tricaprylin: 10 mL/kg

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	4 8 5	5 6 5	5 9 9	6 0 0	6 2 8	6 4 3	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	2 9 6	2 9 7	2 0 0	2 1 6	2 3 5	2 1 8	2 8 5	2 1 3	2 8 6	2 0 9	2 1 0	2 2 8	2 2 4	2 4 0	2 8 1	3 3 2	3 3 0	3 4 4	4 0 2	4 2 2
Alimentary System																												
Esophagus	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	A	+	A	A	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	A	A	+	+	+	A	A
Adenocarcinoma									X																			
Mesothelioma malignant, metastatic, testes																												
Intestine large, rectum	+	A	+	A	A	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	A	A	A	+	+	+	A	A
Intestine large, cecum	+	A	+	A	A	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	A	A	A	+	+	+	A	A
Mesothelioma malignant, metastatic, testes																												
Intestine small, duodenum	+	A	+	A	A	+	+	+	+	+	M	+	+	+	+	+	A	A	+	+	+	A	A	+	M	+	A	A
Intestine small, jejunum	+	A	+	A	A	+	+	+	+	+	M	+	+	+	+	+	A	A	+	+	A	A	A	+	+	+	A	A
Intestine small, ileum	+	A	+	A	A	+	+	+	+	+	M	+	+	+	+	+	A	+	+	+	A	A	A	+	+	+	A	A
Mesothelioma malignant, metastatic, testes																												
Liver	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																												
Mesentery																							+					
Mesothelioma malignant, metastatic, testes																												
Pancreas	+	+	+	M	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Mesothelioma malignant, metastatic, testes																												
Acinus, adenoma																					X							
Acinus, adenoma, multiple																												
Salivary glands	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									X			
Squamous cell papilloma, multiple																												
Stomach, glandular	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Cardiovascular System																												
Heart	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																												
Adrenal cortex	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Pheochromocytoma benign																												X
Bilateral, pheochromocytoma benign																									X			
Islets, pancreatic	+	A	+	M	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Adenoma																												
Parathyroid gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	M	+	+	+	+	+
Pituitary gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Pars distalis, adenoma																												
Pars intermedia, adenoma																												
Thyroid gland	+	A	+	A	M	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	A	A	+	+	+	+	+
C-cell, adenoma																												
Follicular cell, adenoma																												
Follicular cell, carcinoma																												

TABLE C2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Tricaprylin: 10 mL/kg (continued)

Number of Days on Study	7 1 5	7 2 6	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	1 9 1	1 9 8	1 8 8	2 0 2	2 2 9	2 0 3	2 0 5	1 9 2	1 9 3	1 9 4	2 0 6	2 0 7	2 0 8	2 1 1	2 1 5	2 2 1	2 3 3	2 3 3	2 3 6	2 3 9	1 9 5	2 1 7	2 1 9	2 2 0	2 2 1	2 2 7	Total Tissues/ Tumors
Alimentary System																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Intestine large, colon	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Adenocarcinoma																											1
Mesothelioma malignant, metastatic, testes																			X								1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine large, cecum	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Mesothelioma malignant, metastatic, testes																			X								1
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Intestine small, jejunum	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Intestine small, ileum	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Mesothelioma malignant, metastatic, testes																			X								1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Hepatocellular adenoma	X								X					X												X	4
Mesentery					+			+					+						+								5
Mesothelioma malignant, metastatic, testes																			X								1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, testes																			X								1
Acinus, adenoma			X	X				X							X				X				X				7
Acinus, adenoma, multiple	X						X		X	X	X	X	X	X		X				X				X			11
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Squamous cell papilloma			X						X			X	X								X				X	X	8
Squamous cell papilloma, multiple					X	X																					2
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																											
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	51
Endocrine System																											
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Pheochromocytoma benign		X		X	X																	X		X		X	7
Bilateral, pheochromocytoma benign						X	X		X		X		X						X								7
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma									X																		1
Parathyroid gland	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	46
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Pars distalis, adenoma							X		X										X		X						4
Pars intermedia, adenoma																					X						1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
C-cell, adenoma			X															X									2
Follicular cell, adenoma												X															1
Follicular cell, carcinoma										X																	1

TABLE C2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Tricaprylin: 10 mL/kg (continued)

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	4 8 5	4 8 5	5 6 9	5 9 0	6 0 8	6 2 3	6 4 5	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	1 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	4 0 0	4 8 1	3 3 2	3 3 0	3 4 4	0 4 4	2 0 2
General Body System																												
Peritoneum																												
Mesothelioma malignant, metastatic, testes																												
Genital System																												
Epididymis	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes																												
Preputial gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								X				
Prostate	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes																												
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes																												
Testes	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma																		X	X	X		X	X	X	X	X		
Interstitial cell, adenoma						X		X	X					X	X	X	X				X						X	X
Hematopoietic System																												
Blood																												
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node															+	+	+						+			+		
Lymph node, mandibular	+	+	+	A	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Lymph node, mesenteric	+	A	+	M	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes																												
Thymus	+	A	+	A	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+
Integumentary System																												
Mammary gland	M	+	+	M	M	+	M	+	M	+	+	+	M	+	+	M	+	+	M	+	+	+	+	M	+	+	+	+
Fibroadenoma																												
Skin	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																												X
Subcutaneous tissue, fibroma																	X											
Subcutaneous tissue, neurofibrosarcoma																												
Subcutaneous tissue, sarcoma																								X				
Musculoskeletal System																												
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma																							X					
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes																												
Nervous System																												
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Tricaprylin: 10 mL/kg (continued)

Number of Days on Study	7 1 5	7 2 6	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	1 9 1	1 9 8	1 8 8	2 0 2	2 2 9	2 0 3	2 0 5	1 9 2	1 9 3	1 9 4	2 0 6	2 0 7	2 0 8	2 1 1	2 2 5	2 3 1	2 3 3	2 3 6	2 3 9	1 9 5	1 1 7	2 1 9	2 2 0	2 2 1	2 2 7	Total Tissues/ Tumors
General Body System																										
Peritoneum																		+								1
Mesothelioma malignant, metastatic, testes																		X								1
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Mesothelioma malignant, metastatic, testes								X		X								X								3
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Adenoma																			X							2
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Mesothelioma malignant, metastatic, testes																		X								1
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Mesothelioma malignant, metastatic, testes								X										X								2
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Bilateral, interstitial cell, adenoma	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	32
Interstitial cell, adenoma																		X								11
Hematopoietic System																										
Blood		+												+												2
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Lymph node		+		+	+	+								+				+		+				+	+	14
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Mesothelioma malignant, metastatic, testes																		X								1
Thymus	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Fibroadenoma			X		X																					2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Squamous cell papilloma																										1
Subcutaneous tissue, fibroma																										1
Subcutaneous tissue, neurofibrosarcoma		X																								1
Subcutaneous tissue, sarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Osteosarcoma																										1
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Mesothelioma malignant, metastatic, testes																		X								1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53

TABLE C2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Tricaprylin: 10 mL/kg (continued)

Number of Days on Study	2 3 3	2 3 2	2 8 8	2 8 2	2 9 2	3 9 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	4 8 5	4 8 5	5 6 9	5 9 0	6 0 8	6 2 3	6 4 5	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 0 2
Respiratory System																												
Lung	+	+	+	A	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinosarcoma																X												
Mediastinum, mesothelioma malignant, metastatic, testes																												
Nose	+	+	+	A		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	A	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																												
Eye																							+					
Urinary System																												
Kidney	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+
Carcinoma																		X										
Urinary bladder	+	A	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+
Systemic Lesions																												
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																	X								X	X	X	
Lymphoma malignant histiocytic																												
Mesothelioma malignant																												

TABLE C2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Tricaprylin: 10 mL/kg (continued)

Number of Days on Study	7 1 5	7 2 6	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	1 9 1	1 9 8	1 8 8	2 0 2	2 2 9	2 0 3	2 0 5	1 9 2	1 9 3	1 9 4	2 0 6	2 0 7	2 0 8	2 1 1	2 2 5	2 3 1	2 3 3	2 3 6	2 3 9	1 9 5	2 1 7	2 1 9	2 2 0	2 2 1	2 2 7	Total Tissues/ Tumors
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Carcinosarcoma																										1
Mediastinum, mesothelioma malignant, metastatic, testes																		X								1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Special Senses System																										
Eye	+				+																					3
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Leukemia mononuclear		X				X			X					X											X	9
Lymphoma malignant histiocytic																				X						1
Mesothelioma malignant								X		X								X								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
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate[a]	11/50 (22%)	11/49 (22%)	16/49 (33%)	14/51 (27%)
Adjusted rate[b]	31.9%	30.1%	47.8%	53.6%
Terminal rate[c]	8/31 (26%)	5/29 (17%)	13/30 (43%)	11/23 (48%)
First incidence (days)	678	659	597	623
Life table test[d]	P=0.042	P=0.550	P=0.161	P=0.082
Logistic regression test[d]	P=0.019	P=0.543	P=0.127	P=0.044
Cochran-Armitage test[d]	P=0.248			
Fisher exact test[d]		P=0.574	P=0.168	P=0.343
Adrenal Medulla: Pheochromocytoma (Benign, Complex, or Malignant)				
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
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				
Overall rate	1/50 (2%)	0/50 (0%)	3/50 (6%)	4/51 (8%)
Adjusted rate	3.2%	0.0%	9.7%	16.5%
Terminal rate	1/31 (3%)	0/30 (0%)	3/31 (10%)	3/23 (13%)
First incidence (days)	729 (T)	–[e]	729 (T)	715
Life table test	P=0.018	P=0.507N	P=0.304	P=0.106
Logistic regression test	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: Fibroadenoma				
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		P=0.218N	P=0.357N	P=0.195N
Mammary Gland: Fibroadenoma or Adenoma				
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			
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
Mammary Gland: Fibroadenoma, Adenoma, or Carcinoma				
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)
Life table test	P=0.293N	P=0.143N	P=0.510N	P=0.248N
Logistic regression test	P=0.319N	P=0.128N	P=0.521N	P=0.258N
Cochran-Armitage test	P=0.151N			
Fisher exact test		P=0.134N	P=0.500N	P=0.117N
Pancreas: Adenoma				
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 (days)	729 (T)	729 (T)	518	485
Life table test	P<0.001	P=0.129	P=0.003	P<0.001
Logistic regression test	P<0.001	P=0.129	P=0.002	P<0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		P=0.134	P=0.002	P<0.001
Pancreatic Islets: Adenoma				
Overall rate	3/49 (6%)	2/48 (4%)	3/49 (6%)	1/49 (2%)
Adjusted rate	10.0%	5.4%	9.7%	4.3%
Terminal rate	3/30 (10%)	0/30 (0%)	3/31 (10%)	1/23 (4%)
First incidence (days)	729 (T)	632	729 (T)	729 (T)
Life table test	P=0.364N	P=0.497N	P=0.650N	P=0.403N
Logistic regression test	P=0.392N	P=0.520N	P=0.650N	P=0.403N
Cochran-Armitage test	P=0.261N			
Fisher exact test		P=0.510N	P=0.661N	P=0.309N
Pancreatic Islets: Adenoma or Carcinoma				
Overall rate	5/49 (10%)	2/48 (4%)	3/49 (6%)	1/49 (2%)
Adjusted rate	14.6%	5.4%	9.7%	4.3%
Terminal rate	3/30 (10%)	0/30 (0%)	3/31 (10%)	1/23 (4%)
First incidence (days)	625	632	729 (T)	729 (T)
Life table test	P=0.161N	P=0.224N	P=0.355N	P=0.191N
Logistic regression test	P=0.161N	P=0.231N	P=0.365N	P=0.195N
Cochran-Armitage test	P=0.094N			
Fisher exact test		P=0.226N	P=0.357N	P=0.102N
Pituitary Gland (Pars Distalis or Pars Intermedia): Adenoma				
Overall rate	8/50 (16%)	8/47 (17%)	5/49 (10%)	4/51 (8%)
Adjusted rate	21.7%	24.5%	14.3%	17.4%
Terminal rate	4/31 (13%)	6/29 (21%)	3/30 (10%)	4/23 (17%)
First incidence (days)	593	524	518	729 (T)
Life table test	P=0.247N	P=0.558	P=0.310N	P=0.374N
Logistic 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%)
First incidence (days)	541	721	628	608
Life table test	P=0.173N	P=0.417N	P=0.515N	P=0.193N
Logistic regression test	P=0.155N	P=0.415N	P=0.512N	P=0.156N
Cochran-Armitage test	P=0.066N			
Fisher exact test		P=0.394N	P=0.500N	P=0.071N
Preputial Gland: Adenoma or Carcinoma				
Overall rate	8/50 (16%)	6/49 (12%)	6/50 (12%)	2/52 (4%)
Adjusted rate	23.1%	18.7%	16.8%	7.6%
Terminal rate	6/31 (19%)	4/29 (14%)	3/31 (10%)	1/23 (4%)
First incidence (days)	541	687	628	608
Life table test	P=0.108N	P=0.428N	P=0.404N	P=0.132N
Logistic regression test	P=0.092N	P=0.426N	P=0.400N	P=0.109N
Cochran-Armitage test	P=0.034N			
Fisher exact test		P=0.403N	P=0.387N	P=0.040N
Skin: Keratoacanthoma				
Overall rate	2/50 (4%)	1/50 (2%)	3/50 (6%)	0/53 (0%)
Adjusted rate	6.5%	3.3%	9.1%	0.0%
Terminal rate	2/31 (6%)	1/30 (3%)	2/31 (6%)	0/23 (0%)
First incidence (days)	729 (T)	729 (T)	687	–
Life table test	P=0.325N	P=0.512N	P=0.495	P=0.306N
Logistic regression test	P=0.341N	P=0.512N	P=0.484	P=0.306N
Cochran-Armitage test	P=0.227N			
Fisher exact test		P=0.500N	P=0.500	P=0.233N
Skin: Squamous Cell Papilloma				
Overall rate	4/50 (8%)	2/50 (4%)	2/50 (4%)	1/53 (2%)
Adjusted rate	12.2%	5.9%	5.6%	3.8%
Terminal rate	3/31 (10%)	1/30 (3%)	1/31 (3%)	0/23 (0%)
First incidence (days)	691	687	628	674
Life table test	P=0.224N	P=0.353N	P=0.349N	P=0.297N
Logistic regression test	P=0.206N	P=0.347N	P=0.348N	P=0.300N
Cochran-Armitage test	P=0.124N			
Fisher exact test		P=0.339N	P=0.339N	P=0.164N
Skin: Squamous Cell Papilloma, Keratoacanthoma, Trichoepithelioma, or Basal Cell Adenoma				
Overall rate	7/50 (14%)	4/50 (8%)	4/50 (8%)	1/53 (2%)
Adjusted rate	21.6%	12.4%	11.3%	3.8%
Terminal rate	6/31 (19%)	3/30 (10%)	2/31 (6%)	0/23 (0%)
First incidence (days)	691	687	628	674
Life table test	P=0.063N	P=0.280N	P=0.274N	P=0.083N
Logistic regression test	P=0.063N	P=0.265N	P=0.279N	P=0.090N
Cochran-Armitage test	P=0.022N			
Fisher 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 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		P=0.691N	P=0.218	P=0.478N
Skin (Subcutaneous Tissue): Fibroma, Neurofibroma, Neurofibrosarcoma, 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			
Fisher exact test		P=0.339	P=0.218	P=0.528
Stomach (Forestomach): Squamous Cell 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	–	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
Logistic regression test	P=0.071	P=0.071N	–[f]	P=0.934
Cochran-Armitage test	P=0.015N			
Fisher exact test		P=0.059N	P=0.747	P=0.010N

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
Thyroid Gland (C-cell): Adenoma				
Overall rate	6/47 (13%)	7/46 (15%)	8/49 (16%)	2/47 (4%)
Adjusted rate	19.8%	20.7%	24.4%	8.7%
Terminal rate	5/29 (17%)	4/29 (14%)	7/31 (23%)	2/23 (9%)
First incidence (days)	707	678	608	729 (T)
Life table test	P=0.206N	P=0.497	P=0.428	P=0.218N
Logistic regression test	P=0.229N	P=0.457	P=0.397	P=0.227N
Cochran-Armitage test	P=0.102N			
Fisher exact test		P=0.483	P=0.420	P=0.134N
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rate	6/47 (13%)	7/46 (15%)	9/49 (18%)	2/47 (4%)
Adjusted rate	19.8%	20.7%	27.6%	8.7%
Terminal rate	5/29 (17%)	4/29 (14%)	8/31 (26%)	2/23 (9%)
First incidence (days)	707	678	608	729 (T)
Life table test	P=0.227N	P=0.497	P=0.325	P=0.218N
Logistic regression test	P=0.253N	P=0.457	P=0.295	P=0.227N
Cochran-Armitage test	P=0.113N			
Fisher exact test		P=0.483	P=0.319	P=0.134N
All Organs: Mononuclear Cell Leukemia				
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
Logistic regression test	P=0.014N	P=0.171	P=0.522N	P=0.059N
Cochran-Armitage test	P<0.001N			
Fisher exact test		P=0.212	P=0.500N	P=0.001N
All Organs: Malignant Mesothelioma				
Overall rate	4/50 (8%)	2/50 (4%)	2/50 (4%)	3/53 (6%)
Adjusted rate	10.5%	5.0%	6.1%	13.0%
Terminal rate	2/31 (6%)	0/30 (0%)	1/31 (3%)	3/23 (13%)
First incidence (days)	390	593	688	729 (T)
Life table test	P=0.533	P=0.356N	P=0.350N	P=0.641
Logistic regression test	P=0.514N	P=0.290N	P=0.314N	P=0.587N
Cochran-Armitage test	P=0.449N			
Fisher exact test		P=0.339N	P=0.339N	P=0.467N
All Organs: Benign Neoplasms				
Overall rate	48/50 (96%)	45/50 (90%)	49/50 (98%)	43/53 (81%)
Adjusted rate	98.0%	100.0%	100.0%	100.0%
Terminal rate	30/31 (97%)	30/30 (100%)	31/31 (100%)	23/23 (100%)
First incidence (days)	390	524	454	322
Life table test	P=0.041	P=0.457N	P=0.451	P=0.090
Logistic regression test	P=0.048	P=0.396N	P=0.354	P=0.405
Cochran-Armitage test	P=0.011N			
Fisher exact test		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
Logistic regression test	P=0.002N	P=0.269	P=0.237N	P=0.019N
Cochran-Armitage test	P<0.001N			
Fisher exact test		P=0.333	P=0.268N	P=0.001N
All Organs: Benign or Malignant Neoplasms				
Overall rate	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

[a] 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

[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. 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.

[e] Not applicable; no neoplasms in animal group

[f] Value of statistic cannot be computed.

TABLE C4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Tricaprylin[a]

	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				
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		1 (10%)		
Hepatodiaphragmatic nodule	2 (20%)			1 (14%)
Necrosis			1 (10%)	
Mesentery	(1)			(1)
Fat, inflammation, chronic active	1 (100%)			1 (100%)
Pancreas	(10)	(10)	(10)	(7)
Atrophy	1 (10%)			
Inflammation, chronic active		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				
Heart	(10)	(10)	(10)	(7)
Cardiomyopathy	7 (70%)	8 (80%)	10 (100%)	6 (86%)
Endocrine System				
Adrenal cortex	(10)	(10)	(10)	(7)
Vacuolization cytoplasmic		1 (10%)		
Adrenal medulla	(10)	(10)	(10)	(7)
Hyperplasia		2 (20%)		
Islets, pancreatic	(10)	(10)	(10)	(7)
Hyperplasia	1 (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)				
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				
None				
Genital System				
Preputial gland	(9)	(9)	(10)	(6)
Necrosis		1 (11%)		
Prostate	(10)	(10)	(10)	(7)
Hyperplasia		2 (20%)		
Testes	(10)	(10)	(10)	(7)
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%)			
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				
Brain	(10)	(10)	(10)	(7)
Hemorrhage	1 (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)				
Respiratory System				
Lung	(10)	(10)	(10)	(7)
Hemorrhage	1 (10%)			
Infiltration cellular, histiocyte		2 (20%)		2 (29%)
Nose	(10)	(10)	(10)	(7)
Fungus	3 (30%)	1 (10%)	3 (30%)	
Inflammation, acute	3 (30%)	2 (20%)	3 (30%)	
Respiratory epithelium, hyperplasia		1 (10%)	3 (30%)	
Special Senses System				
None				
Urinary System				
Kidney	(10)	(10)	(10)	(7)
Hydronephrosis			1 (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				
Intestine large, colon	(47)	(46)	(48)	(44)
Ulcer			1 (2%)	
Intestine small, duodenum	(49)	(46)	(48)	(42)
Ulcer				1 (2%)
Intestine small, ileum	(46)	(46)	(48)	(42)
Ulcer		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				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%)		3 (6%)
Fibrosis			1 (2%)	1 (2%)
Hepatodiaphragmatic nodule	1 (2%)	5 (10%)	7 (14%)	5 (10%)
Hyperplasia	1 (2%)	5 (10%)	2 (4%)	
Hypertrophy				1 (2%)
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%)		1 (2%)	
Bile duct, hyperplasia	1 (2%)			
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		1 (7%)		
Artery, inflammation, chronic active		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%)		2 (4%)
Stomach, glandular	(50)	(48)	(49)	(50)
Erosion	6 (12%)	3 (6%)	7 (14%)	5 (10%)
Hyperplasia, lymphoid			5 (10%)	
Inflammation, chronic active	2 (4%)	1 (2%)		
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			1 (2%)	
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)

	Untreated Control	2.5 mL/kg	5 mL/kg	10 mL/kg
2-Year Study (continued)				
Endocrine System				
Adrenal cortex	(50)	(49)	(49)	(51)
Hemorrhage	1 (2%)			
Hypertrophy			1 (2%)	1 (2%)
Hypoplasia	1 (2%)			
Vacuolization cytoplasmic, diffuse				1 (2%)
Adrenal medulla	(50)	(49)	(49)	(51)
Hyperplasia	22 (44%)	18 (37%)	22 (45%)	18 (35%)
Islets, pancreatic	(49)	(48)	(49)	(49)
Hyperplasia	6 (12%)	5 (10%)	3 (6%)	1 (2%)
Parathyroid gland	(40)	(47)	(47)	(46)
Cyst				1 (2%)
Hyperplasia		1 (2%)		1 (2%)
Pituitary gland	(50)	(47)	(49)	(51)
Pars distalis, angiectasis	3 (6%)	1 (2%)	3 (6%)	2 (4%)
Pars distalis, congestion		1 (2%)		
Pars distalis, cyst	2 (4%)		2 (4%)	4 (8%)
Pars distalis, hyperplasia	9 (18%)	8 (17%)	10 (20%)	6 (12%)
Pars distalis, vacuolization cytoplasmic			1 (2%)	
Pars intermedia, cyst			1 (2%)	
Pars intermedia, hyperplasia			1 (2%)	
Thyroid gland	(47)	(46)	(49)	(47)
Fibrosis		1 (2%)		
C-cell, hyperplasia	7 (15%)	4 (9%)	9 (18%)	2 (4%)
Follicle, cyst	1 (2%)			
Follicular cell, hyperplasia		2 (4%)		
General Body System				
None				
Genital System				
Preputial gland	(50)	(49)	(50)	(52)
Abscess	3 (6%)	4 (8%)	6 (12%)	3 (6%)
Cyst				1 (2%)
Dilatation		2 (4%)	1 (2%)	2 (4%)
Hyperplasia		1 (2%)		
Inflammation, acute		1 (2%)		
Inflammation, chronic active	2 (4%)		1 (2%)	
Prostate	(49)	(49)	(49)	(52)
Hyperplasia	3 (6%)	7 (14%)	6 (12%)	7 (13%)
Inflammation, acute	1 (2%)	1 (2%)		
Inflammation, chronic active	1 (2%)	1 (2%)		
Seminal vesicle	(49)	(50)	(50)	(52)
Concretion		1 (2%)		
Hyperplasia		1 (2%)		
Inflammation, acute	1 (2%)			
Testes	(49)	(50)	(50)	(52)
Interstitial cell, hyperplasia	4 (8%)	5 (10%)	5 (10%)	8 (15%)
Seminiferous tubule, atrophy	5 (10%)	4 (8%)	1 (2%)	3 (6%)
Seminiferous tubule, giant cell				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				
Lymph node	(24)	(25)	(24)	(14)
Lymphatic, ectasia		1 (4%)		
Mediastinal, angiectasis	2 (8%)	2 (8%)	3 (13%)	7 (50%)
Mediastinal, congestion		1 (4%)		
Mediastinal, ectasia			5 (21%)	
Mediastinal, hyperplasia		1 (4%)		
Mediastinal, hyperplasia, lymphoid		1 (4%)		
Mediastinal, infiltration cellular, mast cell	1 (4%)		2 (8%)	
Mediastinal, infiltration cellular, histiocyte		2 (8%)		
Mediastinal, pigmentation	3 (13%)	2 (8%)	2 (8%)	1 (7%)
Mediastinal, lymphatic, ectasia		1 (4%)		
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%)			
Pancreatic, pigmentation			1 (4%)	
Pancreatic, lymphatic, ectasia	1 (4%)	2 (8%)		
Renal, pigmentation			1 (4%)	
Lymph node, mandibular	(49)	(46)	(49)	(50)
Angiectasis	1 (2%)			
Ectasia	1 (2%)		2 (4%)	
Hyperplasia, lymphoid			2 (4%)	
Infiltration cellular, plasma cell		2 (4%)		
Infiltration cellular, histiocyte		1 (2%)		
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	(44)	(40)	(43)	(44)
Galactocele				2 (5%)
Hemorrhage, focal	1 (2%)			
Skin	(49)	(49)	(49)	(52)
Cyst				1 (2%)
Cyst epithelial inclusion	1 (2%)	1 (2%)	1 (2%)	
Developmental malformation		1 (2%)		
Hyperkeratosis	2 (4%)			2 (4%)
Inflammation, chronic active		1 (2%)	1 (2%)	
Ulcer		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				
Respiratory System				
Lung	(50)	(50)	(50)	(51)
Congestion	1 (2%)		1 (2%)	
Edema			2 (4%)	2 (4%)
Fungus	1 (2%)			
Hemorrhage	1 (2%)	2 (4%)	1 (2%)	1 (2%)
Infiltration cellular, histiocyte	1 (2%)	4 (8%)	4 (8%)	2 (4%)
Inflammation, acute	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Inflammation, chronic active			1 (2%)	
Alveolar epithelium, hyperplasia			3 (6%)	1 (2%)
Mediastinum, inflammation		1 (2%)		
Pleura, inflammation, chronic active		1 (2%)		
Nose	(50)	(49)	(50)	(52)
Fungus	18 (36%)	6 (12%)	9 (18%)	5 (10%)
Hyperkeratosis			1 (2%)	2 (4%)
Inflammation, acute	21 (42%)	9 (18%)	12 (24%)	5 (10%)
Respiratory epithelium, metaplasia, squamous	9 (18%)		3 (6%)	
Special Senses System				
Eye	(1)		(1)	(3)
Hemorrhage				1 (33%)
Necrosis				2 (67%)
Lens, cataract			1 (100%)	1 (33%)

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 in the 2-Year Gavage Study of Dichloromethane in Corn Oil[a]

	2.5 mL/kg	5 mL/kg	10 mL/kg
Disposition Summary			
Animals initially in study	50	50	50
Early deaths			
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
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%)		
Mesentery	(12)	(10)	(7)
Hemangiosarcoma	1 (8%)		
Sarcoma	1 (8%)		1 (14%)
Pancreas	(50)	(50)	(50)
Histiocytic sarcoma	1 (2%)		
Acinus, adenocarcinoma		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)
Cardiovascular System			
Heart	(50)	(50)	(50)
Alveolar/bronchiolar carcinoma, metastatic, lung		1 (2%)	1 (2%)
Schwannoma malignant	1 (2%)		
Endocrine System			
Adrenal gland, cortex	(49)	(45)	(50)

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%)
Islets, 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			
Genital System			
Epididymis	(49)	(50)	(50)
Preputial gland	(48)	(44)	(50)
Adenoma	6 (13%)		3 (6%)
Bilateral, adenoma	1 (2%)	1 (2%)	
Testes	(50)	(49)	(50)
Histiocytic sarcoma	1 (2%)		
Bilateral, interstitial cell, adenoma	36 (72%)	35 (71%)	36 (72%)
Interstitial cell, adenoma	7 (14%)	7 (14%)	8 (16%)
Hematopoietic System			
Blood	(3)	(3)	
Bone marrow	(50)	(50)	(50)
Histiocytic sarcoma	1 (2%)		
Lymph node	(50)	(50)	(50)
Lymph node, mandibular	(50)	(50)	(47)
Lymph node, mesenteric	(49)	(49)	(48)
Histiocytic sarcoma	1 (2%)		
Spleen	(49)	(50)	(50)
Hemangiosarcoma	1 (2%)		
Histiocytic sarcoma	1 (2%)		
Thymus	(47)	(48)	(44)
Histiocytic sarcoma	1 (2%)		

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			
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			
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		1 (2%)	1 (2%)
Carcinoma, metastatic, kidney		1 (2%)	
Carcinoma, metastatic, thyroid gland		1 (2%)	
Histiocytic sarcoma	1 (2%)		
Histiocytic sarcoma, metastatic, liver			1 (2%)
Osteosarcoma, metastatic, uncertain primary site	1 (2%)		
Sarcoma, metastatic, mesentery			1 (2%)
Sarcoma, metastatic, uncertain primary site	1 (2%)		
Nose	(50)	(50)	(50)
Special Senses System			
Ear	(4)	(3)	
Sarcoma	1 (25%)		
Zymbal's gland		(1)	(2)
Carcinoma		1 (100%)	2 (100%)
Urinary System			
Kidney	(50)	(50)	(50)
Lipoma		1 (2%)	
Liposarcoma		1 (2%)	
Renal tubule, carcinoma		1 (2%)	
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[b]	(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%)
Neoplasm Summary			
Total animals with primary neoplasms[c]	48	47	48
Total primary neoplasms	152	155	179
Total animals with benign neoplasms	48	47	48
Total benign neoplasms	125	124	156
Total animals with malignant neoplasms	23	21	20
Total malignant neoplasms	27	31	23
Total animals with metastatic neoplasms	5	6	5
Total metastatic neoplasm	19	16	12
Total animals with malignant neoplasms of uncertain primary site	2		

[a] 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.
[b] 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[a]

Number of Days on Study	1 3 3 3 4 5 5 5 5 5 6 6 6 6 6 6 6 6 6 6 6 7 7 7 3 0 5 8 8 7 7 9 9 9 0 0 0 1 2 2 3 5 7 7 8 9 0 1 2 2 9 2 5 3 2 8 5 5 8 5 5 5 0 2 6 8 7 1 3 0 9 1 4 2
Carcass ID Number	1 2 1 1 1 1 2 1 1 1 1 1 2 1 1 1 2 1 1 1 1 1 1 1 7 0 8 6 4 4 0 3 7 2 1 1 0 8 1 8 0 1 8 3 6 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
Alimentary System	
Esophagus	+ + + + M + + + + + + + + + + + + + + + + + + +
Intestine large	+ + + + + A + + + + + + + + + + + + + + + A + + A
Intestine large, cecum	+ + + + + A + + + + + + + + + + + + + + + A + + A
Mesothelioma malignant, metastatic, testes	
Intestine large, colon	+ + + + + A + + + + + + + + + + + + + + + A + + A
Mesothelioma malignant, metastatic, testes	
Intestine large, rectum	+ + + + + A + + + + + + + + + + + + + + + A + + A
Intestine small	+ A + + A
Intestine small, duodenum	+ A + + A
Mesothelioma malignant, metastatic, testes	
Intestine small, ileum	+ A + + A
Intestine small, jejunum	+ A + + A
Liver	+ +
Hepatocellular carcinoma	
Hepatocellular adenoma	X X
Hepatocellular adenoma, multiple	
Histiocytic sarcoma	X
Schwannoma malignant, metastatic, heart	X
Mesentery	+ + + + + + + +
Hemangiosarcoma	X
Mesothelioma malignant, metastatic, testes	
Sarcoma	X
Pancreas	+ +
Histiocytic sarcoma	X
Mesothelioma malignant, metastatic, testes	
Acinus, adenoma	X
Acinus, adenoma, multiple	
Pharynx	+
Palate, squamous cell papilloma	X
Salivary glands	+ +
Fibroma	
Stomach	+ +
Stomach, forestomach	+ + + + + M + + + + + + + + + + + + + + + + + +
Mesothelioma malignant, metastatic, testes	
Squamous cell papilloma	X
Stomach, glandular	+ +
Mesothelioma malignant, metastatic, testes	
Tongue	+

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

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

Number of Days on Study	7 2 3	7 2 6	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 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	1 4 4	1 8 3	1 1 1	1 2 3	1 3 1	1 3 2	1 3 3	1 3 1	1 7 2	1 7 3	1 7 2	1 4 3	1 4 1	1 5 2	1 5 3	1 5 4	1 6 2	1 6 3	1 6 4	1 9 1	1 9 2	1 9 3	1 9 4	1 9 5	2 0 2	Total Tissues/ Tumors
Alimentary System																										
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Mesothelioma malignant, metastatic, testes	X																									1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma					X																					1
Hepatocellular adenoma																		X								3
Hepatocellular adenoma, multiple				X											X					X						3
Histiocytic sarcoma																										1
Schwannoma malignant, metastatic, heart																										1
Mesentery	+								+	+			+								+					12
Hemangiosarcoma																										1
Mesothelioma malignant, metastatic, testes	X												X													2
Sarcoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Mesothelioma malignant, metastatic, testes	X												X													2
Acinus, adenoma		X						X	X			X						X					X			7
Acinus, adenoma, multiple					X																				X	2
Pharynx																										1
Palate, squamous cell papilloma																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroma																		X								1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Mesothelioma malignant, metastatic, testes	X																									1
Squamous cell papilloma									X																	2
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, testes	X																									1
Tongue																										1

[a] 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 Corn Oil: 2.5 mL/kg (continued)

Number of Days on Study	1 3 3 3 4 5 5 5 5 5 6 6 6 6 6 6 6 6 6 6 6 7 7 7 3 0 5 8 8 7 7 9 9 9 0 0 0 1 2 2 3 5 7 7 8 9 0 1 2 2 9 2 5 3 2 8 5 5 8 5 5 5 0 2 6 8 7 1 3 0 9 1 4 2
Carcass ID Number	1 2 1 1 1 1 2 1 1 1 1 1 2 1 1 1 2 1 1 1 1 1 1 1 7 0 8 6 4 4 0 3 7 2 1 1 0 8 1 8 0 1 8 3 6 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	
Heart	+ +
Schwannoma malignant	X
Endocrine System	
Adrenal gland	+ + + + M + + + + + + + + + + + + + + + + + + +
Adrenal gland, cortex	+ + + + M + + + + + + + + + + + + + + + + + + +
Adrenal gland, medulla	+ + + + M + + + + + + + + + + + + + + + + + + +
Pheochromocytoma benign	X X X X X X X
Bilateral, pheochromocytoma benign	X
Islets, pancreatic	+ +
Adenoma	X X X X
Parathyroid gland	+ + + M M + + + + M + + M + + + + + + + + M + + +
Pituitary gland	+ +
Pars distalis, adenoma	X X X X X X X X
Thyroid gland	+ + + + M + + + + + + + + + + + + + + + + + + A
C-cell, adenoma	X
Follicular cell, adenoma	
Follicular cell, carcinoma	X X
General Body System	
None	
Genital System	
Epididymis	+ +
Mesothelioma malignant, metastatic, testes	
Preputial gland	+ + + + + + M + + + + + + + + + + + + + + + + +
Adenoma	X X
Bilateral, adenoma	X
Prostate	+ +
Seminal vesicle	+ +
Testes	+ +
Histiocytic sarcoma	X
Bilateral, interstitial cell, adenoma	X X X X X X X X X X X X X X X X X X X X X X X X
Interstitial cell, adenoma	X X X X X
Hematopoietic System	
Blood	
Bone marrow	+ +
Histiocytic sarcoma	X
Lymph node	+ +
Mediastinal, mesothelioma malignant, metastatic, testes	
Lymph node, mandibular	+ +
Lymph node, mesenteric	+ + + + + M + + + + + + + + + + + + + + + + + +
Histiocytic sarcoma	X

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	7 2 3	7 2 6	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 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	1 4 4	1 8 3	1 1 1	1 2 3	1 3 1	1 3 2	1 3 3	1 7 1	1 7 2	1 7 3	1 4 2	1 4 3	1 5 1	1 5 2	1 5 3	1 5 4	1 6 2	1 6 3	1 6 4	1 9 1	1 9 2	1 9 3	1 9 4	1 9 5	2 0 2	Total Tissues/ Tumors
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma malignant																										1
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma benign											X	X							X		X			X		10
Bilateral, pheochromocytoma benign																X						X				3
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma											X															5
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	44
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma		X	X		X	X			X		X	X	X			X							X	X		20
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
C-cell, adenoma			X					X					X			X			X							6
Follicular cell, adenoma															X				X					X		3
Follicular cell, carcinoma																										2
General Body System																										
None																										
Genital System																										
Epididymis	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Mesothelioma malignant, metastatic, testes													X													1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma		X								X					X							X				6
Bilateral, adenoma																										1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Bilateral, interstitial cell, adenoma	X		X	X	X		X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	36
Interstitial cell, adenoma		X				X			X																	7
Hematopoietic System																										
Blood														+						+	+					3
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mediastinal, mesothelioma malignant, metastatic, testes	X																									1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1

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	1 3 3 3 4 5 5 5 5 5 6 6 6 6 6 6 6 6 6 6 7 7 7 3 0 5 8 8 7 7 9 9 9 0 0 0 1 2 2 3 5 7 7 8 9 0 1 2 2 9 2 5 3 2 8 5 5 8 5 5 5 0 2 6 8 7 1 3 0 9 1 4 2
Carcass ID Number	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 7 0 8 6 4 4 0 3 7 2 1 1 0 8 1 8 0 1 8 3 6 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
Hematopoietic System (continued)	
Spleen	+ A
Hemangiosarcoma	X
Histiocytic sarcoma	X
Mesothelioma malignant, metastatic, testes	
Thymus	+ + + + + + + + + + + + M + M + + + + + + + + M +
Histiocytic sarcoma	X
Integumentary System	
Mammary gland	+ M + + M + + + + M M + + + + + + + + + + + + + M
Fibroadenoma	X
Skin	+ +
Basal cell carcinoma	
Squamous cell carcinoma	
Squamous cell papilloma	
Subcutaneous tissue, fibroma	X X
Musculoskeletal System	
Bone	+ +
Skeletal muscle	+
Mesothelioma malignant, metastatic, testes	
Nervous System	
Brain	+ +
Respiratory System	
Lung	+ +
Alveolar/bronchiolar adenoma	X X X
Histiocytic sarcoma	X
Mesothelioma malignant, metastatic, testes	
Osteosarcoma, metastatic, uncertain primary site	
Sarcoma, metastatic, uncertain primary site	X
Nose	+ +
Trachea	+ +
Special Senses System	
Ear	+ +
Sarcoma	X
Eye	
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)

Number of Days on Study	7 2 3	7 2 6	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 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	1 4 4	1 8 3	1 1 1	1 2 3	1 3 1	1 3 2	1 3 3	1 7 1	1 7 2	1 7 3	1 4 2	1 4 3	1 5 1	1 5 2	1 5 3	1 5 4	1 6 2	1 6 3	1 6 4	1 9 1	1 9 2	1 9 3	1 9 4	1 9 5	2 0 2	Total Tissues/ Tumors
Hematopoietic System (continued)																										
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																										1
Histiocytic sarcoma																										1
Mesothelioma malignant, metastatic, testes	X																									1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Histiocytic sarcoma																										1
Integumentary System																										
Mammary gland	M	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Fibroadenoma																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell carcinoma																				X		X				2
Squamous cell carcinoma											X															1
Squamous cell papilloma				X							X															2
Subcutaneous tissue, fibroma													X													3
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	49
Skeletal muscle	+												+													3
Mesothelioma malignant, metastatic, testes	X												X													2
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										3
Histiocytic sarcoma																										1
Mesothelioma malignant, metastatic, testes	X																									1
Osteosarcoma, metastatic, uncertain primary site																							X			1
Sarcoma, metastatic, uncertain primary site																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear																							+		+	4
Sarcoma																										1
Eye																							+			1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Mesothelioma malignant, metastatic, testes	X																									1

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	1 3 2	3 0 9	3 5 2	3 8 5	4 8 3	5 7 2	5 7 8	5 9 5	5 9 5	5 9 8	6 0 5	6 0 5	6 0 5	6 1 0	6 2 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	1 4 5	1 4 1	2 0 3	1 3 5	1 7 4	1 2 5	1 1 4	1 1 5	2 0 1	1 8 5	1 1 3	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
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma												X													
Leukemia mononuclear													X					X	X		X	X			
Mesothelioma malignant																									

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	7 2 3	7 2 6	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 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	1 4 4	1 8 3	1 1 1	1 2 3	1 3 1	1 3 2	1 3 3	1 3 7 1	1 7 7 2	1 7 7 3	1 4 4 2	1 4 4 3	1 4 5 1	1 5 5 2	1 5 5 3	1 5 5 4	1 6 6 2	1 6 6 3	1 6 6 4	1 9 9 1	1 9 9 2	1 9 9 3	1 9 9 4	1 9 9 5	2 0 2	Total Tissues/ Tumors
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Leukemia mononuclear		X	X						X					X						X	X			X	X	13
Mesothelioma malignant	X												X													2

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

Number of Days on Study	1 5 5	3 2 3	3 2 7	4 8 4	5 3 6	5 7 0	5 8 0	5 8 0	5 8 5	6 1 5	6 4 3	6 4 7	6 7 3	6 8 2	6 8 2	6 9 2	7 0 1	7 0 4	7 1 0	7 1 7	7 2 1	7 2 8	7 3 0	7 3 0
Carcass ID Number	2 4 1	2 1 2	2 4 5	3 0 4	2 2 2	2 8 5	2 7 4	2 7 5	2 9 4	2 3 5	2 9 5	2 6 5	2 8 4	2 5 5	2 9 2	2 2 5	2 2 4	2 6 3	3 0 5	2 8 3	2 2 1	2 5 4	2 1 3	2 1 4	2 1 5
Alimentary System																								
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	A	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+
Mesothelioma malignant, metastatic, testes							X																	
Intestine large, rectum	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	A	A	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	A	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	A	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma										X										X				
Mesentery						+	+				+			+									+	
Mesothelioma malignant, metastatic, testes							X																	
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes							X																	
Acinus, adenocarcinoma																	X							
Acinus, adenoma														X	X						X			
Acinus, adenoma, multiple																								
Pharynx												+												
Palate, squamous cell papilloma												X												
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes							X																	
Squamous cell papilloma														X										
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	A	+	+	+	+	+
Mesothelioma malignant, metastatic, testes							X																	
Cardiovascular System																								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung					X																			
Endocrine System																								
Adrenal gland	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+
Adrenal gland, cortex	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+
Adrenal gland, medulla	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+
Pheochromocytoma malignant																					X			
Pheochromocytoma benign					X					X														
Bilateral, pheochromocytoma malignant																								
Bilateral, pheochromocytoma benign																				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)

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	7 3 1	
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 8 2	2 9 1	2 9 3	3 0 1	3 0 2	3 0 3	Total Tissues/ Tumors
Alimentary 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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma									X															X		4
Mesentery	+					+						+		+		+										10
Mesothelioma malignant, metastatic, testes																X										2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, testes																X										2
Acinus, adenocarcinoma																										1
Acinus, adenoma			X													X				X						6
Acinus, adenoma, multiple				X	X	X	X	X		X				X			X		X			X	X	X	X	13
Pharynx																										1
Palate, squamous cell papilloma																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, testes																										1
Squamous cell papilloma				X																						2
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Mesothelioma malignant, metastatic, testes																										1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	45
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	45
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	45
Pheochromocytoma malignant																							X			2
Pheochromocytoma benign	X						X												X							5
Bilateral, pheochromocytoma malignant																									X	1
Bilateral, pheochromocytoma benign				X																				X		3

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)

Number of Days on Study	1 5 5	3 2 3	3 2 7	4 8 4	5 3 6	5 7 0	5 8 0	5 8 0	5 8 5	6 1 5	6 4 3	6 4 7	6 7 3	6 8 2	6 8 2	6 9 2	7 0 1	7 0 4	7 1 0	7 1 7	7 2 1	7 2 8	7 3 0	7 3 0
Carcass ID Number	2 4 1	2 1 2	2 4 5	3 0 4	2 2 2	2 8 5	2 7 4	2 7 5	2 9 4	2 3 5	2 9 5	2 6 5	2 8 4	2 5 5	2 9 2	2 2 5	2 2 4	2 6 3	3 0 5	2 8 3	2 1 1	2 5 4	2 1 3	2 1 4	2 1 5
Endocrine System (continued)																								
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma											X		X											
Adenoma, multiple																				X				
Carcinoma																								
Parathyroid gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Pars distalis, adenoma									X		X	X	X		X						X		X	
Pars distalis, adenoma, multiple								X		X														
Pars intermedia, adenoma												X												
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+
C-cell, adenoma									X														X	
C-cell, carcinoma								X													X			
General Body System																								
None																								
Genital System																								
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes							X																	
Preputial gland	M	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+
Bilateral, adenoma																								
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma						X	X							X		X	X	X	X	X	X	X	X	
Interstitial cell, adenoma				X				X			X		X		X									X
Hematopoietic System																								
Blood										+														
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																								
Mammary gland	M	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	M	+	+
Fibroadenoma															X	X								
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																								
Squamous cell papilloma																								
Subcutaneous tissue, fibroma										X			X			X					X			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)

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	7 3 1	
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 8 2	2 9 1	2 9 3	3 0 1	3 0 2	3 0 3	Total Tissues/ Tumors
Endocrine System (continued)																										
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma		X			X			X							X				X							7
Adenoma, multiple																										1
Carcinoma																						X				1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	M	+	+	+	45
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma			X	X			X		X										X			X	X	X	X	16
Pars distalis, adenoma, multiple																										2
Pars intermedia, adenoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell, adenoma	X				X				X				X								X					7
C-cell, carcinoma																										2
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, testes																X			X							3
Preputial gland	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	44
Bilateral, adenoma						X																				1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	49
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	49
Bilateral, interstitial cell, adenoma	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			35
Interstitial cell, adenoma																									X	7
Hematopoietic System																										
Blood											+				+											3
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Integumentary System																										
Mammary gland	+	+	+	+	+	+	M	+	M	M	M	M	+	+	+	M	+	M	+	+	+	M	+	+	+	36
Fibroadenoma																										2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma																								X		1
Squamous cell papilloma																							X			1
Subcutaneous tissue, fibroma											X		X													7

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)

Number of Days on Study	1 5 5	3 2 3	3 2 7	4 8 4	5 3 6	5 7 0	5 8 0	5 8 0	5 8 5	6 1 5	6 4 5	6 4 3	6 7 7	6 8 3	6 8 2	6 9 2	7 0 2	7 0 1	7 1 4	7 1 0	7 2 7	7 2 1	7 2 8	7 3 0	7 3 0
Carcass ID Number	2 4 1	2 1 2	2 4 5	3 0 4	2 2 2	2 8 5	2 7 4	2 7 5	2 9 4	2 3 5	2 9 5	2 6 5	2 8 4	2 5 5	2 9 2	2 2 5	2 2 4	2 6 3	3 0 5	2 8 3	2 2 1	2 1 4	2 5 3	2 1 4	2 1 5
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle							+																		
Mesothelioma malignant, metastatic, testes							X																		
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant																									
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																					X				
Alveolar/bronchiolar carcinoma					X																				
Carcinoma, metastatic, kidney																									
Carcinoma, metastatic, thyroid gland								X																	
Mesothelioma malignant, metastatic, testes							X																		
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																						+			
Eye						+										+									
Zymbal's gland													+												
Carcinoma													X												
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lipoma																									
Liposarcoma																									
Renal tubule, carcinoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X		X			X	X			X	X	X	X					
Mesothelioma malignant							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)

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	
Carcass ID Number	2 2 1	2 3 1	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 8 2	2 9 1	2 9 3	3 0 1	3 0 2	3 0 3	Total Tissues/ Tumors
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																+									2
Mesothelioma malignant, metastatic, testes																X									2
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma malignant														X				X							2
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																									1
Alveolar/bronchiolar carcinoma																									1
Carcinoma, metastatic, kidney		X																							1
Carcinoma, metastatic, thyroid gland																									1
Mesothelioma malignant, metastatic, testes																									1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																									
Ear								+								+									3
Eye																+									3
Zymbal's gland																									1
Carcinoma																									1
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lipoma											X														1
Liposarcoma																								X	1
Renal tubule, carcinoma		X																							1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear											X			X	X						X		X		14
Mesothelioma malignant																X			X						3

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

Number of Days on Study	1 0 5	2 9 0	5 1 2	5 4 5	5 4 6	5 5 5	5 7 4	5 7 9	6 0 5	6 1 5	6 4 4	6 7 0	6 7 8	6 7 8	6 7 9	6 8 0	7 0 1	7 0 5	7 2 4	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	3 3 5	3 7 5	3 1 2	4 0 5	3 5 5	3 8 5	3 4 5	3 4 4	3 3 4	3 2 5	3 5 4	3 4 1	3 5 3	3 4 3	3 5 3	3 7 4	3 7 1	3 6 1	3 8 1	3 1 1	3 1 3	3 1 4	3 1 5	3 2 1	3 2 2	3 2 3
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes																										
Intestine small	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																			X		X					
Hepatocellular adenoma																				X		X				
Histiocytic sarcoma									X																	
Mesentery																			+							
Mesothelioma malignant, metastatic, testes																										
Sarcoma																			X							
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes																										
Acinus, adenocarcinoma																										
Acinus, adenoma										X	X								X							
Acinus, adenoma, multiple				X	X				X			X			X	X	X	X		X	X	X	X	X	X	X
Pharynx					+															+						
Palate, squamous cell carcinoma					X																					
Palate, squamous cell papilloma																				X						
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes																										
Squamous cell papilloma																										
Stomach, glandular	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes																										
Tongue						+																				
Cardiovascular 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)

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	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 0	7 3 0	7 3 0	
Carcass ID Number	3 2 4	3 2 3	3 3 3	3 4 1	3 4 2	3 5 1	3 5 2	3 6 2	3 6 3	3 6 4	3 6 5	3 7 2	3 7 3	3 8 2	3 8 3	3 8 4	3 9 1	3 9 2	3 9 3	3 9 4	3 9 5	4 0 1	4 0 2	4 0 3	4 0 4	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Mesothelioma malignant, metastatic, testes														X												1
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma																										2
Hepatocellular adenoma			X										X													4
Histiocytic sarcoma																										1
Mesentery						+			+					+		+	+				+					7
Mesothelioma malignant, metastatic, testes														X		X										2
Sarcoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, testes														X												1
Acinus, adenocarcinoma										X										X				X		3
Acinus, adenoma						X		X						X						X						7
Acinus, adenoma, multiple	X	X	X	X	X		X		X	X	X	X	X		X	X	X	X	X		X	X		X	X	34
Pharynx																										2
Palate, squamous cell carcinoma																										1
Palate, squamous cell papilloma																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, testes														X												1
Squamous cell papilloma															X											1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Mesothelioma malignant, metastatic, testes														X												1
Tongue																								+		2
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma, metastatic, lung																										1

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

Number of Days on Study	1 0 5	2 9 0	5 1 2	5 4 5	5 4 6	5 5 5	5 7 4	5 7 9	6 0 5	6 1 5	6 4 4	6 7 0	6 7 8	6 7 8	6 7 9	6 8 0	7 0 1	7 0 5	7 2 4	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	3 3 5	3 7 5	3 1 2	3 0 5	3 5 5	3 8 5	3 4 5	3 4 4	3 3 4	3 2 5	3 5 4	3 3 1	3 4 3	3 5 3	3 7 4	3 7 1	3 6 1	3 8 1	3 1 1	3 1 3	3 1 4	3 1 5	3 2 1	3 2 3
Endocrine System																								
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																								
Pheochromocytoma benign						X																		
Bilateral, pheochromocytoma benign																								
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma												X			X	X					X	X		
Adenoma, multiple																							X	
Carcinoma					X																			
Parathyroid gland	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma				X	X			X	X		X			X				X				X		X
Thyroid gland	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
C-cell, adenoma																			X		X		X	
Follicular cell, adenoma																		X	X					
General Body System																								
None																								
Genital System																								
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
Interstitial cell, adenoma									X					X	X			X				X		
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	M	+	+	+	+	M
Integumentary System																								
Mammary gland	+	M	M	+	+	+	+	M	M	+	+	M	+	M	M	M	+	+	+	M	M	M	+	+
Adenoma																		X						
Fibroadenoma						X																		
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibroma								X		X												X		
Subcutaneous tissue, sarcoma																	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)

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	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 0	7 3 0	
Carcass ID Number	3 2 4	3 3 2	3 3 3	3 4 1	3 4 2	3 5 1	3 5 2	3 6 2	3 6 3	3 6 4	3 6 5	3 7 2	3 7 3	3 8 2	3 8 3	3 8 4	3 9 1	3 9 2	3 9 3	3 9 4	3 9 5	4 0 1	4 0 2	4 0 3	4 0 4	Total Tissues/ Tumors
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant									X																	1
Pheochromocytoma benign		X									X								X		X				X	6
Bilateral, pheochromocytoma benign								X																		1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma		X									X						X	X			X	X				11
Adenoma, multiple																										1
Carcinoma						X																			X	3
Parathyroid gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Pituitary gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma							X	X			X					X			X				X		X	16
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
C-cell, adenoma	X					X		X		X							X		X							9
Follicular cell, adenoma																										2
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, testes														X		X										2
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma										X										X	X					3
Prostate	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma	X	X	X	X	X	X			X	X	X		X	X	X	X	X	X	X	X	X	X		X	X	36
Interstitial cell, adenoma								X				X											X			8
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	47
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Integumentary System																										
Mammary gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	37
Adenoma																										1
Fibroadenoma												X	X	X		X			X							6
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibroma		X																					X			5
Subcutaneous tissue, sarcoma																										1

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

Number of Days on Study	1	2	5	5	5	5	5	5	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	
	0	9	1	4	4	5	7	7	0	1	4	7	7	7	7	8	0	0	2	2	2	2	2	2	
	5	0	2	5	6	5	4	9	5	5	4	0	8	8	9	0	1	5	4	9	9	9	9	9	
Carcass ID Number	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	7	1	0	5	8	4	4	3	2	5	3	4	5	7	7	6	8	1	1	1	1	2	2	
	5	5	2	5	5	5	5	4	4	5	4	1	3	3	4	1	1	1	1	3	4	5	1	2	3
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																+					+				
Alveolar/bronchiolar carcinoma, metastatic, lung																X									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																X									
Histiocytic sarcoma, metastatic, liver									X																
Sarcoma, metastatic, mesentery																			X						
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Zymbal's gland											+														
Carcinoma											X														
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma									X																
Leukemia mononuclear							X		X			X	X							X					
Mesothelioma malignant																									

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

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	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 0	7 3 0	
Carcass ID Number	3 2 4	3 3 2	3 3 3	3 4 1	3 4 2	3 5 1	3 5 2	3 6 2	3 6 3	3 6 4	3 6 5	3 7 2	3 7 3	3 8 2	3 8 3	3 8 4	3 9 1	3 9 2	3 9 3	3 9 4	3 9 5	4 0 1	4 0 2	4 0 3	4 0 4	Total Tissues/ Tumors
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																									2
Alveolar/bronchiolar carcinoma, metastatic, lung																									1
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma						X								X				X			X				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																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																									1
Leukemia mononuclear																									5
Mesothelioma malignant														X		X									2

TABLE D3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Dichloromethane in Corn Oil[a]

	2.5 mL/kg	5 mL/kg	10 mL/kg
Adrenal Medulla: Benign Pheochromocytoma			
Overall rate[b]	13/49 (27%)	8/45 (18%)	7/50 (14%)
Adjusted rate[c]	42.6%	25.4%	21.1%
Terminal rate[d]	7/23 (30%)	5/26 (19%)	6/31 (19%)
First incidence (days)	605	536	555
Life table test[e]	P=0.024N	P=0.106N	P=0.036N
Logistic regression test[e]	P=0.055N	P=0.180N	P=0.069N
Cochran-Armitage test[e]	P=0.074N		
Fisher exact test[e]		P=0.221N	P=0.096N
Adrenal Medulla: Malignant Pheochromocytoma			
Overall rate	0/49 (0%)	3/45 (7%)	1/50 (2%)
Adjusted rate	0.0%	10.8%	3.2%
Terminal rate	0/23 (0%)	2/26 (8%)	1/31 (3%)
First incidence (days)	-[f]	721	729 (T)
Life table test	P=0.378	P=0.146	P=0.560
Logistic regression test	P=0.355	P=0.134	P=0.560
Cochran-Armitage test	P=0.301		
Fisher exact test		P=0.106	P=0.505
Adrenal Medulla: Benign or Malignant Pheochromocytoma			
Overall rate	13/49 (27%)	11/45 (24%)	8/50 (16%)
Adjusted rate	42.6%	34.8%	24.3%
Terminal rate	7/23 (30%)	7/26 (27%)	7/31 (23%)
First incidence (days)	605	536	555
Life table test	P=0.053N	P=0.288N	P=0.059N
Logistic regression test	P=0.114N	P=0.433N	P=0.110N
Cochran-Armitage test	P=0.155N		
Fisher exact test		P=0.503N	P=0.150N
Liver: Hepatocellular Adenoma			
Overall rate	6/50 (12%)	4/50 (8%)	4/50 (8%)
Adjusted rate	22.9%	12.3%	12.9%
Terminal rate	4/23 (17%)	2/28 (7%)	4/31 (13%)
First incidence (days)	680	615	729 (T)
Life table test	P=0.168N	P=0.264N	P=0.215N
Logistic regression test	P=0.225N	P=0.311N	P=0.266N
Cochran-Armitage test	P=0.300N		
Fisher exact test		P=0.370N	P=0.370N
Liver: Hepatocellular Adenoma or Carcinoma			
Overall rate	7/50 (14%)	4/50 (8%)	6/50 (12%)
Adjusted rate	27.0%	12.3%	18.8%
Terminal rate	5/23 (22%)	2/28 (7%)	5/31 (16%)
First incidence (days)	680	615	724
Life table test	P=0.224N	P=0.170N	P=0.296N
Logistic regression test	P=0.294N	P=0.204N	P=0.365N
Cochran-Armitage test	P=0.394N		
Fisher exact test		P=0.262N	P=0.500N

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
Lung: Alveolar/bronchiolar Adenoma			
Overall rate	3/50 (6%)	1/50 (2%)	4/49 (8%)
Adjusted rate	7.8%	3.3%	12.9%
Terminal rate	0/23 (0%)	0/28 (0%)	4/31 (13%)
First incidence (days)	483	721	729 (T)
Life table test	P=0.602N	P=0.277N	P=0.607
Logistic regression test	P=0.530	P=0.318N	P=0.493
Cochran-Armitage test	P=0.523		
Fisher exact test		P=0.309N	P=0.489
Lung: Alveolar/bronchiolar Adenoma or Carcinoma			
Overall rate	3/50 (6%)	2/50 (4%)	5/49 (10%)
Adjusted rate	7.8%	5.4%	15.4%
Terminal rate	0/23 (0%)	0/28 (0%)	4/31 (13%)
First incidence (days)	483	536	680
Life table test	P=0.452	P=0.466N	P=0.468
Logistic regression test	P=0.345	P=0.522N	P=0.349
Cochran-Armitage test	P=0.348		
Fisher exact test		P=0.500N	P=0.346
Mammary Gland: Fibroadenoma			
Overall rate	1/50 (2%)	2/50 (4%)	6/50 (12%)
Adjusted rate	3.4%	5.5%	18.0%
Terminal rate	0/23 (0%)	0/28 (0%)	5/31 (16%)
First incidence (days)	699	682	555
Life table test	P=0.081	P=0.568	P=0.106
Logistic regression test	P=0.054	P=0.516	P=0.070
Cochran-Armitage test	P=0.047		
Fisher exact test		P=0.500	P=0.056
Mammary Gland: Adenoma or Fibroadenoma			
Overall rate	1/50 (2%)	2/50 (4%)	7/50 (14%)
Adjusted rate	3.4%	5.5%	20.5%
Terminal rate	0/23 (0%)	0/28 (0%)	5/31 (16%)
First incidence (days)	699	682	555
Life table test	P=0.049	P=0.568	P=0.068
Logistic regression test	P=0.030	P=0.516	P=0.040
Cochran-Armitage test	P=0.026		
Fisher exact test		P=0.500	P=0.030
Pancreas: 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
Life table test	P<0.001	P=0.068	P<0.001
Logistic regression test	P<0.001	P=0.047	P<0.001
Cochran-Armitage test	P<0.001		
Fisher exact test		P=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%
Terminal rate	0/23 (0%)	0/28 (0%)	3/31 (10%)
First incidence (days)	–	701	729 (T)
Life table test	P=0.121	P=0.539	P=0.177
Logistic regression test	P=0.104	P=0.514	P=0.177
Cochran-Armitage test	P=0.086		
Fisher exact test		P=0.500	P=0.121
Pancreas: 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
Life table test	P<0.001	P=0.048	P<0.001
Logistic regression test	P<0.001	P=0.029	P<0.001
Cochran-Armitage test	P<0.001		
Fisher exact test		P=0.013	P<0.001
Pancreatic Islets: Adenoma			
Overall rate	5/50 (10%)	8/50 (16%)	12/50 (24%)
Adjusted rate	14.3%	24.5%	34.7%
Terminal rate	1/23 (4%)	5/28 (18%)	9/31 (29%)
First incidence (days)	595	643	670
Life table test	P=0.135	P=0.389	P=0.146
Logistic regression test	P=0.065	P=0.296	P=0.070
Cochran-Armitage test	P=0.050		
Fisher exact test		P=0.277	P=0.054
Pancreatic Islets: Carcinoma			
Overall rate	0/50 (0%)	1/50 (2%)	3/50 (6%)
Adjusted rate	0.0%	3.6%	8.5%
Terminal rate	0/23 (0%)	1/28 (4%)	2/31 (6%)
First incidence (days)	–	729 (T)	546
Life table test	P=0.115	P=0.539	P=0.161
Logistic regression test	P=0.088	P=0.539	P=0.121
Cochran-Armitage test	P=0.086		
Fisher exact test		P=0.500	P=0.121
Pancreatic Islets: Adenoma or Carcinoma			
Overall rate	5/50 (10%)	9/50 (18%)	15/50 (30%)
Adjusted rate	14.3%	27.8%	41.9%
Terminal rate	1/23 (4%)	6/28 (21%)	11/31 (35%)
First incidence (days)	595	643	546
Life table test	P=0.047	P=0.301	P=0.051
Logistic regression test	P=0.016	P=0.213	P=0.016
Cochran-Armitage test	P=0.011		
Fisher exact test		P=0.194	P=0.011

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): Adenoma			
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, Keratoacanthoma, or Basal Cell Carcinoma			
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): Fibroma			
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	615	579
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		
Fisher exact test		P=0.159	P=0.357
Skin (Subcutaneous Tissue): Fibroma or Sarcoma			
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	615	579
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		
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%
Terminal rate	23/23 (100%)	27/27 (100%)	30/31 (97%)
First incidence (days)	483	484	512
Life table test	P=0.062N	P=0.148N	P=0.086N
Logistic regression test	P=0.415N	P=0.448N	P=0.504N
Cochran-Armitage test	P=0.476		
Fisher exact test		P=0.597N	P=0.500
Thyroid Gland (C-cell): Adenoma			
Overall rate	6/48 (13%)	7/49 (14%)	9/48 (19%)
Adjusted rate	24.4%	23.3%	28.1%
Terminal rate	5/23 (22%)	6/28 (21%)	8/31 (26%)
First incidence (days)	699	585	724
Life table test	P=0.477	P=0.603N	P=0.517
Logistic regression test	P=0.395	P=0.601	P=0.460
Cochran-Armitage test	P=0.268		
Fisher exact test		P=0.516	P=0.288
Thyroid Gland (C-cell): Adenoma or Carcinoma			
Overall rate	6/48 (13%)	9/49 (18%)	9/48 (19%)
Adjusted rate	24.4%	27.5%	28.1%
Terminal rate	5/23 (22%)	6/28 (21%)	8/31 (26%)
First incidence (days)	699	580	724
Life table test	P=0.440	P=0.414	P=0.517
Logistic regression test	P=0.335	P=0.355	P=0.460
Cochran-Armitage test	P=0.239		
Fisher exact test		P=0.303	P=0.288
Thyroid Gland (Follicular Cell): Adenoma			
Overall rate	3/48 (6%)	0/49 (0%)	2/48 (4%)
Adjusted rate	13.0%	0.0%	6.1%
Terminal rate	3/23 (13%)	0/28 (0%)	0/31 (0%)
First incidence (days)	729 (T)	–	705
Life table test	P=0.229N	P=0.087N	P=0.377N
Logistic regression test	P=0.248N	P=0.087N	P=0.410N
Cochran-Armitage test	P=0.316N		
Fisher exact test		P=0.117N	P=0.500N
Thyroid Gland (Follicular Cell): Adenoma or Carcinoma			
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%)
First incidence (days)	598	–	705
Life table test	P=0.046N	P=0.023N	P=0.143N
Logistic regression test	P=0.061N	P=0.027N	P=0.183N
Cochran-Armitage test	P=0.074N		
Fisher exact test		P=0.027N	P=0.218N

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%
Terminal 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.
[b] 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.
[c] 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.
[f] Not applicable; no neoplasms in animal group

TABLE D4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Dichloromethane in Corn Oil[a]

	2.5 mL/kg	5 mL/kg	10 mL/kg
Disposition Summary			
Animals initially in study	50	50	50
Early deaths			
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
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		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%)		
Hepatodiaphragmatic nodule	6 (12%)	4 (8%)	5 (10%)
Infarct			1 (2%)
Inflammation, chronic active		1 (2%)	
Mixed cell focus	20 (40%)	14 (28%)	19 (38%)
Necrosis	2 (4%)		1 (2%)
Pigmentation	1 (2%)		
Thrombosis	1 (2%)		
Mesentery	(12)	(10)	(7)
Thrombosis	1 (8%)		
Fat, inflammation, chronic active		1 (10%)	
Fat, mineralization		2 (20%)	
Fat, necrosis	9 (75%)	7 (70%)	2 (29%)
Fat, pigmentation	1 (8%)		
Pancreas	(50)	(50)	(50)
Hyperplasia		1 (2%)	
Acinus, atrophy	28 (56%)	26 (52%)	21 (42%)
Acinus, hyperplasia	28 (56%)	38 (76%)	44 (88%)
Artery, fibrosis			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%)

[a] 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)
Hyperkeratosis	1 (2%)		1 (2%)
Hyperplasia, basal cell	7 (14%)	3 (6%)	7 (14%)
Hyperplasia, focal, squamous		1 (2%)	1 (2%)
Inflammation, acute			2 (4%)
Ulcer			6 (12%)
Stomach, glandular	(50)	(48)	(48)
Inflammation, chronic active			1 (2%)
Mineralization	1 (2%)		
Necrosis	1 (2%)	1 (2%)	
Ulcer	1 (2%)		
Tongue	(1)		(2)
Hyperkeratosis	1 (100%)		
Cardiovascular System			
Heart	(50)	(50)	(50)
Cardiomyopathy	38 (76%)	39 (78%)	34 (68%)
Thrombosis			1 (2%)
Endocrine System			
Adrenal gland, cortex	(49)	(45)	(50)
Accessory adrenal cortical nodule	1 (2%)		
Adrenal gland, medulla	(49)	(45)	(50)
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%)		
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%)
Follicular cell, hyperplasia	1 (2%)	2 (4%)	
General Body System			
None			

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%)
Hematopoietic System			
Lymph node	(50)	(50)	(50)
Bronchial, pigmentation			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%)		
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%)		
Infarct		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%)	
Musculoskeletal System			
Skeletal muscle	(3)	(2)	(2)
Necrosis	1 (33%)		
Nervous System			
None			

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%)		
Inflammation, chronic active		3 (6%)	
Metaplasia, squamous			1 (2%)
Alveolar epithelium, hyperplasia		4 (8%)	2 (4%)
Mediastinum, hemorrhage	1 (2%)		
Mediastinum, inflammation, acute			1 (2%)
Mediastinum, pigmentation		1 (2%)	
Nose	(50)	(50)	(50)
Fungus	6 (12%)	4 (8%)	3 (6%)
Inflammation, acute	11 (22%)	6 (12%)	9 (18%)
Respiratory epithelium, hyperkeratosis	1 (2%)		
Respiratory epithelium, hyperplasia	4 (8%)	2 (4%)	4 (8%)
Respiratory epithelium, metaplasia, squamous	3 (6%)		
Trachea	(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%)		
Transitional epithelium, hyperplasia			1 (2%)

APPENDIX E
GENETIC TOXICOLOGY

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 μg/plate, or 5.0 mL in the desiccator, was selected as the high dose (a high dose of 16,666 μg/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 μL/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.

All treatment levels within an experiment, including concurrent positive and solvent controls, were replicated. Treated cultures contained 6×10^6 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, 3×10^6 cells were plated in medium and soft agar supplemented with trifluorothymidine (TFT) for selection of TFT-resistant ($TK^{-/-}$) cells; 600 cells were plated in nonselective medium and soft agar to determine cloning efficiency. Plates were incubated at 37° C in 5% CO_2 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 ($P \leq 0.05$) 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 μg/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 ± 2 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 ($P \leq 0.05$) difference for one dose point and a significant trend ($P \leq 0.015$) were considered weak evidence for a positive response; significant differences for two or more doses indicated the trial was positive. A positive trend test in the absence of a statistically significant increase at any one dose resulted in an equivocal call (Galloway *et al.*, 1987). Ultimately, the trial calls were based on a consideration of the statistical analyses as well as the biological informaion available to the reviewers.

RESULTS

Corn oil and safflower oil (100 to 10,000 μg/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 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, 1990). Using a preincubation protocol that did not control for volatility, dichloromethane (100 to 10,000 μg/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 μg/mL) in the presence or the absence of S9 (Anderson *et al.*, 1990).

TABLE E1a
Mutagenicity of Corn Oil in *Salmonella typhimurium*[a]

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

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

TABLE E1b
Mutagenicity of Safflower Oil in *Salmonella typhimurium*[a]

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

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

TABLE E1c
Mutagenicity of Tricaprylin in *Salmonella typhimurium*[a]

Strain	Dose (μg/plate)	Revertants/plate[b] -S9	+30% hamster S9 Trial 1	+30% hamster S9 Trial 2	+30% hamster S9 Trial 3	+30% rat S9 Trial 1	+30% rat S9 Trial 2	+30% rat S9 Trial 3
TA100	0	144 ± 17.7	137 ± 7.0			193 ± 8.5		
	100	169 ± 5.2	135 ± 4.9			197 ± 4.8		
	333	134 ± 17.0	142 ± 6.2			189 ± 6.5		
	1,000	108 ± 1.9	147 ± 5.7			190 ± 3.8		
	3,333	112 ± 1.0	137 ± 5.0			176 ± 4.5		
	10,000	131 ± 5.2	176 ± 2.2			188 ± 9.5		
Trial summary		Negative	Negative			Negative		
Positive control[c]		955 ± 37.8	837 ± 39.5			440 ± 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 ± 3.4	14 ± 2.0			17 ± 1.2		
	1,000	15 ± 2.6	12 ± 0.9	12 ± 2.9	24 ± 1.2	17 ± 2.3	15 ± 1.5	28 ± 5.1
	3,333	14 ± 1.3	15 ± 0.3	18 ± 1.5	45 ± 4.5	20 ± 2.6	19 ± 1.7	37 ± 1.5
	6,666			50 ± 6.0	42 ± 1.9		37 ± 2.2	39 ± 3.4
	10,000	17 ± 1.8	44 ± 9.1	52 ± 2.8	55 ± 1.9	42 ± 1.5	49 ± 5.5	54 ± 3.8
	16,666			85 ± 2.8	107 ± 10.7		76 ± 2.4	95 ± 3.2
Trial summary		Negative	Equivocal	Positive	Positive	Equivocal	Positive	Positive
Positive control		958 ± 34.3	607 ± 16.8	408 ± 39.8	351 ± 8.9	105 ± 3.6	91 ± 9.1	90 ± 10.5
TA97	0	222 ± 6.9	185 ± 6.9			216 ± 5.3		
	100	228 ± 3.8	198 ± 7.3			205 ± 20.4		
	333	223 ± 6.3	210 ± 7.6			224 ± 11.9		
	1,000	210 ± 2.6	216 ± 1.8			184 ± 6.5		
	3,333	212 ± 7.6	203 ± 21.5			168 ± 3.7		
	10,000	225 ± 4.0	197 ± 19.4			152 ± 10.4		
Trial summary		Negative	Negative			Negative		
Positive control		742 ± 42.2	436 ± 2.2			442 ± 3.5		
TA98	0	30 ± 4.7	35 ± 4.0			38 ± 1.9		
	100	27 ± 1.5	34 ± 2.4			41 ± 0.6		
	333	27 ± 0.9	33 ± 6.7			36 ± 3.8		
	1,000	28 ± 4.6	29 ± 1.7			31 ± 3.7		
	3,333	28 ± 1.5	28 ± 3.4			34 ± 1.7		
	10,000	28 ± 2.0	31 ± 4.3			28 ± 1.5		
Trial summary		Negative	Negative			Negative		
Positive control		677 ± 20.6	770 ± 11.3			168 ± 3.5		

[a] Study performed at SRI, International. The detailed protocol is presented in Zeiger *et al.* (1988).
[b] Revertants are presented as mean ± the standard error from three plates.
[c] The positive controls in the absence of metabolic activation were sodium azide (TA100 and TA1535), 9-aminoacridine (TA97), and 4-nitro-*o*-phenylenediamine (TA98). The positive control for metabolic activation with all strains was 2-aminoanthracene.

TABLE E1d
Mutagenicity of Dichloromethane in *Salmonella typhimurium*[a]

Strain	Dose[c]	Revertants/plate[b] -S9	+S9 30% hamster	+S9 30% rat
Test 1 - Study performed using desiccator protocol				
TA100	0.00	115 ± 4.0	119 ± 11.0	147 ± 7.1
	0.05	111 ± 1.2	178 ± 23.0	148 ± 8.4
	0.10	187 ± 6.1	291 ± 12.7	269 ± 15.8
	0.25	155 ± 27.4	325 ± 9.5	233 ± 18.1
	0.50	384 ± 39.3	668 ± 57.7	495 ± 18.3
	1.00	321 ± 46.3	571 ± 71.0	341 ± 39.0
Trial summary		Positive	Positive	Positive
Positive control[d]		682 ± 18.2	630 ± 56.0	505 ± 6.1
TA98	0.00	17 ± 0.3	28 ± 0.0	25 ± 4.2
	0.01			29 ± 1.2
	0.05	19 ± 2.2	32 ± 6.1	24 ± 1.2
	0.10	40 ± 4.2	45 ± 0.7	29 ± 2.4
	0.25	20 ± 3.3	46 ± 0.3	34 ± 2.1
	0.50	43 ± 3.3	75 ± 3.7	
	1.00	27 ± 4.2	54 ± 5.1	
Trial summary		Equivocal	Positive	Negative
Positive control		638 ± 50.7	263 ± 1.5	190 ± 5.0
Test 1 - Study performed using preincubation protocol				
TA100	0	109 ± 3.8	127 ± 7.5	134 ± 4.7
	100	113 ± 9.3	128 ± 3.2	141 ± 6.8
	333	104 ± 3.5	121 ± 6.1	117 ± 12.7
	1,000	103 ± 12.3	129 ± 11.0	114 ± 5.9
	3,333	109 ± 14.5	139 ± 2.3	120 ± 4.4
	10,000	100 ± 10.0[e]	138 ± 12.5	129 ± 12.1
Trial summary		Negative	Negative	Negative
Positive control		422 ± 14.1	590 ± 15.9	490 ± 16.5
TA98	0.00	19 ± 1.2	25 ± 3.2	30 ± 3.7
	0.05			35 ± 1.8
	0.10			56 ± 4.8
	0.25			49 ± 5.5
	0.50			69 ± 4.8
	1.00			27 ± 5.1
	100.00	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	
	10,000.00	15 ± 2.6[e]	24 ± 3.8	
Trial summary		Negative	Negative	Negative
Positive control		667 ± 85.0	274 ± 32.1	93 ± 8.1

TABLE E1d
Mutagenicity of Dichloromethane in *Salmonella typhimurium* (continued)

Strain	Dose	Revertants/plate					
		-S9		+hamster S9		+rat S9	
		Trial 1	Trial 2	10%	30%	10%	30%
Test 2 - Study performed using preincubation protocol							
TA100	0	137 ± 4.4	167 ± 10.2	179 ± 7.9	108 ± 8.2	126 ± 6.9	134 ± 10.4
	100	134 ± 3.2	188 ± 1.2	190 ± 1.3	125 ± 5.5	129 ± 14.3	118 ± 16.1
	333	139 ± 4.0	190 ± 4.5	179 ± 2.6	132 ± 6.8	145 ± 5.7	132 ± 13.3
	1,000	101 ± 1.5	193 ± 3.1	186 ± 7.1	123 ± 3.8	131 ± 9.0	105 ± 12.4
	3,333	118 ± 10.7	188 ± 4.3	169 ± 5.0	113 ± 4.4	105 ± 2.3	116 ± 5.3
	6,666		175 ± 10.8	159 ± 3.6			
	10,000	93 ± 8.4			95 ± 7.5[e]	108 ± 10.1	92 ± 4.6[e]
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		360 ± 14.7	470 ± 11.0	1,180 ± 35.5	579 ± 21.7	594 ± 44.0	404 ± 32.9
TA1535	0	21 ± 1.2	28 ± 2.8	13 ± 1.5	10 ± 2.9	8 ± 0.0	11 ± 1.2
	100	18 ± 3.8	31 ± 2.0	8 ± 1.3	8 ± 1.9	12 ± 1.5	11 ± 1.5
	333	19 ± 2.9	25 ± 2.6	13 ± 0.6	10 ± 2.8	15 ± 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 ± 2.4	25 ± 0.0	10 ± 0.9	10 ± 0.7	12 ± 1.2	12 ± 0.9
	6,666						
	10,000	11 ± 1.2	20 ± 4.9	9 ± 1.5	8 ± 0.3	8 ± 2.3	9 ± 1.2
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		331 ± 16.4	354 ± 19.0	219 ± 9.0	431 ± 35.8	118 ± 8.0	143 ± 4.5
TA1537	0	13 ± 1.9			10 ± 1.5		13 ± 0.3
	100	12 ± 2.5			9 ± 1.5		11 ± 2.7
	333	11 ± 2.0			9 ± 0.3		13 ± 2.8
	1,000	9 ± 1.0			13 ± 0.9		14 ± 0.7
	3,333	10 ± 2.7			8 ± 2.3		8 ± 0.9
	6,666						
	10,000	10 ± 1.9			12 ± 0.6		9 ± 0.6
Trial summary		Negative			Negative		Negative
Positive control		653 ± 32.8			80 ± 11.6		48 ± 8.0
TA97	0	168 ± 2.9	196 ± 10.1	182 ± 4.8	170 ± 17.0	199 ± 15.8	198 ± 11.0
	100	169 ± 4.6	205 ± 3.4	197 ± 4.5	194 ± 8.6	187 ± 2.6	215 ± 4.2
	333	169 ± 4.1	213 ± 1.5	214 ± 3.2	207 ± 2.6	178 ± 9.9	211 ± 6.9
	1,000	169 ± 7.5	216 ± 2.4	212 ± 3.5	187 ± 9.7	227 ± 2.9	203 ± 4.0
	3,333	161 ± 6.4	211 ± 5.2	192 ± 2.5	184 ± 9.6	196 ± 5.0	170 ± 9.8
	6,666						
	10,000	149 ± 1.9	189 ± 9.2	176 ± 3.4	179 ± 7.9	165 ± 25.2	159 ± 8.2
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		818 ± 40.9	661 ± 35.0	694 ± 55.9	530 ± 23.0	519 ± 25.6	473 ± 27.8

TABLE E1d
Mutagenicity of Dichloromethane in *Salmonella typhimurium* (continued)

Strain	Dose	Revertants/plate					
		-S9		+hamster 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 ± 2.2	20 ± 2.6	31 ± 3.9	20 ± 1.8	32 ± 6.4	40 ± 1.5
	333	15 ± 3.8	17 ± 2.1	31 ± 3.0	27 ± 2.2	32 ± 2.9	28 ± 0.7
	1,000	15 ± 4.2	18 ± 3.1	35 ± 3.8	33 ± 2.6	29 ± 0.9	35 ± 4.2
	3,333	14 ± 0.3	19 ± 1.5	32 ± 2.0	22 ± 1.5	32 ± 3.8	31 ± 4.2
	6,666		18 ± 0.9	32 ± 2.7		32 ± 3.2	
	10,000	14 ± 2.1			16 ± 2.2[e]		17 ± 2.3[e]
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		558 ± 20.6	609 ± 23.7	1,029 ± 45.5	454 ± 62.7	385 ± 8.4	170 ± 11.3

[a] The detailed protocol and these data are presented in Zeiger (1990).
[b] Revertants are presented as mean ± the standard error from three plates.
[c] Doses are given as mL/desiccator for the desiccator protocol test and μg/plate for the preincubation protocol tests.
[d] The positive controls in the absence of metabolic activation were sodium azide (TA100 and TA1535), 9-aminoacridine (TA97 and TA1537), and 4-nitro-*o*-phenylenediamine (TA98). The positive control for metabolic activation with all strains was 2-aminoanthracene.
[e] Slight toxicity

TABLE E2
Induction of Trifluorothymidine Resistance in L5178Y Mouse Lymphoma Cells by Dichloromethane[a]

Compound	Concentration	Cloning Efficiency (%)	Relative Total Growth (%)	Mutant Count	Mutant Fraction[b]	Average Mutant Fraction[c]
-S9						
Trial 1						
Ethanol						
		80	110	97	40	
		103	104	92	30	
		98	99	74	25	
		81	87	73	30	31
Methylmethanesulfonate (μg/mL)						
		67	53	521	259	
	5	66	52	564	286	
		54	49	558	342	296*
Dichloromethane (μL/mL)						
	0.5	102	93	128	42	
		81	107	114	47	
		105	122	97	31	40
	1.0	86	91	102	39	
		81	103	100	41	
		80	104	98	41	40
	2.0	65	58	119	61	
		83	61	143	58	
		91	71	140	51	57*
	3.0[d]	Lethal				
		Lethal				
		Lethal				

* Significant ($P \leq 0.05$) positive response

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

[b] Mean ± standard error from three replicate plates of approximately 10^6 cells each.

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

[d] Precipitation of dichloromethane occurred at this dose level.

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						
Trial 2						
Ethanol						
		83	94	74	30	
		80	98	80	33	
		82	96	84	34	
		99	112	92	31	32
Methylmethanesulfonate (μg/mL)						
		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	38	
		100	115	77	26	32
	0.50	88	84	95	36	
		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	
		72	102	93	43	
		83	80	102	41	43
	1.50	97	84	128	44	
		96	93	111	39	
		91	44	144	53	45
	2.00	76	79	95	41	
		81	66	132	55	
		73	55	96	44	47
	3.00[d]	Lethal				
		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						
Trial 3						
Ethanol						
		97	112	67	23	
		88	109	89	34	
		85	78	80	31	
		90	100	97	36	31
Methylmethanesulfonate (μg/mL)						
		94	79	192	68	
	5	76	80	217	95	82[c]
Dichloromethane (μL/mL)						
	1.00	54	59	71	44	
		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[d]	87	34	77	30	
		69	24	104	50	40
		Lethal				
	2.50[d]	85	23	140	55	
		74	35	112	51	
		77	33	129	56	54[c]

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						
Trial 1						
Ethanol						
		69	90	154	75	
		83	93	112	45	
		90	101	82	30	
		95	117	108	38	47
Methylcholanthrene (μg/mL)						
		63	28	643	338	
	2.5	76	43	721	318	
		60	21	697	389	348*
Dichloromethane (μL/mL)						
	0.25	89	82	190	71	
		82	63	114	46	
		83	84	123	49	56
	0.50	81	55	154	64	
		80	70	150	63	
		88	82	138	52	60
	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	
		107	58	257	80	82*
	3.00[d]	80	15	206	85	
		77	25	216	94	
		99	27	185	62	81*

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						
Trial 2						
Ethanol						
		88	92	124	47	
		79	117	111	47	
		86	127	89	35	
		68	63	121	59	47
Methylcholanthrene (μg/mL)						
		50	18	780	517	
	2.5	44	23	721	552	
		71	29	822	385	485[c]
Dichloromethane (μL/mL)						
	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
	1.00	76	83	145	64	
		100	77	181	61	
		79	62	156	66	63
	1.50	76	71	185	81	
		94	72	147	52	
		69	52	147	72	68
	2.00	93	68	202	73	
		78	59	159	68	70
		Lethal				
	3.00[d]	63	14	239	127	
		78	19	187	80	
		67	11	335	166	124[c]

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						
Trial 3						
Ethanol						
		111	94	211	64	
		82	83	165	67	
		104	111	194	62	
		117	113	192	54	62
Methylcholanthrene (μg/mL)						
		65	33	822	425	
	2.5	79	57	624	264	
		84	52	910	360	350*
Dichloromethane (μL/mL)						
	1.00	84	82	154	61	
		91	77	186	68	
		62	66	155	84	71
	1.50	93	82	152	54	
		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[d]	101	51	228	75	
		103	66	196	63	
		87	44	167	64	67
	2.50	81	27	199	82	
		97	37	187	65	
		93	29	150	54	67

TABLE E3
Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by Dichloromethane[a]

Compound	Dose (μg/mL)	Total Cells	No. of Chromosomes	No. of SCEs	SCEs/ Chromosome	SCEs/ Cell	Hrs in BrdU	Relative SCEs/ Chromosome[b] (%)
-S9								
Trial 1								
Summary: Negative								
Negative		50	1,045	381	0.36	7.6	26.0	
Mitomycin-C	0.0005	50	1,030	556	0.53	11.1	26.0	48.06
	0.0050	10	208	296	1.42	29.6	26.0	290.32
Dichloromethane								
	160	50	1,038	432	0.41	8.6	26.0	14.15
	500	50	1,043	411	0.39	8.2	26.0	8.08
	1,600	50	1,033	419	0.40	8.4	26.0	11.25
	5,000	50	1,040	425	0.40	8.5	26.0	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	50	1,048	500	0.47	10.0	26.0	38.24
	0.6	10	210	196	0.93	19.6	26.0	170.44
Dichloromethane								
	160	50	1,049	353	0.33	7.1	26.0	-2.50
	500	50	1,050	368	0.35	7.4	26.0	1.55
	1,600	50	1,045	387	0.37	7.7	26.0	7.30
	5,000	50	1,048	376	0.35	7.5	26.0	3.96
								P=0.146

[a] 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).
[b] SCEs/chromosome of culture exposed to dichloromethane relative to those of culture exposed to solvent
[c] 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[a]

-S9					+S9				
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 - Harvest time: 12.0 hours Summary: Negative					**Trial 1** - Harvest time: 13.0 hours Summary: Negative				
Negative					Negative				
	200	0	0.00	0.0	200	2	0.01	1.0	
Mitomycin-C					Cyclophosphamide				
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
Dichloromethane					Dichloromethane				
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

[a] 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).
[b] 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

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[a]

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

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

TABLE 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[a]

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

* Significantly different (P≤0.05) from the control group by Williams' or Dunnett's test
[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

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[a]

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

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error
[b] n=9
[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 Tricaprylin[a]

	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 ± 2.7	49.2 ± 2.3	51.7 ± 2.0*
Hemoglobin (g/dL)	15.6 ± 0.4	17.3 ± 0.8	16.7 ± 0.6	17.5 ± 0.6*
Erythrocytes ($10^6/\mu L$)	8.77 ± 0.31	9.72 ± 0.41	9.30 ± 0.34	9.91 ± 0.32*
Mean cell volume (fL)	52.3 ± 1.0	51.8 ± 0.7	52.9 ± 0.8	52.3 ± 0.8
Mean cell hemoglobin (pg)	17.8 ± 0.3	17.8 ± 0.3	18.0 ± 0.2	17.7 ± 0.2
Mean cell hemoglobin concentration (g/dL)	34.2 ± 0.3	34.2 ± 0.4	34.1 ± 0.3	33.8 ± 0.3
Reticulocytes ($10^6/\mu L$)	0.22 ± 0.03[b]	0.25 ± 0.03	0.18 ± 0.03[c]	0.24 ± 0.02
Leukocytes ($10^3/\mu L$)	2.91 ± 0.40	2.82 ± 0.21	2.90 ± 0.37	3.50 ± 0.40
Segmented neutrophils ($10^3/\mu L$)	1.26 ± 0.25	1.17 ± 0.15	0.96 ± 0.10	1.79 ± 0.31
Lymphocytes ($10^3/\mu L$)	1.46 ± 0.20	1.40 ± 0.13	1.72 ± 0.29	1.52 ± 0.17
Monocytes ($10^3/\mu L$)	0.17 ± 0.02	0.21 ± 0.02	0.18 ± 0.05	0.15 ± 0.03
Eosinophils ($10^3/\mu L$)	0.02 ± 0.01	0.05 ± 0.01	0.04 ± 0.01	0.04 ± 0.02
Nucleated erythrocytes ($10^3/\mu L$)	0.03 ± 0.02	0.06 ± 0.02	0.03 ± 0.02[c]	0.01 ± 0.01

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
[a] Mean ± standard error
[b] n=8
[c] n=7

APPENDIX H
CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

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 ± 0.001% water. USP methods of titration indicated an acid value of 1.82 ± 0.03 mg KOH/g sample, equivalent to 0.467 ± 0.007% octanoic acid, a saponification value of 345 ± 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 ± 0.02% water. USP methods of titration indicated an acid value of 2.27 ± 0.09 mg KOH/g sample, equivalent to 0.58 ± 0.02% octanoic acid, a saponification value of 358 ± 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 A and a major spot and a minor, a trace, a slight trace, and a very 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 5.6% 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 ± 0.03 mg KOH/g sample, equivalent to 0.155 ± 0.007% octanoic acid, a saponification value of 354 ± 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° C. The bulk chemical was stored in amber glass containers at 4° ± 3° 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° to 250° C at 10° 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 ± 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.

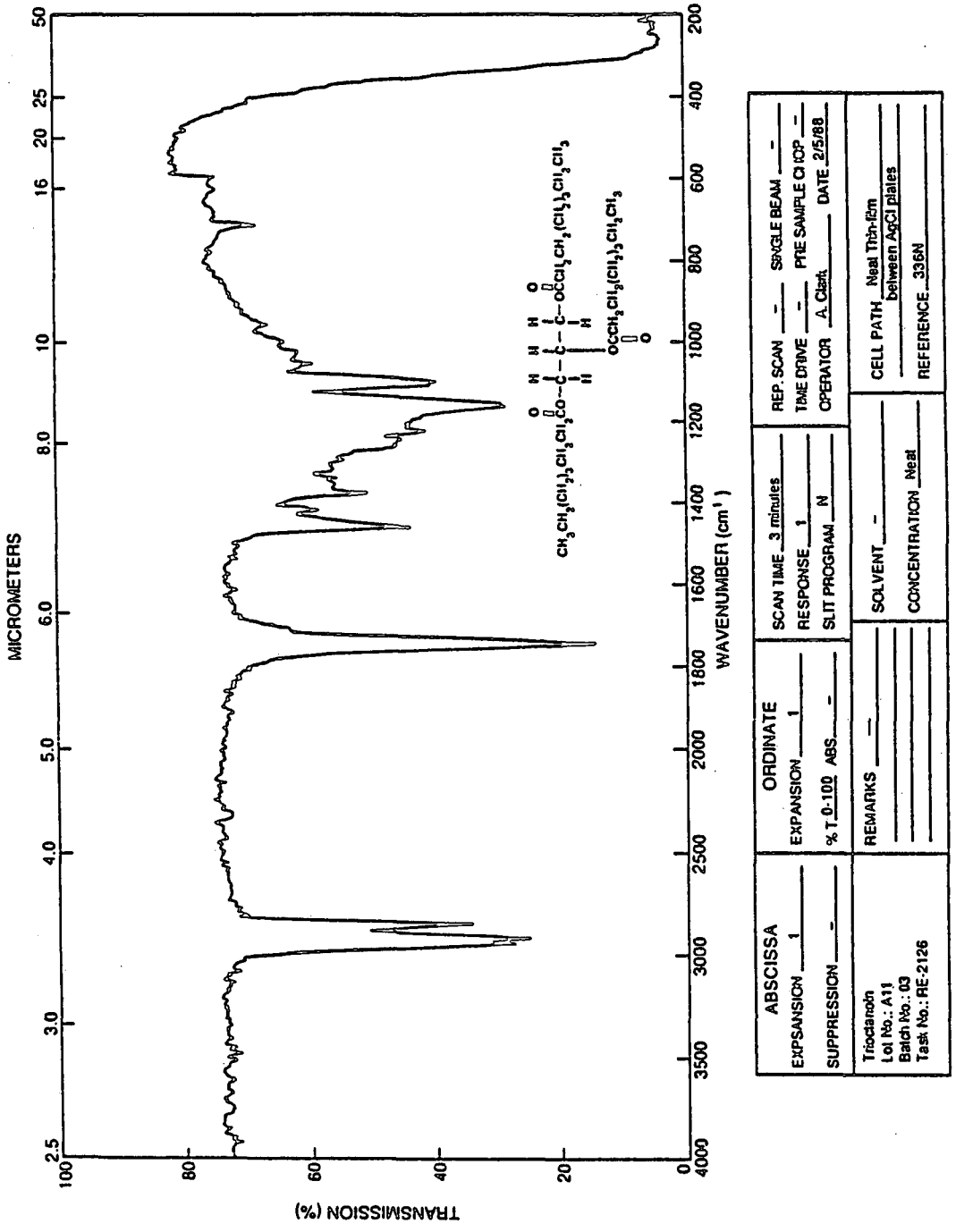


FIGURE III1
Infrared Absorption Spectrum of Tricaprylin

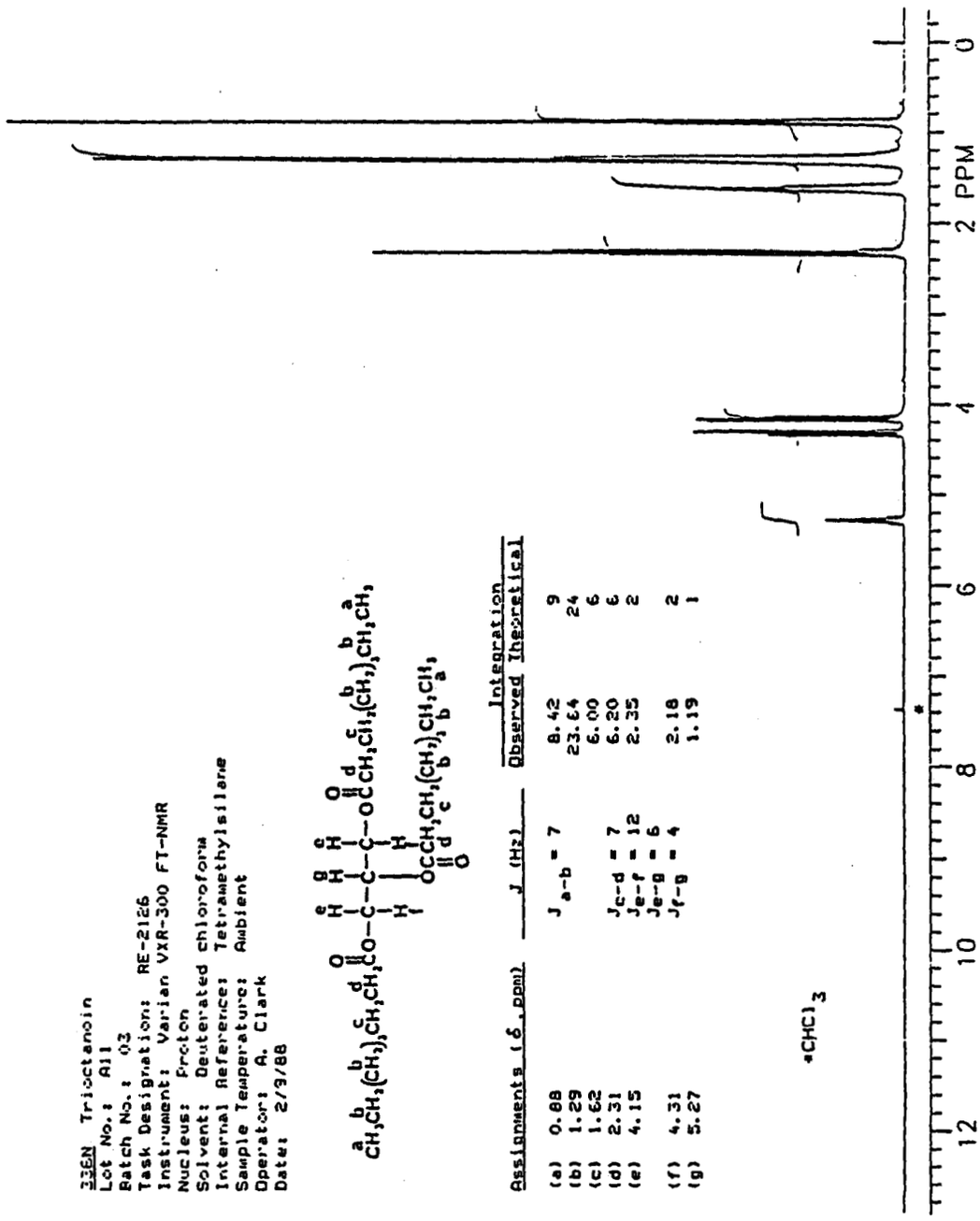


FIGURE II2
Nuclear Magnetic Resonance Spectrum of Tricaprylin

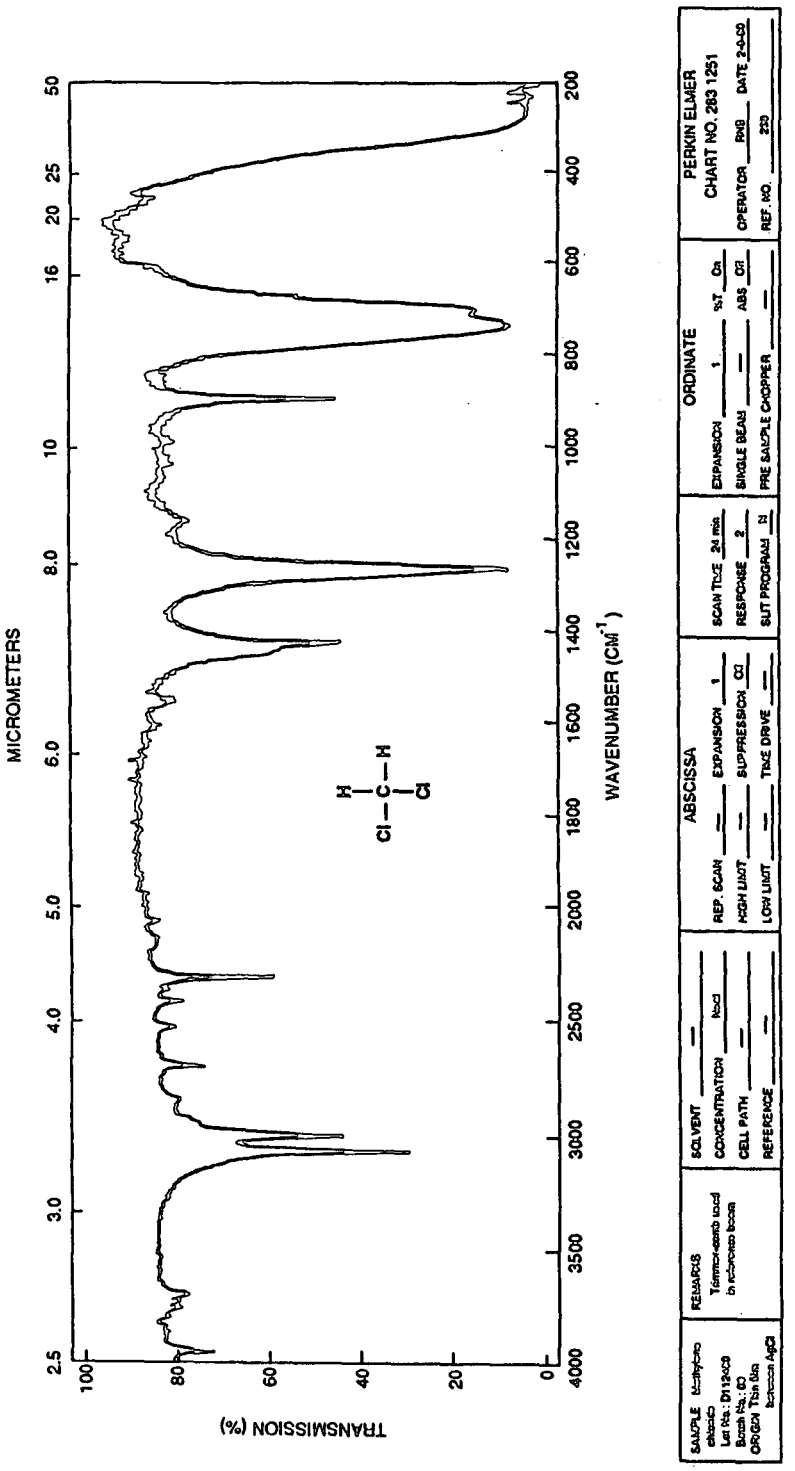


FIGURE H3
Infrared Absorption Spectrum of Dichloromethane

TABLE H1
Characteristics and Approximate Composition of Corn Oil

	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[a]	191	191
Color	1.7 R/12 Y	2.3 R/14 Y
Components		
Glycerides[a]	>98.7%	>98.7%
Unsaponifiable matter[a]	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[b]	<10 ppb[b]
Aflatoxin	<0.5 ppb[b]	<0.5 ppb[b]
Heavy metals (Pb, Cu, Ni, Fe)	<0.1 ppm[b]	<0.1 ppm[b]
Estrogenic activity[a]	None detectable (<5 ppb[b])	None detectable (<5 ppb[b])
Fatty Acid (grams/100 grams of corn oil)		
Total fatty acids	94.3	94.3
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	56.8
Unsaponifiables[a] (% of oil)	**1.25**	**1.25**
Phytosterols	>1.0	>1.0
Stigmasterol[a]	0.07	0.07
β-Sitosterol[a]	0.8	0.8
γ-Sitosterol or Campesterol[a]	0.2	0.2
Tocopherols - total	0.126	0.098
α-Tocopherol	0.032	0.014
γ-Tocopherol	0.091	0.084
δ-Tocopherol	0.003	<0.001
Ubiquinone (coenzyme Q-9)[a]	0.02	<0.02
Squalene[a]	Trace	Trace
Carotenoids[a]	Trace	Trace

[a] From historical experience; not analyzed
[b] Limits of detection

TABLE H2
Preparation and Storage of Dose Formulations 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
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[a] (mg/g)	Determined Concentration[b] (mg/g)	Difference from Target (%)
15 January 1986	17 January 1986	53.7	49.9	–7
		105.6	97.8	–7
		204.5	186.6	–9
	31 January 1986[c]	53.7	48.8	–9
		105.6	96.3	–9
		204.5	188.1	–8
5 March 1986	7 March 1986	53.7	52.4	–2
		105.6	102.2	–3
		204.5	198.4	–3
7 May 1986	8 May 1986	53.7	51.6	–4
		105.6	103.0	–3
		204.5	196.2	–4
2 July 1986	3 July 1986	53.7	52.1	–3
		105.6	101.1	–4
		204.5	194.2	–5
	28 August 1986[c]	53.7	51.6	–4
		105.6	98.4	–7
		204.5	193.1	–6
27 August 1986	28 August 1986	53.7	51.4	–4
		105.6	98.4	–7
		204.5	199.0	–3
22 October 1986	23 October 1986	53.7	49.5	–8
		105.6	96.9	–8
		204.5	187.9	–8
17 December 1986	18 December 1986	53.7	53.8	0
		105.6	104.9	–1
		204.5	199.0	–3
	6 January 1987[c]	53.7	54.9	+2
		105.6	103.3	–2
		204.5	197.5	–3
4 February 1987	4 February 1987	53.7	52.5	–2
		105.6	102.0	–3
		204.5	200.7	–2
8 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 (%)
3 June 1987	3 June 1987	53.7	53.4	–1
		105.6	106.6	+1
		204.5	201.7	–1
	24 June 1987[c]	53.7	51.0	–5
		105.6	102.7	–3
		204.5	199.3	–3
29 July 1987	30 July 1987	53.7	53.1	–1
		105.6	104.1	–1
		204.5	196.7	–4
23 September 1987	24 September 1987	53.7	54.5	+2
		105.6	92.9	–12[d]
		204.5	198.2	–3
28 September 1987[e]	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[c]	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
		105.6	106.3	+1
		204.5	205.8	+1

[a] 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

Date Prepared	Target Concentration (mg/g)	Determined Concentration (mg/g)	
		Study Laboratory[a]	Referee Laboratory[b]
15 January 1986	53.7	49.9	50.0 ± 0.7
2 July 1986	204.5	194.2	194 ± 2
17 December 1986	105.6	104.9	98.6 ± 0.5
3 June 1987	53.7	53.4	51.2 ± 0.4
18 November 1987	105.6	105.7	52.2 ± 0.5
18 November 1987	53.7	53.4	57.7 ± 12.3

[a] Results of duplicate analyses
[b] Results of triplicate analyses

APPENDIX I
FEED CONSUMPTION
IN THE 2-YEAR GAVAGE STUDIES

TABLE I1
Feed Consumption by Male Rats in the 2-Year Gavage Study of Corn Oil

Week	Untreated Control Mean[a]	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
Mean	17.0	16.2	14.6	12.3	9.9

[a] 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	Untreated Control Mean[a]	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

[a] Mean = Average consumption in grams per animal per day

TABLE I3
Feed Consumption by Male Rats in the 2-Year Gavage Study of Tricaprylin

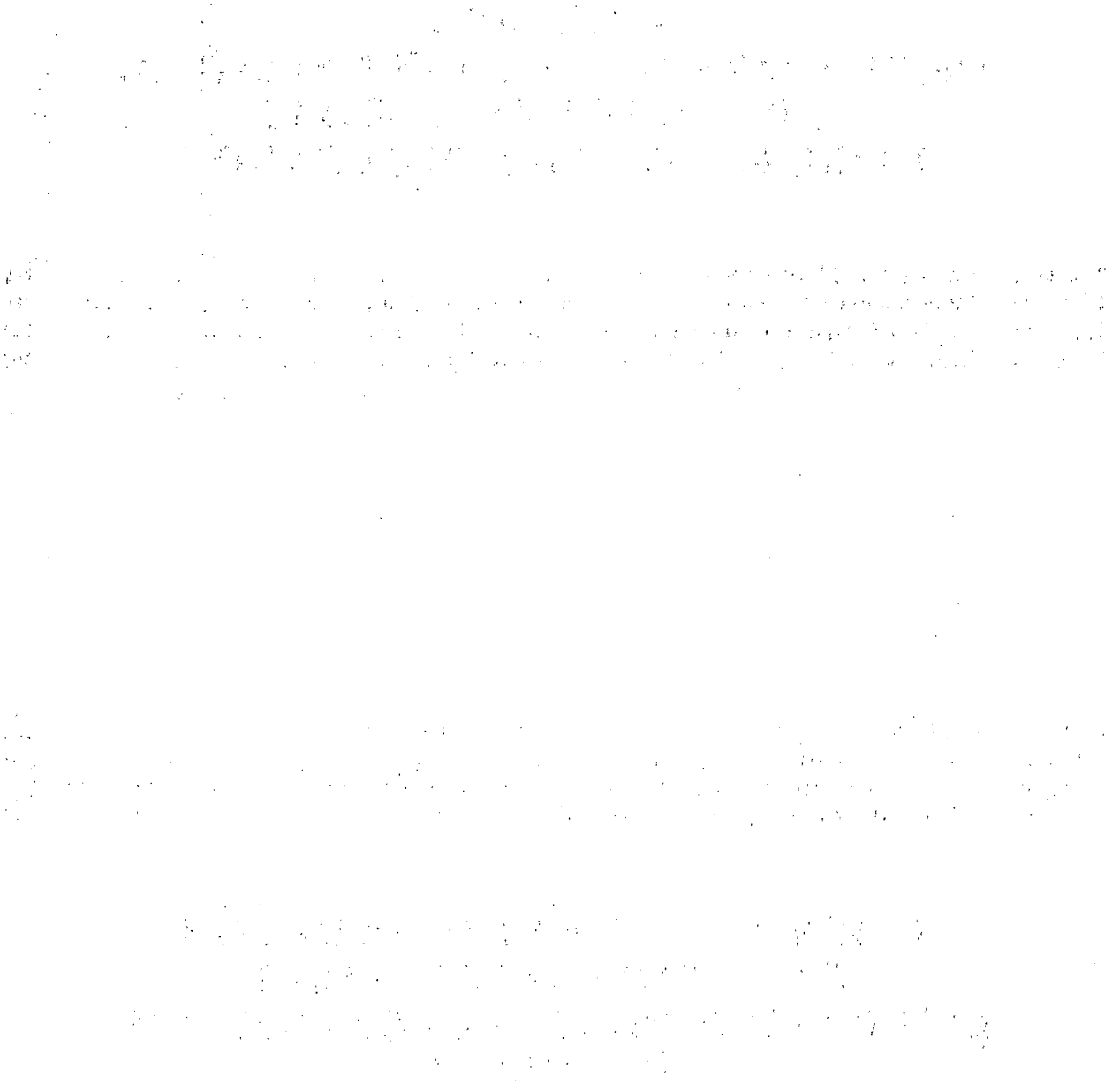
Week	Untreated Control Mean[a]	2.5 mL/kg Mean	5 mL/kg Mean	10 mL/kg Mean
2	14.2	13.7	12.5	11.4
5	16.9	15.9	16.0	14.4
9	17.1	16.5	16.4	13.6
13	13.0	12.1	9.9	8.9
17	20.2	16.9	16.0	13.5
21	15.8	14.9	12.5	10.0
25	18.3	18.3	16.5	13.5
29	17.8	16.2	14.0	12.2
33	17.8	16.3	16.0	13.7
37	18.3	15.6	14.2	12.1
41	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
104	13.5	10.6	9.2	7.6
Mean	17.0	15.1	13.6	11.8

[a] 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[a]	5 mL/kg Mean	10 mL/kg Mean
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
Mean	13.9	12.3	10.1

[a] Mean = Average consumption in grams per animal per day



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[a]

Ingredients[b]	Percent by Weight
Ground #2 yellow shelled corn	24.50
Ground hard winter wheat	23.00
Soybean meal (49% protein)	12.00
Fish meal (60% protein)	10.00
Wheat middlings	10.00
Dried skim milk	5.00
Alfalfa meal (dehydrated, 17% protein)	4.00
Corn gluten meal (60% protein)	3.00
Soy oil	2.50
Dried brewer's yeast	2.00
Dry molasses	1.50
Dicalcium phosphate	1.25
Ground limestone	0.50
Salt	0.50
Premixes (vitamin and mineral)	0.25

[a] NCI, 1976; NIH, 1978
[b] Ingredients ground to pass through a U.S. Standard Screen No. 16 before being mixed

TABLE J2
Vitamins and Minerals in NIH-07 Rat and Mouse Ration[a]

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

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

TABLE J3
Nutrient Composition of NIH-07 Rat and Mouse Ration

Nutrient	Mean ± Standard Deviation	Range	Number of Samples
Protein (% by weight)	22.54 ± 0.70	21.6 – 24.0	32
Crude Fat (% by weight)	5.53 ± 0.28	4.9 – 6.0	32
Crude Fiber (% by weight)	3.45 ± 0.27	2.7 – 4.0	32
Ash (% by weight)	6.64 ± 0.33	6.1 – 7.1	32
Amino Acids (% of total diet)			
Arginine	1.308 ± 0.606	1.210 – 1.390	8
Cystine	0.306 ± 0.084	0.181 – 0.400	8
Glycine	1.150 ± 0.047	1.060 – 1.210	8
Histidine	0.576 ± 0.024	0.531 – 0.607	8
Isoleucine	0.917 ± 0.029	0.881 – 0.944	8
Leucine	1.946 ± 0.055	1.850 – 2.040	8
Lysine	1.270 ± 0.058	1.200 – 1.370	8
Methionine	0.448 ± 0.128	0.306 – 0.699	8
Phenylalanine	0.987 ± 0.140	0.665 – 1.110	8
Threonine	0.877 ± 0.042	0.824 – 0.940	8
Tryptophan	0.236 ± 0.176	0.107 – 0.671	8
Tyrosine	0.676 ± 0.105	0.564 – 0.794	8
Valine	1.103 ± 0.040	1.050 – 1.170	8
Essential Fatty Acids (% of total diet)			
Linoleic	2.393 ± 0.258	1.830 – 2.570	7
Linolenic	0.280 ± 0.040	0.210 – 0.320	7
Vitamins			
Vitamin A (IU/kg)	6,997 ± 2,045	4,430 – 13,000	32
Vitamin D (IU/kg)	4,450 ± 1,382	3,000 – 6,300	4
α-Tocopherol (ppm)	37.95 ± 9.406	22.5 – 48.9	8
Thiamine (ppm)	19.75 ± 2.59	14.0 – 26.0	32
Riboflavin (ppm)	7.92 ± 0.87	6.10 – 9.00	8
Niacin (ppm)	103.4 ± 26.59	65.0 – 150.0	8
Pantothenic acid (ppm)	29.54 ± 3.60	23.0 – 34.0	8
Pyridoxine (ppm)	9.55 ± 3.48	5.60 – 14.0	8
Folic acid (ppm)	2.25 ± 0.73	1.80 – 3.70	8
Biotin (ppm)	0.254 ± 0.042	0.19 – 0.32	8
Vitamin B_{12} (ppb)	38.45 ± 22.01	10.6 – 65.0	8
Choline (ppm)	3,089 ± 328.69	2,400 – 3,430	8
Minerals			
Calcium (%)	1.21 ± 0.12	1.00 – 1.40	32
Phosphorus (%)	0.92 ± 0.06	0.73 – 1.00	32
Potassium (%)	0.883 ± 0.078	0.772 – 0.971	6
Chloride (%)	0.526 ± 0.092	0.380 – 0.635	8
Sodium (%)	0.313 ± 0.390	0.258 – 0.371	8
Magnesium (%)	0.168 ± 0.010	0.151 – 0.181	8
Sulfur (%)	0.280 ± 0.064	0.208 – 0.420	8
Iron (ppm)	360.5 ± 100	255.0 – 523.0	8
Manganese (ppm)	92.0 ± 6.01	81.70 – 99.40	8
Zinc (ppm)	54.72 ± 5.67	46.10 – 64.50	8
Copper (ppm)	11.06 ± 2.50	8.090 – 15.39	8
Iodine (ppm)	3.37 ± 0.92	1.52 – 4.13	6
Chromium (ppm)	1.79 ± 0.36	1.04 – 2.09	8
Cobalt (ppm)	0.681 ± 0.14	0.490 – 0.780	4

TABLE J4
Contaminant Levels in NIH-07 Rat and Mouse Ration

	Mean ± Standard Deviation[a]	Range	Number of Samples
Contaminants			
Arsenic (ppm)	0.46 ± 0.32	0.05 – 1.07	32
Cadmium (ppm)[b]	0.10 ± 0.01	0.10 – 0.20	32
Lead (ppm)	0.34 ± 0.25	0.05 – 1.00	32
Mercury (ppm)	<0.05		32
Selenium (ppm)	0.37 ± 0.10	0.16 – 0.63	32
Aflatoxins (ppb)	<5.0		32
Nitrate nitrogen (ppm)[c]	21.03 ± 9.03	11.0 – 41.0	32
Nitrite nitrogen (ppm)[c]	0.37 ± 0.64	<0.10 – 2.60	32
BHA (ppm)[d]	2.41 ± 1.03	<0.10 – 5.00	32
BHT (ppm)[d]	1.13 ± 0.65	<0.10 – 4.00	32
Aerobic plate count (CFU/g)[e]	63,174 ± 83,703	3,100 – 320,000	31
Aerobic plate count (CFU/g)[f]	90,575 ± 175,516	3,100 – 940,000	32
Coliform (MPN/g)[g]	9.26 ± 26.42	<3.00 – 150	31
Coliform (MPN/g)[h]	43.34 ± 195	<3.00 – 1,100	32
E. coli (MPN/g)[i]	3.03 ± 0.18	<3.00 – 4.00	32
Total nitrosoamines (ppb)[j]	9.75 ± 4.24	3.80 – 19.50	32
N-Nitrosodimethylamine (ppb)[j]	7.91 ± 3.46	2.80 – 16.00	32
N-Nitropyrrolidine (ppb)[j]	1.84 ± 1.35	0.90 – 5.40	32
Pesticides (ppm)			
α-BHC[k]	<0.01		32
β-BHC	<0.02		32
γ-BHC	<0.01		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
HCB	<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 ± 0.16	0.05 – 0.60	32
Endosulfan I	<0.01		32
Endosulfan 2	<0.01		32
Endosulfan sulfate	<0.03		32

TABLE J4
Contaminant Levels in NIH-07 Rat and Mouse Ration (continued)

[a] For values less than the limit of detection, the detection limit is given for the mean.
[b] One lot milled 4 June 1986 contained 0.20 ppm; all others measured 0.10 ppm or less.
[c] Sources of contamination: alfalfa, grains, and fish meal
[d] Sources of contamination: soy oil and fish meal
[e] CFU = colony forming unit; excludes one high value of 940,000 CFU/g obtained in the lot milled 5 November 1987
[f] Includes one high value of 940,000 CFU/g obtained in the lot milled 5 November 1987
[g] MPN = most probable number; excludes one high value of 1,100 MPN/g obtained in the lot milled 5 July 1988
[h] Includes one high value of 1,100 MPN/g obtained in the lot milled 5 July 1988
[i] Includes one value of 4 MPN/g from the lot milled 4 April 1988
[j] All values were correct for % recovery.
[k] BHC = hexachlorocyclohexane or benzene hexachloride
[l] Seventeen lots contained more than 0.05 ppm.

APPENDIX K
SENTINEL ANIMAL PROGRAM

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 Tricaprylin Studies		
Preinitiation	0/5	None positive
5½ months	0/2	None positive
6 months	1/5	RCV/SDA[a]
7 months	0/5	None positive
12 months	0/5	None positive
18 months	0/5	None positive
24 months	0/10	None positive
Dichloromethane 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

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 γ-glutamyl tranferase. 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^2 of tissue and then formulae for quantitative stereology are applied to calculate the focus number per cm^3, 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 carcinogen-induced 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 azaserine-induced 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 camostate-containing 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^3	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 ±0.8

* $p < 0.05$, 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	Other
Lard	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 occuring 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.

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Submitted/In Preparation

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TR No.	CHEMICAL
201	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (Dermal)
206	1,2-Dibromo-3-chloropropane
207	Cytembena
208	FD & C Yellow No. 6
209	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (Gavage)
210	1,2-Dibromoethane
211	C.I. Acid Orange 10
212	Di(2-ethylhexyl)adipate
213	Butyl Benzyl Phthalate
214	Caprolactam
215	Bisphenol A
216	11-Aminoundecanoic Acid
217	Di(2-Ethylhexyl)phthalate
219	2,6-Dichloro-p-phenylenediamine
220	C.I. Acid Red 14
221	Locust Bean Gum
222	C.I. Disperse Yellow 3
223	Eugenol
224	Tara Gum
225	D & C Red No. 9
226	C.I. Solvent Yellow 14
227	Gum Arabic
228	Vinylidene Chloride
229	Guar Gum
230	Agar
231	Stannous Chloride
232	Pentachloroethane
233	2-Biphenylamine Hydrochloride
234	Allyl Isothiocyanate
235	Zearalenone
236	*D*-Mannitol
237	1,1,1,2-Tetrachloroethane
238	Ziram
239	Bis(2-chloro-1-Methylethyl)ether
240	Propyl Gallate
242	Diallyl Phthalate (Mice)
243	Trichlorethylene (Rats and Mice)
244	Polybrominated Biphenyl Mixture
245	Melamine
246	Chrysotile Asbestos (Hamsters)
247	L-Ascorbic Acid
248	4,4′-Methylenedianiline Dihydrochloride
249	Amosite Asbestos (Hamsters)
250	Benzyl Acetate
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252	Geranyl Acetate
253	Allyl Isovalerate
254	Dichloromethane (Methylene Chloride)
255	1,2-Dichlorobenzene
257	Diglycidyl Resorcinol Ether
259	Ethyl Acrylate
261	Chlorobenzene
263	1,2-Dichloropropane
266	Monuron
267	1,2-Propylene Oxide
269	Telone II® (1,3-Dichloropropene)
271	HC Blue No. 1
272	Propylene
273	Trichloroethylene (Four Rat Strains)
274	Tris(2-ethylhexyl)phosphate
275	2-Chloroethanol
276	8-Hydroxyquinoline
277	Tremolite
278	2,6-Xylidine
279	Amosite Asbestos
280	Crocidolite Asbestos
281	HC Red No. 3
282	Chlorodibromomethane
284	Diallylphthalate (Rats)
285	C.I. Basic Red 9 Monohydrochloride
287	Dimethyl Hydrogen Phosphite
288	1,3-Butadiene
289	Benzene
291	Isophorone
293	HC Blue No. 2
294	Chlorinated Trisodium Phosphate
295	Chrysotile Asbestos (Rats)
296	Tetrakis(hydroxymethyl) phosphonium Sulfate & Tetrakis(hydroxymethyl) phosphonium Chloride
298	Dimethyl Morpholinophosphoramidate
299	C.I. Disperse Blue 1
300	3-Chloro-2-methylpropene
301	*o*-Phenylphenol
303	4-Vinylcyclohexene
304	Chlorendic Acid
305	Chlorinated Paraffins (C_{23}, 43% chlorine)
306	Dichloromethane (Methylene Chloride)
307	Ephedrine Sulfate
308	Chlorinated Pariffins (C_{12}, 60% chlorine)
309	Decabromodiphenyl Oxide
310	Marine Diesel Fuel and JP-5 Navy Fuel
311	Tetrachloroethylene (Inhalation)
312	*n*-Butyl Chloride
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314	Methyl Methacrylate
315	Oxytetracycline Hydrochloride
316	1-Chloro-2-methylpropene
317	Chlorpheniramine Maleate
318	Ampicillin Trihydrate
319	1,4-Dichlorobenzene
320	Rotenone
321	Bromodichloromethane
322	Phenylephrine Hydrochloride
323	Dimethyl Methylphosphonate
324	Boric Acid
325	Pentachloronitrobenzene
326	Ethylene Oxide
327	Xylenes (Mixed)
328	Methyl Carbamate
329	1,2-Epoxybutane
330	4-Hexylresorcinol
331	Malonaldehyde, Sodium Salt
332	2-Mercaptobenzothiazole
333	*N*-Phenyl-2-naphthylamine
334	2-Amino-5-nitrophenol
335	C.I. Acid Orange 3

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339	2-Amino-4-nitrophenol
340	Iodinated Glycerol
341	Nitrofurantoin
342	Dichlorvos
343	Benzyl Alcohol
344	Tetracycline Hydrochloride
345	Roxarsone
346	Chloroethane
347	D-Limonene
348	α-Methyldopa Sesquihydrate
349	Pentachlorophenol
350	Tribromomethane
351	*p*-Chloroaniline Hydrochloride
352	N-Methylolacrylamide
353	2,4-Dichlorophenol
354	Dimethoxane
355	Diphenhydramine Hydrochloride
356	Furosemide
357	Hydrochlorothiazide
358	Ochratoxin A
359	8-Methoxypsoralen
360	N,N-Dimethylaniline
361	Hexachloroethane
362	4-Vinyl-1-Cyclohexene Diepoxide
363	Bromoethane (Ethyl Bromide)
364	Rhodamine 6G (C.I. Basic Red 1)
365	Pentaerythritol Tetranitrate
366	Hydroquinone
367	Phenylbutazone
368	Nalidixic Acid
369	Alpha-Methylbenzyl Alcohol
370	Benzofuran
371	Toluene
372	3,3-Dimethoxybenzidine Dihydrochloride
373	Succinic Anhydride
374	Glycidol
375	Vinyl Toluene
376	Allyl Glycidyl Ether
377	*o*-Chlorobenzalmalononitrile
378	Benzaldehyde
379	2-Chloroacetophenone
380	Epinephrine Hydrochloride
381	*d*-Carvone
382	Furfural
384	1,2,3-Trichloropropane
385	Methyl Bromide
386	Tetranitromethane
387	Amphetamine Sulfate
388	Ethylene Thiourea
389	Sodium Azide
390	3,3′-Dimethylbenzidine Dihydrochloride
391	Tris(2-chloroethyl) Phosphate
392	Chlorinated Water and Chloraminated Water
393	Sodium Fluoride
394	Acetaminophen
395	Probenecid
396	Monochloroacetic Acid
397	C.I. Direct Blue 15
398	Polybrominated Biphenyls
399	Titanocene Dichloride
400	2,3-Dibromo-1-propanol
401	2,4-Diaminophenol Dihydrochloride
402	Furan
403	Resorcinol
404	5,5-Diphenylhydantoin
405	C.I. Acid Red 114
406	γ-Butyrolactone
407	C.I. Pigment Red 3
408	Mercuric Chloride
409	Quercetin
410	Naphthalene
411	C.I. Pigment Red 23
412	4,4-Diamino-2,2-stilbenedisulfonic Acid
413	Ethylene Glycol
414	Pentachloroanisole
415	Polysorbate 80
416	*o*-Nitroanisole
417	*p*-Nitrophenol
418	*p*-Nitroaniline
419	HC Yellow 4
420	Triamterene
421	Talc
422	Coumarin
423	Dihydrocoumarin
424	*o*-Benzyl-*p*-chlorophenol
425	Promethazine Hydrochloride
427	Turmeric Oleoresin
428	Manganese (II) Sulfate Monohydrate
430	C.I. Direct Blue 218
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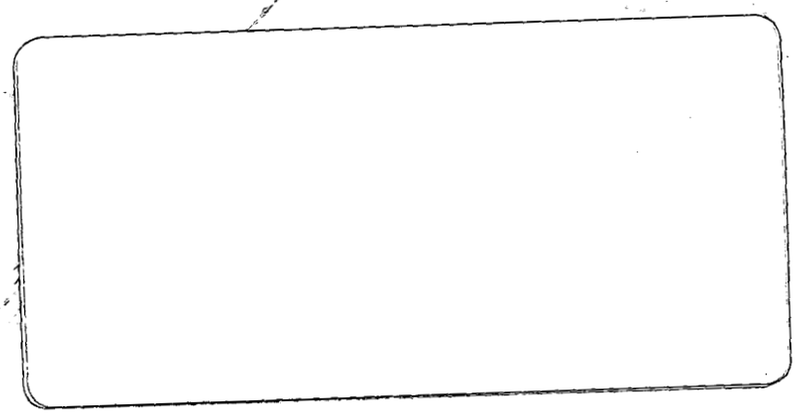

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